THE MESSENGER

Newsletter No. 8

June 2018 — National Center of Competence in Research, RNA & Disease

NCCR
RNA & Disease

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

Dear colleagues

It is my pleasure to introduce the latest issue of The Messenger. *One major highlight is an interview with Chuan He who travels back in time to lead us through the original discovery of m⁶A RNA methylation in the 1970s by others, and how work from his lab in 2011 re-ignited interest in this mark. Rapid progress in this field has now entrenched the m⁶A modification of RNA as a key regulatory mechanism in organisms ranging from yeast to plants and humans. As a network, we have grown over the Phase I of the program and now entering Phase II, where we are even stronger and enriched by the increased number of participating labs. Collaborations between members have increased, as measured by the increasing number of joint publications. To a good measure, this is fostered by the Lab Exchange program of the NCCR that funds collaborative visits to labs within the network. My own lab hosted students in this context and we all found it a very enjoyable experience. Great scientific achievements have been made at the individual level by our members, but together as a network, we can claim to represent some of the best research in RNA biology. A recognition of this comes in the form of the prestigious Otto Naegeli prize conferred on Nenad Ban for his work on the protein synthesis machinery. Numerous other accolades received by our members and research stories are mentioned in this newsletter. Great emphasis is placed on disease mechanisms in the Phase II of the NCCR operations, so exciting times lie ahead. Enjoy reading.*

Ramesh Pillai
Principal Investigator
NCCR RNA & Disease

Interview Chuan He

"There is no room for a zoo of modifications on mRNA."

Chuan He gives us his perspective on the field of messenger RNA methylation and tells us about his career.

The field of mRNA methylation has publication wise exploded since 2011/2012 after what, in the case of m⁶A, seemed to be decades of relative dormancy. Why was this?

When m⁶A was discovered back in 1974, people recognized its importance because you had something so abundant on mRNA and the methyltransferase was found to be essential. I think that molecular biologists in the 70ies and 80ies lacked the tools such as current mass spectrometry techniques for quantification of the chemical modification and importantly, sequencing technologies to map the modification sites and look at their distribution. Back then cloning a gene was a PhD thesis and because there were no better approaches available, the field became sort of dormant. Still, few people were researching it mostly in plants and yeast, and I would say that the mainstream RNA community did not forget about it but somehow put it on the backburner. In 2008 my colleague Tao Pan and I started to think that there were well-known DNA and histone modifications playing critical roles in gene expression and, at the same time, RNA chemical modifications were as diverse if not even more diverse than protein modifications but more than the ones on DNA. It was hard to believe that they mostly serve to fine-tune the structure and function and we thought that there had to be some additional roles. That led us to write a grant to study potential reversible RNA methylation, which was funded in 2009. My lab made a breakthrough in 2011 when we discovered that m⁶A is reversible and from there people started to jump in with modern technologies to map it and study the involved enzymes.

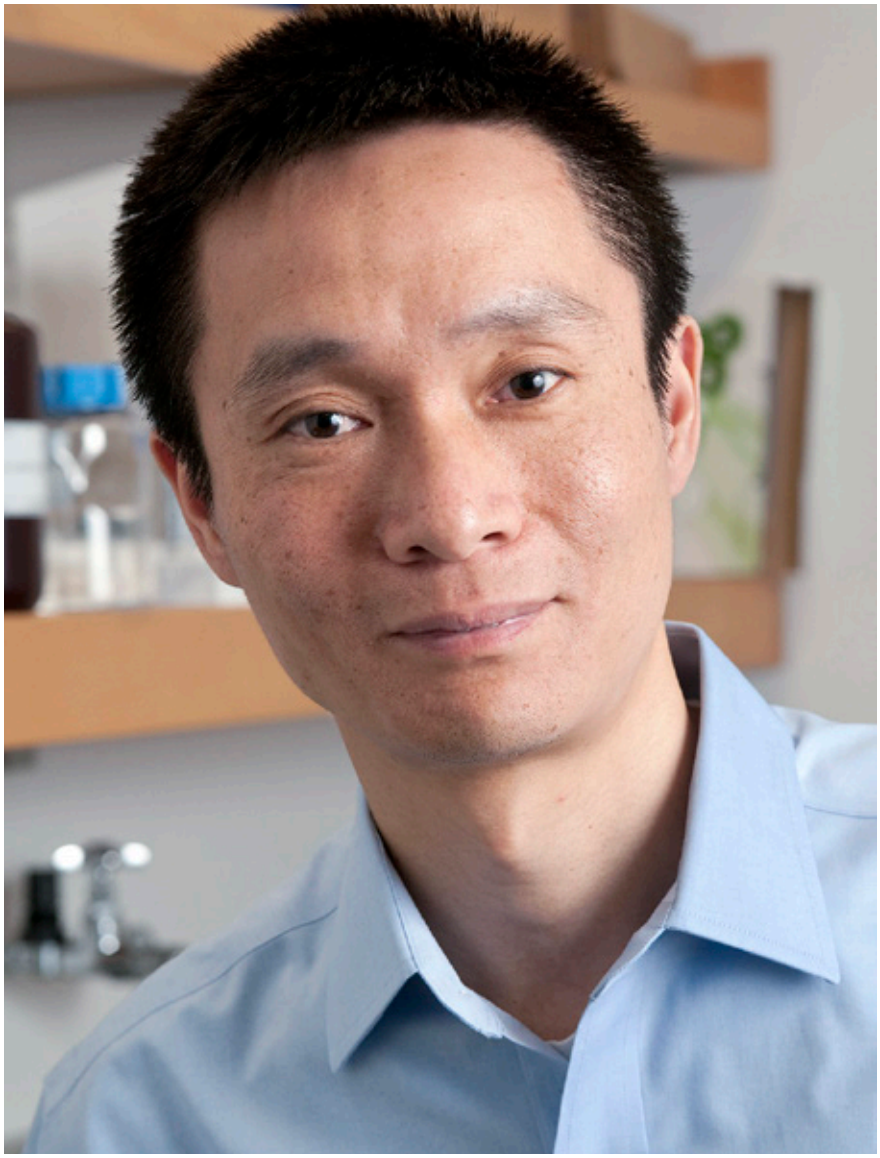
The currently known effects of m⁶A are diverse in affecting transcript stability, translational efficiency, and splicing. Do you have a sort of overreaching theory what the role of m⁶A is for the cell?

