Welcome to the 4th Berlin Summer Meeting, June 23 – 25, 2011

A conference organised by the Berlin Institute for Medical Systems Biology (BIMSB) at the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, funded by:

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Welcome Address

Dear colleagues and guests,

We're looking forward to the 4th Berlin Summer Meeting where we aim to discuss general principles of gene regulation “From RNA to Protein and beyond”.

Within the last decade, RNA biology and post-transcriptional regulation became a major focus in life sciences. At the same time, proteins, their post-translational modifications and interactions are now studied at a global scale. Understanding how the combined action of these regulatory processes affects the physiology of cells, organs and organisms is an important task for systems biology. Another challenge is to develop suitable experimental and computational approaches.

The Berlin Summer Meeting traditionally invites leading scientists to present and discuss experimental and computational approaches in an intense and open atmosphere. We would like to foster intellectual exchange between various areas of biology and stimulating interactions of leading scientists and young researchers in Berlin and beyond.

The Berlin Summer Meeting is coordinated by the Berlin Institute for Medical Systems Biology (BIMSB) at the MDC, Berlin-Buch, Germany. We would like to thank our sponsors and funding agencies for financial support and members of the BIMSB and MDC for organizing this first rate scientific meeting.

With best regards,

Anne Ephrussi
Richard Bonneau
Matthias Hentze
Stefan Kempa
Nikolaus Rajewsky
Matthias Selbach
(The Scientific Committee 2011)

PROGRAMM SCHEDULE – BERLIN SUMMER MEETING 2011

(long talks: 45 minutes + 15 min discussion, short talks: 15 minutes + 5 min discussion)

Thursday, 23 June 2011

08:30 - Registration + Coffee

WELCOME

09:00 – 09:10 **Nikolaus Rajewsky**
Welcome to the 4th Berlin Summer Meeting

RNA-Protein Interaction I (Chair: Matthias Hentze)

09:10 – 10:10 **Matthias W. Hentze**
Regulatory RNA-binding proteins: from mechanistic reductionism to complete mRNA interactomes

10:10 – 11:10 **Henning Urlaub**
Mass spectrometric investigation of protein-RNA cross-links

11:10 – 11:40 Coffee Break

11:40 – 12:40 **Thomas Tuschl**
Characterization of regulatory small RNAs and RNA-binding proteins

12:40 – 13:00 **Claudia Carissimi**
High-throughput biochemical identification of miRNA targets pin-points to miR-21 as a novel modulator of TCR Signaling

13:00 – 14:30 Lunch break & poster session (Number of posters to be announced)

Protein-Protein Interaction (Chair: Matthias Selbach)

14:30 – 15:30 **Gianni Cesareni**
Mapping the human phosphatome on growth pathways

15:30 – 16:30 **Anne-Claude Gavin**
Biomolecular networks from proteins to metabolites

16:30 – 17:00 **Coffee Break**

17:00 – 18:00 **Matthias Mann**
Quantitative proteomics as a versatile method to detect specific protein interactions

18:30 – 20:30 Welcome Reception

Friday, 24 June 2011

09:00 – Registration + Coffee

Gene-regulation connects to cell function and metabolism (Chair: Stefan Kempa)

09:30 – 10:30 **Uwe Sauer**
Where and when does transcription control metabolic function?

10:30 – 11:00 Coffee Break

11:00 – 11:20 **Aouefa Amoussouvi**
Counting of Sic1 mRNA molecules in single budding yeast cells to investigate the influence of transcription variability on the G1/S transition

11:20 – 11:40 **Thorsten Cramer**
Inhibition of glycolysis as a novel form of hepatocellular carcinoma therapy

11:40 – 12:00 **Alessandro Prigione**
Reprogramming of energy metabolism upon induction of pluripotency

12:00 – 13:00 **Karen H. Vousden**
Control of metabolism by p53

13:00 – 14:30 Lunch break & poster session

RNA-Protein Interaction II (Chair: Richard Bonneau)

14:30 – 15:30 **Anne Ephrussi**
oskar *RNP assembly and transport in the* Drosophila *oocyte*

15:30 – 15:50 **Helena Jambor**
Systematic analysis of subcellular gene expression patterns in complex tissues

15:50 – 16:10 **Baiba Vilne**
Regulatory networks of hematopoietic stem cells and their micro-environment

16:10 – 16:30 **Uwe Ohler**
miRNA profiling in plants – from identification to function

16:30 – 17:00 Coffee Break

17:00 – 18:00 **Daniel R. Larson**
A single molecule view of the central dogma in yeast

19:30 – 21:30 Berlin from the Boat: Spree-tour (to be booked separately)

Saturday, 25 June 2011

9:00 - Registration + Coffee

Post-transcriptional Regulation (Chair: Anne Ephrussi)

09:30 – 10:30 **Elisa Izaurralde**
Dissecting the molecular mechanisms of miRNA-mediated gene silencing

10:30 – 11:00 **Coffee Break**

11:00 – 12:00 **Nikolaus Rajewsky**
Post-transcriptional gene regulation by small RNAs and RNA binding proteins

12:00 – 13:00 **Michael Hengartner**
RIP-chip-SRM: a new combinatorial large-scale approach to identify miRNA targets in C. elegans

Lunch

POSTER SESSION WILL TAKE PLACE DURING LUNCH BREAKS.
PLEASE WAIT FOR ANNOUNCEMENTS

Speaker Abstracts

Invited speakers abstracts in alphabetical order

Mapping the human phosphatome on growth pathways

Gianni Cesareni[1], Francesca Sacco[1], Pier Francesco Gherardini[1], Antonella Ragnini-Wilson[1, 2], Serena Paoluzi[1], Luisa Castagnoli[1]

[1]University of Rome, Tor Vergata, Rome, Italy
[2]High-throughput Microscopy Facility, Department of Translational and Cellular Pharmacology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy

The ability to address, on a large scale, the functional consequences of knocking down the expression of any gene of interest has considerably sped up gene annotation in complex eukaryotic systems. Typically, the consequences of interfering, by siRNA, large collections of genes, up to entire genomes, on any convenient phenotypic readout can be investigated by established approaches. Thus, genes may be associated to a function of interest if the alteration of their gene products perturbs the phenotypic readout. The mapping procedure, however, is low resolution because, given the intricacy of the gene interaction web in the cell, two genes affecting the same readout may map to different signaling pathways. We have set out to develop an approach that could map, at a higher detail, gene products onto complex pathways. We focused on the task of mapping the 300 human phosphatase gene products onto the growth pathways that respond to cytokine, growth factors and nutrients. To this end we have used a high content phenotypic screening based on siRNA and automated fluorescence microscopy and we have monitored the cell state after knocking down each of the phosphatase genes. Cell state is a “complex” phenotype defined by a combination of five readouts monitoring the activation of five key “sentinel” proteins chosen for their centrality in the pathways and for the robustness of the activation assay. By modeling the available information on the growth pathways that we are testing we can predict the effects of perturbing each node of interest on the cell state defined by the activation/inactivation pattern of the sentinel proteins. Finally, by matching the experimentally determined cell states with the one predicted by the pathway model we can infer the pathway nodes that are likely to be affected by the phosphatase knock down.

oskar RNP assembly and transport in the *Drosophila* oocyte

Anne Ephrussi

European Molecular Biology Laboratory, Heidelberg, Germany

Intracellular localization of mRNAs coupled with their translational regulation is a highly conserved mechanism that allows precise spatial and temporal control of gene expression within cells. In *Drosophila*, precise localization of the mRNAs encoding key embryonic patterning determinants is required for proper development to proceed. *oskar* mRNA, which encodes the posterior patterning determinant of the fly, is transcribed within the nurse cells and transported via cytoplasmic bridges into the oocyte, in which it is ultimately localized at the posterior pole. The assembly of *oskar* mRNPs competent for posterior transport is a multistep process that begins upon splicing and requires the Exon Junction Complex of proteins. New insight into the role of splicing and of the EJC in mRNA transport will be presented.

Biochemical approaches to biomolecular networks

Anne-Claude Gavin

EMBL Heidelberg Developmental Biology Unit, Heidelberg, Germany

Biology does not rely on biomolecules acting in isolation. Biological function depends on the concerted action of molecules acting in protein complexes, pathways or networks. Biomolecular interactions are central to all biological functions. In human, for example, impaired or deregulated protein–protein or protein–metabolite interaction often leads to disease. Recent strategies have been designed that allow the study of interactions more globally at the level of entire biological systems. We will discuss the use of these biochemical approaches to genome-wide screen in model organisms.

Regulatory RNA-binding proteins: from mechanistic reductionism to complete mRNA interactomes

Matthias W. Hentze

European Molecular Biology Laboratory, Heidelberg, Germany

RNA-binding proteins (RBPs) orchestrate virtually all aspects of RNA biology. These include roles as translational regulators whose functions we have studied by means of “reductionist” biochemical approaches investigating instructive model systems. I will present unpublished work on the elucidation of a new RBP-driven (Sex Lethal) regulatory mechanism that could foreshadow a more generally applying principle for mRNAs harboring upstream open reading frames. I will also speak about rapidly progressing system scale work identifying “all” mRNA binding proteins (the “mRNA interactomes”) of different mammalian cells and yeast, and discuss possible implications for RNA biology and cell metabolism.

RIP-chip-SRM: a new combinatorial large-scale approach to identify miRNA targets in *C. elegans*

Michael O. Hengartner

Institute of Molecular Life Sciences, University of Zurich, Zurich, Switzerland

MicroRNAs (miRNAs) are small, non-coding RNAs that negatively regulate gene expression. As miRNAs are involved in a wide range of biological processes and diseases, much effort has been invested in identifying their mRNA targets. We have developed a novel combinatorial approach, RIP-chip-SRM (RNA binding protein immunopurification + microarray + targeted protein quantification via selected reaction monitoring), to identify *de novo* high confidence miRNA targets in the nematode *Caenorhabditis elegans*. We used differential RIP chip analysis of miRNA-induced silencing complexes from wild type and miRNA mutant animals, followed by quantitative targeted proteomics via selected reaction monitoring to identify and validate mRNA targets of the *C. elegans* bantam homologue miR-58. Comparison of total mRNA and protein abundance changes in *mir-58* mutant and wild type animals indicated that the direct bantam/miR-58 targets identified through this approach are mainly regulated at the level of protein synthesis, not mRNA stability.

Dissecting the molecular mechanisms of miRNA-mediated gene silencing

Joerg Braun[1], Eric Huntzinger[1], Latifa Zekri[1], Elisa Izaurralde[1]

[1]Max Planck Institute for Developmental Biology, Tübingen, Germany

MicroRNAs (miRNAs) are genome-encoded ~22 nucleotide-long RNAs that silence gene expression post-transcriptionally by base pairing with the 3' untranslated regions of target mRNAs. To exert their function, miRNAs associate with Argonaute proteins (AGOs) in miRNA-induced silencing complexes (miRISCs), which silence the expression of mRNAs containing partially or fully complementary miRNA-binding sites. In animals, most miRNAs are only partially complementary to their targets. Our group has shown that in this case the AGO proteins are not sufficient to mediate silencing and require interaction with proteins of the GW182 family. We have also shown that AGO-GW182 complexes mediate silencing by promoting translational repression and mRNA deadenylation. Deadenylation decreases translation efficiency and, in somatic cells, commits the mRNA to decapping and 5’-to-3’ exonucleolytic degradation. Our analysis of GW182 protein function has revealed two domains critical for silencing: an N-terminal GW-repeat-containing region conferring binding to AGOs, and a bipartite silencing domain, consisting of Middle and C-terminal regions, which elicits translational repression and degradation of miRNA targets. Exactly how the bipartite silencing domain of GW182 proteins interferes with translation and accelerates deadenylation is not completely understood. We have recently started to address this question by showing that the silencing domains of GW182 interact with the cytoplasmic poly(A)-binding protein 1 (PABPC1), suggesting GW182 proteins are PABP-interacting proteins (Paips) that interfere with the function of PABPC1 in translation and mRNA stabilization. Furthermore, in a screen for proteins interacting with the GW182 silencing domains we identified subunits of the two major cytoplasmic deadenylase complexes: the PAN2-PAN3 and the CCR4-CAF1-NOT complexes, both of which in turn interact with PABPC1. These interactions are conserved and critical for silencing in D. melanogaster and human cells. Together, our findings indicate that the silencing domains of GW182 proteins provide a binding platform for deadenylation factors and PABPC1, creating an intricate network of protein-protein interactions which causes the rapid deadenylation of miRNA targets.

A single molecule description of the central dogma in yeast: from constitutive gene expression to cell-cycle regulation

Daniel R. Larson

National Cancer Institute, National Institutes of Health, Bethesda, USA

Cellular mRNA levels are achieved by the combinatorial complexity of factors controlling synthesis and decay, yet the small number of molecules involved in these pathways fluctuates stochastically. These fluctuations are in turn transmitted to the protein levels . Here we describe a method of fluctuation analysis of fluorescently-labeled RNA to measure dynamics of nascent RNA – including initiation, elongation and termination -- at an active yeast locus. We find no transcriptional memory between initiation events, in contrast to the transcriptional bursting which has been observed in higher eukaryotes. By measuring the abundance and intra-nuclear mobility of an upstream transcription factor, we observe that the gene firing rate is directly determined by trans-activating factor search times. These data imply that for many housekeeping genes in budding yeast, the steady state distribution of mRNA converges on a Poisson distribution. The model that emerges from these single-cell, single-molecule studies is one in which uncorrelated transcription initiation events, single exponential mRNA decay, and translation probabilities which are uncoupled from mRNA decay, result in the experimentally observed distribution of protein molecules per cell. This simple model of regulation breaks down for cell-cycle genes, whose expression is tightly controlled. We found that two genes responsible for mitotic progression in budding yeast, SWI5 and CLB2 exhibit a mitosis-dependent mRNA stability switch. Their transcripts are stable until mitosis when a precipitous decay eliminates the mRNA complement, preventing carry-over into the next cycle. This work reveals a novel regulatory mechanism of mRNA decay and mitotic division possibly employed by a variety of mRNAs and organisms. By regulating both synthesis and decay, the cell has effective control over protein variation during the cell cycle, suggesting a role for noise minimization in certain highly regulated genes.

