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Mini Review

SRp20: An overview of its role in human diseases

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ABSTRACT

Alternative splicing in mRNA maturation has emerged as a major field of study also because of its implications in various diseases. The SR proteins play an important role in the regulation of this process. Evidence indicates that SRp20 (SFSR3), the smallest member of the SR protein family, is involved in numerous biological processes. Here we review the state-of-the-art of knowledge about the SR proteins, in particular SRp20, in terms of its function and misregulation in human diseases including cancer also in view of its potential as a therapeutic target.

1. Introduction

The alternative splicing (AS) of RNA, a molecular event affecting the expression of most human genes [1], leads to the production of multiple isoforms of mature RNA from a single primary transcript. This event is due to the presence of various splicing sites within precursor mRNAs (pre-mRNAs). Alternative splicing is regulated by interactions between cellular splicing factors and RNA sequences in the pre-mRNA [2,3], and even very mild changes in the levels of splicing factors can perturb AS regulation [4].

Alternative splicing causes important temporal and tissue-specific changes in the human proteome [2,5]. When a protein exists as two or more splicing variants, one splicing variant can exert its function in cooperation with the full-length protein [6], or paradoxically exert opposite functions compared to the full-length counterpart [7]. Splicing reactions in the eukaryotic nucleus are catalyzed by spliceosomes, which are large enzymatic complexes composed of small nuclear RNA (snRNA) molecules and of more than 100 associated auxiliary proteins [8]. Five snRNAs, i.e. U1, U2, U4, U5 and U6, constitute the major spliceosome and participate directly in the splicing reaction by interacting with intron consensus sequences and with each other. An snRNA combined with a protein forms a small nuclear RiboNucleoProtein (snRNP); snRNPs assemble on the pre-mRNA to form the spliceosome.

Among the many proteins associated to the spliceosome, there are two highly conserved protein families: the splicing factors known as Ser/Arg-rich (SR) proteins and heterogeneous nuclear RiboNucleoProteins (hnRNPs) [9]. The SR proteins exhibit dual functionality in pre-mRNA constitutive and alternative splicing. In fact their primary constitutive function is exerted at the level of splice-site selection. They interact with exonic splicing enhancer sequences (ESEs) thereby forming a barrier that prevents exon skipping, thus ensuring the correct 5′ to 3′ linear order of exons in spliced mRNA. In addition, SR proteins regulate the selection of alternative splice sites (different from canonical sites), thus promoting the inclusion of alternative exons. Moreover, SR proteins antagonize the activity of hnRNPs, which are bound to exonic splicing silencers (ESSs), at the level of AS regulation [10]. Here we review the state-of-the-art of knowledge about the SR proteins, in particular SRp20, in terms of its function and misregulation in human diseases including cancer.

2. The SR protein family

The first evidence of the splicing factors function of SR proteins dates back to the early 1990s [11], whereas the name 'SR protein' stems from the recognition of proteins with an RS domain by a

Abbreviations: AS, alternative splicing; PTM, post-translational modifications; RBDs, RNA-binding domains; RRM, RNA recognition motif; RS domain, domain rich in arginine and serine; snRNA, small nuclear RNA; snRNP, small nuclear RiboNucleoProtein; SR-proteins, serine/arginine-rich proteins; SRSF, serine/arginine-rich splicing factor.

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monoclonal antibody that binds to active sites of RNA polymerase II transcription [12]. SF2/ASF was the first SR protein identified [13]. Subsequently, others, i.e. SRp20, SRp40, SRp55 and SRp75, were classified on the basis of their relative MW on SDS/PAGE gel [14]. More recently, Manley and Krainer proposed a simple definition of SR proteins and rationalized the nomenclature associated to these proteins [15]. According to their definition, an SR protein is any protein with one or two N-terminal RNA-binding domains (RBDs; also known as RNA recognition motifs [RRMs]) followed by a downstream arginine/serine-rich (RS) domain characterized by consecutive RS or SR repeats. Based on this stringent definition, there are 12 SR proteins in humans encoded by twelve genes, designated serine/arginine-rich Splicing Factors (SRSFs) 1-12; these are listed in Table 1 and their structural organization is illustrated in Fig. 1.The N-terminal RRM provides substrate specificity by modulating the interactions of SR proteins with short mRNA splicing enhancer sequences [16,17]. The C-terminal RS domain aids protein–protein interactions, thus simplifying spliceosome recruitment [18,19].