Regarding post-transcriptional regulation, I always argue that, on one hand translation initiation controls the entire proteome and, on the other hand, you have miRNAs regulating few or tens of genes. These two processes are critical but in mammalian systems, for example, during differentiation, development, signaling and stress response cells often change the expression of hundreds or even thousands of genes but you do not change the entire proteome, and you do not change only a few. So there seems to be a lack of a mechanism to coordinate this. Moreover, through animal experiments, it was discovered that if you get rid of this methylation machinery, most of the cells are stuck at the stem cell or progenitor stage. If you start looking into biological processes in animal models instead of HeLa and HEK cells, you realize the critical role m⁶A plays in cell differentiation. It has many roles, but the essential one is for cell differentiation and development. Mammalian systems are estimated to have around two hundred different cell types. Each

cell type is thought to have its transcription program produced by waves of expression of various transcription factors that dictate lineage-specific cell differentiation and tissue maturation. Two hundred different cell types require thousands of such transcription factor waves regulating each up to hundreds and thousands of transcripts. We know how these several hundred transcripts are activated by transcription factors under each wave, but we do not how their translation and importantly their decay is coordinated. How could this be done? Conceptually the easiest way to think about this is to put a methyl group to coordinate several hundred transcripts under one wave providing them with a new identity and grouping them for coordinated decay before tackling the next wave. This was probably the initial role. Once you have something available, biology tends to take advantage of it and through evolution, it starts to pick up other functions. Fundamentally, I believe it is a way to coordinate the transcriptome for translation and decay.

What are currently the major open questions?

I think we currently know like thirty percent of what is going on mechanistically. There are still a lot of readers we have no knowledge on and we do not know about a lot of things occurring in the nucleus and cytoplasm. In the nucleus, we do not understand how specific transcripts are selected for methylation and the majority of the demethylation occur there. DNA methylation occurs at tens of millions of sites, but its demethylation concerns a few percents of these. RNA is the same thing. Concerning the demethylases, we do not know why they are in the nucleus and what they are doing. Importantly, if you knock out the methylase transferase and some of these demethylases in the nucleus, the phenotype is much more dramatic than when you knock out the cytoplasmic reader proteins acting in translation and turnover. There is something else fundamentally important going on in the nucleus that we do not quite understand. That is number one. Number two is the question, which I get all the time, where does the selectivity come from? How does the cell know this transcript needs to be methylated and importantly, how do the readers know these are the transcripts? How do these transcripts know they go to translation versus decay? These are questions not only for RNA methylation but also in general for RNA protein complexes. How do they know what set of RNAs experience what kind of environment in the cytoplasm which then leads to what kind of fate? I would say that this is still mostly a mystery.



"The mainstream RNA community did not forget about it but somehow put it on the backburner."

After the discovery that it is reversible, the term RNA epigenetics was coined: can it be called epigenetics in the sense that it has an effect on subsequent generations?

In 2010 I wrote a commentary in Nature Chemical Biology which was probably the first paper ever to propose the idea of dynamic reversible RNA methylation and the editor back then put RNA epigenetics into the title or text. I was a little hesitant back then, but if you look nowadays, it has a lot of common features with DNA methylation: there are writers, readers, and erasers. Not all methylation is erased but dynamically only to a portion, and it affects gene expression. What you do not have is the inheritance; it cannot be inheritable on the RNA level. Later on, people developed the term epitranscriptome, which I like very much, but back then, we were not as smart to come up with this. However, we do have unpublished results in the lab showing that RNA methylation could be "inheritable" through other mechanisms. Experiments in a model organism currently performed in my lab show that if we change RNA methylation, this leads to a dramatic phenotype not previously seen. When we remove the introduced perturbation, the phenotype stays. There is clearly something going on that we do not understand yet. In that sense in a few years maybe we can come back and revisit whether these phenomena are inheritable.

