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Regulation of gene expression by RNA-binding proteins

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INTRODUCTION

Gene expression is a tightly regulated process that governs the production of functional RNA and proteins within cells. Central to this regulation are RNA-Binding Proteins (RBPs), which play diverse roles in the post-transcriptional control of gene expression. RBPs interact with RNA molecules to modulate their processing, stability, localization, and translation, thereby influencing the abundance and activity of gene products. In this narrative, we explore the mechanisms by which RBPs regulate gene expression, their roles in cellular physiology and disease, and the therapeutic potential of targeting RNA-protein interactions.

DESCRIPTION

RBPs interact with RNA molecules through specific RNA-binding domains, such as RNA Recognition Motifs (RRMs), zinc finger domains, and K Homology (KH) domains, which recognize and bind to RNA sequences or structural motifs. These interactions can occur co-transcriptionally in the nucleus or post-transcriptionally in the cytoplasm, depending on the localization and function of the RBP. Once bound to RNA, RBPs can exert a variety of regulatory effects on gene expression, including alternative splicing, RNA editing, polyadenylation, mRNA stability, localization, and translation.

Alternative splicing is a crucial mechanism by which RBPs regulate gene expression and generate proteome diversity. RBPs such as Serine/Arginine-Rich (SR) proteins and heterogeneous nuclear Ribonucleoproteins (hnRNPs) bind to pre-mRNA transcripts and modulate splice site selection, leading to the inclusion or exclusion of specific exons in the mature mRNA. This process can generate multiple mRNA isoforms from a single gene, resulting in protein variants with distinct functions or properties. Dysregulation of alternative splicing is implicated in numerous diseases, including cancer, neurodegenerative disorders, and developmental syndromes, highlighting the importance of RBP-mediated splicing regulation in cellular physiology and pathology.

RNA stability is another critical aspect of post-transcriptional gene regulation mediated by RBPs. RBPs such as AU-Rich Element-Binding Proteins (ARE-BPs) and microRNA (miRNA)-associated RBPs bind to specific sequence elements or secondary structures within mRNA transcripts and modulate their stability and degradation rates. By protecting mRNA transcripts from degradation or targeting them for degradation by the RNA decay machinery, RBPs can influence the abundance and turnover of gene products in the cell. Dysregulation of RNA stability is implicated in various diseases, including inflammatory disorders, cardiovascular diseases, and cancer, underscoring the importance of RBP-mediated RNA turnover in maintaining cellular homeostasis.

RBPs also play critical roles in the regulation of mRNA localization and translation, controlling the spatial and temporal expression of gene products within cells. RBPs such as the Fragile X Mental Retardation Protein (FMRP) and Staufen regulate mRNA transport and localization to specific subcellular compartments, such as dendrites and synapses, where they are translated in response to synaptic activity. Additionally, RBPs such as the Poly(A)-Binding Protein (PABP) and eukaryotic Initiation Factors (eIFs) modulate mRNA translation initiation, elongation, and termination by interacting with translation machinery components and regulatory elements within the mRNA transcript. Dysregulation of mRNA localization and translation is implicated in synaptic plasticity disorders, neurodevelopmental disorders, and cancer, highlighting the importance of RBP-mediated translational control in cellular function and disease pathology.

In addition to their roles in normal cellular physiology, RBPs are increasingly recognized as key regulators of disease-associated pathways and therapeutic targets for intervention. Dysregulation of RBP expression, activity, or localization is implicated in a wide range of human diseases, including cancer, neurodegenerative disorders, autoimmune diseases, and infectious diseases. For example, mutations in RBPs such as TDP-43, FUS, and hnRNPA1 are associated with Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), highlighting the importance of RNA metabolism dysregulation in these neurodegenerative diseases. Moreover, RBPs such as HuR and PTB are overexpressed in various cancers and contribute to tumor progression, metastasis, and chemotherapy resistance by regulating the expression of oncogenes and tumor suppressors.

The therapeutic potential of targeting RNA-protein interactions is increasingly recognized in the development of novel therapeutic strategies for human diseases. Small molecules, peptides, and oligonucleotide-based approaches have been developed to modulate RBP activity, disrupt RNA-protein interactions, or restore normal RNA metabolism in disease states. For example, small molecules that inhibit the RNA-binding activity of specific RBPs, such as the SR Protein Kinase (SRPK) inhibitor SPHINX, have shown promise as potential therapeutics for cancer and neurodegenerative diseases. Moreover, Antisense Oligonucleotides (ASOs) and RNA interference (RNAi) approaches can be used to selectively target and degrade disease-associated RNAs or modulate their splicing, translation, or stability, offering potential treatments for a wide range of genetic and acquired diseases.

CONCLUSION

RNA-binding proteins play diverse and essential roles in the post-transcriptional regulation of gene expression, influencing RNA processing, stability, localization, and translation. Dysregulation of RBP-mediated gene expression control is implicated in numerous diseases, including cancer, neurodegenerative disorders, and autoimmune diseases. Targeting RNA-protein interactions represents a promising approach for developing novel therapeutics to modulate gene expression and treat human diseases. As our understanding of RBP biology continues to advance, so too will our ability to exploit these molecular regulators for therapeutic benefit, paving the way for new treatments and improved outcomes for patients.