Molecular Cancer Research

Review

Emerging Functions of SRSF1, Splicing Factor and Oncoprotein, in RNA Metabolism and Cancer

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Abstract

Serine/Arginine Splicing Factor 1 (SRSF1) is the archetype member of the SR protein family of splicing regulators. Since its discovery over two decades ago, SRSF1 has been repeatedly surprising and intriguing investigators by the plethora of complex biologic pathways it regulates. These include several key aspects of mRNA metabolism, such as mRNA splicing, stability, and translation, as well as other mRNA-independent processes, such as miRNA processing, protein sumoylation, and the nucleolar stress response. In this review, the structural features of SRSF1 are discussed as they relate to the intricate mechanism of splicing and the multiplicity of functions it performs. Similarly, a list of relevant alternatively spliced transcripts and SRSF1 interacting proteins is provided. Finally, emphasis is given to the deleterious consequences of overexpression of the *SRSF1* proto-oncogene in human cancers, and the complex mechanisms and pathways underlying SRSF1-mediated transformation. The accumulated knowledge about SRSF1 provides critical insight into the integral role it plays in maintaining cellular homeostasis and suggests new targets for anticancer therapy. *Mol Cancer Res; 1–10. ©2014 AACR.*

Introduction

Eukaryotic gene expression is a complex process, comprising several intermediary steps between transcription of the pre-mRNA in the nucleus and translation in the cytoplasm. These steps include pre-mRNA processing in the form of 5′-end capping, splicing and 3′-end cleavage/polyadenylation, as well as nuclear export of the mature mRNP. In addition, the mRNA is subject to quality control, which can affect its stability and translation. All of these processes are tightly controlled and coordinated in a tissue-specific and temporal manner, so as to determine the eventual proteomic composition of a cell.

One major class of regulators of mRNA metabolism is the phylogenetically conserved SR protein family (1). The 12 human SR proteins have a modular domain structure, with one or two RNA recognition motifs (RRM) and a C-terminal RS domain comprising multiple Arg–Ser dipeptide repeats (2). Although all the SR proteins are predominantly nuclear and localize to interchromatin granule clusters or nuclear speckles, six of them (SRSF1, SRSF3, SRSF4, SRSF6, SRSF7, and SRSF10) shuttle between the nucleus and the cytoplasm (3–5).

The SR proteins have been characterized as essential splicing factors required for constitutive pre-mRNA splicing. In addition, the SR proteins are key regulators of alternative splicing, the process through which approximately 95% of human genes produce multiple mRNA transcripts by the differential inclusion of exons or exon segments. Although different SR proteins can interchangeably restore constitutive splicing activity to splicing-inactive cytoplasmic S100 HeLa-cell extract, they do show a degree of substrate specificity, especially with respect to regulation of alternative splicing through sequence-specific binding to exonic splicing enhancer sequences (ESE; refs. 6, 7). The nonredundant role of the different SR protein family members is emphasized by the fact that homozygous-knockout mice for *Srsf1, Srsf2,* or *Srsf3* have embryonic lethal phenotypes (8–11).

In addition to their role as splicing regulators, it has become increasingly apparent that SR proteins are involved in other steps of RNA metabolism, such as Pol II transcription, nuclear export of the mature mRNA, as well as nonsense-mediated mRNA decay (NMD), and translation (reviewed in refs. 12 and 13). Furthermore, certain SR proteins have been shown to be involved in maintenance of genomic stability, cell viability, and cell-cycle progression (14–16). The crucial role of SR proteins in normal cell function is enforced by the discovery that several SR proteins have oncogenic potential. This was first demonstrated for SRSF1, formerly known as SF2/ASF, whose regulation and functions are the focus of this review.

SRSF1: The Archetypal SR Protein

SRSF1 is the founding member of the SR protein family, originally identified and isolated by virtue of two of its activities: (i) promoting spliceosome assembly and constitutive pre-mRNA splicing in S100 HeLa cell extract (17, 18) and (ii) regulating alternative splicing of the SV40 early pre-mRNA *in vitro* (19). Although originally characterized as a

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splicing factor, SRSF1 has since been found to possess additional functions, such as regulating mRNA transcription, stability and nuclear export, NMD, and translation, as well as protein sumoylation. SRSF1 was also the first member of the SR protein family to be identified as a proto-oncogene, highlighting the important role of alternative splicing in tumorigenesis (20–22).