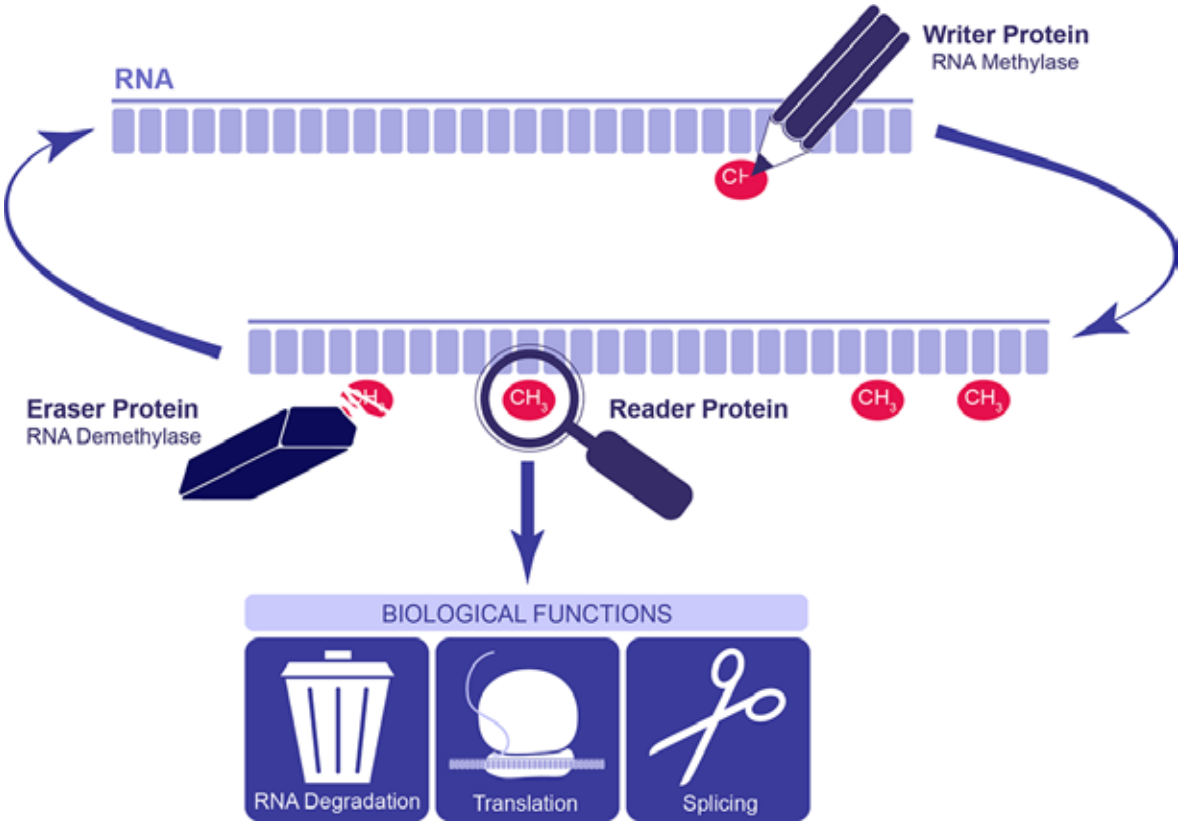


Illustration created by Margot Riggi and kindly provided by Ramesh Pillai.

It is quite intriguing how similar the methyl binding pockets of the m⁶A reader domain YTH and the binding pockets of some histone methylation reader domains are. One could argue that they recognize chemically similar entities but could there also be domains reading out both?

I would be extremely cautious when people look at simple cell lines and declare that we understand everything. The thing I am most excited about right now in the lab is precisely what you just said. I even wrote a commentary for the journal of RNA in which I stressed the importance of what is going on in the nucleus. Before we thought, that transcription controls RNA methylation by methyltransferase recruitment, but they are coupled together. How could they be coupled together? One way would be through what you said multifunctional proteins, but it could also be through other pathways. Several hypotheses are currently tested in the lab. We have incredibly fascinating yet very preliminary results suggesting that RNA methylation could also affect chromatin state. Whether there are proteins capable of recognizing both, I do not know, but I can say that methyltransferases, as well as some of the nuclear readers, are impacting histone marks or other proteins that are related to altering chromatin structure.

"We can research this in HeLa and HEK cells to death, but if there is no biological relevance, there is no meaning to this."

Your lab published on other mRNA modifications such as m¹A and 2'-O methylation. Will it be discovered that there is a whole sort of zoo of RNA modifications as on rRNA and tRNA?

Well, one needs to be a little careful, there is no room for a zoo of modifications on mRNA, since it carries the genetic information from DNA to proteins, so you do not want to introduce modifications taking the chance of generating problems with translation. The other mRNA modifications are less abundant than m⁶A. For instance, m¹A occurs in tissue at about five to ten percent of the level of m⁶A. Recently, two papers came out with single base resolution: there is a Nature paper showing about 20 sites, which is very interesting and nice work but it does not correlate with the mass spectrometry measurements of m¹A's abundance. There is another work in Molecular Cell, which maps a lot more sites in the 5' UTR consistent with our study. Some of these abundant m¹A sites are installed by tRNA methyltransferases, which were highjacked through evolution to act on mRNA. In our lab, we can confirm about six to seven different modifications on mRNA, and there could be other ones, which we do not know about yet. These other known ones are about ten percent as abundant as m⁶A and we suspect that many of them are installed by rRNA and tRNA modification enzymes. For some, there are also seem to be dedicated modification enzymes.

Is there more to come then?

Yes, but the essential one is m⁶A. For the rest, we have yet to see their functional impact on biology. It is important to study RNA methylation but the biological relevance is

most crucial. We can research this in HeLa and HEK cells to death, but if there is no biological relevance, there is no meaning to this. At the end of the day, for these other modifications, we need to know what are their writers, readers and what the biological consequences in animals are when functional alterations occur.

> *"It cannot be inheritable on the RNA level."*

Is the m^{6}A machinery a potential drug target or is it too essential?

It is druggable. Regarding m^{6}A, some of the demethylases and reader proteins are not essential and with the right dosage, even the essential methyl transferase might be a drug target just like EZH and other histone modifiers. We start realizing that RNA methylation plays critical roles in cell differentiation but is also important for proliferation and growth. Recent results suggest that aberrant RNA methylation is another trick cancers use to gain a survival advantage. Therefore, the involved proteins can become potential targets for therapy. Industry started to jump into this, and several start-up companies are either formed or in the process of being created.

