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Function of alternative splicing

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Abstract

Almost all polymerase II transcripts undergo alternative pre-mRNA splicing. Here, we review the functions of alternative splicing events that have been experimentally determined. The overall function of alternative splicing is to increase the diversity of mRNAs expressed from the genome. Alternative splicing changes proteins encoded by mRNAs, which has profound functional effects. Experimental analysis of these protein isoforms showed that alternative splicing regulates binding between proteins, between proteins and nucleic acids as well as between proteins and membranes. Alternative splicing regulates the localization of proteins, their enzymatic properties and their interaction with ligands. In most cases, changes caused by individual splicing isoforms are small. However, cells typically coordinate numerous changes in ‘splicing programs’, which can have strong effects on cell proliferation, cell survival and properties of the nervous system. Due to its widespread usage and molecular versatility, alternative splicing emerges as a central element in gene regulation that interferes with almost every biological function analyzed.

Keywords

Alternative Splicing; pre-mRNA; gene function

1.0 Introduction

The comparison of mRNA with genomic sequences in the late 1970s showed that prior to the export into the cytosol, viral sequences are removed from the pre-mRNA and the remaining sequences are joined together (Berget et al., 1977; Chow et al., 1977). It was quickly found that almost all mammalian polymerase II transcripts undergo this process, called pre-mRNA splicing. Due to splicing, only a small fraction of sequences from the primary transcripts are joined together and exported as exons into the cytosol, forming the mature mRNA. The majority of intervening sequences (introns) remain in the nucleus where they are subsequently degraded (reviewed in (Sharp, 2005)). It is now clear that the vast

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majority of pre-mRNAs contain exons that can be alternatively included into the mature mRNA or removed from it, which is called alternative splicing.

Frequently transcripts contain several alternative exons and their usage can be combined, largely increasing the diversity of the mRNA expressed from the genome and giving alternative splicing a central role in forming complex organisms. Alternative splicing patterns constantly change under physiological conditions, allowing an organism to respond to changes in the environment by determining which part of the genome it expresses. Most of the changes in alternative splicing are studied in artificial experimental systems, but alternative exon usage changes in real life scenarios. The stress of exams on medical students causes a change in alternative pre-mRNA splicing of the phosphatidylinositol 3-kinase-related protein kinase (SMG-1). This change may have later effects on nonsense-mediated RNA decay and the p53 pathway (Kurokawa et al., 2010).

Alternative splicing can play a role even before life and after death. The importance of alternative splicing before fertilization is illustrated by Nitric Oxide Synthase 1 where splicing isoforms are involved in controlling the erectile function (Hurt et al., 2006). The role after death is shown by the poor meat quality of turkeys that underwent transport and heat stress prior to slaughtering. This stress changes the splicing patterns of ryanodine receptors, ultimately leading to an increase of water content in the meat and lowering the quality (Strasburg and Chiang, 2009).

A change in alternative splicing can lead to human diseases, as summarized in section 3.1.4. However, changes in alternative splicing can be exploited for useful purposes, as they could be part of a pest control approach that generates male flies with a splicing defect eliminating female offspring (Fu et al., 2007).

Most of the splicing isoforms are only known through sequence comparison. The realization of alternative splicing's importance resulted in more functional studies of alternative exons reviewed here. This paper extends an earlier review published about seven years ago (Stamm et al., 2005) and shows impressive progress in the field. Functions of alternative exons published prior to 2005 are not covered here (but can be found in (Stamm et al., 2005)). They are summarized in Supplemental Figure 1.

Despite more than 20,000 publications dealing with alternative splicing, we still do not know the function of most alternative exons. However, key features emerge: most changes caused by alternative splicing are subtle and often hard to detect, changes in alternative splicing of different genes are controlled by 'splicing programs' centered around 50-300 regulatory proteins that work in combination. These splicing programs controlling different genes can have drastic physiological effects.

We will first give a brief summary of alternative splicing regulation and then describe functions of alternative exons that were experimentally determined during the past seven years.

2.0 Mechanism of alternative splicing

An alternative exon can only exert a function on the protein level after it is recognized by the splicing machinery and included in the mRNA. We therefore briefly summarize the mechanism of alternative pre-mRNA splicing. Previous work resulted in an explosion of mechanistical insights into alternative splicing regulation, which has been covered in excellent reviews (Matlin et al., 2005; Li et al., 2007b; Graveley, 2009; Wahl et al., 2009). Readers interested in a more basic introduction to alternative splicing and RNA are referred to specialized books covering the subject (Elliott and Ladomery, 2011; Stamm et al., 2012).

Human exons are between 50 and 300 nt in length, averaging about 137 nt (Berget, 1995). Thus they represent short sequences of the pre-mRNA that are surrounded by larger introns, which have an average length of 3,400 nt (Deutsch and Long, 1999). A large macromolecular complex, the spliceosome, recognizes exons and removes the intervening sequences (introns) while the pre-mRNA is synthesized by RNA polymerase II in the nucleus. The spliceosome is composed of at least 170 proteins and five snRNAs (small nuclear RNAs) (Behzadnia et al., 2007). Exons are defined by three major sequence elements: the 5' splice site, the 3' splice site and the branch point (Figure 1). The spliceosome recognizes these elements and assembles in a stepwise manner on the nascent pre-mRNA. First, the U1 snRNP binds to the 5' splice site, then splicing factor 1 binds to the branch point, which facilitates binding of the U2AF factor on the 3' splice site. This E (early) complex is committed to the splicing reaction by the substitution of SF1 by U2 snRNP, resulting in the prespliceosomal A complex. Through the exchange and recruitment of more factors, the A complex is transformed into the splicosomal B complex that removes the intron and joins the exons in a transesterification reaction.

2.1 Common features of alternative exons determined by genome-wide analysis

Alternative spliced exons share the sequence features of constitutively used exons, but, in general, these sequences deviate more from the consensus sequences (i.e. are weaker), which implies a lowered affinity to the spliceosome resulting in reduced recognition. The branch point of constitutive exons is typically within 40 nt of the 3' splice site, but this distance can be much larger in alternative exons, up to 400 nt. In these cases, there are no AG nucleotides between the branch point and the 3' splice site, called the AG dinucleotide exclusion zone (Gooding et al., 2006). The higher phylogenetic conservation of branch points preceding alternative exons reflects a difference between constitutive and alternative exons, which indicates that the cis-elements marking alternative exons are so weak they cannot tolerate more perturbations (Kol et al., 2005).

Similarly, splice sites and exonic enhancers are generally weaker in alternative exons (Wang et al., 2005b), an evolutionarily conserved feature (Garg and Green, 2007). This conservation indicates it is an evolutionary advantage for an exon to be used alternatively.

An important finding of genome-wide analysis was the discovery of evolutionary conserved intronic regions, which suggests deep intronic regions contribute to splicing regulation (Sugnet et al., 2006; Yeo et al., 2007), (Sironi et al., 2005; Venables, 2007; Voelker and Berglund, 2007). These motifs are typically not discovered by in vitro methods that can

analyze only shorter sequences and could explain the mechanism of action of disease-causing deep intronic sequences. (Kashima et al., 2007; Spina et al., 2007; Davis et al., 2009).

2.2 Proteins regulating alternative splicing

The 5' splice site, the 3' splice site and the branch point sequences follow only loose consensus sequences. Therefore, additional factors are required for exon recognition, which are brought into play by RNA sequence elements that can be either exonic or intronic. These short sequences bind to proteins that stabilize the binding of U1, U2 or SF1 to form the A complex. Likewise, binding of proteins to splicing silencers that block A complex formation inhibit exon recognition. The proteotypical exon enhancing proteins are SR-proteins and contain a domain rich in arginine and serine, called RS-domain. In contrast, most hnRNPs bind to splicing silencers and inhibit exon recognition. As a general rule, SR-proteins and SR-domain containing proteins promote exon inclusion and hnRNPs antagonize exon inclusion. However, there are numerous exceptions to this rule, for example the GTPase Rac1, where a critical exon is regulated by the completion of two SR-proteins, SRp20 and ASF/SF2 (Goncalves et al., 2009) and the myosin phosphatase targeting subunit-1 (MYPT1), which is regulated by antagonism between the two hnRNPs PTB and TIA-1 (Shukla et al., 2005). Furthermore, SF2/ASF and htra2-beta, two SR-proteins cause exon skipping of several exons regulated by ceramide (Sumanasekera et al., 2012).

