Ling-Ling Chen: Shaping a career in RNA biology

Marie Anne O'Donnell

Chen studies the formation and biological activities of noncoding RNAs.

Ling-Ling Chen was born in Shangqiu, an ancient city in China where the first fire was lit by a human. Studying apoptosis in the optic nerve at Lanzhou University ignited Chen's interest in science and she published her first paper as an undergrad before moving on to the Shanghai Institute of Materia Medica, Chinese Academy of Sciences. With the comprehensive training in molecular biology she acquired there, Chen moved to Gordon Carmichael's laboratory at the University of Connecticut Health Center in Farmington to specialize in RNA biology as a postgraduate student focusing on the processing, editing, and functions of noncoding RNA. Although Chen liked biology, she was not really considering a career in academic research. But Carmichael stoked Chen's enthusiasm for science by encouraging her to explore new directions and she "had a feeling of freedom in thinking and doing experiments in [her] own way." Chen investigated the function of Alu elements, a class of very common DNA elements in the human genome, and showed that inverted repeated Alu elements in the 3′-untranslated regions of mRNAs can form intramolecular double-stranded RNAs. These RNA structures retain mRNAs in nuclear substructures called paraspeckles, which store mRNAs that are not needed immediately in the cytoplasm. The key to Alu element–mediated gene regulation was a long noncoding RNA (lncRNA) called NEAT1 that acts as a scaffold to organize these paraspeckles. Chen's postgraduate studies uncovered this novel paradigm of gene regulation but, more importantly, she developed a can-do attitude during this time that continues to motivate her to be a productive scientist. After a short period of postdoctoral work in Carmichael's laboratory, Chen circled back to Shanghai to continue identifying new types of lncRNAs with her own group.

We contacted Chen to learn more.

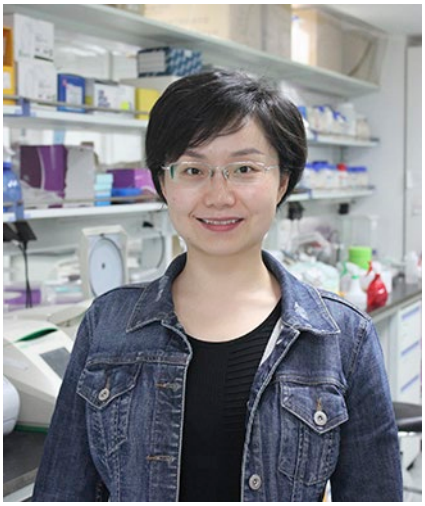
What drew to you to study noncoding RNA and what are you currently working on?

In my opinion, one of the most exciting advances in molecular biology in 2009 was the discovery of mRNA-like lncRNAs that originate from intergenic regions, called lincRNAs. I worked on NEAT1 at that time and the long isoform of NEAT1 is nonpolyadenylated. So I asked the question, "Do all lncRNAs look similar to mRNAs?" and searched for novel types of lncRNAs in nonpolyadenylated transcriptomes. I had acquired an independent grant that enabled me to develop methods to visualize and characterize nonpolyadenylated RNAs (1) and led to the discovery of a series of novel RNA species in my laboratory (2–6). These RNA species do not have their own promoters, but are derived from long primary RNA polymerase II transcripts by unusual RNA processing pathways. Rather than using canonical 5′-end m^7G-capping or 3′-end polyA tailing for maturation, their stabilization is achieved by several other mechanisms, including capping by small nucleolar RNA–protein (snoRNP) complexes at both 5′ and 3′ ends (2, 3) or only the 5′ ends (4), or by forming circular structures that protect them from degradation (5, 6). Importantly, we have revealed that some of these new RNAs can impact cellular processes and functions and their mis-regulation is associated with human diseases.

"Our cells are so smart that all these distinct stable RNA species can be produced from introns and exons by seamlessly coupled eukaryotic mRNA processing"

What is up next for you?

Studies on lncRNAs are advancing at a rapid pace, but the characteristics of each class of lncRNA and their functional implications are underappreciated. In my laboratory, we will continue to characterize the life cycle of different lncRNAs, how they are regulated, and their mechanism of action in depth. For instance, it is becoming increasingly clear that the function of lncRNAs is associated with their subcellular localization and many of the new RNAs we work with have important roles in gene regulation but are never exported to the cytoplasm (see the illustration of lncRNAs). How nuclear retention of lncRNAs is achieved, regulated, and related to their function remains largely unknown. In addition, different circular RNA species derived from polymerase II primary transcripts are widely expressed (5, 6) and we are investigating how they are generated and degraded and through which proteins they execute their functions. Finally, we will continue working on sno-processed lncRNAs, including snoRNA-ended lncRNAs, derived from introns and polycistronic transcripts (2–4). Some of these are specifically deleted in Prader–Willi syndrome (PWS), a neurodevelopmental genetic disorder. These RNAs form a striking nuclear accumulation in cells and sequester multiple RNA binding proteins and we hope to dissect the role of each lncRNA to the molecular and disease phenotype of PWS. By studying different types of RNAs with a variety of genome-wide, biochemical, and cell biological approaches, we aim to identify general rules that govern lncRNA and circular RNA processing and how they function in health and disease.

