Current Cancer Drug Targets, 2020, *20*, 729-740

REVIEW ARTICLE

The Roles of Alternative Splicing in Tumor-immune Cell Interactions

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ARTICLE HISTORY

Received: January 30, 2020
Revised: May 09, 2020
Accepted: May 11, 2020

DOI:
10.2174/1568009620666200619123725

Abstract: Alternative splicing (AS) plays a significant role in the hallmarks of cancer and can provide neoantigens for immunotherapy. Here, we summarize recent advances in immune system associated tumor specific-antigens (TSAs) produced by AS. We further discuss the regulating mechanisms involved in AS-mediated innate and adaptive immune responses and the anti-tumoral and pro-tumoral roles in different types of cancer. For example, ULBP1_RI, MLL5Δ21spe, NKp44-1Δ5, MHC-IΔ7, CD200SΔ1, 2, PVR α/β/γ/δ and IL-33 variants 1/2/3 act as regulators in solid tumors and IPAK4-L and, FOXP1ΔN100 exhibit functions in hematological cancers.

Keywords: Alternative splicing, tumor cells, immune system, immunotherapy, neoantigens, Tumor specific-antigens (TSAs).

1. INTRODUCTION

Immunotherapy has transformed the treatment of many advanced cancers [1]. Immunotherapeutic anticancer approaches, such as therapeutic vaccines and T cell receptor engineered T cells (TCR-T cells), rely heavily on suitable target antigens [2]. Currently, there are three main types of tumor antigens: *i.e*. antigens derived from tumor-specific somatic mutation, cancer germline antigens (CGAs), and antigens derived from viral genes expressed by viral-infected tumor cells. Clinical studies have shown remarkable outcomes in cancer patients receiving either TCR-T cell therapy targeting CGAs [3, 4] or neoantigen-based vaccines [5-7]. Neoantigens are tumor-specific antigens (TSAs) that do not exist in normal human genomes. In non-virus-related tumors, neoantigens are derived from novel protein sequences formed by tumor-specific DNA damage. For virus-related tumors, such as cervical cancer, neoantigens can also come from viral open reading frames [8]. The major obstacle for the broader applicability of tumor immunotherapies is the lack of targetable neoantigens for many cancer types.

To date, mutation-derived neoantigens have received considerable attention, with neoepitopes derived from mRNA processing events. Alternative splicing (AS) is a regulated process that occurs during gene expression. It results in a single gene coding for multiple proteins and affects more than 90% of human coding genes [9]. Introns and exons are selectively included or excluded in the AS process [10]. Therefore, pre-mRNAs are modified into various isoforms and then translated into proteins during AS, in order to meet cell diversity demands [11]. Previous studies have identified and categorized five types of AS events, including exon skipping (SE), intron retention (RI), alternative 3' splice site (A3SS), alternative 5' splice site (A5SS), and mutually exclusive exon (MXE) events [12]. In addition, AS regulates most hallmarks of cancer, including proliferation, apoptosis, hypoxia, angiogenesis, immune escape and metastasis [13-15]. Following the rapid development of sequencing technology, various studies have shown that cancer-specific AS can produce neoantigens. For example, Jayasinghe *et al*. analyzed 8 656 tumor samples and found that splice-site-creating mutations can produce more neoantigens than other types of mutations [16]. Hoyos *et al*. also reported that tumor-specific splicing has the potential to generate a large new class of tumor-specific neoantigens [17]. From another perspective, for cancers that exhibit low prevalence of somatic mutations and copy number variations but widespread mRNA splicing aberrations (*e.g*., B cell acute lymphoblastic leukemia), the expanded target scope of immunotherapies may lead to more efficient development [18]. Thus, AS-derived neoantigens may offer a much broader scope for immunotherapy applications.

The human immune system, which includes innate and adaptive immunity, is a host defense system comprised of biological structures and processes that protect against disease [19]. Neoantigens from tumor cells affect the efficacy of both the innate and adaptive immune systems. In neoantigen-expressing tumors, natural killer (NK) cell stimulation can

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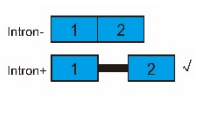
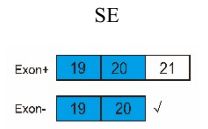
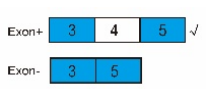
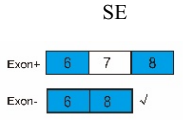
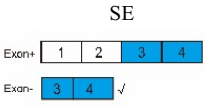
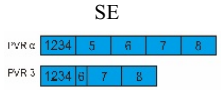
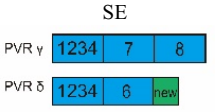
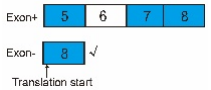
1873-5576/20 $65.00+.00

Table 1. Role of alternative splicing (AS) in human tumor immunity.