How was the transition from chemistry to a more life science focus for you and your lab?

I was trained as a synthetic chemist during my PhD at MIT, and after graduating, I was considering materials versus catalysis versus biology; and I saw this large potential in biology. I then did a couple of years of biochemistry during my postdoc, and when I started my lab, we were doing mostly synthetic work because that was what I was most comfortable with, but we always performed biological experiments on the side. We were working a little bit on DNA damage, structural biology and then switched to five years of microbiology, which also included genetic work. In 2008 I got tenure, which is a milestone in one's career, I closed down my chemistry lab because I did not feel like I can make the type of contribution that would satisfy me in the chemistry field. For the first eight years of my career from chemistry to structural biology and microbiology, I was continually looking for something that could potentially give me an identity and allow me to leave a mark in science. Then epigenetics came, which from a chemistry point of view makes sense: In the human genome, you have three billion base pairs, we have tens and trillions of cells and the complexity has to come from chemical modifications. The diversity and complexity of chemical modifications of biological macromolecules were the general direction we decided to go into. Tao Pan and I used to have lunch every week talking about this and inspiring each other and so we decided to explore RNA modifications and from there on, we were very lucky with the findings we made starting with the reversibility of m^{6}A methylation.

What made you initially become a scientist?

In China, for kids of my generation doing well in school it was almost a straightforward path to become scientists. In college, I started realizing that I wanted to do something which is quite flexible, challenging and intellectually rewarding. Only later in my career, I began appreciating the type of freedom you have as a scientist to explore your interests. I also dislike when things are foreseeable and in science, you do not know where you stand in a couple of years.

Who had a significant influence on your career?

My generation was inspired by Chinese-American Nobel prize recipients. They were like national pride. Then my parents, who are not scientists but well educated, provided me with a good environment. Back then, there were not so many options for young people in China as today. It concerns me that, also in the US, many talented young kids s do not go into science anymore.

What caused this change?

The business world, which makes it easier for people to be awarded for their work and compensated better. It has become less trendy to go into science, and young people tend to go more into business, IT, finance and consulting. Business is taking over the world in a way. I do not blame the young people, but at the same time, science also needs young talents.

Do you encourage your kids to go into science?

I do, but my wife has different thoughts when she looks at the lives of scientists, which are quite stressful. I do not know about researchers in Switzerland, but in the US, it is stressful and very competitive. Five to ten percent of the time you are enjoying the rewards, but most of the time you work hard, it is stressful, and you travel a lot.

How do you perceive the increasing competition to acquire funding in the USA?

I feel bad when I started as an assistant professor the funding was fine with an approval rate of around twenty percent, and there were plenty of private foundations supporting young researchers. I think that the biomedical research has gone a little bit out of control in the US. The NIH budget has doubled and kept increasing. That was great for biomedical research, but at the same time, every medical school and university involved tried expanding it. University faculty members have stable support as they teach, but there are many soft money places doing great science, but the expansion has gone a little bit too fast. The result is that at most biomedical research institutes everybody complains about the lack of funding. Yet everybody is guilty of trying to expand it. I wished the system had undergone more steady progress instead of this rapid expansion. It does dramatically drive life science forward, but concomitantly creates so many PhD students and postdocs. Nowadays it is unfortunate that it takes six to eight years in some biological disciplines to get a PhD and another five to six years as a postdoc before becoming an assistant professor. By that time, you are close to forty years old and even older when you obtain your first NIH R01 grant, which is a very competitive process. That turns back many young people when they look at this. I do not think that this is necessary and I wish there were ways to shorten the time to obtain a PhD, and the postdoc does not need to be so long. Of course, we want NIH to keep increasing funding, but at the same time, I would wish that research institutions and universities would think twice before they expand. Many places realized the problem now and tied up their budgets and expansion plans.

Interview: Dominik Theler

Chuan He

Biography

In 2000, Chuan He obtained his PhD in chemistry from the Massachusetts Institute of Technology, Cambridge under the supervision of Stephen J. Lippard. He then moved to the lab of Gregory L. Verdine at Harvard University for a postdoc and in 2002 became an assistant professor at the University of Chicago. In 2008, he was promoted to associate professor and in 2010 to full professor. He is the director of the Institute for Biophysical Dynamics at the University of Chicago and the Synthetic and Functional Biomolecules Center at Peking University. In 2014, he became an investigator of the Howard Hughes Medical Institute.

