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•EDITORIAL•

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Noncoding RNA: from dark matter to bright star

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The central dogma states that genes encoded in the DNA should be first transcribed into messenger RNA (mRNA) and then translated into functional proteins (Crick, 1970). This dogma has been written in numerous textbooks and learned by myriad students. However, along with the completion of the human genome project in June 2000, an astonishing fact was revealed: only 1.5% of the human genome encodes for proteins (Lander et al., 2001; Venter et al., 2001). This fact raised three fundamental questions: (i) why does the human genome have so few protein-coding genes? (ii) how to explain the apparent differences between humans and other species using the limited coding genes? (iii) what are the roles of the noncoding regions in our genome? In the past two decades, several international consortia such as ENCODE, FANTOM, and EPIC (Carninci et al., 2005; EPIC Planning Committee, 2012; ENCODE Consortium, 2004), as well as many individual research groups, have tried to answer the three questions mentioned above using various state-of-the-art sequencing technologies (Telese et al., 2013). Although it is still far away to get clear answers, we do have some exciting clues from those large scale studies on the 98% noncoding part of the genome, which often referred to as "dark matter."

Chinese scientists have been actively joining the race for annotating new noncoding genes in the "dark matter" part, which turned out to be transcribed pervasively for generating a massive amount of noncoding RNAs (ncRNAs) (Djebali et al., 2012). Among them, China has made tremendous contributions in discovering new small nucleolar RNAs (snoRNAs), microRNAs (miRNAs), Piwi-interacting RNAs (piRNAs), heterochromatin-derived 24 nt small RNA in plants, tRNA-derived small RNAs (tsRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) (Chen et al., 2016; He et al., 2007; Li et al, 2008., 2015; Wang et al., 2004; Wei et al., 2014; Yang et al., 2006; Zhang et al., 2013). In contrast to protein-coding genes, the noncoding gene numbers are still steadily increasing day by day. For example, according to the latest release of NONCODEv5, human lncRNA pools have 172, 216 transcripts encoded by 96, 308 noncoding genes (Fang et al., 2018). Although American scientists first observed circular forms of RNA using electron microscopic in eukaryotic cells (Hsu and Coca-Prados, 1979), China is now leading the circRNA research. Drs. Ling-Ling Chen, Ge Shan, and Fangqing Zhao's groups had identified tens of thousands of new circRNAs in mammalian cells (Ji et al., 2019; Li et al., 2015; Zhang et al., 2013). More importantly, two circRNAs, cia-cGAS and circPan3, have been demonstrated to be critical for immune regulation in knockout mice by Dr. Zusen Fan's team (Xia et

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al., 2018; Zhu et al., 2019). Currently, accumulating evidence indicates that ncRNAs play critical roles in dosage compensation, cell differentiation, cell proliferation, tissue regeneration, and adaptive immunity (Chen et al., 2018; Chen and Xue, 2016; Rinn and Chang, 2012).

Six years ago, the National Natural Science Foundation of China (NSFC) sponsored a vital and timely Major Research Program on ncRNA named "Regulatory mechanism of noncoding RNA in genetic information transfer" in 2014. This initiative aims to answer the following key questions: (i) how many novel ncRNAs are present in all kingdom of life? (ii) what are the biogenesis pathways for the new ncRNAs? (iii) what are the functional mechanisms of ncRNAs in regulating vital life activities? Toward these questions, the Major Research Plan has invested 28.6 million of US dollars awarded for 101 ncRNA projects in the past six years. With this focused funding in a specific research direction, the ncRNAs now become one of the brightest stars, and China has the world's largest community of ncRNA innovation center since 2016.