The active concentration of splicing regulatory proteins can be influenced by the cell through different expression levels or through sequestration in cellular organelles, which resulted in the concept that alternative splicing is regulated by the ratios of antagonistic splicing factors. PTB (polypyrimidine tract binding protein) is an hnRNP and a well-studied example of the regulation by antagonistic proteins. For example, PTB competes with RBM4 for a CU-rich regulatory element in alpha-tropomyosin (Lin and Tarn, 2005), with TIA1 for a U-rich cis-element in myosin phosphatase (Shukla et al., 2005) and in FAS (Izquierdo et al., 2005) with U2AF for regulation in the src gene (Sharma et al., 2005) and with SRp30c for regulation of the hnRNPA1 gene (Paradis et al., 2007). Antagonism can also occur among SR-proteins, for example between SRp20 and SF2/ASF in the rac1b gene (Goncalves et al., 2009). Splicing regulatory proteins cannot only antagonize each other, but can also enhance their action on an exon, where they act like coactivators. This is exemplified by Fox-3 and PSF that together promote usage of a neuron-specific exon in the myosin heavy chain (Kim et al., 2011).

The importance of the concentration of splicing factors is further highlighted by the fact that most splicing factors autoregulate their expression levels, often by generating inactive variants as seen in FOX proteins (Damianov and Black, 2010), SF2/ASF (Sun et al., 2010) and tra2-beta1 (Stoilov et al., 2004). As the splicing factors work within protein, RNA complexes, their action depends on the binding site's sequence context.

Global analysis of drosophila cells shows that different splicing factors control a variable number of pre-mRNAs and that many alternative exons are regulated by multiple trans-acting factors, suggesting the relative ratios of these factors control exon usage (Blanchette et al., 2005).

2.3 Emerging role of RNA in alternative splicing reaction

Despite the large progress that has been made in determining the regulation of model exons, our mechanistical understanding is not complete. The comparison between exonic splicing regulatory sequences and alternative splicing usage in human and chimpanzee shows that changes in *cis*-elements are not associated with alternative exon variations between the two species (Irimia et al., 2009), suggesting the existence of other regulatory factors.

The current models of splice site selection outlined in Figure 1 propose proteins as the main regulators. However, there are less than 50 proteins known that regulate alternative splicing and less than 300 proteins known that bind RNA (Chen and Manley, 2009; Graveley, 2009), which contrasts with the more than 2,500 identified transcription factors (Babu et al., 2004). RNA itself could be involved in this regulation and there is emerging evidence of a larger role of non-coding RNA in exon selection. These RNA elements can be located on the pre-mRNA and regulate the binding of U1 snRNP by stabilizing the interaction of U1 with competing 5' splice sites (Yu et al., 2008). The RNAs can also be generated from other transcripts and then regulate pre-mRNAs (reviewed in (Khanna and Stamm, 2010)).

miRNAs are a well-studied group of small RNAs and were shown to influence alternative splicing. For example, miR-124 acts on the splicing regulator PTB (Makeyev et al., 2007) and influences PTB-dependent splicing events indirectly. miR-10a/10b, miR-28 and miR-505 target SF2/ASF (Verduci et al., 2010; Meseguer et al., 2011) and influence SF2/ASF dependent exons. Similarly, miR-23a/b regulates the expression of CUGBP and ETR-3-like proteins that control the majority of alternative splicing in the developing muscle (Kalsotra et al., 2010).

Longer RNAs that regulate alternative splicing include MALAT1 that regulates the phosphorylation of SR-proteins (Tripathi et al., 2010), as well as fragments of snoRNAs that regulate numerous alternative exons (Kishore et al., 2010).

RNA elements within a pre-mRNA influence splice site selection, often by influencing the secondary structure (reviewed by (Buratti and Baralle, 2004)). Most proteins regulating alternative splicing bind to single stranded RNA and changing the RNA structure can “mask” such binding sites by forming double-stranded RNA structures (Hiller et al., 2007b). The effect of secondary structure is well studied for the DSCAM pre-mRNA, where the structure of the pre-mRNA regulates alternative exon usage. In the DSCAM pre-mRNA, one alternative exon is chosen from 48 alternative exons by the formation of a double-stranded RNA structure between a conserved sequence in the pre-mRNA and the alternative exon (Graveley, 2005). The 5' splice site of tau exon 10 is possibly determined by its sequestration in a secondary structure (Varani et al., 1999) that is possibly opened by the RNA helicase p68/DDX5 (Kar et al., 2011). However, there is experimental evidence that regulatory proteins contribute to exon 10 regulation by binding near the proposed secondary structure, which is currently investigated (Wang et al., 2011).

Finally, metabolites can change pre-mRNA structures. Three *Neurospora crassa* genes contain a thiamine aptamer in introns located at the 5' end of genes involved in thiamine metabolism. Two of these introns have alternative 5' splice sites. The thiamine aptamer

sterically blocks one of the alternative 5' splice sites in the absence of thiamine pyrophosphate. Upon binding of thiamine phosphate, the aptamer changes its conformation, making the alternative 5' splice site accessible to the splicing machinery. Thus, a metabolite can change alternative splicing by changing the secondary structure of a pre-mRNA (Cheah et al., 2007).

Since not all short non-coding RNAs have been identified, it is likely that RNAs play a larger role in splice site selection than previously thought. A new cloning method provided evidence for widespread expression of dsRNAs in mouse brain, suggesting that pre-mRNA regulation by antisense RNAs is much more common than previously anticipated (Shen et al., 2011). tRNAs are another emerging regulation by RNA where the initiator tRNA, devoid of a loaded methionine, can regulate alternative splicing events that depend on the AUG start codon for their usage (Kamhi et al., 2010).

2.4 Alternative splicing is integrated with other mechanisms of gene expression

Alternative exon usage is coordinated with other events of gene expression, most notably transcription. Two models have been suggested for the mechanism: the recruitment model and the kinetic model. The recruitment model assumes splicing factors assemble at the CTD (carboxy terminal domain) of RNA polymerase II and are released onto the nascent pre-mRNA during transcription. As these factors influence splice sites in a concentration dependent manner, the pre-loading of the CTD influences alternative exon usage (Das et al., 2006; Das et al., 2007b). The kinetic model postulates that protein complexes need time to assemble on an exon, which leads to its recognition. Everything that slows down a polymerase would give more time for the recruitment of the regulatory complexes and would favor alternative exon usage, as these exons usually depend more strongly on auxiliary factors (reviewed in (Kornblihtt, 2006; Kornblihtt, 2007)). The kinetic model attained considerable attention as genome-wide studies showed that exons associate with different histone modifications than introns (Kolasinska-Zwierz et al., 2009). DNA that encodes constitutive exons shows a higher degree of nucleosome occupancy than alternative exons or introns (Tilgner et al., 2009; Chen et al., 2010). Furthermore, exons associate with distinct histone modifications that are at least partially evolutionarily conserved (Andersson et al., 2009; Kolasinska-Zwierz et al., 2009; Huff et al., 2010). These histone marks could contribute to the regulation of alternative splicing (Luco et al., 2010). (Reviewed in (Kornblihtt et al., 2009; Schor et al., 2010)).

Histone modifications are not the only epigenetic modifications associated with alternative splicing. For example, the methylation pattern of honeybees correlates with splice sites and, most interestingly, is regulated by the different intake of royal jelly in workers and queens during development (Lyko et al., 2010). Therefore, it becomes clear that epigenetic modifications correlate with alternative splicing and influence the process mechanistically. This should be kept in mind when analyzing the function of alternative exons, as the exon usage could simply reflect an overall change in chromatin structure that changes alternative splicing as a 'side effect'.

