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# *Review of LncRNA Subcellular Localization*

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***Abstract:*** Long non-coding RNAs (LncRNAs) are a class of RNA molecules typically longer than 200 nucleotides that are unable to be translated into proteins. They regulate various biological processes in the cell, such as gene expression, epigenetic modifications, cell differentiation, and tissue development, through multiple mechanisms. The function of LncRNAs is closely related to their subcellular localization. LncRNAs located in the nucleus or cytoplasm participate in processes such as epigenetic regulation, transcriptional regulation, and RNA processing, or regulate mRNA stability, translation efficiency, and signal transduction. In recent years, the role of LncRNAs in diseases like cancer and neurological disorders has gained increasing attention. Studying their subcellular localization is crucial to understanding their function. This review summarizes the mechanisms and functions of LncRNA subcellular localization, introduces commonly used experimental methods (such as fluorescence in situ hybridization, immunofluorescence staining, and cell fractionation), as well as computational methods (such as prediction models based on machine learning and deep learning), and discusses the latest research advancements and future directions in LncRNA subcellular localization. Additionally, we introduce related databases for LncRNA subcellular localization, such as LncLocate, RNALocate, and LncAtlas, which further advance the development of LncRNA localization studies.

## 1. Introduction

Long non-coding RNAs (LncRNAs) are RNA molecules primarily longer than 200 nucleotides that lack the ability to be translated into proteins [1]. LncRNA molecules play a crucial role in the life activities of organisms, exerting significant effects on gene expression regulation, epigenetic modifications, cell differentiation, and tissue development through a variety of complex functions [2]. In recent years, studies have shown that LncRNAs play vital roles in the pathophysiology and biological processes of the blood system, nervous system, and various cancers, providing new perspectives for disease mechanism analysis and the development of therapeutic targets [3].

The functional roles of LncRNAs are influenced by several factors, including their primary sequence [3], secondary structure [4], subcellular localization [5][6], interactions with RNA-binding proteins (RBPs), as well as their expression levels and spatiotemporal specificity [7]. The primary

sequence and secondary structure determine the ability of LncRNAs to specifically bind with other molecules such as DNA, RNA, or proteins; subcellular localization directly affects the context of their action, such as epigenetic regulation in the nucleus or translation regulation in the cytoplasm [8]. Meanwhile, interactions between LncRNAs and RBPs can form functional complexes that enhance their biological effects. The expression levels and spatiotemporal regulation of LncRNAs enable precise regulatory roles in different tissues and physiological states. This complex, multi-factorial regulatory network determines the diverse functional manifestations of LncRNAs in biological processes.

The subcellular localization of LncRNAs is a critical prerequisite for their functional roles. The specific distribution of different LncRNAs in subcellular regions, such as the nucleus, cytoplasm, and mitochondria, determines how they exert their functions [9]. For example, LncRNAs localized in the nucleus primarily participate in epigenetic regulation and transcriptional control, while those in the cytoplasm typically regulate mRNA stability, translation efficiency, or mediate protein-protein interactions [10]. By studying the subcellular localization patterns of LncRNAs, we can gain deeper insights into their functional mechanisms and explore their potential roles in diseases [11].

This paper aims to systematically summarize the mechanisms, functions, and research methods related to LncRNA subcellular localization. First, we will discuss the mechanisms behind LncRNA localization in regions such as the nucleus and cytoplasm. Then, we will analyze the impact of localization on the execution of their functions. Finally, we will introduce the currently commonly used methods for studying LncRNA subcellular localization

## 2. Mechanisms of LncRNA Subcellular Localization

LncRNA subcellular localization refers to its specific distribution in different subcellular regions, such as the nucleus and cytoplasm, which plays a decisive role in the execution of LncRNA functions [12]. In the nucleus, LncRNAs typically participate in processes such as epigenetic regulation, transcriptional control, and RNA processing by binding to chromatin remodeling complexes, transcription factors, or RNA polymerase[13]. In the cytoplasm, LncRNAs mainly regulate mRNA stability, translation efficiency, and mediate protein interactions, playing roles in signal transduction and metabolic regulation[14]. Furthermore, LncRNAs can also localize to other subcellular compartments, such as mitochondria and the endoplasmic reticulum, where they regulate processes related to energy metabolism and protein processing [15].

### 2.1. Mechanism of Nuclear Localization

LncRNAs localized to the nucleus typically achieve nuclear localization through specific signal sequences and molecular chaperones. LncRNAs can bind to chromatin remodeling complexes and participate in epigenetic regulation [16]. Additionally, some LncRNAs directly regulate target gene expression by interacting with transcription factors or RNA polymerase II. For example, XIST is a classic nuclear-localized LncRNA that induces X-chromosome inactivation by binding to the PRC2 complex [17]. In the nucleus, LncRNAs exert their functions through various pathways, such as epigenetic regulation, transcriptional control, and RNA processing. For instance, XIST regulates X-chromosome inactivation by binding to chromatin remodeling complexes, while MALAT1 participates in alternative splicing and mRNA processing. Nuclear-localized LncRNAs also regulate chromatin three-dimensional structure to promote the regionalized expression of genomic functions [18].