RNA research in China has a long and glorious history. In 1968, a collaborative research team of about 20 peoples from four institutes, one university, and one factory was established and led by Profs. Yinglai Wang, Debao Wang, and You Wang (Qi, 2010). They aimed to answer the most challenging question in the world at that time: whether nucleic acid can be synthesized artificially? After 13 years of hard work, the first yeast alanine tRNA identical to its natural molecule was synthesized *in vitro* and reported in Chinese in *Chin Sci Bull*, 1982. This scientific achievement is a milestone in China and even in the world, especially considering the historical circumstances and harsh research conditions. The *de novo* synthesis of a full nucleic acid molecule with complete activities not only opened the door for synthesizing other RNA molecules but also demonstrated that nucleic acid could be directly produced rather than by isolating from natural organisms. Besides, Prof. Wangyi Liu from Shanghai Institute of Biochemistry, along with an American research group almost at the same time, demonstrated the crucial role of magnesium ions on stabilizing the tertiary structure of RNA (Liu and Wang, 1964; Nishimura and Novelli, 1963). Of note, Liu's work was initially published in Chinese in *Acta Biochimica et Biophysica Sinica* (Liu and Wang, 1963). In the early 1970s, Prof. Dizhou Tong's team found that the injection of nucleic acids from carp into the fertilized eggs of goldfish influence its caudal fin formation (Tung and Niu, 1975). In the 1990s, Prof. Runsheng Chen from the Institute of Biophysics joined several genome sequencing projects and started to develop algorithms to predict new noncoding genes (Sun et al., 1995). In the same period, Prof. Enduo Wang from Shanghai Institute of Biochemistry focused on studying aminoacyl-tRNA synthetases and its interaction with cognate tRNAs (Gu et al., 1996). As a critical application of ncRNAs, Dr. Lianghu Qu established a novel RNA sequencing method for RNA structure evolution and phylogenetic studies (Qu et al., 1983; Qu et al., 1990; Qu et al., 1991).

After entering the 21st century, China first made breakthroughs in identifying diverse ncRNAs. For example, Drs. Lianghu Qu and Youxin Jin's groups identified hundreds of snoRNA genes in different eukaryotes, including yeast, fruit fly, worm, *Arabidopsis thaliana*, rice, mouse, and human (Chen et al., 2003; Gu et al., 2005; Huang et al., 2004; Li et al., 2007; Liang et al., 2002; Qu et al., 2001; Zhou et al., 2004). Besides, Dr. Qu's group first identified stress-induced tRNA-derived RNAs (sitRNA) as a novel class of small RNAs involved in the differentiation of *Giardia* (Li et al., 2008; Liao et al., 2014). Prof. Runsheng Chen's group cloned 161 ncRNAs, including snoRNA, stem-bulge RNAs (sbRNAs), and snRNA-like RNAs (snlRNAs) in *C. elegans* by Sanger sequencing, and they estimated that the *C. elegans* genome encoded around 2,700 small ncRNAs (Deng et al., 2006). Using a highly parallel pyrosequencing technology, Dr. Yijun Qi's group identified 4,000 small RNAs, including 200 miRNAs in *Chlamydomonas* (Zhao et al., 2007). Furthermore, Dr. Qi's group discovered a novel class of double-strand break-induced small RNAs in *Arabidopsis* and human cells, for which they referred to as diRNAs (Wei et al., 2012). Dr. Xiaofeng Cao's group provided compelling evidences to dissect miRNA, tasiRNA, phasiRNA and 24 nt siRNA biogenesis pathways in rice and prove the concept that TE-derived siRNAs globally fine-tune nearby gene expression (Liu et al., 2007; Liu et al., 2005; Song et al., 2012; Wei et al., 2014). Besides this original discovery, Drs. Chen Ling-Ling and Li Yang's groups jointly identified a new class of lncRNAs, which they named as sno-lncRNAs because there is a box C/D or box H/ACA snoRNAs at their both ends (Yin et al., 2012). They demonstrated that several sno-lncRNAs might be related to a rare genetic disorder Prader-Willi syndrome. In 2012, Dr. Chen-Yu Zhang's team reported a striking observation, in which, they found that microRNAs can be secreted and packaged into microvesicles and then delivered into other cells (Zhang et al., 2010). This original research lays the foundation for the concepts of exosome andexosomal RNA. Most recently, Dr. Lianghu Qu's team discovered the LTR retrotransposon-derived lncRNAs involved in DNA HR repairosome to regulate DNA repair and genome integrity (Deng et al., 2019).