2.5 Global analysis indicates that alternative exons are jointly regulated in networks of exons

The development of new technologies, especially genome-wide splicing arrays, deep-sequencing and CLIP (Cross link and immunoprecipitation) analysis (Moore and Silver, 2008; Liu and Elliott, 2010), and the emergence of high-throughput sequencing (Sultan et al., 2008) provided new insights into the global regulation of alternative exons and their function. For example, it was found that 76% of all genes are expressed during brain development, with a striking coordination of alternatively spliced exons that implies they are functionally relevant (Johnson et al., 2009). Similar coordinated changes in expression of alternative splicing were observed in a cell model of myogenic differentiation (Bland et al., 2010): during differentiation of a primary model of human erythrocytes (Yamamoto et al., 2009), during epithelial mesenchymal transition (Warzecha et al., 2010), during chemically induced cell death that results in a coordinated change of splicing of apoptotic factors (Moore et al., 2010) and after stimulation with insulin (Hartmann et al., 2009). The analysis of these model systems showed that numerous alternative exons changed to achieve a biological outcome simultaneously. Some of the exons changed under different experimental conditions could just be co-regulated, without a direct contribution to the phenotype.

Similar to functional networks of alternative exons, there are networks of exons regulated by a common factor. These exons could be identified by CLIP analysis that shows the *in vivo* binding profiles between a protein factor and RNAs, especially when coupled with microarray analysis that shows functional changes. In the CLIP method, an RNA binding protein is cross-linked *in situ* to the pre-mRNA, the complexes are immunoprecipitated, the RNA isolated and cloned or subjected to direct sequencing in HITS/CLIP. CLIP was pioneered for NOVA (Ule et al., 2003; Licatalosi et al., 2008; Ruggiu et al., 2009) and has since been applied to numerous other factors, including TIA-1 (Wang et al., 2010), hnRNPC (Konig et al., 2010), PTB (Xue et al., 2009; Llorian et al., 2010), SF2/ASF (Sanford et al., 2009) and FOX2 (Yeo et al., 2009). Functionally, the role of given splicing factors on alternative splicing have been determined by array analysis after knockdown of a splicing factor by siRNA. These experiments identified new target genes of splicing factors, as for SAM68 (Chawla et al., 2009).

The CLIP method allows detailed evolutionary comparisons. For example, the targets of the mammalian NOVA-1 and its *Drosophila* ortholog Pasilla have been compared. Interestingly, NOVA-1 and Pasilla regulate a completely different set of genes in both organisms, but recognize exons with similarly arranged regulatory sequences. This indicates that sequences regulated by a splicing factor evolve rapidly, whereas the regulatory principle is highly conserved (Brooks et al., 2011).

Almost all genome-wide studies of alternative splicing are based on assays that detect changes in mRNA expression. As protein expression from RNA is regulated by a wide variety of mechanisms, such as miRNA action, nonsense-mediated decay and translational efficiency, it is important to test whether the proteome reflects the changes in alternative splicing. The emerging proteomic studies indicate that indeed the proteome reflects the diversity seen on the RNA level (Tress et al., 2008; Severing et al., 2011).

2.6 Outlook

Despite the large body of work accumulated in the past 10 years, more amazing features of the splicing process are being discovered. Trans-splicing, the connection of two different mRNAs, has been long known in trypanosomes, but there is evidence it can also occur in humans and drosophila (Horiuchi and Aigaki, 2006; Al-Balool et al., 2011). Related to trans-splicing, a rearrangement of exon order different from their genomic order has been observed (Dixon et al., 2005). Pre-mRNA splicing is strictly a nuclear event, but can occur in the cytosol of platelets, which are devoid of a nucleus (Denis et al., 2005). Finally, there is evidence that splicing can bypass the 3' end formation signals and connect the RNA of two neighboring genes, which could create fusion transcripts from adjacent genes (Frith et al., 2007).

Most of the mechanistical insight into alternative splicing derived from biochemical experiments and transfection studies, where the behavior of millions of molecules is averaged. These studies are now being refined by single molecule analysis. By visualizing the binding of PTB on its target pre-mRNA, evidence was found that PTB stabilizes RNA loops that flank an exon (Cherny et al., 2010), which questions earlier studies that proposed PTB creates one larger loop containing the regulated exon (Wagner and Garcia-Blanco, 2001).

Most of the functional studies of splicing isoforms are performed in cell models that are easy to manipulate. To obtain a more physiological picture, an increasing amount of mouse models has been generated (reviewed in (Moroy and Heyd, 2007)). These studies sometimes gave surprising results, for example, they generated a mouse line that showed an increased sensitivity to dioxin (Pohjanvirta, 2009). Similarly, mice expressing only selected mu-receptors responded to heroin, but not to the chemically related morphine, which reflects the preference of most human addicts (Pan et al., 2009). More challenging insights can be expected when functional studies move from cells to whole organisms in the future.

Tremendous progress has been made in determining the mechanisms of splice site selection and in determining the genome-wide regulation of alternative exons during the past years. The data suggest that most alternatively spliced isoforms are part of a program that changes the isoform repertoire of multiple genes. These coordinated changes have to be taken into account when analyzing the function of a given exon. It is possible that a functional change is not caused by a single exon, but by the coordinated change of multiple, coregulated alternative exons. The coregulated exons may not be apparent in an experiment. Now we can at least start to predict the regulation of exons based on their sequence elements and can determine exons that are coregulated by a splicing factor experimentally (Das et al., 2007a). The field can therefore start to analyze the physiological functions of coordinated changes in alternative splicing.

3.0 Function of alternative splicing

3.1 General principles

The overall function of alternative splicing is to increase the diversity of the mRNA expressed from the genome. Due to the combinatorial control mechanisms that regulate

alternative exon recognition, splicing programs coordinate the generation of mRNA isoforms from multiple genes. Evolution can select some of these isoforms to fulfill defined functions. Other isoforms could simply represent co-regulated exons without any direct function. It is also possible that a specific isoform shows only a functional effect when expressed with other isoforms generated by a coordinated change in splicing. The magnitude of alternative splicing regulation ranges from subtle modifications of protein functions, for example in ion channels to making binary on/off switches, observed in apoptosis genes.

3.1.1 Genome-wide overview of functions—Genome-wide studies indicate protein-parts encoded by alternative exons are predominantly located in coiled regions on the outside of the protein. Therefore, alternative exons do not change the general structure of the protein, but mainly influence local structures on the protein surface (Wang et al., 2005d). Alternative exons are often located in unstructured protein regions, allowing the introduction of protein domains without disrupting the overall protein structure (Romero et al., 2006). Together, this indicates the major function of alternative splicing is to modify, but not to radically change the function of a protein. Evolutionary analysis supports this notion, as human-mouse comparison shows that short alternative exons preserving the reading frame are conserved between human and mouse, indicating that small, incremental changes are caused by alternative splicing (Zhang et al., 2007a).

3.1.2 Alternative splicing as a part of evolution—Alternative splicing is an evolutionarily old process and likely appeared in the common ancestor of eukaryotes (Irimia et al., 2007). The function of individual exons can be determined by evolutionary comparison (reviewed in (Keren et al., 2010)). All comparisons rely on the hypothesis that functionally important alternative exons will be conserved in evolution. In contrast, non-functional exons will be eliminated by purifying selection. A frequently used property of alternative exons is the symmetry of an exon. An exon is symmetric when it can be divided by three, which indicates it keeps the reading frame. In general, conserved alternative exons in reading frames are symmetrical, whereas exons in non-protein coding regions and species-specific exons show a higher fraction of non-symmetrical exons (Magen and Ast, 2005; Xing and Lee, 2005).

The amount of alternative splicing increases from invertebrates to vertebrates (Kim et al., 2007a), suggesting the generation of new alternative exons could be a driving force in evolution. A characteristic of primates is the occurrence of Alu elements that comprise about 10% of the human genome (Hasler et al., 2007). These Alu insertions can evolve into exons, which contribute to generating a more complex transcriptome in primates (Lev-Maor et al., 2003; Dagan et al., 2004).

Mouse-human comparison showed that about 11% of cassette exons are alternatively used in one species, but constitutively used in the other species. This demonstrates that alternative splicing contributes to species-specific differences (Claverie-Martin et al., 2005; Lei and Vorechovsky, 2005; Pan et al., 2005; Mola et al., 2007). Within one species, alternatively spliced exons are conserved mostly in the nervous system. In contrast, testis and cancer cell lines show the least amount of conserved alternative splicing. For testis, this could suggest a deliberate increase of variation in expression to allow for evolutionary selection. The diverse

expression of alternative exons in cancer cells could be caused by a general breakdown of surveillance mechanism, but could also allow the selection of cancer cells likely to grow in an organism (Kan et al., 2005).