SRSF1: Structure and Functions

The multiple functions of SRSF1 are a consequence of its RNA-binding potential, nuclear-cytoplasmic shuttling, and interactions with diverse proteins, as dictated by its structure. The modular domains of SRSF1 consist of two RRMs: (i) a canonical RRM at the N-terminus, followed by a pseudo-RRM and (ii) a C-terminal RS domain that is shorter than that of most other SR proteins (Fig. 1). Although both RRMs are required for efficient RNA binding and splicing (23, 24), the pseudo RRM, or RRM2, has a dominant role in dictating substrate specificity *in vivo* (25, 26). Indeed, recent NMR structural analysis showed that RRM2 specifically binds to GA-rich ESE sequences, and follow-up transfection assays showed that it is sufficient to elicit changes in alternative splicing of a subset of SRSF1 target genes (27).

Crosslinking immunoprecipitation and high-throughput sequencing (CLIP-seq) analysis in human and murine cells revealed widespread binding of SRSF1 preferentially to the exonic regions of the transcriptome (28, 29). The mapping of *in vivo* SRSF1-binding sites also enabled identification of GGAGA as the SRSF1 binding consensus motif, consistent with earlier studies (6, 30–32). As a regulator of RNA splicing, SRSF1 promotes exon definition and the use of proximal alternative 5′ splice sites or 3′ splice sites in a concentration-dependent manner, in part through recognition of degenerate ESE sequence elements on its pre-mRNA targets. In the case of cassette exons with one or more cognate ESEs, SRSF1 promotes their inclusion; however, if binding occurs preferentially on the flanking constitutive exon(s), SRSF1 tends to promote skipping of the alternative exon (21, 28). Table 1 lists some of the known alternatively

spliced genes that are targets of SRSF1 and contribute to its biologic functions.

Upon binding a cognate ESE, SRSF1 modulates splicing at the early stages of spliceosome assembly and facilitates splice-site selection, in part through recruitment of core spliceosomal proteins. The interaction of SRSF1 with other proteins was initially believed to be mediated solely by the RS domain. However, SRSF1 deletion mutants lacking the entire RS domain retain their splicing activity (23–25, 33, 34). Furthermore, a study by Cho and colleagues strongly indicates that it is the RRMs of SRSF1 that mediate the interaction with the U1-70K component of the U1 snRNP and formation of the Early (E) spliceosomal complex, with the RS domain playing a regulatory role (35). In addition, the RS domain is required for nuclear-cytoplasmic shuttling of SRSF1 and regulates its subnuclear localization (25).

SRSF1 undergoes various posttranslational modifications (PTM) that in turn regulate its subcellular localization and functions. These include extensive phosphorylation of the Ser residues in the RS domain by enzymes like Clk/Sty 1, 2, 3, and 4 kinases in the nucleus (36, 37), SRPK 1 and 2 kinases in the cytoplasm (38, 39), topoisomerase 1 (40), as well as dephosphorylation by the phosphatases PP1 and PP2A (41, 42). SRSF1 transitions between intermediate phosphorylation states, influencing its interaction with other proteins, RNA-binding properties, and target specificity, as well as subcellular location (43–46). Cytosolic phosphorylation of approximately 12 Ser residues in the N-terminal portion of the RS domain by SRPK 1 and 2 generates a hypophosphorylated form of SRSF1, which is imported into the nucleus through association with transportin-SR (47, 48). Hypophosphorylated SRSF1 accumulates in nuclear speckles and further phosphorylation of the RS domain Ser residues by Clk/Sty generates a hyperphosphorylated form of the protein. Hyperphosphorylated SRSF1 then moves from the nuclear speckles to active sites of transcription, where it promotes the splicing reaction. During splicing, SRSF1 transitions back to its hypophosphorylated state, which is associated with the postsplicing functions of SRF1, as well as its nuclear export bound to spliced mRNA.
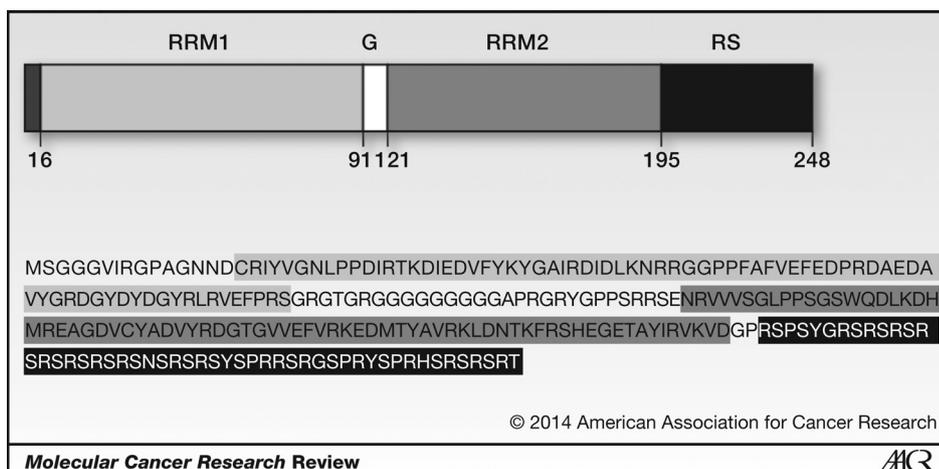