Whether SR proteins exert a specific or non-specific function remains to be established. It has been suggested that their role is non-specific in mRNA splicing [3,16], whereas other studies suggest that some SR proteins play specialized roles [20,21]. Most of the serine residues of SR proteins are phosphorylated in the RS domain and this affects their function in the spliceosome. Despite evidence that RS domain phosphorylation may control splicing [22], its role in this process needs further investigation. Differently, the role of phosphorylation in the entry of SR proteins into the nucleus is well-established. This post-translational mechanism (PTM), in fact, enhances the interactions between the RS domain and transportin, i.e. the nuclear import receptor [23,24]. The phosphorylation mechanism and the structure of SR protein kinases have been recently reviewed by Ghosh and Adams [25].

The splicing of pre-mRNA is an essential, precisely regulated molecular process occurring before mRNA translation that produces functional mRNA molecules via the specific removal of introns and ligation of exons. It is a crucial regulatory step in eukaryotic gene expression [26]. After the discovery that genes are constituted by introns and exons, the concept that one gene generates multiple forms of mRNA transcripts gradually became plausible [27]. Alternative splicing of pre-mRNA can help to explain the incongruity between gene content and organism complexity at protein level [28,29].

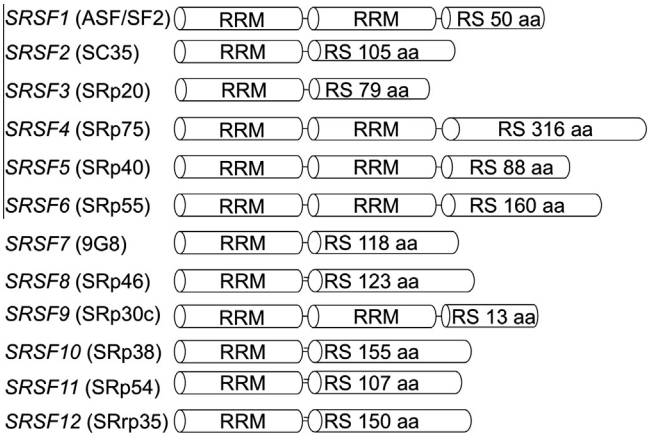

Fig. 1. SR proteins domain structure. Gene symbols and protein names (in parenthesis) are reported followed by the schematic representation of the domain structures of the known members of SR family. The SR proteins have one or two N-terminal RNA recognition motifs (RRMs) and one C terminal RS domain. The RRM motif identifies and binds specific RNA sequences. The RS domain interacts with other proteins and facilitates recruitment of the spliceosomal components.

It is thought that most genes of the human genome undergo alternative splicing [2,30] and that, on average, a given gene gives rise to 4 alternatively spliced variants that differ in their sequence and therefore in the activities of the coded proteins. Four types of AS events have been described: alternative 5′ splice site selection, alternative 3′ splice site selection, cassette-exon inclusion or skipping, and intron retention [29]. For an in-depth account of the role of SR proteins in constitutive and alternative splicing see the article by Long and Caceres [3].

While AS plays a significant role in normal cellular development, changes or defects in this process have also been linked to human disease, including cancer [31,32]. Consequently, aberrant mRNAs, splicing factors and other RNA processing factors have become targets for new therapeutic approaches for various human diseases.

Table 1
SR protein and gene symbols. For each protein the annotated function is summarized based also on information obtained from the EMBL-EBI database.