3.1.3 Splicing in individuals—Individuals belonging to the same species show differences in alternative splicing. When 250 exons from 22 human individuals were compared, 6 out of 70 alternative exons showed consistent differences among individuals (Hull et al., 2007). There are now numerous examples, where a certain haplotype contributes to differences in alternative splicing patterns (Hull et al., 2007; Douglas et al., 2009; Iwata et al., 2009) (reviewed in (Graveley, 2008)). These studies suggest that differences in alternative splicing patterns contribute to differences in gene expression and phenotypes among individuals. In the future it will be interesting to see how single nucleotide polymorphisms contribute to alternative splicing and differences among individuals.

3.1.4 Splicing in disease—Given the widespread functions of alternative splicing, it is not surprising that aberrant regulation of alternative splicing leads to human disease. This connection to human health is being increasingly recognized and has been covered in numerous reviews (Wang and Cooper, 2007; Kim et al., 2008a; Cooper et al., 2009; Tazi et al., 2009; Barta and Schumperli, 2010; Dhir and Buratti, 2010; Hallegger et al., 2010; Raponi and Baralle, 2010; Tazi et al., 2010; Ward and Cooper, 2010). In most cases, changes in alternative splicing are caused by point mutations, which have been collected in databases (Bechtel et al., 2008b; Bechtel et al., 2008a).

Changes of alternative splicing in cancer cells are well-studied, as a deregulation of alternative splicing is a hallmark of cancer (Klinck et al., 2008; Venables et al., 2009; Misquitta-Ali et al., 2011) (reviewed in (Kim et al., 2008b; David and Manley, 2010)). Several protein isoforms generated by alternative splicing are crucial for cancer progression and are the subject of experimental therapeutic intervention. For example, the RON tyrosine kinase gene can generate a constitutively active kinase due to the skipping of an alternative exon (Collesi et al., 1996). The exon, controlled by the splicing factor SF2/ASF, determines the epithelial to mesenchymal transition, which is the invasiveness of the cancer cells (Ghigna et al., 2005). It is now investigated whether manipulating this splicing event changes tumor progression.

Most tumors rely on anaerobic glycolysis for their energy requirements, which acidifies the surrounding media (Gatenby et al., 2006). Therefore tumors have a lower requirement of oxygen and a different expression profile than glycolytic enzymes. One of these enzymes is pyruvate kinase, which is upregulated in some cancer cells (Christofk et al., 2008). Currently it is controversial whether a splice variant or the total pyruvate kinase is upregulated (Bluemlein et al., 2011), but functional studies showed a reversal from the embryonic to the adult splicing forms of pyruvate kinase slows cancer growth in mouse models (Christofk et al., 2008). The deregulation of pyruvate kinase splicing could indicate a cancer-specific program, as the trans-acting factors regulating the splicing event are under the control of c-myc (David et al., 2010) (Clower et al., 2010).

The lower pH of the tumor's microenvironment influences alternative splicing by changing the intracellular localization of numerous splicing factors. Most splicing factors are nuclear under steady state conditions, but they shuttle between the nucleus and the cytosol, typically driven by phosphorylation (Stamm, 2008). For example, under hypoxia (Daoud et al., 2002) and chemically induced acidic conditions (Hirschfeld et al., 2009), the splicing factor tra2-beta1 accumulates in the cytosol and is depleted in the nucleus. As a result, the splicing of its target genes is altered. Important for cancer, the matricellular protein Cyr61 (cysteine rich 61) that promotes metastasis changes its splicing pattern to an isoform supporting metastasis (Hirschfeld et al., 2009). Therefore, changes in the tumor microenvironment could contribute to the deregulation of alternative splicing in cancer.

Lists of alternative exons deregulated in different cancer cells have been compiled in the literature (see for example (Xu and Lee, 2003; Klinck et al., 2008; Venables et al., 2009)).

Several neurological diseases are characterized by changes in alternative splicing. One of the best-investigated diseases is Myotonic Dystrophy type 1 (DM1). There, a CTG expansion in the 3' untranslated region of the DMPK gene causes a sequestration of two splicing regulatory proteins: CUGBP1 and MBNL1. As a result, a network of alternative splicing events is changed, which causes abnormalities in heart development and skeletal muscle (reviewed (Ranum and Cooper, 2006; Poulos et al., 2011)).

3.2 Overall changes of cellular properties

The influence of splice variants on global cellular processes has been studied using transfection assays that either overexpress or remove a splicing isoform. The readout of these experiments is typically cell proliferation, which can have a significant physiological relevance, for example in cancer. However, the detailed molecular mechanisms for the observed effect remain unclear.

Well-studied examples include apoptosis, where alternative splicing can act like an on/off switch for several genes encoding pro-apoptotic or anti-apoptotic enzymes. For example, alternative inclusion of parts of the active center of caspase 3 generates pro- and anti-apoptotic forms (Vegran et al., 2005). However, the overall contribution of alternative splicing to apoptosis is more complex, as splice variants can increase (Mosley and Keri, 2006) or inhibit apoptosis (Lee et al., 2010a). The role of splicing isoforms is not absolute, but depends on the cell type where the isoforms are expressed (Caldas et al., 2007) (Figure 2, Table 1).

The role of intronic SNPs (single nucleotide polymorphism) in modifying alternative splicing is an emerging area of research. Its potential importance is illustrated by a deep intronic SNP in the oxidized low-density lipoprotein (lectin-like) receptor 1 gene. The SNP is associated with exon 5 skipping that correlates with acute coronary syndromes, where the new shorter variant called LOXIN protects cells from apoptosis. Although it is not fully clear how the SNP influences splice site selection mechanistically, the example shows that inherited variations of alternative splicing contribute to complex human diseases (Mango et al., 2005).

Alternative splicing isoforms have been implicated in almost all aspects of cancer development: cell proliferation, cell invasiveness, methylation defects and chemotherapy resistance. It is often difficult to discern whether a particular splice site selection causes the observed effect or is merely the result of the cancerous transformation. In addition to functional examples in Table 1B, extensive isoform profiling of cancer cells has been performed ((Xu and Lee, 2003; Klinck et al., 2008; Venables et al., 2009)). Related to the role in cancer development, the role of isoforms in angiogenesis that controls blood supplies to tumors has been documented.

Similar to molecularly well-characterized examples, different mechanisms are used to modify cellular processes, for example destabilization of the protein (Lin et al., 2009a), addition of inserts in functional domains (Vegran et al., 2005; Mosley and Keri, 2006; Krieg et al., 2009) or activation of signaling pathways (Datta et al., 2006).

Finally, it should be pointed out that not all splicing isoforms have a measurable effect, for example there was no observable difference between TREX2 isoforms (Chen et al., 2007). As such negative results are difficult to publish, they are likely under reported.

3.3 Change in transcription factors

Transcription is regulated by the formation of protein complexes on the promoter sequences of DNA. As these protein complexes are assembled by combining several weak interactions to form one high-affinity complex, they offer multiple regulation points for alternative splicing variants that generally have moderate influence on binding to DNA or other proteins in the complex (Figure 3).

Changes in alternative splicing alter the structure of the transactivation domain, which influences the activation of RNA polymerase II in either a negative or positive way (Table 2, A). Skipping of alternative exons that encode the DNA binding domain leads to transcription factors that have lost their ability to bind to promoters. These isoforms can either be inactive (Figure 3, B) or act in a dominant negative way. This is usually achieved by replacing the transcription factor isoform with a DNA binding domain from the transcription factor complex (Figure 3, C). Nuclear receptors are particularly well-studied. They typically form after multimerization of cytosolic receptors initiated by ligand binding that leads to their translocation into the nucleus. The protein interaction in the multimerization domains is subject to regulation by alternative splicing and usually leads to inactive variants. However, typical for alternative splicing regulation, alternative exons do not just inactivate a factor, but can also modulate its activity (Goodson et al., 2005). Since such effects are subtler, they are likely under reported (Figure 3, D).

Intracellular and intranuclear localization can be regulated by alternative splicing, which leads to inactive transcription factors when accumulated in the cytosol. The FOXP2 variants show a drastic example of such a regulation that also includes sequestration. The loss of the DNA binding domain results in the cytoplasmic localization of FOXP2 variants. Since these variants still contain a dimerization domain, they can form complexes in the cytosol, which downregulates the transcriptional activity of the full-length form (Vernes and Fisher, 2009).

