Alternative Splicing in Breast Cancer 23

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Abstract

Alternative splicing of pre-mRNA is an essential event that leads to protein diversity and regulation of the cellular processes in mammals. With the advent of the next generation sequencing technologies, the role of alternative splicing is gaining a momentum. Regulation of alternative splicing is a complex process involving the core spliceosome machinery and multiple regulatory factors that enable the tightly controlled splicing of introns/exons. Any aberrant alteration in this process can result in diseases such as cancer. Indeed, accumulating evidence suggests that alternative splicing plays an important role in all hallmarks of cancer including proliferative signaling, resisting cell death, inducing angiogenesis, and activating invasion and metastasis. These changes may occur due to mutations or altered expression levels of key regulatory genes of spliceosome machinery or splicing factors. In this review, we summarize recent findings that have implicated the critical role of alternative splicing in breast cancer and discuss current understandings and its potential utility in breast cancer.

Keywords

Alternative splicing · Breast cancer · Alternative splicing events · Spliceosome machinery · Splicing factors

23.1 Introduction

The splicing mechanism is the process in which introns are separated from the exons; the latter go on to form mature mRNAs. Alternative splicing (AS) is a mechanism by which selective inclusion/ exclusion of exons and introns during splicing of the pre-mRNAs leads to the production of more than one isoform. It plays an

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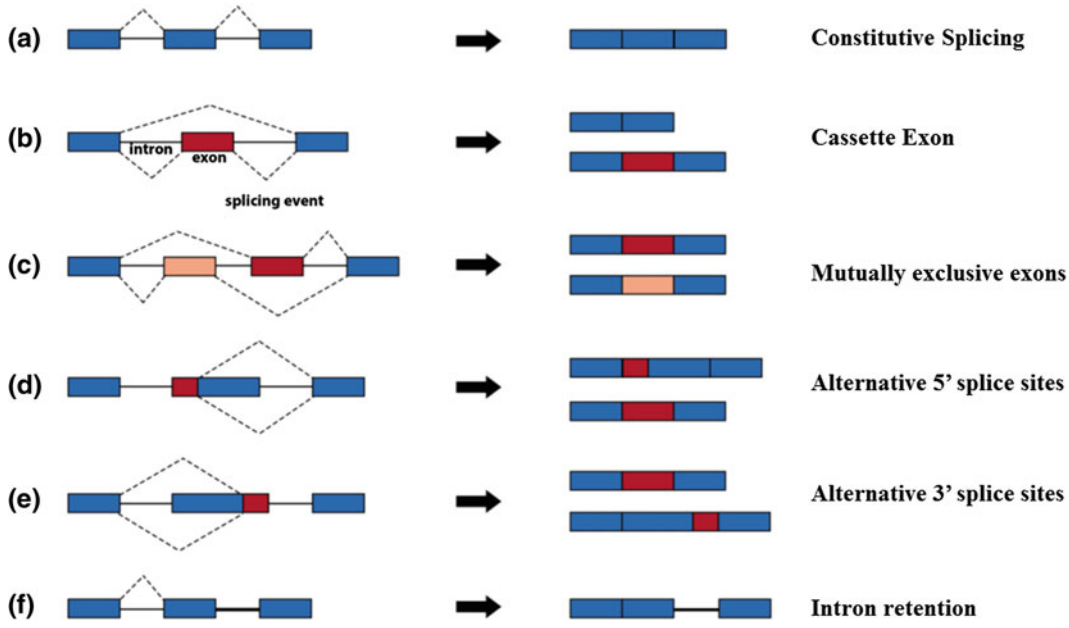