Protein name	Gene symbol	Function
ASF, SF2, SRp30a	SRSF1	Plays a role in preventing exon skipping, ensuring the accuracy of splicing and regulating AS. Isoform ASF-2 and isoform ASF-3 act as splicing repressors.
SC35, PR264, SRp30b	SRSF2	Necessary for the splicing of pre-mRNA. Required for formation of the earliest ATP-dependent splicing complex, interacts with spliceosomal components bound to both the 5′- and 3′-splice sites during spliceosome assembly. It also is required for ATP-dependent interactions of both U1 and U2 snRNPs with pre-mRNA. Interacts with other spliceosomal components. The phosphorylated form (by SRPK2) is required for cellular apoptosis in response to cisplatin treatment. Exerts transcription corepressor activity.
SRp20	SRSF3	Involved in RNA processing in relation with cellular proliferation and/or maturation.
SRp75	SRSF4	Involved in AS site selection during pre-mRNA splicing. Represses the splicing of MAPT/Tau exon 10.
SRp40, HRS	SRSF5	Involved in constitutive splicing, can modulate the selection of AS sites.
SRp55, B52	SRSF6	Involved in constitutive splicing, can modulate the selection of AS sites. Represses the splicing of MAPT/Tau exon 10. RNA binding.
9G8	SRSF7	Required for pre-mRNA splicing. Can also modulate AS *in vitro*. Represses the splicing of MAPT/Tau exon 10. RNA binding; zinc ion binding.
SRp46	SRSF8	AS regulator, regulates its own expression at the level of RNA processing and the splicing of fibronectin and CD45 genes. May act, at least in part, by interaction with other R/S-containing splicing factors. Represses the splicing of MAPT/Tau exon 10.
SRp30c	SRSF9	Involved in constitutive splicing, can modulate the selection of AS sites. Represses the splicing of MAPT/Tau exon 10.
TASR1, SRp38, SRrp40	SRSF10	Involved in constitutive and regulated RNA splicing.
P54, SRp54	SRSF11	May function in pre-mRNA splicing.
SRrp35	SRSF12	Seems to antagonize SR proteins in pre-mRNA splicing regulation.

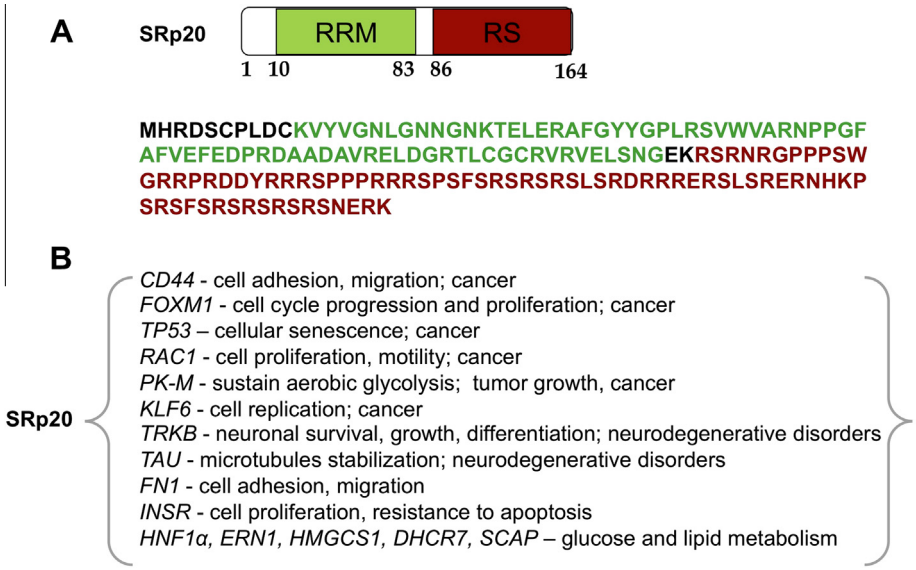

Fig. 2. SRp20 features. (A) The protein has an RNA recognition motif (RRM) in the N-terminus and an arginine/serine-rich domain (RS) at the C-terminus. In green are the amino acids of the RRM domain and in red those of the RS domain. (B) Genes known to be regulated by SRp20 are listed with their biological function and implication in diseases.

3. SRp20 and its cell regulatory functions

SRp20 (also called SRSF3) is the smallest member of the highly conserved SR-rich splicing factor family and is constituted by one RRM at the N-terminus and one RS domain at the C-terminus. The protein is composed of 164 amino acids, about half of which belong to the RS domain (Fig. 2A); its molecular weight is about 19 kDa and it is extensively phosphorylated on serine residues in the RS domain. SRp20 regulates the splicing of numerous genes [33–43]. It affects AS by interacting with RNA cis-elements in a concentration- and cell differentiation-dependent fashion [44]. A summary of genes regulated by SRp20 is shown in Fig. 2B. At the end of the 90s, Jumaa and Nielsen showed that SRp20 regulates the AS of its own mRNA, thereby providing the first demonstration of auto-regulatory activity of an SR protein [33–35]. In fact, SRp20 promotes the inclusion of exon 4 of its own mRNA and reduces the expression of the full-length SRSF3 protein [35].

Besides its regulation of RNA splicing, SRp20 is also involved in other important cellular functions. It has been implicated in protein translation [45], termination of transcription [46] and insulin signaling [47]. In a proteomic analysis of insulin signaling in human hematopoietic cells, SRp20 and CLIC1 were identified as novel downstream effectors of insulin-dependent signals. Importantly, the insulin-induced reduction in SRp20 enhances insulin-dependent accumulation of cyclin D3 [47].