Immune Type	Splice Isoform	Splice Patterns	Splicing Regulator	Role	Study Type	Reported Effect	Refs.
Innate	ULBP1_RI	 RI	ATF4 RBM4	Pro-tumoral	Tumor-derived human cell line-HAP1 cells	Tumor cells escape NK cell surveillance by increasing ULBP1_RI isoform	[38, 39]
Innate	MLL5$^{\Delta 21spe}$	 SE	Not mentioned	Anti-tumoral	Normal tissues; Human melanoma cells (WM1361); Human lung adenocarcinoma cells (H441); Mouse EL4 cells	NKp44 binds with MLL5$^{\Delta 21spe}$ to activate NK cells	[54, 55]
Innate	NKp44-1$^{\Delta 5}$	 SE	Cytokine (IL-15, IL-18, TGF-β)	Pro-tumoral	HeLa cells; Breast cancer cells (MCF7); Human melanoma cells (A375)	NKp44-1$^{\Delta 5}$ binds with PCNA to inhibit NK cell lysis	[48, 52, 53]
Innate	IPAK4-L	 Full-length	U2AF1	Pro-tumoral	AML; Normal hematopoietic cells	Mutation of U2AF1 leading to IRAK4-L isoform production and innate immunity activation.	[58]
Adaptive	MHC-I$^{\Delta 7}$	 SE	Not mentioned	Anti-tumoral	Melanoma treatment model of C57BL/6	MHC-I$^{\Delta 7}$ is recognized by TCR, inducing stronger anti-tumor immune responses	[68]
Adaptive	CD200S$^{\Delta 1,2}$	 SE	Not mentioned	Anti-tumoral	Human carcinoma tissues; Rat C6 glioma cell lines; Glioma rat model; Wistar rats model with lung metastasis	CD200S activates CD8^{+}T cells, CD200L induces immunosuppressive response	[76-78]
Adaptive	PVR α, δ	 SE	ATF6	Anti-tumoral	Hepatocellular carcinoma (HCC) cells	Transmembrane PVR (PVR α, δ) activates CTLs by binding to CD226	[84, 86, 89, 91]
Adaptive	PVR β, γ	 SE	IFNγ	Pro-tumoral	Melanoma cells	Soluble isoform (PVR β, γ) suppresses CTLs by increasing expression of inhibitory receptor TIGIT	[84, 86, 89, 91]
Adaptive	IL-33 variant 1/2/3	 SE	Not mentioned	Dual effect	CRC cells; NSCLC cells; Breast cancer cells	IL-33 promotes or inhibits tumorigenesis.	[94-101]
Adaptive	FOXP1$^{\Delta N100}$	 SE	Not mentioned	Pro-tumoral	DLBCL cells; human B cells; Mouse lymphoma models	FOXP1$^{\Delta N100}$ can activate B cells and lead to development of DLBCL.	104, [105]

✓represents splice pattern corresponding to splice isoform on left column. 'New' aindicates new insert sequence.

RI: intron retention; SE: exon skipping; ATF: activating transcription factor; MLL5: mixed-lineage leukemia-5; spe: special; NK cell: natural killer cell; MHC: major histocompatibility complex; CD200S: truncated forms of CD200; CD200L: full-length CD200; TIGIT: T cell Ig and ITIM domain; PVR: poliovirus receptor; IFN γ: interferon γ; CTLs: cytotoxic T lymphocytes. DLBCL: diffuse large B cell lymphoma; U2AF1: U2 small nuclear RNA auxiliary factor 1; IRAK4-L: long isoform of interleukin-1 receptor-associated kinase 4; CRC: colorectal cancer; NSCLC: non-small cell lung cancer; HCC cell: hepatocellular carcinoma.

enhance the number and function of tumor-specific T cells, causing tumor growth inhibition [20]. Here, to characterize the roles of AS in tumor-immune interactions, we categorized them into innate and adaptive immunity contexts.

AS events and corresponding functions are summarized in Table **1**. All illustrations were created using Adobe Illustrator CS6.

