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Review

The interplay between non-coding RNAs and alternative splicing: from regulatory mechanism to therapeutic implications in cancer

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Abstract

Alternative splicing (AS) is a common and conserved process in eukaryotic gene regulation. It occurs in approximately 95% of multi-exon genes, greatly enriching the complexity and diversity of mRNAs and proteins. Recent studies have found that in addition to coding RNAs, non-coding RNAs (ncRNAs) are also inextricably linked with AS. Multiple different types of ncRNAs are generated by AS of precursor long non-coding (pre-lncRNAs) or precursor messenger RNAs (pre-mRNAs). Furthermore, ncRNAs, as a novel class of regulators, can participate in AS regulation by interacting with the cis-acting elements or trans-acting factors. Several studies have implicated abnormal expression of ncRNAs and ncRNA-related AS events in the initiation, progression, and therapy resistance in various types of cancers. Therefore, owing to their roles in mediating drug resistance, ncRNAs, AS-related factors and AS-related novel antigens may serve as promising therapeutic targets in cancer treatment. In this review, we summarize the interaction between ncRNAs and AS processes, emphasizing their great influences on cancer, especially on chemoresistance, and highlighting their potential values in clinical treatment.

Keywords: Alternative splicing, Non-coding RNA, Cancer, Drug resistance, Chemotherapy, Targeted therapy, Immunotherapy

Background

Gene expression is tightly regulated at multiple levels during physiological processes, whose dysregulation is associated with several diseases, including cancer [1]. RNA splicing, a fundamental step of gene expression, involves the removal of introns from precursor messenger RNAs (pre-mRNAs) and the merging of the exons to form mature mRNAs [2-4]. Alternative selection of spliced exons, also known as alternative splicing (AS), can result in different protein products from a single primary transcript, and thus AS acts as a predominant post-transcriptional regulatory mechanism of gene expression [5, 6].

In addition to coding RNAs, non-coding RNAs (ncRNAs) are also inextricably linked with AS. Non-coding RNAs (ncRNAs) are functional RNAs that do not encode proteins. The advancement in high-throughput sequencing in the last decades has allowed us to identify a large number of ncRNAs, including long non-coding RNAs (lncRNAs),

microRNAs (miRNAs), circular RNAs (circRNAs), small nucleolar RNAs (snoRNAs) and small nuclear RNA (snRNAs), which are generated by AS of pre-lncRNAs or pre-mRNAs [7-11]. Recent studies have shown that ncRNAs, originally considered as transcriptional "junks", play vital roles in gene expression regulation, including AS [12-17]. Extensive interactions between ncRNAs and AS have been reported, which contribute to the complexity of gene regulation in cancer. Therefore, deciphering their interplay would help to determine cancer pathogenesis of cancer and provide new insights into cancer therapy. In this review, we summarize the molecular mechanisms and potential roles of the interaction between ncRNAs and AS in the development, progression and multi-drug resistance (MDR) of various cancers and discuss the latest development in therapeutic strategies targeting AS or AS-related ncRNAs.

The regulation mechanism of RNA splicing

Pre-mRNA splicing in the eukaryotic cell was first discovered in 1977 using an electron microscope [18-20]. To date, our understanding of RNA splicing has been greatly improved. As seen in Figure 1, RNA splicing is a highly regulated process, which requires coordination between spliceosomes, cis-acting elements, and trans-acting proteins to remove introns from pre-mRNAs and merge the protein-coding exons to generate mature mRNAs [21].

The introns contain three important sites, the 5' splice site (5'SS), branch point site (BPS), and 3' splice site (3'SS), which are short conserved sequences (Figure 1A). In general, the RNA splicing process is a two-step transesterification reaction that begins with a nucleophilic attack at the 5' SS (also known as the splice donor) by a 2'-hydroxyl group of the BP adenosine. This reaction creates a cleaved 5' exon and a lariat structure containing the intron and the 3' exon. Subsequently, the 3'-hydroxyl group on the detached 5' exon attacks the 3' SS (also referred as the splice acceptor), which removes the intron and ligates the exons to produce a mature mRNA [22, 23].

In the splicing process, the generation of spliceosome plays an important function (Figure 1B). The spliceosome is a large multimeric ribonucleoprotein (RNP) complex which consists of five small nuclear ribonucleoproteins (snRNPs), including U1, U2, U4/U6, and U5. The U1 and U2 snRNPs recognize the 5'SS and the BP sequence, respectively, and functionally generate the pre-spliceosome. The pre-spliceosome then associates with the preassembled U4/U6/U5 tri-snRNP to form the fully assembled spliceosome to execute the splicing function [24-27].

In addition, some other important cis-acting elements on pre-mRNA such as intronic splice enhancers and silencers, exonic splice enhancers and silencers (ISEs, ISSs, ESEs, and ESSs, respectively) are important for the splicing regulation by recruitment of splicing factors such as serine/arginine-rich (SR) proteins and heterogenous nuclear ribonucleoproteins (hnRNPs) (Figure 1A). The SR proteins contain one or more RNA recognition motifs that bind to ESEs and ISEs on the pre-mRNA to recruit other SFs. The hnRNPs are generally more diverse in their RNA-binding domain and preferentially interact with the splicing silencers [28-30].

More than 95% of human genes undergo AS, which contributes to the diversity of RNA transcripts and protein products [31-33]. Figure 1C illustrates different types of AS, including exon skipping (ES), intron retention (IR), alternative 5' or 3' splice site selection (A5SS or A3SS) and mutually exclusive exons (MXE) [15, 34]. AS is regulated by cis-acting elements in pre-mRNAs and trans-acting factors, whose mutation or deregulation could lead to aberrant AS events and is usually associated with tumorigenesis.

NcRNAs produced by RNA splicing

Similar to mRNAs, the majority of ncRNAs are produced by the splicing of primary transcripts (also known as host genes). In this section, we discuss the splicing mechanisms underlying the biogenesis of various ncRNAs, including lncRNAs, circRNA, snoRNAs and sno-derived RNAs (sdRNAs), and clarify their biological significance in tumorigenesis and progression (Figure 2, Table 1 and 2).

AS of lncRNAs from pre-lncRNAs

LncRNAs are >200 nucleotide-long RNA transcripts that do not encode proteins. They are generated from the splicing of pre-lncRNAs (Figure 2A). AS of lncRNAs produces different isoforms of lncRNAs that might exert different functions in cancer [35-39]. For example, a multi-exon lncRNA *PXN-AS1*, which is regulated by SFs MBML3 and DDX17, could be spliced into multiple isoforms in hepatocellular carcinoma (HCC) [35]. MBNL3 promotes the inclusion of the exon 4 of *PXN-AS1* to produce *PXN-AS1-L*, which inhibits myeloid cell leukemia (Mcl)-mediated cell apoptosis in a *PXN*-dependent manner [35]. Whereas DDX17 induces the retention of the intron 3 of *PXN-AS1* to produce a novel aberrant isoform, *PXN-AS1-IR3*, which promotes HCC metastasis by inducing *MYC* transcription activation [36].