A recent study demonstrated that SRp20 (SRSF3) and SF2/ASF (SRSF1) associate with chromatin before and after, but not during, mitosis [48]; this interaction implies that these proteins could be involved in the regulation of chromatin structure and function and thus may play a role in cell cycle control. SRp20 is involved in mRNA polyadenylation [49], which implicates it in pre-mRNA processing and, more in general, in terminal exon recognition. SRp20 also acts as a shuttle in the TAP-dependent mRNA export from nucleus to cytoplasm [50–52]. Its role in embryogenesis was revealed by a study showing that SRp20-null mouse embryos did not form blastocytes, and died at morula stage [53].

4. SRp20 in human disease including cancer

The biological relevance of AS is supported by observations linking aberrant AS to human diseases, including tumorigenesis [32,54–58]. In this context, a variety of SRp20 functions are associated with their alterations in human or animal diseases. Proteins SRp20, 9G8 and ASF/SF2 were proposed as activators of the AS of the adhesion molecule CD44. In fact, the *CD44* gene alternative exon v9 contains a splicing enhancer responsive to these three SR proteins [36,37].

The human *TAU* gene, which encodes a protein of 441 amino acids, contains 16 exons, three of which undergo AS thereby generating different isoforms of tau proteins. In the search for potential therapeutic targets for tauopathies, Yu and colleagues studied the splicing mechanism of *TAU* and found that SRp20 participates in the AS of *TAU* by promoting the exclusion of exon 10 [38]. SRp20 is also involved in the alternative splicing of fibronectin [39], insulin receptor [40], and Rac1 [41]. SRp20 activates the inclusion of exon 10 of the pyruvate kinase M (*PK-M*) gene to promote the expression of the oncogenic PK-M2 isoform, thus fostering aerobic glycolysis and tumor growth [42]. SRp20 has also been implicated in the neurodegenerative disorder Alzheimer's disease. In fact, SRp20 regulates the splicing of *TRKB* to generate TrkB-Shc transcripts that are involved in this disorder [43]. Lastly, SRp20 controls the early-to-late switch in human papillomavirus by regulating the gene expression of the virus via interaction with A/C-rich RNA elements [44].

Since mutations in oncogenes and tumor suppressors can lead to cancer, it is hardly surprising that also mutations at exon–intron junctions that affect splicing can cause cancer. The expression of the splicing factor SRp20 is triggered by oncogenic signaling pathways such as the Wnt signaling pathway that drives the formation of several cancers [37,41,59]. Importantly, SRp20 protein levels correlate with the extent of β-catenin/TCF4 signaling in the colorectal cancer cell lines SW480, HT29, and DLD1, which are widely used to study this signaling [37]. Moreover, our studies confirmed a direct cause-effect relationship between Wnt pathway activation and increased SRp20 expression, and demonstrated that SRp20 expression was higher in colon cancer stem-like cells than in non-cancer stem-like cells [59]. Furthermore, we found that SRp20 silencing slowed down cell proliferation, thereby implicating SRp20 in the tumorigenicity of cancer stem-like cells isolated from CaCo-2 cells [59, for cancer stem cells studies see also 60,61].

Jia and colleagues discovered the role of SRp20 in proliferation [62]. They demonstrated that it promotes the G2/M transition by

affecting the expression of the cell cycle regulators FoxM1, Cdc25B and PLK1. Therefore, SRp20 is critical for the control of the G2/M phase transition and for the prevention of cell apoptosis. Moreover, when looking at SRp20 function in the splicing of human papillomavirus (HPV) RNA, Jia and collaborators found a remarkable increase in SRp20 expression in cervical cancer tissues [62]. This phenomenon is not limited to HPV-induced cancers; SRp20 is over-expressed also in lung, breast, stomach, skin, bladder, colon, liver, thyroid, and kidney tumor tissue, and in B-cell lymphoma cells [62]. SRp20 over-expression is required for ovarian cancer cell growth and maintenance of transformation properties [63,64]. In fact, ovarian cancer cells with reduced SRp20 expression grow slowly, do not grow in an anchorage-independent fashion, undergo apoptosis and are less tumorigenic [63]. SF2/ASF, SRp20 and SC35 were also found to be specifically up-regulated in a model of cervical tumor progression and are also over-expressed in high-grade cervical lesions, which indicates that they may have oncogenic functions. Given the changes associated with SR proteins, the latter may be used as biomarkers for diagnosis of cervical tumor progression [65].