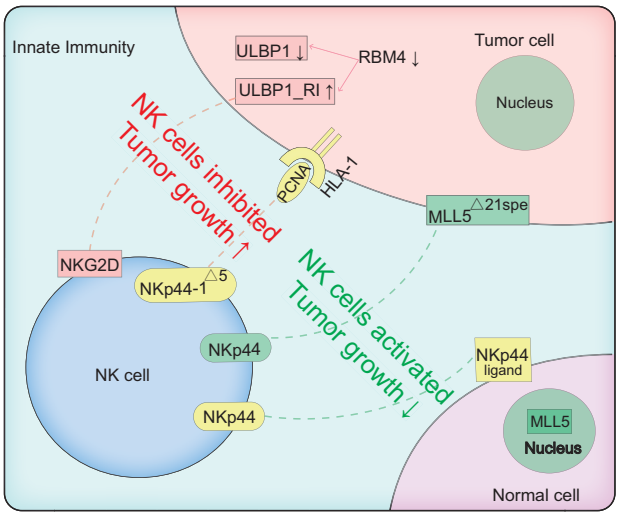


Fig. (1). Schematic of AS between innate immunity and tumor cells. Red and green dotted lines represent inhibition and activation of NK cells, respectively.↑ represents promoted tumor growth, ↓ represents inhibited tumor growth or downregulation of RBM4. Tumor cells downregulate RBM4 and subsequently increase ULBP1_RI. ULBP1 is an NKG2D ligand on tumor cell surface, and is recognized by NKG2D on the surface of NK cells, which are then activated. ULBP1_RI and ULBP1 combine competitively with NKG2D, and ULBP1_RI functions as a negative regulator of NK cells. Green: in normal cells, MLL5 protein is in the nucleus. In the tumor environment, abnormal isoform of MLL5 (MLL5$^{\Delta 21spe}$) is highly expressed on cell surface, and activates NKp44^{+} NK cells. NK cells are activated by combination of NKp44 and corresponding ligand located in normal membrane. NK cells expressing alternative NKp44 isoform (NKp44-1$^{\Delta 5}$) can be inhibited by proliferating cell nuclear antigen (PCNA) ligands, which are often highly expressed on tumor cell surface. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. AS AND TUMOR INNATE IMMUNE RESPONSES

Innate immune cells, including macrophages, dendritic cells (DC), and NK cells, contribute to spontaneous and acute antitumor responses by releasing mediators of inflammation, such as cytokines and chemokines, which activate and recruit local immune cells [21]. NK cells have received renewed interest recently as they do not rely on antigen specificity and can directly kill malignant or transformed cells by releasing cytotoxic granules [22]. NK cells also exhibit the capacity to preferentially kill cancer stem-like cells [23]. Several studies have successfully exploited NK cell functions against neuroblastoma [24, 25], glioblastoma [26, 27], and lung cancer [28]. Lacking antigen-specific receptors, NK cells use a set of innate receptors to sense and respond to changes in the tumor-immune microenvironment. Specifically, activated receptors (*e.g.*, NKG2D and natural cytotoxicity receptors (NCRs)) and inhibited receptors (*e.g.*, major histocompatibility complex, MHC-I) on the surface of NK cells are in a state of dynamic balance, which determines the functional state of these cells [29]. Given the ability of NK cells to detect and destroy a range of cancerous tissues, mechanistic insight into how cancer cells regulate NK cell activity at the AS level and the pharmacological modulation of these activities represent an underexplored potential in immunotherapy. The splicing events involved in innate immunity are illustrated in Fig. (**1**).

2.1. NK Cells in Solid Tumors

2.1.1. Tumor Cells Escape NK Cell Surveillance by Increasing Expression of ULBP1_RI Isoform

NK cells are regulated by a balance of signals from activating and inhibitory receptors, which recognize cognate ligands expressed by potential target cells [30, 31]. One of the best-studied NK-activating receptors is NKG2D, which is also expressed in certain T cell subsets [32]. NKG2D ligands are often highly expressed in tumor cells (such as melanoma), but not in normal cells [33]. The structure of NKG2D ligands is similar to that of the MHC-Ⅰ protein. Humans have eight NKG2D ligands, whereas mice have 5_6 different ligands [34]. As a human NKG2D ligand, ULBP1 has two isoforms: *i.e.*, ULBP1 and ULBP1_RI (intron-retained isoform) (Table **1**) [35]. The relative expression between these two isoforms confers the level of NK cell activation. High ULBP1 expression is associated with elevated NK activation, whereas ULBP1_RI corresponds to the deactivation of NK cells. Both RBM4 and ATF4 are regulators of ULBP1 expression: AFT4 directly binds to the promoter of ULBP1 to promote transcriptional activation, whereas RBM4 inhibits the formation of splicing isomer ULBP1_RI [36]. Tumor cells can escape NK cell surveillance by decreasing the expression of RBM4, resulting in lower and higher expression of ULBP1 and ULBP1_RI, respectively [35]. Yong *et al.* found that low expression of RBM4 is associated with poor prognosis in gastric cancer [37] and is mediated by controlling cancer-related splicing [36].

The ULBP ligand family contains ULBP1, ULBP2, ULBP3, and RAET1E. RAET1E can be transformed into a truncated and soluble form by AS, termed RAET1E2, which is found in many human cancer cell lines, such as liver carcinoma, gastric adenocarcinoma, and ovarian carcinoma [38]. RAET1E2 can also inhibit NKG2D-mediated NK cytotoxicity resulting in an immune escape mechanism in tumors [38]. Although the innate immune system has become an area of intense interest in immunotherapy, the mechanisms involved in the enhancement of NK cell capacity to inhibit or kill tumor cells need further exploration.

2.1.2. NKp44 and NKp44-1$^{\Delta 5}$ Function as Positive and Negative Regulators of NK Cells, Respectively

NK cells are activated by various receptors, including the NCR family, which is comprised of NKp46 (NCR1, CD335), NKp44 (NCR2, CD336), and NKp30 (NCR3, CD337) [39]. NKp44 is encoded by the NCR2 gene located on chromosome 6 in the human MHC class II locus and is exclusively expressed in activated NK cells [40, 41]. NKp44 expression is associated with a marked increase in cytolytic activity in NK cells [42, 43]. In addition, non-covalent binding with DAP-12 is essential for NKp44-mediated NK activation [44].

