Golestan University of Medical Sciences

Jorjani Biomedicine Journal

Online ISSN: 2645-3509

Role of Aberrant Alternative Splicing in Cancer

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Article Type:

Letter to Editor

Article History:

Received: 15 Mar 2021
Revised: 30 Mar 2021
Accepted: 1 Apr 2021

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DOI: 10.29252/jorjanibiomedj.9.2.1

Abstract

Alternative splicing can alter genome sequence and as a consequence, many genes change to oncogenes. This event can also affect protein function and diversity. The growing number of study elucidate the pathological influence of impaired alternative splicing events on numerous disease including cancer. Here, we would like to highlight the significant role of alternative splicing in cancer biology and emphasize the necessity for conducting more research into target alternative splicing as a treatment for cancer.

Keywords: cancer, Alternative splicing[MeSH]

Highlights

95% of human genes transcribe more than one transcript and generate variant protein isoforms tumors have irregular splicing pattern alternative splicing process are common occurrence and can be used as novel therapeutic biomarkers.

Statement

I would like to highlight the significance of role of alternative splicing in cancer.

The eukaryotic genome is well-defined by the existence of small exons between long non-coding introns. After splicing, introns are discarded and exons are joined together. RNA splicing is a category of RNA processing in which a newly generated precursor messenger RNA (pre-mRNA) transcript is altered into a mature messenger RNA (mRNA) and, throughout this process; pre-mRNAs convert to mature mRNAs via intron excision and exon ligation. RNA splicing occurs either through or instantly after transcription in almost all mammalian cells within the nucleus (1, 2). After alternative splicing, around 95% of human genes transcribe more than one transcript and generate variant protein isoforms with identical or completely altered functions (3). A significant cause of illnesses is due to imperfections in mRNA splicing (4). It has been illustrated that tumors have irregular splicing pattern in comparison with normal tissues (5). Apparently the unbalanced expression of splicing variants or improper expression of the right isoforms is the part of cancer cell biology (6). Moreover, transcriptome sequences have demonstrated that gene mutations aligned with cancer-specific alternative splicing process are common occurrence and can be used as novel therapeutic biomarkers (7). Proliferation / Differentiation in the body is affected by numerous genes which are involved in splicing regulation (2). Tumor-associated genes may express splice isoforms that either favor or impede the development of cancer cells. For instance, numerous apoptosis regulators can express proapoptotic or antiapoptotic isoforms (8). A broadly cited example is Bcl-x, one of the member of Bcl-2 family proteins, which controls the permeability of the mitochondrial outer membrane. Even though the Bcl-xS splice isoform is proapoptotic, the Bcl-xL isoform is antiapoptotic since it stops mitochondrial constituents from being released that will lead to apoptosis (9). An entire cancer-associated phase, such as the epithelial to mesenchymal transformation (EMT), may also be affected consistently by aberrant alternative splicing (10). While the list of EMT-related genes that have alternative splicing variants related with cancer development is very extended (11). We would like to emphasize limited number of the most significant and well-studied events up to date : i exon 11 skipping E-cadherin, a cell-to-cell adhesion molecule that is down-regulated in EMT, brings about a splice variant that is up-regulated in great number of cancers and is contrary associated with wild-type expression (12). (ii) CD44, a transmembrane glycoprotein implicated in cell movement and invasion, has numerous variable exons lead to a multitude of splice isoforms (13) (iii) a remarkable example of a splice isoform used as a signaling mediator rather than last effector is Rac1b, whose expression is stimulated by metalloproteinase-3 and in turn up-regulates Snail and induces EMT (14).

During past decades there has been a noticeable increase in the number of publications that highlight the role of alternative splicing in cancers. It seems that alterations in the expression and activity of

critical splice factors or their modifiers (factor kinases and phosphatases) could lead to malignant cellular transformation. Therefore, a systemic deregulation of alternative splicing should be regarded as another characteristic of neoplasm. Against the evidence which reveals the connection between cancers and alternative splicing, the pharmaceutical sector has yet to completely apply the potential of manipulating alternative splicing for anti-cancer therapies. In this regard it is a very good idea that future research investigate the possibilities under the light of splicing modification in diverse type of cancers and funders invest more resources in this basic research.

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How to cite:

khorasani M, Alaei M, shojaee M. Role of aberrant Alternative Splicing in cancer. *Jorjani Biomedicine Journal*. 2021; 9(2): 1-4.