He Lab Website

Research highlights

Research highlights from NCCR laboratories

Roland Fischer

Cleaving with preferences

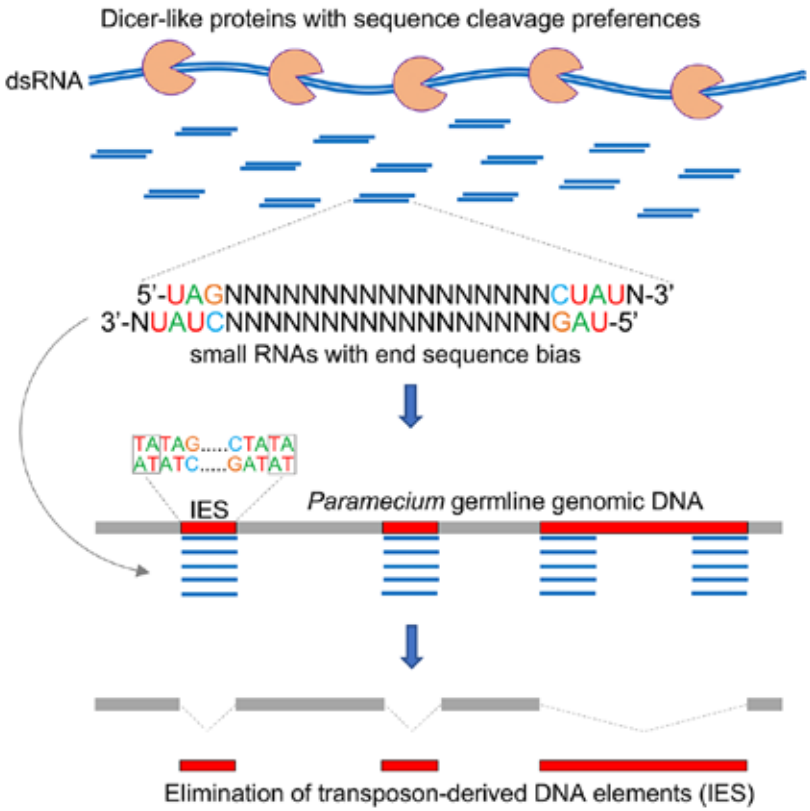
In eukaryotes, RNA interference-derived small RNAs (sRNAs) play a critical role in development, gene expression, and genome stability. Dicer proteins have an important role as well, as they produce small RNAs (sRNAs) from long double-stranded RNA (dsRNA) templates. The enzymes are best known for their role as endoribonucleases in small RNA pathways, where they regulate biogenesis of a wide range of small RNAs derived from various sources.

Up to now though, Dicer proteins have never been shown to have sequence cleavage preferences. In a new Cell paper, Cristina Hoehener, Iris Hug, and Mariusz Nowacki from the Institute of Cell Biology of the University of Bern now report three Dicer-like enzymes in Paramecium with pronounced sequence cleavage preferences. These preferences lead to the production of RNAs precisely matching ends of transposon-derived short DNA elements with corresponding end base preferences. The researchers propose a biological role for these newly characterised enzymes and their sequence-biased cleavage products. Through in vitro assays they tested whether the sequence specificity is a consequence of a specific Dicer cleavage, or as in other organisms, due to selection by Argonaute proteins. They could exclude the latter and were able to show that Paramecium Dicer-like proteins have sequence specificity for their target dsRNA, which contributes to the efficiency and precision of the DNA elimination machinery.

The observed features make Paramecium Dicers more similar to restriction enzymes, although their sequence requirements are not as stringent as in the case of bacterial restriction endonucleases cleaving dsDNA. It remains to be determined how the Paramecium Dicer-like enzymes recognize the dsRNA target in a sequence-specific manner.

As for the biological role, the researchers propose the facilitation of the precise elimination of germline-specific DNA. The Nowacki group had previously reported an sRNA class (internal eliminated sequence [IES] sRNAs [iesRNAs]), arising later during Paramecium development, which originates from and precisely delineates germline DNA (IESs) and complements the initial sRNAs in targeting DNA for elimination. They suggest that the Dicer-like proteins evolved together with the excision machinery to be able to efficiently eliminate those DNA elements from the genome. Analysis of developmental-specific sRNAs in Paramecium had already shown that the sRNAs map preferentially to the very ends of IESs. The researchers therefore believe that sequence specific Dicer proteins have evolved to produce sRNAs that help recognizing the ends of excised DNA. This mechanism will ensure that IES ends are marked precisely by small RNAs and target their elimination in a precise fashion. This allows to optimize the mechanism of RNA-guided DNA elimination by only producing sRNAs that are useful. More importantly, it ensures production of small RNAs marking the DNA ends very precisely, which may be essential, because most IESs are located within coding regions of the genome.

As a side note the researchers suggest that the ability of Dicer-like proteins to cleave at specific sequences within a long dsRNA template could provide an opportunity for future protein engineering to produce enzymes with unique sequence preferences.



Graphical abstract from Hoehener C. et al. (2018) Cell, 173(1), 234-247 published under the CC BY-NC-ND 4.0 license.

Hoehener C. et al. (2018) Cell, 173(1), 234-247 (open access)

Research highlights

How to undo splicing deficits

With the ever better understanding of regulated gene expression, it has become increasingly clear that RNA is much more than a passive intermediate. Amongst these transcription-translation regulation processes, splicing is a particularly crucial step – crucial, but also tricky. Splicing deficits could be associated with a wide range of maladies, so finding ways to deal with these deficits might open up new clinical paths with big therapeutic potential. The most promising candidates for this are small unusually structured drugs called oligonucleotides which have the power to shift the splicing process. If this shift becomes controllable we might dispose of a clinical tool to undo changes due to mutations in disease processes.

