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NCCR
RNA & Disease

National Center of Competence in Research
The role of RNA in disease mechanisms

Dear colleagues

It is my pleasure to open this year's first newsletter of the NCCR RNA & Disease. We are now finishing the third year of our 1st phase and we can be very pleased with what the NCCR has brought to our field in Switzerland. With over a dozen of associated groups and now eight junior groups (soon nine with the recruitment of a new assistant professor at the ETH Zurich), we have more than doubled the number of research groups in our network from the original sixteen groups at the start of the NCCR.

Being part of a research network when starting your lab is a strong asset. I personally immensely benefited from such opportunities during my assistant professorship when after two years I could join as a junior PI the NCCR Structural Biology and one year later the European network on alternative-splicing EURASNET. Both networks helped me shape my research and were at the origin of many projects that I still pursue today. EURASNET also allowed me to meet for the first time Adrian Krainer or Jørgen Kjems, who are now among our advisory board members. The spirit we hope to bring to our NCCR is certainly inspired by the fruitful experiences I gained from these two previous networks. I certainly hope that our NCCR will be as positive for our junior groups as those two were for me. Our young colleagues are also important to increase the momentum of our NCCR as they all bring new expertise and a different angle that enrich our own research. I do have active collaborations with three of the eight junior PIs and would not be surprised if by the end of phase 2, I will have active collaborations with the remaining six, too.

Frédéric Allain
Co-director NCCR RNA & Disease

Junior Principal Investigators of the NCCR RNA & Disease

Fostering the new generation of Swiss RNA researchers

A major goal of the NCCR RNA & Disease is to raise the next generation(s) of scientists in the field of RNA and Disease.

Besides training young scientists at the master, PhD and postdoc level, for which we offer lectures, training courses, workshops, summer schools, seminars, and lab exchange grants, another important group of researcher that we particularly care about are our junior principal investigators (junior PIs). By supporting and mentoring promising junior group leaders, the NCCR contributes to the future of its research field. Our junior PIs were all within their first four years of running their independent research group at the time they applied to join the NCCR and obtaining a tenured position is their next career challenge. David Gatfield is the first of our NCCR's junior PIs to achieve this crucial career transition and we congratulate him for his new position as tenured associate professor at the University of Lausanne since February 2017.

The junior PI groups not only benefit from receiving NCCR funding for their research but also by gaining access to the network's activities and facilities. The junior PIs also profit from the advice and feedback from the more senior principal investigators of the network and they are encouraged to ask one of them to be their mentor. In exchange, the junior PIs are an extremely valuable addition for the NCCR by expanding the network's research and expertise areas and the collaborative projects resulting from this.

Given the importance of our junior PIs, we decided to feature them in this issue of *The Messenger* by presenting short portraits of the five junior PIs who joined the NCCR in 2015 and three longer articles on the new junior PIs. Jeffrey Chao and Marc-David Ruepp were the two successful candidates of last year's call for junior PIs. They will formally join the NCCR at the beginning of year 4 in May. The third new junior PI is Rory Johnson who holds the NCCR-sponsored assistant professor position at the University of Bern since last November.

Jeffrey Chao – NCCR RNA & Disease Junior PI

Tracking single RNAs in living cells to elucidate their life cycle

Besides RNA metabolism, another continuum in Jeffrey Chao's research is the study of biological macromolecules by applying complex methods based on electromagnetic waves.

After graduating with a bachelor's degree in molecular biology from Pomona College in 1999, Jeff went on to do his PhD in the lab of Jamie Williamson at the Scripps Institute in San Diego. There he made use of waves situated at rather opposite extremes of the spectrum of known electromagnetic waves by applying X-ray crystallography and biomolecular Nuclear Magnetic Resonance Spectroscopy to study protein-RNA interactions with atomic resolution. Jeff then worked in Robert Singer's lab at the Albert Einstein College of Medicine in the Bronx first as a postdoctoral fellow and then as an instructor. There he continued with structural studies and in addition started to develop and apply methods to study single mRNAs in living cells by using fluorescence microscopy adding another part of the spectrum of electromagnetic waves used in his research. In January 2013, Jeff started his own lab at the Friedrich Miescher Institute in Basel.

