Aberrant alternative splicing in cancer: Splicing events and their regulatory mechanisms (Review)

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Abstract. Alternative RNA splicing provides cells with transcriptomic and proteomic diversity by adding another layer of regulation to gene expression. Accumulating evidence has revealed that defects in alternative splicing contribute to a variety of features of cancer development, including the modulation of cancer heterogeneity, evasion of apoptosis of cancer cells, rewiring cancer metabolism and facilitating cancer metastasis via fine-tuning the epithelial-to-mesenchymal transition process. In this review, well-known aberrant alternative splicing events associated with multiple aspects of cancer progression were presented based on available data obtained from an extensive literature search used to construct splicing regulatory networks for each of these events. The study aims to provide a more comprehensive understanding of cancer-associated splicing networks and more precise guidance for targeting these events for cancer treatment.

Contents

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1. Introduction

As a specific type of pre-mRNA splicing, alternative splicing involves the flexible decision to include or exclude a certain piece of the RNA sequence to greatly increase protein diversity in human cells (1). Through alternative splicing, multiple protein isoforms, which may have similar or distinct functions, are generated from a single gene; these isoforms may have enhanced or decreased levels of expression in physiological processes, including early development (2), and in diseases such as cancer and neurodegeneration (3). Alternative RNA splicing is a fine-tuned process that utilizes a pool of ribonucleoproteins and splicing factors in addition to the components of the basic RNA-spliceosome. Dysregulation of alternative RNA splicing has been frequently identified during cancer development due to cis-element sequence mutations in a specific splicing region or alterations in splicing regulatory components, which may affect multiple splicing events (4). The occurrence of aberrant splicing events not only affects primary tumor progression but can also boost epithelial-to-mesenchymal transition (EMT) to promote tumor metastasis (5,6). Numerous reviews have summarized the role of alternative splicing in different aspects of cancer. Lee and Abdel-Wahab (7), Marzese *et al* (8) and Cherry and Lynch (9) have systematically summarized the mechanisms of alternative RNA splicing, dysregulation of cancer-related splicing events and current therapeutic manipulation of aberrant alternative splicing to treat cancer. Urbanski *et al* (4) delineated altered splicing regulatory components, tumor-associated splicing events and therapeutic targets to modulate tumor-related splicing. EMT is widely associated with tumor metastasis, and alternative RNA splicing, with its high regulatory flexibility, has been shown to contribute to EMT via a well-described mechanism (5,10).

Although understanding the regulatory networks of alternative splicing events is critical, to the best of our knowledge, no review has presented a panoramic perspective on cancer-related alternative splicing network regulation. A comprehensive understanding of the currently known regulatory networks is critical for us to better comprehend how these aberrant splicing events occur and how to more precisely target dysregulated alternative splicing in cancer. The current study extensively reviewed the well-established cancer-associated splicing events and explored the literature to summarize the

current understanding of the specific events favored by cancer cells to provide an overview of cancer-related alternative splicing regulatory networks.

2. Introduction to alternative RNA splicing

RNA splicing is a biological process that occurs in eukaryotic genes, during which pre-mRNAs exclude all introns and join all exons to make mature mRNAs. This process is catalyzed by the spliceosome, which is composed of numerous proteins, Small nuclear RNAs and small nuclear ribonucleoproteins (snRNPs), such as U1, U2, U4, U5 and U6 (11). Based on RNA splicing, alternative splicing occurs due to the existence of cis-acting elements, including intronic splicing enhancers (ISEs), intronic splicing silencers (ISSs), exonic splicing enhancers (ESEs) and exonic splicing silencers (ESSs), and fluctuations in trans-acting splicing factors. The cooperation of specific splicing factors and element sequences results in seven types of alternative splicing, including exon skipping, intron retention, alternative 5' splice sites, alternative 3' splice sites, mutually exclusive exons, alternative promoters and alternative polyadenylation, which markedly enhance protein diversity (12). As discussed above, alternative splicing is essential for physiological processes, while its dysregulation, e.g., loss-of-function mutations in components of the spliceosome, such as the A, C and U2 complex, and additional splicing factors, contributes to diseases such as cancer (13).

Epi-transcriptomic regulation, including RNA modifications and RNA editing, was recently demonstrated to regulate alternative RNA splicing (14). Compared to RNA editing, the relevance of m6A RNA modification to alternative splicing is more extensively investigated. The m6A RNA modification is regulated by methyltransferases, such as methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3), methyltransferase 14, N6-adenosine-methyltransferase non-catalytic subunit (METTL14) and methyltransferase 16, RNA N6-adenosine (METTL16), demethylases, such as FTO α-ketoglutarate dependent dioxygenase and alkB homolog 5, RNA demethylase, and m6A binding proteins, such as YTH N6-methyladenosine RNA binding protein (YTHD)Fs and YTHDCs (15). Via m6A deposition at proximal splice sites, METTL3 influences thousands of splicing events of cancer cells to promote breast cancer progression (16). As a m6A binding protein, YTHDC1 was reported to promote serine and arginine rich splicing factor 3 (SRSF3) but suppress SRSF10 RNA binding activity, and affect splicing regulation near the related m6A modification sites (17). Epi-transcriptomic regulation adds another layer of complexity to alternative RNA splicing regulation, but this topic will not be extensively discussed in this review.

3. Splicing events related to apoptosis

Fas cell surface death receptor (FAS). The human FAS protein (also known as Apo-1/CD95) belongs to the nerve growth factor and TNF receptor superfamily and induces apoptosis through binding to FAS ligand (18). *FAS* generates a variety of splicing variants due to the deletion of exons 3, 4, 6 or 7, and of these, the FASExo6Del variant is the most extensively studied. The FASExo6Del lacks a membrane binding region and is soluble (sFAS) inside cells, which blocks the apoptotic function of full-length FAS in cancer cells (19). FAS exon 6 inclusion is modulated by the Ewing sarcoma protein EWS, which can bind to splice sites flanking exon 6 and recruit splicing factors, including U1snRNP and U2AF65 (20). Izquierdo *et al* (21) reported that TIA1 cytotoxic granule associated RNA binding protein (TIA-1)/TIA-1 cytotoxic granule associated RNA binding protein like 1 promotes FAS exon 6 inclusion via the uridine-rich sequence in the 5' splice site of intron 6, while polypyrimidine tract binding protein 1 (PTBP1) facilitates exon 6 skipping by binding to an ESS. The skipping of FAS exon 6 can also be induced by RNA binding motif protein 17 (RBM17), whose activity is inhibited by ERK- and p38-modulated phosphorylation but enhanced by Cdc2-like kinase 1 (CLK1) phosphorylation, to promote cancer cell migration and invasiveness (22-24). In addition, other splicing factors, including SRSF6, RBM5 and heterogeneous nuclear RNP A1 (hnRNPA1), have been reported to promote FAS exon 6 skipping. SRSF6 binds to the 5' splice site of the cassette exon, RBM5 functions via the exon 6 sequence and a weakly associated 3' splice site, while hnRNPA1 binds to the 5' splice site on exon 5 (25-27). The binding of RBM5 to FAS can be inhibited by a long noncoding (lnc)RNA, an antisense (AS) transcript of FAS, FAS-AS1, in B-cell lymphoma (28). SRSF7 promotes exon 6 skipping to promote colon and lung cancer cell survival (29). Hepatitis B virus core protein (HBc) slightly increases FAS exon 6 skipping to generate sFAS by increasing the expression of PTBP1 (30). Thus, cancer cells can escape apoptosis by utilizing a group of splicing factors that augment the generation of the soluble FASExo6Del isoform, which blocks FAS-mediated apoptosis.