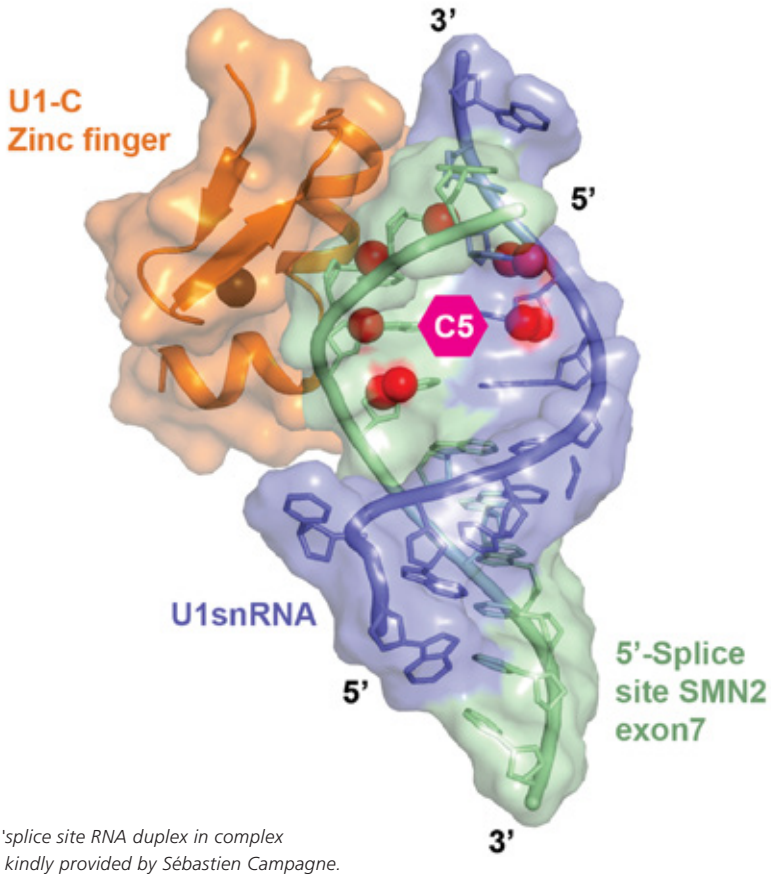
One of these diseases is spinal muscular atrophy (SMA), a rare genetic condition caused by the mutation or deletion of the survival of motor neuron 1 (SMN1) gene. SMA is characterized by progressive degeneration of spinal motoneurons. Humans carry two nearly identical copies of the SMN genes: SMN1 and SMN2. SMN1 expresses the full-length SMN protein, whereas SMN2 leads to a mRNA that is translated into a truncated and unstable protein. This is due to a C-to-T transition at position 6 of exon 7, causing exon 7 to be predominantly skipped. The nucleotide substitution in SMN2 results in the production of around 80–90% of truncated proteins and only 10–20% of functional full-length proteins.

In a recent Nature communications paper, a research group from Roche in collaboration with the Allain group from the Institute of Molecular Biology & Biophysics at ETH Zürich reports a striking success in targeting these kind of deficits. Their report suggests that a splicing deficit of an individual gene can be selectively targeted through small molecule interactions with RNA:protein complexes. In the paper the researchers stress that as mis-splicing is the cause of many disease-causing mutations, the work has the potential to have widespread implications in the research and development of such RNA-targeting therapies.

Small molecule splicing modifiers have been previously described, but they targeted the general splicing machinery with a low specificity for individual genes. The group of molecules found and described by the joint group is much more promising for therapeutic use. By using a combination of RNA splicing, transcription, and protein chemistry techniques, the researchers were able to show that these molecules directly bind to two distinct sites of the SMN2 pre-mRNA, thereby stabilizing a yet unidentified ribonucleoprotein complex that is critical to the specificity of these small molecules for SMN2 over other genes. They as well found that the molecules function via interaction with a tertiary RNA structure comprising the ESE2 region of exon 7, and an RNA helix that binds the U1 snRNP complex. This interaction of small molecules with the mRNA:protein complex is critical for the high selectivity of the small molecules for SMN2, which is higher than that of compounds that interact only at the 5'ss site.

In addition to the therapeutic potential of these molecules for treatment of SMA, the work has wide ranging implications in understanding how small molecules can interact with specific quaternary RNA structures. This is potentially relevant in cases of previously considered undruggable small molecule targets.

Sivaramakrishnan M. et al. (2017) Nature Communications 8(1), 1476 et al. (2017) (open access)



NMR-guided model of the U1-5'splice site RNA duplex in complex with U1-C and SMN-C5. Picture kindly provided by Sébastien Campagne.

Research highlights

TRICK and TREAT

Keeping up with all the advances in science can be overwhelming. Sometimes, little things like acronyms can help people remember. When FMI Junior group leader Jeff Chao and his collaborators had developed a method for imaging the first round of translation in living cells and animals in 2015, they called it TRICK: Translating RNA Imaging by Coat protein Knock-off. Now comes the second delivery – and this time they decided to call it: TREAT, of course. With the new method the researchers are able to measure mRNA degradation, in single cells again, which nicely complements the TRICK method they developed earlier. With this a complete accounting of an individual transcript's life from birth to death is now possible.

As reported in Molecular Cell, Chao's group developed a fluorescent biosensor that allows the distinction of intact transcripts and degradation intermediates to study the dynamic life of mRNA within a cell. With the help of this sophisticated fluorescent microscopy method they are now able to capture the complex spatial and temporal dynamics of the degradation of single mRNA molecules in living cells. This is of special interest, as degradation of mRNA might play a more important role in regulation processes than previously thought. As Jeff Chao points out, "It has become increasingly clear that the regulation of mRNA degradation, particularly during development or rapid environmental changes, can dramatically influence RNA levels." While many of the RNA degradation steps have been characterized, we have so far been missing a clear picture of when and where degradation happens.