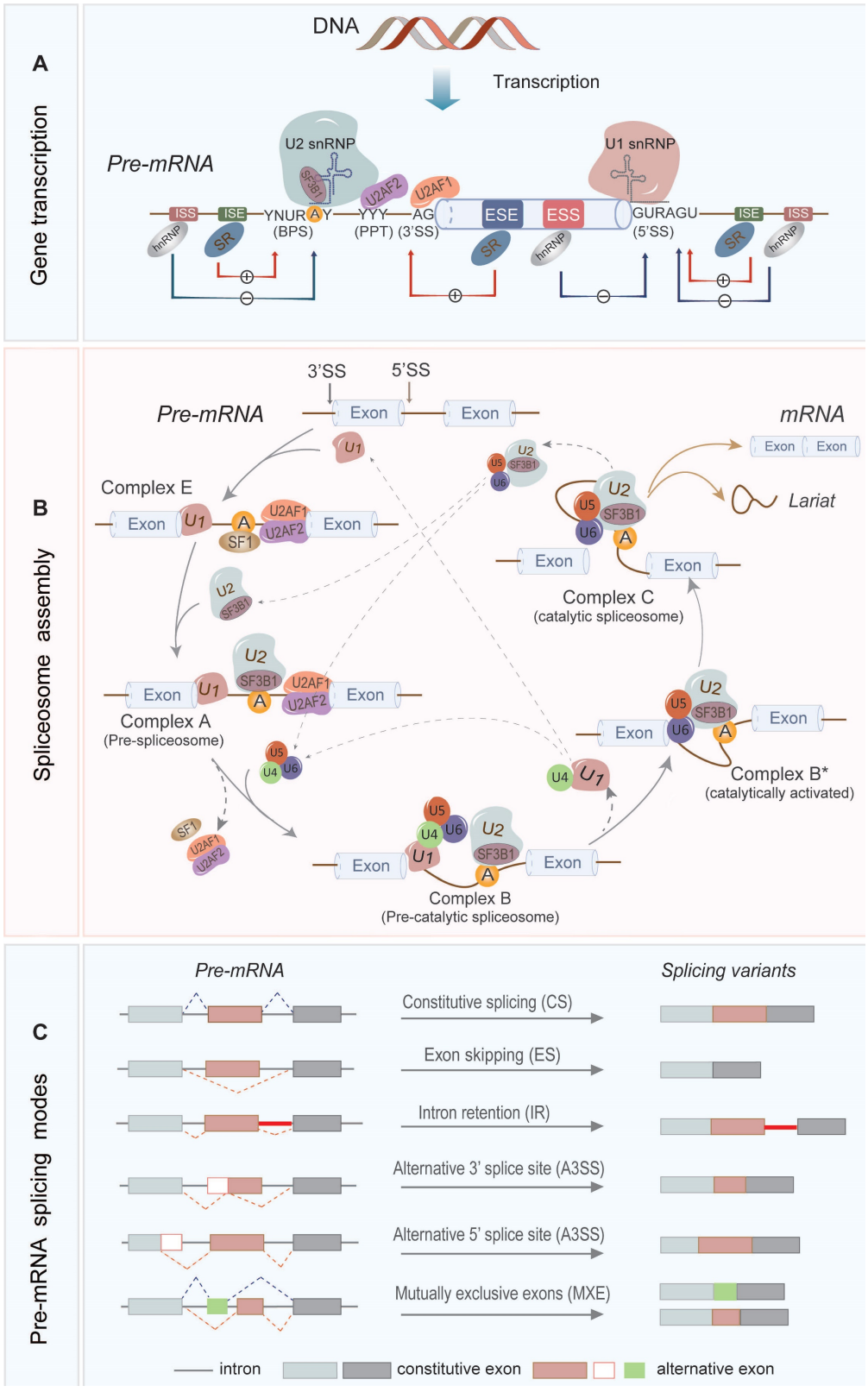

Figure 1. The regulation mechanism and mode of RNA splicing. **(A)** The cis-acting elements on the primary transcription product include a 5' splice site (5'SS), 3' splice site (3'SS), branch point site (BPS), polypyrimidine tract (PPT), and splicing regulatory elements (SREs) in the proximity of splice site. The SREs are subdivided into intronic and exonic splice enhancers and silencers (ISEs, ISSs, ESEs, and ESSs, respectively). SR proteins as splicing activators enhance the utilization of splice sites by preferentially combining with ESEs and ISEs; and conversely, hnRNPs as splicing repressors inhibit the binding to the splice sites by interacting with ESSs and ISSs. **(B)** U1 snRNP recognizes 5'SS and binds it via base pairing, while SF1, U2AF2 and U2AF1 combines separately the BPS, PPT and 3'SS, forming early complex E. Then U2 snRNP replaces SF1 and binds to the BPS to form complex A. The U4/U6–U5 tri- snRNP complex is subsequently recruited to form a pre-catalytic spliceosome. The complex B is rearranged to form catalytically activated complex B*, which catalyzes the first transesterification reaction to produce Complex C, followed by the second transesterification reaction. Lastly, exons are interlinked to form mature mRNA, and the introns are degraded rapidly as the lariat and snRNPs are recovered. **(C)** RNA splicing consists of constitutive splicing (CS) and alternative splicing (AS), and various AS modes are generated based on the multiple splice sites and ways of exon linking, including exon skipping (ES), alternative 5' or 3' splice site selection (A5SS or A3SS), mutually exclusive exons (MXE) and intron retention (IR).

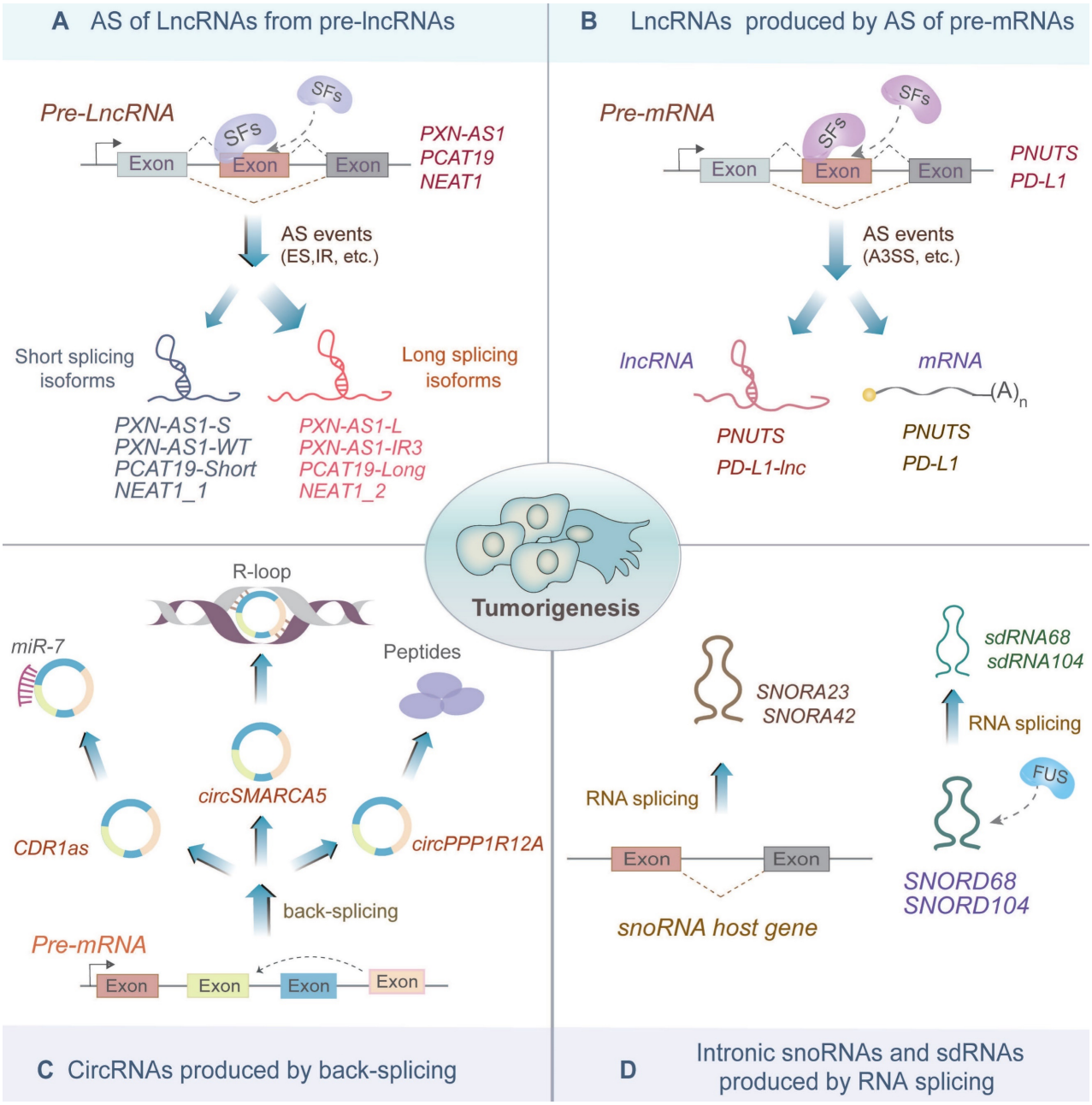

Figure 2. Non-coding RNAs produced by RNA splicing. **(A)** Precursor long non-coding RNAs (pre-lncRNAs) undergo splicing factor-mediated alternative splicing, which triggers the L/S switch. The long splicing isoforms, such as *PXN-AS1-L*, *PXN-AS1-IR3*, *PCAT19-Long* and *NEAT1_2*, have been reported to promote tumorigenesis. **(B)** LncRNAs *PNUTS* and *PD-L1-lnc* generated by bifunctional pre-mRNA splicing can promote carcinogenesis. **(C)** CircRNAs produced by backing splicing of host genes are involved in the regulation of several biological processes. For instance, *CDR1as, circSMARCA5* and *circPPP1R12A* affect cancer progression through sponging miR-7, forming an R-loop with parental DNA, and producing peptides, respectively. **(D)** SnoRNAs **(***SNORA23* and *SNORA42*) are produced by splicing of the intronic region of the host genes, while sno-derived RNAs (sdRNAs) *sdRNA68* and *sdRNA104* are produced by FUS-mediated self-splicing of some snoRNAs. Both snoRNAs and sdRNAs are reported to alter the process of tumorigenesis in some cancers.