Bridging integrator 1 (BIN1). BIN1 is a nucleocytoplasmic adaptor protein that participates in apoptosis. The *BIN1* gene contains 19 exons and can generate >10 different isoforms due to alternative splicing (31). Aberrant *BIN1* alternative splicing has been found to contribute to tumor progression and metastasis in multiple tumor types (32,33). SRSF1 was demonstrated to promote exon 12a inclusion, which antagonizes apoptosis and leads to tumor progression in multiple tissues (34,35). SRSF1 activity can be affected by the centrosomal kinase NIMA related kinase 2 (NEK2), which can promote SRSF1-mediated *BIN1* exon 12a inclusion by phosphorylation (36). Similarly, hnRNPA2/B1 enhances exon 12a inclusion to produce the antiapoptotic BIN1 isoform in glioma cells (37). In hepatocellular carcinoma, the RNA binding protein non-POU domain containing octamer binding (NONO) was shown to increase *BIN1* exon 12a inclusion via the DExH-box helicase 9/NONO/splicing factor proline and glutamine rich axis (38). RBM25 commonly functions as a tumor suppressor in acute myeloid leukemia, as it regulates apoptosis-related pre-mRNA splicing. Specifically, knockdown of RBM25 facilitates the generation of BIN1 exon 12 containing isoforms that increase cancer cell proliferation and decrease apoptosis (39).

Bcl-2-like protein 1 (BCL2L1). BCL2L1 belongs to the Bcl-2 superfamily, which plays a central role in apoptosis and is essential for development and tissue homeostasis (40,41). *BCL2L1* can generate two variant transcripts via the

alternative 5' splice site of exon 2: The antiapoptotic Bcl-x long isoform (Bcl-xL) and the proapoptotic Bcl-x short isoform (Bcl-xS) (42). SRSF2 was shown to induce the generation of Bcl-xS via the induction of E2F transcription factor 1 (E2F1) in lung cancer cells (43). RBM10, a known tumor suppressor, can regulate the ratio of Bcl-xL to Bcl-xS to a proapoptotic level (44). By contrast, a truncated RBM10 variant with concomitant EGFR mutations favors the generation of an antiapoptotic Bcl-xL to Bcl-xS ratio, which leads to an incomplete response to kinase inhibitor therapy in patients with lung cancer (45). Splicing factor 3b subunit 1 (SF3B1), as one of the most frequently mutated splicing factors in tumors, is overexpressed in glioblastoma. An increase in the Bcl-xS/Bcl-xL ratio induces apoptosis when SF3B1 activity is inhibited both *in vitro* and *in vivo* (46). In patients with head and neck cancer (HNC), SRSF10 is upregulated to generate Bcl-xL, the cancer-specific isoform, which promotes HNC progression via the ERK1/2/early growth response 1 (EGR1)/SRSF10 axis (47). Lv *et al* (48) reported that SRSF1-mediated production of Bcl-xL suppresses autophagy in lung cancer cells, which contributes to tumorigenesis, and to the progression of gefitinib-resistant cancer cells, during which SRSF1 splicing activity can be enhanced by NEK2 phosphorylation (36). Another RNA binding protein, RBM4, has been demonstrated to promote the generation of Bcl-xS to induce apoptosis by antagonizing the splicing activity of SRSF1 on Bcl-x, which inhibits tumorigenesis (49). Similarly, PTBP1 also increases the generation of Bcl-xS by binding to the polypyrimidine tract located between the two alternative 5' splice sites of Bcl-x exon 2 and competing with SRSF1 for binding (50). Another tumor suppressive splicing factor, poly(rC) binding protein 1 (PCBP1), modulates signal transducer and activator of transcription 3 (STAT3) splicing by producing the STAT3β isoform via exon 23 skipping, which further elevates the Bcl-xS to Bcl-xL ratio and inhibits cancer cell proliferation (51). The tumor suppressor RBM25 stimulates the generation of Bcl-xS, and knockdown of RBM25 was found to increase Bcl-xL, which decreases apoptosis (52). This finding is consistent with RBM25-regulated BIN1 exon 12 inclusion (39). PTBP3 and hnRNPK have been reported to repress Bcl-xS generation, which inhibits apoptosis (53,54); furthermore, accumulated SET nuclear proto-oncogene protein can synergize with the effect of hnRNPK (55). The expression of hnRNPA1, a nucleocytoplasmic shuttling protein, was found to be elevated in patients with chronic myelogenous leukemia. Interference with the shuttling activity of hnRNPA1 could decrease Bcl-xL expression and affect hematopoietic cell survival (56). The switching of Bcl-xL to Bcl-xS is also enhanced by KH RNA binding domain containing, signal transduction associated 1 (also known as Src-associated in mitosis 68 kDa protein), whose splicing activity is decreased by protein arginine methyltransferase 2 (57), the Src family kinase Fyn (58), the transcription factor zinc finger and BTB domain containing 7A (also known as FBI-1) (59) and lncRNA BC200 (60). By contrast, hnRNPA2/B1 was reported to increase the generation of Bcl-xL, which is promoted by Fyn (58) and BC200 (60). In addition, melanoma differentiation-associated gene 7 (also known as IL-24) was demonstrated to decrease the Bcl-xL/Bcl-xS ratio by downregulating the ceramide-sensitive RNA trans-factor SF3B1, whose activity is also maintained by the pan-protein kinase C (PKC) member PKCτ in non-small cell lung cancer (NSCLC) cells (61,62). In addition to splicing factor regulation, lncRNAs can also mediate the alternative splicing of BCL2L1. The lncRNA LINC00162 decreases the level of the antiapoptotic Bcl-xL splicing isoform by enhancing hnRNPH1 splicing activity, which sensitizes cancer cells to 5-aza-2'-deoxycytidine treatment (63). Overexpression of intronic Bcl-xS-inducing lncRNA (also known as intronic BCL-XS-inducing lncRNA) enhances the generation of Bcl-xS, leading to apoptosis (64). In summary, alternative splicing of BCL2L1 is regulated by a complex network that affects cancer cell apoptosis and survival during cancer progression.