Recent research has revealed that AS can occur during transcription of the NCR2 gene, resulting in transcripts that encode receptor isoforms with inhibitory functions. For example, the alternative isoform of NKp44 that lacks exon 5 (NKp44-1$^{\Delta 5}$) can inhibit NK cell activation, which is triggered by proliferating cell nuclear antigen (PCNA) (Table **1**) [45]. PCNA is an inhibitory ligand of higher NKp44 expression found on the surface of tumor cells [46] and interacts with the NKp44-1$^{\Delta 5}$ isoform. Mechanically, in the presence of NKp44-1$^{\Delta 5}$, PCNA in tumor cells is presented by human histocompatibility leukocyte antigen-1 (HLA-1) and is then recruited to the NK immunological synapses (NKIS), which, in turn, induce an inhibitory effect on NK cells [47].

The expression of NKp44-1$^{\Delta 5}$ can be affected by cytokines, such as IL-15, IL-18, and TGF-β [48]. IL-15 improves NKp44-1$^{\Delta 5}$ levels, whereas IL-18 plays a role in its downregulation [48]. NKp44-1$^{\Delta 5}$ also contributes to a shift in peripheral blood NK cells towards decidua basalis NK [48]. Shemesh *et al*. found that NKp44-1 expression is significantly associated with poorer survival in acute myeloid leukemia (AML) patients [49]. In addition, overexpression of NKp44-1 in NK-92 cells can reverse the inhibitory effect of NK-92 cells on PCNA mediation, leading to poor lytic immune synapse formation [49].

NKp44-mediated NK cell activation is also regulated by mixed-lineage leukemia-5 (MLL5$^{\Delta 21spe}$) although MLL5 is not the major ligand of NKp44 [50]. MLL5 $^{\Delta 21spe}$ lacks an exon 21spe at the C-terminus and encodes a highly conserved 1168-amino acid protein (Table **1**). This specific 21spe fragment was previously reported in GenBank (accession no. AAR13894.1). In normal cells, MLL5 is specifically expressed in the nucleus, whereas MLL5$^{\Delta 21spe}$ is located on the tumor cell surface and is recognized by NKp44 [51]. Therefore, NK cells can recognize the MLL5$^{\Delta 21spe}$ isoform on the tumor cell surface and thus activated to eliminate these cells.

Other MLL5 isoforms such as MLL5β reported in human papillomavirus induced cervical cancer, function as important active regulators of oncogene E6 and E7 transcription [52]. Full-length MLL5 is comprised of 25 exons, whereas MLL5β is truncated at exon 14 due to the insertion of 26 nucleotides [52]. MLL5$^{\Delta 21spe}$ functions differently from MLL5β because of its unique subcellular localization on the cell-surface.

Taken together, in the battle between NK and tumor cells, AS plays a critical role in the activation of NKp44-mediated NK cell response. Thus, providing additional MLL5$^{\Delta 21spe}$ isoforms or designing molecules to compete with the NKp44-1$^{\Delta 5}$-PCNA sites represent potential approaches for cancer immunotherapies.

2.2. Innate Immune Pathways in Hematological Cancers

Spliceosome mutations in myeloid malignancies, such as AML, are a form of oncogenic mutation. A recent study on AML samples found that mutant U2 small nuclear RNA auxiliary factor 1 (U2AF1) induces an exon 4-contained AS isoform of interleukin-1 receptor-associated kinase 4 (IRAK4), which encodes the IRAK4-L protein, to activate innate immunity [53]. IRAK4 activates the NF-κB and MAPK pathways *via* the mediation of downstream signaling of the Toll-like receptor (TLR) superfamily [54]. IRAK4 can be divided into two spliced isoforms depending on whether exon 4 is contained or excluded: *i.e*., IRAK4-L and IRAK4-S (**Table 1**) [53]. IRAK4-S can control innate immune responses in normal hematopoietic cells, whereas IRAK4-L mediates NF-κB maximal activation, resulting in uncontrolled innate immune responses in malignant hematopoietic cells [55]. IRAK4-L also exhibits high expression in breast and colon cancer cells, indicating an association with oncogenicity [53]. Furthermore, mutant U2AF1 (S34F) AML cells acquire a dependency on IRAK4-L and are sensitive to IRAK4 inhibitors, suggesting potential therapeutic strategies [53].

3. AS AND TUMOR ADAPTIVE IMMUNE RESPONSE

Adaptive immunity can be divided into T cell-mediated cytotoxic responses and B-cell-mediated antibody responses. The proliferation of primary T cells can be activated by a specific combination of TCRs and MHC on the surface of antigen-presenting cells (APCs) [56]. MHC restriction in antigen recognition means that $CD4^+$ T cells recognize MHC class II molecules and $CD8^+$ T cells recognize MHC class I molecules [57]. For B cell-mediated adaptive immunity (known as humoral immunity), when pathogens and antigens enter the body, specific B cells are induced to differentiate into plasma cells and antibodies and antigens are produced to prevent pathogenic infection [58]. Memory cells are also produced when the primary immune response is activated. When the same antigen reappears, the memory cells respond quickly to produce a powerful counterattack [59]. The splicing events involved in adaptive immunity are illustrated in Fig. (**2**).