### 2.2. Mechanism of Cytoplasmic Localization

In the cytoplasm, LncRNAs typically complete their localization with the help of signal recognition particles (SRPs) or RNA-binding proteins (RBPs)]. These LncRNAs are involved in regulating mRNA translation, stability maintenance, and signal transduction. For example, HOTAIR influences the translation efficiency of specific mRNAs through interactions with RBPs, thus exerting regulatory effects[20].

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In the cytoplasm, LncRNAs typically complete their localization with the help of signal recognition particles (SRPs) or RNA-binding proteins (RBPs) [19]. These LncRNAs are involved in regulating mRNA translation, stability maintenance, and signal transduction. For example, HOTAIR influences the translation efficiency of specific mRNAs through interactions with RBPs, thus exerting regulatory effects [20].

Some LncRNAs localize to mitochondria or other specific organelles, such as the endoplasmic reticulum and Golgi apparatus. These LncRNAs usually possess specific sequence or structural features, interacting with mitochondrial transport complexes or other specific molecular chaperones to achieve their localization[21]. For instance, the LncRNA RMRP has been found to localize to mitochondria, where it participates in the replication and transcription regulation of mitochondrial DNA. The subcellular localization of LncRNAs generally depends on their nucleotide sequences and higher-order structures[22]. Key nuclear localization signals (NLS) or nuclear export signals (NES) are important factors affecting their distribution. Moreover, the interaction domains between

LncRNAs and RBPs, as well as their secondary structures (such as stem-loop structures), play critical roles in their precise localization[23].

LncRNAs localized to the cytoplasm mainly regulate mRNA stability, translation efficiency, and signal transduction. For example, the LncRNA TINCR stabilizes specific mRNAs by binding to the STAU1 protein, affecting epithelial cell differentiation[24] LncRNA GAS5 competitively binds to glucocorticoid receptors, inhibiting downstream signal transduction, and regulating cell metabolism and growth[25]. LncRNAs localized to mitochondria participate in regulating mitochondrial genome replication, transcription, and energy metabolism. For instance, LncRNA RMRP not only participates in the transcription initiation of mitochondrial DNA but also mediates mitochondrial protein synthesis through the generation of short RNA molecules [26]. Dysfunction of mitochondrial LncRNAs may be associated with metabolic diseases and aging[27]. .

LncRNA functions often depend on their specific subcellular localization. Some LncRNAs show inhibitory effects when regulating transcription in the nucleus, while in the cytoplasm, they may promote mRNA stability or protein translation. This localization-dependent functionality highlights the central role of LncRNA's subcellular distribution in its biological effects. Abnormal LncRNA localization is often closely related to various diseases. For example, in cancer, some LncRNAs lose their normal function or gain new functions that promote tumor growth and metastasis due to abnormal localization. Studying the mechanisms of LncRNA localization and its role in diseases helps in the development of precise diagnostic biomarkers and therapeutic targets[10].

## 4. Research Methods for LncRNA Subcellular Localization

Research methods for ncRNA subcellular localization can be broadly classified into traditional experimental methods and modern methods based on machine learning and deep learning algorithms. Traditional experimental techniques include fluorescence in situ hybridization (FISH)[18], immunofluorescence staining[23], cell fractionation[26], subcellular component separation [27], and RNA-binding protein immunoprecipitation (RIP) [28], while machine learning methods take advantage of the continuous advancements in high-throughput sequencing technologies and the existing ncRNA subcellular localization data.

Specifically, in situ hybridization involves designing specific probes to detect the spatial distribution of ncRNAs within cells, making it a classic method for studying ncRNA localization. This method, combined with fluorescent or enzyme labeling systems, allows precise localization of ncRNAs at the single-cell leve[2]. While it is highly sensitive, probe design is demanding, and the experimental procedure is complex. Cell fractionation separates the cell nucleus, cytoplasm, mitochondria, and other subcellular compartments, followed by RT-qPCR or RNA-Seq to detect the distribution of ncRNAs in different fractions. This method is quantitatively accurate, but RNA degradation or cross-contamination can occur during the process[5]. RIP combined with high-throughput sequencing (RIP-Seq) can indirectly infer the localization of ncRNAs by detecting interactions between ncRNAs and specific RNA-binding proteins. This method provides functional insights but requires attention to the dynamic nature of RNA-protein interactions[8]. Modern super-resolution microscopy techniques, such as STORM (Stochastic Optical Reconstruction Microscopy) or PALM (Photoactivated Localization Microscopy), have significantly improved the resolution of ncRNA localization studies, allowing precise mapping of ncRNA distribution within cells. However, these methods typically require high-cost instruments and complex imaging analysis[10].