A very recent study demonstrated that SRp20 regulates cellular senescence [66]. The process of cellular senescence is the ability of cells to enter a state of irreversible proliferation arrest; importantly the mechanisms underlying cellular senescence are involved in protection against cancer. SRp20 regulates cellular senescence through alternative splicing of *TP53*, thereby generating p53β [66]. In detail, SRp20 downregulation induces the generation of p53β and is an endogenous mechanism to promote cellular senescence [66], which suggests that SRp20 is involved in tumorigenesis and that it is a direct regulator of p53.

ASF/SF2 and SRp20 are two antagonistic splicing factors that regulate Rac1b expression in colorectal tumor cells. Rac1 is a member of the Rho family of small GTPases that are involved in signaling pathways that control proliferation, actin-dependent cell motility, invasiveness of tumor cells as well as gene transcription. The AS variant Rac1b is over-expressed in a subset of colorectal tumors and is required to sustain tumor cell viability and subsequent tumor progression [41].

Acute myeloid leukemia (AML) also known as acute myelogenous leukemia is the most common type of blood cancer affecting adults, and its incidence increases with age. There is growing evidence of a link between AML and aberrant alternative splicing of pre-mRNA, which may result from aberrant expression of splicing factors, these being the real mediators of splicing reactions. Compared to healthy controls, the expression of splicing factors SRSF1, SRSF3 and SRSF4 mRNAs is significantly decreased in newly diagnosed AML patients [67]. This aberrant expression may be related to the abnormal expression of oncogenes in AML and could be useful for the early diagnosis, prognosis, and therapy of this disorder.

The AS of kruppel-like factor 6 (KLF6) tumor suppressor is a key event in hepatocellular carcinoma (HCC). In fact, SRp20 contributes to cell proliferation in physiologic liver growth and HCC through SRSF1-mediated AS of *KLF6* [68]. Moreover, SRp20 loss in liver leads to aberrant splicing of genes involved in glucose/lipid metabolism (*HNF1α*, *ERN1*, *HMGCS1*, *DHCR7* and *SCAP*) thus impairing the morphological and functional differentiation of hepatocytes [69].

5. Concluding remarks

The finding that most human pre-mRNA transcripts are alternatively spliced prompted efforts to understand the significance of AS in various biological processes. In this scenario, there is growing interest in the molecular components that orchestrate the regulation of AS. The splicing factor SRp20 has long been studied as a regulator of pre-mRNAs AS, but only in recent years has SRp20 been linked to cancer. The data summarized in this review support the link between SRp20 and cancer and the existence of a role of SRp20 in the general splicing machinery in tumorigenesis. Understanding and identifying the molecular mechanisms governing SRp20-dependent signaling will have an impact on the clinical management of cancer patients and on the identification of the most promising molecular targets for treatment.