MCL1 apoptosis regulator, BCL2 family member (MCL1). MCL1 is a member of the antiapoptotic BCL-1 family and can generate a proapoptotic splicing variant called MCL1S via exon 2 skipping (65). Upregulation of the full length MCL1 (MCL1L) has been demonstrated in various human tumor types (66), and the development of antisense oligonucleotides that can shift MCL1L splicing to MCL1S to trigger cancer cell apoptosis has been extensively investigated (67,68). Numerous hnRNP family members, including hnRNPF, hnRNPH1 and hnRNPK, regulate MCL1 splicing. Thus, knocking down these splicing factors in breast cancer cells results in a switch of MCL1 splicing that favors MCL1S (69). As a proto-oncogene, SRSF1 is involved in the generation of the antiapoptotic isoform MCL1L, as well as other cancer-specific splicing events (70,71). SRSF1 stability is increased by the lncRNA DGCR5 in esophageal squamous cell carcinoma to regulate MCL1 splicing (72). SRSF5 also promotes the generation of MCL1L in breast cancer cell lines (70). By contrast, decreased expression of SRSF2 in renal cancers was demonstrated to enhance alternative splicing of several apoptosis-related genes including MCL1, into antiapoptotic isoforms (73). Moore *et al* (71) also validated that SF3B1 knockdown favors the splicing of MCL1 to MCL1S, which indicates that SF3B1 is a valuable target for inducing cancer cell apoptosis by switching MCL1 splicing (74,75). RBM4 was found to promote MCL1S generation by binding to GU-rich elements in MCL1 exon 2. This process can be interrupted by the upregulation of serine-arginine protein kinase 1 (SRPK1), which shuttles nuclear RBM4 to the cytoplasm in breast cancer cells (76). The stability of MCL1 splicing variants is also regulated by micro (mi)RNAs, including miR-23b, which downregulates MCL1S in lung cancer cells (77), and miR-29b, which promotes MCL1S generation to sensitize HeLa cells to etoposide treatment (78). In addition, dynamic histone acetylation can affect MCL1 splicing. H3 and H4 acetylation of H3K4me3 nucleosomes, located around MCL1 alternative exon 2, was shown to increase MCL1L generation in colon and breast cancer cells (79). Thus, cancer cells can fine-tune the alternative splicing of MCL1 at different levels, including splicing factors, miRNA and histone modifications, to escape apoptosis.

MDM2 proto-oncogene (MDM2) and MDM4. MDM2 and MDM4 work both cooperatively and independently to inhibit and degrade the tumor suppressor protein p53 (80). MDM2 has been reported to give rise to >40 splicing variants. Most MDM2 isoforms lack the p53 binding site and are involved

with malignant tumor progression (81). Studies on MDM2 alternative splicing in cancer progression are currently limited. MDM4 is another negative regulator of p53, which was reported to be upregulated in various cancers (82). MDM4 gives rise to a myriad of splicing variants, and of these, the short isoform of MDM4 (MDM4-S), which excludes exon 6, has been proven to be oncogenic and even more potent than full-length MDM4 (83). RBM11 has been reported to enhance the generation of MDM4-S to promote glioblastoma progression (84). Knockdown of pre-mRNA processing factor 19 or RNA-binding protein with serine-rich domain 1 promoted the skipping of exon 6 to produce MDM4-S in cancer cells (85,86). Of note, the RNA binding protein zinc finger matrin-type 3, a downstream target of p53, promotes the production of MDM4-S, which mediates nonsense-mediated mRNA decay of full-length MDM4, thereby enhancing p53 stability to form a positive feedback loop suppressing tumor progression (87). In a genome-wide short interfering RNA screen, Siebring-van Olst *et al* (88) identified that silencing SF3B1, SF3B6, snRNP D3 polypeptide or SF3A3 increased the generation of MDM4-S, indicating that these splicing factors can inhibit the generation of this splice variant. Considering the variety of MDM2 and MDM4 alternative splicing variants, their splicing regulations are far less investigated, which is partially due to the complexity of the variable exons and ambiguous effects of the splicing variants in cancer progression.

Caspase family members. Caspases are a family of protease enzymes that are essential for the execution of apoptosis. Among them, caspase-2 (CASP2), CASP8 and CASP-9 have been investigated for their alternative splicing regulation. Several alternative splicing isoforms of CASP2 exist, and one of the major splicing variants contains exon 9, which introduces a stop codon to generate the antiapoptotic CASP2S isoform (89). The Wu laboratory discovered a 100-nt region located in intron 9 (In100) that can facilitate exon 9 skipping. They further demonstrated that PTBP1 can be recruited to the In100 element to promote exon 9 skipping (90). The Wu laboratory further revealed that SRSF1 and SRSF2 promote exon 9 skipping and that hnRNPA1 increases exon 9 inclusion, which drives proapoptotic or antiapoptotic effects, respectively, in serum-deprived HeLa cells (89). The tumor suppressor RBM5 was shown to promote the generation of full-length CASP2 to induce apoptosis in cancer cells (91).

CASP8 also produces multiple splicing variants. An antiapoptotic splicing variant, caspase-8 L (CASP8L), is generated due to the aberrant inclusion of intron 8, which introduces a premature stop codon before the CASP8 C-terminal domain (92). Upregulation of CASP8L has been demonstrated in multiple types of cancers, where CASP8L suppresses apoptosis by interfering with the binding of CASP8 to FADD (93). SRSF2 was demonstrated to decrease the generation of CASP8L due to the regulation of the transcription factor E2F1 (43). Stacey *et al* (94,95) discovered that the single nucleotide polymorphism rs700635[C] is significantly associated with retention of intron 8 of CASP8 and is correlated with an increased risk of breast cancer and cutaneous basal-cell carcinoma.

CASP9 is activated on the apoptosome complex, and failure to activate CASP9 leads to degenerative and developmental disorders and cancer (96). *CASP9* can generate a short isoform, CASP9b, via the skipping of exons 3, 4, 5 and 6. The apoptotic peptidase activating factor 1 and baculoviral IAP repeat containing 2 binding domains are preserved on CASP9b, which antagonizes the activity of the full-length CASP9a to suppress apoptosis (97,98). Massiello and Chalfant (99) demonstrated that the downregulation of SRSF1 is critical for the inclusion of the four exons described above to generate CASP9a in A549 cells and is also essential for ceramide-induced exon inclusion. The activity of SRSF1 can be further regulated by Akt signaling-induced phosphorylation in NSCLC (100). Furthermore, SRSF2, whose expression is upregulated by the transcription factor E2F1, promotes the production of CASP9a (43). In addition, hnRNPL was demonstrated to promote the skipping of four exons to increase CASP9b levels (101). Of note, hnRNPU competes with hnRNPL by binding to the cis-element in exon 3 of CASP9 to increase the expression of CASP9a. This process is also regulated by Akt signaling in NSCLC (102). Taken together, reports show that SRSF1 and SRSF2 are the most common factors that participate in alternative splicing of caspase family RNAs.

4. Splicing events related to cell signal transduction

RAS factors. RAS family oncoproteins included KRAS proto-oncogene, GTPase (KRAS), HRAS and NRAS, which belong to the small GTPase superfamily and are consistently activated in various human cancers (103). Multiple isoforms of RAS family members generated by alternative splicing add another layer of complexity to the therapeutic targeting of RAS factors (104). Although five isoforms can be produced from *NRAS* due to alternative splicing of exons 2, 3, 4 and 5 (104), limited investigations on the splicing regulation of *NRAS* have been reported. Similarly, limited investigations of *KRAS* splicing have been published. Two isoforms can be produced from *HRAS* by the inclusion of the intron D exon (IDX) to produce p19 HRAS and by skipping to generate the full-length p21 HRAS (105,106). The p19 HRAS lacks the last four exons due to the in-frame stop codon in IDX. p19 HRAS was reported to suppress the activity of p21 HRAS (107). Bach-Elias's group published two reports that focused on the alternative splicing regulation of *HRAS*. They revealed that hnRNPA1 and p68 could suppress IDX inclusion, whereas SRSF2, SRSF4, hnRNPH1 and FUS RNA binding protein (also known as translocated in liposarcoma) could promote IDX inclusion by binding to the IDX downstream ISS 'rasISS1' (108,109).