Since launched in 2014, the Major Research Program has dramatically promoted the basic and translational research of ncRNA in China. Here we summarize recent conceptual advances of several made-in-china works funded by the program. Dr. Mofang Liu's group identified several novel mutations at the D-box of the *Piwi* gene from male infertility patients. They demonstrated that those mutations stabilized piwi protein and led to histone-to-protamine exchange de-

ficiency by sequestering RNF8 in the cytoplasm (Gou et al., 2017). This study not only first linked the Piwi mutations to human infertility but also shed new light on the long and fundamental puzzle of histone-to-protamine exchange during male germ cell development. Moreover, Dr. Liu's group recently further demonstrated that Piwi/piRNA complex could activate the translation of a subset of spermiogenic mRNAs via the cooperation of eIF3f and HuR in a developmental stage-specific manner (Dai et al., 2019). This observation changed the way we think about the role of piRNA complexes in development. Besides these prime examples in the direction of ncRNA and medicine, the Major Research Program also led to the radical breakthrough in ncRNA and agronomy. Dr. Qifa Zhang's group found that PMST1 and LDMAR lncRNAs regulate photoperiod-sensitive male sterility of the two-line hybrid rice (Fan et al., 2016). This study cracks the genetic basis of photosynthetic nuclear sterility in hybrid rice, which puzzled scientists for nearly 30 years, and nobody could imagine ncRNAs can play such transcendent roles. Recently, Dr. Yueqin Chen's group revealed that miR-408 could positively regulate grain yield by increasing panicle branches and grain numbers in rice (Zhang et al., 2017). In line with several novel findings from other Chinese groups (Jiao et al., 2010; Liu et al., 2005; Liu et al., 2019), it reminds us that miRNAs could be used as a powerful breading resource in agronomy.

The examples mentioned above are just a glimpse of the scientific achievements funded by the Major Research Program. This issue of *Science China Life Sciences* includes three review articles and three research articles that explore the functional mechanisms of ncRNA dark matter. Li et al. summarized the recent technological progress of various epitranscriptomic tools (Li et al., 2020). In this direction, supported by the Major Research Program, Dr. Yun-Gui Yang and Chengqi Yi's groups have developed several transcriptome-wide approaches for identifying RNA modifications such as m6A, m1A, and m5C (Li et al., 2017; Liu et al., 2020; Yang et al., 2017). Dr. Yun-Gui Yang's group also demonstrated that m6A reader YTHDC1 could regulate alternative splicing of 2000 cassette exons (Xiao et al., 2016). As RNA alternative splicing tends to be dysregulated in cancers, in this issue, Wang et al. summarized the recent mechanistic progress and available tools such as antisense oligonucleotides and small interference RNAs (siRNAs) to reverse splicing defects in cancer cells (Wang et al., 2020). In another review article, Saw et al. further summarized the clinical progress of siRNA therapeutics (Saw and Song, 2020). Similar to the size of siRNA, Li et al. identified a group of novel microRNA-like RNAs (milRNA) in *Arthrobotrys oligospora* that are involved in its lifestyle transition (Ji et al., 2020). Recently, there are several lncRNA encoded microproteins (< 100 amino acids) were reported (Yeasmin et al., 2018). However, whether and how the microprotein functions in cancer cells are still unclear. Xu et al. identified a novel microprotein KRASIM from 20,000 novel sORF in HCC cells. They demonstrated that it could repress tumor cell growth and proliferation via the KRAS pathway (Xu et al., 2020). CRISPR-Cas is an RNA-mediated defense system in archaea and bacteria. In this issue, Yang et al. solved the crystal structure of Cas1 in complex with branched DNA and provided novel insights on the mechanisms of spacer adaptation (Yang et al., 2020).

These reviews and research articles attribute more importance of ncRNAs in gene expression. In contrast to the dogma described for the 1.5% of the human genome coding part, the enormous ncRNAs generated from the noncoding part have their distinct regulatory principles. Considering the single-stranded nature and the base-pairing potentials, we speculate that the functionality of ncRNAs may mostly rely on its self-interactions and *trans* interactions with other large molecules such as proteins and mRNAs. Therefore, studying the tertiary structure of ncRNAs and its dynamic interactions with other molecules may enable us to understand the regulatory principles of ncRNAs in the cells.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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