At the FMI, the Chao lab aims to characterize the lifecycle of individual mRNAs from transcription through translation to degradation with spatial and temporal resolution in single cells. These studies rely on cells that express transcripts containing unique RNA sequences that can be recognized by chimeric fusions of the cognate high-affinity RNA-binding protein with a fluorescent protein. The presence of multiple copies of the RNA sequence allows imaging of single reporter transcripts and tracking them over time using fluorescence microscopy experiments. The Chao lab has pioneered the use of multi-color single-molecule RNA imaging to move beyond simply visualizing mRNAs to being able to ask specific questions about the fate of the transcripts. In collaboration with the Ephrussi and Singer labs, they developed the TRICK (translating mRNA imaging by coat protein knock-off method) technique for imaging the first round of translation[1]. The reporter transcript contains two different RNA tags that enable labeling of a transcript in both the coding sequence and the 3'-UTR with spectrally distinct fluorescent proteins (red and green). Once the reporter RNA is transcribed the green fluorescent protein sensor binds to the coding region and the red fluorescent sensor to the 3'-UTR making it appear yellow. Subsequently, during the first round of translation, the green fluorescent sensor is knocked-off by the ribosome and the reporter transcript appears red, allowing determination of the location and time of this event. The Chao lab is currently working to develop additional biosensors to study other events in the life cycle of an mRNA also in the context of their NCCR funded research. In another branch of their research the Chao lab studies RNA-protein complexes through the use of structural approaches. Chao states that the NCCR offers the possibility through collaboration to modify and adapt the imaging methods developed in his to study different processes and answering new questions.

[1] Halstead J.M. et al. (2015) Science, 347(6228), 1367-71

Website Chao Lab

"The NCCR brings together many leading RNA labs not just in Switzerland, but in the world. This vibrant scientific community will provide both inspiration and critical feedback, which I will surely benefit from."

Rory Johnson – NCCR RNA & Disease Junior PI

Long noncoding RNAs and their role in human diseases

Legend holds that some of the gold reserves of the Swiss National Bank are stored beneath the Parliament Square in Bern.

No rumor is that Bern since November 2016 is the location of a lab called GOLD (Genomics of Long noncoding RNA and Disease) headed by Rory Johnson. He graduated in 2000 with a Master of Science in Physics from Imperial College London, performing his Masters Thesis on protein-engineering in the lab of Stephen J. Curry. Subsequently, Rory was awarded a Wellcome Trust 4-Year PhD scholarship to work with Noel J. Buckley (University of Leeds, UK), where he used microarray and bioinformatic approaches to investigate genome regulation by the transcription factor REST (RE1 Silencing Transcription Factor). For his postdoc he moved to the Genome Institute of Singapore where he was first a postdoctoral researcher and then a research associate in the lab of Lawrence W. Stanton. During this time he became interested in the little-known field of long non-coding RNAs (lncRNAs). From 2010 until 2016 he was Staff Scientist and *Ramon y Cajal* Researcher at the Centre for Genomic Regulation in Barcelona. Here he participated in several international consortia: ENCODE (the Encyclopedia of DNA Elements), GENCODE (annotation of lncRNAs) and PCAWG (PanCancer Analysis of Whole Genomes). At the end of 2016, Rory set up his own lab at the Department of Clinical Research of the University of Bern, and affiliated with the Department of Medical Oncology of the University Hospital Bern.

The GOLD lab uses a combination of bioinformatics and wet lab experiments to discover long noncoding RNAs (lncRNAs) involved in disease, with an emphasis on cancer. In order to study such lncRNAs experimentally, the lab developed a vector system called DECKO (Double Excision CRISPR Knockout), which enables one to silence lncRNAs of interest. Importantly, DECKO is also amenable to high-throughput functional screens. This introduces the need for a bioinformatics tool to efficiently design the large number of targeting sequences; to this end the team has developed the CRISPETa pipeline, which can also be used through a web interface[1].

Another approach to identify lncRNAs involved in disease is the analysis of large=scale genomics datasets by dedicated bioinformatics tools. Using this approach a bioinformatics pipeline called ExInAtor was developed and used to predict "cancer driver" lncRNAs by analyzing 1123 genomes derived from 23 cancer types[2]. Consult the research highlights on page 9 of this newsletter for more information regarding the publication describing these findings. Additional research efforts in the Johnson lab involve contributing high quality annotation of genomes, the use of RNA sequencing data as clinical diagnostics and the large-scale study of sub-cellular localization of lncRNAs, which could provide important clues regarding their mechanisms of action.

Of the two projects carried out in the context of the NCCR RNA & Disease, one will take the functional screening approach in cells to identify lncRNAs functions and the other aims at bioinformtically predicting further lncRNAs driving cancer, which will then be validated experimentally. Several collaborations with other NCCR RNA & Disease labs are planned as well as with oncologists at the University Hospital Bern. Johnson mentions that the NCCR organized events are facilitating being up to date on the latest developments in the field.

"So far the meetings with principal investigators in the context of the NCCR has been extremely rewarding for me, and I feel that I have made a network of scientific contacts throughout the country extremely quickly."

[1] *Pulido-Quetglas C. et al. (2017) PLOS Computational Biology 13(3), e100534*
[2] *Lanzós A. et al. (2017) Scientific Reports (7), 41544*

Website GOLD Lab

CRISPETa Webserver

Marc David Ruepp – NCCR RNA & Disease Junior PI

RNA metabolism and neurological diseases

Since the beginning of his scientific career, Ruepp has been fascinated by RNA. Graduating with a major in Biochemistry from the University of Bern in 2005, Ruepp decided to follow his passion and performed his doctoral studies in the group of Prof. Dr. Daniel Schümperli (University of Bern) from 2006 to 2009.

