Preface

Splicing of the primary RNA transcript, i.e., removal of introns and joining of exons to produce mature mRNAs competent for translation into proteins, is a quasi-systematic step of gene expression in higher eucaryotes. The full biological significance of splicing has not been appreciated until it was discovered that alternative splicing, that process which allows a primary transcript to yield several distinct mRNAs and consequently several different proteins, is a widespread mechanism. Although we had already recently published in this same series (2003, Volume 31 Ph. Jeanteur, ed.) a book dedicated to the regulation of alternative splicing, we thought it timely to follow up in this direction by focusing on pathological and therapeutic aspects.

Interestingly, estimates of the proportion of human genes that can undergo at least one alternative splicing event increased from about 50%, as mentioned in the preface to this previous book, to 75% in most recent ones, suggesting that alternative splicing is the rule rather than the exception for mammalian genes. An obvious benefit is the creation of protein diversity but there is another side to the coin. The flexibility required for the large repertoire of potential alternative splice sites that goes with a high level of sequence degeneracy at splice junctions has two important consequences.

The first one is that point mutations, or even "neutral" polymorphisms, can be sufficient to abrogate weak alternative sites or, conversely, to create new ones with pathological consequences. It should be noted that most current state-of-the-art transcriptomics is limited to a global quantitative assessment of mRNA sequences originating from a given transcription unit and overlooks the qualitative diversity generated by alternative splicing. Many ongoing studies now address this issue to provide the basic knowledge of alternative splicing events essential for complex multigenic diseases like cancer. The paper by Bracco et al. describes methods and core facilities for quantitation of splice variants expression while that by Novoyatleva et al. examines the generality of missplicing as a cause of human disease.

The second one is that additional information is required to define splice sites to be used among a wealth of cryptic ones, especially in very large introns. This information is provided by regulatory sequences recognized by protein factors. Both these types of elements define potential therapeutic targets: anti-sense strategies are an obvious approach to target RNA sequences in the pre-messenger that has been examined for quite some time already. A detailed account of this type of strategy is given by Garcia-Blanco. In contrast, targeting protein factors by small chemicals is much more novel and is specifically addressed in the chapter by Soret, Gabut, and Tazi.

Targeting human monogenic hereditary diseases offers a wealth of distinct situations where specific therapeutic strategies can be envisioned

mostly at the proof-of-concept stage. The following chapters address, albeit not exhaustively, various pathological situations where splicing aberrations have been well characterized: neurological conditions involving missplicing of genes coding tau proteins (Andreadis), spinal muscular atrophy (Wirth et al.) or myotonic dystrophy (Kuyumcu-Martinez and Cooper), muscular dystrophy (Wilton and Fletcher), premature aging phenotypes (De Sandre-Giovannoli and Levy) of cystic fibrosis (Nissim-Rafinia and Kerem).

Although no chapter is exclusively focused on cancer, the number of gene alterations involved in the development of any single solid tumor is so high and diverse that there are many opportunities for missplicing events. In the face of such a complexity, therapeutic approaches based on redirecting alternative splicing will probably come in the longer term after proof-of-concepts have been obtained in the better-defined and simpler situations offered by the monogenic diseases mentioned above.

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