Moreover, AS of lncRNA *PCAT19* also generates two isoforms, namely *PCAT19-short* and *PCAT19-long*, which exhibit reciprocal expression in pancreatic cancer (PCa) [37]. The *PCAT19-long* isoform interacts with HNRNPAB to activate a subset of cell-cycle genes associated with PCa progression, such as CHEK1 and AURKB, while the *PCAT19-short* isoform possesses potential tumor suppressive function [37]. In addition, *NEAT1*, a well-known oncogenic lncRNA, produces two isoforms, *NEAT1_1* and *NEAT1_2* [40, 41]. Among these, *NEAT1_2* is significantly upregulated in papillary thyroid carcinoma (PTC) and non-small cell lung cancer (NSCLC) compared with that in noncancerous tissues [38, 39, 42]. In PTC, *NEAT1_2* significantly promotes cell growth and metastasis by acting as a sponge of *miR-106b-5p* to derepress ATAD2 expression [39]; while in NSCLC, RBM10 regulates AS of *NEAT1* to downregulate NEAT1_2 expression, ultimately affecting the invasion and metastasis of NSCLC by suppressing the

activation of the PTEN/PI3K/AKT/mTOR signaling pathway [38].

LncRNAs produced by AS of pre-mRNAs

Recent studies revealed that some pre-mRNAs are bifunctional and could serve as precursors of both mRNAs and lncRNAs [43, 44] (Figure 2B). For instance, *PNUTS* is a bifunctional pre-mRNA encoding both *PNUTS* mRNA and *lncRNA-PNUTS* [43]. In breast cancer, the *PNUTS* mRNA switches to *lncRNA-PNUTS*, which serves as a competitive sponge for miR-205, thereby promoting tumor epithelial-mesenchymal transition (EMT) [43]. In lung adenocarcinoma (LUAD), bifunctional *PD-L1* pre-mRNA produces *PD-L1-lnc,* a lncRNA isoform, in addition to *PD-L1* mRNA [44]. *PD-L1-lnc* is induced by IFNγ and binds to MYC to enhance its transcriptional activity, consequently activating its downstream genes and promoting LUAD cell proliferation and invasion [44]. Altogether, these findings uncovered the novel lncRNA-mediated functions of pre-mRNAs in cancer.

Table 1. LncRNAs involved in the dysregulated alternative splicing events for carcinogenesis and progression

LncRNA	Mechanism	Target genes	Patterns	Biology function	Related diseases or processes	Refs
PXN-AS1	interacts with SF MBNL3	pre-PXN-AS1 → PXN-AS1-L	ES: exon 4 (-)	promotes proliferation and tumorigenesis	Hepatocellular carcinoma	[35]
	interacts with DDX17	pre-PXN-AS1 → PXN-AS1-IR3	IR: intron 3	activates MYC pathway	Hepatocellular carcinoma	[36]
PCAT19	produces long isoform that interacts with HNRNPAB	pre-PCAT19 → PCAT19-Long	/	activate a subset of cell-cycle genes	Prostate cancer	[37]
NEAT1	produces two isoforms and the long has tumor-promoting effect	pre-NEAT1 → NEAT1_2	/	promotes cell growth and metastasis	Non-small cell lung cancer, Papillary thyroid cancer	[38, 39]
lncRNA-PNUTS	produced by hnRNPE1-mediated AS of PUNTS	PNUTS pre-mRNA → lncRNA-PNUTS	A3SS (exon 12)	promotes tumor progression	Breast cancer, Epithelial-Mesenchymal Transition	[43]
PD-L1-lnc	produced by AS of PD-L1	PD-L1 pre-mRNA → PD-L1-lnc	/	enhances c-Myc transcriptional activity	Lung adenocarcinoma	[44]
Linc01232	suppresses the degradation of HNRNPA2B1	A-Raf pre-mRNA → A-Raf FL	ES (-)	activates MAPK/ERK signaling pathway	Pancreatic cancer	[54]
DGCR5	binds with SRSF1 to increase its stability	Mcl pre-mRNA → Mcl-1L	ES: exon 2 (-)	inhibits cell apoptosis	Esophageal squamous cell carcinoma	[55]
SNHG6	recruits and binds to hnRNPA1	PKM pre-mRNA → PKM2	MXE (exon 9,10)	enhances aerobic glycolysis	Colorectal cancer	[56]
PLANE	recruits and binds to hnRNPM	NCOR2 pre-mRNA → NCOR2-202 (-)	A5SS (intron 45)	promotes proliferation and tumorigenicity	Pan-cancer	[119]
BC200	recruits and binds to hnRNPA2B1	BCL-X pre-mRNA → BCL-XL	A5SS (exon 2) (-)	promotes cell proliferation	Breast cancer, Apoptosis	[120]
LincRNA-uc002yug.2	binds to SRSF1 and MBNL	RUNX1 pre-mRNA → RUNX1a	/	promotes cell proliferation and tumor growth	Esophageal cancer	[121]
PNCTR	recruits RBPs PTBP1and down-regulates them	CHEK2 pre-mRNA → CHEK (-)	ES: exon 8 (-)	promotes cell survival	Pan-cancer	[57]
TPM1-AS	combines competitively with RBM4	TPM1 pre-mRNA → TPM1 V2 and V7 (-)	MXE (exons 2a,2b)	inhibits cancer cell migration and formation of filopodia	Esophageal cancer	[122]
KASRT	interacts with SRSF1and down-regulates it	KLF6 pre-mRNA → KLF6-SV1	IR (-)	modulates P21/CCND1 pathway	Osteosarcoma	[123]
LINC01133	combines competitively with SRSF6	/	/	inhibits epithelial–mesenchymal transition and metastasis	Colorectal cancer	[124]
lncRNA AB074169 (lncAB)	combines competitively with RBP KHSRP and decreases its expression	p21 pre-mRNA→ p21 (CDKN1a) (-)	/	inhibits cell proliferation and tumor growth	Papillary thyroid cancer	[125]
CCAT1	targets miR-490 and up-regulates hnRNPA1 expression	/	/	promotes cell migration	Gastric cancer	[61]
LOC90024	encodes SRSP which interacts with SRSF3	Sp4 pre-mRNA → L-Sp4	ES: exon 3 (-)	promotes cancer tumorigenesis and progression	Colorectal cancer	[67]
HOXB-AS3	encodes HOXB-AS3 peptide which competitively binds to hnRNPA1	PKM pre-mRNA → PKM2 (-)	MXE (exon 9,10)	regulates cancer metabolism reprogramming	Colorectal cancer	[68]
asFGFR2	creates a chromatin environment and inhibits SF MRG15-PTB binding	FGFR2 pre-mRNA → FGFR2-IIIb	ES: exon IIIb (-)	suppresses cell proliferation and migratory potential	Hepatocellular carcinoma	[69, 71]
ENST00000501665.2	binds to RBPs of SWI/SNF chromatin remodeling complex	OIP5 pre-mRNA →OIP5	/	enhances expression of the oncogene	HEK293 cell	[70]
Fas-AS1	forms RNA-RNA duplexes with Fas pre-mRNA and recruits SPF45	Fas pre-mRNA → sFas	ES: exon 6	inhibits cell apoptosis	Apoptosis	[74]
ZEB2	forms RNA-RNA duplexes with ZEB2 pre-mRNA	ZEB2 pre-mRNA → ZEB2	IR	downregulates E-cadherin expression	Epithelial-Mesenchymal Transition	[75]
UXT-AS1	forms RNA-RNA duplexes with UXT pre-mRNA	UXT pre-mRNA → UXT2	A5SS	promotes cell proliferation and inhibits cell apoptosis	Colorectal cancer	[76]

* (-) refers to down-regulated AS products of target genes or suppressed AS events.

