What is Alternative Splicing, and Why is it Important?

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Genetic information of an organism is stored in the genes, the functional subunits of the genome, arranged in the strands of the DNA double helix in the nucleus. This information is transcribed from DNA into a messenger RNA (mRNA) template by a process called transcription. However, in eukaryotes, before the mRNA can be translated into proteins, non-coding portions of the sequence, called introns, must be removed and protein-coding parts, called exons, joined by RNA splicing to produce a mature mRNA.

The discovery of alternative splicing

RNA splicing was first discovered in 1970s in viruses and subsequently in eukaryotes. Not long after, scientists discovered alternative patterns of pre-mRNA splicing that produced different mature mRNAs containing various combinations of exons from a single precursor mRNA. The first example of alternative splicing of a cellular gene in eukaryotes was identified in the IgM gene, a member of the immunoglobulin superfamily. Alternative splicing (AS) therefore is a process by which exons or portions of exons or noncoding regions within a pre-mRNA transcript are differentially joined or skipped, resulting in multiple protein isoforms being encoded by a single gene. This mechanism increases the informational diversity and functional capacity of a gene during post-transcriptional processing and provides an opportunity for gene regulation (**Figure 1**).

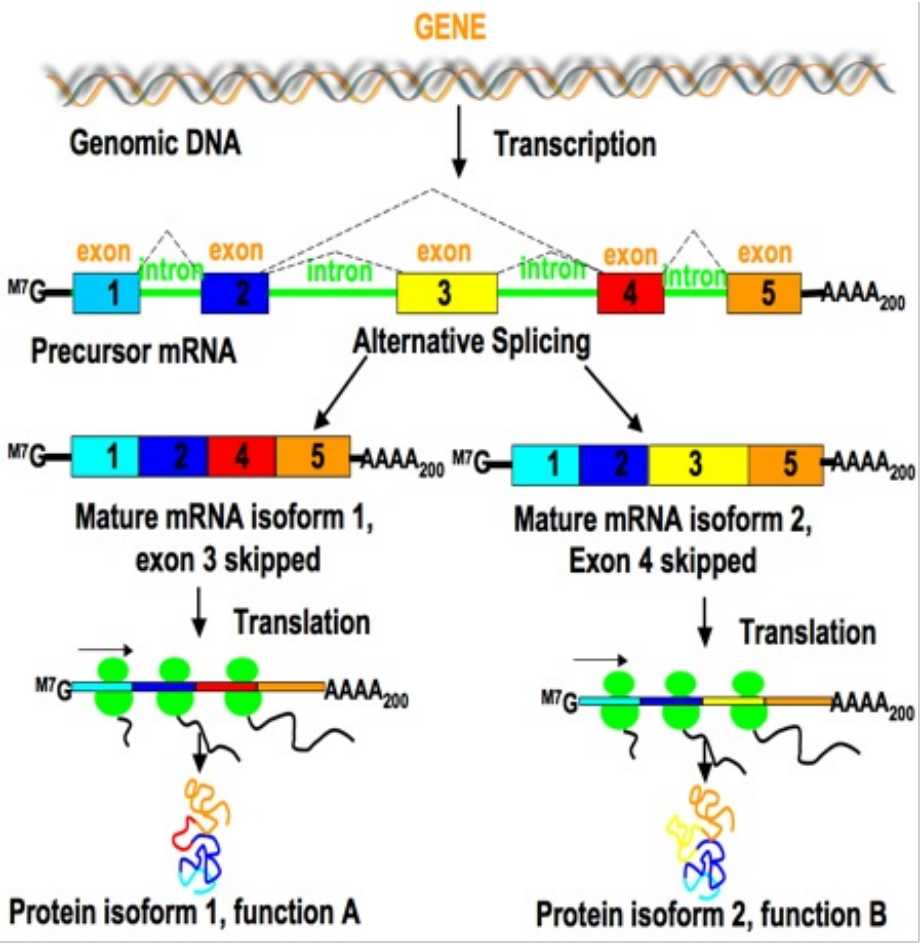

Figure 1. Alternative Splicing generates transcriptome diversity and provides an opportunity for gene regulation. Alternative splicing can generate mRNAs encoding proteins with different, even opposite functions. Figure used by permission.*

Alternative splicing generates a tremendous amount of proteomic diversity in humans and significantly affects various functions in cellular processes, tissue specificity, developmental states, and disease conditions.

The mechanism of alternative splicing

During alternative splicing, cis-acting regulatory elements in the mRNA sequence determine which exons are retained and which exons are spliced out. These cis-acting regulatory elements alter splicing by binding different trans-acting protein factors, such as SR (Serine-Arginine rich) proteins that function as splicing facilitators, and heterogeneous nuclear ribonucleoproteins (hnRNPs) that suppress splicing. Inhibition of silencing could be achieved sterically, when binding of splicing inhibitors to splicing silencers located in close proximity to splicing enhancers blocks the binding of snRNPs and other activator proteins or prevents the spliceosome assembly. The final decision to include or splice an alternative exon is thus determined by combinatorial effects, cellular abundance, and competitive binding between SR activators and hnRNP inhibitors. The outcome of alternative splicing depends on the stoichiometry and interactions of splicing activators and inhibitors as well as the steric conformation and accessibility of the splicing sites.

The importance of alternative splicing

It is thought that at least 75% of roughly 30,000 human genes undergo alternative splicing to encode two or more splice isoforms, with striking variation across tissue types and developmental stages. Recent advances in high-throughput technologies have facilitated studies of genome-wide alternative splicing. These studies estimate that greater than 95% of human multi-exon genes express multiple splice isoforms. Furthermore, there is evidence for alternatively splicing events that are often differentially regulated across tissues and during development, as well as among individuals and populations, suggesting that individual isoforms may serve specific spatial or temporal roles. Alternative splicing is known to be involved in the regulation of normal physiological functions as well as pathologies. For example, a number of alternatively spliced genes in immunity are known. Studies indicate that alternative splicing of CD44, a protein involved in T cell homing with 10 variable cassette exons and six distinct protein isoforms, is crucial for T cell function. The variable exons of CD44 all encode portions of the membrane-proximal extracellular domain of the protein, and the presence of some of the variable exons has been shown to increase the association of CD44 with various proteins. Isoform expression has been shown to be activation dependent, such that the naive T cells mainly express the smallest CD44 isoform that lacks all variable exons, whereas activated T cells express multiple CD44 isoforms, indicating that CD44 alternative splicing is important for activation.

While these examples demonstrate the utility of alternative splicing in humans, the scope and exact role of this regulatory mechanism still remains to be investigated on a genome-wide scale. Current technological advances suggest that alternative splicing is more widespread than initially thought and is likely to be involved in a number of human pathologies.

Stay tuned for the next article in this series, when we'll talk about what alternative splicing means for your experiments.

* "Post-transcriptional mechanisms of gene regulation and information control in immunity", by *Grigoryev, Yevgeniy A.*, Ph.D., **THE SCRIPPS RESEARCH INSTITUTE**, 2011, 282 pages; 3488985, http://gradworks.umi.com/34/88/3488985.html