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Role of Alternative Splicing in Mirtron Formation and Arm Selection of Precursor MicroRNAs

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Introduction

Alternative splicing is a fundamental mechanism that allows a single gene to produce multiple distinct mRNA isoforms, thereby increasing the complexity and diversity of the transcriptome. This process, which involves the selective inclusion or exclusion of exons during mRNA processing, plays a crucial role in regulating gene expression and cellular function. In the context of microRNA (miRNA) biogenesis, alternative splicing has a significant impact on the formation of mirtrons and the selection of miRNA arms, processes that are essential for the proper regulation of gene expression. Mirtrons, a subclass of microRNAs, are formed through a splicing-dependent mechanism, which makes them distinct from canonical miRNAs. Understanding the role of alternative splicing in mirtron formation and arm selection of precursor miRNAs provides critical insights into the regulation of gene expression and the potential for therapeutic manipulation of miRNA pathways. MicroRNAs are small, non-coding RNAs that regulate gene expression at the post-transcriptional level by binding to complementary sequences in the 3' Untranslated Regions (UTRs) of target mRNAs. The canonical pathway of miRNA biogenesis begins with the transcription of primary miRNAs (pri-miRNAs), which are processed into precursor miRNAs (pre-miRNAs) by the enzyme Drosha in the nucleus. These pre-miRNAs are then exported to the cytoplasm, where they are further processed by the enzyme Dicer into mature miRNAs. However, not all miRNAs follow this canonical pathway. A subset of miRNAs, known as mirtrons, bypass the Drosha-mediated cleavage step and are formed through the direct splicing of introns from precursor mRNAs. This unique biogenesis pathway involves the excision of a small RNA sequence from the intronic region, which is then processed into a pre-miRNA by the splicing machinery of the cell.

Description

Alternative splicing refers to the phenomenon where different combinations of exons are included or excluded from the final mRNA transcript, leading to the production of multiple isoforms from a single gene. This process is regulated by a complex network of cis-regulatory elements, trans-acting factors, and splicing enhancers or silencers. The regulation of alternative splicing is crucial for normal cellular function, as it can significantly alter the protein-coding potential of a transcript, as well as affect the production of non-coding RNAs such as miRNAs. In the context of mirtron formation, alternative splicing plays a key role in determining which sequences are included or excluded from the precursor miRNA. By modulating the splicing pattern of a given transcript, cells can generate distinct miRNA isoforms with different target specificities and functional roles. One of the most important aspects of alternative splicing in miRNA biogenesis is its effect on the arm selection of precursor miRNAs. miRNAs are produced from both the 5' and 3' arms of the precursor hairpin structure. The selection of which arm is processed into the mature miRNA is a critical step in determining the functional specificity of the miRNA. Each arm of the precursor has the potential to generate a distinct miRNA species, each with a different sequence and, therefore, different target mRNAs. The decision of which arm is selected for processing is influenced by a variety of factors, including the sequence of the precursor, the abundance of the two arms, and the activity of RNA-binding proteins that regulate miRNA biogenesis [1].

Alternative splicing can impact arm selection by altering the balance of precursor miRNA isoforms. For example, splicing events that lead to the inclusion or exclusion of specific exons within the precursor can change the relative abundance of the two arms, thereby influencing which arm is more likely to be selected for processing. In some cases, alternative splicing may produce precursor miRNAs with different stem-loop structures or different lengths, which could favor the selection of one arm over the other. Additionally, the splicing of particular introns may expose or hide specific binding sites for RNA-binding proteins, further influencing the selection of the miRNA arm. In this way, alternative splicing provides an additional layer of regulation in miRNA biogenesis, allowing for fine-tuned control of miRNA expression and function. The relationship between alternative splicing and arm selection is not limited to mirtron formation alone. In canonical miRNA biogenesis, splicing events within the primary miRNA transcript can also impact the processing of the pre-miRNA. For instance, the inclusion or exclusion of specific exons or introns during splicing can modify the structure of the pre-miRNA, which may in turn affect the selection of the mature miRNA arm. Moreover, alternative splicing can influence the expression of RNA-binding proteins involved in miRNA processing, such as the Dicer and Argonaute proteins. By modulating the abundance or activity of these proteins, alternative splicing can indirectly affect the processing of both canonical and non-canonical miRNAs [2].

