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Review

Minor spliceosome and disease

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ABSTRACT

The U12-dependent (minor) spliceosome excises a rare group of introns that are characterized by a highly conserved 5′ splice site and branch point sequence. Several new congenital or somatic diseases have recently been associated with mutations in components of the minor spliceosome. A common theme in these diseases is the detection of elevated levels of transcripts containing U12-type introns, of which a subset is associated with other splicing defects. Here we review the present understanding of minor spliceosome diseases, particularly those associated with the specific components of the minor spliceosome. We also present a model for interpreting the molecular-level consequences of the different diseases.

Contents

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1. Introduction

Pre-mRNA splicing is an essential step in the gene expression pathway of all eukaryotes. During splicing, the non-coding intron sequences are recognized and removed from precursor mRNA (pre-mRNA) by the spliceosome, a large ribonucleoprotein complex. Defects in splicing of one or more mRNA species are a major cause of human diseases and present estimates suggest that up to 60%, are associated with pre-mRNA splicing [1,2]. In addition to monogenic disorders, genetic variants altering splicing are also thought to be an important contributor to complex diseases and cancer [3,4]. The majority of disease-associated splicing defects are *cis*-acting mutations within a single gene that disrupt either the splice site consensus sequences or splicing regulatory elements located in introns or exons [5]. Notably, exonic mutations interpreted as missense, nonsense or silent also commonly affect splicing [4,6,7]. The outcome of *cis*-acting splicing mutations is often either a formation of abnormal or non-functional protein species or accelerated decay of the affected individual mRNAs. In contrast, mutations in splicing factors, spliceosome components or spliceosome assembly factors often lead to widespread defects in the processing of large numbers of pre-mRNAs [8–10].

Most metazoan species contain two distinct pre-mRNA splicing machineries known as the major (U2-dependent) and minor (U12-dependent) spliceosomes, which recognize and excise either the major (U2-type) or minor (U12-type) class of introns, respectively. In contrast to the major introns, U12-type introns are characterized by divergent and highly conserved 5′ splice site (5′ss) and branch point sequences (BPS) (Fig. 1A; [11]). These introns also lack the characteristic polypyrimidine tract (PPT) that is present in U2-type introns immediately upstream of the 3′ splice site (3′ss). Minor introns constitute only ~0.35% of all human introns and have been reported to be present in 700–800 genes, each of which typically carry only a single U12-type intron and multiple U2-type introns. U12-type introns are enriched in genes that represent a rather restricted set of functional classes and pathways. Particularly they are present in genes related to 'information processing functions', such as DNA replication and repair, transcription, RNA processing, and translation, but can also be found in genes related to cytoskeletal organization, vesicular transport, and voltage-gated ion channel activity, as suggested originally by Burge et al., [12] and verified later [13,14]. Both the identities of genes carrying U12-type introns and their positions within the genes are evolutionarily conserved [15].

The overall organisational and functional features of both spliceosomes are highly similar. Both are composed of five small nuclear RNA (snRNA) molecules that associate with protein factors to give rise to small nuclear ribonucleoproteins (snRNPs). Within the minor spliceosome, four of the five snRNAs are unique. Specifically, U11, U12, U4atac, and U6atac replace the major spliceosome counterparts U1, U2, U4 and U6 snRNAs, respectively. U5 snRNA is shared between the two spliceosomes. Of the 200–300 proteins associated with spliceosomes, most are thought to be shared between the two systems and only 7 proteins, associated with U11 and U12 snRNPs, are unique to the minor spliceosome [16,17].

The highly similar spliceosome composition is reflected in the conserved assembly pathway and catalytic mechanism. Both spliceosomes are assembled sequentially starting from intron recognition, followed by formation of a catalytically active spliceosome and joining of the exons flanking the excised intron. With minor introns, the 5′ss and BPS are co-operatively recognized by a pre-formed U11/U12 di-snRNP [18], contrary to the sequential recognition of these sequences by individual U1 and U2 snRNPs in major introns. Since the PPT is lacking in minor introns, the U2AF1/2 heterodimer that recognizes the PPT and 3′ss of major introns does not associate with minor introns. Instead, an integral U11/U12 di-snRNP protein component, Urp/ZRSR2 takes up the role of 3′ss recognition with minor introns [19]. Following this initial recognition, both splicing pathways proceed with association of a tri-snRNP, either U4atac/U6atac.U5 or U4/U6.U5 (Fig. 1B; [20,21]). Further rearrangements in RNA–RNA and RNA–protein interactions lead to the formation of a catalytically active spliceosome and catalytic excision of the intron [20,22,23].

Here, we review the role of the minor spliceosome in human diseases, with a specific focus on diseases caused by mutations in the integral components of the minor spliceosome. Given that most protein components and U5 snRNA are shared with the major spliceosome, there are also several diseases where mutations disrupting shared components can potentially affect the functions of both spliceosomes. Those have been discussed in detail elsewhere [24].

2. Minor spliceosome in human disease

The direct targets for human diseases specific for the minor spliceosome are the unique snRNA and protein components. This includes several components of the U11/U12 intron recognition complex and the U4atac and U6atac snRNAs in the minor tri-snRNP. The U11/U12 di-snRNP contains, in addition to the U11 and U12 snRNAs, seven integral proteins (65K, 48K, 59K, 35K, 31K, 25K and 20K) that are unique to the minor spliceosome [25,26]. Additionally, the Urp/ZRSR2 protein associated with the U11/U12 di-snRNP has been reported to function in both minor and major spliceosomes, with an essential role for U12-type intron 3′ss recognition [19].

To date five human diseases with mutations in the specific components of the minor spliceosome have been described (Table 1). Three of them affect the components of the U11/U12 di-snRNP, namely the U11/U12-65K protein (*RNPC3*; [27]), U12 snRNA (*RNU12*; [28]) and Urp protein (*ZRSR2*; [29]); while two diseases are attributed to mutations in the U4atac snRNA (*RNU4ATAC*; [30–32]). Each of these diseases is hypomorphic, leading only to a partial loss of minor spliceosome function because correctly spliced mRNAs can be detected in the patient cells. We briefly introduce each disease and later discuss the impact of disease mutations on the assembly of the minor spliceosome and the fate of affected mRNAs.

Apart from mutations in the core minor spliceosome components, we also describe the few reported human diseases caused by mutations at the splice sites of U12-type introns, though we note that this appears to be underexplored territory given the small number of cases reported so far. Finally, we mention the emerging role for the minor spliceosome in cancer and autoimmune disorders as well as neurodegenerative diseases.

2.1. Diseases affecting the intron recognition step

2.1.1. Isolated growth hormone deficiency

Recessive mutations in the *RNPC3* gene, encoding U11/U12-65K, one of the seven minor spliceosome-specific proteins, have been associated with isolated growth hormone deficiency (IGHD) and associated pituitary hypoplasia. The 65K protein is part of a molecular bridge that connects the U11 and U12 snRNPs into a di-snRNP (Fig 1B; [33]). Initially, *RNPC3* mutations were detected in a single family only [27], but additional cases with overlapping mutations and similar phenotypes have been described subsequently [34]. IGHD is a condition characterized by a shortage or absence of growth hormone, with the absence of associated pituitary hormone deficiencies. Genetically, IGHD is a diverse disease and can result from either recessive or dominant mutations in various genes involved in pituitary development or function [35].

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