Table 2. CircRNAs, miRNAs and snoRNAs involved in the dysregulated alternative splicing events in cancer

Type	NcRNA	Mechanism	Target genes	Patterns	Biology function	Related diseases or processes	Refs
CircRNA	CircSMARCA5	combines competitively with SRSF1	VEGFA pre-mRNA → Iso8a (-)	ES: exon 8	inhibits angiogenesis	Glioblastoma multiforme	[58]
	CircURI1	combines competitively with hnRNPM	VEGFA pre-mRNA → VEGFAe7IN (-)	ES: exon 7	suppresses cell migration	Gastric cancer	[126]
	CircMYH9	combines competitively with hnRNPA2B1	p53 pre-mRNA → p53 (-)	/	promotes tumor growth by modulating Serine and glycine metabolism and redox homeostasis	Colorectal cancer	[127]
	CIRC-UBR5	recruits splicing regulatory factor QKI, NOVA1 and U1 SnRNA	/	/	regulates tumor differentiation	Non-small cell lung cancer	[128]
	CircRNA100146	targets miR-361-3p, miR-615-5p and up-regulates SF3B3 expression	/	/	promotes cell proliferation and invasion	Non-small cell lung cancer	[62]
MiRNA	miR-92a	reduces RBM4 expression	PTB pre-mRNA → nPTB	ES: exon 10 (-)	increases the invasion, migration, and mitochondrial activity	Colorectal cancer	[60]
	miR-193a-3p	reduces SRSF2 expression	BCL-X, caspase 9 pre-mRNA → BCL-XL, caspase 9a	A5SS (exon 2); ES (-)	promotes cisplatin resistance	Gastric cancer	[81]
	miR-30a-5p, miR-181a-5p, miR-216b-5p	decreases SRSF7 expression	SPP1 pre-mRNA → SPP1-c	MXE (exon 3,5)	decreases cell proliferation rate	Renal cancer	[129]
	miR-30c	decreases SRSF1 expression	/	/	suppresses cell survival and proliferation	Prostate cancer	[130]
	miR-1296	reduces SFPQ expression	/	/	promotes cell proliferation, invasion, migration	Colorectal cancer	[131]
	miR-133b	reduces SF3B4 expression	/	/	promotes cell proliferation and metastasis	Hepatocellular carcinoma	[132]
SnoRNA	SNORD104, SNORD68	interacts with RBP FUS	pre-snoRNAs → sdRNAs (sdRNA104, sdRNA68)	/	affects cell growth and proliferation	Colorectal cancer	[52]
	SNORD27	combines competitively with U1 snRNA and SFs	E2F7 pre-mRNA → E2F7	ES (exon 12)	regulates E2F7-dependent cell cycle regulation	Cell cycle	[59]
	SNORA70E	/	PARPBP-88 pre-mRNA → PARPBP-15	ES (exon 4)	promotes tumorigenesis and progression	Ovarian cancer	[133]

* (-) refers to down-regulated AS products of target genes or suppressed AS events.

CircRNAs produced by back-splicing

CircRNAs are closed-loop RNA molecules produced by back splicing of the parental genes, in which the downstream splice site is reversed and joined to the upstream splice site [10]. Previously, circRNAs were regarded as accidental "splicing noise" or by-products with few biological functions. However, increasing evidence suggests that circRNAs exert vital roles, such as miRNAs sponging, transcription regulation, and peptides encoding [45-47] (Figure 2C). For instance, circRNA *CDR1as* sponges *miR-7* to enhance the stability of *miR-7* targets including *E2F3, CKAP4*, and *TGFBR2*, thus promoting tumor growth and progression [45, 48]. Additionally, *CircSMARCA5*, derived from the back-splicing of exon 15 and exon 16 of *SMARCA5*, binds to the genomic location of *SMARCA5* to form an R-loop, which pauses transcription at exon 15 of *SMARCA5* and produces truncated nonfunctional proteins, thus increasing sensitivity to cisplatin chemotherapy of breast cancer [46]. Moreover, *CircPPP1R12A* is generated by reverse splicing exon 24 and 25 of *PPP1R12A* pre-mRNA, and encodes a 73-amino acid peptide, called circPPP1R12A-73aa [47]. CircPPP 1R12A-73aa promotes proliferation and metastasis of colon cancer through activating the Hippo-YAP signaling pathway [47]. Therefore, circRNAs produced by splicing exhibit significant effects associated with carcinogenesis.

Intronic snoRNAs and sdRNAs produced by RNA splicing

The majority of snoRNAs are processed from the introns of snoRNA host genes (SNHGs) [49] (Figure 2D). For example, *SNORA23* is generated by the splicing of the intronic region of the *IPO-7* gene, and its elevated levels significantly promote cancer cell survival and invasion in pancreatic ductal adeno-carcinoma [50]. Furthermore, *SNORA42* is spliced from the intron 10 of the *KIAA0907* gene, and its elevated levels play oncogenic roles via driving the malignant phenotype in NSCLC cells [51]. Therefore, snoRNAs spliced from SNHGs perform essential functions during tumor development.

A preprint by Plewka P et al. argued a novel molecular mechanism of snoRNA self-splicing (Figure 2D), in which snoRNAs *SNORD104* and *SNORD68* interacted with RNA-binding protein (RBP) FUS and were further spliced into smaller sdRNAs (*sdRNA104* and *sdRNA68*, respectively) [52]. FUS-dependent *sdRNA68* and *sdRNA104* regulated the expression of two colorectal cancer (CRC)-promoting genes, including *KCNQ10T1-001* antisense transcript and

BRE mRNA [52, 53]. Therefore, sdRNAs, as spliced products of snoRNAs, play critical pathological functions during tumor proliferation and progression.

Collectively, a numerous of ncRNAs generated by RNA splicing serve as potential prognostic and therapeutic biomarkers, indicating potential candidate targets for tumor prevention and treatment.

Regulation of alternative splicing by ncRNAs

Recent studies have identified that ncRNAs exert their functions as regulators of AS events. As illustrated in Figure 3, ncRNAs regulate AS of pre-mRNAs by influencing the trans-acting factors or cis-acting elements, thus resulting in abnormal splicing of certain oncogenes or tumor suppressors (Table 1 and 2).

NcRNAs regulate AS through influencing trans-acting factors

NcRNAs alter the expression and function of splicing factors (SFs) via interacting with SFs as "Interactors" or "Hijackers", participating in competing endogenous RNA (ceRNA) regulatory network, encoding functional peptides and chromatin remodeling, thereby triggering tumor-associated alternative pre-mRNA splicing events.