Quantitative proteomics as a versatile method to detect specific protein interactions

Matthias Mann[1], Marco Yannick Hein[1], Nina Hubner[1], Maximiliane Hilger[1], Jürgen Cox[1]

[1]Proteomics and Signal Transduction, Max-Planck Institute of Biochemistry, Martinsried, Germany

Mass spectrometry-based proteomics, particularly in a quantitative and high resolution format, has become a very powerful technology to study gene expression at it ‘end point’ - the level of proteins. Accurate expression changes can now be measured for the entire yeast proteome and for a very large fraction (more than 10,000 proteins) of mammalian genomes. Furthermore, MS-based proteomics can analyze post-translational modifications on a very large scale – for example, more than 10,000 phosphorylation sites can readily be quantified in a cell line and in vivo. Here we describe the current state of the technology as exemplified by the proteomics pipeline developed at the Max Planck Institute in Martinsried with an emphasis on recent developments in instrumentation and computational proteomics. The main focus of the talk will be on using quantitative proteomics data not for protein expression measurement but rather for the detection of specific protein interactions. In this format, protein quantification (in our case by SILAC labeling or in a label-free format) is applied to distinguish background binders from true binders. By quantification of binders to bait molecules vs. a control bait, the need for stringent washes is reduced and transient binders can still be detected. We will describe application of our generic workflow to interactions with specific DNA elements in the genome (such as GWAS derived SNPs or QTLs), RNA structures, post-translational modifications as well as to stimulus dependent interactions in signaling pathways. Finally, we will discuss prospects and ongoing work aimed at a first pass of the ‘human interactome’.

Post-transcriptional gene regulation by small RNAs and RNA binding proteins

Nikolaus Rajewsky

Berlin Institute for Medical Systems Biology at the Max Delbrück Center for Molecular Medicine, Berlin, Germany

In recent years it has become apparent that a large fraction of all genes in animals is regulated post-transcriptionally by small RNAs.

Furthermore, animal genomes contain hundreds of genes with RNA binding domains. It is clear that many of these RNA binding proteins have important and specific functions in mRNA localization and stability as well as in regulating protein production. However, only recently technologies have become available to probe post-transcripitonal regulatory networks on a genome-wide scale.

I will briefly review previous efforts to understand more about the function of microRNAs in post-transcriptional gene regulation. I will then present ongoing work where we use high throughput quantitative proteomics, next-generation sequencing and computational approaches to unravel the biological function of small RNAs and RNA binding proteins in well-defined *in vivo* systems such as *C. elegans*.

Where and when does transcription control metabolic function?

Uwe Sauer

Institute of Molecular Systems Biology, ETH Zurich, Zurich, Switzerland

Compared to other biological networks, the topological structure and function of metabolism is unusually well understood. The true challenge in understanding how metabolic fluxes are modulated is the complexity arising from multiple overlapping regulatory mechanisms and metabolic feedback into these regulatory networks (1). Here I will focus on identifying the key regulation mechanisms that actually control metabolic fluxes. By combining various omics methods with computational analysis, we are able to delineate actively controlling regulation events from the much larger number of occurring regulation events. Examples to be covered include flux regulation through transcriptional regulation and phosphorylation of enzymes in yeast and *E. coli*. Based on computational network analysis, such regulation is unevenly distributed through the network, focussing on those reactions that require the largest flux change upon nutritional changes. Finally, I will highlight the potential of a novel method for high-throughput metabolomics (i.e. 2000 ion peaks per minute) in large-scale mapping of active regulation.

References:
1. Heinemann M & Sauer U. **Curr. Opin. Microbiol**. 13: 337 (2010)

Characterization of regulatory small RNAs and RNA-binding proteins

Thomas Tuschl

Laboratory of RNA Molecular Biology, Howard Hughes Medical Institute, The Rockefeller University, New York, USA

Our laboratory studies how RNA-binding proteins (RBPs) and small-RNA-containing ribonucleoprotein complexes (RNPs) regulate messenger RNAs (mRNAs) in human cells. We develop experimental approaches to precisely define the RNA recognition elements (RREs) bound by RBPs and RNPs and examine their regulatory function at a transcriptome level. Current studies focus on characterizing RBPs that control mRNA stability or where mutations cause genetic diseases, such as fragile X syndrome and amyotrophic lateral sclerosis. The identification of posttranscriptional regulatory networks will increase our understanding of the molecular causes of disease and may lead to the rational design of new therapeutic agents. Finally, we are establishing a platform for discovery and use of RNA as a biomarker by recording and quantifying alteration in transcript isoforms and their abundance in normal and disease conditions using deep sequencing followed by RNA fluorescence in situ hybridization in large pathological tissue collections.

Mass spectrometric investigation of protein-RNA cross-links

Henning Urlaub[1,2]

[1]*Bioanalytical Mass Spectrometry Group, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany*
[2]*Bioanalytics, Department of Clincal Chemistry, University Medical Center Göttingen, Göttingen, Germany*

UV-induced cross-linking of protein–RNA complexes is widely used to study protein–RNA interactions. Mass spectrometry (MS) has been successfully applied to characterise the cross-links obtained on the molecular level and thus allows for unambiguously identification of the cross-linked protein and also the protein region and/or the amino acid in direct contact with RNA. Here, several strategies will be presented for the mass spectrometric detection of protein-RNA cross-links and a computational approach to identify cross-links by database search subsequent to their analysis by MS. Furthermore, detailed insights of how various amino acids are covalently attached to RNA after UV-light induced cross-linking will be provided.

Control of Metabolism by p53

Eric C Cheung, Arnaud Vigneron, Eyal Gottlieb, Karen H Vousden

The Beatson Institute for Cancer Research, Glasgow, Scotland, UK

The p53 protein is an important tumor suppressor that functions in a number of ways to prevent cancer development. Under conditions of severe or sustained stress, p53 can drive cell death and senescence, thereby removing the damaged and potentially transformed cell. However, recent evidence has also revealed an important role for basal p53 levels in helping cells to survive the effects of less acute stress. Under these conditions, p53 plays an important anti-oxidant role – so helping cells to cope with the constitutive oxidative stress associated with normal proliferation and growth. p53 also plays a role in the control of several metabolism pathways. By helping to promote oxidative phosphorylation and dampen glycolysis, p53 opposed the shifts in metabolism that are characteristic of transformed cells. p53 also helps to coordinate the response to starvation by inhibiting cell proliferation and growth, while promoting certain catabolic responses.

The ability of p53 to promote survival and modulate metabolism could contribute to tumor suppression by helping cells to prevent or repair stress and damage. However, this raises the possibility that the inappropriate or deregulated expression of some of these activities of p53 may also support cancer progression. We have been investigating the activities of TIGAR, a protein that functions to protect cells from cell death. TIGAR can act as a fructose-2,6-bisphosphatase, driving the pentose phosphate pathway (PPP), promoting NADPH production to restore reduced glutathione and protecting the cell from ROS-associated apoptosis and autophagy. Other activities of TIGAR that may also contribute to the survival function are presently under investigation. While transcription of *TIGAR* can be p53-regulated in human cells, cancer cells also frequently show robust expression of TIGAR despite being null or mutant for p53 and we have found over-expression of TIGAR in a number of cancer cell lines (regardless of p53 status) and in a significant proportion of malignant colon cancers. It therefore seems possible that inappropriate expression of TIGAR might contribute to tumor cell growth and survival, and we are examining possible oncogenic functions of TIGAR in various cell based and *in vivo* models.

This work was supported by Cancer Research UK

Short Talk Abstracts

Invited Short-Talkers in Alphabetical Order

Counting of Sic1 mRNA molecules in single budding yeast cells to investigate the influence of transcription variability on the G1/S transition

Aouefa Amoussouvi[1,2], Gabriel Schreiber[3], Matteo Barberis[3], Claudia Beck[3], Szymon Stoma[3], Edda Klipp[3], Andreas Herrmann[2]

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[2]Humboldt University Berlin, Institute of Biology, Molecular Biophysics, Berlin, Germany
[3]Humboldt University Berlin, Institute of Biology, Theoretical Biophysics, Berlin, Germany

Some recent single-molecule methods have been developed. These new techniques revealed that transcription level of many genes is rather low and that a cell-to-cell variability of the number of mRNA exists among genetically identical populations of cells. The goal of our project is to better understand the regulation mechanism of the yeast cell cycle. We are currently focusing on two genes, Sic1 and Cln2, involved in the transition between the G1 and the S phases in the early stage of the cell cycle. We investigate the robustness of yeast cell cycle progression despite noisy gene expression, and for this purpose, we combine modeling and experimental approaches. We took advantage of the MS2 system and applied it on S. cerevisia. The MS2 strategy integrates hairpin building sequences in the 3'UTR of the gene of interest. These hairpin loops are binding sites for a MS2 coat protein coupled to a triplet of GFP molecules, MS2-CP-GFP(x3). Thus, single mRNA granules can be detected by fluorescence microscopy due to the local accumulation of GFP molecules. We investigated the distribution of transcripts in synchronized and unsynchronized populations. Moreover we also followed single particles of Sic1 mRNA over time to understand their behavior in the cells. Finally, we used our experimental results to develop a stochastic model for the G1/S transition centered on the fluctuation of Sic1 transcription level and the resulting noise.

High-throughput biochemical identification of miRNA targets pin-points to miR-21 as a novel modulator of TCR signalling

Claudia Carissimi[1], Teresa Colombo[1], Valerio Fulci[1], Gianluca Azzalin[1], Nicoletta Carucci[1], Vincenzo Barnaba[2], Giuseppe Macino[1]

[1]Sapienza Università di Roma, Dipartimento di Biotecnologie Cellulari ed Ematologia, Sezione di Genetica Molecolare, Rome, Italy
[2]Sapienza Università di Roma, Dipartimento di Medicina Interna, Rome, Italy

Identification of target genes is currently one of the most challenging tasks in microRNA (miRNA) biology. Aiming to unravel the function of miR-21, whose expression is rapidly induced upon T-lymphocyte activation by T-cell Receptor (TCR) engagement, we used a biochemical approach to identify miR-21 targets. Following ectopic expression of miR-21 in a T-lymphocyte cell line (Jurkat), we immuno-purified and profiled RNA Induced Silencing Complexes (RISC) associated mRNAs. We compared mRNA abundance in immunoprecipitated RISCs from Jurkat cells over-expressing either miR-21 or control shRNA. Bioinformatic analysis highlighted that miR-21 overexpression is mirrored by the specific enrichment for its seed matches in the 3'UTR of RISC-associated mRNAs. Interestingly, putative miR-21 target genes thus identified are significantly enriched in functional annotation for T-cell activation, particularly TCR signal transduction. To verify whether miR-21 expression actually affects TCR signalling, we measured lymphocyte activation markers (IL-2 production, CD69 expression and AP-1 activity) in Jurkat cells over-expressing miR-21, and indeed we found evidences supporting a role of miR-21 as a negative regulator of TCR signalling. Consistently, a loss of function approach in primary human T-lymphocytes shows that titration of miR-21 by a lentiviral “sponge” significantly increases TCR mediated activation. Despite extensive reports on the anti-apoptotic activity of miR-21 in solid tumours, we failed to detect any effect of miR-21 on apoptosis both in Jurkat cells and primary T-lymphocytes. This is in agreement with the fact that biochemical purification of miR-21 targets did not yield any significant enrichment for genes involved in this biological process and confirms the notion that miRNA function is strictly dependent on cellular context. In summary, by using a prediction independent, biochemical approach to miRNA target identification, we inferred and proved a novel function for miR-21 in human T-lymphocytes.

Systematic analysis of subcellular gene expression patterns in complex tissues

Helena Jambor[1], *Pavel Mejstrik*[1], *Stephan Saalfeld*[1], *Pavel Tomancak*[1]

[1]*Max-Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany*

Cell fate specification and tissue formation during animal development are determined by the dynamic regulation of gene expression. In addition, local expression domains can also control cell polarisation events. Such subcellularly restricted protein activity is established for example by coupling mRNA localisation and translational control. To understand the principles of tissue formation and polarity establishment, we are determining global and subcellular mRNA localisation patterns in the *D.melanogaster* ovary in a genome-wide approach. The ovary of fruit flies is ideally suited for this project as the large dimensions of the egg-chamber and the high abundance of each mRNA, transcribed from polyploid chromosomes, permit screening at low resolution. Furthermore, the architecture of cells of the egg-chamber is well described, allowing us to correlate mRNA localization sites with subcellular structures. We have developed a method for large-scale isolation of egg-chambers for subsequent fluorescent *in situ* hybridisation (FISH) and implemented a pipeline for high-throughput screening and image processing. The expression patterns will be annotated using a controlled vocabulary and made available in a public database. In the pilot screen we probed 480 genes of which 208 gave a signal in FISH experiments. Half of the expressed genes showed a subcellularly asymmetric distribution of the mRNA within the egg-chamber. We are currently determining whether the mRNA localisation of candidates is functional by fluorescently tagging the genes in their genomic context and then analysing the protein expression patterns in transgenic animals.

MiRNA profiling in plants -- from identification to function

David Corcoran, Natalie Breakfield, Philip Benfey, Uwe Ohler[1]

Duke University, Institute for Genome Sciences & Policy, Biostatistics & Bioinformatics, Durham, USA

The crucial role of RNA-based gene regulation is now clearly established. While the class of microRNAs has been widely studied in animal model systems, plants provide a unique perspective: plant miRNAs largely regulate target gene expression in an siRNA-like manner, and largely target transcription factors, making it much easier to place them within regulatory networks. Last not least, efficient cell sorting techniques allow it to obtain expression profiles at high resolution.

We here applied deep sequencing to identify small RNAs in all major cell types of a complete model organ system, the root of A. thaliana. To identify new miRNAs, we identified potential precursor foldbacks as a first step; different from animals, plant miRNA precursors pose a real challenge as they can vary in size from 70-700 nt, and frequently contain more than one mature miRNA.

A Bayes classifier then combined distinct features reflecting primary sequence, secondary structure, and processing of precursors, to assign log-odds scores to foldbacks. From ~20 libraries resulting in ~200 million aligned reads, we identified more than 150 high-scoring candidates, with 70 of them consistently predicted across replicates. The large scale of the data also allowed for the refined annotation of many of the ~250 known Arabidopsis miRNAs. In addition to miRNAs, plants also harbor endogenous siRNAs, and we have characterized the class of trans-acting siRNAs in particular.

Our results show that most known and new plant miRNAs exhibit specific spatial and developmental expression patterns. Disruption of several newly identified ones results in a growth phenotype, and demonstrates the crucial role of miRNAs in plant development. Plant miRNAs largely target transcription factors, and our work above is complemented by ongoing studies aimed at deciphering the respective quantitative contribution of miRNAs and transcription factors in developmental regulatory networks.