3.1. T Cells in Solid Tumors

3.1.1. MHC-I$^{\Delta 7}$-expressing DCs Present Antigen More Efficiently and Easily than Normal DCs

As APCs, DCs with MHC-I on the membrane surface play important roles in activating T lymphocytes [60]. The function of MHC-I is mainly determined by the highly conserved amino acid sequence in its cytoplasmic tail encoded by exons 6 and 7 [61]. Deletion of the cytoplasmic tail results in reduced function or even loss of MHC-I [62]. However, the exon 7-deleted splice variant of MHC-I (MHC-I$^{\Delta 7}$) is still capable of presenting internal and external antigens and has a remarkable antigen-presenting ability, which can be recognized by the TCRs of $CD8^+$ T cells and can induce stronger anti-tumor immunity (Table **1**) [63]. Mechanically,

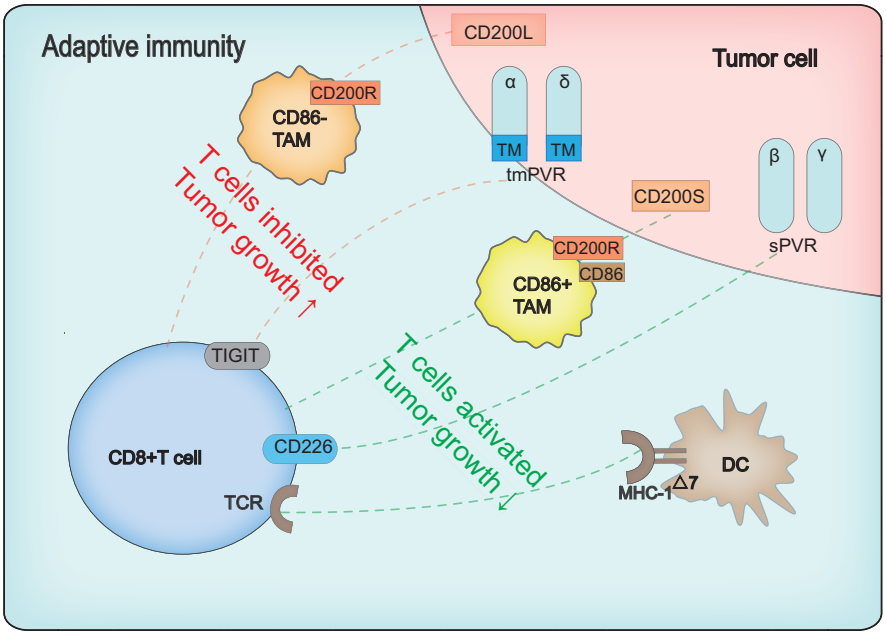


Fig. (2). Schematic of AS between adaptive immunity and tumor cells. Red and green dotted lines represent inhibition and activation of CD8+T cells, respectively.↑represents promoted tumor growth, ↓represents inhibited tumor growth. Three molecular mechanisms are involved. First, two CD200 isoforms, *i.e.*, CD200L and CD200s, function as CD8+ T cell inhibitory and stimulatory regulators. Combination of full-length CD200 (CD200L) and CD200 receptor (CD200R) expressed on CD86 tumor-associated macrophages (TAMs) leads to inhibition of CD8+ T cells. The truncated form of CD200 (CD200S), with exon 1 and 2 deleted, endows TAMs with DC-like morphology, resulting in increased expression of CD86, a co-stimulatory factor, and thus activation of CD8+ T cells. Second, the poliovirus receptor (PVR) has four AS isoforms: *i.e.*, α, β, γ, and δ. PVRα and PVRδ are transmembrane PVRs (tm PVR), which locate and activate the immune response by binding to CD226; the remaining isoforms are soluble PVRs (sPVR), which lack a transmembrane domain and inhibit cytotoxic T lymphocyte (CTL) anti-tumor immune responses. Finally, exon 7-deleted splice variant of MHC-I (MHC-IΔ7) endows APCs with superior capacity in antigen-presentation, and interact with TCR more efficiently, thus inducing CD8+ T cells to produce a stronger anti-tumor immune response. MHC-I$^{\Delta 7}$ also prompts APCs to secrete more cytokines to stimulate CD8+ T cells. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

MHC-I$^{\Delta 7}$ not only improves the bioavailability of presented antigen peptides, but also induces the release of cytokines, such as IFN-γ, when the concentration of antigen peptides is extremely low [63].

This superior property of MHC-I$^{\Delta 7}$ has been applied to DC-based anti-tumor vaccines, which effectively extend survival in the B16 melanoma tumor mouse model [63-65]. These results suggest that the MHC- I cytoplasmic tail encoded by exon 7 could be targeted directly in DC vaccines [66], which may improve their ability to stimulate the cytotoxic T lymphocyte (CTL) response and enhance anti-tumor immunity.