Fig. 23.1 Main alternative splicing events **a** Constitutive splicing; **b** cassette alternative exon; **c** mutually exclusive exons; **d** alternative 5′ splice site; **e** alternative 3′ splice site and **f** intron retention

important role in regulating cellular processes in a tissue-specific manner (Black 2003; Pan et al. 2008). In particular, recent high-throughput sequencing technologies revealed that about 92–94 % of human genes are alternatively spliced (Blencowe 2006; Pan et al. 2008; Wang et al. 2011; Irimia and Blencowe 2012). In this process, inclusion or exclusion of exons or portions of exons or introns within a pre-mRNA transcript can result in multiple protein isoforms being encoded by a single gene. This process is tightly regulated in normal cells. Most exons are constitutive, being always spliced or included in the mature mRNA (Fig. 23.1a). However, aberrant regulation of AS may result in several diseases including cancer. The major alternative splicing patterns or events (Fig. 23.1b–f) are grouped into five types. If an exon is sometimes excluded or included, this indicates that the exon expression is regulated and also termed as cassette exon (Fig. 23.1b). In some cases, cassette exons are mutually exclusive (Fig. 23.1c); this might hold true for more than one exons. Exons can be longer or shorter affecting their splice sites. Alterations in 5′-terminal exons result in alternative promoter sites (Fig. 23.1d). On the other hand, alternative splicing of the 3′-terminal exons can lead to alternative polyadenylation sites (Fig. 23.1e). In addition, some regulatory events result in inclusion of an intron, a splicing pattern called intron retention (Fig. 23.1f).

Aberrant alternative splicing events in cancer may impact the alteration of genes and proteins both at the expression and functional level. These events are regulated by a complex process involving the core spliceosome machinery and multiple regulatory factors (Irimia and Blencowe 2012). A schematic was depicted in Fig. 23.2 to summarize the key regulatory players at the exon level.

The core spliceosome machinery is a large dynamic macromolecular RNA-protein complex composed of five small nuclear RNAs (snRNAs) and over 100 associated proteins. The association of these small RNAs with the protein factors comprise the RNA-protein-complex called small nuclear ribonucleic proteins (snRNPs). Splice sites of a gene are the binding sites for the spliceosome machinery. Splicing factors (SFs), a subset of RNA binding proteins (RBPs), control