Reprogramming of energy metabolism upon induction of pluripotency

Alessandro Prigione[1,2,5], Björn Lichtner[1,2], Heiner Kuhl[1,3], Eduard A. Struys[4], Markus Ralser[1,2], James Adjaye[1,2], Hans Lehrach[1,2], Bernd Timmermann[1,3]

[1]Max Planck Institute for Molecular Genetics, Berlin, Germany
[2]Department of Vertebrate Genomics
[3]Next Generation Sequencing Group
[4]VU Medical Center, Amsterdam,The Netherlands

Somatic cells reprogrammed to pluripotency likely undergo metabolic transformation events in order to sustain the burden of their increased anabolic requirements. Accordingly, we previously showed that somatic mitochondria are extensively remodeled within human induced pluripotent stem cells (iPSCs), suggesting the occurrence of a metabolic shift from respiration to glycolysis. Here, we applied next generation sequencing (NGS) technology and identified that mitochondrial DNA (mtDNA) sequence variants are unequally distributed within iPSCs. This phenomenon, reminiscent of the replicative segregation of mitochondria occurring during oocyte maturation, further underscores iPSC heterogeneity and might be important to monitor during the derivation of safe clinical-grade iPSCs. We then integrated transcriptional, metabolic, and functional data, and unveiled that iPSC generation induces a global reconfiguration of bioenergetic metabolism resembling the Warburg effect. Human embryonic stem cells (hESCs) and iPSCs showed a remarkable increase of PDK1, which re-routes the bioenergetic flux towards glycolysis and has been recently associated with enhanced reprogramming efficiency. Finally, a small molecule inducer of the HIF-1α response, which stimulates glycolysis and up-regulates PDK1, significantly improved human iPSC generation. Overall, induction of pluripotency appeared to be associated not with a unique mtDNA profile but rather to an overall re-adaptation of the bioenergetic pathways to the acquired pluripotent state. These results provide further evidence for a major metabolic shift during reprogramming and indicate that altering distinct aspects of metabolic signaling can enhance the reprogramming process, suggesting an instrumental role for metabolic transformation in the establishment of pluripotency.

Inhibition of glycolysis as a novel form of hepatocellular carcinoma therapy

Ines Rudolph[1,2], Katjana Daskalow[1,2], Bertram Wiedenmann[1], Volker Schmitz[3], Esther Raskopf[3], Thorsten Cramer[1,2]

[1]Charité - Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Hepatologie und Gastroenterologie, Berlin, Germany
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Hepatocellular carcinoma (HCC) is a fatal disease due to prevailing diagnosis at advanced tumor stages and primary chemoresistance. Better understanding of the molecular mechanisms that govern HCC resistance is needed to design innovative treatment options. Enhanced glycolysis is a hallmark of cancer and we could show overexpression of glycolysis-related factors in human HCC. However, a causal role of glycolysis in the pathogenesis of HCC has not been elucidated thus far. Therefore, we analyzed the anti-proliferative efficacy of the glycolysis inhibitor 2-deoxyglucose (2-DG) against HCC in vitro and in vivo. 2-DG treatment resulted in robust reduction of proliferation in vitro, partially explained by a G1 arrest. As shown in Western Blot analysis, the glycolytic inhibitor stabilized hypoxia-inducible factor 1 (HIF-1) protein under normoxic conditions. Hypoxia is a hallmark of cancer and known to contribute to chemoresistance. Functional inactivation of HIF 1 in vitro was achieved via lentivirally delivered shRNA. In HIF-1-deficient cells, 2-DG displayed higher anti-proliferative potency and induced more apoptotic cell death compared to wildtype cells. Furthermore, we could identify 2-DG as a potent radio- and chemosensitizer in vitro. In good accordance, inhibition of glycolysis via 2-DG reduced tumor growth in a murine orthotopic HCC model. In addition, 2-DG-induced inhibition of proliferation showed enhanced efficacy upon hepatocyte-specific inactivation of HIF-1in a murine transgenic HCC model. In summary, we deduct a significant anti-tumorigenic effect of glycolysis inhibition on hepatocellular carcinoma and characterize HIF-1 as a pivotal mechanism for resistance against anti-glycolytic therapy. The chemo- and radiosensitizing impact of 2-DG warrants its validation as an adjuvant therapeutic agent in clinical studies of HCC, preferably in combination with pharmacological inhibitors of HIF-1.

Regulatory networks of hematopoietic stem cells and their micro-environment

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Hematopoietic stem cells (HSC) are thought to be regulated by extracellular cues from the 'niche,' which trigger downstream signal transduction cascades within the HSC. Current studies have, so far, not resulted in comprehensive understanding of the signaling networks dictating HSC fate. In the present work, theoretical systems-biology and experimental hematology approaches are combined to determine the role of the niche in orchestrating HSC epigenetic machinery and the cell cycle. Thus, time-course gene expression analysis of co-cultured Lin-Sca1+cKit+ (LSK) and HSC-supportive UG26-1B6 stromal cells was performed. Microarray results were independently confirmed by RT-qPCR, demonstrating ~80% agreement for the selected candidate genes. HSC activity and functionality was confirmed by colony forming cell (CFC) assay and in vivo transplantation assay. Search space reduction using clustering analysis suggests that the most intense molecular cross-talk between LSK and stromal cells occurs during the first 24 h of co-culture. In LSK cells, gene function enrichment analysis revealed up-regulation of transcripts associated with cell adhesion and migration, TGFβ signaling, metabolism, as well as MAPK- regulated cell proliferation. At the same time, epigenetic regulators mediating gene silencing were among the down-modulated transcripts. Interestingly, similar analysis in stromal cells demonstrated molecular signatures also involved in cell adhesion, migration and proliferation, as well as Wnt, TGFβ and mTOR signaling. In both, LSK and stromal cells, among the most significantly up-regulated transcripts was an ECM-associated TGFβ and Wnt signaling intermediate. By integrating gene expression data with various sources of prior knowledge (e.g., PPI and pathway databases, semantic text mining) an in silico hypothesis was generated predicting the putative role of this factor in HSC mobilization by regulating the G0/G1 phase transition of the cell cycle and the epigenetic modifications accompanying it. Current work is focused on the experimental validation and further refinement of the network.

Poster Abstracts

P1
doRiNA - a web front-end for complex queries on miRNA and RBP target sites

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MicroRNAs (miRNA) are a class of short (~22nt) non-coding RNAs that post-transcriptionally control gene expression. RNA binding proteins (RBP) may interact with single-stranded or double-stranded RNA to control every aspect of RNA life. Binding sites on target genes can be experimentally determined (e. g. by PAR-CLIP for RBPs) or computationally predicted (e. g. by PICTAR2 for miRNAs). We integrate data on Protein-RNA as well as miRNA-RNA interactions from both sources into one common framework: The *doRiNA* database (Database of RNA interactions, http://dorina.mdc-berlin.de). *doRiNA* currently contains target sites of four RBPs (AGO1-4, IGF2BP1-3, PUM2 and QKI) as well as target site predictions of all miRNAs from mirbase for three different conservation levels (fish, chicken, human). Any user-selected combination of RBP and miRNA sites can be searched by two different set options: Either searching for target genes, which may bind ANY of the regulators (union operation), or target genes, which are bound by EACH user-given regulator (intersect operation). Moreover, the user can confine the search space of target sites by supplying lists of gene symbols and/or NCBI refseqs. Search results are displayed in a table incorporating links to a local (i. e. in-house) installation of the UCSC Genome Browser. We continue working on *doRiNA* to extend the search capabilities.

P2
Tools for data analysis, warehousing and integration for large-scale system biology projects

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Complex, multi-omics level systems biology projects pose considerable challenges to the annotation, handling, warehousing, and integrated pre-processing and analysis of the generated experimental data. Within the GoFORSYS project, we developed several bioinformatics analysis and infrastructure solutions (QuantPrime, QuantPipe, ChlExDa and ChlamyCyc) that aim at both aspects with the goal to also allow an efficient bridging between them. QuantPrime is a RT-qPCR (Reverse Transcription quantitative PCR) primer design pipeline for medium to high-throughput quantification projects. It includes automated specificity checking (using BLAST) and selects preferably primers not amplifying genomic DNA. It is freely available at http://www.quantprime.de. QuantPipe is a RT-qPCR data pre-processing and analysis pipeline which automates data extraction, quality control (including melting curve checks, amplification efficiency checks among others) and normalization. ChlExDa (Chlamydomonas Experimental Data) is a systems biology oriented experimental data store developed for the GoFORSYS project. While centered on locally gathered *Chlamydomonas reinhardtii* data, it can import, describe and export any kind of numeric data related to a specific experimental sample (e.g. omics data) or on a timeline (e.g. online fermenter data). It abstracts the actual data from its application by storing it linked to local ontologies, which can be dynamically mapped to public ontologies (e.g. genome annotations, KEGG, GO, etc. ontologies) for analyis. This allows for later updates or additions of the analysis ontologies without re-importing of the original data. ChlamyCyc provides a curated and integrated systems biology repository for Chlamydomonas, enabling and assisting in systematic studies of fundamental cellular – in particular metabolic – processes. The ChlamyCyc database and web-portal is freely available: http://chlamycyc.mpimp-golm.mpg.de.

P3
Identification and characterization of the mRNA-bound proteome of human cells

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Vertebrate genomes encode at least several hundred RNA-binding proteins (RBPs). RBPs play a key role in the regulation of spatial and temporal changes in protein synthesis through control of mRNA maturation, transport, stability and translation. The comprehensive and unbiased identification of all components of the protein-mRNA interactome is a prerequisite for a systems-level understanding of post-transcriptional regulatory processes. Here, we present an approach to identify the proteomic composition of the protein-mRNA interactome. Our method relies on the incorporation of photoreactive nucleosides, 4-thiouridine and 6-thioguanosine, into nascent RNA of living cells, which allows to efficiently crosslink RBPs to RNA by UV radiation at 365 nm. mRNA and crosslinked proteins are recovered by oligo(dT) bead precipitation under highly stringent conditions and the cross-linked proteins were characterized by mass spectrometry. The majority of the 650 identified proteins are “bona fide” RBPs including splicing factors, RNA helicases, and translation initiation factors. In addition, we identified several proteins in HEK293 cells for which neither an RNA-binding activity has been previously reported nor an RNA-binding domain is readily detectable. We are currently identifying the mRNA targets of a number of these RBP candidates**.**

P4
Absolute quantification of protein isoforms by targeted proteomics: A method development

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Quantitative measurement of proteins in a high-throughput manner:
Different approaches in the proteomics field are currently used in order to identify proteins in a complex mixture. The most common approach is the proteome wide identification of tryptic peptides by mass spectrometry (MS). The so called "shotgun" proteomics approach is one of the major method used to generate peptide MS spectra. These spectra will be further processed to identify the proteins in the mixture. It has the advantage being a primarily non-restrictive method for the identification of proteins. However, being an untargeted approach and with limited sensitivity it generates only partially overlapping, incomplete and relatively quantitative datasets. In contrast to this, the targeted proteomic approach using the technique of selected reaction monitoring (SRM) aims to identify only a determined subset of peptides, thus proteins, in a complex mixture. Consequently, one key advantage is the higher sensitivity and thus the identification of low abundance proteins, such as elements of signal transduction pathways e.g. Myc. Furthermore, with the help of spiked-in standards SRM can be used to create a calibration curve for each of the peptides, hence providing a tool for absolute quantification of the proteins of interest.

Aim of the method development and relevance of this technical setup:
The goal is to set up a method which is suitable for the absolute quantification of the protein isoform repertoire of the human central carbon metabolism (termed CCM-isome). As a first step we identified isoform specific unique proteotypic peptides of the CCM-isome with the help of experimental data, the KEGG database and the PeptideAtlas. Subsequently, these peptides were synthesized as isotopically labeled peptides which were used to develop the SRM assays. Moreover, these peptides were used to construct a calibration curve for the different isoforms and thus allowing the absolute quantification of these protein isoforms; as it has been shown that a single isoform switch (PKM1, adult form, to the PKM2 splice isoform, embryonic one) can be sufficient to shift cellular metabolism and promote tumorigenesis. This approach will be used to measure the isoform expression profile of a human cell line under different conditions. The derived quantitative data will be further analyzed and will deliver important model parameters for the scientific community. We are convinced that it is promising to deepen our understanding of isoform usage for further drug development.

P5
Computational methods towards a biological interpretation of gene expression data: Application to *in vitro* foam cell formation

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Microarray data analysis makes it possible to query the expression level of large numbers of genes simultaneously and to evaluate the response of a biological system to an external stimulus or condition. Although microarrays are standard tools, selecting the most appropriate method(s) for analysis to enable meaningful biological insight is not straightforward, and it is important to perform a thorough quality assessment of the data before interpretation. The insights gained are most meaningful when multiple levels of biology are interpreted (single genes, ontology, and pathways) to understand the mechanisms and estimate the effects of stimuli beyond RNA levels. Here, we present the methods used to quality check and analyze a large dataset from an *in vitro* study of foam cell formation, which is one of the initial steps of atherosclerosis. The objective was to estimate the relevance of the formation of foam cells *in vitro* compared to what is known from *in vivo* studies. In short, macrophages are activated and absorb large quantities of modified lipids, such as oxidized low-density lipoprotein (oxLDL), by endocytosis. The debris accumulated when foam cells are subjected to apoptosis is the basis for plaque rupture in vascular tissues, which can lead to myocardial infarction and other possibly fatal atherosclerotic diseases. Cigarette smoke is a known risk factor for atherosclerosis, so another objective of the study was to understand whether smoke has an effect on foam cell formation and to learn more about the underlying mechanisms. Macrophages were therefore exposed to modified LDL and to smoke at different doses, and gene expression was analyzed over time. For application to foam cell formation, we emphasize the need for in-depth quality control of microarray data and the use of multiple tools to investigate biology at different levels in order to gain a better understanding of the mechanisms underlying foam cell formation and the effect of cigarette smoke exposure.