Figure 1. Modular domain structure of SRSF1. Primary structure of the SRSF1 protein highlighting the two N-terminal RNA recognition motifs (RRMs) and the C-terminal RS domain.

RRM1   G   RRM2   RS

16   91 121   195   248

MSGGGVIRGPAGNNDCRIYVGNLPPDIRTKDIEDVFYKYGAIRDIDLKNRRGGPPFAFVEFEDPRDAEDA
VYGRDGYDYDGYRLRVEFPRSGRGTGRGGGGGGGGGGAPRGRYGPPSRRSENRVVVSGLPPSGSWQDLKDH
MREAGDVCYADVYRDGTGVVEFVRKEDMTYAVRKLDNTKFRSHEGETAYIRVKVDGPRSPSYGRSRSRSR
SRSRSRSRSNSRSRSYSPRRSRGSPRYSPRHSRSRSRT

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Table 1. Selected splicing targets of SRSF1 and their roles in SRSF1-mediated tumorigenesis

Target	Function	SRSF1-induced splicing change	Property of SRSF1-induced isoform	References
BCL2L1	Apoptosis regulator	Enhanced inclusion of full-length exon 2	Antiapoptotic	Leu et al. (85)
BCL2L11	Apoptosis regulator	Increased inclusion of novel alternative 3' exon	Antiapoptotic	Anczuków et al. (22)
BIN1	Apoptosis regulator	Increased exon 12A inclusion	Antiapoptotic	Karni et al. (20); Anczuków et al. (22)
CASP2	Apoptosis regulator	Skipping of a novel 61-bp exon	Proapoptotic	Jiang et al. (86)
CASP9	Effector of apoptosis	Increased inclusion of cassette exons 3–6	Proapoptotic	Massiello et al. (87)
CCND1	Cell-cycle regulator	Intron 4 retention	Cell-cycle regulator; pro-oncogenic	Olshavsky et al. (88)
CD3ζ	Signaling transducer of T-cell receptor	Suppressed alternative splicing within 3'-UTR	Codes for functional CD3ζ protein of T-cell receptor	Moulton et al. (89)
CD44	Cell–cell interaction, cell adhesion, and migration	Increased exon v9 inclusion	Epithelial-specific isoform	Galiana-Arnoux et al. (90)
DFFA	Inhibitor of caspase-activated DNase	Intron 5 exclusion	CAD inhibitor, no chaperone activity	Li et al. (15)
ENG	Part of TGFβ receptor complex; important in angiogenesis	Retention of terminal intron	Promotes endothelial senescence	Blanco et al. (91)
FN1	Structural component of extracellular matrix, integrin signaling	Inclusion of EDA exon	Promotes cell invasion	Lopez-Mejia et al. (92)
MAPT	Stabilization of microtubules	Increased exon 10 inclusion	Microtubule stabilization	Kondo et al. (93)
MKNK2	Effector in MAPK signaling pathway	Increased inclusion of mutually exclusive exon 13b	Activates p38a-MAPK; pro-oncogenic	Karni et al. (20); Maimon et al. (94)
MST1R	Receptor for macrophage stimulating protein	Skipping of exon 11	Promotes metastasis	Ghigna et al. (21)
RPS6KB1	Kinase of ribosomal protein S6	Inclusion of novel exons 6a and 6c	Activates mTORC1; pro-oncogenic	Karni et al. (20); Ben Hur et al. (58)
SLC39A14	Ion carrier, Zn transport in prostate cells	Increased inclusion of mutually exclusive exon 4b	Biomarker for colorectal cancer	Thorsen et al. (95)
TEAD1	Transcriptional enhancer	Increased exon 5 inclusion	Unknown	Karni et al. (20)

