Medical care, Drug discovery

Study of intracellular architecture by noncoding RNAs

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Abstract

Among numerous long noncoding RNAs (lncRNAs) produced by the human genome, some act as the scaffold of intracellular structures. Soft matter physics theory and experimental verification have revealed that micellarization by RNA-protein complex is the key to construction of a massive lncRNA-based structure. On the other hand, functional analyses of the lncRNA-based structures revealed that it regulates thermal stress responsive gene expression by sponge function via methylated lncRNAs.

Background & Results

Numerous lncRNAs were discovered in the post-genome era. We have identified lncRNAs that induce phase separation to form intracellular structures. In this study, we show that the lncRNA-induced phase separation by RNA occurs through micellarization, which is different from the typical liquid-liquid phase separation by proteins broadly studied. It can be a pioneering result as the basis of phase separation research. On the other hand, we addressed the mechanism of action of the phase separated structures in cells. Our results show importance of intracellular phase separation in which the temperature-dependent gene expression is controlled by the sponge mechanism of the structure via RNA methylation. Our results can be the basic knowledge for understanding the molecular mechanism and biological function of intracellular phase separation.

Significance of the research and Future perspective

Decoding the human genome in the early 21st century revealed that only 2% of the human genome encodes protein information. Subsequently, numerous lncRNAs were discovered to be synthesized from the noncoding regions of the genome, and its function as a "genomic dark matter " attracted a great deal of attention. We have discovered for the first time in the world a lncRNA that acts as the scaffold of the intracellular structure. On the other hand, the intracellular phase separation has been studied and become an active research field in cell biology. The phase separation is considered to be a general mechanism of cell space compartmentalization as a mechanism for transiently forming an isolated space in a crowded intracellular environment. Intracellular phase separation is induced by biopolymers such as intrinsically disordered proteins and RNAs. It was clarified that the above-mentioned structure formation by the lncRNA was achieved by phase separation, and also that the lncRNA induces the phase separation. In this study, the mechanism of lncRNA-dependent structural formation was clarified by soft matter physics theory and its verification experiments, and revealed that the paraspeckle nuclear body is formed by micellarization of the RNA-protein complex. Our study paved the way for the theoretical design of RNA-based phase separated structures. On the other hand, we also analyzed the role of the phase-separated structure in the cell. We found that the nuclear stress bodies (nSBs) formed on the heat-inducible lncRNA acts as a “molecular sponge” to regulate temperature-dependent gene expression through sequestration of regulatory proteins via methylated lncRNAs. In addition to the function of the protein phosphorylation reaction as a "crucible" that we previously reported, nSBs broadly control temperature-dependent gene expression by two independent mechanisms of action, "sponge" and "crucible". Our research clearly showed the biological significance of the lncRNA-induced phase separation in the cells.

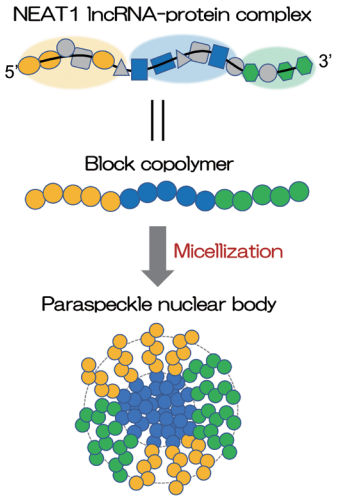

Figure 1.Paraspeckle nuclear body is formed through micellization of NEAT1 lncRNA-protein complex (block copolymer)

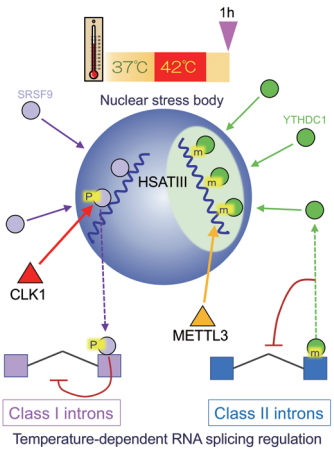

Figure 2. Nuclear stress body is formed upon thermal stress exposure and regulates gene expression during stress recovery through crucible function of protein phosphorylation and sponge function mediated by RNA methylation both of which occur in the phase separated environment.

Patent	
Treatise	Yamazaki, Tomohiro; Yamamoto, Tetsuya; Yoshino, Hyura et al. Paraspeckles are constructed as block copolymer micelles. The EMBO Journal 2021; 40(12): e107270. doi: 10.15252/embj.2020107270 Ninomiya, Kensuke; Iwakiri, Junichi; Aly, Mahmoud K et al. m6A modification of HSATIII lncRNAs regulates temperature-dependent splicing. The EMBO Journal 2021; 40(15): e107976. doi: 10.15252/embj.2021107976
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