During this period, he mainly focused on mRNA 3' end formation. His specific interests for misregulated RNA metabolism and neurodegenrative diseases emerged while he contributed towards a study on a somatic gene therapy approach for spinal muscular atrophy during his time in the Schümperli lab. For his postdoctoral research, Ruepp remained faithful to his interests and joined the group of Prof. Dr. Oliver Mühlemann (University of Bern) in 2010, where he studied nonsense mediated mRNA decay. At the same time Ruepp's urge to understand relations between RNA metabolism and neurological diseases intensified and he therefore developed his own research focus. Since 2014, he is an independent junior group leader at the Department of Chemistry and Biochemistry at the University of Bern. The long-term objective of his reaserach is to elucidate the selective motor neuron death in Amyotrophic Lateral Sclerosis (ALS), a fatal disease that leads to progressive muscle wasting and paralysis. Towards this end, the Ruepp group pursues two principal objectives: deciphering the physiological function(s) of the FUS (Fused in Sarcoma) protein and elucidating the pathogenic mechanisms associated with ALS-associated FUS mutations.

FUS is an hnRNP-like RNA-binding protein and when mutated it can lead to the development of Amyotrophic Lateral Sclerosis (ALS). Unraveling the biological functions of FUS will allow to study which of these functions are affected by ALS-associated mutations and how this in turn leads to neurodegeneration. A collaborative project of the Ruepp and Schümperli groups has revealed contributions of FUS towards replication-dependent histone gene expression by interacting with U7 snRNPs and histone specific transcription factors[1]. The recent discovery of the Ruepp group that FUS is involved in splicing of minor intron containing pre-mRNAs revealed a new potential pathomechanism in ALS[2]. Furthermore, misregulated minor-intron splicing has emerged as a common feature in neurological diseases including for example SMA (Spinal Muscular Atrophy) and TDP-linked ALS.

The NCCR RNA & Disease – funded project of the Ruepp lab will focus on pathomechanistic aspects of ALS causing mutations in FUS. Within the RNA & Disease, Ruepp's research integrates in and complements well the RNA metabolism cluster where it will intensify already existing collaborations and has great potential to connect to the current project portfolio on RNA binding proteins and neurological diseases. His research will also reinforce the disease link of the network. Besides benefitting from the scientific excellence and having the opportunity to exploit from mentoring by internationally renowned scientists, Ruepp also recognizes the opportunities for the researchers in his group: "The possibility for my students to enroll in the RNA Biology PhD program and participate in NCCR RNA & Disease events such as the annual retreat, allows them to learn from and interact with top-class RNA scientists and facilitates the exchange with other students promoting bottom-up collaborative projects".

"The NCCR RNA & Disease is a network of excellence and I feel privileged to be a member. Being part of this Swiss-wide consortium consisting of scientists at all career stages facilitates the exchange with other junior group leaders in the same field as well as to learn and receive mentoring from established and internationally renowned scientists."

[1] Raczynska K.D. et al. (2015) Nucleic Acids Research 43(20), 9711-28
[2] Reber S. et al. (2016) EMBO Journal 35(14), 1504-21

Website Ruepp Lab

Constance Ciaudo

Functions of RNA interference factors in mammalian stem cells

Constance Ciaudo is since April 2013 assistant professor at the Institute of Molecular Health Sciences at ETH Zurich. Her laboratory works on understanding the role of RNA interference factors and RNA binding proteins in fundamental mechanisms in mammalian stem cells such as regulation of pluripotency and maintenance of genomic integrity. Thus, her research contributes knowledge for the future use of stem cell for treating diseases, sheds light on embryogenesis processes and uncovers new roles of RNA proteins binding to it in cellular processes. The Ciaudo lab recently published a paper on the non-canonical function of a subunit of the microprocessor complex in controlling exit of stem cells from pluripotency[1]. This paper is featured as a research highlight on page 8 of this newsletter. An example of a fruitful NCCR collaboration was the Ciaudo lab applying their expertise in mammalian stem cell biology to assess the biological effect of a compound discovered in the lab of Jonathan Hall. The compound targets a RNA protein interaction known to be important in the differentiation of stem cells and applying the compound to murine embryonic stem cells induced their differentiation[2]. Ciaudo states that access to the NCCR supported technology platforms is a very valuable benefit from being part of the NCCR. For her lab the RNA synthesis platform provides important research reagents.

[1] Cirera-Salinas D. et al. (2017) Journal of Cell Biology 216(2), 355-366
[2] Roos M. et al. (2016) ACS Chemical Biology 11(10) 2773-2781

Ciaudo Lab Website

"The NCCR RNA & Disease is a network of excellence and I feel privileged to be a member. Being part of this Swiss-wide consortium consisting of scientists at all career stages facilitates the exchange with other junior group leaders in the same field as well as to learn and receive mentoring from established and internationally renowned scientists."