P6
Dissecting the molecular mechanisms of miRNA-mediated gene silencing

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MicroRNAs (miRNAs) are genome-encoded ~22 nucleotide-long RNAs that silence gene expression post-transcriptionally by base pairing with the 3' untranslated regions of target mRNAs. To exert their function, miRNAs associate with Argonaute proteins (AGOs) in miRNA-induced silencing complexes (miRISCs), which silence the expression of mRNAs containing partially or fully complementary miRNA-binding sites. In animals, most miRNAs are only partially complementary to their targets. Our group has shown that in this case the AGO proteins are not sufficient to mediate silencing and require interaction with proteins of the GW182 family. We have also shown that AGO-GW182 complexes mediate silencing by promoting translational repression and mRNA deadenylation. Deadenylation decreases translation efficiency and, in somatic cells, commits the mRNA to decapping and 5’-to-3’ exonucleolytic degradation. Our analysis of GW182 protein function has revealed two domains critical for silencing: an N-terminal GW-repeat-containing region conferring binding to AGOs, and a bipartite silencing domain, consisting of Middle and C-terminal regions, which elicits translational repression and degradation of miRNA targets. Exactly how the bipartite silencing domain of GW182 proteins interferes with translation and accelerates deadenylation is not completely understood. We have recently started to address this question by showing that the silencing domains of GW182 interact with the cytoplasmic poly(A)-binding protein 1 (PABPC1), suggesting GW182 proteins are PABP-interacting proteins (Paips) that interfere with the function of PABPC1 in translation and mRNA stabilization. Furthermore, in a screen for proteins interacting with the GW182 silencing domains we identified subunits of the two major cytoplasmic deadenylase complexes: the PAN2-PAN3 and the CCR4-CAF1-NOT complexes, both of which in turn interact with PABPC1. These interactions are conserved and critical for silencing in D. melanogaster and human cells. Together, our findings indicate that the silencing domains of GW182 proteins provide a binding platform for deadenylation factors and PABPC1, creating an intricate network of protein-protein interactions which causes the rapid deadenylation of miRNA targets.

P7
Sm protein iCLIP reveals the spliceosomal snRNP profile of mouse brain

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The core machinery of pre-mRNA splicing is formed by spliceosomal snRNPs (small nuclear ribonucleoproteins), each of which is composed of an RNA component, Sm proteins, and additional proteins specific for each snRNP. The Sm proteins form a highly stable heptameric ring composed of SmB/B', D1, D2, D3, E, F and G. The Sm ring specifically interacts with uridine-rich sites on snRNAs (termed Sm sites). The positioning of individual Sm proteins and snRNP-specific proteins on snRNAs has initially been deduced from *in vitro* cross-linking experiments. Here, we used iCLIP (individual nucleotide resolution UV cross-linking and immunoprecipitation) to analyze the binding positions on RNAs associated with Sm proteins *in vivo*. For this purpose, we utilized an antibody against SmB/B' to immunoprecipitate RNPs from UV cross-linked mouse brain at postnatal day 7. This allowed us to analyse binding of Sm proteins and other associated snRNP-specific proteins for all major and minor spliceosomal snRNAs. In addition to these snRNP cross-linking maps we will present the genome-wide analysis of iCLIP data to predict novel RNA targets of the Sm complex.

P8
Local absence of secondary structure permits translation of mRNAs that lack ribosome-binding sites

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The initiation of translation is a fundamental and highly regulated process in gene expression. Translation initiation in prokaryotic systems usually requires interaction between the ribosome and an mRNA sequence upstream of the initiation codon, the socalled ribosome-binding site (Shine-Dalgarno sequence). However, a large number of genes do not possess Shine-Dalgarno sequences and it is unknown, how start codon recognition occurs in these mRNAs. We have performed genome-wide searches in various groups of prokaryotes in order to identify sequence elements and/or RNA secondary structural motifs that could mediate translation initiation in mRNAs lacking Shine-Dalgarno sequences. We find that mRNAs without a Shine-Dalgarno sequence are generally less structured in their translation initiation region and show a minimum of mRNA folding at the start codon. Using reporter gene constructs in bacteria, we also provide experimental support for local RNA unfoldedness determining start codon recognition in Shine-Dalgarno-independent translation. Consistent with this, we show that AUG start codons reside in single-stranded regions, whereas internal AUG codons are usually in structured regions of the mRNA. Taken together, our bioinformatics analyses and experimental data suggest that local absence of RNA secondary structure is necessary and sufficient to initiate Shine-Dalgarno-independent translation. Thus, our results provide a plausible mechanism for how the correct translation initiation site is recognized in the absence of a ribosome-binding site.

P9
Characterization of new potential SHP2 substrates by a MS-based quantitative approach

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SHP2 belongs to the Protein tyrosine phosphatase family (PTPs). These enzymes contribute to the maintenance of regulated levels of tyrosine phosphorylation by acting in concert and in competition with the more extensively studied family of protein tyrosine kinases (PTKs). SHP2 is one of the rare PTPs that promotes the activation, rather than the down-regulation, of growth pathways. In particular this phosphatase is a well characterized positive regulator of the RAS/MAPK pathway. Deregulation of SHP2 results in several pathological conditions, but despite the wealth of genetic data, the details of the physiological mechanisms, whose disruption or imbalance, lead to disease still remain an unsolved puzzle. The single main issue which does not allow us to make a satisfactory correlation between SHP2 and disease phenotype is the limited knowledge of physiological substrates and of the molecular partners/adaptors that contribute to activity modulation, localization in the cell and substrate selection. To this aim, we applied a quantitative phosphoproteomic approach to monitor alterations in the global tyrosine phosphorylation of SHP2 mutant mouse embryonic fibroblasts in comparison with their wild-type isogenic counterparts. Three proteins (CDK2, PAXI and MK14) were found to harbor hyperphosphorylated phosphotyrosine sites in mutant cells and were functionally linked to SHP2, as direct or indirect substrates. In particular SHP2-dependent MK14 dephosphorylation can suggest a new mechanism by which SHP2 positively regulates the RAS/MAPK pathway. Additional information about the SHP2 interaction network were provided by a parallel mass spectrometry analysis of the purified phosphatase complex, an analysis that allowed us to associate to SHP2 new interesting cellular functions in addition to the well-established role of modulator of the RAS pathway.

P10
Inefficient nonsense mediated decay promotes transcriptional robustness of human genes

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The Nonsense Mediated Decay (NMD) pathway degrades transcripts that contain a premature termination codon. However the efficiency of NMD's surveillance of gene expression varies both among and within human genes. We hypothesized that human genes should bear the signature of this variable surveillance with respect to their usage of "fragile" codons that can be mistranscribed into a STOP codon. Here, we observe that human single-exon genes have evolved to become robust to nonsense transcriptional errors, because they show a significant depletion of fragile codons relative to multi-exon genes. A similar depletion is evident in last exons of multi-exon genes. Both observations can be attributed to NMD deficiency. Furthermore, histone genes, which are immune to NMD, are particularly robust to transcriptional errors. Our study shows that human genes are exposed to the fitness effects of transcriptional errors, a phenomenon that may have been underestimated until now, in molecular evolution in general and in selection for genomic robustness in particular.

P11
Theoretical aspects of mRNA degradation

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In the process of gene expression, one important determinant of the protein level is the stability of messenger RNA. Experimentally, the stability can be analyzed by the decay of the mRNA level over time after further synthesis had been inhibited. Alternatively, one can track the amount of radioactively labeled mRNA over time. On the one hand, it was found that different mRNA species can vary substantially in their life time. Furthermore, it has also been noted frequently that the decrease of mRNA level does not generally show an exponential decay. On the other hand, a variety of putative mechanisms and responsible enzymes for degradation have been revealed in the different organisms. Additionally, for effective degradation typically several modifications have to be performed to the mRNA. This can be viewed as an aging of the mRNA. In this contribution, we present a stochastic model where we relate the decaying mRNA level to the messages' life time distribution. The theoretical framework is general as we do not restrict to a particular degradation process. Furthermore, we can also link the mRNA stability to the age and rest-life distribution of an ensemble of transcripts. In a further step, we suggest a general model that describes degradation as a multistep process. Each step represents a modification of the mRNA - thereby changing the degradation efficiency. Finally, we provide instructive examples - representing the exo- and endonuclelytic degradation pathway. As a result, the presented approach allows to extract information about the underlying degradation mechanisms from the experimentally observed decay pattern. Moreover, our method is suitable to improve the analysis of mRNA life time experiments.

P12
Statistical tests for detecting differential RNA-transcript expression

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As a fruit of the current revolution in sequencing technology, transcriptomes can now be analysed at an unprecedented level of detail. These technological advances have been exploited in diverse ways. Examples of such include the detection of differentially expressed genes across biological samples, and the quantification of the abundances of various RNA transcripts within single genes. A natural next step is now to extend the detection of differential abundance, focusing on individual transcripts within one gene. However, robust strategies to solve this problem have not yet been defined. In this work, we present two novel statistical tests to address this important methodological gap: a ‘gene-structure-sensitive’ Negative-Binomial (NB) test that can be used to detect differential transcript expression when the gene structure is known and a non-parametric kernel-based test, called Maximum Mean Discrepancy (MMD), for cases when the gene structure is incomplete or unknown. Both methods can account for biological variance and cope with replicates. Our analysis shows that both MMD and the NB-test identifies genes with differential transcript expression considerably better than approaches based on transcript quantification, such as rQuant and Cuffdiff. In this work we furthermore present some applications of the before mentioned methods and show some common pitfalls of RNA-Seq experiments. Here, we proposed two novel approaches to test for differential expression on the level of transcripts. While the NB-test exploits existing transcript annotation, the MMD test can be used in settings where details about transcripts are not available. On simulated reads and investigation of real data, we achieved promising results using these methods, highlighting their potential as discovery and statistical testing tool. Furthermore we show applications of those methods and point to some common problems of RNA-Seq experiments.

P13
Performance and qualities of different alignment and SNV calling algorithms using short read high-throughput sequencing data

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The use of high-throughput "second generation" sequencing for the identification of alterations in cancer genomes is rapidly increasing and with this a large amount of genomic data is generated which needs to be handled with specially developed bioinformatics tools. In order to detect germline and somatic mutations of cancer tissues, one depends on the accuracy of alignment and single nucleotide polymorphism (SNV) calling algorithms. Sequencing errors and genetic aberrations present a strong challenge for these algorithms. We analyzed targeted enrichment sequencing data of 29 prostate cancer patients and validated 698 SNVs by mass spectrometry. Using BWA ("Burrows Wheeler Aligner") and Bowtie for short read alignment in combination with different SAMtools versions for variant calling we found BWA producing much less false positive SNVs compared to the Bowtie algorithm. We developed a logistic regression approach for refined SNV calling which is able to improve specificity and recall.

P14
CodY regulon in bacillaceae

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Transcription factor CodY is a global regulator of nutrient limitation and amino acid metabolism in Firmicutes studied mostly in B. subtilis. Starting with a set of 42 experimentally verified binding sites in B. subtilis, CodY regulon was analysed in Bacillaceae using comparative genomics methods. We show that CodY regulon in Bacillaceae consists of at least 135 clusters of orthologous operons having conserved binding sites. The function of 15% of them is unknown. Of others, 30% of operons are involved in amino acid metabolism. 20% of operons are related to transport. CodY regulates transcription of 10 other transcription factors in B. subtilis.

P15
Identification of microRNA–controlled immune cell functions *in vivo*

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The immune system is composed of distinct cell lineages that display a large spectrum of biological activities; even cells which are closely related ontogenically can display mutually exclusive functions. For example, monocytes include two subtypes, which either suppress or promote inflammation and can protect the host against infection and injury but also stimulate the progression of chronic inflammatory diseases. Factors that regulate monocyte functional heterogeneity are largely unknown, but their identification may offer therapeutic options for tailoring immune responses to a desired phenotype. In this context, microRNAs are interesting candidates because they regulate multiple target genes and methods are being developed that allow to therapeutically interfere with their expression in vivo and in patients. Here we used a three-step 'functional genomics' approach to address the biological relevance of microRNAs in monocyte subsets: 1) we used computational methods to characterize the expression of (non-)coding sequences in monocyte populations; 2) we manipulated candidate regulatory molecules in vivo e.g. utilizing miRNA knockout mice or locked nucleic acid miRNA agonists; and 3) we evaluated simultaneously control and modified monocytes to determine the role of regulatory molecules in defined in vivo microenvironments. The approach identified miR-146a as a key regulatory component that is differentially regulated in monocyte subsets and that controls the monocyte response both quantitatively and qualitatively. Thus this microRNA represents an important candidate target for therapeutic modulation of monocyte responses.

P16
Impact of translation kinetics on the ribosomal traffic

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The rate by which the ribosomes elongate the nascent chain depends on the codon context and is non-uniform along the coding sequence. According to current models of ribosomal translation, this implies that the distribution of the ribosomes along the mRNA is not uniform. Interestingly, slow-translating codons are overrepresented at the beginning of the majority of the coding sequences. To experimentally assess the impact of the mRNA sequence and of the initial slow-translating region, we substituted fast-translating with synonymous slow-translating clusters of codons along the coding sequence of a model gene encoding the OmpA protein. The mutants mRNAs were up-regulated by ~60 times using pET expression system compared to the intrinsic cellular OmpA-mRNA. The mRNA fractions translated by different number of ribosomes were determined by means of qRT-PCR after fractionation of polysome profiles. Constructs with slow-translating region downstream of the initiation site are translated by a lower number of ribosomes, emphasizing the significance of codon context for the regulation of the ribosome traffic. To assess the ribosome distribution on a transcriptome-wide level we are currently performing deep-sequencing analysis of the ribosome-protected fragments. Our results indicate that the nucleotide sequence contains an additional level of information to regulate the efficiency of translation via adjustment of the ribosomal traffic.

P17
Ribonomics of the plastid-encoded RNA polymerase

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The plastid genome is transcribed by three different RNA polymerases, the plastid-encoded RNA polymerase (PEP) and two nucleus-encoded RNA polymerases (NEPs). PEP is a eubacterial-type multimeric enzyme retained from the ancestral prokaryotic endosymbiont, for which the core subunits are encoded by the plastid *rpoA*, *rpoB*, *rpoC1* and *rpoC2* genes. Taking advantage of homologous recombination in tobacco chloroplasts, we have C-terminally tagged the tobacco PEP alpha subunit (RpoA) with the hemagglutinin (HA) epitope. Phenotypes of transplastomic plants are indistinguishable from WT. We analyzed the spatio-temporal expression of the tagged alpha subunit by western analysis and demonstrated that RpoA:HA is present in the soluble fraction, but is dramatically more abundant in the membrane fraction of chloroplasts. RpoA:HA can readily be immunoprecipitated from both fractions of chloroplast extracts. In an attempt to survey PEP-dependent nascent transcripts on a genome-wide level, we developed a tobacco chloroplast whole genome tiling array and probed for nucleic acids enriched in RpoA:HA precipitates. The identified nucleic acids correspond to genetically identified targets of PEP, but map predominantly to 3'-ends of plastid genes. Implications for PEP-dependent transcription are discussed**.**

P18
Strong negative feedback from Erk to Raf confers robustness to MAPK signalling

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Protein levels within signal transduction pathways vary strongly from cell to cell. We analysed how signalling pathways can still process information quantitatively despite strong heterogeneity in protein levels. Mathematical analysis of isolated de- and phosphorylation cycles predicts that phosphorylation of a signalling molecule is proportional to the protein concentration. We systematically perturbed the protein levels of Erk by siRNA. We found that the steady-state phosphorylation of Erk is very robust against perturbations of Erk protein level, suggesting that there are mechanisms that provide robustness to the pathway against protein fluctuations. Using mathematical modelling and experimental analysis, which included analysis of Erk phosphorylation under Mek overexpression, measuring transcript levels of negative feedback regulators, and application of generic inhibitors of transcription and translation, we could exclude kinetic effects and transcriptional negative feedback as mechanisms of robustness. We found that cells are robust as long as the signal passes through Raf-1. In contrast, cells where the pathway is activated by a mutation in B-Raf loose robustness. Molecular analysis of the system shows that a single post-translational feedback to Raf mediates robustness. Thus, robustness is provided through a fast posttranslational mechanism although variation of Erk levels occurs on a timescale of days.

