Chapter XVII
Alternative Splicing and Disease

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ABSTRACT

Alternative splicing is an important part of the regular process of gene expression. It controls time and tissue dependent expression of specific splice forms and depends on the correct function of about 100 splicing factor proteins of which many are the product of alternative splicing itself. It is therefore not surprising that even minor sequence disturbances can cause mis-spliced gene products with pathological effects. We survey some common diseases which can be traced back to a malfunction of alternative splicing including cystic fibrosis, beta-thalassemia, spinal muscular atrophy and cancer. Often cancer also results from even mis-spliced splicing factors leading to randomly spliced non-functional isoforms of several genes.

INTRODUCTION

The hypotheses of Beadle and Tatum (1941), that one gene codes for a single uniquely defined protein, has been disproved many times during the past 30 years by discovering a number of ways how one single gene gives rise to different gene products. The differences may result at the transcriptional level, during RNA pre-processing, m-RNA translation or post-translational protein processing and folding. A recent review by Boeckmann et al. (2005) describes the most important ways of gene product modification.

Alternative splicing increases the diversity of gene products by deriving different final mRNAs from the same pre-mRNA transcript by alternative definition of introns which are spliced out to derive the

final mRNA used for translation. But whereas the process of splicing, the interaction of different pro-teins forming the spliceosome and removing an intron, is investigated and described in great detail by Staley and Guthrie (1998), Will and Luhrmann (2001), Nilsen (2003) and Tazi et al. (2005), the process of how the splice sites are selected is not yet fully understood.

For each single splicing reaction the spliceosome is newly formed in interaction with the pre-mRNA and acts in two basic steps as seen in Figure 1. Cleavage of the donor site and ligation of the 5' end of the intron to the branch side (step 1) is followed by removal of the intron by cleavage of the acceptor site, the 3' end of the intron, and the ligation of the neighboring exons (step 2). About hundred interacting molecular splicing factors, many of them are snRNPs, are known to steer this complex process. Four important signals on the pre-mRNA intron are essential to attract these splicing factors to form the spliceosome and to perform splicing. Theses are the donor site at the 5' end of the intron, the branch point with the nucleotide A located about 17-40 nucleotides upstream of the acceptor site, the polypy-rimidine region, and the acceptor site itself which defines the 3' end of the intron. Exonic and intronic splicing enhancer or silencer sequence motifs additionally affect attraction of all splicing factors. If hit by mutations, all changed sequence signals are prone to change the pattern of splicing and to seriously affect protein expression, eventually causing death and disease.

Krawczak et al. (1992) reported about 15% of all known diseases causing point mutations to directly hit splice sites. This early publication did not consider mutations of exonic or intronic splicing enhancer or silencer signals known to be very important today. The Human Gene Mutation Database published by Stenson et al. 2003 contains 61106 registered mutations of which 5822 affect splicing events. From this set 3633 are point mutations of the GT donor and the AG acceptor splice sites. Skipped exons induced by

Figure 1. The two major steps of splicing; cleavage at the donor site (5' splice site) and forming the lariat structure (step 1) followed by removing the intron and ligating the exons (step 2)
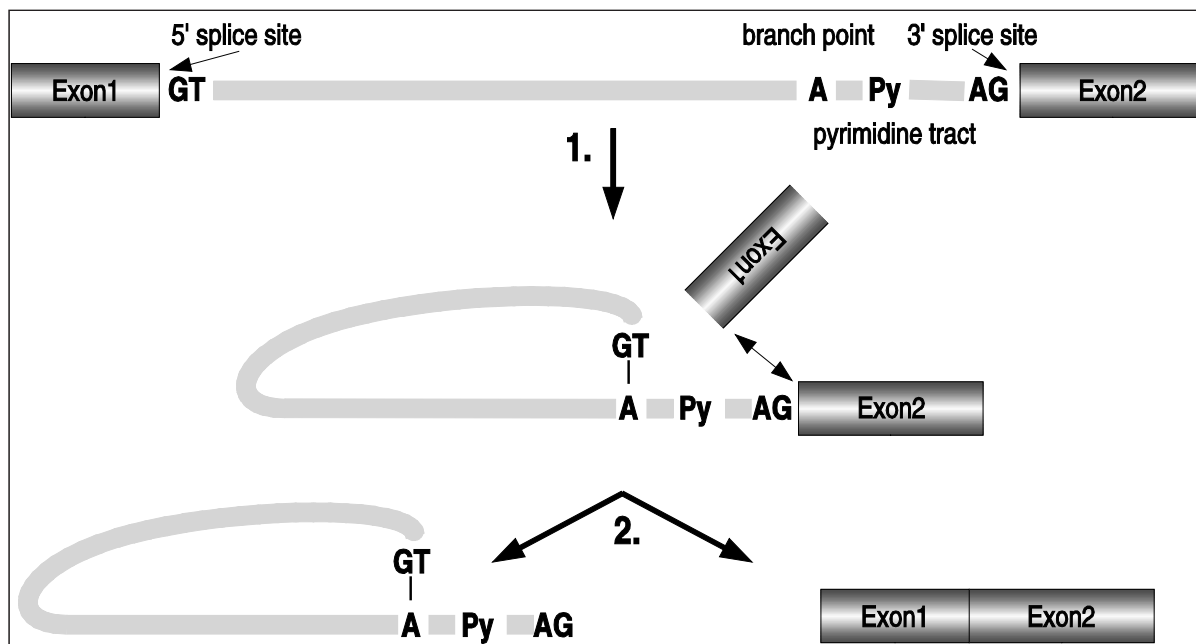
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