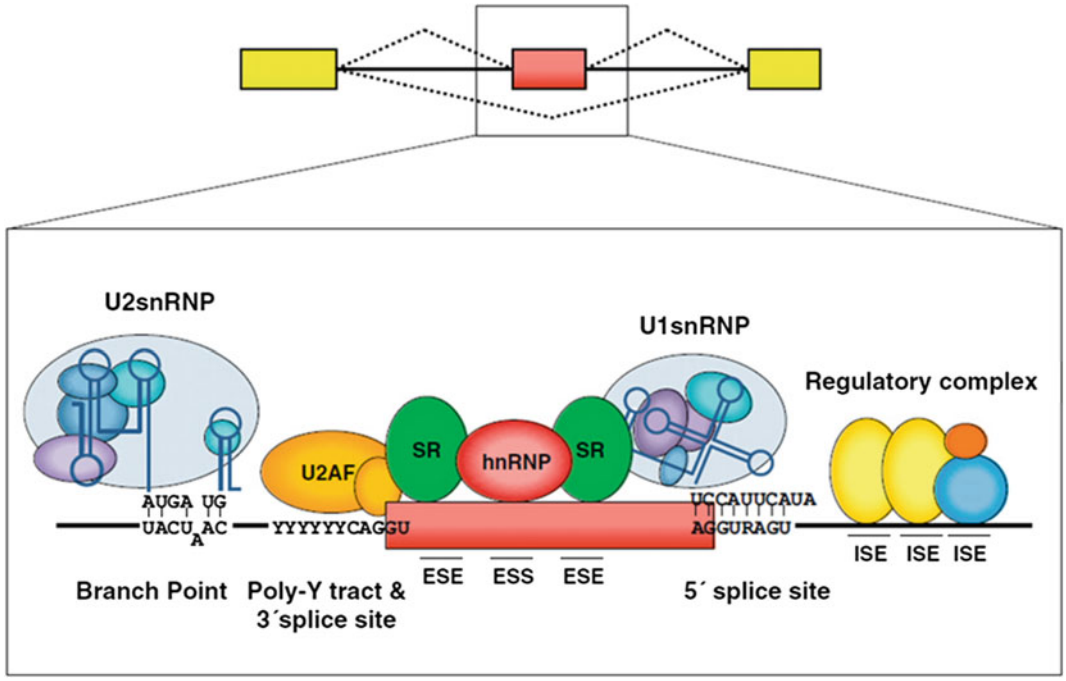

Fig. 23.2 Schematic representation of core spliceosomal components and its binding proteins. Splicing factors can either promote or repress splice site selection depending on the location of their binding sites with respect to splicing signals. *ISE* Intronic splicing\enhancer; *ISS* Intronic splicing silencer; *ESE* Exonic splicing enhancer; *ESS* Exonic splicing silencer; SR, Ser/Arg-repeat containing protein; *hnRNP* Heterogeneous ribonucleoprotein (hnRNP); and U2AF, U2 snRNP auxiliary factor. Adapted from Irimia and Blencowe Current Opinion in Cell Biology

the choice of splice sites and impact the recruitment of the spliceosome to splice sites (Chen and Weiss 2015; Liu and Cheng 2013; Zhang and Manley 2013; Cartegni et al. 2002; Irimia and Blencowe 2012). SFs exert their effect by binding specific RNA sequences, or motifs, known as exonic splicing enhancers (ESEs), exonic splicing silencers (ESS), intronic splicing enhancers (ISEs) and intronic splicing silencers (ISSs) (Cartegni et al. 2002; Irimia and Blencowe 2012). Bound SFs can either activate or inhibit the interaction between spliceosome and pre-mRNAs (McManus and Graveley 2011). Some of them can have dual function based on the location of the motifs they bind. Several splicing factors have been well established in humans (Venables et al. 2008; Twyffels et al. 2011), and categorized into two major families: serine-arginine protein (SR) and heterogeneous ribonucleoprotein (hnRNP). SRs usually promotes splicing, while hnRNPs usually inhibit the splicing process by binding to silencer sequences (Cartegni et al. 2002; David and Manley 2010; Irimia and Blencowe 2012). The decision of alternative splicing also requires cis-acting RNA splicing regulatory elements (SREs) which influence the splicing of exons/introns in the mRNA (Cho et al. 2014). Cis-acting regulatory elements are located on 200–300 nucleotides adjacent to observed splice sites. They also can alter splicing by binding to different *trans*-acting proteins which are remotely located and act as splicing enhancers or silencers. The ultimate decision for splicing regulation is combinatorial and context-dependent based on the cooperation and competition of splicing factors. All these factors increase the diversity and functional capacity of a gene during post-transcriptional processing and exert tight gene regulation.

Mutations of SF genes or alterations in expression levels of the proteins may contribute to aberrant AS. These proteins are guided by additional factors that can also interact with mRNAs at specific motifs to regulate the inclusion or exclusion of exons in the final transcript. Alterations in the levels and activity of these SFs thus provide another means of AS deregulation. Changes in splice sites or motifs of SFs in a given gene may also affect the alternative splicing. Besides binding to SFs, other characteristics of the protein may be altered including ligand binding, enzymatic activity, subcellular localization, and/or protein-protein interactions. This further may alter many processes that can switch cells from normal to malignant phenotype.

Deregulation of alternative splicing due to these factors may result in cancers including breast cancer. Several studies have revealed splice variants specific to tumors in several cancers including breast cancer which impact hallmarks of cancer such as proliferation, apoptosis, cell-cycle-control, metabolism, angiogenesis, and invasion (Chen and Weiss 2015; Dutertre et al. 2010; Germann et al. 2012; Swami et al. 2009; Liu and Cheng 2013; Oltean and Bates 2014; Venables et al. 2008; Zhang and Manley 2013). In this chapter, we will review the regulatory factors and alternative splicing events in breast cancer, its promises and limitations in the clinical practice.