David Gatfield

Post-transcriptional gene regulation and circadian rhythms

„The membership carries a certain prestige, provides visibility within the home university and across Switzerland, and is a fantastic platform for collaborative endeavors."

Since February 2017, David Gatfield is an associate professor at the Center for Integrative Genomics at the University of Lausanne, the same institute where he previously held the position of an SNSF assistant professor. Research in the Gatfield lab focuses on the post-transcriptional regulation of gene expression in the context of biological timekeeping by circadian clocks. A specific interest lies in translational regulation. Of note, daily gene expression oscillations form the molecular basis of the daily variations detected across vital processes in the mammalian body, touching on metabolism, physiology and behavior; it is thus a specific interest of the Gatfield lab to explore connections between rhythmic RNA regulation and human health. Furthermore, environmental cues influence aspects of these rhythms, and their analysis is integrated in the experimental approaches as well. In recent publications, the Gatfield lab described novel roles for temporal regulation of translation efficiency and for upstream open reading frames in biological timekeeping in mouse liver and kidney[1–3]. The Gatfield lab will venture together with the Mühlemann group in a study that assesses how NMD and circadian clocks are connected, and team up with Ulrike Kutay to assess the translational specificities of ribosomal variants. Gatfield mentions that being a member of the NCCR was especially important during 2016 when the future location of his lab was uncertain. During this period he could not apply for grants and the NCCR funding allowed him to keep core personnel employed, which are now the basis for efficient rebuilding of the group. Moreover, for David Gatfield also the moral support was helpful during this crucial career transition.

[1] Castelo-Szekely V. et al. (2017) Genome Biology, in press
[2] Janich P. et al. (2016) Genomics Data 8, 41-4
[3] Janich P. et al. (2015) Genome Research 25(12), 1848-59

Website Gatfield Lab

Martin Jinek

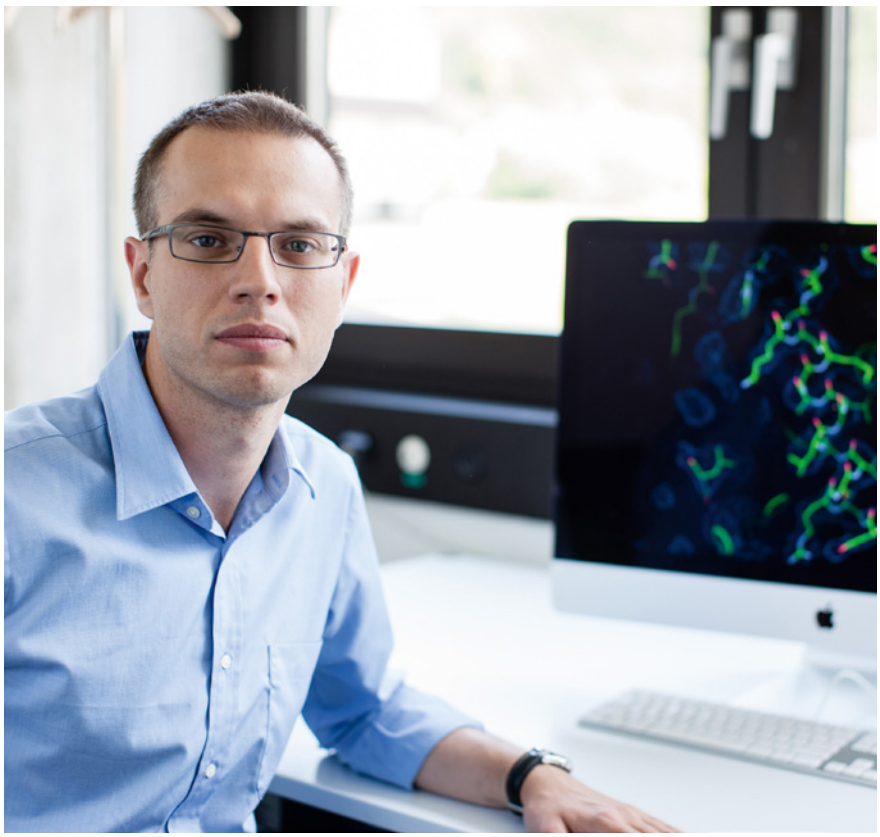
Roles of protein-RNA complexes in cellular processes

Martin Jinek is since February 2013 tenure track assistant professor at the Institute of Biochemistry at the University of Zurich.