In addition to PTMs of the RS domain, SRSF1 is also methylated at three Arg residues in the inter-RRM linker region (49). Global proteomic analysis revealed SRSF1 to be methylated at R93, R97, and R109 residues. Mutation of these residues leads to cytosolic accumulation of the protein, and consequently higher translation stimulation, with a concurrent decrease in its nuclear functions, including alternative splicing and stimulation of NMD. These findings suggest that differential methylation of SRSF1 modulates SRSF1 nuclear-cytoplasmic shuttling and its functions in each cellular compartment.

The Many Roles of SRSF1

Though initially identified as a splicing regulator, the interaction of SRSF1 with many different proteins presum- ably enables it to regulate several cellular functions (Fig. 2, Table 2).

SRSF1 and nonsense-mediated mRNA decay

Besides splicing, SRSF1 is also a player in the NMD mRNA quality surveillance mechanism, wherein mRNA transcripts containing a premature termination codon (PTC) are subjected to degradation. Overexpression of *SRSF1* greatly enhances NMD of two well-characterized PTC-containing NMD substrates, β-globin and GPX1 (50). This activity of SRSF1 is independent of its shuttling ability, but requires an intact RS domain. Though the exact mechanism for SRSF1-mediated NMD enhance- ment is still under investigation, it has been shown that SRSF1 associates with CBP80-bound mRNA and the
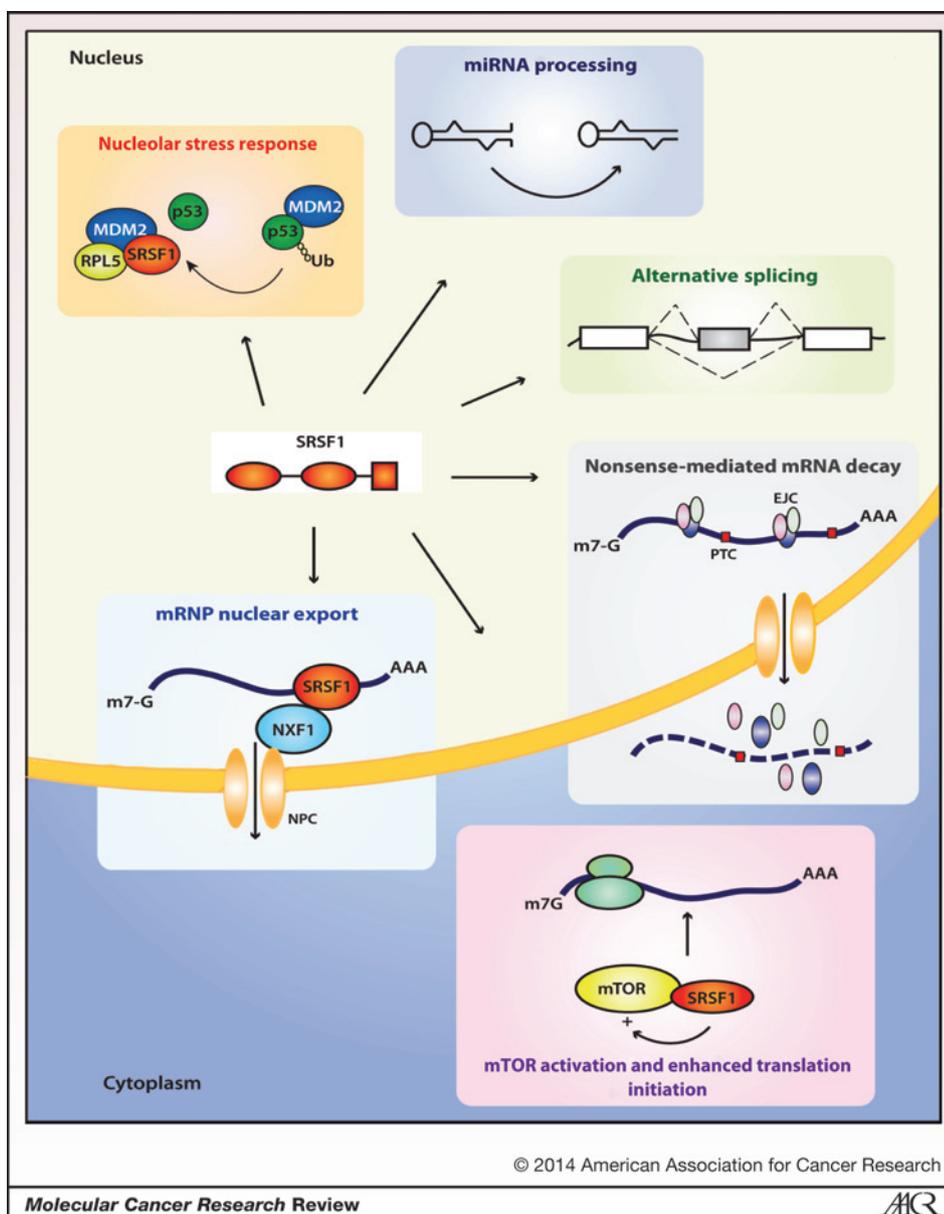