The effect of alternative splicing is not limited to protein isoforms, but extends to ncRNA (non-coding RNA). ncRNAs bind to transcription factors where different ncRNA isoforms generated by alternative splicing can modulate the activity of a transcription factor (Feng et al., 2006a; Hashimoto et al., 2009a) (Figure 3, E).

Most of the studies were performed by transfection analysis. It is important to keep in mind that alternative splicing frequently occurs in a cell-type or tissue-specific way, as illustrated by the MYB gene. The MYB gene modulates transcriptional activities through at least six alternative exons, which are used differentially in lymphomas and during hematopoietic differentiation. This example shows how cell-type specific splice site selection can contribute to cell-type specific transcriptional programs (O'Rourke and Ness, 2008). Alternative splicing of transcription factor isoforms contributes to regulatable on/off switches that can be triggered by extracellular signals. For example, the TFII-I gene in resting cells generates two isoforms, the cytosolic delta isoform and the nuclear beta isoform. The beta isoform blocks activation of the *c-fos* gene. Upon growth factor stimulation, the beta isoform moves from the nucleus to the cytosol and the delta isoform from the cytosol to the nucleus. In the nucleus, the delta isoform activates *c-fos* (Hakre et al., 2006). This example also illustrates that changes in transcriptional activity are only visible after cellular stimulation.

3.4 Change in localization of proteins

Alternative splicing can change the intracellular localization of proteins by altering localization signals, sequences for post-translational modification or interaction sites with other proteins (Figure 4). These changes can result in all or nothing effects, for example when an exon introduces a nuclear localization site (Miyake et al., 2005). More often these changes are gradual, where alternative exons shift the relative distribution of protein isoforms among cellular compartments, such as in the *ING4* variants (Unoki et al., 2006). Proteins often acquire new functions in different compartments. For example, the *lipin* gene generates a nuclear and a cytoplasmic variant due to inclusion of an alternative exon. The nuclear form acts as a transcription factor, whereas the cytosolic form has phosphatidate (PA) phosphatase activity (Han and Carman, 2010; Zhang et al., 2012) (reviewed in (Csaki and Reue, 2010)). In this gene, the alternative splicing of the crucial exon is regulated by the splicing factor *tra2-beta1*, which is downregulated in obese subjects (Pihlajamaki et al., 2011). This suggests a deregulation of a splicing factor can control fat metabolism by sending a key regulatory protein into different cellular compartments.

Most of the studies investigating the intracellular localization of splice variants analyze used tagged cDNA, mostly GFP, myc and Flag tags. In contrast to pre-mRNAs, these cDNA constructs do not undergo nonsense-mediated decay. It is therefore crucial to test that the endogenous mRNAs are actually expressed as a protein.

A special case of localization is the association of proteins with membranes (Table 3, C-E). By deleting membrane-binding domains, alternative splicing can control membrane association of proteins. The soluble proteins can either accumulate in the cytosol or be secreted, depending on their membrane topology. This mostly results in a loss of function of the normally membrane-bound protein. However, the soluble proteins can have dominant

effects, as shown in the MET oncogene, where a soluble, secreted form inhibited the signaling of the membrane-bound form (Tiran et al., 2008). Finally, the localization among different membrane compartments is regulated by alternative splicing, which leads to the accumulation of the variants in different cellular organelles (Table 3, D).

A change in localization due to splice site selection can have severe physiological consequences. For example, unusual intron retention creates a soluble, secreted form of the erythropoietin receptor that is released into the blood where it competes with the full-length receptor, which contributes to erythropoietin resistance in end-stage kidney diseases (Khankin et al., 2010).

3.5 Change in enzymatic properties

Alternative splicing can change enzymatic properties (Figure 5). The best studied class of enzymes affected by alternative splicing are kinases, which are frequently inactivated by inclusion or deletion of alternative protein parts in their active center. In most cases, a change in usage of the alternative exon completely abolishes the activity (Table 4, A). However, in some cases the activity is only modulated, typically reduced (Ghosh et al., 2006) (Dolzhanskaya et al., 2006). Frequently, described enzymatic inactive forms are generated by premature stop codons. Care should be taken in analyzing these isoforms to ensure the shortened variants are actually expressed as mRNAs as they could be degraded (Schneider et al., 2005), typically by NMD (nonsense mediated decay). Other mechanisms that influence the activity are the control of enzyme secretion or the control of substrate binding (Lira et al., 2008).

Kinases can be regulated by autoinhibition. A removal of this domain generates constitutively active enzymes (Table 4, B).

In few instances, alternative isoforms have a dominant negative effect on the active isoform, which is achieved by the formation of heterodimers (Table 4, C). Finally, alternative splicing can change the substrate specificity of enzymes, for example in the cytosolic phospholipase A2 beta (Ghosh et al., 2006).

3.6 Alternative exons that encode protein domains

Alternative exons frequently encode part of protein domains. These exons are usually identified by database comparison and their function is deduced from the general function of the domain that is deleted by exon skipping. Table 5 lists examples of identified domains where a change of binding to a defined interaction partner was not determined. Tables 6 and 2B list changes in binding domains that alter the interaction with DNA, other proteins and defined ligands. The role of the domain is illustrated in Figure 6.

3.7 Change in binding to other proteins

As most alternative exons are localized on the protein surface, alternative splicing can regulate the binding to other proteins. Exons can encode complete interaction domains or part of binding domains, which changes the interaction with other proteins (Table 6, A; Figure 6A, B). In most cases, the binding affinity is modulated but the binding is not

abolished completely. Several cases have been reported where a change in alternative splicing outside a known protein domain changes the interaction with other proteins, summarized in Table 6, B.

Similar to a change in protein binding is the influence of alternative splicing on binding of low molecular weight ligands or hormones (Figure 6C). The classical example is the insulin receptor, where skipping of the alternative exon 11 generates a receptor that shows the highest affinity for IGF-II (insulin-like growth factor II) (reviewed in (Belfiore et al., 2009)). This system is more complicated in vivo as the insulin receptor and the IGF-IR (insulin-like growth factor I receptor) can form heterodimers. There is no difference among the splice variants in these heterodimers (Slaaby et al., 2006), demonstrating the ability of alternative exons to 'fine-tune' a biological response.

Another interaction regulated by alternative splicing is the binding of proteins to DNA, which can be controlled by alternative exons in the DNA binding domain, summarized in Table 2, B. In addition, binding to membranes is influenced by alternative splicing and changes the localization of the proteins, summarized in Table 3.

3.8 Change in channel proteins

In general, the effects evoked by alternative splicing are relatively small. Electrophysiological techniques can analyze channel proteins and determine the properties of a few or even a single molecule. Alternative splicing can change every aspect of ion channels: gating times, gating voltages, ion sensitivity and inhibition by other substances (Table 7, Figure 7). Similar to other events generated by alternative splicing, some variants can exhibit dominant effects, for example variants of the glutamate transporter SLC1A3 (Vallejo-Illarramendi et al., 2005).

3.9 Influence on mRNA function

Alternative splicing not only occurs in the coding regions of pre-mRNA, but also in the untranslated regions, summarized in Table 8. An emerging theme is the regulation of mRNA stability through miRNAs, which can be affected by alternative splicing of the miRNA-binding sites, frequently located in the UTR, as has been seen in the SLC11A2 gene (Andolfo et al., 2010).

3.10 Other functions of alternative exons

Alternative exons were found to change the stability of proteins by different mechanisms, that includes a change in the C-terminus making proteins more susceptible to degradation, as seen for the migration and invasion inhibitory protein MIIP (Song et al., 2005) and the iodotyrosine deiodinase (Gnidehou et al., 2006) (Table 9, A).

3.11 General conclusion

These examples demonstrate that alternative splicing influences almost all aspects of protein functions, making it a central element in gene expression. Given the widespread usage of alternative splicing that affects almost every gene, the experimentally verified examples here

are only the tip of the iceberg. It is likely that genome-wide approaches will unveil new functions and new regulatory modules in the future.