The Jinek laboratory investigates the function of protein-RNA complexes in cellular processes using structural, biochemical and functional approaches. One the research interests of the lab is prokaryotic CRISPR-Cas systems, which are bacterial defense mechanisms against viruses. These systems have recently emerged as powerful molecular tools for precision genome engineering, which provided entirely new possibilities for basic research and could also be applied for therapeutic purposes. The focus of Jinek's studies is the genome editor nuclease Cas9, whose molecular structure and mechanism was uncovered by the lab in 2014 [1]. In 2016 the group published further structural work on engineered Cas9 variants [2]. The Jinek lab additionally studies eukaryotic RNA processing and modification pathways. The current NCCR-funded research project in the Jinek lab, which is carried out in collaboration with the research group of Ulrike Kutay, investigates proteins involved in ribosome biogenesis. Another area of research is the m(6)A RNA methylation, a dynamic RNA modification that plays important roles in regulating the function and stability of eukaryotic mRNAs. The group recently determined the structure of the writer complex that mediates m6A methylation [3]. Collaborations with other NCCR groups will explore this and other topics in the future. Jinek points out that participation in NCCR organized events has provided valuable interactions for him and his group and an opportunity to receive feedback from other NCCR researchers.

[1] Anders C. et al. (2014) Nature 513(7519), 569-73
[2] Anders C. et al. (2016) Molecular Cell 61(6), 895-902
[3] Sledz P. and Jinek M. (2016) eLife 5, e18434

Website Jinek Lab



"My research group and I very much appreciate the NCCR seminar series, which has a great track record of bringing in distinguished scientists from the RNA field."

Ana Claudia Marques

Contributions of long-noncoding RNAs to homeostasis and disease

Advances in next-generation sequencing technologies have revealed that a large proportion of the human transcriptome, of which only a small part codes for proteins, consists of intergenic long non-coding RNAs (lincRNAs). Although only <1% of them have been functionally characterized, lincRNAs have been shown to regulate gene expression programs through diverse mechanisms. The role of these non-coding transcripts in cellular homeostasis, phenotypic variation and disease is the research topic of Ana Claudia Marques, who is a SNSF assistant professor since October 2014 at the Department of Computational Biology in the University of Lausanne. Her lab employs a combination of computational and experimental approaches to shed light on this enigmatic class of transcripts. The Marques lab recently published a bioinformatics study that revealed a subset of human complex trait-associated lincRNAs are involved in cis-regulation of gene expression through the modulation of local chromosomal architecture[1]. NCCR funds the Marques lab to investigate the contributions of lincRNAs to cell cycle progression. The group has ongoing collaborations with the Ciaudo and Polymenidou labs. In addition to her research, Ana contributes to the overall success of the NCCR as its delegate for equal opportunities. Ana appreciates that her and her group members can participate in NCCR organized events, such as the annual retreats, summer schools and workshops. However, her only regret is that due to being based in Lausanne, it is less practicable for them to attend the NCCR seminars held in Bern and Zurich.

[1] *Tan J.Y. et al. (2017) Cell Reports 18(9), 2280-2288*

Website Marques Lab

"The NCCR membership has provided opportunities to present and discuss my ongoing research and future plans to trusted peers. The constructive criticism that I have received is invaluable at this early stage of my independent research career."

Magdalini Polymendiou

RNA binding proteins and neurodegenerative diseases

„I think it is the collaborations (both ongoing and 'budding'), which enable research that would not be possible without this NCCR."

Magdalini Polymenidou is an SNSF assistant professor at the Institute of Molecular Life Sciences of the University of Zurich since September 2013. Her lab studies the molecular mechanisms underlying amyotrophic lateral sclerosis (ALS) and frontotemporal dementia, which are fatal and currently incurable neurodegenerative diseases. In both diseases accumulations of RNA-binding proteins such as TDP-43 and FUS occur. Moreover, in the most common genetic form of these diseases, an atypical form of RNA translation takes place leading to the production of dipeptide repeat proteins (DPRs), which are abnormal and toxic protein products. The Polymenidou group together with other groups published a review article summarizing the current knowledge of the involvement of small RNAs in disease including cardiovascular, inflammatory, muscle and neurodegenerative diseases[1]. The Polymenidou lab uses ex vivo mouse and human nervous system cultures as novel disease models to study these processes. In the context of the NCCR the dynamic functional polymerization of TDP-43 was discovered in collaboration with the lab of Frédéric Allain. The manuscript describing these findings was recently accepted for publication in Nature Communications[2]. Magdalini Polymenidou appreciates the vibrant scientific community of the NCCR RNA & Disease, from whose more senior members she receives valuable input but also profits from the peer group of junior PIs within the network. One of her PhD students received through the NCCR an SNF mobility grant, which enabled a half year-long stay at the Massachusetts General Hospital in Boston in a collaborator lab.