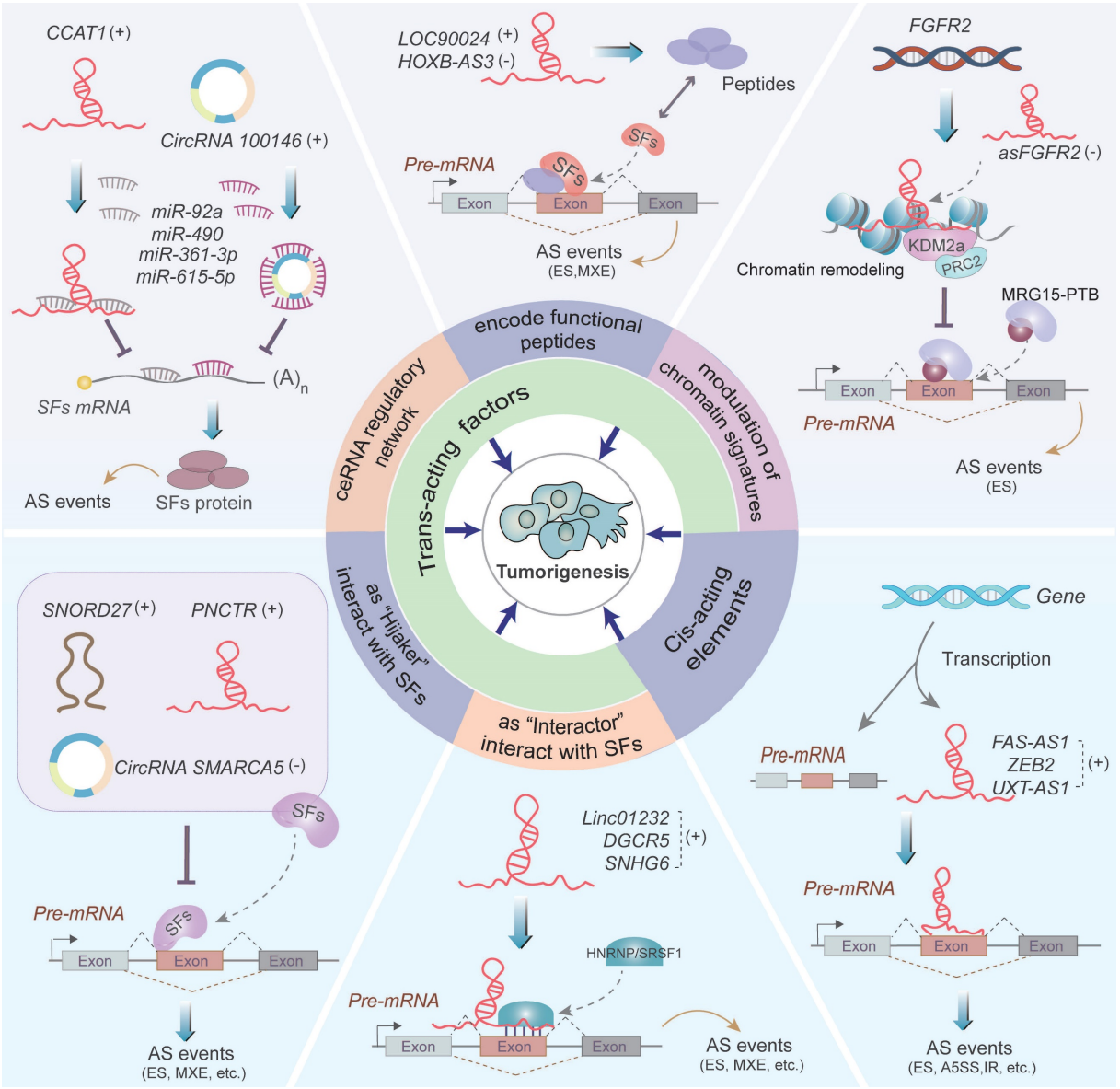

Figure 3. Regulation of alternative splicing by ncRNAs. Noncoding RNAs including lncRNAs, circRNAs, miRNAs, and snoRNAs regulate the occurrence of carcinogenesis-related AS events through two main splicing regulatory mechanisms. One way is to interact with the trans-acting factors, comprising acting as "Interactors" or "Hijackers" of SFs, participating in ceRNA regulatory network, encoding functional peptides and modulating chromatin signatures, all of which influence the expression and function of SFs. The second way is ncRNAs form dsRNA duplexes with the cis-acting elements, thus affecting tumorigenesis. The symbols (+) and (-) denote that ncRNAs act as oncogenes and tumor suppressor genes, respectively.

NcRNAs acting as "Interactors" of SFs

NcRNAs recruit and stabilize SFs, and positively regulate the process of pre-mRNA splicing as "Interactors" of SFs, consequently influencing the pathogenesis process of tumorigenesis and progression [54-56] (Figure 3). Exemplified by linc01232, which significantly upregulates HNRNPA2B1 protein expression by suppressing its ubiquitin-mediated degradation in PCa cells [54]. Subsequently, the stabilized HNRNPA2B1 participates in the AS of *A-Raf* pre-mRNA and facilitates the formation of full-length *A-Raf* (*A-Raf FL*) isoform, thus promoting PCa cells metastasis [54]. Besides, lncRNA *DGCR5* indirectly regulates AS of *Mcl-1* pre-mRNA by interacting with serine- and arginine-rich splicing factor 1 (SRSF1) to increase its stability, and contributes to the generation of the full length of *Mcl-1* (*Mcl-1L*, anti-apoptotic isoform), thus facilitating the carcinogenesis of esophageal squamous cell carcinoma (ESCC) [55]. Additionally, lncRNA *SNHG6* interacts with hnRNPA1, which triggers hnRNPA1-mediated splicing of *PKM* pre-mRNA and promotes the expression of PKM2 over PKM1, consequently enhancing aerobic glycolysis in CRC cells [56].

NcRNAs acting as "Hijackers" of SFs

Accumulating studies have supported that ncRNAs, including lncRNA, circRNAs and snoRNAs, function as "Hijackers", which competitively bind to SFs and thereby inhibit the interaction between SFs and target pre-mRNAs in the context of tumorigenesis and development [57-59] (Figure 3). For example, lncRNA *PNCTR* recruits many RBPs PTBP1 to the peri-nucleolar compartment and blocks its binding with *CHEK2* pre-mRNA [57]. The interaction between PTBP1 and *CHEK2* pre-mRNA results in the upregulation of a CHEK2 isoform containing exon 8 and enhances the cell survival of cancer cells [57]. Furthermore, it has been convincingly found that *circSMARCA5* hijacks SRSF1 and impedes the binding of SRSF1 protein to vascular endothelial growth factor A (*VEGFA*) pre-mRNA, thus reducing the ratio of pro-angiogenic (Iso8a) to anti-angiogenic (Iso8b) isoforms and inhibiting angiogenesis in glioblastoma multiforme (GBM) cells [58]. In addition, *SNORD27* is a C/D box snoRNA that competitively binds to *U1* snRNAs and several SFs to form RNP complexes in HeLa cells [59]. The RBPs facilitate the skipping of exon 12 in *E2F7* pre-mRNA and inhibit the inclusion of silent exon in *MAP4K3, ZBTB37, FER,* and *ABCA8* pre-mRNAs, thereby influencing E2F7-dependent cell cycle regulation [59].

NcRNAs alter SF expression by the ceRNA mechanism

The expression of SFs is regulated by various types of ncRNAs, which can functionally influence the outcomes of AS in cancer [60-62] (Figure 3). MiRNAs suppress SF expression by directly attaching to the 3'-untranslated region (3'-UTR) of the SF transcripts [60, 63]. For instance, miR-92a reduces the expression of RNA-biding motif 4 (RBM4) by targeting the *RBM4* mRNA, which leads to elevated levels of exon 10-included nPTB transcript via an AS-coupled nonsense-mediated decay (NMD) mechanism [60]. Subsequently, nPTB affects the splicing of *FGFR2* and *PKM2* and promotes the isoform *FGFR2* and *PKM2* of these two genes, respectively, thereby altering metabolic signature of CRC cells [60]. More importantly, the ceRNA machinery can alter SF expression involving ncRNAs such as lncRNA, circRNAs, and pseudogenes, and these transcripts regulate each other through competing for shared miRNA regulators at the post-transcriptional level. Since microRNA response elements (MREs) exist on mRNAs, lncRNAs, circRNAs etc., and these RNAs can competitively sponge miRNAs by recognizing the same MREs [64-66]. Thus, lncRNAs and circRNAs can functionally act as ceRNAs to sponge miRNAs and therefor modulate the expression of miRNA-targeted SF mRNAs [61, 62]. Taking lncRNA *CCAT1* as an example, it sponges miR-490 and indirectly upregulates the expression of *hnRNPA1* and subsequently facilitates hnRNPA1-mediated AS events, leading to the migration and metastasis of gastric cancer [61]. Similarly, *circRNA100146* directly sponges miR-361-3p and miR-615-5p and leads to promoting SF3B3 expression, consequently accelerating NSCLC cell proliferation and invasion through SF3B3-mediated AS regulation [62].

NcRNAs affect the function of SFs by encoding functional peptides

NcRNAs can encode "hidden" peptides that regulate RNA splicing [67, 68]. As shown in Figure 3, *LOC90024* encodes a splicing regulatory small protein (SRSP) that enhances the binding of SRSF3 to the exon 3 of *Sp4* pre-mRNA, which induces the generation of long Sp4 isoform (encoding L-Sp4 protein), whereas suppresses short Sp4 isoform (encoding S-Sp4 peptide), ultimately promoting CRC tumorigenesis and progression [67]. LncRNA *HOXB-AS3* encodes a conserved 53-aa peptide named HOXB-AS3, which competitively recognizes the arginine residues in the RGG motif of hnRNPA1 and antagonizes hnRNPA1-dependent *PKM* splicing, leading to the inhibition of PKM2 isoform and glucose metabolism in CRC cells [68]. Taken together, these studies suggest that the

ncRNAs-encoded functional peptides play important roles in AS regulation and may serve as novel targets for peptide-based anti-tumor drugs in the future.