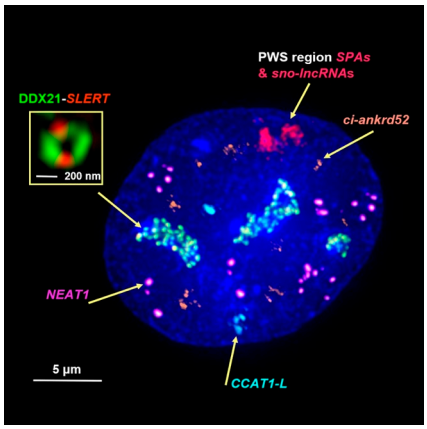


Ling-Ling Chen in the laboratory. Photo courtesy of Ling-Ling Chen.

What kind of approach do you bring to your work?

I trained as an RNA biologist and our research is rooted in molecular biology, but in the laboratory we use every approach

modonnell@rockefeller.edu



An illustration of lncRNAs with potential roles in gene regulation that exhibit nuclear localization patterns in human cells. The image is composed from different images captured by advanced microscopy. Image courtesy of Run-Wen Yao.

necessary. For instance, we routinely use imaging, including super-resolution microscopy, to visualize detailed subcellular localization patterns of RNAs, which provides useful clues about their functional activities (2–5). Importantly, as the molecular and genomic properties and mechanisms of action of these noncoding RNAs are so different from those of protein-coding genes, we need to continuously invent novel methods to investigate their potential functions. Understanding the biogenesis of each different category of noncoding RNA is critical for the development of methods that permit their functional annotation.

What did you learn during your PhD and postdoc that prepared you for being a group leader?

In addition to the training in RNA biology I received at UConn, two other unique experiences there supported my start as an independent scientist. First, I received a grant that funded my salary and science for two years right after I received my PhD. Although I stayed in the same laboratory for postdoctoral training, I could largely pursue my own new research directions. I was promoted to Assistant Professor in residence one year later and then joined the Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, in February 2011. So my independent career started quite soon after the completion of graduate school. I learned grant writing, management skills, and how to interact with other faculty members in the department during this period. Second, before I was ready to choose to stay in academia, I finished an MBA degree in management during my graduate studies. At that time, I thought that the PhD–MBA dual degree would make me more competitive in the future job market. Although I ended up as a scientist, the MBA training did help me become a group leader in the beginning. I think that running a laboratory is very much like managing a small business where you need to generate ideas, identify your niche, raise money, set up the right culture, recruit the right team to work with you, and work with passion.

What has been the biggest accomplishment in your career so far?

So far, the most exiting accomplishment has been the methods we developed for the genome-wide discovery and characterization of nonpolyadenylated RNAs, which led to the identification of sno-processed lncRNAs and circular RNAs. We are figuring out how these molecules form, what role they play in gene regulation, and how they may influence disease. We were excited to learn that our cells are so smart that all of these distinct stable RNA species can be produced from introns and exons by seamlessly coupled eukaryotic mRNA processing. On the other hand, it was also important to find out that some sno-processed lncRNAs are conspicuously absent in people with the neurodevelopmental genetic disorder PWS.

What has been the biggest challenge in your career so far?

Although it is satisfying to see that circular RNAs are broadly expressed and have functional potential, we ultimately want to learn what they do in cells. However, because they are expressed with cognate linear transcripts and have unique structural features, one of our biggest challenges is how to develop methods to study the function of these RNA circles without affecting their resident genes.

"MBA training helped me become a group leader . . . it is very much like managing a small business"

What is the best advice you have been given?

Focus on the topics that interest you and work with passion. Ideas are important, but having the skills and methods to test your ideas is critical.

What hobbies do you have?

I like hiking and reading. Hiking and reading books that are not related to science can temporarily separate me from my laboratory and clear and refresh my mind. Since my daughter was born two years ago, I spend nearly all my downtime reexploring the world with her by sensing her feelings.

What do you think you would be if you were not a scientist?

Because I had the MBA training, I would be a consultant, I guess. But I really don't know whether I would be good at it. It could be very challenging.

What has been your biggest accomplishment outside of the laboratory?

My family. I am very fortunate to have met my husband, Li Yang, in my first year of college back in 1997 and we married in 2001, one year after I graduated. Li has been super supportive throughout my graduate school and career development. He is also a great scientist and we collaborate. Our lovely daughter was born in 2015 and we have been learning how to balance our careers with family life.

Any tips for a successful research career?

Self-motivation, self-confidence, persistence, and working with passion are critical. As a woman scientist, don't be discouraged by apparent difficulties when you want to have a family. Build support networks with family and friends when you need to spend a lot of intense time with your children in the first few years. Our parents from both sides helped a lot in the past two years after my daughter was born.

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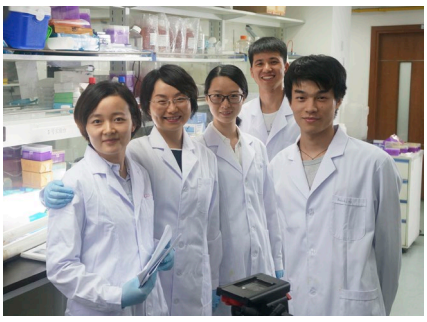

Ling-Ling Chen (second left) with her graduate students (left to right) Jia-Lin Zhang, Chun-Jie Guo, Xiang Li, and Yang Wang. Image courtesy of Chu-Xiao Liu.