23.2 Alternative Splicing in Breast Cancer

23.2.1 Mutations in RNA Splicing Factors

Recent next-generation sequencing technologies have revealed the presence of somatic mutations in the components of spliceosome machinery and splicing factors (Malcovati et al. 2011; Papaemmanuil et al. 2011; Yoshida and Ogawa 2014; Yoshida et al. 2011). These mutations mostly involve components that are involved in the initial steps of pre-mRNA splicing, such as 3' splice-site recognition and occur in a mutually exclusive manner. Among the mutated splicing factors, *U2AF1, SRSF2, SF3B1, and ZRSR2* genes were common mutational hotspots in myeloid neoplasms such as myelodysplastic syndrome (MDS). Although these mutations were frequent (45–85 %) in myeloid neoplasms, they exist in other hematologic malignancies and solid tumors, albeit at different frequencies (Quesada et al. 2012; Ramsay et al. 2013; Scott and Rebel 2013; Wang et al. 2011; Yoshida and Ogawa 2014). Mutations in splicing factor 3b, subunit 1 (*SF3B1*) occurred in 15 % of chronic lymphocytic leukemias (CLLs) (Quesada et al. 2012), and in solid cancers such as uveal melanomas (9.7 %) (Furney et al. 2013; Harbour et al. 2013), pancreatic cancers (4 %) (Biankin et al. 2012), and breast cancers (2 %) (Cancer Genome Atlas 2012; Stephens et al. 2012). Mutations in other splicing genes, such as the U2 small nuclear RNA auxiliary factor 1 gene (*U2AF1*), the serine/arginine-rich splicing factor 2 gene (*SRSF2*), and the U2 small nuclear ribonucleoprotein auxiliary factor 35 kDa subunit-related protein 2 gene (*ZRSR2*), have also been identified in a lower frequency than *SF3B1* mutations (Yoshida and Ogawa 2014; Yoshida et al. 2011).

SF3B1 is the only splicing factor that has been reported to be among the top 35 mutated genes using next-generation sequencing on 510 breast tumors (Cancer Genome Atlas 2012). However, the frequency was low (2 % of all tumors). Of the 15 non-silent mutations, the majority were missense mutations. Patients with estrogen receptor ER+ and HER-2+ subtypes harbored the majority of these mutations. The *SF3B1* was also among the 18 significantly mutated genes in untreated ER+ breast tumors from 77 patients accrued from two neo-adjuvant aromatase inhibitor clinical trials (Ellis et al. 2012). A recent study re-analyzed the mutations in spliceosomal components using public exome and whole genome sequencing data (Maguire et al. 2015). Their data also confirmed that *SF3B1* was the most commonly mutated gene in the spliceosomal complex in breast cancer, in particular in ER + breast tumors. Furthermore, *SF3B1* mutations were associated with differential splicing of genes in ER+ breast tumors including

TMEM14C, *RPL31*, *DYNL11*, *UQCC*, *ABCC5* and *CRNDE*. Some of these splice variants have also been observed in other cancers with *SF3B1* mutations (Furney et al. 2013).

23.2.2 Altered Gene Expression Levels in RNA Splicing Factors

Accumulating evidence implicates that aberrant expression of genes regulating alternative splicing is another factor that impacts the alternative splicing events in breast cancer. In our study, the splicing factor *SF3B1* was upregulated in acquired endocrine resistant models as well as in cases with Onco*type* DX high-recurrence scores (Gokmen-Polar et al. 2015). However, we did not observe any prognostic correlation of *SF3B1* expression in our analyses using breast tumors from TCGA and Affymetrix microarray datasets. Interestingly, splicing factor 3b, subunit 3 (*SF3B3*), a SF3B subunit interacting with SF3B1, was also upregulated in these models. As in the case of *SF3B1*, high expression of *SF3B3* correlated with the Onco*type* DX high-recurrence cases. In contrast to *SF3B1*, high expression of *SF3B3* correlated with poor prognosis in patients with ER+ breast cancer.

Other alterations in expression of splicing factors or components of spliceosome machinery, have also been reported in breast cancer (Grosso et al. 2008). These alterations are assumed to affect the splicing pattern of other genes that are involved in tumor development and progression. Alternatively, they might act as oncogenes. For example, splicing factor SF2/ASF is upregulated in various human tumors, and impacts alternative splicing of the tumor suppressor *BIN1* and the kinases *MNK2* and *S6K1*. While *BIN1* isoforms lost their tumor-suppressor activity, the *MNK2* isoform promotes MAPK-independent eIF4E phosphorylation and the *S6K1* isoform has demonstrated oncogenic properties (Karni et al. 2007).