NcRNAs alter the function of SFs by modulation of chromatin signatures

LncRNAs participate in the establishment of cell-specific splicing events by regulation of chromatin conformation signatures [69, 70]. An antisense lncRNA, *asFGFR2,* recruits histone demethylase KDM2a and polycomb repressive complex 2 (PRC2) to the *FGFR2* locus creating an adverse chromatin environment that antagonizes the recruitment of splicing regulatory factor complex MRG15-PTB [69] (Figure 3). This regulatory mechanism eventually promotes the generation of exon IIIb-containing isoform *FGFR2 IIIb*, which inhibits tumorigenicity of HCC cells [69, 71]. Besides, *ENST00000501665.2,* a splicing form of lncRNA *OIP5-AS1,* facilitates the interaction of chromatin-remodeling complexes SWI/SNF with the promoter of *OIP5* by directly binding to multiple nuclear RBPs including SMARCA4, a component of the SWI/SNF multi-subunit molecular complex, which leads to activated transcription and splicing of *OIP5* oncogene [70].

Altogether, these findings demonstrate that ncRNAs influence the expression and function of SFs to regulate multiple cancer-related AS events through different mechanisms, adding complexity into the ncRNAs-AS network.

NcRNAs regulate AS via cis-acting elements

Cis-natural antisense transcripts (cis-NATs) are a new class of RNAs transcribed from the opposite strand of a coding gene and regulate gene expression by forming the double-stranded RNA (dsRNA) with the complementary region [72, 73]. Cis-NATs can regulate AS of their antisense pre-mRNA, involved in diverse cellular functions during carcinogenesis [74-76] (Figure 3). Villamizar O et al. discovered that *FAS-AS1* (SAF), a cis-NAT transcribed from the antisense strand of *FAS*, interacts with *FAS* pre-mRNA to form RNA duplexes. These duplexes recruit SPF45 to mediate exon skipping of *FAS* and upregulate soluble Fas (sFas) protein to protect cells against FasL-induced apoptosis [74]. Similarly, lncRNA *ZEB2 (Sip1)* interacts with the 5'-untranslated region (5'-UTR) of *ZEB2* to form a dsRNA [75]. This interaction blocks the splicing of a large intron located in the 5'UTR of *ZEB2* which contains an internal ribosome entry site (IRES) critical for Zeb2 expression, thus promoting EMT of cancer cells through upregulating Zeb2 protein levels [75]. Moreover, lncRNA *UXT-AS1,* transcribed from the antisense strand of *UXT*, binds to the cis-acting element within *UXT* pre-mRNA [76]. The binding reduces the pro-apoptotic *UXT1* transcripts, meanwhile increases the pro-proliferative *UXT2* transcripts, thereby accelerating CRC progression [76]. Altogether, these publications reveal a novel mechanism of ncRNAs-mediated regulation of AS in cancer cells by RNA duplex formation with the parental pre-mRNA.

NcRNA-regulated AS events mediate drug resistance in oncology

Chemotherapy and targeted therapy are frequently used in cancer treatment. However, multi-drug resistance (MDR) continues to hinder the clinical effects of chemotherapy. AS provides an opportunity for the pro-oncogenes to gain a new function that facilitates cancer cells evade from chemotherapy [77]. For instance, Androgen receptor splice variant 7 (ARV7) is associated with abiraterone resistance in castration-resistant prostate cancer [78]. Besides, Δ16HER2 splice variant is associated with lapatinib resistance in breast cancer [79]. Therefore, owing to the important roles and promising clinical value of AS in drug resistance, as well as above mentioned extensive interplay between ncRNAs and AS, we summarized the interactive network of ncRNA-AS in drug resistance. This may provide new insights into understanding the MDR mechanism and identifying novel targets for preventing or reversing drug resistance in cancers (Figure 4 and Table 3).

NcRNAs trigger AS of cell death-related genes to mediate chemoresistance

Apoptosis-evading cancer cells have a critical role in chemoresistance. NcRNAs regulate the AS events of apoptosis-related genes such as the *BCL-2* family, pro-apoptotic caspases, and *FAS*, thus altering the process of apoptosis and affecting the efficacy of chemotherapeutic drugs [80-82] (Figure 4). LncRNA *UCA1* is abnormally upregulated in cisplatin-resistant oral squamous cell carcinoma (OSCC) cells and sponges miR-184 to enhance SF1 expression. This augments SF1-mediated splicing of *BCL-2* family genes containing *Mcl-1* and increases BCL2 protein expression, thereby preventing apoptosis [80, 83, 84]. Furthermore, *miR-193a-3p* interacts with SRSF2 to increase the anti-apoptotic variant of *BCL-X* (*BCL-XL*) and decrease the pro-apoptotic variant of *caspase 9* (*caspase 9a*), leading to cisplatin resistance in $CD44^+$ gastric cancer cells [81]. Interestingly, EZH2, the catalytic subunit of the PRC2 involved in H3K27 methylation, hyper-methylates the lncRNA *FAS-AS1* promoter and represses the FAS-AS1 expression in chemo-resistant B-cell lymphoma [82]. The reduced FAS-AS1 expression causes increasing of soluble Fas receptor (sFAS) in a RBM5-dependent manner, which

further suppresses apoptosis and leads to acquirement of chemoresistance [82, 85].

Autophagy is another fundamental mechanism that affects the sensitivity of cancer cells to anticancer agents, inhibition of which can also trigger apoptosis in cancer cells [86]. Increasing studies have indicated that the interplay of ncRNAs-AS mediates drug resistance in cells by regulating autophagy [87, 88]. For example, lncRNA *CRNDE* interacts with SRSF6 protein and reduces its stability, thus reducing AS of *PICALM* and inhibiting S-to-L isoform switch [87]. Finally, *CRNDE* suppresses 5-FU/oxaliplatin resistance via attenuating autophagy flux in gastric cancer cells [87]. Another study suggested that estrogen inhibits lncRNA *EGOT* in a dose-dependent manner in breast cancer [88]. Low expression of *EGOT* interferes with pre-ITPR1/EGOT dsRNA formation and hnRNPH1 recruitment, consequently reducing autophagosome accumulation by downregulating ITPR1 protein, and ultimately enhancing paclitaxel resistance [88].

