Mini Review

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Hereditary Abnormalities Disorders and Infectious Diseases in the Proliferation of Coronary Vessels

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Abstract

Advances in genomics, bioinformatics and genome editing have revealed new dimensions of gene regulation. Post-transcriptional modification of mRNA transcripts by alternative splicing is an important regulatory mechanism of mammalian gene expression. In general, there is growing interest in elucidating the role of alternative splicing in transcriptome regulation. Considerable effort has been expended to study this process in heart development and heart failure. However, only a few studies provide information on alternative splicing products and dysregulation in congenital heart disease (CAD). Although sophisticated reports have demonstrated a critical role for RNA-binding proteins (RBPs) in coordinating splicing junctions during cardiac development and dysfunction, the impact of RBP dysregulation or genetic mutations on CAD is limited. increase. not fully addressed. Here, we review our current understanding of alternative splicing and the role of RBP in heart development and CAD. We describe the perinatal splicing transition and its dysregulated effects on CAD. In addition, we summarize the findings of the splice variants responsible for key transcription factors involved in CAD. A better understanding of the role of alternative splicing in cardiac development and CAD may lead to new advances in the prevention and treatment of neonates with CAD.

Keywords: congenital heart defects • transcriptome • splicing variants • genome

Introduction

The genomic era has opened new avenues of understanding new mechanisms--including post-transcriptional regulation by alternative splicing mechanisms [1]. RNA splicing, orchestrated by the splicing machinery, is a tightly regulated post-transcriptional modification process in which introns are removed from nascent pre-mRNAs, resulting in the generation of mature mRNAs for translation and protein synthesis [2].In contrast to standard "constitutive" splicing. Alternative splicing exhibits temporal regulation during cell differentiation and coordinates tissue homeostasis and organ development by fine-tuning cell properties, physiological functions and developmental trajectories. On the other hand, dysregulation of splicing networks can lead to impaired organ formation and function. Various physiological conditions and environmental cues can alter splicing decisions, resulting in the generation of multiple mRNA isoforms from a single gene in a tissue-specific and context-dependent manner. This supports the notion that alternative splicing plays a key role in proper organ formation and function at key stages of mammalian development [3].

The transcripts of most mammalian protein-coding genes undergo one or more types of alternative splicing. Several alternative splicing styles or patterns are described. Among them, the most commonly encountered are her five patterns: (1) exon skipping (SE), (2) mutually exclusive exon usage (MEX), (3) alternative 5′ splice site selection (5′SS), (4) alternative 3′ splice site selection (3′SS), (5) intron retention (IR). Notably, ES is the most common pattern in which specific exons, called cassette exons, are included or skipped in the mature transcript depending on splicing decisions. MEX is rarer than ES. One cassette exon is included in this pattern and the other cassette exon is skipped in the mature

transcript. The use of alternative splicing start or end sites affects the 5′ and 3′ ends, respectively, to produce shorter or longer exons from the same transcript [4]. Finally, IR occurs when intronic spacing is retained in mature transcripts that can be translated or processed by nonsense-mediated attenuation mechanisms. Alternative splicing reactions are catalyzed by spliceosomes. Spliceosome assembly involves a complex interaction of small nuclear ribonucleoprotein particles (snRNPs, U1, U2, U4/U6, and U5) and other associated proteins. Spliceosome formation and its mechanism of action have been elegantly studied and characterized using cryo-electron microscopy studies [5].

Alternative splicing is a ubiquitous process in organs, tissues, and cell types. In humans, it is estimated that more than 95% of protein-coding gene transcripts undergo alternative splicing, resulting in proteome complexity. Therefore, establishing the partition of this process in human organ development and disease remains challenging. Indeed, not all splicing products lead to functionally intact protein isoforms at the translational level due to several reasons, amongst them [6].

The splicing event may produce a non-coding transcript lacking a functional open reading frame; the splicing event may lead to a functional non-coding transcript that modulates chromatin accessibility or competes with other RNAs; the splicing event may affect transcript stability leading to antisense mediated decay; the splicing event may alter the subcellular localization of the mature mRNA impairing its translation or function; the nonsense-mediated decay of premature stop codon-containing transcripts; and the splicing events may be overestimated as a result of amplification artifacts [7].

Develop from Parallel Splicing Throughout Cardiac Development

Cardiac development is a highly dynamic process in which extensive remodeling of the transcriptome occurs in a spatiotemporally regulated manner. These changes are primarily driven by transcriptional and post-transcriptional modification mechanisms, including alternative mRNA splicing.

Advanced genome-wide sequencing and functional genomics tools have revealed key splicing junctions during the differentiation of human embryonic stem cells into cardiac progenitors. They also revealed significant differences in alternative splicing patterns between fetal and adult hearts. RI events were detected more frequently in fetal hearts compared with adult hearts. Furthermore, cell proliferation processes were enhanced with fetal-specific alternative splicing events. In contrast, adult-specific events were enhanced in energy-related categories. Key cell cycle regulators including calcium channel beta 2 (CACNB2), tropomyosin 1 (TPM1), disabled-1 (Dab1), and pumilio RNA-binding family member 1 (PUM1), calcium/calmodulin-dependent protein kinase 2D (CAMK2D) A factor, and subunit 11 of the anaphase promoting complex (ANAPC11), shows significant differences in splicing between fetal and adult hearts. Similarly, sarcomere-associated proteins are developmentally regulated through alternative splicing, including cardiac troponin T (cTnT). Exon 5 of cTnT is predominantly expressed in the embryonic heart and encodes a protein domain that increases the sensitivity of embryonic cTnT-containing myofilaments to calcium compared to the less sensitive adult cTnT myofilaments, thereby Adjusts the shrinkage properties of Recently, single-cell RNA-seq analysis of 996 samples representing the cellular composition of fetal-like (hiPSC-derived cardiac progenitor cells), healthy adult hearts, and diseased heart failure revealed cellular heterogeneity in fetal and adult hearts. Gender was brought up further [8].