4.0 Databases for work on alternative splicing

The experimental analysis of splicing problems has been greatly facilitated by user-friendly, Web-based analysis tools and databases, summarized in Table 10. Databases for alternative splicing were mostly generated computationally from different species (Table 10, A), but have also been generated from protein databases (Table 10, B). Importantly, numerous specialized databases listed in Table 10, B, help in analyzing alternative splicing functions and are useful to put a splicing event into a bigger picture.

Finally, software tools are available to analyze splicing events, which are listed in Table 10, C. With a few exceptions listed in Table 10, all resources are available for free on the Web.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CLIP	Cross link and immunoprecipitation
CTD	carboxy terminal domain
Cyr61	cysteine rich 61
ESE	exonic sequence enhancer

HITS-CLIP	High-throughput sequencing of RNA isolated by crosslinking immunoprecipitation
hnRNP	heterogenous ribonuclear proteins
IR	insulin receptor
ISS	inhibitory splicing sequence
ncRNA	non-coding RNA
NLS	nuclear localization signal
NMD	nonsense mediated decay
NoLS	nucleolar localization signal
NOVA	neuro-oncological ventral antigen 1
NR	nuclear receptors
PTB	polypyrimidine tract binding protein
SNP	single nucleotide polymorphism
SR	serine arginine rich
U2AF	U2 auxillary factor

Highlights

- Almost every human pre-mRNA undergoes alternative splicing
- The overall function of alternative splicing is to increase the diversity of mRNAs expressed from the genome
- Changes caused by individual splicing isoforms are typically small
- Splicing changes are coordinated, generating significant biological effects through combination
- Alternative splicing interferes with almost every biological function analyzed

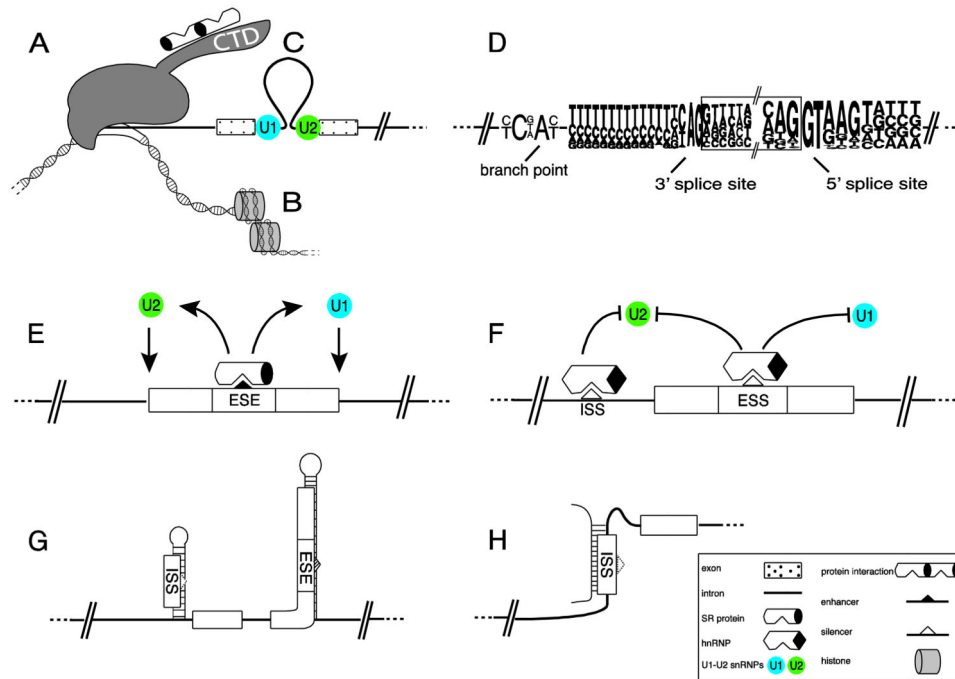


Figure 1. Control elements of alternative exons

The usage of alternative exons is controlled by the combination of multiple factors. **A:** RNA polymerase II assembles splicing factors on its CTD, which can predetermine the splicing outcome of a nascent pre-mRNA. This example shows SR-proteins, but other factors assemble as well. **B:** Exon boundaries correlate with DNA nucleosome occupancy and alternative exon usage is influenced by chromatin marks. **C:** Large intron regions can loop out to bring exons together. **D:** An exon is defined by three crucial elements: the branch point, the 3' splice site and the 5' splice site, which follow consensus sequences indicated. **E:** Exons need additional factors to be recognized. These factors bind to exonic or intronic sequences. In this example, two SR-proteins bind to exonic enhancers (ESE: exonic splicing enhancer) and help stabilize binding of U2 and U1 snRNP. **F:** Exon usage can be repressed by exonic splicing silencers (ESS) and intronic splicing silencers (ISS) that prevent U1 or U2 snRNP binding. **G:** RNA secondary structures can mask exonic or intronic splicing enhancer and silencer, as proteins binding to these RNA elements typically recognize single stranded RNA. **H:** small RNAs can bind to splicing regulatory elements located on different mRNAs.

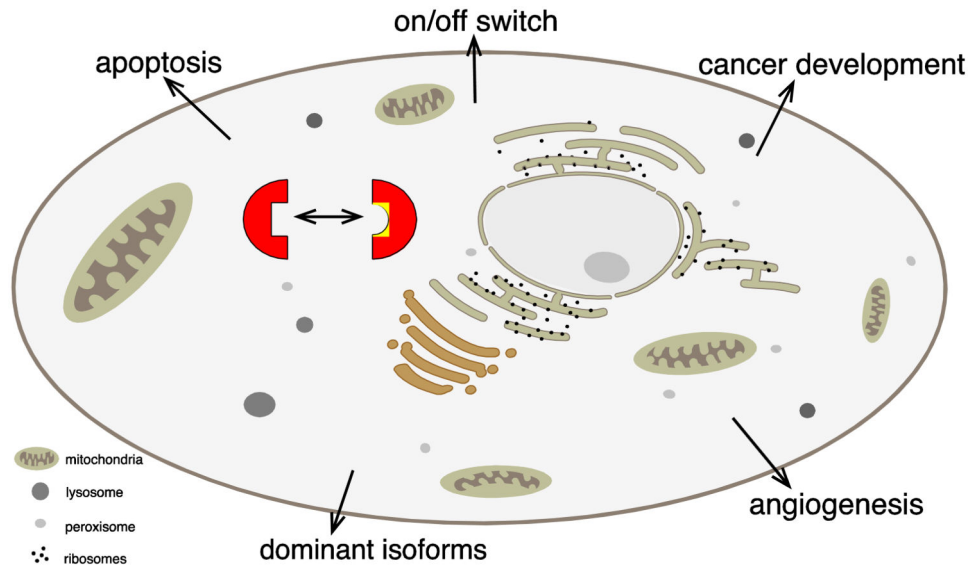


Figure 2. Overall changes in cellular properties due to alternative splicing

A eukaryotic cell is schematically depicted. Alternative splicing changes protein isoforms (red half squares) by introducing new protein sequences (yellow) that are encoded by alternative exons. Changes in global cellular processes are arranged similar to Table 1 that lists specific examples.