Heterogeneous ribonucleoproteins (hnRNPs) are another major group of splicing factors that are involved in different steps of pre-mRNA processing and cellular functions (Carpenter et al. 2006; Grosso et al. 2008). The hnRNP proteins are also involved in various biological processes required for tumor progression. Splicing factor *SRSF1* is upregulated in human breast tumors, and its overexpression promotes transformation of mammary cells (Anczukow et al. 2015). A recent study reported the expression profile of ten splicing factors (both SRs and hnRNPs) and eight RNA-binding proteins in breast cancer cells (Silipo 2015). Taken together, these studies emphasize that alterations (mutations or altered expression) in core spliceosomal complex genes and its associated genes may contribute to aberrant alternative splicing in breast cancer progression.

23.3 Alternative Splicing Events in Breast Cancer

Aberrant alternative splicing events have been associated with the initiation and progression in breast cancer (Dutertre et al. 2010). We will enumerate some examples for each type of alternative splicing events and emphasize their contribution in breast cancer development and progression (Table 23.1).

23.3.1 Cassette Exons

23.3.1.1 Exon Skipping

The breast cancer susceptibility genes, *BRCA1* and *BRCA2*, are good illustrative examples for exon skipping. *BRCA1* RNAs from most tumors show splicing alterations (Bonnet et al. 2008; Easton et al. 2007; Lovelock et al. 2006; Tommasi et al. 2008; Caux-Moncoutier et al. 2009; Anczukow et al. 2008). For example, the full-length *BRCA1* gene encodes 24 exons. Exon 18 skipping in *BRCA1* can enhance (SF2/ASF) or inhibit (hnRNPA1 and hnRNPH/F) binding of splicing factors to the mRNA (Liu et al. 2001; Millevoi et al. 2010). In addition, skipping of exon 11 has been associated with cell death and proliferation. Besides exon 11 and 18 skipping, other splice variants of *BRCA1* have been

Table 23.1 Aberrant alternative splicing events in breast cancer

Gene name	Alternative splicing event	References
BRCA1	**Cassette exon** Skipping of exon 18 and exon 11 IRIS isoform- skipping of multiple exons	Liu et al (2001), Millevoi et al. (2010), Tammaro et al. (2012), Ahlborn et al. (2015), Romero et al. (2015)
CD44	**Cassette exon** Inclusion of variable exons 9 (exon 6–14) in humans	Inoue and Fry (2015), Olsson et al. (2011), Screaton et al. (1993)
FGFR2	**Mutually exclusive exons** FGFR2 IIIb or IIIc	Fletcher et al (2013)
HER-2	**Intron retention** Herstatin-retention of intron 18, p100-retention of intron 15	Jackson et al. (2013), Doherty et al. (1999), Aigner et al. (2001)
Bcl- 2-like *Bcl-xL versus* *Bcl-xS*	**Alternative 5′ splice sites** 5′ splice sites in exon 2	Boise et al. (1993), Adams and Cory (2007), Akgul et al. (2004)
VEGF	**Alternative 3′ splice sites** Proximal/distal 3′ splice site	Biselli-Chicote et al. (2012), Harper and Bates (2008), Nowak et al. (2008)

identified including *BRCA1* full length (inclusion of all exons), partial skipping of exon 11, skipping of exons 9, 10, and partial skipping of exon 11 and IRIS isoforms (skipping of exons 12–24, but retaining a short segment from intron 11) (Tammaro et al. 2012). Additional studies are emerging regarding novel *BRCA1* variants inducing splicing defects (Ahlborn et al. 2015; Romero et al. 2015; Tammaro et al. 2012). However, the clinical significance of these variants and the relevance of these mutations are unknown. With the exception of IRIS, the importance of other *BRCA1* splicing events in cancer development needs to be further determined.