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References

[1] E.T. Wang, R. Sandberg, S. Luo, et al., Alternative isoform regulation in human tissue transcriptomes, Nature 456 (2008) 470–476.
[2] Z.M. Zheng, Regulation of alternative RNA splicing by exon definition and exon sequences in viral and mammalian gene expression, J. Biomed. Sci. 11 (2004) 278–294.
[3] J.C. Long, J.F. Caceres, The SR protein family of splicing factors: master regulators of gene expression, Biochem. J. 417 (2009) 15–27.
[4] E.L. Heinzen, D. Ge, K.D. Cronin, et al., Tissue-specific genetic control of splicing: implications for the study of complex traits, PLoS Biol. 6 (12) (2008) e1000001.
[5] A.M. Celotto, B.R. Graveley, Alternative splicing of the drosophila dscam pre-mRNA is both temporally and spatially regulated, Genetics 159 (2001) 599–608.
[6] K. Fujita, A.M. Mondal, I. Horikawa, et al., P53 isoforms delta133 p53 and p53 beta are endogenous regulators of replicative cellular senescence, Nat. Cell Biol. 11 (2009) 1135–1142.
[7] C. Akgul, D.A. Moulding, S.W. Edwards, Alternative splicing of Bcl-2-related genes: functional consequences and potential therapeutic applications, Cell. Mol. Life Sci. 61 (2004) 2189–2199.
[8] M.S. Jurica, M.J. Moore, Pre-mRNA splicing: awash in a sea of proteins, Mol. Cell 12 (2003) 5–14.
[9] A.J. Matlin, F. Clark, C.W. Smith, Understanding alternative splicing: towards a cellular code, Nat. Rev. Mol. Cell Biol. 6 (2005) 386–398.
[10] U. Pozzoli, M. Sironi, Silencers regulate both constitutive and alternative splicing events in mammals, Cell. Mol. Life Sci. 62 (2005) 1579–1604.
[11] X.D. Fu, The superfamily of arginine/serine-rich splicing factors, RNA 1 (1995) 663–680.
[12] M.B. Roth, C. Murphy, J.G. Gall, A monoclonal antibody that recognizes a phosphorylated epitope stains lampbrush chromosome loops and small granules in the amphibian germinal vesicle, J. Cell Biol. 111 (1990) 2217–2223.
[13] A.R. Krainer, G.C. Conway, D. Kozak, Purification and characterization of pre-mRNA splicing factor SF2 from hela cells, Gene. Dev. 4 (1990) 1158–1171.
[14] A.M. Zahler, W.S. Lane, J.A. Stolk, et al., SR proteins: a conserved family of pre-mRNA splicing factors, Gene. Dev. 6 (1992) 837–847.
[15] J.L. Manley, A.R. Krainer, A rational nomenclature for serine/arginine-rich protein splicing factors (SR proteins), Gene. Dev. 24 (11) (2010) 1073–1074.
[16] J.F. Caceres, A.R. Krainer, Functional analysis of pre-mRNA splicing factor SF2/ASF structural domains, Embo J. 12 (1993) 4715–4726.
[17] P. Zuo, J.L. Manley, The human splicing factor ASF/SF2 can specifically recognize pre-mRNA 5′ splice sites, Proc. Natl. Acad. Sci. USA 91 (1994) 3363–3367.
[18] J.Y. Wu, T. Maniatis, Specific interactions between proteins implicated in splice site selection and regulated alternative splicing, Cell 75 (1993) 1061–1070.
[19] J.D. Kohtz, S.F. Jamison, C.L. Will, et al., Protein-protein interactions and 5′ splice-site recognition in mammalian mRNA precursors, Nature 368 (1994) 119–124.
[20] H.Y. Wang, X. Xu, J.H. Ding, et al., SC35 plays a role in T cell development and alternative splicing of CD45, Mol. Cell 7 (2001) 331–342.
[21] X. Xu, D. Yang, J.H. Ding, et al., ASF/SF2-regulated CaMKII delta alternative splicing temporally reprograms excitation-contraction coupling in cardiac muscle, Cell 120 (2005) 59–72.
[22] A. Massiello, C.E. Chalfant, SRp30a (ASF/SF2) regulates the alternative splicing of caspase-9 premRNA and is required for ceramide-responsiveness, J. Lipid. Res. 47 (2006) 892–897.
[23] N. Kataoka, J.L. Bachorik, G. Dreyfuss, Transportin-SR, a nuclear import receptor for SR proteins, J. Cell. Biol. 145 (1999) 1145–1152.
[24] M.C. Lai, R.I. Lin, S.Y. Huang, et al., A human importin-beta family protein, transportin-SR2, interacts with the phosphorylated RS domain of SR proteins, J. Biol. Chem. 275 (2000) 7950–7957.
[25] G. Ghosh, J.A. Adams, Phosphorylation mechanism and structure of serine-arginine protein kinases, FEBS J. 278 (4) (2011) 587–597.