[1] *Hruska-Plochan M. et al. (2015) Swiss Medical Weekly 145, w14192*

[2] *Afroz T. et al. (2017) Nature Communications, in press*

Website Polymenidou Lab

Research highlights

Research highlights from NCCR laboratories

Roland Fischer

A noncanonical way out of pluripotency

Mouse embryonic stem cells (mESCs) deficient for DGCR8, a key component of the microprocessor complex, present strong differentiation defects. However, the exact reasons impairing their commitment remain elusive. An analysis of newly generated mutant mESCs conducted by the group of Constance Ciaudo (ETH Zurich) revealed that DGCR8 is essential for the exit from the pluripotency state. The group suggests a new noncanonical function of DGCR8 in addition to its established function in microRNA biogenesis.

As in real life, in the cell machinery too there are canonical and noncanonical ways of accomplishing things. The correct functioning of a machinery – and thus life in general – usually depends on the interplay of both, whereas from a scientist's point of view the latter is probably more interesting. The group of Constance Ciaudo from the Institute for Molecular Health Sciences of the ETH Zurich has shown in a paper recently published in the Journal of Cell Biology how a noncanonical function of DGCR8 proteins controls the mouse embryonic stem cells (mESCs) exit from pluripotency.

But first to the orthodox side of things: The canonical miRNA pathway is crucial for stem cell biology, regulating features such as pluripotency factors and cell fate commitment; no surprise therefore that its misregulation contributes to human diseases. miRNAs are processed from primary transcripts in the nucleus by the microprocessor complex. This protein complex in the cell nucleus is composed of the ribonuclease enzyme Drosha and the RNA-binding protein DGCR8 and cleaves primary miRNA substrates to pre-miRNA. These are exported into the cytoplasm, where the enzyme DICER processes them into mature miRNAs, to be then incorporated into the RNA-induced silencing complex, leading to the destabilization or translational repression of their mRNA targets.

Ciaudo and her group were intrigued by recent scientific work about the identification of posttranslational modifications (phosphorylation) of the DGCR8 protein and especially by the discovery of noncanonical functions for DGCR8 in specific biological systems. In their paper, they now present a new role for the DGCR8 protein, independent of DROSHA, regulating the exit from pluripotency of mESCs. Interestingly they have found that the impaired differentiation of Dgcr8_ KO mESCs is independent of its function in miRNA biogenesis. The crucial newly found mechanism involves Tcf7l1 pre-mRNA, a core component of the pluripotency network. It turned out that proper phosphorylation of the DGCR8 protein is required for its binding to Tcf7l1.

To understand the molecular mechanisms causing the differentiation defects in Dgcr8 mutant mESCs the group generated new mutant cells deleted for the Dgcr8 gene using CRISPR/Cas9 genome engineering. Several molecular analyses indicated that these mutant mESCs complemented with impaired phosphorylated form of DGCR8 are not able to exit the pluripotency state, despite a restoration of miRNAs expression, cell proliferation, and proper cell cycle distribution. So the group came up with the hypothesis that the exit from pluripotency impairment might actually be independent of the role of DGCR8 in the miRNA biogenesis pathway and that the phosphorylation of DGCR8 could represent another mechanism ensuring tight control of the exit from pluripotency in mESCs.

Using RIP (RNA immunoprecipitation) experiments, they were able to demonstrate the direct interaction of DGCR8 protein with the Tcf7l1 mRNA in wildtype and Drosha_KO mESCs, indicating that this interaction is independent of the microprocessor complex. There are two isoforms of Tcf7l1, and DGCR8 facilitated the splicing of the long Tcf7l1, an event necessary for the differentiation of mESCs. To finally demonstrate the importance of the two Tcf7l1 isoforms in mESC commitment, they forced the expression of the short isoform in WT and Dgcr8_KO mESCs in an inducible manner or down-regulate the long isoform and thereby demonstrate that the up-regulation of the short Tcf7l1 isoform and the down-regulation of the long Tcf7l1 isoform promote the exit from pluripotency and differentiation of mESCs. With all this collected experimental data, Ciaudo and her colleagues believe they can now explain the previously observed impaired differentiation process of Dgcr8_KO mESCs. More interestingly, the results reveal a new noncanonical function of DGCR8 essential for the exit from pluripotency of mESCs.

Cirera-Salinas D. et al. (2017) Journal of Cell Biology 216(2), 355-366

Research highlights

Identifying the drivers amongst the passengers

A new method developed by Rory Johnson, leader of the GOLD (Genomics of Long noncoding RNA and Disease) Lab at the at the University of Bern, can identify cancer genes in noncoding regions of DNA. The statistical method is the first to be specifically designed to identify cancer driver long noncoding RNAs (lncRNAs) from tumour genome cohorts.

Cancer begins with a series of genetic mutations that enable a cell to escape the normal constraints on its growth and migration. The big challenge in the domain of genetic cancer research is to identify which "driver genes" are the targets of these mutations – such genes represent new targets for therapy. While much effort has been put into identifying conventional protein-coding genes connected to cancer development, the majority noncoding regions of DNA have up until now been neglected. Notably long noncoding RNAs (lncRNAs) represent a vast unexplored genetic space that may hold missing drivers, but few such "driver lncRNAs" have been identified.