Rac family small GTPase 1 (RAC1). RAC1 is a small GTPase whose signaling is upregulated in various cancers, which promotes cancer cell survival, proliferation and invasion (110). RAC1b is an alternative spliced variant generated by the inclusion of an additional exon after exon 3 (i.e. exon 3b) in tumors. This isoform activates RAC1 downstream signaling pathways in the absence of signal stimuli (111,112). Two SR proteins, SRSF1 and SRSF3, function antagonistically in the splicing of RAC1 exon 3b. The former promotes inclusion, while the latter promotes the skipping of exon 3b in colorectal tumor cells. In one study, inhibition of the PI3K pathway increased SRSF1 and RAC1b levels, while activation of Wnt/β-catenin/transcription factor 4 transcription increased SRSF3 expression

and decreased RAC1b levels (113). SRSF1-mediated RAC1b generation is also induced by SRPK1 and glycogen synthase kinase-3 (GSK3)β activation, where SRPK1 phosphorylates SRSF1 to enhance nuclear translocation (114). Other splicing factors have also been shown to regulate RAC1 exon 3b alternative splicing in cancer cells. hnRNPA1 was shown to repress RAC1b generation by binding to exon 3b. This process can be inhibited by splA/ryanodine receptor domain and SOCS box containing 1-mediated hnRNPA1 ubiquitylation (115) and by treatment with MMP3 (116), which stimulates RAC1b expression and EMT in pancreatic cancer cells (117,118). The inverse correlation between hnRNPA1 and RAC1b was further validated in breast cancer biopsies (116). PTBP1 was reported to promote colon tumorigenesis via RAC1 exon 3b inclusion, in conjunction with two other events, NUMB endocytic adaptor protein (NUMB) exon 9 inclusion and pyruvate kinase M (PKM) exon 10 inclusion, which will be discussed later (119). Epithelial splicing regulatory protein 1 (ESRP1) was found to inhibit exon 3b inclusion in RAC1 to decrease the generation of RAC1b (120). This promotes cell colonization but suppresses migration of ovarian cancer cells (121). By contrast, ESRP1 increases RAC1b generation in colorectal cancer cells (CRC) to promote CRC tumorigenesis (122). Furthermore, ESRP1/2 is critical for the inclusion of RAC1 exon 3b in breast cancer cells (123). The above research suggests that ESRP1 regulates RAC1 exon 3b alternative splicing in a cell type-specific manner. Other reported factors that enhance RAC1b generation include the neural-associated transcription factor forkhead box (Fox)D1, which promotes melanoma metastasis, (124) and DIS3-like 3'-5' exoribonuclease 2, which recruits hnRNPU to pre-RAC1 mRNA to promote hepatocellular carcinoma progression (125). In addition to these extensively reported splicing factors, inflammatory cytokines, including IL-6 and TGF-β1, were demonstrated to indirectly promote RAC1b production in cancer cells through downstream signaling cascades (126,127).

p120 catenin. p120 catenin is a cadherin-associated protein encoded by the gene catenin δ1 that can enhance the mobility and invasiveness of mesenchymal cancer cells (128). Due to N-terminal splicing events that introduce four alternative translation start sites, p120 can generate a series of isoforms, 1, 2, 3 and 4. Isoforms 3 and 4 are normally expressed in epithelial cells and full-length isoform 1 is expressed in mesenchymal cells (128,129). The effects of p120 catenin isoforms on the promotion of EMT and tumor invasiveness have been extensively studied. However, limited research on the generation of p120 catenin tumor-associated isoforms has been published, with the exception of a few reports on ESRP1 and ESRP2 (130). Loss of ESRP1 and ESRP2 was reported to promote the generation of mesenchymal isoform 1 of p120, to mediate EMT and tumor progression (130).

MAPK interacting serine/threonine kinase 2 (MKNK2). *MKNK2* normally produces two splicing variants (SVs), namely MKNK2a and MKNK2b, which arise from the alternative usage of two 3' exons (131). The MKNK2b isoform lacks the MAP kinase binding site. Although the function of MKNK2a in tumorigenesis is ambiguous, MKNK2b has been recognized as a pro-oncogenic kinase due to its deficiency of a p38α-MAPK binding site but retention of eukaryotic translation initiation factor 4E phosphorylation activity (132,133). SRSF1 promotes MKNK2b splicing. This process is modulated by an increase in SRPK1/2 and a decrease in protein phosphatase 1, catalytic subunit, α isoform-modulated phosphorylation (134).

5. Splicing events related to metabolism

PKM. The *PKM* gene encodes pyruvate kinase, the enzyme that catalyzes the final step in glycolysis. In most human tissues, two alternative SVs can be generated by the mutual inclusion of exon 9 or exon 10 to produce variant M1 (PKM1) or variant M2 (PKM2), respectively (135). PKM1 is constitutively expressed in cells and tissues with high energy demand, including muscle and neurons, while PKM2 mainly functions in early embryonic development, as well as in carcinogenesis, to drive cancer-favorable metabolism (136). Three hnRNP proteins, PTBP1, hnRNPA1 and hnRNPA2, promote the inclusion of exon 10 by binding to sequences flanking exon 9 to promote PKM2 generation. The expression of these genes can be upregulated by the oncogenic transcription factor c-Myc binding protein (c-Myc) (137). Additional research from the same group revealed that, if present at higher levels, hnRNPA1/A2 and PTBP1 bind to sites in and around exon 9 to drive its exclusion, thereby decreasing the expression of proteins that bind to the proximal sites of exon 9 and can induce exon 9 inclusion. This indicates that splicing factors can fine-tune splicing events in a dose-dependent manner (138). Sun *et al* (139) reported that miR-124, miR-137 and miR-340 target the above three hnRNP proteins to decrease PKM2 production and inhibit the Warburg effect in CRC cells, which adds another layer of regulation to the alternative splicing of PKM. In addition, the activity of PTBP1 can be antagonized by RBM4, which promotes the switch of PKM2 to PKM1 (140). Furthermore, the stability of hnRNPA1 can be regulated by the E3 ligase ZFP91 zinc finger protein, atypical E3 ubiquitin ligase, which decreases PKM2 generation in hepatocellular carcinoma (141). Another splicing factor, RBM X-linked, was reported to competitively inhibit the splicing activity of hnRNPA1 on PKM to suppress tumorigenesis (142). Establishment of sister chromatid cohesion N-acetyltransferase 2, a protein that may have acetyltransferase activity and may be required for the establishment of sister chromatid cohesion, was demonstrated to increase the splicing activity of hnRNPA1 on PKM in lung cancer (143). The centrosomal kinase NEK2, which is a component of the hnRNPA1/2 and PKM pre-mRNA splicing complex, was also shown to promote the generation of PKM2. The transcription of NEK2 is regulated by c-MYC, which demonstrates that MYC proto-oncogene, bHLH transcription factor (MYC) is the hub of PKM2 generation and of rewiring cancer cell metabolism (144). PTBP1 was also reported to promote PKM2 expression in drug-resistant pancreatic cancer cells and can be activated by the ETS transcription factor ELK1 (ELK1)/MYC pathway in colon cancer cells (119,145). The microRNA miR-133b and the deacetylase SMAR1 were reported to target PTBP1 and downregulate its expression to repress PKM2 generation in tumor cells (146,147). SRSF3 was shown to promote the inclusion of exon 10 to generate PKM2 in tumor cells by binding to the ESE in exon 10 in cooperation with PTBP1 and hnRNPA1 (148,149). SRSF3-mediated