Figure 2. The multifunctional SR protein SRSF1. Splicing-dependent and -independent functions of SRSF1 in the nucleus and the cytoplasm. EJC, exon junction complex; NFX1, nuclear exchange factor 1; NPC, nuclear pore complex; PTC, premature termination codon.

Table 2. Protein interactions and functions of SRSF1

Interacting partner	SRSF1-interacting domain	Function	References
MDM2	RRM1	Nucleolar stress; oncogene-induced senescence	Fregoso et al. (64)
mTORC kinase	RRM2	Activation of mTOR signaling pathway; enhanced cap-dependent translation	Michlewski et al. (56)
PIAS1	RRM2	Protein sumoylation	Pelisch et al. (63)
PP2A	RRM2	Interaction with SRSF1 inhibits PP2A, leading to activation of mTOR signaling pathway	Michlewski et al. (56)
RPL5	RRM1	Nucleolar stress; oncogene-induced senescence	Fregoso et al. (64)
RRP1B	Unknown	Splicing of metastasis regulators	Lee et al. (96)
TAP/NXF1	Linker between RRM1 and RRM2	Nuclear export of mRNP	Huang et al. (52)
TOP1	RRM1 and RRM2	SRSF1 interaction inhibits DNA cleavage activity of Topo 1	Trzcinska-Daneluti et al. (97)
Transportin-SR	RS	Nuclear import	Lai et al. (47)
U1-70K	RRM1 and RRM2	RNA splicing	Cho et al. (35)
UBC9	RRM2 and RS	Protein sumoylation	Pelisch et al. (63)

nuclear adaptor TAP, thereby promoting the pioneer round of translation (51).

SRSF1 and nuclear export of mRNA

The ability of SRSF1 to shuttle between the nucleus and the cytoplasm is a major contributor to its multifunctional character. Nuclear to cytoplasmic translocation of SRSF1 is mediated through its interaction with the TAP/NXF1 receptor (52). In the process, SRSF1 serves as an export adaptor; facilitating the nuclear export of spliced mRNAs to which it is bound. Considering that nuclear export of SRSF1 requires partial dephosphorylation of its RS domain (53, 54), differential phosphorylation of SRSF1 can serve as a regulatory mechanism for nuclear export of mRNPs.

SRSF1, mTOR, and translation

The presence of some SRSF1 in the cytoplasm suggests a role for it in the cytoplasmic processes of RNA metabolism, such as translation. Consistent with this idea, SRSF1 was found to associate with polyribosomes in cytoplasmic extracts and to enhance translation of ESE-containing luciferase reporters (55). Enhanced cap-dependent translation by SRSF1 has been attributed to its ability to activate the mTORC1 signaling pathway through both splicing-dependent and -independent mechanisms (56, 57). This includes regulating alternative splicing of the MAPK MNK2 to promote the formation of the MNK2b isoform, which phosphorylates the translation initiation factor eIF4E, enhancing its activity in translation initiation (20, 57). SRSF1 also regulates the splicing of S6 kinase 1 to generate short isoforms, which bind mTORC and enhance 4EBP1 phosphorylation, also resulting in enhanced translation initiation (56–58). Finally, SRSF1 was reported to directly interact with the mTORC1 complex, leading to increased phosphorylation of its substrates S6K1 and 4EBP1, in addition to interacting with and inhibiting the activity of the phosphatase PP2A, an antagonist of the mTORC1 target S6K1 (56).