P19
Multiple reference genomes and transcriptomes for *Arabidopsis thaliana*

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We have sequenced the genomes of 18 inbred accessions of *Arabidopsis thaliana* at ~40x coverage using paired-end Illumina sequencing with different insert sizes. We developed an assembly pipeline that uses iterative read mapping and de novo assembly to accurately recover genome sequences with an error rate close to 1 in 10kb in single copy regions of the genome, and 1 in 1kb in repetitive or transposon rich loci, as assessed with independent data. Naive projection of the coordinates of the 27,416 protein coding genes in the reference annotation onto the 18 genomes predicted large effect disruptions in 8,652 (32%), suggestion that *A. thaliana* can survive prevalent gene disruptions. We developed a pipeline for de novo annotation combining computational gene prediction and RNA-seq data from plant seedlings. We re-annotated each genome, finding that whilst there is considerable variation in gene structure, compensating changes help to ensure that many altered transcripts still retain function. Thus 8,757 genes had at least one additional or modified transcript in at least one accession. We also investigated transcript's diversity in relation to the variation of their 40,578 inferred protein sequences, finding 3,840 (9.5%) proteins that had less than 50% amino-acid sequence identity with the corresponding TAIR10 proteins. Protein diversity varied across gene models and we found isoforms with severe disruptions to occur with low frequency. To complement the genotype-focused analysis, we investigated the quantitative transcriptome variation using RNA-seq. We found 20,963 (78%) of all protein genes to be expressed in at least one strain, with 9,360 (45%) exhibiting significant variation between strains. Mapping causal variants that affect gene expression, we identified variants associated with expression polymorphisms near 941 (10%) of differentially expressed genes. These candidate cis-eQTLs are tightly mapped, and analysis of the location of eQTLs relative to local gene models revealed an excess of associations in regulatory regions.

P20
The function of chriz/Z4 complex in drosophila melanogaster interphase chromosomes

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For the study of interphase chromatin organization, Drosophila provides a number of advantages, like excellent genetics, versatile molecular tools and cytological approaches to interphase chromosomes. We study the role of proteins specifically bound to the euchromatic parts of interphase chromosomes. The chromodomain protein Chriz and the zinc finger protein Z4, together with BEAF-32 and the histone H3S10 kinase Jil-1 constitute a complex that is required for phosphorylation of sections of interphase chromatin and for the maintenance of interphase chromatin structure. Z4 and Jil-1 kinase physically interact with the Chriz protein, which is at the core of the complex. To investigate the role of each of the proteins in the complex and their interplay, dsRNA-induced gene silencing (RNAi) in Drosophila S2 cells was performed. It is found that knockdown of Chriz results in strong (80%) downregulation of Z4 and Jil-1 along with significant decrease in H3S10 phosphorylation. The Z4 RNAi-mediated knockdown in contrast does not affect Chriz and Jil-1 levels, and H3S10 phosphorylation is also not reduced. This points to an independent role of Z4 in the complex presumably related to another type of epigenetic modification. The complex was found by ChIP to bind to many genes in their promoter region and also at more upstream sites. Currently we investigate the correlation between the presence of the complex and the activity of genes bound.

P21
Are there any smallRNA oscillators?

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Small non-coding RNAs (sRNAs) participate globally in the gene-regulatory network of bacteria. Mechanistically, these sRNAs are postulated to regulate gene expression mainly by binding mRNAs and thereby modulating the half-life of the sRNA-mRNA complexes. Still very little is known about the precise mechanisms and functions. It is known that in many microorganisms, the expression of genes oscillates globally. Here we discuss about the role of sRNAs as drivers of these global oscillations in gene expression. We developed a model that describes how the product of a non-oscillatory transcribed gene x can oscillate forced by an sRNA that is produced in an oscillating manner. We analyse whether this modulation will lead to oscillations of the levels of gene x's mRNA and protein levels, and investigate the conditions under which oscillations might be found. Furthermore, we incorporate a self-sustained sRNA oscillator and find a set of specific patterns associated with the resulting oscillations. Our results suggest that sRNA-driven oscillations are a feasible mechanism by which cells might control oscillations in a cost-effective and precise manner.

P22
Protein-RNA interaction map of the RNA helicase MOV10

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RNA helicases represent a class of enzymes that functions in virtually all aspects of RNA metabolism, including transcription, splicing, RNA transport, translation and RNA turnover. RNA helicases unwind RNA structures and/or disrupt and remodel ribonucleoprotein complexes. Since their RNA targets and RNA sites of action remain largely elusive, it has been difficult to assign specific biological functions to many of these enzymes. MOV10 is the mammalian homolog of the Drosophila Armitage and Arabidopsis SDE3 proteins, which both have been shown to function in RNAi pathways. Interestingly, MOV10 have been found to localize to cytoplasmic P-body granules and to interact with AGO2, suggesting a role for MOV10 in miRNA mediated regulation. Nevertheless, the function of MOV10 remains unknown. Recent advantages in characterization of protein-RNA interactions have allowed exact mapping of protein-RNA interactions on a transcriptome-wide scale using a method based on photoactivatable-ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) in combination with next-generation sequencing. Here, we report a comprehensive MOV10 protein-RNA interaction map in human cells using PAR-CLIP, providing the first transcriptome-wide report of a mammalian RNA helicase protein-RNA interaction map. We find that MOV10 predominantly binds to sites in the 3'UTRs of mRNA transcripts in addition to a smaller proportion of binding sites in the coding sequences. We observe a large overlap between our identified MOV10 targets and AGO2 targets, further supporting a role for MOV10 in miRNA mediated regulation.

P23
Distinct cell growth programs identified by global gene expression analysis

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Regulated cell growth is critical for normal cell physiology and its dysregulation is a hallmark of human cancers. Changes in gene expression associated with growth rate confound studies that aim to relate specific inputs to changes in the behavior of transcriptional networks. We used experimental control of cell growth rate by means of chemostat cultures to characterize differential gene expression in different nitrogen sources with unprecedented specificity. We performed minimal perturbation studies in steady-state cultures to study the remodeling of global gene expression associated with transient increases in nitrogen availability. To analyze these data we developed a new method that enables statistical comparison of gene expression levels in steady-state and dynamic conditions using standard methods of linear regression. Application of this method to dynamic growth data identified significant differences in mitochondria-related gene expression suggesting a rapid transition from respirative to fermentative growth independent of carbon availability. By means of high-resolution time series analysis we find evidence that mRNA degradation plays an important role in the transition between gene expression states associated with distinct metabolic growth programs. Our study provides new insights into the regulation of cell growth and methods for its analysis.

P24
Petri nets for spatio-temporal modeling of the genetic regulatory networks

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The analysis of genetic regulatory networks, responsible for cell differentiation and development in prokaryotes and eukaryotes, will much benefit from the recent up scaling to the genomic level of experimental methods in molecular biology. One of the hottest research topics in Genome Science is the interaction between genes. Genetic Regulatory Network (GRN) is one of the recent focuses to understand metabolic pathways and bioprocesses. GRNs act as analog biochemical computers to specify the identity and level of expression of a group of targeted genes. Actually there few systems that are interested to the GRN modeling. Despite this systems described explicitly the modeling used techniques; they not define how represent the biological knowledge required to model the GRN. The goal of our project is to study the dynamic of the GRN by giving a spatio-temporal model, able to represent the gene expression evolution caused by external factors. We present a prototype for the study of dynamical systems to predict the functional robustness of genetic networks against variations of internal and external parameters. Biomedical knowledge is encapsulated in tens of millions of publications with various degrees of coherence and computability. The most difficulty is to identify the biological knowledge and in particular the GRN knowledge.The ontology’s are a very powerful formalisms of representation knowledge domains as complex and rich that the cellular biology. In this paper we proposed a new approach for the spatio-temporal modeling and simulating the dynamic of the genetic networks. One of our contributions concerns the knowledge representation based on ontology. Thanks to an annotated ontological meta-model we resolved the ambiguity problem in biologic domain, through a shared semantics. This approach was validated on the ABC model of Arabidopsis thaliana flower. We realised an hybrid analyse (qualitative and quantitative). For the qualitative analysis we used the PETRI nets and the experimental results to do the quantitative results. We contributed also by the gene classification depending on interpretations results. Actually this interpretation is manual and his major advantage is to help decisions makes and will be in the coming future. Keywords: gene expression, PETRI Nets, spatio-temporal modeling, Genetic Regulatory Networks (GRNs), knowledge representation, ontology.

P25
How your diet shapes your mouth: Effects of different food types on the omnivorous nematode *pristionchus pacificus*

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The nematode *Pristionchus pacificus*, a so called roundworm of the family Diplogastridae, is able to feed on different microorganisms: bacteria, fungi, amoebae - or other nematodes. In the lab it is easily cultivated on agarplates seeded with *E. coli*, growing to adulthood in 72-82 hours at 20-22°C. In the wild the nematode lives in soil. However, when food is scarce and the population is overcrowded it pursues necromeny: the development stops in juvenile stages, initiating the so called Dauer stage which is non-feeding. The Dauers then use beetles like *Exomala orientalis* for transportation to open up new food sources. When the beetle dies and its carcass attracts microorganisms the Dauers feed on those and continue development to adulthood. It has been observed that, depending on the present food and the life-cycle they have gone through, the larvae exhibit one of two distinct mouth forms when exiting the last juvenile stage. In my work I analyse the molecular adaptations with regard to the nematodes' buccal morphology prevailing with certain food types being presented. Therefore I expose them to either bacteria, yeast or amoebae. Furthermore, worms will go through one of three different life-cycles: the direct one (on normal "foodplates"), the J2-arrest (hatching embryos are starved in liquid medium; development stops in J2 stage; arrested J2s are transferred to foodplates) or the Dauer-stage (embryos at a high density hatch in liquid medium containing little food; due to overcrowding they will enter Dauer stage; Dauers are transferred to foodplates). When the worms have reached the adult stage RNA is isolated, the small RNA as well as mRNA populations are sequenced and the abundance patterns are determined. RNA species that appear in strikingly different amounts will be analysed further by quantitative PCR to gain information on the genes involved in the adaptational processes. I will present preliminary analysis results from this experiment.

P26
Experimental tests of the bicoid morphogen hypothesis

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The fly body plan is established early in embryogenesis by a series of transcription factors, several of which are expressed in gradients. One transcription factor, Bicoid (Bcd), is distributed as a long-range gradient that extends along much of the anterior posterior axis. Bicoid has been proposed to provide "morphogen-like" patterning activities, and intense efforts are underway in numerous labs to quantify the gradient and mathematically model the responses of Bcd-dependent target genes. I will discuss two major experimental approaches that are designed to directly test the most critical assumptions of the model. Briefly, our results suggest that Bcd concentration in the wildtype gradient is in excess at every position along the AP axis, and that target genes are not positioned primarily by Bcd concentrations. We further identify three repressors, Capicua, Runt, and Kruppel, all of which are present in middle regions of the embryo, and present evidence that these repressors antagonize Bcd-dependent activation to form sharp gene expression boundaries. We propose that combinatorial interactions between Bcd and these repressors are critical components of the regulatory system that precisely registers multiple Bcd target gene expression boundaries with respect to each other.

P27
Induction of oxidative stress proteins during degradation of fluoranthene by micrococcus sp. and pseudomonas putida

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Environmental pollution by crude oil, refined petroleum products and polycyclic aromatic hydrocarbons (PAHs) is a global problem. Studies have identified bacterial remediation as a promising alternative clean-up strategy. It is therefore imperative to study underlying mechanism by which individual microbes respond to PAHs in order to formulate bioremediation protocols that would be sustainable, safe and cost effective. The induction of oxidative stress proteins by Micrococcus sp. and P. putida during degradation of fluoranthene was investigated using electrophetic, HPLC and mass spectrophotometry technique. Micrococcus sp. and P. putida degraded 100 mg/L fluoranthene in mineral salt media to 2.5 ± 0.8 and 0.02 ± 0.07 mg/L respectively after 7 days of incubation. There was significant ($P <= 0.05$) increase in total intracellular protein, catalase and glutathione-S-transferase activities in both isolates in the presence of fluoranthene. Protein profiles of isolates cell extracts from fluoranthene media showed induction of new proteins compared to controls. This study has revealed potential of the isolates to withstand toxicity of fluoranthene by expressing unique proteins and their impending use in efficient remediation of PAHs polluted sites. Keywords: Bacteria, Environmental Pollution, Oxidative Stress, Polycyclic Aromatic Hydrocarbons, Proteins.

P28
Evaluation of the effects of LC-MS data pre-processing with applications in quantitative proteomics studies

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LC-MS (Liquid Chromatography-Mass Spectrometry) remains one of the most important analytical platforms for elucidating the functions and structures of biological systems. But despite intensive research, it is generally conceded that current methods of data-analysis miss out on much of the information contained in the large data-sets produced with this technology and that many of the estimates produced can be of quite variable quality. This is due in part to the high complexity of the systems studied, but also to the extensive pre-processing that is routinely applied to the output data. Thus, while software packages such as OpenMS and MaxQuant provide largely automated sets of routines for extracting features of interest from the raw data and for storing them in an easily analyzable format, considerable caution must be employed in interpreting the results of downstream analyses. Through a detailed inspection of raw and processed Orbitrap data we identify potential artifacts that risk confounding downstream analyses and using robust regression models propose a heuristic error model for the reported peptide intensities. Using data collected as part of a dilution study, we demonstrate how such a model can be used to rank peptides for their adherence to linear behavior, and outline potential applications of such rankings in quantitative proteomics studies. We furthermore consider the value that may be added to such studies from detailed modeling of non-unique peptides, which are often discarded in quantitative studies. While some work in this direction has already been done, there has so far been limited emphasis on accounting for the statistical distribution of the acquired data. Nor have there been extensive attempts at exploiting prior information in the form of plausible ranges of protein abundances.