switching from PKM1 to PKM2 is enhanced by the binding of the lncRNA activating regulator of DKK1 (150). The ERK1/2/EGR1/SRSF10 axis also contributes to cancer-related PKM2 isoform generation, as the expression of SRSF10 is upregulated to promote exon 9 skipping (47). Other factors, including IGF2BP3, which promotes lung tumorigenesis (151) and SAM68, which enhances glycolysis and proliferation in CRC cells, have been reported to promote PKM2 production (152). The alternative splicing of PKM is also regulated by the overall methylation status of the intragenic DNA. PKM2 generation was reported to switch to PKM1 upon deletion of the intragenic DNA methylation-mediated binding of brother of regulator of imprinted sites (153). Taken together, reports show that cancer cells rewire their energy metabolism by producing the PKM2 isoform and that this process is extensively regulated via multiple mechanisms.

6. Splicing events related to cell motility and migration

ENAH. Enabled homolog (ENAH or MENA), is an actin regulatory protein, whose corresponding gene is actively spliced, giving rise to multiple isoforms that affect tumor progression. ENAH 11a (inclusion of exon 11a) and ENAH^{INV} (inclusion of exon 4) are two representative isoforms with distinct functions. The former is highly expressed in primary epithelial tumors, while the latter is preferentially expressed in invasive tumors (154). As global regulators of an epithelial splicing regulatory network, ESRP1 and ESRP2 were found to promote the production of the ENAH 11a isoform to reduce cell invasiveness (155). However, matrix stiffness reduces ESRP1 expression and ENAH 11a generation during tumor cell intravasation (156). PTBP1 was also found to modulate ENAH exon 11a skipping by binding to polypyrimidine tracts located upstream of intron 11 and downstream of exon 11a to promote lung cancer migration and invasiveness (157). RNA binding fox-1 homolog 2 (RBFOX2) enhances ENAH exon 11a inclusion via a cis-element located in intron 11a, and its activity can be regulated by the oncogenic kinase CLK2 (158,159). Yang *et al* (160) reported that breast cancer cells lacking lin-28 homolog A (LIN28A) exhibit skipping of ENAH exon 11a, which suggests that LIN28A is important for the inclusion of ENAH exon 11a.

NUMB. The protein encoded by the *NUMB* gene plays essential roles in cell division and cell-fate determination (161). Due to alternative splicing of exons 6, 10 and 12, six protein isoforms can be generated from *NUMB*: NUMB1 (full length), NUMB2 (skipping of exon 12), NUMB3 (skipping of exon 6), MUMB4 (skipping of exons 6 and 12), NUMB5 (skipping of exons 10 and 12) and NUMB6 (skipping of exons 6, 10 and 12) (162). NUMB was originally considered to be a tumor suppressor (163), while NUMB5 and NUMB6 function to promote cancer cell migration and invasion (164). Another NUMB splicing variant, in which, exon 9 is included, promotes cancer cell proliferation and was first identified in lung cancer, and conversely, exon 9 skipping inhibits cell proliferation (165). RBM5, RMB6 and RBM10 exert antagonistic effects on NUMB exon 9 splicing. While RBM5 and RBM6 promote the inclusion of NUMB exon 9, RBM10 promotes the skipping of exon 9, which either promotes or suppresses lung cancer cell proliferation, respectively (166). PTBP1, whose expression can be induced by the transcription factors ELK1 and MYC, is also essential for the inclusion of NUMB exon 9, which promotes cell proliferation in colon cancer (119,167). SRSF1 regulates multiple exon alternative splicing events in *NUMB* by enhancing the inclusion of NUMB exon 9 (167) and the skipping of NUMB exon 12 in cancer cells (168). As *NUMB* is an actively spliced gene in cancer, numerous studies have also revealed the splicing regulation of NUMB exon 12. Since the effect of NUMB exon 12 skipping on tumorigenesis is controversial, the regulation of exon 12 splicing is not discussed in this review.

7. Splicing events of cell cycle regulators

Cyclin D1 (CCND1). CCND1, which is a mediator of cell cycle control and is required for cell cycle G1/S transition, is upregulated in various types of cancer (169). The *CCND1* gene primarily generates two SVs, i.e., full-length CCND1 (CCND1a) and a C-terminal truncated CCND1 (CCND1b), the latter of which is an oncogenic cyclin isoform (170). The G870A polymorphism, located within the CCND1 splice site, modulates its splicing, where the AA genotype gives rise to increased expression of CCND1b mRNA (171,172). Furthermore, the generation of CCND1b mRNA associated with the G870 allele is promoted by association with SRSF1 in human prostate cancer cells (173). The splicing factor SAM68 can also enhance the expression of CCND1b by interacting with the proximal region of CCND1 intron 4 in prostate cancer cells (174). In one discordant study, RBM11 promoted the aggressiveness of glioblastoma but increased the CCND1a/b ratio, which indicates the existence of other regulatory mechanisms (84).

8. Splicing events of transcription factors

STAT3. STAT3 regulates multiple biological processes, including cell proliferation and growth. *STAT3* generates a variety of SVs. The two major variants, full length STAT3α and the shortened STAT3β, are generated due to an alternative acceptor site in exon 23, which causes a frameshift and the introduction of seven new amino acids and a stop codon (175,176). Full-length STAT3α has been extensively reported to participate in tumorigenesis, whereas STAT3β was demonstrated to exert a dominant negative effect on STAT3α to provide tumor suppressor activity (176). While most publications have recognized the distinct functions of STAT3α and STAT3β, limited research has been performed to investigate how these two variants are generated. One publication stated that PCBP1 could promote STAT3α to STAT3β switching in cancer cells by binding to the exonic splicing suppressor in exon 23 of *STAT3* (51). PCBP1 can further inhibit the translation of STAT3 through its 5'UTR in cancer cell lines, which indicates dual levels of transcriptional regulation by this RNA binding protein (177).