SRSF1 and miRNA processing

Besides playing a role in virtually every aspect of mRNA metabolism, SRSF1 also facilitates the processing of certain small noncoding RNAs (59). miRNAs are processed from longer precursors called pri-miRNAs, transcribed by RNA Pol II (60). The pri-miRNA is then processed, first in the nucleus by the RNase Drosha, and then in the cytoplasm by another RNAse, Dicer, to generate the mature miRNA. SRSF1 binds to some pri-miRNAs and serves as an auxiliary factor to promote the Drosha-mediated cleavage step of pri-miRNA processing. While this study specifically focused on the processing of the mir7 miRNA, miRNA expression profiling revealed this to be a more general function of SRSF1, affecting processing of other miRNAs, such as miR221 and miR222.

SRSF1 and genome stability

While the discovery that SRSF1 regulates RNA processing and function at several levels, other than splicing, is intriguing, what is even more startling is the identification of SRSF1's roles in many other biologic processes. These include cell-cycle stage-specific chromatin association and SRSF1-mediated maintenance of genomic stability (14, 61). Chicken DT-40 cells depleted of SRSF1 were observed to be hypermutagenic, with accumulation of DNA double-strand breaks and wide-scale genomic rearrangements (14). Further investigation revealed a role for SRSF1 in maintaining genomic stability by preventing the formation of R-loops; these are structures formed by hybridization between the DNA template strand and the nascent RNA, which can trigger genomic instability. Deposition of SRSF1 cotranscriptionally from the CTD of RNA Pol II to the nascent mRNA transcript enables it to prevent the formation of R-loops, instead triggering assembly of pre-mRNPs.

SRSF1 and chromatin association

The association of SRSF1 with interphase chromatin may be another way in which SRSF1 participates in the surveillance of genome integrity (61). SRSF1 was reported to bind to interphase chromatin, dissociate from mitotic chromosomes, and reassociate with postmitotic chromatin. This association–dissociation is regulated by M-phase–specific phosphorylation of Histone H3 on Ser 10 by Aurora kinase B. SRSF1 depletion decreased chromatin-association of the HP1 proteins, the basic units of heterochromatin organization. SRSF1 is also enriched at active gene loci, through its association with the chromatin-associated protein Psip1/Ledgf, which specifically recognizes and binds trimethylated H3K36 residues (62). Though the functional implications of these observations are still unknown, it was proposed that the cell-cycle–specific association of SRSF1 with chromatin could reflect a potential role in chromatin organization and cell-cycle progression, as well as in transcriptional regulation and, as mentioned above, in the maintenance of genomic stability. Furthermore, the recruitment of SRSF1 to actively transcribed genes by Psip1 might serve as an additional mechanism for modulating alternative splicing (62).

SRSF1 and protein sumoylation

The ability of SRSF1 to interact with various proteins has helped to uncover its unanticipated role in several additional cellular pathways. Through its interaction with the E2 SUMO-conjugating enzyme Ubc9, SRSF1 stimulates protein sumoylation (63). In doing so, it displays characteristics of an E3 ligase, acting as a cofactor to facilitate the process. In addition, SRSF1 interacts with and regulates the function of the E3 sumo ligase PIAS1.

SRSF1 and nucleolar stress

Similarly, by characterizing the interaction between SRSF1 and the ribosomal protein RPL5, we recently described a role of SRSF1 in the nucleolar stress pathway, wherein SRSF1 stabilizes the interaction between RPL5 and the E3 ubiquitin ligase MDM2 (64). Sequestration of MDM2 in this complex results in stabilization of the p53 tumor suppressor, which then mediates the stress response.

Regulation of SRSF1 Expression

Consistent with the many processes that it regulates, SRSF1 is an essential gene and Srsf1-null mice are embryonic lethal (11). Tissue-specific deletion of Srsf1 in mouse heart leads to lethality about 6 to 8 weeks after birth, due to heart failure (11). These mice have defective Ca^{2+} metabolism, seemingly due to mis-splicing of the Ca^{2+}/calmodulin-dependent kinase IIδ (CAMKIIδ), leading to a defective contractile apparatus and cardiomyopathy. Knockdown of the SRSF1 ortholog in C. elegans also leads to late embryonic lethality (65). Furthermore, loss of SRSF1 expression in chicken DT-40 cells triggers cell-cycle arrest in the G_2 phase and apoptosis (14). On the other hand, overexpression of SRSF1 in immortal rodent fibroblasts or human mammary epithelial cells leads to oncogenic transformation, with increased cellular proliferation and protection against apoptosis (20–22).