In addition to experimental approaches, bioinformatics methods can be used to analyze the primary sequence, secondary structure, and key signal sequences (such as NLS or NES) of ncRNAs to predict their subcellular localization. These methods rely on existing experimental data and machine learning models, such as LocARNAs [12] or iLoc-lncRNA. Deep learning algorithms,

such as CNNs (Convolutional Neural Networks) or Transformers, have been employed to build models for predicting ncRNA localization. These methods integrate ncRNA sequence features, protein interaction networks, and epigenetic information to enhance prediction accuracy. For example, DeepLncLoc combines multimodal data to efficiently distinguish between nuclear and cytoplasmic localization.

## 5. LncRNA Subcellular Localization Databases

LncRNA subcellular localization databases are designed to assist researchers in understanding the localization of long non-coding RNAs (LncRNAs) within cells, thereby revealing their biological functions and mechanisms of action. These databases offer various functionalities and sources of information, combining experimental data with computational prediction models. Lnclocate [10] uses machine learning algorithms to predict the potential subcellular localization of LncRNAs based on the analysis of their sequence features and secondary structures. It supports multiple localization types, including the nucleus, cytoplasm, and exosomes, and is known for its high predictive accuracy. LncRNADisease [11] primarily focuses on the relationship between LncRNAs and diseases but also provides information on their subcellular localization. By integrating existing experimental data, it presents the localization and functions of LncRNAs in various disease contexts, which helps in understanding their roles in pathological processes. RNALocate [18] integrates experimental data on LncRNA subcellular localization and provides localization information based on cell type and experimental conditions. It categorizes various subcellular locations, such as the nucleus, cytoplasm, and exosomes, and is widely used in studies exploring the role of LncRNAs in different cellular environments. LncAtlas [26] focuses on LncRNA expression profiles and subcellular localization, leveraging high-throughput experimental data to uncover the distribution of LncRNAs across different cell types. It provides localization information in various cellular subregions and includes experimentally validated high-quality data.

These databases provide invaluable resources for LncRNA subcellular localization research, covering aspects from gene expression and secondary structure to deep learning predictions. They offer both experimentally verified and predicted localization information, providing researchers with efficient data support to gain a comprehensive understanding of LncRNA functions and their dynamic localization within cells.

## 6. Conclusions

The study of LncRNA subcellular localization has become a crucial area for understanding their biological functions and mechanisms of action. This review explores the mechanisms, functions, and research methods of LncRNA subcellular localization, focusing on their specific distribution and roles in cellular compartments such as the nucleus, cytoplasm, mitochondria, and endoplasmic reticulum. Research shows that the localization of LncRNAs not only determines their roles in processes like gene expression regulation, transcriptional control, and RNA processing but also plays a key part in biological processes such as cell signaling and energy metabolism. Additionally, abnormal LncRNA localization is closely linked to several diseases, particularly cancer. Investigating the mechanisms of LncRNA localization and their roles in diseases can help develop new diagnostic and therapeutic strategies.

Current methods for studying LncRNA subcellular localization include traditional experimental techniques (such as fluorescence in situ hybridization, immunofluorescence staining, and subcellular fractionation) as well as computational methods based on machine learning and deep learning. Traditional experimental methods provide high-resolution evidence for LncRNA localization but are complex to perform and limited by specific experimental conditions. In contrast,

computational methods based on bioinformatics and deep learning provide large-scale, high-throughput localization information and have become an essential complement to experimental approaches.

As research on LncRNAs continues to advance, future directions are likely to focus on the following areas:

1) Efficient and Accurate Localization Prediction: Current deep learning-based LncRNA subcellular localization prediction methods still have room for improvement. Future research may enhance the accuracy and generalizability of localization predictions by integrating multimodal data, protein interaction networks, and epigenetic information. Furthermore, with advances in computational power, more refined model designs and larger datasets will drive progress in LncRNA localization research.

2) Dynamic Studies of LncRNA Localization: LncRNA localization within cells is not static; it is influenced by various physiological and pathological states. Future research should focus on the dynamic changes in LncRNA localization across different cell cycles, physiological conditions, and disease states, and how these changes impact the functional execution of LncRNAs.

3) Formation and Function of Multifunctional Complexes: The function of LncRNAs often depends on their interactions with RNA-binding proteins (RBPs). Future studies could explore the role of LncRNA-RBP and protein complexes in subcellular localization and function, especially the mechanisms of complex assembly and disassembly in different cellular compartments.

4) Disease-Associated LncRNA Localization: Abnormal localization of many LncRNAs in diseases could be a key factor in their dysfunction. Future studies on the subcellular localization changes of LncRNAs in diseases (such as cancer and neurodegenerative diseases) could provide insights into their role in pathological processes and identify new therapeutic targets.Integration of Experimental and Computational Methods: Future LncRNA subcellular localization research should emphasize the integration of experimental methods with computational predictions. Experimental data can validate the predictions made by computational models, while computational methods can analyze and mine large volumes of experimental data. This interdisciplinary collaboration will accelerate advancements in LncRNA localization research.

In summary, research on LncRNA subcellular localization will offer a more comprehensive understanding of their roles in cellular functions and disease mechanisms. With ongoing technological development and innovation, LncRNA research is poised to make a significant impact in both biological and medical fields in the future.

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