Krüppel-like factor 6 (KLF6). KLF6 is a nuclear transcriptional regulator that functions as a tumor suppressor in multiple cancers (178). Due to alternative splicing of exons 2 and 3, *KLF6* can generate three SVs, i.e., KLF6-SV1

(missing parts of exon 2 and exon 3), KLF6-SV2 (missing part of exon 2) and KLF6-SV3 (missing exon 3). Among these isoforms, KLF6-SV1 is considered oncogenic, while KLF6-SV2 promotes cancer cell apoptosis (179). The KLF6 IVS1-27G>A single nucleotide polymorphism in the intron upstream of exon 2 facilitates the binding of SRSF5 to enhance the generation of the KLF6-SV1 and KLF6-SV2 isoforms (180). SRSF1 increases the production of KLF6-SV1 in Ras-activated hepatocellular carcinoma (181). The expression level of SF3B1 is positively correlated with that of KLF6-SV1 in patients with hepatocellular carcinoma, and silencing or blocking SF3B1 decreases KLF6-SV1 levels, which is consistent with the tumor-promoting activity of SF3B1 (182).

9. Splicing events of cell membrane receptors and ligands

Vascular endothelial growth factor A (VEGFA). VEGFA is important for angiogenesis and produces a group of splicing variants due to the alternative splicing of exons 6, 7 and 8. The splicing variants can be divided into two groups, proangiogenic $VEGFA_{xxx}a$ and antiangiogenic $VEGFA_{xxx}b$, depending on 3' splice site usage in exon 8 (183). SR splicing factors were demonstrated to regulate the splicing of VEGFA, and while SRSF1 and SRSF5 favor $VEGFA_{xxx}a$ production, SRSF6 upregulates $VEGFA_{xxx}b$ by binding to the 3'UTR downstream of the stop codon in exon 8b (184). The activity of SRSF1 is regulated by multiple mechanisms in different types of cancer, including SRPK1 activation in lung and prostate cancer (185,186), lncRNA metastasis associated lung adenocarcinoma transcript 1-mediated SRSF1 stabilization in breast cancer (187) and circular RNA cerebellar degeneration related 1 activation in lung cancer (188). The level of $VEGFA_{xxx}b$ can also be upregulated by SRSF2, whose translation efficiency is controlled by E2F1 in lung tumor cells (189). TIA-1 generates two isoforms, full-length TIA-1 (flTIA-1) and short TIA-1 (sTIA-1), among which flTIA-1 induces VEGFA165b expression, while sTIA-1 suppresses this process (190). The alternatively spliced isoforms of TIA-1, which are involved in the regulation of VEGFA pre-mRNA splicing, add another layer of complexity to this splicing regulatory network. RBM10 levels are negatively correlated with VEGFA165a in endometrial tumors, and its regulation of the VEGFA165a/b ratio has been further validated *in vitro* (191).

Fibroblast growth factor receptors (FGFRs). The family of *FGFRs* contains four members, FGFR1-4, among which FGFR 1-3 normally generate the IIIb and IIIc isoforms due to alternative splicing of the exons encoding the third Ig-like domain region, which does not occur in FGFR4 (192). Compared with FGFR3 and FGFR4, significantly more studies have investigated the regulatory mechanisms of FGFR1 and FGFR2 alternative splicing in cancer development. The FGFR2 IIIb and IIIc isoforms contain either exon 8 or exon 9, respectively (192). The former is mostly expressed in epithelial cells, while the latter is expressed in mesenchymal cells (193). Isoform switching of FGFR2 has been demonstrated in EMT of cancer cells (194). Multiple cis-elements that affect FGFR2 alternative splicing have been identified. A core sequence of 18 nucleotides within the intronic splicing activator and repressor element, located between exon 8 and exon 9, is essential for the generation of the IIIb isoform in DT3 cells (195). Carstens *et al* (196) discovered that another cis-element, ISS-1, which is located upstream of exon 8, can suppress the generation of the IIIb isoform via the recruitment of PTBP1 through its pyrimidine-rich sequence. Another cis-element, ISE/ISS-3, which was identified in the intronic region between exon 8 and exon 9, enhances the splicing of exon 8 and represses the splicing of exon 9 (197). ESRP1 and ESRP2 were reported to enhance the generation of the IIIb isoform by binding to this ISE/ISS-3 motif (198). Upstream of ISE/ISS-3, a UGCAUG motif can recruit the protein RBFOX2 to mediate FGFR2 IIIc to IIIb switching, which implies a role in mesenchymal-epithelial transition (199). Coupled with hnRNPA1, KH-type splicing regulatory protein (KHSRP) is also critical for the expression of the FGFR2 IIIb isoform to maintain an epithelial state, whereas TGF-β induction silences the expression of KHSRP to induce EMT (200). However, most research on FGFR1 alternative splicing during tumorigenesis concerns a different FGFR1 splicing event involving either the inclusion (FGFR1α) or exclusion (FGFR1β) of the α-exon rather than the classical splicing of isoforms IIIb and IIIc (201). FGFR1β enhances breast cancer metastasis, which can be promoted by the EMT inducer TGF-β1, while FGFR1α inhibits tumor growth (202). The 69-nucleotide ESE on α-exon is required for its inclusion via the recruitment of SRSF6 in glioblastoma cells (203). The splicing factor PTBP1 exerts distinct effects on FGFR1 splicing under different conditions, by suppressing the production of FGFR1β in breast cancer cells but inducing FGFR1β generation in glial cell transformation (204,205).

Macrophage stimulating 1 receptor (MST1R, also known as RON). RON is a membrane tyrosine kinase receptor of the MET proto-oncogene, receptor tyrosine kinase family that has been found to promote the progression of numerous cancers (206). *RON* generates various splicing variants via the selective skipping of multiple exons, including two tumor-associated isoforms, namely RONΔ160, which is generated by skipping exons 5 and 6, and RONΔ165, which is generated by skipping exon 11; both of these variants have been shown to promote tumorigenesis, and particularly, tumor-cell invasiveness (207,208). SRSF2 promotes the inclusion of RON exon 11 by interacting with the CGAG sequence on exon 11 (209). Exon 11 skipping is promoted by the binding of SRSF1 to a splicing enhancer located in exon 12 of RON to induce EMT and tumor metastasis, during which SRSF1 activity can be regulated by AMPK (210,211). In addition, SRSF1 promotes the skipping of exons 5 and 6 to produce RONΔ160 (212). hnRNPA2/B1 was demonstrated to enhance exon 11 skipping to produce RONΔ165, activate Akt/PKB signaling and induce EMT in HNC cells (213). Of note, hnRNPA1 can antagonize SRSF1 activity and decrease the expression level of hnRNPA2/B1 to promote RON exon 11 inclusion and mesenchymal-epithelial transition (214). The expression level of hnRNPA1 is further regulated by GSK3α and -β, which results in increased hnRNPA1 expression when the former is silenced and decreased hnRNPA1 expression

Table I. Regulation of cancer-related alternative splicing events.