P29
Systems biological integration of genetic and epigenetic alterations in prostate cancer identifies central cancer patterns

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Genetic and epigenetic alterations are the basis for the development of malignancies. With new high throughput sequencing tools at hand it has become possible to characterize complete genomes within reasonable time-frames, and, moreover, to generate maps of different information levels of the same tissue material: The identification of mutations, genomic structural variations, gene expression alterations, changes in methylation patterns within one technology has improved the throughput and scientific possibilities to a great extent. With a proof of concept study on more than 30 prostate cancer tissues we provide views of cancerous and benign states over several layers and show that the integration of different data sets enables a complete view of malignant cells. We identified robust alterations encompassing several pathogenetic motifs which might provide the basis for the development of tumor markers.

P30
RGASP evaluation of RNA-Seq read alignment algorithms

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As the amount of high throughput sequencing (HTS) data is rapidly growing, the need for its fast and accurate analysis becomes increasingly important. Inside a wide spectrum of algorithms developed to align reads from RNA-Seq experiments, algorithms capable of performing spliced alignments form a particularly interesting subgroup. The results of these techniques are very valuable for downstream transcriptome analyses. Unfortunately, most of the original publications were not accompanied by a comparison of alignment performance and result quality. The *RNASeq Genome Annotation Assessment Project* (RGASP, carried out by the Wellcome Trust Sanger Institute) was launched to assess the current progress of automatic gene building using RNA-Seq as its primary dataset. Its goal was to assess the success of computational methods to correctly map RNA-Seq data onto the genome, assemble transcripts, and quantify their abundance in particular datasets. The input data originated from three model organisms (Human, Drosophila, and *C. elegans*) and comprised data from different sequencing platforms (Illumina, SOLiD and Helicos). As part of RGASP, also alignments of a variety of different methods, including *BLAT*, *GEM*, *PALMapper*, *SIBsim4*, *TopHat*, and *GSnap*, were submitted; here we present the results of the analysis we performed on these submissions. Besides different descriptive statistical criteria, as sensitivity and precision of intron recognition, mismatch and indel distribution, we also compared the alignments among each other, e.g., with respect to the agreement of intron predictions and multiple mappings of reads. We further investigated the influence of different alignment filtering strategies to the alignment performance in general but also respective to downstream analyses as transcript prediction and quantification. Our comparisons showed a great diversity in the behavior of the different alignment strategies, with surprisingly small agreement between a subset of methods. We can show that different filtering strategies influence the performance significantly and can drastically increase the precision of transcript prediction and transcript quantification. Additionally, the evaluation of the transcript annotations derived from these alignments allows us to correlate alignment accuracy with the precision of exon, transcript, and gene prediction. We will discuss specific features of the different alignment strategies that most influence the success of subsequent analysis steps. The tools developed for this analysis are incorporated into the Galaxy instance at http://galaxy.fml.mpg.de. Further details will be available from http://www.fml.mpg.de/raetsch/suppl/srm-eval.

P31
Transcriptome-wide competition between hnRNP C and U2AF^{65} controls the inclusion of cryptic exons

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In the nucleus of eukaryotic cells, heterogeneous nuclear ribonucleoprotein (hnRNP) particles are associated with all nascent transcripts. Despite their abundance, however, it remained unclear how these particles control pre-mRNA processing. In order to obtain a systemic view of their activity, we developed individual-nucleotide resolution UV-cross-linking and immunoprecipitation (iCLIP) to monitor binding of the core component, hnRNP C. Integration of the protein-RNA interaction map with functional data derived from alternative splicing microarrays revealed that hnRNP C can silence alternative exons by binding to uridine-rich poly-pyrimidine tracts at the 3' splice site. One possible mechanism for this activity could involve competition with U2AF^{65}, a protein that is required to bind to the poly-pyrimidine tract and to recruit the U2 snRNP subunit of the spliceosome. To test whether hnRNP C and U2AF^{65} indeed compete for poly-pyrimidine-tract recognition, we performed quantitative iCLIP mapping of U2AF^{65} binding in wild-type and hnRNP C knockdown HeLa cells. Consistent with our hypothesis, we found a strong increase of U2AF^{65} binding in the absence of hnRNP C specifically at poly-pyrimidine tracts of hnRNP C-silenced exons. In addition, we detected competition with U2AF^{65} at a large number of deep intronic sites, indicating that hnRNP C is crucial to prevent the recognition of cryptic exons (see also conference contribution from Kathi Zarnack). Taken together, our data describe a novel function for hnRNP C as a transcriptomic sentinel that directly competes with the splicing machinery to prevent inclusion of cryptic exons and to maintain splicing fidelity.

P32
Investigation of UV induced protein-RNA cross-linking by mass spectrometry

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UV induced cross-linking is a common method for the analysis of protein-RNA contact sites. Upon UV irradiation, the formation of novel covalent bonds between nucleic acid bases and amino acid residues is induced. Mass spectrometry (MS) has proven to be a sensitive and unbiased method to identify the generated cross-links. This method can be applied on larger and more complex protein-RNA assemblies to identify i) proteins that are in direct contact to RNA and ii) their corresponding RNA binding region and motifs. However, the low yield of UV cross-linking and the absence of suitable data analysis tools for computational identification of cross-linked heteroconjugates present various challenges. The proportion of low abundant cross-linked heteroconjugates over the excess of non-cross-linked peptides and RNA oligonucleotides can be enhanced by enrichment procedures e.g. using titanium dioxide. This approach is successfully applied in our cross-linking studies of spliceosomal subcomplexes, i.e. human U1, U2 and U5 small nuclear ribonucleoprotein (snRNP) particles as well as in other protein-RNA assemblies investigated in our laboratory. In addition, photo reactive base-analogues such as 4-thio-uracil and 6-thio-guanine can be incorporated into the RNA in order to enhance the cross-linking yield. Standard database search engines cannot be easily applied for the identification of cross-links. MSMS spectra of cross-linked heteroconjugates are usually dominated by the peptide fragments. However, the precursor masses are shifted by the different masses of the cross-linked RNA moieties of variable compositions. We employed an algorithm that subtracts the masses of all possible nucleotide combinations from the experimental precursor mass of potential cross-links. By submitting the modified precursor masses together with the unaltered MSMS information into database search, cross-linked peptides are identified.

P33
Investigation of interactions between proteins and G-quadruplex motifs in the 5‘ UTR of mRNAs

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Guanine-rich nucleic acids can adopt four-stranded structures called G-quadruplexes. It has been shown that G-quadruplex forming sequences occur with high prevalence in regulatory elements e. g. oncogene promotors, telomeres and 5’ and 3’ UTRs of mRNAs. G-quadruplex motifs in mRNAs have only recently been recognized as a new posttranscriptional regulatory mechanism of gene expression. We were able to demonstrate that a G-quadruplex in the 5’ UTR of the zic-1 mRNA inhibits its translation in eukaryotic cells. The G-quadruplex motif is evolutionary conserved and thermodynamically very stable. Dual-luciferase assays were employed to show that the 5’ UTR containing the G-quadruplex motif represses protein synthesis. Quantitative RT-PCR confirmed that the reduction of protein synthesis is due to regulation on the translational level and not a consequence of reduced transcription. More recently, we started to study the interaction between proteins and G-quadruplex motifs. The investigation of this interaction is necessary to understand the role of G-quadruplexes in translation. Proteins binding to different types of G-quadruplexes were isolated by pull-down assays and subsequently identified by MALDI-TOF mass spectrometry. Some of the isolated proteins have already been described to bind to G-quadruplex motifs composed of DNA, while others seem to be specific for RNA. This is particularly the case for several ribosomal proteins, which are likely to originate from the stalled ribosome. Some of the most prominent protein candidates have been overexpressed to investigate the mode and strength of interaction in more detail. Taken together, G-quadruplex motifs in the 5’ UTR of mRNAs can be considered to add a new level of regulation of gene expression to recently discovered regulatory RNA elements such as riboswitches and aptazymes.

P34
Automated bacterial gene annotation

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Annotation of newly sequenced genomes is an important step for the investigation of prokaryotic species. Several methods for prediction of protein coding genes have been established. Due to their universal nature, the quality of predictions can be further improved using lineage-specific models. This accounts especially for species that live under extreme environmental conditions or show genetic anomalies. Desirable improvements are more exact gene positioning and the detection of genes with unusual features. Putative gene functions can be assessed using homologous data, however results significantly depend on the choice of representative reference species which is a non-trivial task. Here we present a combined approach: BacProt uses homologous genes to generate a lineage-specific prediction model that improves prediction quality. The tool complements the annotation with basic ncRNAs and introduces a new method for synteny-based ncRNA detection.

P35
Coordination of DNA replication, siRNA production and histone modification by the Rik1-Dos2 complex

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Histone modification marks play an essential role in many chromatin processes. During DNA replication, both heterochromatin and euchromatin are disrupted ahead of the replication fork and then reassembled into their original epigenetic states behind the fork. How the histone marks are faithfully inherited during each generation is still poorly understood. In fission yeast RNA interference (RNAi)-mediated histone methylation is cell-cycle regulated. Centromere repeats are transiently transcribed at S phase and processed into small interference RNAs (siRNAs) by RITS and RDRC complexes. The small RNAs, in concert with silencing factors, including Dos1/Clr8, Dos2/Clr7, Rik1 and Lid2, promote heterochromatic H3K9 methylation by a histone methyltransferase, Clr4. H3K9 methylation serves as a binding site for Swi6, a structural and functional homolog of metazoan Heterochromatin Protein 1 (HP1). We identified a silencing complex, which contains Dos2, Rik1, Mms19, Cdc20 (DNA polymerase epsilon) and Cdc27 (DNA polymerase delta). The complex regulates heterochromatic siRNA generation, and is required for DNA replication and heterochromatin assembly. Our findings provide a molecular link between DNA replication, siRNA production and histone methylation, and suggest a novel mechanism underlying the coordination of the these processes, shedding light on how epigenetic marks are inherited during each cell cycle.

P36
From face to interface recognition: A differential geometric approach to predict RNA binding surfaces

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Protein-RNA interactions play a critical role in all steps of the gene expression pathway. RNA binding proteins interact with their partners via distinct regions on their surface that are characterized by an ensemble of chemical, physical and geometrical properties. While DNA-binding interfaces have been extensively studied, characterizing RNA-binding surfaces is still a great challenge. In this study, we introduce a novel methodology based on differential geometry, a method which is commonly used in face recognition, to uniquely predict RNA-binding interfaces, distinguishing them from DNA-binding surfaces. Applying the method on experimentally solved three dimensional structures of proteins we successfully classify single-stranded RNA (ssRNA) binding proteins from DNA binding proteins, with 83% accuracy. We show that the method is insensitive to conformational changes that occur upon binding and can be applicable for de novo prediction of RNA-binding proteins. Remarkably, when concentrating on the well-studied nucleic-acid binding motif, the zinc finger motif, we distinguish successfully between RNA- and DNA-binding interfaces possessing the same binding motif even within the same protein, as demonstrated for the RNA polymerase transcription-factor, TFIIIA. In conclusion, we present a novel methodology to characterize protein surfaces, which can successfully predict RNA-binding surfaces and accurately tell apart ssRNA from dsDNA binding interfaces. The strength of our method in recognizing fine-tuned differences on nucleic acids-binding interfaces make it applicable for many other molecular recognition problems. We show the implications of the method for predicting drug binding sites on protein-RNA interfaces.

P37
Rapid peptide in-solution isoelectrofocusing fractionation for deep proteome analysis

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Despite the advancements in mass spectrometry technology, sample fractionation in a prerequisite for a deep coverage of a proteome, especially in case of high complexity as for the human one. In a traditional MS-based approach, proteins are separated by 1D-SDS gel before online MS analysis (GeLC-MS); more recently, with the introduction of a device for peptide isoelectofocusing, the peptide mixture is fractionated after protein digestion on a strip this approach and allowed a deeper proteome coverage respect the GeLC-MS. Anyway both methods still require long working times. Here we describe the application of an in-solution isoelectrofocusing method for a simple and fast peptide fractionation prior to liquid chromatography-mass spectrometry (LC-MS/MS) analysis. This analysis enables the identification of more than 5700 proteins and more than 44000 peptides in less than 24 hours of measurement time. With such a high average number of identified peptides per protein, this approach allows identification of splice variants that are still not annotated; moreover, using a stable isotope-label in cell culture (SILAC) sample, ~4200 protein (or ~75%) are reliably quantified and other ~600 can be quantified after a manual control.

P38
A systems biology approach to screen for miR17-92 targets in Lymphoma by a combination of qProteomics and transcriptomics

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A correlation between aberrant microRNA (miR) expression and cancer has been frequently reported. The miR17-92 cluster (composed of miR17, miR18, miR19a, miR19b, miR20a and miR92) is located in a genomic region amplified in several human B-cell lymphomas. In a mouse B-cell lymphoma model, enforced expression of the miR17–92 cluster acts synergistically with c-myc to accelerate tumor development. Of the few targets identified so far, a significant portion is cancer-related. We employ a functional genomics approach combining SILAC-based quantitative proteomics and transcriptomics to extend the analysis of miR17-92 targets and thus shed light on its role in c-myc full-blown B-cell lymphoma. We obtained a high-confidence quantitative proteome of about 4700 proteins, and a corresponding transcriptome of about 10000 transcripts. Comparative analysis of the proteome and transcriptome revealed that the cellular response is predominantly at the protein level, with significantly higher down-regulation in predicted protein targets of miR17/20a and miR19a/19b, as compared to non-targets. The intersection between predicted miR-targets and down-regulated proteins produced a list of 187 miR17-92 candidate targets. Validation of miR-engagement in observed down-regulation is ongoing by using RISC-IP coupled with qPCR. Interestingly, among them we found several proteins (e.g. RRM2, ATAD2) that participate in cell proliferation control, acting as either oncogenes or tumor suppressors depending on the context and on the expression level. Moreover, the emerging response from molecular targets largely coincides with phenotypic analyses: miR17-92 overexpression results in reduced cell proliferation and in slower G1/S transition, having as a consequence loss of cells which overexpress the cluster in competition assays performed in vitro and in vivo. This suggests that, in this context, the miR17-92 cluster has a protective role.

