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Review

Alternative RNA splicing and gastric cancer

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ABSTRACT

Alternative splicing (AS) linked to diseases, especially to tumors. Recently, more and more studies focused on the relationship between AS and gastric cancer (GC). This review surveyed the hot topic from four aspects: First, the common types of AS in cancer, including exon skipping, intron retention, mutually exclusive exon, alternative 5 ' or 3′ splice site, alternative first or last exon and alternative 3′ untranslated regions. Second, basic mechanisms of AS and its relationship with cancer. RNA splicing in eukaryotes follows the GT-AG rule by both *cis*-elements and *trans*-acting factors regulatory. Through RNA splicing, different proteins with different forms and functions can be produced and may be associated with carcinogenesis. Third, AS types of GC-related genes and their splicing variants. In this paper, we listed 10 common genes with AS and illustrated its possible molecular mechanisms owing to genetic variation (mutation and /or polymorphism). Fourth, the splicing variants of GC-associated genes and gastric carcinogenesis, invasion and metastasis. Many studies have found that the different splicing variants of the same gene are differentially expressed in GC and its precancerous diseases, suggesting AS has important implications in GC development. Taking together, this review highlighted the role of AS and splicing variants in the process of GC. We hope that this is not only beneficial to advances in the study field of GC, but also can provide valuable information to other similar tumor research.Although we already know some gene splicing and splicing variants play an important role in the development of GC, but many phenomena and mechanisms are still unknown. For example, how the tumor microenvironment and signal transduction pathway effect the forming and function of AS? Unfortunately, this review did not cover the contents because the current study is limited. It is no doubt that clarifying the phenomena and mechanisms of these unknown may help to reveal the relationship of AS with complex tumor genetic variation and the occurrence and development of tumors.

Contents

Abbreviations: AS, alternative splicing; pre-mRNAs, primary gene transcripts; GC, gastric cancer; CS, constitutive splicing; snRNPs, small nuclear ribonucleoproteins; U2AF, U2 small nuclear ribonucleoproteins auxiliary factor; ESE, exonic splicing enhancer; SRps, serine/arginine-rich proteins; hnRNP, heterogeneous nuclear ribonueleoprotein; SNPs, single nucleotide polymorphisms; SRSF, serine/arginine-rich splicing factor; ASVs, alternative splicing variants; CD44v6, the CD44 splice variant 6.

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1. Introduction

Alternative splicing (AS) involves the organization of exons from primary gene transcripts (pre-mRNAs) in different arrangements to produce structurally and functionally distinct mRNA and protein variants. AS is a basic mechanism of gene expression control in eukaryotes, and enables increased complexity of gene expression, facilitates higher efficiency of transcription, and promotes protein diversity. AS may also be involved in the pathogenesis of many diseases.

In 1977, Phillip Sharp and Richard Roberts discovered the concept of "split genes" almost simultaneously [2–4]. Since then, AS has been found to play important roles in human diseases such as Mediterranean anemia [5], type II diabetes [6], Alzheimer's disease [7], Duchenne–Aran disease [8], retinitis pigmentosa [9], and cancer [10–14]. Many studies have associated AS with the occurrence, development, and metastasis of multiple cancer types. This suggests that AS could be a useful target for cancer diagnosis, treatment, and prognosis prediction [15].

Gastric cancer (GC) is a common malignancy, having the fourth-highest incidence and the second-highest mortality of cancers worldwide [16]. GC results from complex interactions between host and environmental factors, involving multifactorial and multistep processes that are influenced by genetic heterogeneity, a complexity of phenotypic characteristics, and racial diversity [17]. Multiple splice variants have been found associated with GC in recent years [18,19]. In this review, we discuss AS and its regulation, provide examples of several genes that undergo AS and are associated with GC, and explain how splice variants can alter the biological behavior of GC.

2. Types and regulation of alternative splicing

2.1. Types of alternative splicing

Eight common types of alternative transcript events have been described: exon skipping, intron retention, mutually exclusive exon, alternative 5′ splice site (A5SS), alternative 3′ splice site

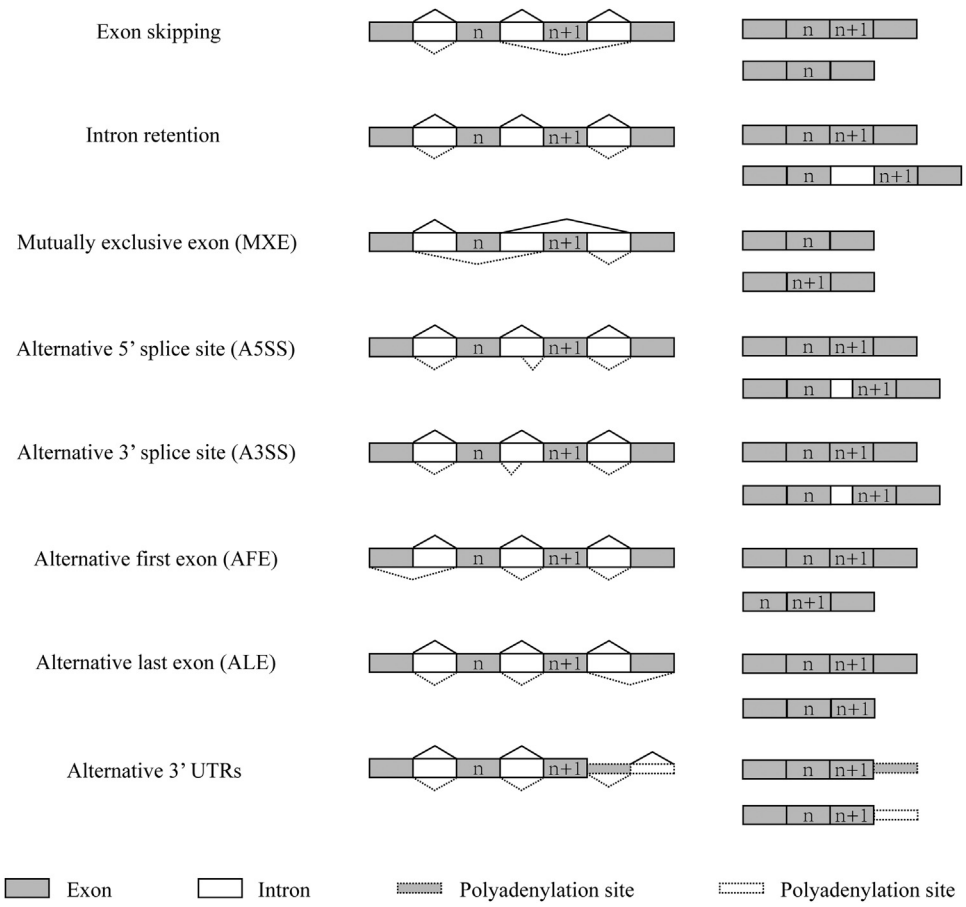

Fig. 1. Types of pre-mRNA alternative splicing. Eight common types of alternative transcript events and the mode of alternative splicing variants are shown.