Gene	AS event	Role in cancer	Splicing factors	Upstream modulators of splicing factors	(Refs.)
FAS	Exon 6 inclusion	Promotes apoptosis	EWS, TIA-1/TIAR	ND	(20,21)
	Exon 6 skipping	Suppresses apoptosis	RBM17[a], SRSF6, RBM5, hnRNPA1, SRSF7, PTBP1[b]	ERK[a] ↓, p38[a] ↓, CLK1[a] ↑, HBc[b] ↑	(22-27,29,30)
BIN	Exon 12a inclusion	Suppresses apoptosis	SRSF1[a], hnRNPA2/B1, NONO	NEK2[a] ↑	(34-38)
	Exon 12a skipping	Promotes apoptosis	RBM25	ND	(39)
BCL2L1	Bcl-xL (alternative 5' splice site on exon 2)	Suppresses apoptosis	SF3B1[a], SRSF10, SRSF1[b], PTBP3, hnRNPK, hnRNPA1, hnRNPA2/B1[c]	MDA-7[a] ↓, PKCτ[a] ↑, NEK2[b] ↑, Fyn[c] ↑, BC200[c] ↑	(36,46-48,53-56,58,60-62)
	Bcl-xS (alternative 5' splice site on exon 2)	Promotes apoptosis	SRSF2[a], RBM10, RBM4, PTBP1, PCBP1, RBM25, SAM68[b], hnRNPH1[c]	E2F1[a] ↑, PRMT2[b] ↓, Fyn[b] ↓, FBI-1[b] ↓, BC200[b] ↓, LINC00162[c] ↑	(43,44,49-52,57-60,63)
MCL1	MCL1L (exon 2 inclusion)	Suppresses apoptosis	hnRNPF, hnRNPH1, hnRNPK, SRSF1[a], SRSF5, SF3B1	DGCR5[a] ↑	(69-72,74,75)
	MCL1S (exon 2 skipping)	Promotes apoptosis	SRSF2, RBM4[a]	SRPK1[a] ↓	(73,76)
CASP2	CASP2S (exon 9 inclusion)	Suppresses apoptosis	hnRNPA1	ND	(89)
	CASP2 full length (exon 9 skipping)	Promotes apoptosis	PTBP1, SRSF1, SRSF2, RBM5	ND	(89-91)
CASP9	CASP9a (full length)	Promotes apoptosis	SRSF2[a], hnRNPU[b]	E2F1[a] ↑, Akt[b] ↓	(43,102)
	CASP9b (exon 3,4,5,6 skipping)	Suppresses apoptosis	SRSF1[a], hnRNPL	Akt[a] ↑	(99-101)
HRAS	p21 (intron D exon skipping)	Oncogene	hnRNPA1, p68	ND	(108,109)
	p19 (intron D exon inclusion)	Inhibitor of p21	SRSF2, SRSF4, hnRNPH1, FUS	ND	(108,109)
RAC1	Exon 3b skipping	Upregulated in cancer	SRSF3[a], hnRNPA1[b]	TCF4[a] ↑, SPSB1[b] ↓, MMP3[b] ↓	(113,115-118)
	Exon 3b inclusion (RAC1b)	GTPase activated isoform	SRSF1[a], PTBP1, hnRNPU[b]	SRPK1[a] ↑, GSK3β[a] ↑, DIS3L2[b] ↑, FOXD1, IL6, TGFβ1	(113,114,119,124-127)
MKNK2	MKNK2b	Pro-oncogenic	SRSF1[a]	SRPK1/2[a] ↑, PP1α[a] ↓	(134)
PKM	PKM1 (inclusion of exon 9)	Dominant in mature, differentiated cells	RBM4, RBMX	ND	(140,142)
	PKM2 (inclusion of exon 10)	Dominant in embryos and cancer cells	PTBP1[a,d], hnRNPA1[a,b,c], hnRNPA2[a,c], SRSF3[e], SRSF10, IGF2BP3, SAM68	c-MYC[a] ↑, miR-124[a] ↓, miR-137[a] ↓, miR-340[a] ↓, ZFP91[b] ↓, ESCO2[b] ↑, NEK2[c] ↑, ELK1[d] ↑, miR-133b[d] ↓, SMAR1[d] ↓, LNCAROD[e] ↑	(47,119,137-139,141,143-152)
ENAH	ENAH 11a (inclusion of exon 11a)	Dominant in primary epithelial tumors	ESRP1, ESRP2, RBFOX2[a], LIN28A	CLK2[a] ↑	(155,158-160)
NUMB	Exon 9 inclusion	Promote cancer cell proliferation	RBM5, RBM6, PTBP1[a], SRSF1	ELK1[a] ↑, MYC[a] ↑	(119,166,167)

Table I. Continued.

Gene	AS event	Role in cancer	Splicing factors	Upstream modulators of splicing factors	(Refs.)
	Exon 9 skipping	Inhibit cancer cell proliferation	RBM10	ND	(166)
CCND1	CCND1b	Oncogenic	SRSF1, SAM68	ND	(173,174)
KLF6	KLF6-SV1 (missing part of exon 2 and 3)	Oncogenic	SRSF5, SRSF1, SF3B1	ND	(180-182)
VEGFA	$VEGFA_{xxx}a$ (3' splice site usage in exon 8)	Proangiogenic	SRSF1[a], SRSF5	SRPK1[a] ↑, MALAT1[a] ↑, circCDR1[a] ↑	(184-188)
	$VEGFA_{xxx}b$ (3' splice site usage in exon 8)	Antiangiogenic	SRSF6, SRSF2[a]	E2F1[a] ↑	(184,189)
FGFR2	FGFR2IIIb (inclusion of exon 8)	Dominant in epithelial cells	ESRP1, ESRP2, RBFOX2, hnRNPA1, KHSRP[a]	TGFβ[a] ↓	(198-200)
	FGFR2IIIc (inclusion of exon 9)	Dominant in mesenchymal cells	PTBP1	ND	(196)
FGFR1	FGFR1α (inclusion of α exon)	Inhibit cancer growth	SRSF6	ND	(203)
RON	Exon 11 inclusion	Oncogenic acitivity	SRSF2, hnRNPA1[a], hnRNPC1/C2	GSK3α[a] ↓, GSK3β[a] ↑	(209,214-216)
	Exon 11 skipping (RONΔ165)	Stronger oncogenic activity	SRSF1[a], hnRNPA2/B1, hnRNPH1, SF3B1	AMPK[a] ↑	(210,211,213, 217,218)
ERBB2	Exon 16 skipping (Δ16HER-2)	Promotes tumorigenesis	SRSF3, hnRNPH1 (Inh)	ND	(221)
	Intron 8 retention (herstatin)	Inhibits cancer cell proliferation	hnRNPA1, SRSF1 (Inh)	ND	(222)