P39
A protein interaction map for the human chemical synapse

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Central to all neuronal functions are the trillions of synapses within the human brain that transmit chemical signals. This process is performed and regulated by complex networks of proteins in the pre- and post-synaptic termini. In the past ten years efforts in synaptic-proteomics have been focused on identifying the constituents of synaptic sub-compartments; the synaptic vesicle, pre-synaptic active site and post-synaptic density. Over 2000 gene products have been identified in the chemical synapse, but the binary interactions between these players have not previously been studied on a global scale. To gain more insight into multi-protein complexes formed at the synapse we have adopted a high-throughput screening strategy; over 700 proteins were tested for pairwise interaction in yeast and human cell lines. Selection of interacting protein pairs for further study was based upon a scoring system which took into account six factors: 1) known interactions between orthologues, 2) the presence of domains known to interact in each of the proteins, 3) co-expression, 4) co-localisation, 5) shared biological function and 6) distance in an interaction network made up of all known interactions. The interactions we detected are now being used to predict the locality of multi-protein complexes within the synapse. We have also established assays based on sub-cellular fraction and immunostaining to verify our predictions *in vivo.* The protein interaction network generated and validated by this study could provide insight into synapse dysfunction, which is central to the etiology and progression of neurological disorders including neurodegeneration, autism and schizophrenia.

P40
Terminal exon pausing: functional coupling of transcription and splicing leads to widespread cotranscriptional splicing.

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Pre-mRNA splicing is catalyzed by the spliceosome, which can assemble on pre-mRNA co-transcriptionally. However, whether splicing generally occurs during transcription has not been previously addressed. Indeed, splicing catalysis is expected to occur post-transcriptionally in yeast, where the shortness of terminal exons should leave insufficient time for splicing. We have isolated endogenous S. cerevisiae nascent RNA and determined gene-specific splicing efficiencies and transcription profiles, using high density tiling microarrays. Surprisingly, we found that splicing occurs co-transcriptionally for the majority of intron-containing genes. Analysis of transcription profiles revealed Pol II pausing within the terminal exons of these genes. Intronless and inefficiently spliced genes lack this pause. *In silico* simulations of transcription and splicing kinetics confirm that this pausing event provides sufficient time for splicing before termination. The discovery of terminal exon pausing demonstrates functional coupling of transcription and splicing near gene ends. We are currently investigating the role of elongation factors in terminal exon pausing.

P41
Profiling the human classical tyrosine phosphatases substrate specificity

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Reversible tyrosine phosphorylation is a pervasive posttranslational mechanism underlying cell physiology. Phosphoprotein homeostasis is regulated by two enzyme families, kinases and phosphatases. A thorough description of the mechanisms responsible for substrate selection by kinases and phosphatases is central to our understanding of signal transduction. Our work has focused on classical Protein Tyrosine Phosphatases (PTPs), a family of 37 enzymes catalyzing the dephosphorylation of tyrosine residues. Deregulation of PTPs is critically involved in many human diseases such as cancer and autoimmunity. As a consequence this enzyme family is receiving increased attention as potential drug target. Classical phosphatases can exhibit some substrate specificity in vivo by combining an intrinsic enzymatic specificity with a network of protein interactions bringing the enzymes in close proximity of their substrates. However, the relative importance of these two mechanisms is not established. We have used a new high throughput technology based on high-density phosphopeptide chips to determine the recognition specificity of 16 members of the PTP family. In addition we have carried out an extensive survey of the scientific literature to extract interaction information that could contribute to place PTPs in the context of the human protein interaction network. This combined approach has allowed to estimate the relative contribution of intrinsic and network-mediated specificity in determining in vivo substrate selection.

P42
Quantitative comparison of selected genomic-wide protein domain co-occurrences in 18 species

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Transcription factors (TF) typically cooperate to activate or repress the expression of genes. They play a critical role in developmental processes. To compare the set of transcription factors between species, we currently rely on genome annotiation of equal quality. To overcome this problem, we propose to perform gene prediction followed by the detection of functional domains via HMM-based annotation of SCOP domains. In this contribution we will demostrate that this methods leads to consistent estimates for quantitative comparison. To emphasize the applicability, we analyzed the protein domain distribution of putative TFs by quantitative and boolean means. In particular, we utilize systematic studies of protein domain occurrences and co-occurrences to study avoidance or preferential co-occurence of certain protein domains within TFs. Among seven major classes of DNA-binding domains, we observed specific co-occurence of zinc-finger and KRAB domains in human and zinc-finger and winged helix domains in *Phytophthora* and *Leishmania*. On the other hand, we found the tendency of avoidance among zinc-finger and Tetratricopeptide repeat (tpr) domains for human.The quantitative comparison of protein sets among species can be used to study their evolution. In this respect, signals for preferential co-occurrence can arise from recent proliferation by gene duplication as in the case of the primate-specific krab-znf family of transcription factors.

P43
Multi-purpose single nucleotide polymorphism calling enhanced by probabilistic integration of base call quality scores

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We develop a novel method for single nucleotide polymorphisms (SNPs) detection in Next Generation Sequencing (NGS) data, which includes error probabilities of sequenced bases to accurately discriminate true polymorphisms from sequencing errors. Cross sample comparison of NGS data to identify variant positions (e.g. SNPs) is a common task in high-throughput sequence analyses. Several applications such as variant detection in forward genetic screens, medical resequencing or population allele frequency estimation benefit from our approach, which aims at discriminating signal from noise (sequencing errors) on as little prior assumptions as possible. A novel application in conjunction with Photoactivatable-Ribonucleoside-Enhanced Crosslinking and Immunoprecipitation (PAR-CLIP), which profiles RNA-Protein interactions, is presented in detail. In contrast to methods that calculate test-statistics on the counts of observed bases (A, C, G, T), in our novel approach we exclusively utilize the error probabilities from sequencing experiments that are provided by the employed NGS platform to implement a qualitative measure of sequencing errors in our model of experimentally determined polymorphic positions. During a head to head comparison of two samples a probability vector (p(A), p(C), p(G), p(T)) for each sample is calculated from pileups of sequenced reads. Those two probability vectors are utilized to calculate a test-statistic to identify polymorphic positions while controlling for sequencing errors by adjusting a threshold. Our initial evaluation on synthetically generated data shows promising results on homozygous allele frequencies and currently we are embedding our model in a sound multinomial probabilistic framework. We implemented our QS-enhanced SNP-model in a tool called “ACCUSA2” that uses the Java-based Picard-Framework that enables efficient processing of SAM/BAM files.

P44
Monitoring pyruvate utilization in living mouse – a case study for stable isotope tracer experiments in vivo

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Analyzing dynamics of metabolism in vivo is challenging but also very promising to deliver a deeper understanding of the metabolic network. With this aim usually cell-cultures or organisms are fed with substrates containing stable or radioactive isotopes and their uptake and metabolization to endogenous compounds is measured. Small changes in metabolic fluxes do not always lead to detectable differences in metabolite levels but they can often be seen in differential label incorporation rates. Here we present a Stable Isotope Resolved Metabolomics (SIRM) approach in mice. Wildtype mice were injected with ^{13}C-labeled Pyruvate and label-incorporation was measured in blood plasma and liver tissue at different time points to learn more about the dynamics and time-scale of metabolic processes of the mouse-liver in vivo. Applying GC-TOF-MS (Gas Chromatography coupled to a Time Of Flight Mass Spectrometer) we are able to monitor most of the metabolites of the central carbon metabolism in a non-targeted manner. We can also find unexpected labeled products of the metabolism, leading to a better knowledge of pathway usage and flexibility. The used analytical strategies, the workflow we are using and the first results of the mice-labeling experiment are reported here. We found that the largest fraction of pyruvate is used in the tricarboxylic acid (TCA) cycle whereas only a minor fraction is used for gluconeogenesis. Monitoring the dynamics we can conclude that we had chosen exactly the right time-scale. The knowledge gained in this study will be beneficial for further experiments, e.g. other mouse lines, serving as human tumor models, as well as for cell-cultures and in perspective also for human patients as shown recently.

P45
Structure-function characterization of poliovirus genome RNA-element

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Poliovirus is a small non-enveloped icosahedral virus with positive single strand RNA genome. Protein-RNA interactions play a crucial role in virus life cycle. In particular, recognition of the genome cloverleaf-like cis-element *oriL* by viral protein 3CD is essential for the genome replication initiation. It was shown that the apical tetraloop of domain d of *oriL* is involved in this interaction but detailed mechanism remains unknown. The aim of our research is to determine features of the apical region of domain d significant for the 3CD-*oriL* recognition and viral replication. Defined structures of the relevant tetraloops of enteroviral genomes belong to one particular structural class of the three existing stable classes. We engineered viral genomes containing tetraloops of all these classes with/without flanking base pair variations. Kinetics of viral genome replication and affinity to recombinant 3CD protein were measured. We performed preliminary molecular dynamics simulations studies of RNA ligands and showed that their biochemical features are correlated with structural properties. Our study contributes to understanding of molecular mechanism of the poliovirus replication initiation and the general protein-RNA recognition problem.

P46
Long non-coding RNAs with enhancer-like function

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A number of recent genome-wide studies identify long non-coding RNAs based on expression analysis and chromatin marks. We have used the annotation of the human genome of HAVANA, based on data of the GENCODE project to identify long non-coding RNAs that are located in regions not overlapping known protein coding genes. By custom microarray approaches we show these long non-coding RNAs to be differentially expressed in primary human keratinocytes upon induction of differentiation. Using siRNAs to knock down a number of the identified long non-coding RNAs in human cells we have identified seven that mediate positive regulation of nearby genes. These long non-coding RNAs have effects similar to those of classical defined enhancers, mediating their effects through the processed RNA transcript. Enhancers are classically defined as regulatory DNA elements, mediating orientation independent regulation of gene expression over a distance, properties that are recapitulated by the identified long non-coding RNAs. Recent experimental approaches have shown that a large number of enhancers can be identified from ChIP-seq data for enhancer-binding proteins and associated histone methylation marks. Comparisons of genome-wide ChIP-seq data with expression profiling from RNA-seq studies suggest the transcription of enhancers to be a common phenomenon. With the possibility of delineating enhancer functions through knock-down studies, the repertoire of enhancer interaction studies will be widely expanded.

P47
Hypoxia-inducible factor 1α promotes gastric cancer chemoresistance via modulation of p53 and NF-κB

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Introduction: Chemoresistance is a pivotal obstacle in oncology. Molecular characterization of pathways regulating chemoresistance is a central prerequisite to improve cancer therapy. The hypoxia-inducible factor HIF-1α has been linked to chemosensitivity while the underlying molecular mechanisms remain largely elusive. Material and Methods: RNA interference was applied to inactivate HIF-1α or p53 in the human gastric cancer cell lines AGS and MKN28. The chemotherapeutic agents 5-fluorouracil and cisplatin were used and chemosensitivity was assessed by cell proliferation assays as well as determination of cell cycle distribution and apoptosis. Expression of p53 and p53 target proteins was analyzed by western blot. NF-κB activity was characterized by means of electrophoretic mobility shift assay. Results: Inactivation of HIF-1α in gastric cancer cells resulted in robust elevation of chemosensitivity. Accordingly, HIF-1α-competent cells displayed a significant reduction of chemotherapy-induced apoptosis. Remarkably, this phenotype was completely absent in p53 mutant cells while inactivation of p53 per se did not affect chemosensitivity. HIF-1α markedly suppressed chemotherapy-induced activation of p53 and p21 as well as the retinoblastoma protein, eventually resulting in cell cycle arrest. Reduced formation of reactive oxygen species in HIF-1α-competent cells was identified as the molecular mechanism of HIF-1α-mediated inhibition of p53. Furthermore, loss of HIF-1α abrogated, in a p53-dependent manner, chemotherapy-induced DNA-binding of NF-κB and expression of anti-apoptotic NF-κB target genes. Accordingly, reconstitution of the NF-κB subunit p65 reversed the increased chemosensitivity of HIF-1α-deficient cells. Conclusion: In summary, we identified HIF-1α as a potent regulator of p53 and NF-κB activity under conditions of genotoxic stress. We conclude that p53 mutations in human tumors hold the potential to confound the efficacy of HIF-1-inhibitors in cancer therapy.

P48
The speed of ribosomes

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During protein synthesis a ribosome doesn't always proceed at the same speed. Instead, elongation rates depend on a multitude of factors like the concentrations of translation-related molecules. We present a model that allows to calculate codon-specific elongation rates based on aminoacyl-tRNA (aa-tRNA) concentrations and codon usages. The model takes into account the effect of non-cognate aa-tRNAs that compete with cognate aa-tRNA for ribosomes and regards simultaneously translating ribosomes that reduce the number of available aa-tRNA molecules. Using available in vivo data we computed the elongation rates for Escherichia coli and performed stochastic simulations of the translation process.

P49
Effects of human argonaute 2 phosphorylation on small RNA-guided gene silencing

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The discovery of small RNAs, namely small-interfering RNAs (siRNAs) and microRNAs (miRNAs), revealed a new possibility of post-transcriptional gene silencing by regulating gene expression at the messenger RNA (mRNA) level. Therefore, they play important roles in biological processes including embryonic development, cell metabolism or apoptosis. Therefore, it is very likely that small RNA-guided gene silencing is regulated itself. Argonaute (Ago) proteins are the proteinogenic key factors mediating small RNA-guided gene silencing. This marks Agos as a potential target of regulatory pathways - especially Ago2, the only human Ago protein with cleavage activity. Post-translational protein modifications offer an efficient way for regulating protein function. Ago2 shows indeed several modifications: Hydroxylation at proline-700 and ubiquitinylation have influence on Ago2 stability, phosphorylation at serine-387 is crucial for P-body localization. Our group identified further phosphorylation sites of Ago2 by mass spectrometry. By generating phospho-mutants, we could show that the phosphorylation of tyrosine-529 (Y529) in the MID domain and serine-798 (S798) in the PIWI domain of Ago2 seems to influence the cleavage activity. By mutating Y529 to glutamate (Y529E), mimicking the phosphorylated state, the binding of the 5' phosphate of the small RNA is inhibited. Probably repulsive forces, due to the negative charge of the phospho-mimicking group and the 5' phosphate of the small RNA, cause the binding defect. Consequently, Ago2 shows no cleavage activity, neither *in vitro* nor *in vivo*. Also the glutamate mutant of S798 (S798E), mimicking the phosphorylated state, shows a defect in cleavage activity *in vitro*. Currently, we focus on the molecular background for the reduced cleavage activity of S798E. In further studies, we will embed Ago phosphorylation to specific signaling pathways in order to better understand the network of cellular processes which regulate gene expression.

P50
Small RNAs in plant organells: Degradation products protected by RNA binding proteins?