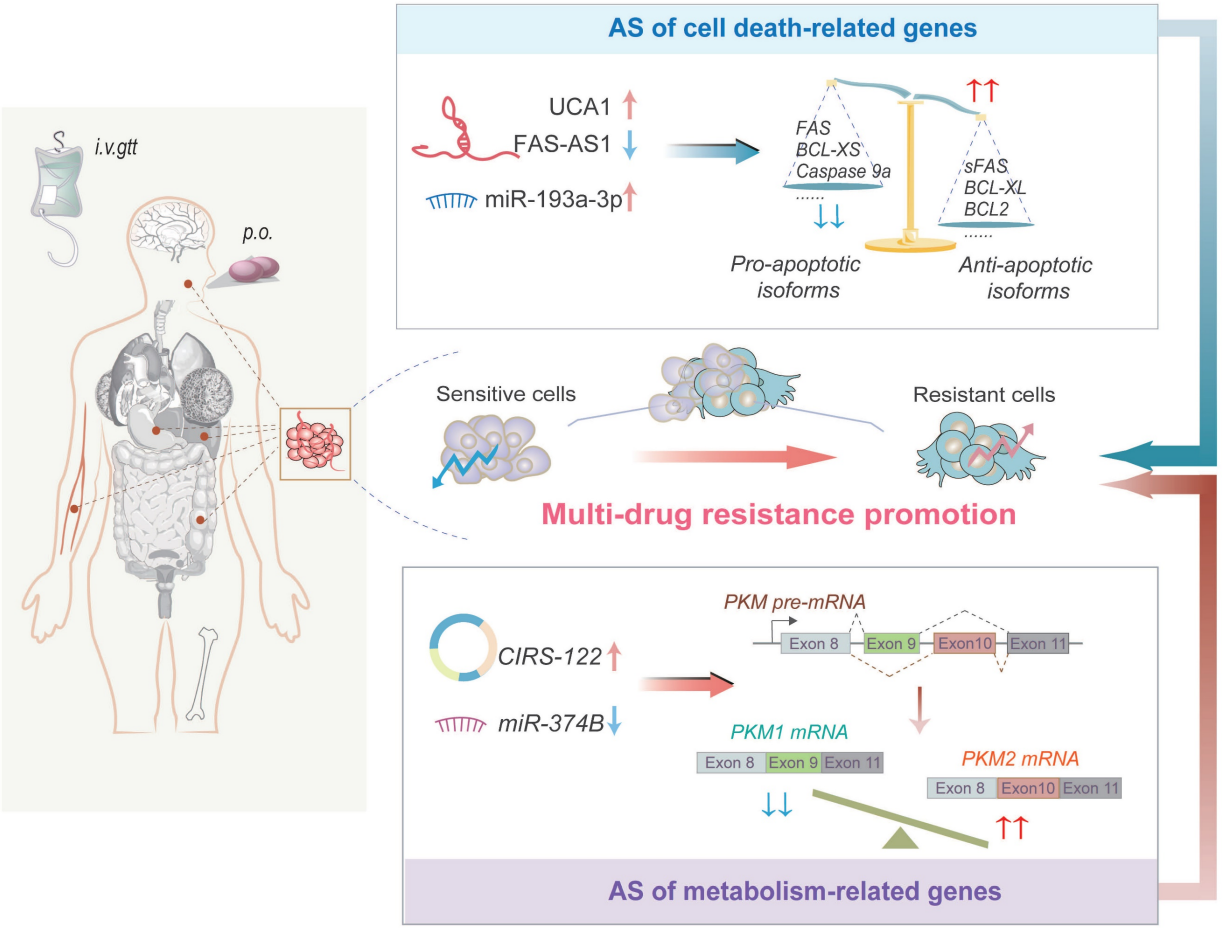

Figure 4. NcRNA-regulated AS events mediate drug resistance in oncology. Some lncRNAs, miRNAs and circRNAs impact drug resistance of cancer cells by triggering AS of cell death-related genes and metabolism-related genes. AS of cell death-related genes decreases the ratio of pro-/anti-apoptotic splicing isoforms to promote apoptotic tolerance in tumor cells, while AS of metabolism-related genes causes the upregulation of *PKM2* expression to promote glycolysis in cancer cells.

Table 3. NcRNA-regulated AS events involved in drug resistance in cancer

NcRNA	Mechanism	Target genes	Biology function	Drugs	Related diseases	Refs
UCA1	targets miR-184 and up-regulates SF1 expression	Mcl pre-mRNA → Mcl-1L	increases BCL2 protein expression	Cisplatin	Oral squamous cell carcinoma	[80, 83]
miR-193a-3p	reduces SRSF2 expression	BCL-X, caspase 9 pre-mRNA → BCL-XL, caspase 9a	suppresses cell apoptosis	Cisplatin	Gastric cancer	[81]
Fas-AS1	low levels of it promote RBM5-mediated AS	Fas pre-mRNA → sFas	causes impaired Fas signaling in chemoresistance	Cytotoxic drugs	B-cell lymphoma	[82, 85]
CRNDE	interacts with SRSF6 and reduces its stability	PICALM pre-mRNA → PICALML (-)	reduces autophagy flux	5-FU/oxaliplatin	Gastric cancer	[87]
EGOT	forms pre-ITPR1/EGOT dsRNA and recruits hnRNPH1	ITPR1 pre-mRNA → ITPR1	promotes autophagy to increase drug sensitivity	Paclitaxel	Breast cancer	[88]
miR-374B	decreases hnRNPA1 expression	PKM pre-mRNA → PKM2 (-)	antagonizes PKM2-mediated glycolysis pathway	Sorafenib	Hepatocellular carcinoma	[94]
CIRS-122	targets miR-12	PKM pre-mRNA → PKM2	promotes glycolysis	Oxaliplatin	Colorectal cancer	[95]

*(-) refers to down-regulated AS products of target genes.

NcRNAs trigger AS of metabolism-related genes to facilitate chemo- and targeted resistance

Cancer cells depend on aerobic glycolysis for ATP production and promoting rapid growth, which are also critical for the development of chemo- and targeted resistance [89]. *PKM* is a critical enzyme in glycolysis metabolism, its splicing is crucial for metabolic regulation [90]. AS of *PKM* pre-mRNA generates two isoforms, *PKM1* and *PKM2*, containing exon 9 and exon 10, respectively. Interestingly, *PKM2* encodes a protein that can catalyze glycolysis, and is correlated with poor prognosis in cancer patients, whereas *PKM1* encodes a protein that can promote oxidative phosphorylation [91-93]. Hence, aberrant AS of *PKM* pre-mRNA triggered by ncRNAs can alter the sensitivity of cancer cells to chemotherapeutic agents [94, 95] (Figure 4). A study found that hnRNPA1 can bind to the flanking sequence of exon 9, resulting in exon 10 inclusion and thus sustaining a high PKM2/PKM1 ratio [96]. However, miR-374b represses hnRNPA1 expression through targeting its 3'UTR, subsequently inhibiting *PKM2* and glycolysis to re-sensitize sorafenib-resistant HCC cells [94]. It seems beyond dispute that AS of *PKM* regulated by miR-374b overexpression plays a significant role in overcoming sorafenib resistance in HCC. Another study indicated that *CIRS122* (hsa_circ_0005963) produced by back splicing upregulates the expression of *PKM2* by sponging miR-122, which stimulates glycolysis and leads to oxaliplatin resistance in CRC cells [95]. This intercellular signal delivery could thus be used as a potential strategy for treating oxaliplatin-resistant CRC [95]. Overall, these findings support that ncRNAs promote drug resistance in tumor cells by enhancing *PKM2*-mediated glycolysis, highlighting their potential as targets to reverse drug resistance in cancer cells.

Targeting AS of ncRNAs or AS-related ncRNAs for cancer therapy

Aberrant AS events are emerging as additional hallmarks of various cancers [33, 97-101]. Currently, strategies targeting AS, such as small molecule targeting SFs or spliceosome, splice-switching antisense oligonucleotides (SSOs) and RNA or protein isoforms have exhibited potential values in clinical treatment (Figure 5). H3B-8800 is an orally available small molecule targeting SF3B1, which has entered phase I of clinical trials for the treatment of hematological malignancies [102, 103]. Besides, SSOs are typically synthetic short-stranded RNAs that are designed to base-pair with cis-acting elements of target pre-mRNA, thus facilitating the conversion of splicing isoforms via blocking the binding of SFs to the pre-mRNA [104]. Li et al. found that *BCL-X* SSO targeting the exon 2 of *BCL-X* pre-mRNA significantly elevates the *BCL-XS*/*BCL-XL* ratio and promotes glioma cell apoptosis [105]. In addition, antisense oligonucleotides (ASOs) targeting RNA isoforms are also emerging as pharmacological agents [106]. Li et al. identified an oncogenic lncRNA AC104041.1, and designed LNA-modified ASO targeting two splice variants of AC104041.1 which exhibited potent anti-tumor activity for head and neck squamous carcinoma (HNSCC) [107]. Moreover, alternative tumor-specific antigens (TSAs) have recently been evaluated and considered to be bona fide targets of anti-cancer immunity [108, 109]. Volpe G et al. reported that in Philadelphia chromosome-positive hematological malignancies, novel BCR-ABL transcripts are generated by AS, whose translational products contain C-terminal amino acid sequence derived from the out of reading frame (OOF) of the *ABL* gene [110]. The presence of OOF-peptide can stimulate specific cytotoxic T lymphocyte reaction, suggesting that the BCR-ABL-OOF isoforms may be novel neoantigens for chronic myeloid leukemia therapy [110]. Some recent studies showed that small molecule inhibitors can also be used as a potential source of tumor antigens and can be used in immunotherapy [111, 112]. Elizabeth A et al. found that triple-negative breast cancer (TNBC) cells produce many intron-retained double-strand RNAs when treated with H3B-8800 [111]. These new antigens in turn activate the antiviral immune response and further induce exogenous apoptosis [111]. Moreover, Lu X et al. revealed that sulfonamide derivative, Indisulam (E7070), degrades RBM39 in a dose-dependent manner and induces new antigens in cancer cells, thereby stimulating anti-tumor immune response and enhancing the efficacy of immune checkpoint inhibitors [112]. Additionally, agents that mediate splicing isoform-specific degradation have also been developed [113]. For instance, the AR-V7 degrades both AR-V7 isoform and full-length AR for prostate cancer, while DT2216 degrades the anti-apoptotic splicing isoform BCL-XL for liquid and solid cancers [114]. Therefore, these small molecules have shown promising effects of reducing the tumor burden in a variety of cancers [114].