Johnson and former colleagues from Barcelona – he has only recently set up the GOLD Lab in Bern – have now developed a statistical method specifically designed to identify cancer driver lncRNAs from tumour genome cohorts. The software called ExInAtor aims to address the unique opportunity of discovering cancer driver lncRNAs within and across tumour types using mutation data generated by projects such as ICGC (International Cancer Genome Consortium).

"It is only very recently that we have the possibility to scan entire genomes and can therefore search a full catalogue of mutations", says Johnson. This is accomplished by sequencing the entire genomes of matched pairs of normal and tumour samples, and then comparing them to identify tumour mutations. The Group used ExInAtor to predict drivers from the GENCODE annotation across 1112 entire genomes from 23 cancer types. Using a stratified approach, the group identified 15 high-confidence candidates: 9 novel and 6 known cancer-related genes, including well-known driver lncRNAs such as *MALAT1, NEAT1* and *SAMMSON*. They also showed for the first time, that driver lncRNAs are distinguished by elevated gene length, evolutionary conservation and expression.

ExInAtor identifies genes with excess load of somatic single nucleotide variants (SNVs). Though signals in noncoding regions of the DNA are relatively weak and noisy, Johnson believes that they are in control of the problem of false positives. "But there are probably many false negatives", acknowledges Johnson, "that is something we would like to improve." Although ExInAtor was designed with lncRNAs in mind, it makes no use of functional impact predictions and hence is agnostic to the protein-coding potential of the genes it analyses. The group took advantage of this versatility to further test ExInAtor's precision, by comparing predictions to the gold-standard catalogue of the Cancer Gene Census (CGC) – with positive results.

The distinguishing features of cancer-related lncRNAs are reminiscent of similar findings for protein coding genes. Evolutionary conservation and high steady-state RNA levels are generally interpreted in this context as evidence for functionality of lncRNAs. It remains unclear how many lncRNA drivers remain to be discovered, and which have tumour-specific or pan-cancer activity. "We expect that future studies will yield many more candidate lncRNAs than produced here: although the datasets we have used represent a large proportion of all presently available tumour genomes, future projects will be larger and produce mutation calls of better quality," says Johnson.

At the present time, the group are using ExInAtor to hunt for lncRNAs in an international collaboration called PCAWG (Pan-Cancer Analysis of Whole Genomes) that have sequenced thousands of entire tumour genomes. So far the results are promising, with dozens of new driver lncRNAs identified. "We plan to spend the next couple of years improving the sensitivity of ExInAtor to a point where we hope to identify essentially all the cancer driver lncRNAs that may be out there."

Lanzós A. et al. (2017) Scientific Reports (7), 41544

Unconscious bias

It is much easier to see unconscious bias in others, simply because we are not conscious of our own bias.

As scientists we all rely on the power of our brains to help us to make sense of data and as humans our brains are obviously integral in making sense of the world around us. Every day our brains process large amounts of information. To do this effectively the brain develops short cuts. These are based on our past experiences, as well as cultural norms and stereotypes. These shortcuts are processed unconsciously and therefore happen much faster than our conscious thoughts.

These shortcuts are very helpful. For example if we meet a friend we can quickly ascertain his mood. This is fast thinking.

Some information requires the slow processing. If you carry out the following calculation *"19x36 ="* you will notice there is a perceivable effort. The answer does not spring to mind unconsciously. As this takes effort wherever possible the brain will operate using fast thinking, leaving this effortful, conscious, slower thinking for more important or complex tasks.

Fast thinking can lead to us making assumptions in situations and about people. Whilst these are essential to daily living, sometimes the brain works too fast, leading to mistakes. For example if you hear the word parent, or engineer what image comes to mind?

Rather than view each person we meet as an individual we make assumptions about them and these are unconscious and are based on stereotypes, our cultural environment and our personal internal landscape. This can result in subtle and unconscious bias, which affects both our high level thinking and smaller more subtle behaviours.

In our workshop in Kandesteg at the 2nd NCCR RNA & Disease annual retreat we demonstrated the brain's lazy processing with many participants failing to answer correctly a simple calculation because of assumptions about what they thought they saw or heard about the starting point. Much research has shown positive effects of diversity on teams and organisations. The group explored their usual group of friends/advisors in a work context for diversity, crossing out those who were most like them to find out the diversity of advice and help that they may be experiencing.

Detecting bias

It is much easier to see unconscious bias in others, simply because we are not conscious of our own bias. To find out more about your own biases take the Implicit Association Test https://implicit.harvard.edu/implicit/takeatest.html

You can also monitor your own thinking and speech.

Notice the justifications you use for decisions, particularly those about other people. If you seem to put a lot of effort into your justification it could be you are digging yourself out of a bias-induced hole.