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Small RNA species as regulators of gene expression like miRNAs have been described from a variety of species. Recently, short RNAs with similar size have been described as footprints of a specific class of RNA binding proteins called pentatricopeptide repeat proteins (PPR) (Pfalz et al., EMBO J. 2009). PPR proteins are particularly prevalent in plants (more than 450 members in Arabidopsis), where they are imported into mitochondria and chloroplasts. PPR Proteins can act as roadblocks against exonucleases, protecting their target RNAs from degradation (Barkan A., Plant Physiol. 2011). Eventually, breakdown of the messages will inevitably occur and leave behind small RNA species, footprints of PPR proteins. We have analysed RNA seq datasets available for current plant model species for the presence of such footprints in chloroplasts. We found about 50 clusters of small chloroplast RNAs, the majority in intergenic regions. These clusters have relative sharp 5’ and 3’ ends and coincide with known or predicted binding sites of PPR proteins. By 5’ and 3’ RACE and comparisons with transcript ends known from the literature, we demonstrate that ends of RNA footprints and of mature mRNAs coincide. By comparing Arabidopsis and rice small RNA clusters we show conservation for a subgroup of these clusters while others seem to be lineage-specific. We noticed not only interspecific conservation, but found also different clusters with sequence similarities within a species. This indicates that one protein could serve different but related sequences in one species. Taken together the presented data support a model in which RNA binding proteins protect transcript segments against degradation. It is unclear, whether these novel RNA species serve regulatory functions or are only the useless remainder of chloroplast road blocks against exonucleases.

P51
The influence of the local sequence environment on RNA loop structures

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RNA folding is assumed to be a hierarchical process. The secondary structure of an RNA molecule, signified by base-pairing and stacking interactions between the paired bases, is formed first. Subsequently, the RNA molecule adopts an energetically favorable three-dimensional conformation in the structural space determined mainly by the rotational degrees of freedom associated with the backbone of regions of unpaired nucleotides (loops). To what extent the backbone conformation of RNA loops also results from interactions within the local sequence context or rather follows global optimization constraints alone has not been addressed yet. Because the majority of base stacking interactions are exerted locally, a critical influence of local sequence on local structure appears plausible. Thus, local loop structure ought to be predictable, at least in part, from the local sequence context alone. To test this hypothesis, we used Support Vector Machines (SVM) and Random Forests (RF) on a nonredundant data set of unpaired nucleotides extracted from 97 X-ray structures from the Protein Data Bank (PDB) to predict discrete backbone angle conformations given by the discretized [eta] /θ-pseudo-torsional space. Predictions on balanced sets with four to six conformational classes using local sequence information yielded average accuracies of up to 64% (SVM) [55% (RF)], thus significantly better than expected by chance (17%–25%). Bases close to the central nucleotide appear to be most tightly linked to its conformation. Our results suggest that RNA loop structure does not only depend on long-range base-pairing interactions; instead, it appears that local sequence context exerts a significant influence on the formation of the local loop structure**.**

P52
SplamiR - Predicting a new class of plant microRNAs

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MicroRNAs (miRNAs) are a class of non-coding RNAs, usually 21nt long. They have been identified in a number of plants, animals and viruses where they are important regulators of various cellular processes. MiRNAs mediate the down-regulation of target mRNA sequences through hybridization. Recently, miRNA genes with primary transcripts that contain large introns have been discovered. These primary unspliced miRNAs (pri^{u}-miRNAs) do not show the typical hairpin structure. At present, *ab initio* methods for the computational detection of novel plant miRNAs focus on the identification of the hairpins and, therefore, intron-containing precursors are not recognized. Hence, more sophisticated methods for the detection of spliced miRNAs are required. To tackle this problem, we present SplamiR, the first method for the computational prediction of spliced miRNAs. SplamiR is applicable to all plant genomes and is able to predict spliced and non-spliced miRNAs for any designated target gene. The SplamiR pipeline consists of two main phases: in phase one, all potential stems in genomic sequence are collected. In phase two, stems with high complementarity to a given target gene are identified. By means of pattern recognition tools, putative intronic sequences are removed from the miRNA candidates and these resulting sequences are checked for the capability to fold into the typical hairpin structure. We applied SplamiR to the genomes of rice and maize where all known spliced members of the MIR444 family were correctly identified. Furthermore, we found a previously undiscovered miRNA sequence for maize whose expression is supported by an expressed sequence tag (EST). In summary, the presented pipeline is the first bioinformatic approach for the prediction of this new class of miRNAs. SplamiR is applicable to many plant genomes for the detection of spliced and unspliced miRNAs when given the target mRNA.

P53
Length dependent translation of mRNA

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Several sets of data show that the steady state amount of proteins per mRNA is negatively correlated with the length of the message. This would mean that, statistically, longer genes are less expressed than shorter ones. One possible explanation for this observation is that the rate of protein synthesis decreases statistically with the length of the mRNA, in agreement with the experimental observation that the ribosome density is also decreasing. On the other hand, the time scale that ribosomes need to reach the end of the mRNA, which is proportional to the length of the message, interferes with the time scales associated to the degradation process of the mRNA. Thus, the turnover of mRNA may have a direct influence on the translation rate. In this contribution, we present a mechanistic model for protein synthesis coupled to mRNA degradation. The model shows that unspecific endonucleolitic degradation interrupts the translation of the messages and thus affects the rate of protein synthesis in a length-dependent way. The functional relationship between translation rate and length of the mRNA is then compared with data from E. coli and show a statistically good agreement. Moreover, we have subsequently assumed that degradation occurs by means of de-capping, which is one of the main mRNA degradation pathways in eukaryotes. In this case, the model still shows a negative correlation, which is however weaker than in prokaryotes.

P54
Thiolation-proteomics in sarcoplasmic reticulum from skeletal muscle.

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Muscle contraction is a physical phenomenon that is initiated by electrical activity occurring on the surface of muscle cell membrane and extending their effect on internal membranes specifically the Sarcoplasmic Reticulum (SR), which is the main storage of Ca^{2+}. Prolonged muscle activity, results in force of contraction decline becoming refractory to further stimulation and protect the muscle from damage. This physiological process is known as fatigue. Muscle proteome is one of the most complexes of the animal tissues, needed to the proper function. Muscle fiber contractile and cytoskeleton protein machinery needed an accurate regulation of intracellular (Ca^{2+}) by the SR. The proteome of the SR consist mainly of two groups of proteins; membrane and soluble, all with a regulatory function for Ca^{2+}. SR proteins undergo posttranscriptional changes such as phosphorylation and thiolation. In the present study we analyze the SR proteins containing vicinal thiol-groups (VT-G) which are regulated by redox potential. The VT-G of interest is mainly present at the protein surface allowing the formation of reversible disulfides. From highly purified isolated SR we made SDS-PAGE analysis and label VT-G using a radioactive thiol-specific reagent to label protein-SH. N-iodoacetyl-3-(I^{125})iodotyrosine ((I^{125})IAIT), and differentiate monothiols from dithiols. The major SR membrane protein regulating Ca^{2+} are; Ryanodine Receptor-Ca^{2+}.channel (RyR) for muscle contraction and SERCA for Ca^{2+} uptake in muscle relaxation, both are VT-G proteins (VTGP). Interestingly, the major SR luminal Ca^{2+}-binding protein (Calsecuestrin) does not have any thiol. Triadin and Junctin, the two SR RyR-regulated proteins are not VTGP. However the SERCA1 associated protein ä-Sarcoglycan that has been shown to influence SERCA structural conformation is a VTGP. We will discuss the physiological meaning in muscle of thiolation-proteomics in SR, considering VT-G proteins as nano-switches for muscle function.

P55
Proteomics characterization of the *escherichia coli* RNA degradosome

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RNA degradation is an essential component of post-transcriptional control of gene expression. In *Escherichia coli*, RNA degradation involves a multi-protein complex consisting of four proteins: the main enzyme is the endonuclease RNase E which interacts with the exonuclease PNPase, helicase RhlB, and enolase. The interaction between these components is highly dynamic, and their detailed roles are still unclear. In particular, it is still a matter of debate to what extent PnPase and RhlB form an independent degradation complex in case RNase E function is compromised. To increase our understanding of degradosome function, we examined mutants of the four main enzymes (RNase E, PnPase, RhlB, and enolase) in their impact on protein expression, comparing these results to data on RNA expression and half-life. Our results paint a complex picture of the RNA degradation machinery, but support functional ties between PnPase and RhlB.

P56
Hunting 6S RNAs in bacteria

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6S RNA is a highly abundant non-coding RNA in bacteria, which was already discovered in Escherichia coli in the late 1960s, but its function remained unclear for many years. It was discovered that 6S RNA interacts with the RNA polymerase (RNAP) and thereby regulates gene expression [1]. The sequence of 6S RNA of all bacteria is highly divergent, in contrast to its conserved secondary structure, which contains a single-stranded central bulge within a highly double-stranded hairpin molecule [2] and allows the formation of a stable complex with RNAP [3]. Residues located in the -35-region upstream of the 6S RNA are essential for binding [4], whereas the release of RNAP is controlled by pRNAs, for which the 6S RNA itself serves as template [5].
The aim of this work was to detect 6S RNA in all bacteria. Therefore, we used different approaches, including sequence homology, motif and pattern searches by e.g. covariance models as well as a global search by hand. Furthermore, we analyzed the syntenic regions of the 6S RNAs with Proteinortho [6] to obtain more information about their genomical location.
Here we present a complete overview of the occurrence of the 6S RNA within bacteria. We show common features concerning sequence, number of copies, regulation and syntenic conservation, which differ between the bacterial classes.

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P57
Global profiling of miRNA and the hairpin precursor: insights into miRNA processing and novel miRNA discovery

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MiRNAs constitute an important class of small regulatory RNAs that derive from hairpin precursors (pre-miRNAs). To date, hundreds of different miRNAs have been identified in various species. Recent studies have sought to reveal novel aspects of miRNA biogenesis as well as modification. To gain further insight into miRNA processing, we sequenced the small RNAs of two distinct size ranges corresponding to mature and precursor miRNA respectively. Of 167 million reads of length between 17 and 30nt derived from 10 different adult mouse tissues, 53% were derived from 507 miRNA loci annotated in miRbase 16. In contrast, only approximately 1% of 58 million reads of size ranging from 30 to 94nt were mapped to 272 distinct miRNA loci. With such a limited sequencing depth of miRNA precursors, however, we observed their processing intermediates including previously reported ago2-cleaved-pre-miRNAs. In addition, by combining the sequencing data derived from mature and precursor miRNA, we identified with high confidence miRNA editing events and elucidated the different pattern of untemplate modification at 3' end of both mature miRNAs and their precursors. Finally, based on our mature and precursor sequencing data, and without using genome reference sequence information, we predicted 437 mature miRNAs, of which 403 have been deposited in miRBase and 34 were novel candidates with supporting sequencing reads corresponding to the mature as well as precursor forms. Therefore, our approach has high potential in the identification of miRNAs from the organisms without an available genome reference sequence.

P58
mRNA-seq analyses reveal a novel role of hnRNP C in transcriptome maintenance

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Heterogeneous nuclear ribonucleoprotein C (hnRNP C) is one of the most abundant proteins in the nucleus where it nucleates so-called hnRNP particles on all nascent transcripts. We could previously show that sequence-specific positioning of these particles plays a role in alternative splicing. Combining protein-RNA interaction mapping using iCLIP with splicing evidence from splice-junction microarrays, we demonstrated that hnRNP C can silence alternative exons by binding to uridine tracts at the 3' splice site (see also conference contribution from Julian König). In addition to previously known alternative exons, we found hnRNP C binding sites at deep intronic positions, suggesting that binding of hnRNP C within introns prevents the recognition of cryptic splicing signals. Since our initial microarray analysis was restricted to detecting *a priori* annotated exons, we now performed mRNA-seq experiments to compare the transcriptome of hnRNP C knockdown and control HeLa cells. Consistent with our hypothesis, we observed excessive usage of novel splice sites and inclusion of cryptic exons, including for instance a disease-related pseudoexon in the *PTS* gene. We used RT-PCR quantifications and mini-gene constructs to verify these events. In addition, we found the formation of novel junctions resulting in skipping of constitutive exons, indicating that hnRNP C is crucial for maintaining general transcript structure. Taken together, our data suggest a novel role for hnRNP C as a transcriptomic sentinel that prevents inclusion of cryptic exons to maintain splicing fidelity.

P59
Analysis of the metabolic response of human cells to glucose and oxygen levels

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The central metabolism is the principal source of energy and building blocks for cell growth and survival. In a healthy state cellular metabolism is tightly regulated to guarantee physiological function but also efficient usage of available resources. Metabolic deregulations are cause or response to many diseases. An impaired metabolic activity can lead to loss of the physiological activity, cell damage or inefficient substrate utilization. However, the underlying mechanisms inducing metabolic dys-functions are not well understood. To gain deeper insights in the dynamics of metabolism we adapted available techniques for stable isotope labeling, proteome and metabolome analysis to measure the metabolic activity in a dynamic manner. Cell physiology and metabolic activity are strictly regulated and imbalances have severe consequences for the cell. The regulation of metabolism is complex, because it appears at all biological layers. We observed that metabolic activities are not necessarily reflected in the abundance of transcripts, proteins or even in the steady-state levels of metabolites. Beyond being regulated simply by the expression levels of enzymes, the cellular metabolic pattern is influenced also by the isoform composition of the enzymatic network and its regulatory mechanisms. With our experiment we aimed to elucidate the metabolic dynamics of human cells in response to glucose and oxygen. Therefore we measured HEK293 cells upon 21 different conditions of oxygen and glucose: We determined measured flux distributions absolute quantities of metabolites and relative expression level of isozymes. Furthermore we identified known and not described regulatory events within the central carbon metabolism of HEK293 cells.

P60
Depletion of the ternary complexes limits the speed and efficiency of translational elongation

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The translation of genetic information according to the sequence of the mRNA template occurs with high accuracy and fidelity. Critical events in each elongation cycle of translation are charging of transfer RNA (tRNA), codon reading and tRNA-regeneration for a new cycle. Using both deterministic and stochastic approaches we developed a generic model that accurately describes the dynamics of single elongation steps, thus providing a systematic insight into the sensitivity of the mRNA translation rate to dynamic environmental conditions. Alterations in the concentration of the available aminoacylated tRNA can transiently stall the ribosomes during translation which results, as suggested by the model, in two outcomes: stress-induced change in the tRNA availability triggers the ribosomal dissociation, whereas extensive demand for one tRNA species results in a competition between frameshift to an aberrant open-reading frame and ribosomal drop-off. Using the bacterial *Escherichia coli* system, we experimentally validated the model and draw parallels between these two possible mechanisms. This general model can be applied to both prokaryotic and eukaryotic systems, providing the potential to understand the dynamics of translational elongation and its sensitivity to environmental factors in a systematic way.

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