In addition to these AS-targeting strategies, ncRNAs as novel splicing regulators also hold new promise in cancer therapeutic (Figure 5). In B-cell lymphoma, 3-Deazaneplanocin A (DZNep) and ibrutinib could inhibit EZH-mediated methylation of lncRNA *FAS-AS1* promoter and upregulate *FAS-AS1*, thus enhancing FAS-mediated apoptosis of cancer cells [82, 115, 116]. These findings indicate that

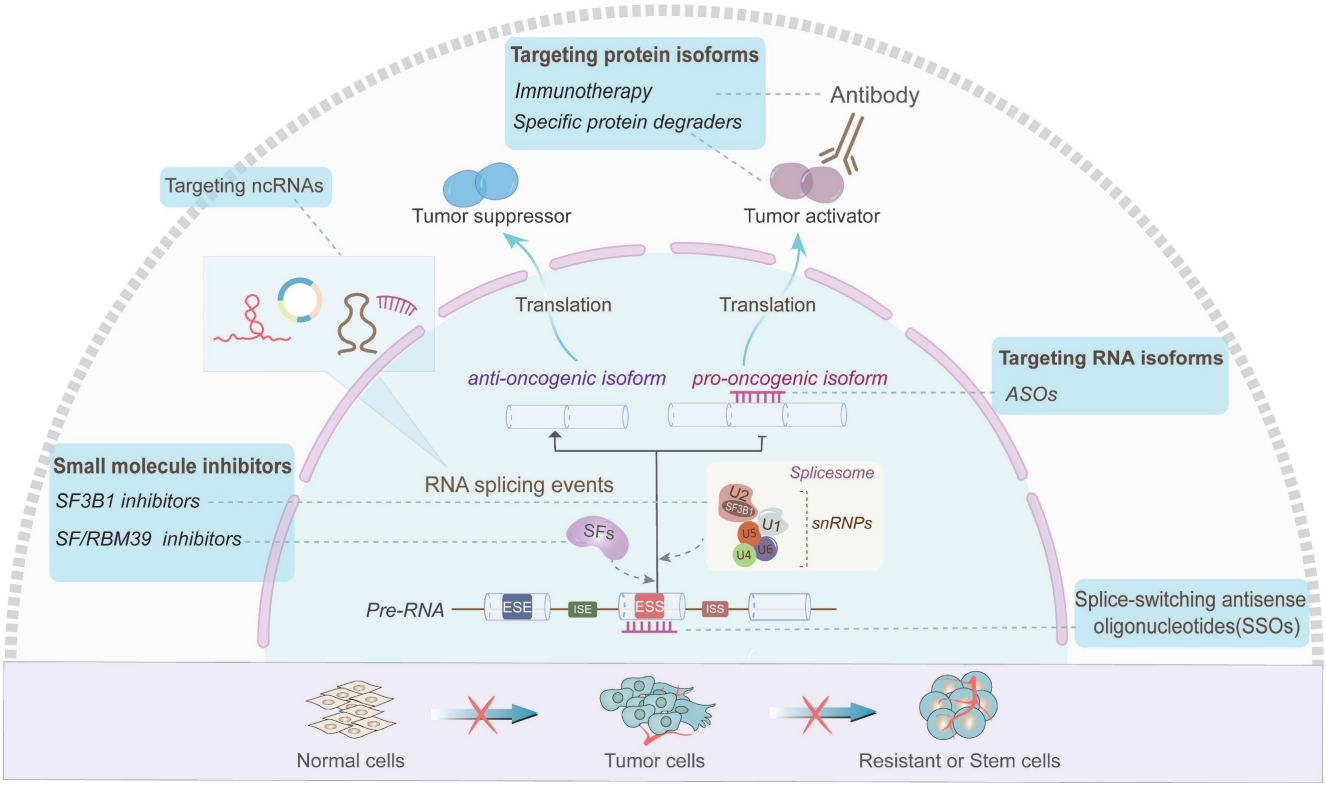

Figure 5. Strategies targeting AS of ncRNAs or AS-related ncRNAs for cancer therapy. Several antitumor strategies have been developed to alter AS events at distinct levels and consequently reverse the course of drug-resistant cells or carcinogenesis. These strategies include small molecule inhibitors of targeting SFs (such as RBM39) and splicesomal components (such as SF3B1), splice-switching antisense oligonucleotides (SSOs) targeting splicing "switch", antisense oligonucleotides (ASOs) targeting specific RNA isoforms, specific antibodies and protein degraders targeting oncogenic protein variants, and RNA therapies targeting AS-related ncRNAs.

FAS-AS1 might be a promising target for lymphoma treatment and provide a rationale for the synergistic combination of EZH inhibitors and chemotherapy for lymphoma treatment.

Conclusions and perspectives

Previously studies focused on AS related-coding genes, yet ncRNA-associated AS events have gained increasing interest, especially in the field of tumor epigenetics. This review highlights the interaction between ncRNAs and AS in cancer and summarizes distinct types of ncRNAs-mediated mechanisms involved in the aberrant regulation of AS events in various cancers. Owing to the extensive interactions between ncRNAs and AS and their mutual influence on cancer progression, AS-related ncRNAs have emerged as predictive biomarkers of chemotherapy and as potential targets for combination therapy. Hence, we also discussed the interplay of ncRNAs and AS in drug-resistant cells and the recent developments in cancer therapies targeting AS or AS-related ncRNAs.

Currently, researches on ncRNAs-AS network are conducted at a single gene level, since original papers usually performed rescue experiments to prove the concept. However, this simple model of single gene cannot fully reflect the complexity of the ncRNAs-AS interactive network or explain their important roles in cancers. Therefore, the mechanisms and functions of ncRNAs-AS network need to be further investigated, especially using bioinformatics to identify AS isoforms or AS-related ncRNAs that serve as prognostic biomarkers or therapeutic targets [117, 118]. Recently, Deng et al. developed a comprehensive database LncAS2Cancer, which provides information regarding AS of lncRNAs across human cancers, as well as predicts the potential interaction between lncRNA and AS in cancers [118]. However, to systematically explore the interplay between ncRNAs and AS, the development of high through-put sequencing methods detecting ncRNA-pre-mRNA or ncRNA-SF interaction is demanded. Nevertheless, the evidence to date is sufficient to demonstrate the importance of ncRNA-AS interplay in cancer. The development of effective drugs or strategies to target AS events of ncRNAs or AS-related ncRNAs, and their combination with current chemo-, targeted-, or immuno- therapies hold the promise for combating cancer in the future.

Abbreviations

AS, Alternative splicing; NcRNAs, Non-coding RNAs; SR, Serine/arginine-rich; pre-mRNA, precursor messenger RNA; RNP, Ribonucleoprotein;

snRNP, Small nuclear ribonucleoprotein; SF, Splicing factor; hnRNP, Heterogeneous nuclear ribonucleoprotein; SRE, Splicing regulatory element; ss, splice site; BPS, Branch point site; PPT, Polypyrimidine tract; ISE, Intronic splicing enhancer; ISS, Intronic splicing silencer; ES, Exon skipping; ESE, Exonic splicing enhancer; ESS, Exonic splicing silencer; A5SS, Alternative 5' splice site; A3SS, Alternative 3' splice site; IR, Intron retention; MXE, Mutually exclusive exon; LncRNA, Long non-coding RNA; miRNA, MicroRNA; circRNA, Circular RNA; snRNA, Small nuclear RNA; snoRNA, Small nucleolar RNA; PTC, Papillary thyroid carcinoma; HCC, hepatocellular carcinoma; EMT, Epithelial-mesenchymal transition; LUAD, Lung adenocarcinoma; SdRNA, SnoRNA-derived RNA; SNHG, SnoRNA host gene; ceRNA, Competing endogenous RNA; SRSF1, Serine- and arginine-rich splicing factor 1; RBP, RNA-binding protein; 3'-UTR, 3'-untranslated region; RBM4, RNA-binding motif 4; MREs, microRNA response elements; NSCLC, Non-small cell lung cancer; CRC, Colorectal cancer; Pancreatic cancer, PCa; ESCC, Esophageal squamous cell carcinoma; GBM, Glioblastoma multiforme; NMD, Nonsense- mediated decay; SRSP, Splicing regulatory small protein; PRC2, Polycomb repressive complex 2; dsRNA, Double-stranded RNA; cis-NAT, cis-natural antisense transcript; MDR, Multi-drug resistance; ARV7, Androgen receptor splice variant 7; OSCC, Oral squamous cell carcinoma; HNSC, Head and neck squamous carcinoma; TNBC, Triple-negative breast cancer; OOF, Out of reading frame; FasL, Fas ligand; DZNep, 3-Deazaneplanocin A; SSO, Splice-switching antisense oligonucleotide; ASO, Antisense oligonucleotides.

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Author contributions

H.W. and M.L. conceived the structure of the manuscript. M.L., H.H. and S.Z. wrote the manuscript. H.W., H.H., M.W., B.F. and X.H. provided the guidance throughout the revision of this manuscript. H.Z. and J.L. revised the paper. M.L. and H.W. prepared the figures. All authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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