Mitigating bias

- Become aware of your biases and take responsibility for them
- Widen your experience of people unlike you (expand your in-group)
- Use slow thinking to reflect on how you would feel in any given biased situation and make reasoned arguments against your own decisions
- Identify common ground with people unlike you
- Read the reference works below and watch the Royal Society video

References

Royal Society Video

Blindspot: Hidden Biases of Good People, Mahzarin Banaji & Anthony Greenwald

Thinking Fast and Slow, Daniel Kahneman

Inclusion Nudges, Tinna Neilsen & Lisa Kepinski

3 Keys to Defeating Unconscious Bias, Sondra Thiederman

Dr. Sue Hewitt, develomenta, Denbigh, UK
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Announcements

People

We would like to welcome Profs. Mark Rubin and Peter Scheiffele as new associate members of the NCCR RNA & Disease.

Mark Rubin has been appointed as the new director of the Director of the Department of Biomedical Research at the University of Bern (formerly Department of Clinical Research) and leader of the Bernese Center for Precision Medicine. His research interests focus on the role of genomic and transcriptomic alterations in prostate cancer as well as developing novel diagnostic tools and treatment options.

Peter Scheiffele is full professor for cell and developmental neurobiology at the Biozentrum of the University of Basel. His lab has a large interest in the role RNA metabolism, especially alternative splicing in neuronal cell homeostasis as well as the alterations occurring in neurodevelopmental disorders.

We congratulate Nenad Ban for being awarded the Ernst Jung Prize for Medicine, Michael N. Hall for receiving the Szent-Györgyi Prize for Progress in Cancer Research, and Helge Grosshans for obtaining an ERC Advanced Grant.

Support Grants:

The NCCR RNA & Disease is co-organizing partner of the 2017 Riboclub Meeting taking place in Orford, Canada, from September 25–28. The NCCR RNA & Disease will issue travel grants for PhD students and postdocs from NCCR member and associate member labs to support their attendance. Submission of an abstract is a pre-requisite to receive a travel grant. The application deadline for the travel grants is May 11, 2017 and applicants will be informed about the outcome before the abstract submission deadline of the meeting June 30, 2017. Link to application and further information

Please visit our webpage for more information on the Lab exchange program, the Doctoral mobility grant and measures in equal opportunities.

Announcements

First steps in computational biology for RNA Research training course

The NCCR RNA & Disease and the Swiss Institute of Bioinformatics (SIB) are co-organizing a training course for researchers with no prior experience with Unix or R. The workshop takes place May 15-16, 2017 in Lausanne. Link to application and further information
Link to application and further information

Biomed ETHZ mailing list server

A new mailing list server for enhancing the information exchange among the biomedical research community in Zürich was set up by Prof. em. Daniel Schümperli. The Biomed ETHZ mailing list server should be used to inform the other subscribers about seminars and placing requests for materials and instrument usage.
Click here to subscribe to Biomed ETHZ

Jobs

Predoc program
The NCCR will soon open the application for its newly established PreDoc program. Participants will during one year rotate through three participating NCCR member and associate member labs. More information regarding the program and the application process will be available on the NCCR website beginning of May. The application deadline for this round of the Predoc program is July 1, 2017.

PhD program in RNA Biology
Find out more on our website.

Professorhip in RNA Biochemistry – University of Bern
Open rank faculty position in RNA and disease at the Department of Chemistry and Biochemistry.

Application deadline June 12, 2017
Link to announcement

Upcoming events organized by the NCCR RNA & Disease

> NCCR seminar series spring semester 2017 at the University of Bern and ETH Zurich. Speakers: Profs., Juan Valcarcel and Stuart Wilson (Invited by the RNA Biology PhD program students).

> 2nd NCCR RNA & Disease **Summer School** "RNA & RNP architecture: from structure to function to disease", August 28 – September 1 2017 Saas-Fee (Registration closed)

> The NCCR will present parts of its research to the public in the form of stands both at the Scientifica – Zurich Science Days, September 2–3 2017, ETH & University of Zurich and the Night of Research, September 16 2017, University of Bern.

> 2017 RiboClub Meeting, "RNPs: the Good, the Bad and the Ugly. Insights into RNA-protein complex assembly and function in health and disease." September 25–28, Orford, Canada

> The 19th Swiss RNA Workshop, February 2 2018, University of Bern

NCCR RNA & Disease Internal Events

> General Assembly Meeting, June 12 2017, La Neuveville

> 3rd NCCR RNA & Disease Retreat, February 4–6 2018, Kandersteg

Past events organized or supported by the NCCR RNA & Disease

> The 18th Swiss RNA Workshop, January 27 2017, University of Bern

> 2nd NCCR RNA & Disease Retreat, January 29–31 2017, Kandersteg

> 3rd NCCR RNA & Disease Site Visit, February 23–24 2017, Zurich

> NCCR seminar series spring semester 2017 at the University of Bern and ETH Zurich. Speakers: Profs. Brenda Bass, Irene Bozzoni, Christopher Burge, Thomas Cech.

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