Presumably to prevent the deleterious consequences of its misregulation, the level of SRSF1 is tightly controlled within the cell. SRSF1 negatively autoregulates its expression through multiple posttranscriptional and translational mechanisms (66). SRSF1 regulates splicing of its own transcript and keeps a check on its overexpression by promoting the expression of PTC-containing splice isoforms that are targeted to NMD. SRSF1 also regulates its expression at the translational level, by shifting the association of its mRNA from polysomes to monosomes, indicative of decreased translation efficiency. Furthermore, the SRSF1 transcript itself is subject to silencing by the miR7 miRNA, which as outlined above, is one of the miRNA targets processed more efficiently through SRSF1 binding, thereby generating a negative-feedback loop (59).

SRSF1 and Cancer

Despite the abovementioned regulatory mechanisms to maintain constant SRSF1 levels, SRSF1 is overexpressed in many different cancer types, and it is a potent proto-oncogene (20–22, 67). SRSF1 is located on Chromosome 17q23, a locus that is commonly amplified in certain tumors, correlating with poor prognosis (20, 68). We found that slight overexpression of SRSF1 results in oncogenic transformation of immortalized rodent fibroblasts and human mammary epithelial cells, with the cells acquiring higher proliferative capacity, resistance to apoptosis, and forming malignant tumors upon orthotopic transplantation into mouse models. Furthermore, SRSF1 overexpression in lung adenocarcinoma cells results in a more aggressive phenotype and confers resistance to anticancer drugs like carboplatin and paclitaxel (67).

Among the positive regulators of SRSF1 that contribute to its overexpression in cancer are the oncogenic transcription factor MYC and the splicing regulator Sam68 (69, 70). We found SRSF1 to be a direct transcriptional target of MYC, containing two functional noncanonical E-boxes in its promoter. MYC, which is itself a potent oncogene aberrantly expressed in cancer, positively associates with SRSF1 expression in lung and breast tumors, and is responsible for SRSF1 overexpression in at least a subset of lung tumors (69). SRSF1 expression is also regulated at the level of splicing, in response to the splicing factor Sam 68 (70). Sam68 activity switches alternative splicing of the SRSF1 transcript from the NMD-targeted isoforms to the full-length, translatable isoform, thus resulting in an increase in SRSF1 protein levels. MYC- and Sam68-mediated SRSF1 overexpression is associated with oncogenic phenotypes, such as increased cell proliferation, anchorage-independent growth, cell motility and invasion, and epithelial–mesenchymal transition (EMT).

The strong oncogenic potential of SRSF1 is in all likelihood a cumulative reflection of its various different functions. However, the splicing function of SRSF1 has been the most extensively characterized in this context, and multiple SRSF1-regulated alternative splicing events have been

identified that contribute to its role in tumorigenesis (Table 1). Among these are several apoptosis regulators: *BIN1, BCL2L11* (BIM), and *MCL1* (20, 22, 71). *SRSF1* over-expression promotes the formation of the nonapoptotic isoforms of these three genes: the BIN1 +12A isoform, which is unable to interact with and activate MYC-mediated apoptosis, the BIM γ1 and γ2 isoforms, which lack the BH3 domain required for proapoptotic function, and the anti-apoptotic MCL1L isoform.

Another important malignant tumor characteristic regulated by SRSF1 is cell motility and invasion. SRSF1 alters the splicing of the macrophage-stimulating protein tyrosine kinase receptor RON, promoting skipping of exon 11 (21). The resulting protein isoform induces EMT and enhances cell motility. SRSF1 also regulates alternative splicing of factors affecting cellular signaling pathways, proliferation, and cell-cycle progression. As mentioned above, these factors include *RPS6KB1*, which encodes the protein S6 kinase 1, a downstream effector in the PI3K/Akt/mTOR signaling pathway, and *MKNK2*, an effector in the MAPK/ERK pathway (19). We identified a novel, short S6K1 isoform that is positively regulated by SRSF1. This p31-S6K1 isoform has recently been shown to be oncogenic and is an important mediator of SRSF1-mediated transformation (20, 58).