[26] A.E. House, K.W. Lynch, Regulation of alternative splicing: more than just the ABCs, J. Biol. Chem. 283 (2008) 1217–1221.
[27] W. Gilbert, Why genes in pieces?, Nature 271 (1978) 501
[28] B.R. Graveley, Alternative splicing: increasing diversity in the proteomic world, Trend. Genet. 17 (2001) 100–107.
[29] T.W. Nilsen, B.R. Graveley, Expansion of the eukaryotic proteome by alternative splicing, Nature 463 (2010) 457–463.
[30] Q. Pan, O. Shai, L.J. Lee, et al., Deep surveying of alternative splicing complexity in the human transcriptome by high-throughput sequencing, Nat. Genet. 40 (2008) 1413–1415.
[31] J.F. Caceres, A.R. Kornblihtt, Alternative splicing: multiple control mechanisms and involvement in human disease, Trend. Genet. 18 (2002) 186–193.
[32] J.P. Venables, R. Klinck, C. Koh, et al., Cancer associated regulation of alternative splicing, Nat. Struct. Mol. Biol. 16 (2009) 670–676.
[33] H. Jumaa, J.L. Guenet, P.J. Nielsen, Regulated expression and RNA processing of transcripts from the Srp20 splicing factor gene during the cell cycle, Mol. Cell. Biol. 17 (1997) 3116–3124.
[34] H. Jumaa, P.J. Nielsen, Regulation of SRp20 exon 4 splicing, Biochim. Biophys. Acta 1494 (2000) 137–143.
[35] H. Jumaa, P.J. Nielsen, The splicing factor SRp20 modifies splicing of its own mRNA and ASF/SF2 antagonizes this regulation, EMBO J. 16 (16) (1997) 5077–5085.
[36] D. Galiana-Arnoux, F. Lejeune, M.C. Gesnel, et al., The CD44 alternative v9 exon contains a splicing enhancer responsive to the SR proteins 9G8, ASF/SF2, and SRp20, J. Biol. Chem. 278 (2003) 32943–32953.
[37] V. Gonçalves, P. Matos, P. Jordan, The beta-catenin/TCF4 pathway modifies alternative splicing through modulation of SRp20 expression, RNA 14 (2008) 2538–2549.
[38] Q. Yu, J. Guo, J. Zhou, A minimal length between tau exon 10 and 11 is required for correct splicing of exon 10, J. Neurochem. 90 (2004) 164–172.
[39] M. de la Mata, A.R. Kornblihtt, RNA polymerase II C-terminal domain mediates regulation of alternative splicing by SRp20, Nat. Struct. Mol. Biol. 13 (2006) 973–980.
[40] S. Sen, I. Talukdar, N.J. Webster, SRp20 and CUG-BP1 modulate insulin receptor exon 11 alternative splicing, Mol. Cell. Biol. 29 (2009) 871–880.
[41] V. Goncalves, P. Matos, P. Jordan, Antagonistic SR proteins regulate alternative splicing of tumor-related Rac1b downstream of the PI3-kinase and Wnt pathways, Hum. Mol. Genet. 18 (19) (2009) 3696–3707.
[42] Z. Wang, D. Chatterjee, H.Y. Jeon, et al., Exon-centric regulation of pyruvate kinase M alternative splicing via mutually exclusive exons, J. Mol. Cell. Biol. 4 (2) (2012) 79–87.
[43] J. Wong, B. Garner, G.M. Halliday, et al., Srp20 regulates TrkB pre-mRNA splicing to generate TrkB-Shc transcripts with implications for Alzheimer's disease, J. Neurochem. 123 (2012) 159–171.
[44] R. Jia, X. Liu, M. Tao, et al., Control of the papillomavirus early-to-late switch by differentially expressed SRp20, J. Virol. 83 (1) (2009) 167–180.
[45] K.M. Bedard, S. Daijogo, B.L. Semler, A nucleo-cytoplasmic SR protein functions in viral IRES-mediated translation initiation, EMBO J. 26 (2007) 459–467.
[46] M. Cui, M.A. Allen, A. Larsen, et al., Genes involved in pre-mRNA 3′-end formation and transcription termination revealed by a lin-15 operon Muv suppressor screen, Proc. Natl. Acad. Sci. USA 105 (2008) 16665–16670.
[47] K. Saeki, E. Yasugi, E. Okuma, et al., Proteomic analysis on insulin signaling in human hematopoietic cells: identification of CLIC1 and SRp20 as novel downstream effectors of insulin, Am. J. Physiol. Endocrinol. Metab. 289 (3) (2005) 419–428.
[48] R.J. Loomis, Y. Naoe, J.B. Parker, et al., Chromatin binding of SRp20 and ASF/SF2 and dissociation from mitotic chromosomes is modulated by histone H3 serine 10 phosphorylation, Mol. Cell 33 (4) (2009) 450–461.
[49] H. Lou, K.M. Neugebauer, R.F. Gagel, et al., Regulation of alternative polyadenylation by U1 snRNPs and SRp20, Mol. Cell. Biol. 18 (1998) 4977–4985.
