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Review

Function of alternative splicing

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Abstract

Alternative splicing is one of the most important mechanisms to generate a large number of mRNA and protein isoforms from the surprisingly low number of human genes. Unlike promoter activity, which primarily regulates the amount of transcripts, alternative splicing changes the structure of transcripts and their encoded proteins. Together with nonsense-mediated decay (NMD), at least 25% of all alternative exons are predicted to regulate transcript abundance. Molecular analyses during the last decade demonstrate that alternative splicing determines the binding properties, intracellular localization, enzymatic activity, protein stability and posttranslational modifications of a large number of proteins. The magnitude of the effects range from a complete loss of function or acquisition of a new function to very subtle modulations, which are observed in the majority of cases reported. Alternative splicing factors regulate multiple pre-mRNAs and recent identification of physiological targets shows that a specific splicing factor regulates pre-mRNAs with coherent biological functions. Therefore, evidence is now accumulating that alternative splicing coordinates physiologically meaningful changes in protein isoform expression and is a key mechanism to generate the complex proteome of multicellular organisms.
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1. Introduction

1.1. Abundance of pre-mRNA splicing

An average human gene contains a mean of 8.8 exons, with a mean size of 145 nt. The mean intron length is 3365 nt, and the 5′ and 3′ UTR are 770 and 300 nt, respectively. As a result, a "standard" gene spans about 27 kbp. After pre-mRNA processing, the average mRNA exported into the cytosol consists of 1340 nt coding sequence, 1070 nt untranslated regions and a poly (A) tail (Lander et al., 2001). This shows that more than 90% of the pre-mRNA is removed as introns and only about 10% of the average pre-mRNA are joined as exonic sequences by pre-mRNA splicing. Human cells are not only capable of accurately recognizing the small exons within the larger intron context, but are also able to recognize exons alternatively. In this

Abbreviations: CGRP, calcitonin-gene-related peptide; DSCAM, Down syndrome cell adhesion molecule; GDNF, glial cell line-derived neurotrophic factor; GMAP-210, Golgi-microtubule-associated-protein of 210 kDa; GnRH, gonadotrophin releasing hormone; HER2, human epidermal growth factor receptor; ICAD, inhibitor of caspase-activated DNAse; IL-4, interleukin 4; LDL, low-density lipoprotein; NMD, nonsense-mediated decay; PECAM-1, platelet/endothelial cell adhesion molecule-1; RUST, regulated unproductive splicing and translation; TSH, thyroid stimulating hormone; VEGF, vascular endothelial growth factor.

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process, an exon is either incorporated into the mRNA, or is excised as a part of an intron. Initially, this was thought to be only a minor processing pathway affecting about 5% of all genes (Sharp, 1994), but over time, it became clear that it is highly abundant. Bioinformatic analysis shows that 59% of the 245 genes present on chromosome 22 are alternatively spliced, and DNA microarray experiments indicate that 74% of all human genes are alternatively spliced (Johnson et al., 2003). The high frequency of alternative splicing in humans is also supported by EST-based database analysis, indicating that 35–60% of all human gene products are alternatively spliced (Mironov et al., 1999; Brett et al., 2000; Kan et al., 2001; Modrek et al., 2001), suggesting that alternative splicing of human genes is the rule and not the exception. On average, a human gene generates two to three transcripts. However, extreme cases exist: The human neurexin3 gene can potentially form 1728 transcripts due to alternative splicing at four different sites. In *Drosophila*, the Down syndrome cell adhesion molecule (DSCAM) can potentially generate 38016 isoforms due to alternative splicing (Celotto and Graveley, 2001). This number is larger than the total number of genes present in *Drosophila*. Alternative splicing is observed in all tissues, but tissue-specific splicing is most prevalent in brain cells (Stamm et al., 2000; Xu et al., 2002). EST data comparison strongly indicates that similar levels of alternative splicing occur in evolutionarily distinct species, such as human, mouse, *Drosophila* and *C. elegans*, emphasizing the importance of alternative splicing throughout evolution (Brett et al., 2002). The increased recognition of alternative splicing is reflected by the steady growth in the number of publications describing alternative splicing. It increased from 16 publications in 1985 to 1073 in 1998. Since then, about 1000 publications per year deal with various aspects of alternative splicing.