Alternative splicing transitions during cardiac development are regulated by multiple RBPs that exhibit large temporal changes in expression levels and exert functions in a cooperative or antagonistic manner [9]. Of the approximately 1500 RBPs expressed in the heart, 390 heart-specific RBPs have been identified. Examples of cardiac RBPs that have been studied primarily in heart development include CELF1 (CUGBP Elav-like family member-1), MBNL1 (muscleblind-like protein-1), RBFOX1, RBFOX2, RBM20, and RBM24. increase. Role in splicing transitions during pre- and postnatal heart development. CELF protein was repressed in the postnatal heart, while MBNL1 was induced. Importantly, both MBNL1

and CELF are regulated by her RBM20-mediated alternative splicing during heart development. Thus, loss of RBM20 function in the adult heart results in a reversion to the embryonic splicing pattern. Rbfox1 has also been identified as a key regulator of the conserved splicing process of transcription factor Mef2 family members, emerging as a key player in reversing global fetal gene programming in pressure-overload heart failure [10].

Fetal Conduction Disorders Induced by Replicating Iterations

A novel splice junction variant of KCNH2 encoding Kv11.1 was discovered in an extended family that affects the relative abundance of full-length Kv11.1a and truncated Kv11.1a USO isoforms [11]. This was determined by competition between alternative KCNH2 splicing and alternative polyadenylation mechanisms. Splicing defects can also affect voltage-gated sodium channels. A recent report showed that the non-muscle isoform of RBFOX2 [RBFOX240] was upregulated in cardiac tissue from patients with myotonic dystrophy 1 (DM1), resulting in increased CELF1 and global suppression of miRNAs. was shown. Modeling in mice showed that overexpression of the Rbfox240 isoform caused inappropriate splicing of voltage-gated sodium channel transcripts, creating a proarrhythmic state that altered the channel's electrical properties, resulting in conduction defects [12].

Arrhythmogenic dysplasia of the right ventricle (ARVD) is a rare genetic disorder in which RV cardiomyocytes are replaced by fibro-adipose tissue, resulting in ventricular arrhythmias. ARVD cases with dominant inheritance and incomplete penetrance are caused by heterozygous mutations in PKP2. Interestingly, the first reported case of ARVD with recessive inheritance was caused by a homozygous cryptic splice variant of PKP2 (c.2484C>T), originally annotated as a synonymous variant. I was. However, further analysis of subject mRNAs revealed disruption of the PKP2 reading frame and altered PKP2 splicing outcomes caused by this cryptic splice-site variant [13].

Similar to prenatal development, alternative splicing junctions play important roles as regulatory elements of the transcriptome in early postnatal development of the mouse heart. Dramatic hemodynamic changes occur during this time, resulting in profound changes in cellular respiratory, metabolic, proliferative, and functional properties [14]. These changes are associated with highly coordinated alternative splicing programs that generate essential protein isoform transitions that play critical roles in postnatal heart growth and maturation. Recently, bulk RNA-sequencing has revealed the transcriptome dynamics of mouse heart cells, cardiomyocytes and cardiac fibroblasts at different prenatal and postnatal stages. Significant changes in cardiomyocyte splicing occur within the first month of life, indicating a critical role for alternative splicing in cardiomyocyte maturation, whereas cardiac fibroblast splicing transitions occur within the first month of life. continue beyond. Finally, it should be noted that alternative splicing products are likely to have functional consequences during postnatal heart development when splicing junctions occur simultaneously in multiple organs. B. Splicing events in the developing heart and brain [15].

Conclusions

Alternative splicing is a ubiquitous method that performs crucial roles in transcriptome law and proteome diversity. The modern literature proof helps the crucial regulatory roles of opportunity splicing in cardiovascular improvement and CHDs. Splicing transition is managed with the aid of using a complicated and tricky community of RBPs, which orchestrate the splicing transition in their goals for the duration of coronary heart improvement and may be dysregulated in CHDs. Pathogenic variations of RBPs may also modify the splicing choices in their goals and account for sizable developmental perturbation main to CHDs. Pathogenic splicing variations of key center cardiac transcription elements and structural genes may be causal to CHDs.

Taking into attention the present demanding situations in organising the partition of his essential method in human coronary heart improvement and disease, big efforts tailor-made to a complete baseline knowledge of tissue-precise and mobileular-precise opportunity splicing transitions and their physiologic roles for the duration of coronary heart improvement are essential. Utilizing

modern-day sequencing technology, inclusive of single-mobileular and long-examine RNA sequencing; analyzing RNP covalent interactions in post-transcriptional gene law, and using purposeful genomics and CRISPR-primarily based totally methods for modulating splicing are predicted to spread the complexity of opportunity splicing-mediated transcriptome law mechanisms on the mobileular-kind precise degree and screen their purposeful affects on mobileular conduct and destiny for the duration of improvement and their contributions to human CHDs. Multilayered collaborative bioinformatics, purposeful genomics, and mechanistic methods for analyzing RBPs dysregulation and elucidating the causal effect of newly located splicing variations in CHDs are vital to find new mechanisms and pave the manner to novel diagnostic and centered methods for toddlers with CHDs.

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