[50] Y. Huang, R. Gattoni, J. Stevenin, et al., SR splicing factors serve as adapter proteins for TAP-dependent mRNA export, Mol. Cell 11 (2003) 837–843.
[51] G.M. Hautbergue, M.L. Hung, A.P. Golovanov, et al., Mutually exclusive interactions drive handover of mRNA from export adaptors to TAP, Proc. Natl. Acad. Sci. USA 105 (2008) 5154–5159.
[52] L. Escudero-Paunetto, L. Li, F.P. Hernandez, R.M. Sandri-Goldin, SR proteins SRp20 and 9G8 contribute to efficient export of herpes simplex virus 1 mRNAs, Virology 401 (2) (2010) 155–164.
[53] H. Jumaa, G. Wei, P.J. Nielsen, Blastocyst formation is blocked in mouse embryos lacking the splicing factor SRp20, Curr. Biol. 9 (1999) 899–902.
[54] J.P. Venables, Unbalanced alternative splicing and its significance in cancer, BioEssays 28 (2006) 378–386.
[55] K. Thorsen, K.D. Sorensen, A.S. Brems-Eskildsen, et al., Alternative splicing in colon, bladder, and prostate cancer identified by exon array analysis, Mol. Cell. Proteomics 7 (2008) 1214–1224.
[56] L. Xi, A. Feber, V. Gupta, et al., Whole genome exon arrays identify differential expression of alternatively spliced, cancer-related genes in lung cancer, Nucleic Acids Res. 36 (2008) 6535–6547.
[57] C.J. David, M. Chen, M. Assanah, et al., HnRNP proteins controlled by c-Myc deregulate pyruvate kinase mRNA splicing in cancer, Nature 463 (2009) 364–368.
[58] C.J. David, J.L. Manley, Alternative pre-mRNA splicing regulation in cancer: pathways and programs unhinged, Gene. Dev. 24 (2010) 2343–2364.
[59] C. Corbo, S. Orrù, M. Gemei, et al., Protein cross-talk in CD133+ colon cancer cells indicates activation of the Wnt pathway and upregulation of SRp20 that is potentially involved in tumorigenicity, Proteomics 12 (12) (2012) 2045–2059.
[60] M. Gemei, P. Mirabelli, R. Di Noto, et al., CD66c is a novel marker for colorectal cancer stem cell isolation, and its silencing halts tumor growth *in vivo*, Cancer 119 (4) (2013) 729–738.
[61] G. Galizia, M. Gemei, L. Del Vecchio, et al., Combined CD133/CD44 expression as a prognostic indicator of disease-free survival in patients with colorectal cancer, Arch. Surg. 147 (1) (2012) 18–24.
[62] R. Jia, C. Li, J.P. McCoy, et al., SRp20 is a proto-oncogene critical for cell proliferation and tumor induction and maintenance, Int. J. Biol. Sci. 6 (7) (2010) 806–826.
[63] X. He, A.D. Arslan, M.D. Pool, et al., Knockdown of splicing factor SRp20 causes apoptosis in ovarian cancer cells and its expression is associated with malignancy of epithelial ovarian cancer, Oncogene 30 (3) (2011) 356–365.
[64] X. He, P.L. Ee, J.S. Coon, et al., Alternative splicing of the multidrug resistance protein 1/ATP binding cassette transporter subfamily gene in ovarian cancer creates functional splice variants and is associated with increased expression of the splicing factors PTB and SRp20, Clin. Cancer Res. 10 (14) (2004) 4652–4660.
[65] S. Mole, M. McFarlane, T. Chuen-Im, et al., RNA splicing factors regulated by HPV16 during cervical tumour progression, J. Pathol. 219 (3) (2009) 383–391.
[66] Y. Tang, I. Horikawa, M. Ajiro, et al., Downregulation of splicing factor SRSF3 induces p53b, an alternatively spliced isoform of p53 that promotes cellular senescence, Oncogene (2012) 1–7.
[67] J. Liu, B. Huang, Y. Xiao, et al., Aberrant expression of splicing factors in newly diagnosed acute myeloid leukemia, Onkologie 35 (6) (2012) 335–340.
[68] Ú. Muñoz, J.E. Puche, R. Hannivoort, et al., Hepatocyte growth factor enhances alternative splicing of the Kruppel-like factor 6 (KLF6) tumor suppressor to promote growth through SRSF1, Mol. Cancer Res. 10 (9) (2012) 1216–1227.
[69] S. Sen, H. Jumaa, N.J. Webster, Splicing factor SRSF3 is crucial for hepatocyte differentiation and metabolic function, Nat. Commun. 4 (2013) 1336, http://dx.doi.org/10.1038/ncomms2342.