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EDITORIAL

Regulatory roles of lncRNA in nuclear function

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Long non-coding RNA (lncRNA) plays multiple functional roles in biological processes and pathogeneses of diseases. As part of those functions, ncRNA modulates nuclear long-range DNA contacts, heterochromatin assembly, and gene expression by participating in the formation of three-dimensional chromatin organization and configuration and guiding various factors in ncRNA-driven compartments (Quinodoz et al. 2021). Those nuclear compartments are formed and shaped by ncRNA-constructed high-concentration territories and ncRNA-band regulators. lncRNA also contributes to the regulation of chromatin network structure, function, and reorganization during development. Further research in lncRNA biogenesis provides new insights into uncovering the regulatory roles of lncRNA processing, localization, macromolecule interactions and structural modules in nuclear function, intracellular signals, and cellular phenomes. The nuclear paraspeckle assembly transcript 1 (NEAT1) acts as a competing endogenous RNA in carcinogenesis and cellular toxicity by altering paraspeckle assembly through phase separation. With hybridization-proximity labeling technologies, an extensive repertoire of incompletely processed, adenosine-to-inosine-edited transcripts was evidenced at the interface between the encoding chromosomal regions and the NEAT1-containing paraspeckle compartment (Yap et al. 2022). NEAT1 plays a decisive role in the assembly of paraspeckles as small subnuclear structures without a membrane and in the orientation of gene regulator and transcript spatialization and temporalization by gathering RNA-binding proteins, localizing the functional territory, and forming ribonucleoprotein complexes. The nuclear function is highly dependent upon the dynamics of NEAT1-regulated/associated proteins and mRNAs, the reshaping of the territory, and/or the activity of NEAT1-dominated interactomes. It has the potential to map NEAT1 interactome, compartment-specific proximity ligations, and direct RNA-RNA interactions between NEAT1 and RNA targets; explore molecular mechanisms of paraspeckle organization and function; and define the formation of biomolecular condensates.

lncRNAs regulate the reoccurrence and metastasis of cancer cells directly by altering oncogene expression by reshaping lncRNA-driven nuclear compartments, of which the process can be influenced by diverse factors. For example, lncRNA Xist as a competing endogenous RNA for miR-210 is

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downregulated by miR-210 in cancer cells, while the inhibition of miR-210 could promote the function of Xist transcripts in the nucleus and cytoplasm (Eliason et al. 2022). Xist consequently increases the expression of nucleoside diphosphate kinase A (NME1) through H3K4me3 and H3K27ac modifications in the NME1 proximal promoter. The regulatory processes and factors have great importance and significance in clinical and translational medicine for discovering new diagnostic biomarkers and therapeutic targets. A high concentration of Xist is required to form intrachromosomal compartment-specific territories and maintain the spatialization and templatization of the compartment close to its transcription islets together with other binding factors and proteins, leading to the occurrence of X-chromosome inactivation. As one of the molecular mechanisms by which the heritable gene is silenced, a number of Xist RNA-binding proteins form the condensates through self-aggregation and heterotypic protein–protein interactions (Pandya-Jones et al. 2020). It is possible that multi-lncRNAs have the recruitment function of lncRNA-specific ubiquitous RNA-binding proteins to contribute to the formation of condensates and the regulation of compartment functions. It is more important to define the mechanisms of switch-off/on in the regulation of lncRNA-dependent or non-dependent territories, condensates, compartments, and chromatin 3D configurations during dynamic regulations of nuclear functions or during rapid development of cancer cell growth and migration.

The regulation of lncRNA in the maintenance of 3D chromatin configuration and function varies among lncRNAs, interactions, and lncRNA-driven territories. The dimensional changes of genome organization and reorganization can result from the intra- and/or extracellular microenvironmental instabilities and challenges, which can consequently cause alterations of cell gene expression, biogenesis, sensitivity, tolerance, resistance, or toxicity to drugs (Wang and Wang 2018) as well as pathogeneses of diseases (Wang 2019; Tian et al. 2022). Of the various regulators, the CCCTC-binding factor (CTCF) plays a decisive role in the maintenance of 3D genome structures in physiological and pathophysiological conditions (Wang et al. 2019; Cao et al. 2020). Hepatocyte nuclear factor 4 alpha-derived lncRNA (HNF4A-AS1) promotes the transactivation of CTCF, changing of HNF4A and other gene mRNA expression, and improvement of cancer patient survival, by increasing the interaction between heterogeneous nuclear ribonucleoprotein U and CTCF after the binding, accelerating glycolysis and metabolism, and preventing carcinogenesis (Song et al. 2020). It seems that the binding of mRNAs with their derived lncRNA and interaction with CTCF/cohesion complex are critical to stabilize the chromatin organization and chromosome conformation. Such biological function is dependent upon the size, type, class, and location of lncRNAs; upon the mono-allelic expression of lncRNA, and upon the lncRNA interactions and allelic association patterns with nearby or corresponding lncRNAs, mRNAs, and proteins in the nucleus. As one of the genome organization factors, lncRNAs with architectural transcription factors like CTCF regulate the cooperation/coordination large-scale chromosome compartmentalization by targeting triplex helix structure hotspots for colocalization (Farabella et al. 2021). Through these triplex-forming mechanisms, lncRNAs contribute to the spatiotemporal organization/reorganization of genome by directly influencing the interactions between RNA-RNA, RNA-DNA, or RNA-proteins.

As part of the three main nuclear functions, lncRNAs play important roles in the regulation of the RNA processing by targeting RNA methyltransferases to influence epigenetic modification, controlling the methyladenosine-dependent RNA structural switches to regulate RNA–protein interactions, and being in regulatory sites to maintain chromatin-associated functions. lncRNAs are essential in the process of chromatin assembly, e.g., lncRNA-dependent nuclear body architectures, to regulate chromatin targeting and remodeling by inducing the binding of ATP-dependent chromatin remodelers and enhancers, to promote chromatin remodeling-reliant DNA repair by stimulating the formation of high mobility group box-1 protein-dominated complex and its translocation, and to coordinate gene silencing and subsequent heterochromatin formation by spreading lncRNA to target distal regions of inactivation. lncRNA-regulated gene expression is highly dependent upon the locations and specificity of lncRNA-oriented interactions, lncRNA-modulated chromatin functions, and lncRNA-controlled complex switch. By deepening our understanding of the complexity of lncRNA-regulated nuclear functions and defining lncRNA-associated/interacted factors in the nucleus, new insights

can be made to see the mysteries of cell biology and to explore mechanisms of toxicology, new sources for lncRNA-specific diagnostic biomarkers and therapeutic targets, and new potentials for the development of nuclear therapies. Thus, we emphasize the importance of lncRNA-regulated nuclear functions and expect more advances in understanding to be translated into clinical application.

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