23.3.1.2 Exon Inclusion and Complex Splicing Patterns

CD44, a cell surface receptor, has been gained attention as a breast cancer stem cell marker and chemo-resistance and is under extensive study as a therapeutic target. CD44 has been used as biomarkers to identify and characterize the breast cancer stem cell (CSC) phenotype (Al-Hajj et al. 2003; Shipitsin et al. 2007). Breast cancer cells with *CD44+/CD24-* subpopulation express higher levels of pro-invasive genes and have highly invasive properties specific to ER− cell lines (Sheridan et al. 2006). However, overexpression of *CD44* has been implicated in both tumor suppression and progression (Horak et al. 2008). Relevance of *CD44* in breast carcinomas is still unclear in part due to the complex splice pattern observed in breast cancer.

CD44 pre-mRNA contains 19 exons, 9 of which are alternatively spliced (Loh et al. 2015). Based on the inclusion of variable exons, a number of isoforms are generated. The standard isoform of *CD44 (CD44s)* contains 10 constant exons (exons 1–5 and 15–20), whereas the variant *CD44v* isoforms includes exons 5a and 14 (exon v1–v10). Exon 5a (v1) is not expressed in humans (Screaton et al. 1993; Inoue and Fry 2015). Several groups have assessed the role of *CD44* in breast cancer progression in vivo using mouse models (Brown et al. 2011; Warzecha et al. 2009). Different splice variants of *CD44* have also been associated with different subtypes of breast cancer (Olsson et al. 2011). High expression of standard (CD44s) isoform was

present in tumors with strong HER-2 staining and in a subgroup of basal-like tumors. Expression was associated with ALDH1 expression. In contrast, other *CD44* variants are associated with luminal A subtype and with tumors with high CD44+/CD24- subpopulation. In breast cancer cell lines, the untransformed (MCF10A) and non-metastatic (MCF-7) cell lines harbor different isoform pattern (*CD44v6* isoform, which includes all of the v6-containing mRNA isoforms- c5v6v7v8v9v10c6) compared to metastatic MDA-MB-231 cell lines. The splicing factor epithelial splicing regulatory protein 1 (*ESRP1*) and *hnRNPA1* are important in controlling the *CD44* isoform switch and critical for regulating the EMT phenotype in cell line models (Warzecha et al. 2009). The switch of *CD44v* to *CD44s* variants has been reported to induce EMT phenotype (Brown et al. 2011). In contrast, other studies reported that *CD44v* isoforms can mediate metastasis (Zhang et al. 2014, 2015; Tjhay et al. 2015). Orthotropic transplantation of a *CD44v*(+) subpopulation of 4T1 breast cancer cells, but not that of a *CD44v*(−) subpopulation, in mice results in efficient lung metastasis accompanied by expansion of stem-like cancer cells proving the role of the variant isoform in cancer metastasis (Yae et al. 2012). In summary, *CD44* splicing is very complex and further analysis is necessary to understand the role of *CD44* splice variants in breast cancer.

23.3.2 Mutually Exclusive Exons

Fibroblast Growth Factor Receptor 2 (*FGFR2*), a member of the fibroblast growth factor receptors, has been shown to be altered in breast cancer (Fletcher et al. 2013). *FGFR2* is one of the examples in breast cancer where the alternative splicing of two mutually exclusive exons (FGFR2 IIIb or IIIc) alters its ligand binding ability and its biological function. Switching of FGFR2 IIIb to IIIc plays a role in EMT process and results in mammary tumor development (Cha et al. 2008; Moffa et al. 2004; Wei et al. 2012).

23.3.3 Intron Retention

Intron retention is common in most of the tumors except in breast tumors (Dvinge and Bradley 2015). Breast tumors were associated with decreased intron retention relative to normal controls. For example, Herstatin is a naturally occurring truncated HER-2 protein generated from alternative *HER-2* mRNA transcripts that retain intron 8 (Jackson et al. 2013; Doherty et al. 1999). Herstatin can act as an inhibitor of full-length HER-2 by interfering with dimerization, and tyrosine phosphorylation (Guidi et al. 1997). In particular, Herstatin levels are significantly higher in noncancerous breast cells compared to carcinoma cells (Koletsa et al. 2008), p100, another truncated HER2 mRNA splice variant, exhibits the retention of intron 15 and inhibits the tumor cell proliferation and oncogenic signaling (Aigner et al. 2001). Further studies are necessary to understand its prognostic and predictive value in breast cancer.