1.2. Mechanism of splice-site selection

The mechanism of splicing has been determined in great detail (Jurica and Moore, 2003; Nilsen, 2003). In contrast, it is not yet fully understood how splice sites are selected. The major problem is the degeneracy of splicing regulatory sequences, such as the 5′, 3′ splice sites, branch points and exonic/intronic sequence elements. These can only be

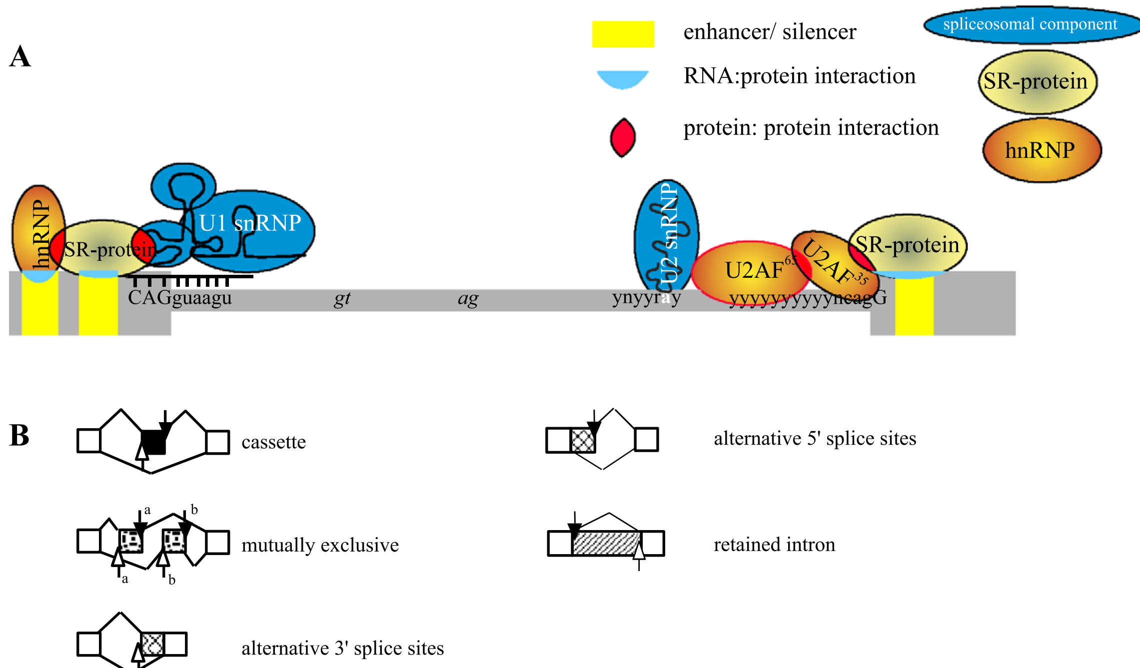

Fig. 1. Splice-site selection. (A) Exons are indicated as boxes, the intron as a thick line. Splicing regulator elements (enhancers or silencers) are shown as yellow boxes in exons or as thin boxes in introns. The 5′ splice site (CAGguaagu) and 3′ splice site $(y)_{10}$ncagG, as well as the branch point (ynyyray), are indicated (*y*=c or u, *n*=a, g, c or u). Upper-case letters refer to nucleotides that remain in the mature mRNA. Two major groups of proteins, hnRNPs (orange) and SR or SR-related proteins (green), bind to splicing regulator elements; the protein–RNA interaction is shown in blue. This protein complex assembles around an exon enhancer, stabilizing the binding of the U1 snRNP close to the 5′ splice site, e.g., due to protein–protein interaction between an SR protein and the RS domain of U170K (shown in red). This allows the hybridization (thick black line with stripes) of the U1 snRNA (black) with the 5′ splice site. The formation of the multiprotein–RNA complex allows discrimination between proper splice sites indicated at exon–intron borders and cryptic splice sites (small *gt ag*) that are frequent in pre-mRNA sequences. Factors at the 3′ splice site include U2AF, which facilitates binding to U2 snRNP to the branchpoint sequence. In exons with weak polypyrimidine tracts, the binding of U2AF is facilitated by the SR proteins binding to exonic enhancers. Green: SR and SR-related proteins; orange: hnRNPs; blue: protein–RNA interaction; red: protein–protein interaction; thick black line with stripes: RNA–RNA hybridization. (B) Types of alternative splicing events: Alternative exons are shown as boxes with different shading. Flanking constitutive exons are shown as white boxes. The open arrow indicates the position of the alternative 3′ splice site analyzed; a closed arrow indicates the position of the 5′ splice sites analyzed.

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