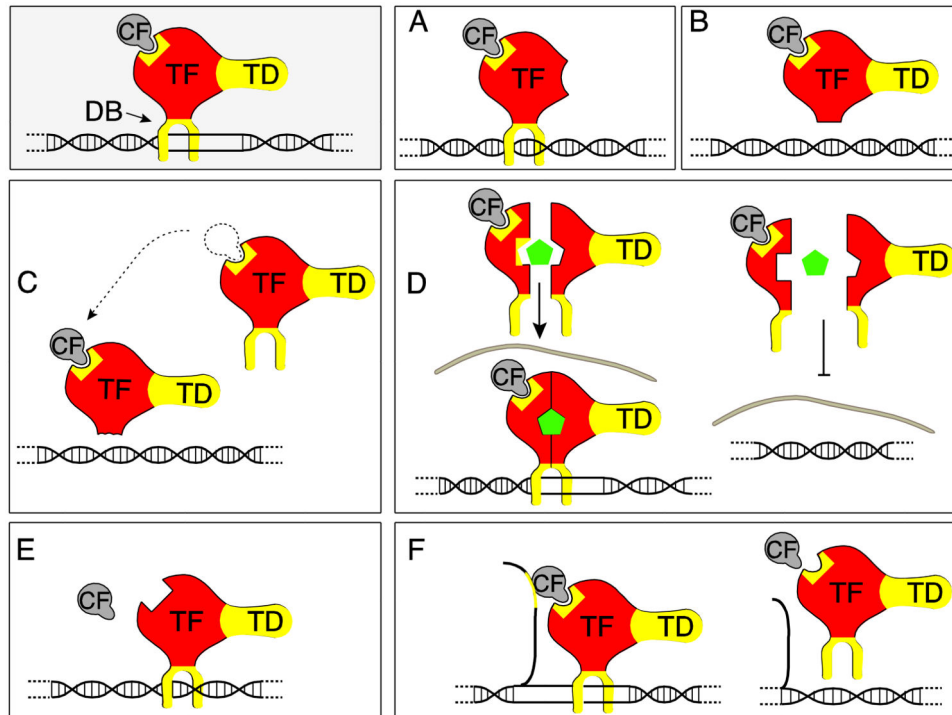


Figure 3. Changes in transcription factors

The gray box schematically depicts the general structure of a transcription factor complex. TD: transactivation domain; CF: Co-factor; TF: core transcription factor, DB: DNA binding domain. Components of transcription factors that undergo alternative splicing with well-studied effects are indicated in yellow. The numbering (A-F) of the Figure refers to Table 2 that lists specific examples.

A. Change in transactivation domain

B. Loss in DNA binding

C. Generation of dominant negative isoforms, here a factor that lost its DNA binding domain, but can still compete for cofactors (indicated by arrow).

D. Alternative splicing of nuclear receptors. In this example, the ligand binding domain is subject to alternative splicing (yellow area) that interferes with ligand binding (green pentagon), which regulates translocation of the dimerized receptor complex into the nucleus (indicated by gray nuclear membrane).

E. The binding of transcriptional cofactors is regulated by alternative splicing.

F. ncRNAs can direct transcription factors to DNA, which is regulated by alternative splicing of the ncRNAs.

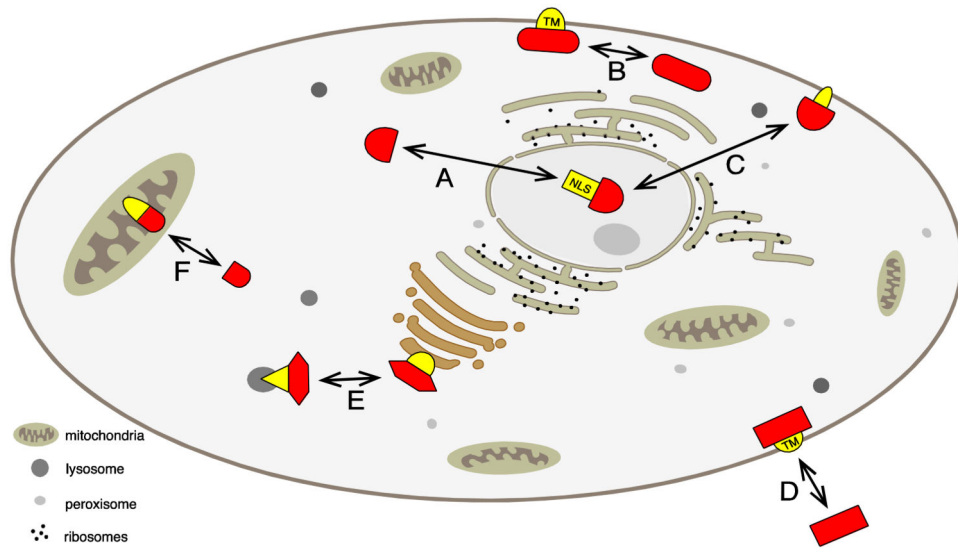


Figure 4. Changes in intracellular localization due to alternative splicing

A eukaryotic cell is schematically shown. Proteins that undergo alternative splicing are shown in red, parts encoded by alternative exons are shown in yellow. The Figure is arranged similar to Table 3, in clockwise arrangement.

- A. Change between cytosol and nucleus, typically by altering a nuclear localization signal (NLS).
- B. Change between plasma membrane and cytosol, typically by changing a transmembrane region (TM).
- C. Change between nucleus and membrane associated forms.
- D. Generation of soluble, secreted forms, typically by changing a transmembrane region (TM).
- E. Localization between different internal membranes.
- F. Localization in the mitochondria, typically by regulating a mitochondrial-targeting signal (MTS).

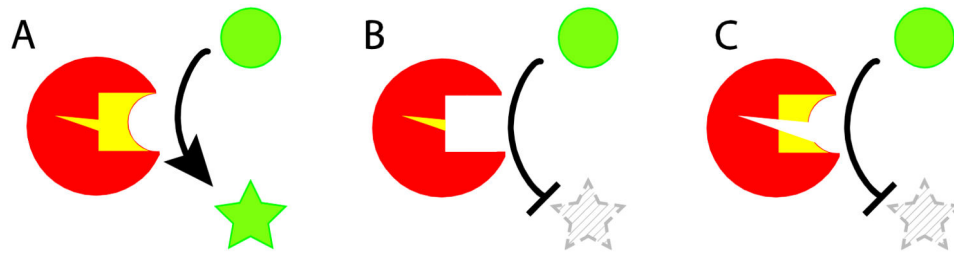


Figure 5. Change of enzymatic activity due to alternative splicing

The alternative exon is shown as a red circle, parts encoded by alternative exons are shown in yellow. **A:** The enzyme converts a substrate (circle) into a product (star). **B:** Alternative splicing influences the substrate binding, which prevents substrate formation (striped star). **C:** Alternative splicing changes the catalytic center (short triangle), which prevents substrate formation (examples in Table 4A).

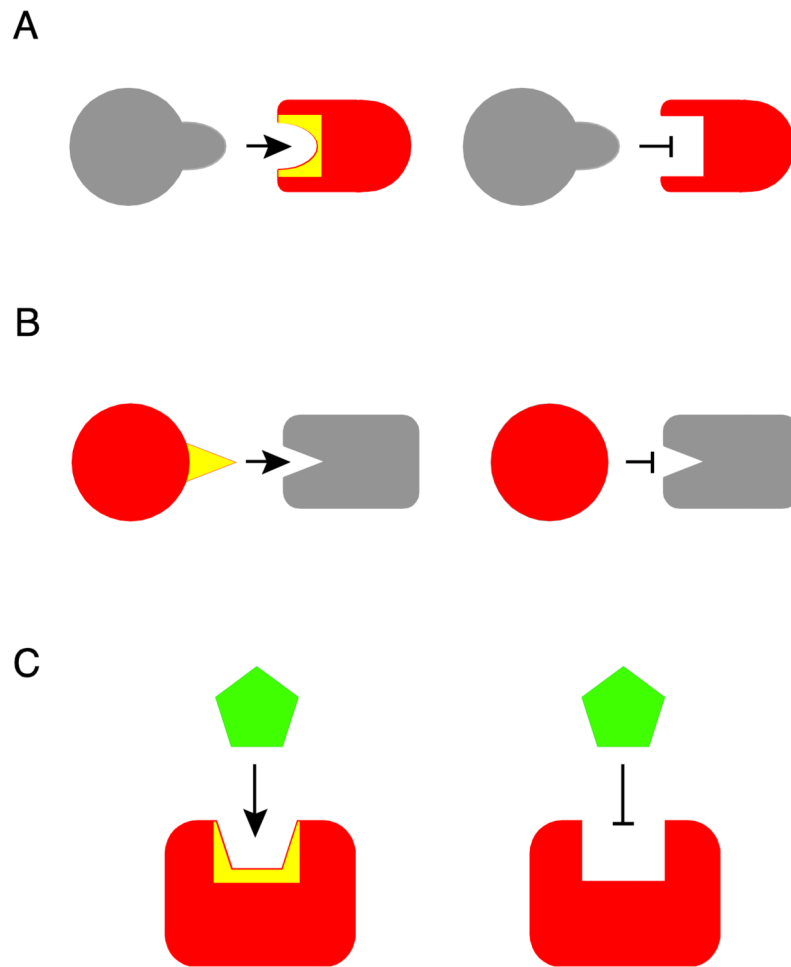


Figure 6. Regulation of protein-protein and protein-ligand interaction by alternative splicing
Examples are given in Table 6, A-B.

