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Alternative Splicing Minireview Series: Combinatorial Control Facilitates Splicing Regulation of Gene Expression and Enhances Genome Diversity*

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Precursor mRNA splicing is the process through which introns are removed from primary transcripts and the exons that encode amino acid sequences are joined together to generate mature, protein-coding mRNAs (1). This process must be extraordinarily precise to ensure accurate decoding of mRNA sequences into functional proteins during translation, but also remarkably flexible, with the ability to recognize and excise introns of variable lengths and sequences. Nearly 90% of human gene sequences consist of introns that must be removed through splicing, and the majority of mutations associated with hereditary human disease are linked to splicing defects (2).

Splicing takes place in the spliceosome, which is a complex of five small nuclear RNAs and associated core proteins and several hundred proteins that assembles on nascent pre-mRNAs during transcription. The splicing pathway is an exquisitely orchestrated series of assembly and conformational rearrangement events, punctuated by the chemical transformations of cleavage of phosphodiester bonds at exon/intron junctions and phosphodiester bond formation during exon ligation. In the first chemical step of splicing, the 5′-exon/intron boundary is cleaved through nucleophilic attack by the 2′-hydroxyl of a specific branch-point adenosine located within the intron to generate a 5′-exon fragment and a lariat intermediate that contains intron and 3′-exon sequences and the branched adenosine (Fig. 1). In the second chemical step, cleavage at the 3′-exon/intron boundary occurs through nucleophilic attack of the 3′-hydroxyl of the 5′-exon at the 3′-splice site, which ligates the exons and releases the intron in the form of a lariat. Self-splicing of certain Group II introns occurs through identical chemical steps in the absence of proteins, suggesting that the RNA components of the spliceosome also mediate catalytic chemistry. Since proteins are not essential for catalysis, spliceosomal proteins are likely to contribute to splicing fidelity and link splicing to other steps of mRNA biogenesis, transport, translation, and turnover.

The splice sites at the exon/intron boundaries and the branch-point consensus sequences in pre-mRNA are only weakly conserved and are far too simple to specify splice sites uniquely. It has become clear that co-transcriptional spliceosome assembly itself helps to ensure accuracy as intron and exon sequences associate with specific proteins that are deposited onto nascent transcripts. Splice sites are also recognized by complementary base pairing with spliceosomal small nuclear RNAs and proteins as splice sites are brought into the active site to proceed through the chemical steps of splice site cleavage and ligation.

The human proteome is more diverse than can be explained by the complexity of the genome due to alternative splicing, which is the process of joining different combinations of exons to produce different mature mRNA sequences from the same primary transcript (Fig. 2). The ability to generate a variety of exon combinations from a single primary transcript through alternative splicing allows a single gene to encode multiple protein isoforms. By including particular exons, alternatively spliced mRNAs can encode protein isoforms with different membrane- or ligand-binding domains, altered covalent modification sites or compartmentalization signals, or modified protein or nucleic acid interaction surfaces. Alternative splicing also can down-regulate expression of a gene by introducing a premature stop codon into an mRNA that triggers nonsense-mediated mRNA decay.

Thus, alternative splicing is a fundamental aspect of post-transcriptional gene regulation with significant functional and biomedical implications. This series of minireviews explores recent advances in understanding mechanisms and regulation of alternative splicing and the critical roles that alternative splicing plays in coordinating gene expression with physiology.

The minireview entitled “Combinatorial Control of Exon Recognition” contributed by Klemens J. Hertel (University of California, Irvine) focuses on the parameters that determine initial exon recognition and how these factors combine to influence splicing outcomes (3). This minireview explains the mechanisms that ensure that exons are recognized with the precision needed to ensure proper mRNA decoding during translation but with the flexibility to allow expression of protein isoforms that are appropriate for specific biological contexts.

Amy E. House and Kristen W. Lynch (University of Texas Southwestern Medical Center) focus on the diversity of mechanisms for alternative splicing regulation in their minireview entitled “Regulation of Alternative Splicing: More than Just the ABCs” (4). These authors explore how signals within precursor mRNAs interact with RNA and protein components of the core splicing machinery and with auxiliary protein factors to allow regulation of alternative splicing at points throughout the splicing pathway from stepwise assembly of the spliceosomal complex on pre-mRNA through the second exon/intron cleavage step.

Stefan Stamm (University of Kentucky) explains the interplay between signal transduction pathways and the splicing...
mechanism in the minireview entitled “Regulation of Alternative Splicing by Reversible Protein Phosphorylation” (5). This minireview presents recent advances in understanding how various kinases and protein phosphatase I interact with splicing factors to integrate cellular signals with post-transcriptional gene regulation at the level of alternative splicing.

In the last minireview of the series, entitled “Genome-wide Analysis of Alternative Pre-mRNA Splicing,” Claudia Ben-Dov, Britta Hartmann, Josefin Lundgren, and Juan Valcárcel (Centre de Regulación Genómica, Barcelona, Spain) present a genome-wide view of alternative splicing (6). These authors explain how progress in elucidating patterns of alternative splicing enabled by advances in high-throughput technologies such as large-scale sequencing and splicing-sensitive microarrays provides deeper understanding of the prevalence, functional relevance, and regulation of alternative splicing and its significance for human disease.

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FIGURE 1. Precursor mRNA splicing pathway. Pre-mRNA splicing occurs through two sequential phosphate transesterification reactions. In the first chemical step, the 2'-hydroxyl of a unique branch-point adenosine within the intron carries out nucleophilic attack on the phosphodiester at the first splice site. This reaction cleaves the pre-mRNA at the exon/intron boundary to produce free Exon 1 and a lariat intermediate that contains the Exon 2 sequence and the intron with 2'-, 3'-, and 5'-ester linkages to the branch-point adenosine. In the second step, the 3'-terminal hydroxyl of Exon 1 carries out nucleophilic attack on the Exon 2/intron junction in a reaction that is the chemical reverse of the first step. The second step releases the intron in the form of a lariat and ligates the exons.

FIGURE 2. Alternative splicing. Exons that contain protein-coding sequences in the genome are indicated by colored rectangles. Precursor mRNAs contain protein-coding exon sequences separated by noncoding introns, which comprise ~90% of the primary transcript sequence. A single gene can give rise to a variety of mature mRNAs, which each contain a subset of exons that are then translated into different protein isoforms.