The human leukocyte antigen-G (HLA-G) in melanoma cells is also regulated at the mRNA splicing level and can boost anti-tumoral immunity [67]. Melanoma cells can rapidly switch cell-surface-located HLA-G1 to intra-cellular HLA-G2, which can restore tumor sensitivity to NK lysis [67]. HLA-G1 is a full-length HLA-G isoform, whereas HLA-G2 is a splicing isoform lacking an exon 3α2 domain [68]. Therefore, modulating HLA splicing isoforms may be an efficient way in which to boost tumor immunity.

3.1.2. CD200S can Activate CD8$^+$ T Cells and, CD200L can Induce Immunosuppressive Responses

CD200 is a transmembrane protein expressed in a large range of tissues, including lymphoid cells, neurons, and endothelial, and mainly functions in immune recognition by binding to its receptor (CD200R) [69]. Tumor cells express two CD200 isoforms, including full-length CD200 (CD200L) and a truncated form of CD200 (CD200S), which occur due to frame-shift mutations during exon 2 and 3 splicing and the emergence of termination codons (Table **1**) [70]. CD200L expression in mouse tumor cells inhibits activation of tumor-specific T cells, whereas CD200S can release the CD200-CD200R inhibitory interaction and reverse the inhibitory state of immune cells [71]. Tumor-associated macrophages (TAMs) isolated from CD200S-enriched C6 tumor cells exhibit higher-level expression of MHC IIα and CD11c, resulting in the activation of CD8+T cells [70]. Glioma model rats transplanted with CD200S cells survive for longer periods than those transplanted with CD200L [70]. In addition, CD200S endows CD200R$^+$ TAMs with DC-like morphology and activates CD8$^+$ CTLs [70].

CD200S can also activate the anti-tumor immune response in a novel type of lung metastasis in Wistar rats, leading to an effective reduction in lung metastasis [72]. Next-generation sequencing has also shown that the expression levels of chemokines and granzyme B in CD200S-rich tumors are much higher than those in CD200-L tumors [72]. Notably, CD200S promotes enrichment of multiple DC subsets expressing CD11c, MHC II, CD8, and/or CD103 in tumors [72]. This provides an attractive cancer therapy mechanism to reverse the immunosuppressive state by targeting CD200L or enforcing the CD200S isoform.

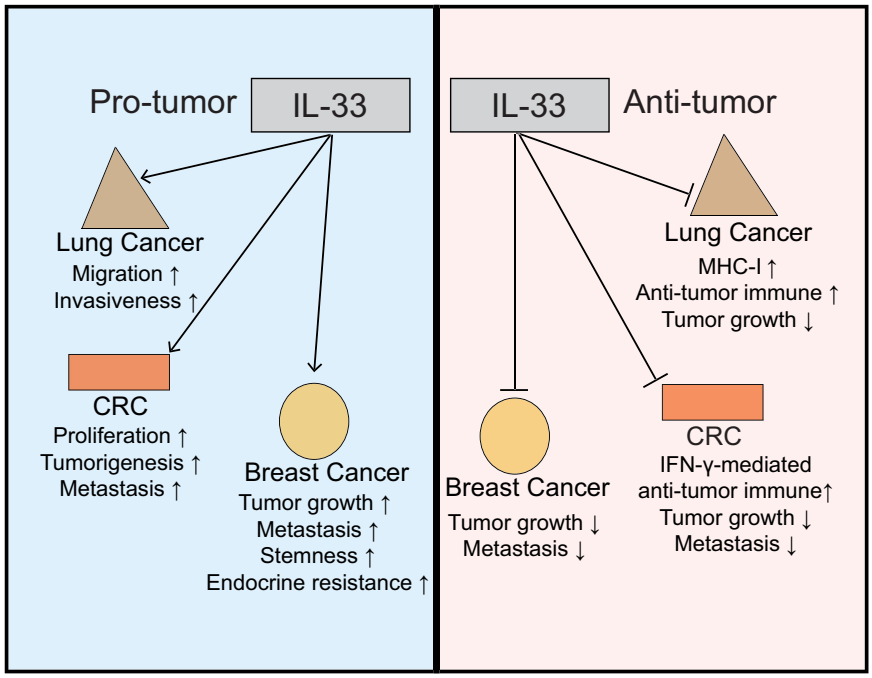


Fig. (3). Opposite functions of IL-33 in tumors. For example, in lung cancer, CRC, and breast cancer, as shown on left, IL-33 can promote tumorigenesis, invasion, metastasis, and drug resistance. On the right, IL-33 inhibits tumors by enhancing the anti-tumor immune response mediated by MHC-1 or IFN-γ. CRC: colorectal cancer. Drugs including FR901464 (SSA), meayamycin B targeting SF3B1, isoginkgetin and 1, 4-heterocyclic, which are involved in step 1 and step 2 splicing [10]. Thus, manipulating AS is a promising immunotherapeutic target with potential research value. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.1.3. Transmembrane-located Poliovirus Receptor (PVR) Activates CTLs by Binding to CD226, Whereas Soluble Isoform Suppresses CTL Immunity