[a-e]The upstream modulator regulates the splicing activity of corresponding factor if they have the same footnotes. ↑, the splicing activity is increased; ↓, the splicing activity is decreased; Akt, AKT serine/threonine kinase; AMPK, protein kinase AMP-activated catalytic subunit alpha 2; BCL2L1, Bcl-2-like protein 1; BIN, Bridging integrator 1; CASP, caspase; CCND1, cyclin D1; circCDR1, circular RNA cerebellar degeneration related 1; CLK, CDC like kinase; DGCR5, DiGeorge syndrome critical region gene 5; DIS3L2, DIS3 like 3'-5' exoribonuclease 2; E2F1, E2F transcription factor 1; ELK1, ETS transcription factor ELK1; ENAH, enabled homolog; ERBB2, Erb-b2 receptor tyrosine kinase 2; ERK, EPH receptor B2; ESCO2, establishment of sister chromatid cohesion N-acetyltransferase 2; ESRP, epithelial splicing regulatory protein; EWS, EWS RNA binding protein 1; FAS, Fas cell surface death receptor; FBI-1, zinc finger and BTB domain containing 7A; FGFR, fibroblast growth factor receptor; FOXD1, forkhead box D1; FUS, FUS RNA binding protein; Fyn, FYN proto-oncogene, Src family tyrosine kinase; GSK, glycogen synthase kinase; HBc, Hepatitis B virus core protein; hnRNP, heterogeneous nuclear ribonucleoprotein; HRAS, HRas proto-oncogene, GTPase; IGF2BP3, insulin like growth factor 2 mRNA binding protein 3; Inh, inhibit target isoform generation; KHSRP, KH-type splicing regulatory protein; KLF6, Krüppel-like factor 6; LIN28A, lin-28 homolog A; LNCAROD, lncRNA activating regulator of DKK1; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MCL1, MCL1 apoptosis regulator, BCL2 family member; MDA-7, melanoma differentiation-associated gene 7; MMP3, matrix metallopeptidase 3; MKNK2, MAPK interacting serine/threonine kinase 2; MYC, MYC proto-oncogene, bHLH transcription factor; ND, not determined; NEK2, NIMA related kinase 2; NONO, non-POU domain containing octamer binding; NUMB, NUMB endocytic adaptor protein; PCBP1, poly(rC) binding protein 1; PKC, pan-protein kinase C; PKM, pyruvate kinase M; PP1α, protein phosphatase 1 catalytic subunit alpha; PRMT2, protein arginine methyltransferase 2; PTBP, polypyrimidine tract binding protein; RAC1, Rac family small GTPase 1; RBFOX2, RNA binding fox-1 homolog 2; RBM, RNA binding motif protein; RON, macrophage stimulating 1 receptor; SAM68, KH RNA binding domain containing, signal transduction associated 1; SF3B1, splicing factor 3b subunit 1; SMAR1, BTG3 associated nuclear protein; SPSB1, splA/ryanodine receptor domain and SOCS box containing 1; SRPK, SRSF protein kinase; SRSF, serine and arginine rich splicing factor; TCF4, transcription factor 4; TGFβ, Transforming growth factor beta superfamily; TIA-1/TIAR, TIA1 cytotoxic granule associated RNA binding protein/TIA1 related; VEGFA, vascular endothelial growth factor A; ZFP91, ZFP91 zinc finger protein, atypical E3 ubiquitin ligase.

when the latter is silenced (215). Other reported hnRNPs that regulate RON alternative splicing include hnRNPC1/C2, which promotes RON exon 11 inclusion (216), and hnRNPH1, which enhances the skipping of RON exon 11 in glioma cells (217). SF3B1-specific inhibitor treatment decreases the level of RONΔ165 in cancer cells, which indicates that SF3B1 is also essential for the skipping of RON exon 11 (218). The abovementioned splicing factors mainly promote RON exon 11

inclusion or skipping, to suppress or promote cancer progression, respectively.

Erb-b2 receptor tyrosine kinase 2 (ERBB2). ERBB2, also called human EGFR2 (HER2) or neu, is overexpressed in various types of cancer and is associated with enhanced tumor metastasis, poor prognosis and recurrence (219). Three *ERBB2* splice variants have been reported, including Δ16HER-2 with exon 16 skipping, herstatin with intron 8 retention and p100 with intron 15 retention (220). ERBB2 splice isoforms play different roles in cancer progression. Δ16HER-2 is associated with high tumorigenesis and cancer metastasis, while herstatin and p100 inhibit tumor cell proliferation (221). A PubMed search revealed only two investigations concerning the mechanism that regulates ERBB2 alternative splicing. The first two splicing factors reported to regulate ERBB2 alternative splicing are SRSF3 and hnRNPH1, both of which can bind to ERBB2 pre-mRNA. Knockdown of SRSF3 promotes the switch from the Δ16HER-2 isoform to the p100 isoform to inhibit cell proliferation, while knockdown of hnRNPH1 increased the Δ16HER-2 level in breast cancer cells (221). Using RNase-assisted RNA chromatography and mass spectrometry assays, Silipo *et al* (222) revealed that hnRNPI, hnRNPH1, hnRNPD, hnRNPA2/B1, hnRNPA1 and SRSF1 bind to exon 8/intron 8 and intron 8/exon 9 boundaries. Among them, hnRNPA1 promotes intron 8 retention to produce the tumor suppressor variant herstatin, while SRSF1 partially decreases the level of herstatin (222). Although the tumorigenic function of ERBB2 splicing variants has been extensively studied, further investigation of its splicing regulatory mechanism is warranted for a more profound understanding of carcinogenesis.

10. Conclusions and future perspectives

Cancer cells leverage a variety of abnormal cell activities to boost primary tumor proliferation, escape apoptosis, initiate distant metastases and develop therapeutic resistance. Aberrant regulation of alternative RNA splicing serves as one of the major carcinogenic mechanisms, as this regulation provides a dynamic and flexible regulatory network. Alternative RNA splicing is directly regulated by splicing factors that bind to RNA to control alternative exon recognition and splicing. During this process, the activity of splicing factors is orchestrated at various levels in cancer development, including through genomic mutations, kinases or proteins that affect their activity and stability, miRNAs and lncRNAs (Table I). The multiple levels of splicing regulation reviewed in this paper led us to the following conclusions: i) SRSF1, as one of the most well-known splicing factors, boosts virtually all of the cancer-related splicing events reviewed here, which suggests that SRSF1 is a promising therapeutic target in cancer. As the first member of the SR protein family that was identified as a proto-oncogene, SRSF1 was discovered to be overexpressed and activated by posttranslational modifications in various types of cancer, which suggests that multiple approaches can be used to target SRSF1-mediated cancer favoring splicing events (223). ii) Given that the effects of various splicing factors, such as SRSF2, RBM5 and PTBP1, on cancer-associated splicing events can be discordant, further investigations are needed to determine how to target these splicing factors to reverse cancer-associated splicing events. iii) A significant group of cancer splicing events, including those involving the caspase family, RAS family, CCND1, STAT3, KLF6 and ERBB2, requires active investigation. Future studies will fill gaps in our knowledge of these splicing regulatory networks. iv) The effect of a specific splicing isoform, such as MKNK2a, NUMB exon 12 or CD44 multi-exon splicing [reviewed elsewhere (224)] in different types of carcinoma can be controversial. Thus, further examination is required when these splicing events are targeted to treat individual patients.

Current publications on splicing regulatory mechanisms are extensive. From a holistic view of the entire splicing regulatory network, these publications are likely only the tip of the iceberg. Future investigations should provide a more comprehensive understanding of dysregulated alternative splicing in cancer progression, as well as how to effectively and safely target this critical process therapeutically.

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Authors' contributions

YS and XH both performed the literature search and drafted the manuscript. XH contributed to the conception of the study. YS helped with the table content organization. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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