SRSF1-mediated activation of the mTORC1 pathway is an essential contributor to its oncogenic activity (20, 22). Inhibition of mTORC1 signaling by rapamycin treatment abrogates SRSF1′s ability to transform cells both *in vitro* and *in vivo*. mTORC1 is a key regulator of cell growth and translation, and its activation by SRSF1 promotes translation of the antiapoptotic factor Survivin in non–small cell lung carcinomas, making them insensitive to cell death cues (72). Recently, SRSF1 was also shown to enhance translation of β-catenin through mTOR activation, leading to activation of the Wnt signaling pathway, an important contributor to oncogenesis (73).

Analysis of various SRSF1 domain-deletion mutants revealed that RRM1 is critical for oncogenic activity in mammary epithelial cells and in a liver-progenitor xenograft model (22, 74). SRSF1 mutants lacking RRM1 (ΔRRM1) are impaired in their ability to alter splicing of the apoptosis regulators BIM1 and BIN1. The differential effect of ΔRRM1 and ΔRRM2 mutants on splicing of SRSF1 indicates the different substrate specificity of these two RRMs. To distinguish between the nuclear functions of SRSF1 (e.g., splicing, NMD) and the cyto-plasmic functions (e.g., translation), in the context of oncogenesis, a nuclear-retained SRSF1 chimeric protein (SRSF1-NRS1), fused to the nuclear retention signal of the nonshuttling SR protein SRSF2 (75) was used, with surprising results. In a three-dimensional mammary epi-thelial cell model, the SRSF1-NRS1 protein was as com-petent as wild-type SRSF1 in inducing transformation, indicating that it is the nuclear functions of SRSF1 that mediate its oncogenic role. However, a recent report by Shimoni-Sebag and colleagues showed that the SRSF1-NRS1 protein is unable to promote tumor formation in hepatocellular xenografts (74). SRSF1-mediated oncogen-esis in this model was attributed to the activation of the Raf-MEK-ERK signaling pathway. The SRSF1-NRS1 protein failed to activate this pathway, indicating that its activation is a cytosolic function of SRSF1. These findings emphasize the multiple pathways through which SRSF1 exerts its oncogenic role, and indicate that different pathways are essential for transformation in different contexts.

Considering the severe outcome of *SRSF1* overexpression, we were excited to discover an antitumorigenic pathway of oncogene-induced senescence that cells trigger to resist transformation (76). Excessive SRSF1 leads to formation of the abovementioned ternary SRSF1–RPL5–MDM2 complex, and the sequestration of MDM2 in this complex stabilizes its ubiquitination target, the cell-cycle regulator p53. We found that p53 induction is one of the primary responses to *SRSF1* overexpression in primary human and murine fibroblasts, and results in cells entering a state of premature cellular senescence. SRSF1-mediated oncogenesis therefore seems to be dependent upon inactivation of the p53 tumor suppressor pathway, a finding that can potentially be exploited when developing therapies against SRSF1-driven or -dependent tumors.

Concluding Remarks

The emerging role of alternative splicing and splicing regulators in cancer is opening up a new therapeutic avenue. The splicing profile of cancer cells has been found to differ extensively from that of nontransformed cells, indicating the importance of alternate isoforms in tumor initiation and progression (77, 78). We are well on our way to character-izing the oncogenic activity of the SR protein SRSF1, and its role in human cancers is becoming increasingly clear. In addition, the roles of other members of the SR protein family, as well as other splicing regulators, in cancer are being explored. *SRSF3, SRSF6*, as well as *HNRNPH* and *HNRNPA2B1* have all been described as potent oncogenes (79–82). While *SRSF1* is an important contributor to breast and lung cancer progression, *SRSF6* is frequently amplified in, and promotes, lung and colon tumors, and HNRNPH and HNRNPA2B1 overactivity is associated with glioblas-tomas. Furthermore, recurrent somatic mutations in *SRSF2* have been observed in myelodysplasias (83) as well as tumors of the lymphoid lineage (84), strongly suggesting a role in pathogenesis. The multifunctional character of SRSF1 and other SR proteins underscores the role of splicing as a central regulator of gene expression and cellular homeostasis. Inves-tigating the mechanisms through which SR proteins induce cellular transformation will hopefully reveal new therapeutic candidates and strategies for combating cancer.

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