Human PVR is a transmembrane glycoprotein belonging to the immunoglobulin superfamily [73]. Recently, PVR has attracted growing attention due to its broad involvement in cancer, *e.g.*, cell adhesion and migration and adaptive immunity [74-79]. The PVR has four main AS isoforms: *i.e.*, α, β, γ, and δ. The α and δ isoforms are transmembrane PVRs (tm PVR) due to the existence of a transmembrane sequence encoded by exon 6. The other two isoforms are soluble PVRs (s PVR), which lack a transmembrane domain (Table **1**) [80, 81]. Transmembrane PVRs function as active regulators of CTL binding to membrane-located CD226 [82]. For example, hepatocellular carcinoma (HCC) escapes immune surveillance by reducing the expression of transmembrane PVRs [78]. Soluble PVRS is highly expressed in serum in tumor patients, including those with lung, gastrointestinal, breast, or gynecological cancer, resulting in the inhibition of the CTL anti-tumor immune response [83]. However, the ligands that bind to soluble PVRs remain to be clarified.

PVR not only functions as an immune regulator, but its ligands expressed in CTLs also play controversial roles. For example, TIGIT serves as an inhibitory ligand of PVR and dominates immunosuppression compared to CD226 (activator); furthermore, TIGIT+ CD226- CTLs occur in melanoma, indicating a suppressive immune state [84]. However, whether the competitive effect between TIGIT and CD226 is associated with different PVR isoforms remains unclear. Importantly, clinical trials (NCT01491893) [85] suggest that the genetically modified poliovirus vaccine may be a promising cancer treatment.

3.1.4. Dual Effect of IL-33 in Tumor Immunity

Interleukin-33 (IL-33) is a damage-associated molecular pattern (DAMP) molecule belonging to the atypical IL-1 family. In addition to playing an important role in tissue damage, allergy, infection, and immunity, it is also involved in pleiotropic immunomodulatory regulation [86, 87].

Previous studies have shown that IL-33 plays a role in tumor promotion and inhibition, depending on the tumor type, targeted immune cells, and cytokines (Fig. **3**). In breast cancer, IL-33 promotes tumor growth and metastasis [88]. For example, overexpression of IL-33 in ER+ human breast cancer cell lines can induce resistance to tamoxifen through stem cell properties [89]. However, IL-33 can also reduce the growth and metastatic ability of breast cancer as it maintains a favorable microenvironment for cooperation between CD8+ T and NK cells to help eliminate tumors [90]. In colorectal cancer (CRC), IL-33 performs two opposite roles: *i.e.*, promotion of tumor formation, proliferation, and metastasis [91, 92] and protection through IFN-γ-mediated anti-tumor immunity [93]. The dual role of IL-33 has also been found in lung cancer [87, 94].

IL-33 possesses three mRNA transcript variants through AS [87]. Several studies have suggested that the multifunctions of IL-33 are related to its three isoforms (*i.e.*, variant 1: NM_001314044.1; variant 2: NM_001199640.1; variant 3: NM_001199641.1) (Table **1**) [87]. For example, Afferni *et al*. [87] extracted data from ISO Expresso [95] and revealed that the expression levels of IL-33 variants 2 and 3 increase in thyroid, liver, breast, and bladder cancers, whereas the only variant 1 is expressed in normal tissues. This indicates that specific abnormal splicing of IL-33 may be associated with the progression of these tumors.

3.2. B Cells in Hematological Cancers

Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma. Forkhead transcription factor (FOXP1) is a potential oncogene in various types of cancer [96]. The N-terminal 100 amino acids of FOXP1 are absent in the small isoform ($FOXP1^{\Delta N100}$) but not in the full-length isoform [97]. $FOXP1^{\Delta N100}$ is encoded by FOXP1 mRNA lacking exon 6, resulting in translation starting from exon 8 (Table **1**). $FOXP1^{\Delta N100}$ is highly expressed in DLBCL patients and predominantly activates B cells, thus contributing to the development of DLBCL [98]. These insights illustrate the high value of FOXP1 in assessing prognosis and treatment strategies for DLBCL patients.

4. DISCUSSION

Based on a review of recent literature, AS appears to serve as a double-edged sword in the regulation of tumor immunity. Abnormal variant ULBP1 in tumor cells can activate NK cells and thus has a killing effect on tumors, whereas abnormal variants of NCRs from NK cells can inhibit the activation of NK cells and allow tumors to escape. Even different isoforms produced by the same mRNA can have the opposite effects (*e.g*., IL-33); therefore, AS can be a weapon used by both tumor cells and immune cells.

Many clinical applications target AS for therapeutic purposes. For example, tumors with deletion of exon 14 show high sensitivity to the MET inhibitor [99, 100]. A similar example of BRAF V600E in melanomas has been also reported [101]. Furthermore, small molecules designed to regulate RNA splicing have achieved good results in preclinical studies. For example, Salton *et al*. reported a comprehensive collection of AS-targeted small molecule.