23.3.4 Alternative 5′ Splice Sites

The apoptosis regulator gene Bcl-2-like 1 or Bcl-x, which belongs to the Bcl-2 family of proteins, can act as an anti-apoptotic (Bcl-xL) or pro-apoptotic (Bcl-xS) protein by regulating caspase activation. These two isoforms are generated based on the alternative splicing pattern of Bcl-x in the 5′ splice sites in exon 2. Overexpression of the longer isoform Bcl-xL has been reported in several cancers including breast cancer, whereas the shorter isoform Bcl-xS is downregulated in cancer (Boise et al. 1993; Adams and Cory 2007; Akgul et al. 2004; Cloutier et al. 2008; Ma et al. 2010). The alternative splicing of Bcl-x has been well documented in affecting survival or evading

apoptosis, one of the key hallmarks of cancer (Hanahan and Weinberg 2000, 2011).

23.3.5 Alternative 3′ Splice Sites

Vascular endothelial growth factor (VEGF) is a well-known stimulator of tumor angiogenesis, tumor growth and metastasis in cancer, all of which are hallmarks of cancer. Overexpression of VEGF is an early event in breast cancer progression and a prerequisite step to tumor invasion (Guidi et al. 1997). Elevated expression of VEGF can be associated with shorter relapse-free survival and overall survival times in breast cancer patients with both positive and negative lymph nodes (Gasparini et al. 1997; Konecny et al. 2004; Relf et al. 1997). *VEGF* pre-mRNA is regulated by alternative splicing (Biselli-Chicote et al. 2012; Harper and Bates 2008). The *VEGF* gene contains eight exons having two competing 3′ splice sites (proximal and distal) in exon 8 (Houck et al. 1991). The proximal 3′ splice site of exon 8 generates the *VEGF* isoforms that are pro-angiogenic, whereas the distal 3′ splice site produces the *VEGF*β isoforms that are anti-angiogenic. Splicing factors *SRSF1* and *SRSF5* (SRp40) have been shown to control the splicing of *VEGF* exon 8 proximal 3′ splice site and promote the production of *VEGF* (Nowak et al. 2008). *VEGF* splicing is complex and alternative splicing of other exons (exon 6 and 7) increases its functional diversity.

23.4 Future Directions; Promises and Limitations

High throughput technologies such as massively parallel RNA-sequencing have emphasized the importance of alternative splicing in biological models and human disease by providing an extensive information of small RNAs and associated proteins that are involved in RNA splicing process. Alterations of these proteins by mutations or gene expression level affect the alternative splicing events leading to altered function and protein-protein interactions of several proteins. In particular, mutations in spliceosome components have opened new therapeutic opportunities in cancer. Much work needs to be done to understand the clinical utility of key splice variants in tumor development, progression and metastasis. In particular, major challenges need to be overcome to remove significant bottlenecks for the clinical utility of cancer-specific splice variants. First, computational biology methods need to be refined and standardized among the different databases and platforms. Second, identification of gene expression alterations at the exon level need to be coupled with biological endpoints such as proliferation, apoptosis or recurrence/metastasis. For example, in breast cancer, a decrease in the proliferation rate following neoadjuvant endocrine therapies can be associated with alterations at the exon level. Exon markers can unravel the dual roles of some of the prognostic and predictive markers in breast cancer initiation, progression and metastasis. Third, experimental models need to be developed that can determine and validate the biological significance of these exon markers. However, the complexity arises when multiple exons are skipped or included. This might suggest that it is important to not only identify clinical significance at the exon level as well as at the transcript level. Fourth, databases at the transcript level need to be developed from tumors of retrospective and prospective clinical trials with the outcome follow-up. These databases are critical to understand their ultimate clinical utility both at the discovery and validation stage.

In conclusion, overcoming of all of these challenges requires the extensive collaboration of computational scientists, mathematicians, cancer biologists, pathologists and clinicians.

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