The regulation of mirtron formation and arm selection by alternative splicing is an area of active research, and many questions remain regarding the precise mechanisms involved. Recent studies have begun to elucidate the factors that influence splicing decisions in the context of miRNA biogenesis. For example, certain splicing factors have been identified that preferentially promote the formation of mirtrons by enhancing the splicing of introns that contain miRNA sequences. These factors can act as activators or repressors of mirtron formation, depending on the specific sequence context and the cellular environment. In addition, recent work has highlighted the importance of specific RNA motifs and structural elements within the precursor miRNA that are involved in the selection of the mature miRNA arm. These elements can interact with splicing factors, RNA-binding proteins, and other regulatory molecules, influencing the efficiency and accuracy of arm selection. In addition to its role in mirtron formation and arm selection, alternative splicing also contributes to the broader regulation of miRNA expression. In many cases, alternative splicing events within miRNA-producing genes can generate different miRNA isoforms, each with distinct regulatory properties. For example, a single miRNA gene may produce several different precursor miRNAs through alternative splicing, with each precursor generating distinct mature miRNAs with different target specificities. This allows for the generation of a diverse repertoire of miRNAs from a single genetic locus, enabling the cell to fine-tune its gene expression profile in response to various environmental or developmental cues. Moreover, the regulation of alternative splicing can contribute to the tissue- and stage-specific expression of miRNAs, allowing for the precise regulation of gene networks in different cellular contexts [3].

The interplay between alternative splicing and miRNA biogenesis has important implications for understanding gene regulation in health and disease. Many diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases, have been linked to dysregulation of splicing and miRNA expression. In particular, aberrant splicing events can lead to

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the production of miRNAs with altered or inappropriate target specificities, contributing to the development of disease. For example, changes in the splicing of miRNA precursors can lead to the generation of miRNAs that promote tumorigenesis by targeting tumor suppressor genes or that disrupt normal neuronal development by targeting key genes involved in synaptic plasticity. Understanding the molecular mechanisms that link alternative splicing to miRNA biogenesis and arm selection could provide valuable insights into the molecular basis of these diseases and lead to the development of novel therapeutic strategies. One potential therapeutic approach is the targeting of splicing regulators or RNA-binding proteins that control mirtron formation and arm selection. By modulating the activity of these factors, it may be possible to influence miRNA expression and restore normal gene regulation in diseased cells. For example, small molecules or RNA-based therapies could be developed to selectively alter the splicing of specific miRNA precursors, thereby promoting the formation of miRNAs with desirable properties. In cancer therapy, for instance, such approaches could be used to enhance the expression of tumor-suppressive miRNAs or inhibit the production of oncogenic miRNAs. Similarly, in neurodegenerative diseases, modulating the splicing of miRNA precursors could help to restore normal neuronal function and prevent disease progression [4,5].

Conclusion

Alternative splicing plays a crucial role in the formation of mirtrons and the selection of miRNA arms during miRNA biogenesis. By influencing the splicing of precursor miRNAs and the subsequent selection of mature miRNAs, alternative splicing adds an important layer of regulation to gene expression. This process allows cells to generate a diverse range of miRNA isoforms with distinct regulatory functions, contributing to the precise control of gene expression in response to environmental and developmental cues. As research into the interplay between alternative splicing and miRNA biogenesis continues to evolve, it holds promise for the development of new therapeutic strategies for a variety of diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases. Understanding the molecular mechanisms that govern mirtron formation and arm selection will be critical for harnessing the full potential of miRNAs in therapeutic applications.

Acknowledgement

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Conflict of Interest

None.

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