Gene-modified human polioviruses have been shown to be effective in targeting PVR-positive tumor cells [77, 102-104]. Furthermore, there are many proposed patents for AS and cancer [105]. For example, a new Bax isoform (BaxΔ2) has been reported in colon cancer cell lines. Bax Δ2 can impair cancer cell sensitivity to chemotherapeutic drugs that target caspase 8 [106]. Antibodies against Bax Δ2 can be used to detect Bax Δ2 expression levels in circulating tumor cells isolated from patients, which is helpful for guiding clinical treatment strategies [106].

Tumor immunology is an emerging field that has revolutionized cancer treatment. Most immunotherapy strategies have focused on T cell engineering [107]. However, research on NK cells has gradually increased, with such cells demonstrating a direct killing effect on tumor cells, without relying on specific antigen recognition [108]. Thus, NK cells exhibit efficient elimination of distal metastasis and circulating tumor cells. In addition, the importance of macrophages in immunotherapy should not be ignored. For example, our previous study showed that extensive mutual AS editing exists between macrophages and breast cancer cells [109].

Taken together, we discussed the tumor-immune cell crosstalk from an AS point-of-view. As AS events produce many more recurrent neoantigens than are produced by point mutations [110], greater attention should be paid to AS-derived neoantigens. Although immunotherapies targeting AS-derived neoantigens face technological and biological challenges, screening new AS-based antigens as targets of immunotherapy will benefit tumor patients [111]. In addition, specific AS events and their roles in immunity regulation need careful classification. Promisingly, the generation of Spinraza, a drug for spinal muscular atrophy (SMA), highlights the possibility of splicing as a therapeutic target. Spinraza is an antisense oligonucleotide, which plays a therapeutic role by targeting the splicing of pre-SMN2 mRNA to increase the production of the full-length SMN protein [112]. With increasing research on the molecular functions of genes and proteins with abnormal AS, more potential immunotherapeutic targets of AS will emerge [113].

AS defects are often found in human cancers. They may be caused by a mutation in splicing regulatory elements of specific cancer genes or abnormal alteration of splicing events. RNA splicing regulators have emerged as a new class of oncoproteins and tumor suppressors that can regulate the RNA isoforms involved in cancer hallmarks. In addition, AS is a comprehensive and dynamic process rather than a static one. Thus, under clinical treatment application, how to target AS events or splicing regulators effectively in order to produce stable treatment, is worth further exploration.

CONCLUSION

We systematically elucidated the splicing events of several specific genes that promote or inhibit tumors between tumor-immune cell interactions. We analyzed the innate and adaptive immune responses of a variety of tumors, including solid and hematologic tumors. Cancer-specific antigens produced by AS exhibit considerable potential in the development of novel therapeutic approaches for the treatment of cancers.

AUTHOR CONTRIBUTIONS

Honglei Zhang, Jianyun Nie and Baowei Jiao designed and supervised the work. Yue Wang and Honglei Zhang wrote the manuscript. Yue Wang created the three illustrations for this manuscript. Xiyin Li, Wenhuan Wang and Hairui Wang retrieved literature and analyzed the data. All authors read and approved the final manuscript.

LIST OF ABBREVIATIONS

A3SS	=	Alternative 3’ splice sites
A5SS	=	Alternative 5’ splice sites
AML	=	Acute myeloid leukemia
APC	=	Antigen-presenting cells
AS	=	Alternative splicing
ATF	=	Activating transcription factor
CD200L	=	Full-length CD200
CD200R	=	CD200 receptor
CD200S	=	Truncated forms of CD200
CGAs	=	Cancer germline antigens
CRC	=	Colorectal cancer
CTL	=	Cytotoxic T lymphocytes

DAMP = Damage-associated molecular pattern
DC = Dendritic cells
DLBCL = Diffuse large B cell lymphoma
HCC = Hepatocellular carcinoma
HLA = Human leukocyte antigen
HPV = Human papillomavirus
IFN γ = Interferon γ
IRAK4 = Interleukin-1 receptor-associated kinase 4
MHC = Major histocompatibility complex
MLL5 = Mixed-lineage leukemia-5
MXE = Mutually exclusive exon
NCRs = Natural cytotoxicity receptors
NK cell = Natural killer cell
NKIS = NK immunological synapse
NSCLC = Non-small cell lung cancer
PCNA = Proliferating cell nuclear antigen
PVR = Poliovirus receptor
RBM4 = RNA-binding motif 4
RI = Intron retention
s PVR = Soluble PVR
SCMs = Splice-site-creating mutation
SE = Exon skipping
TAMs = Tumor-associated macrophages
TCR = T cell receptor
TIGIT = T cell Ig and ITIM domain
tm PVR = Transmembrane PVR
TSAs = Tumor-specific antigens
U2AF1 = U2 small nuclear RNA auxiliary factor 1

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by the National Natural Science Foundation of China [grant No.81960479, No.81760480 and No.81360392] (to Jianyun Nie); [grant No. 31801249] (to Honglei Zhang).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We would also like to acknowledge the efforts of Dr. Christine Watts for language editing.

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