In the last years the development of quantitative fluorescent microscopy techniques to image single molecules of RNA has allowed many aspects of the mRNA lifecycle to be directly observed in living cells. But the new method helps to bridge a gap that has eluded scientist's efforts so far. Single-molecule fluorescent in situ hybridization (smFISH) has enabled some aspects of mRNA degradation to be characterized, but the loss of signal resulting directly from the process being studied has prevented this approach from being widely applied. For their new method, Chao and his colleagues took advantage of a viral RNA structure that forms a knot-like structure. This pseudo-knot prevents the degradation of mRNA by Xrn1, a 5'-3' exoribonuclease. "And with the help of a multicolored biosensor containing these viral pseudo-knots, we were able to distinguish between intact mRNA transcripts and mRNA transcripts that are being degraded", Chao explains. To visualize degradation, the scientists engineered a transcript that is labeled with two RNA-binding proteins fused to two distinct fluorescent tags: one of the proteins – PP7 (tagged with green fluorescent protein) – binds to the coding region of the mRNA, while the other – MS2 (with a red tag) – binds to the 3' untranslated region. Between PP7 and MS2, the scientists introduced the viral pseudo-knots. Thus labeled, the individual untranslated mRNAs appear yellow. As the RNA is degraded by XRN1, the green-tagged PP7 is displaced. However, at the position of the pseudo-knot, XRN1 degradation halts, which allows the detection of a quantifiable color change from yellow to red. And thus the scientists called this technique TREAT for 3(Three)'-RNA End Accumulation during Turnover.

The researchers describe their methods to establish this system in mammalian cell lines and Drosophila melanogaster oocytes, but they believe the principles can be applied to any experimental system. The method already led to interesting insights: The group has found that individual degradation events occur independently in the cytosol and that the degraded mRNAs did not accumulate in processing bodies. This is important because the processing bodies, membrane-less compartments that form during phase transitions, were thought to play a direct role in RNA degradation.

Horvathova I. et al. (2017) Molecular Cell, 68 (3), 615-625

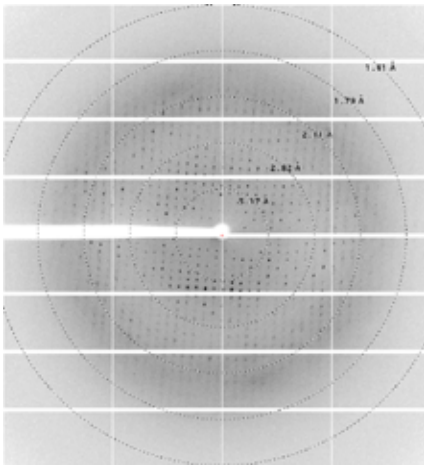
Picture kindly provided by the Chao lab.

NCCR Technology Platforms

High-Throughput Crystallization Platform

As of phase 2, the high-throughput crystallization platform of the NCCR RNA & Disease offers expanded services including remote inspection of screening experiments, the acquisition of initial synchrotron data and on a collaborative basis full structure determination.

The expanded services will be provided by the Protein Crystallization Center (PCC) and the laboratory of Martin Jinek at the Institute of Biochemistry of the University of Zurich. Users can contact the platform by sending an email to rna.xtal@bioc.uzh and registering with the PCC to get advice on sample requirements and choice of screens. Plate-based crystallization screens will be set up at the PCC by the use of pipetting robots allowing for drop volumes as low as 50 nanoliters per well and incubated in Rock Imagers with automated imaging capabilities, including UV. Images can be remotely accessed through a web interface, and the users can consult with the platform on preliminary hits obtained. Afterwards, refinement screens could be conducted, suitable crystals fished and mounted for initial synchrotron screening. Full crystal optimization and data collection with subsequent structure determination can be performed on a collaborative basis with the Jinek group. The platform's services are free of charge except for the PCC's screening services, which are accessible at a very favorable rate to member and associate member labs of the NCCR RNA & Disease.

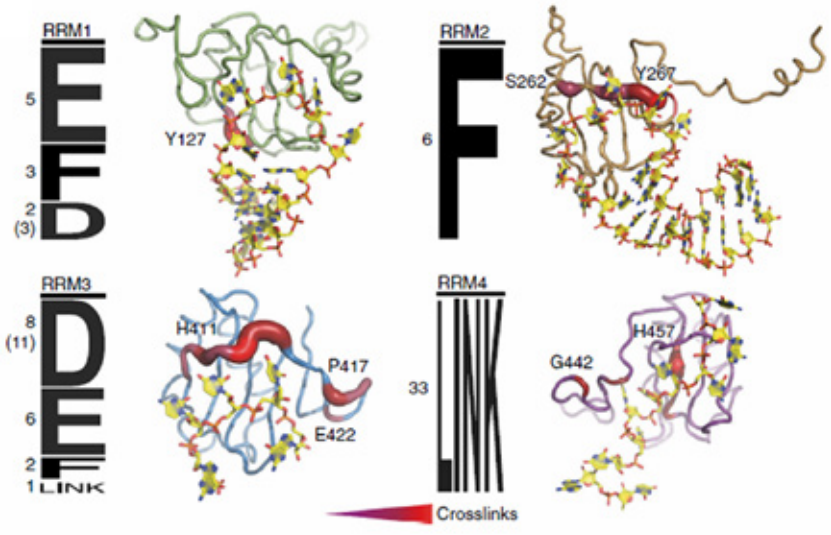


Diffraction pattern kindly provided by Carmela Garcia-Doval (Jinek lab).

Structural Mass Spectrometry Platform

Starting from phase 2 the NCCR RNA & Disease researchers have access to a new platform for structural mass spectrometry, which will provide structural data obtained from protein-RNA and protein-protein crosslinking experiments followed by mass spectrometry analysis.

The platform is headed by Alexander Leitner, senior scientist in the group of Ruedi Aebersold at the Institute of Molecular Systems Biology at ETH Zurich. They together with the Allain lab developed the crosslinking of segmentally isotope-labeled RNA and tandem mass spectrometry (CLIR-MS/MS) method (Dorn G. et al. (2017) Nature Methods), which is now offered as a platform service. The method allows for analysis of protein-RNA interactions with single amino acid and nucleotide resolution. Given sufficient crosslinks, the method allows for structural modeling of the complexes investigated. The platform also further develops the method in close collaboration with the labs of Frédéric Allain and Jonathan Hall. Researchers as well have access to chemical cross-linking of protein-protein complexes (XL-MS) for obtaining interaction information and distance restraints of multi-subunit assemblies. For example, Alexander Leitner applied XL-MS to obtain structural information on mammalian mitochondrial ribosomes in collaboration with the lab of Nenad Ban (Greber B.J. et al. (2015) Science). Researchers interested in the platform's services can contact Alexander Leitner by email: leitner@imsb.biol.ethz.ch



PTBP1 binding mapped on the EMCV-IRES RNA with CLIR-MS/MS). Used by permission from Springer Nature: Dorn G. et al. (2017) Nature Methods, 14 (5), 487–490.

3rd NCCR RNA & Disease Retreat

Fostering the Network Spirit

Talk Session at the Gemeindesaal Kandersteg

The third NCCR RNA & Disease retreat took place in Kandersteg from February 4th to 6th 2018 with over 130 participants. The retreat serves as an essential event bringing NCCR researchers together and fostering collaborations. The program consisted of thirty oral presentations including keynotes by Scientific Advisory Board members Jørgen Kjems and Adrian Krainer. During the two poster sessions over sixty posters were presented. On Monday afternoon participants engaged in outdoor activities such as skiing, sledging and hiking. Next year a joint retreat with the Vienna RNA research community will take place from January 30th to February 3rd 2019 in Fuschlsee close to Salzburg.

Participants on frozen Lake Oeschinen

Discussions taking place during one of the poster sessions.

Announcements

People

We are grateful to Sarah Woodson, Johns Hopkins University, Baltimore, USA for accepting the invitation to become a member of the Scientific Advisory Board of the NCCR RNA & Disease.

We would like to welcome Pauline Jullien, who is an SNSF assistant professor at the Institute of Plant Sciences, University of Bern as a new associate member of the NCCR RNA & Disease. Her group researches plant reproduction and epigenetics.

We bid farewell to Marc-David Ruepp, who took up a senior lecturer position at King's College London as of March 2018.

We congratulate Nenad Ban for being awarded the Otto Naegeli Prize for Medical Research 2018, Raffaella Santoro for being granted an ERC Advanced Grant, Marc Bühler for being elected EMBO Member and Martin Jinek, who was promoted to associate professor at the University of Zurich as of April 2018.

Esteban Finol, who is pursuing his PhD in the lab of Frédéric Allain, became the new PhD students representative of the NCCR RNA & Disease. We would like to thank his predecessor Stefan Reber (Ruepp group) for his contributions.

It is our sad duty to inform you that Elisa Izaurralde (MPI Tübingen) has passed away on April 30. Elisa was a member of our NCCR's review panel and a highly respected and much appreciated researcher in the field of RNA biology. Her untimely death is a great loss for the RNA community, she will be missed.

Support Grants

Giovanna Brancati (Grosshans lab), Esteban Finol (Allain lab) and Daniel Spies (Ciaudo lab) received NCCR RNA & Disease lab exchange grants.

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

Swiss RNA Workshop

The 19th edition of the Swiss RNA Workshop took place on February 2nd 2018 in Bern with nearly 200 participants. Keynotes were given by Julius Brennecke (IMBA, Vienna, Austria) and Sarah Woodson (Johns Hopkins University, Baltimore, USA). We thank the RNA Society for the financial support received through its RNA salon initiative. The 20th Swiss RNA Workshop will be on January 25th 2019 in Bern.

Elections by the General Assembly

At its meeting on March 28th 2018, the general assembly decided to include the delegate for Knowledge and Technology Transfer Jonathan Hall in the NCCR's steering committee. David Gatfield was elected as delegate and Oliver Mühlemann as co-delegate for Communication. Frédéric Allain was appointed co-delegate for Equal Opportunities and Rory Johnson as co-delegate for Knowledge & Technology Transfer.

Inclusion of Two Associate Members in the General Assembly

The NCCR RNA & Disease decided to include two of its associate members in the general assembly. The associate members elected Vikram Panse and Raffaella Santoro as their representatives in the general assembly.

Upcoming events organized or supported by the NCCR RNA & Disease

> NCCR Seminar Series:
Ling-Ling Chen (Shanghai Institute of Biochemistry and Cell Biology, China), October 1, University of Bern & October 2, 2018 ETH Zurich
Matthias Hentze (EMBL Heidelberg, Germany), November 12, University of Bern & November 13, 2018 ETH Zurich
Marina Rodnina (MPI for Biophysical Chemistry Göttingen, Germany), December 3, University of Bern & December 4, 2018, ETH Zurich

> Special Seminar by Phillip A. Sharp MIT, Cambridge, USA: October 30th ETH Zurich

> The 20th Swiss RNA Workshop: January 25 2019, University of Bern.

NCCR RNA & Disease Internal Events

> Joint retreat with the with the Vienna RNA research community, January 30–February 3 2019, in Fuschlsee, Austria

Jobs

Predoc program
Application can be submitted for the second edition of the Predoc program of NCCR RNA & Disease until July 1st 2018.
Find out more on the Predoc program website

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

Check the jobs's section of the NCCR RNA & Disease webpage for other openings.

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