- A. Alternative splicing of the domain-binding pocket regulates protein interactions.
- B. Alternative splicing of domains that bind to binding pockets regulates protein interactions.
- C. Alternative splicing changes binding of a ligand (green pentagon) to a protein (red).

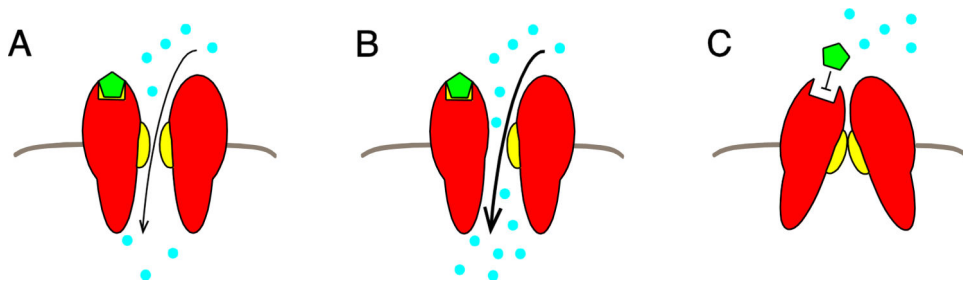


Figure 7. Change of ion channels due to alternative splicing

The ion-channel is shown in red and the channel opening indicated by yellow half circles. The triangle indicates a ligand-binding site; the ligand is shown as a hexagon. **A:** Channel in its open conformation. Dots indicate the flow of ions. **B:** Alternative splicing changes the pore, which in this case leads to a larger flux. **C:** A change in the ligand-binding site prevents channel opening.

Table 1

Cellular processes changed by alternative splicing

A. Apoptosis		
Name	Function	Reference
Birc2 (baculoviral IAP repeat containing 2) Mus musculus	Exon in the CARD (Caspase activation and recruitment domain) domain increases anti-apoptotic activity	(Mosley and Keri, 2006)
BIRC5 (baculoviral IAP repeat containing 5)	Alternative splicing generates two isoforms, which interact with the wild-type and regulate proliferation and apoptosis	(Caldas et al., 2005)
BIRC5 (baculoviral IAP repeat containing 5)	BIRC5 exon 2B inclusion causes loss of anti-apoptotic potential	(Vegran et al., 2005)
CASP10 (Caspase 10, apoptosis-related cysteine peptidase)	Truncated protein generated by new exon inclusion enhances NF- κ B activity	(Wang et al., 2007)
CASP3 (caspase 3, apoptosis-related cysteine peptidase)	Deletion of CASP3 exon 6 in the catalytic site generates a protein with anti-apoptotic function	(Vegran et al., 2005)
CASP3 (caspase 3, apoptosis-related cysteine peptidase)	Exon skipping rises a short isoform and increases chemoresistance	(Vegran et al., 2006)
CASP6 (Caspase 6, apoptosis-related cysteine peptidase)	Alternative spliced isoform inhibits the wild-type protein activation	(Lee et al., 2010a)
CFLAR (CASP8 and FADD-like apoptosis regulator)	The CFLAR longer form lacking a cysteine residue is inactive and inhibits apoptosis	(Sharp et al., 2005)
CMTM8 (CKLF-like MARVEL transmembrane domain containing 8)	Deletion of exon 2 induces apoptosis	(Li et al., 2007a)
DAPK1 (death-associated protein kinase 1)	Alternative splicing in the kinase domain generates a new isoform, which induces wild-type isoform destabilization	(Lin et al., 2009a)
HYAL1 (hyaluronoglucosaminidase 1)	Exon skipping induces cell cycle arrest and apoptosis	(Lokeshwar et al., 2006)
KLF6 (Kruppel-like factor 6)	Different 5' site use causes cell apoptosis and reduces cell proliferation	(Hanoun et al., 2010)
MADD (MAP-kinase activating death domain)	Exon 13 and 16 inclusion generates a pro-apoptotic form inhibiting cell proliferation	(Mulherkar et al., 2006; Mulherkar et al., 2007)
OLR1 (oxidized low density lipoprotein (lectin-like) receptor 1)	Exon skipping has anti-apoptotic effect	(Mango et al., 2005)
RIPK2 (receptor-interacting serine-threonine kinase 2)	Exon 2 skipping leads to a form lacking kinase domain and caspase activity	(Krieg et al., 2009)
TP73 (tumor protein p73)	Alternative splicing isoforms in C-terminus region, alpha and beta, have anti- and pro-apoptotic function, respectively	(Nyman et al., 2005)
B. Competition between isoform functions (switch function)		
Name	Function	Reference
GHRH (growth hormone releasing hormone)	Intron retention rises a truncated protein that is a dominant negative	(McElvaine and Mayo, 2006)
Hrh3 (histamine receptor H3) Mus musculus	Alternative splicing creates different C-terminus proteins that act as a dominant negative	(Bakker et al., 2006)
NPPB (Natriuretic peptide B)	Exon-skipped isoform attenuates expression and secretion of wild-type isoform	(Torrado et al., 2010)
PPARG (peroxisome proliferator-activated receptor gamma)	Exon inclusion gives rise a dominant negative form	(Kim et al., 2006)

<i>A. Apoptosis</i>		
Name	Function	Reference
SLC6A2 (solute carrier family 6 (neurotransmitter transporter, noradrenaline), member 2)	Short isoform has dominant negative effect on long isoform	(Sogawa et al., 2010)
SLC6A3 (solute carrier family 6 (neurotransmitter transporter, dopamine), member 3)	Short isoform has dominant negative effect on long isoform	(Sogawa et al., 2010)
Vipr2 (vasoactive intestinal peptide receptor 2) Mus musculus	Alternatively spliced isoform is a competitive interactant of wild-type	(Huang et al., 2006b)
<i>C. Cancer/ Cell proliferation</i>		
Name	Function	Reference
AR (androgen receptor)	Exon gives rise to a constitutive ligand-independent form and improves therapy-resistant prostate cancer	(Dehm et al., 2008)
CCND1 (Cyclin D1)	Alternative splicing generates a protein lacking exon 5 and enhances cell invasiveness	(Kim et al., 2009)
CD83 (CD83 molecule)	Alternative splicing of two exons in transmembrane and cytosolic domains inhibit T cell proliferation	(Dudziak et al., 2005)
CD99 (CD99 molecule)	Deletion in cytoplasmatic domain generates a truncated protein and enhances tumor malignancy	(Scotlandi et al., 2007)
CD99 (CD99 molecule)	Alternative splicing generates a short intracytoplasmatic domain and promotes breast cancer	(Byun et al., 2006)
Cyld (cylindromatosis (urban tumor syndrome)) Mus musculus	Splice variant causes an increase of B cell survival	(Hovelmeyer et al., 2007)
DNMT3B (DNA (cytosine-5-)methyltransferase 3 beta)	Exon 5 deletion creates a new isoform expressed in cancer cells and contributes to the genomic DNA methylation defects	(Gopalakrishnan et al., 2009)
ERBB4 (v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian))	Exon skipping in phosphotylinositol-3 kinase binding site enhances proliferation	(Muraoka-Cook et al., 2009)
ESR2 (estrogen receptor 2 (ER beta))	Exon 6 is anti-proliferative	(Treck et al., 2007)
ESR2 (estrogen receptor 2 (ER beta))	Exon inclusion has an anti-tumor effect	(Treck et al., 2008)
GLI1 (GLI family zinc finger 1)	Exon 3 and part of exon 4 are protective against transforming process	(Lo et al., 2009)
H2AFY (H2A histone family, member Y)	Alternative splicing generates two isoforms, one of which blocks cell growth	(Novikov et al., 2011)
KLF6 (Kruppel-like factor 6)	Alternatively spliced isoform enhances cell proliferation	(Naria et al., 2005)
MET (met proto-oncogene (hepatocyte growth factor receptor))	Exon 14 exclusion in the juxtamembrane domain enhances oncogenic activity	(Lee et al., 2006)
MITF (microphthalmia-associated transcription factor)	Alternative exon encoding six amino acids reduces DNA synthesis and influences proliferation	(Bismuth et al., 2005)
MST1R (macrophage stimulating 1 receptor (c-met-related tyrosine kinase))	Exon skipping enhances cancer proliferation	(Xu et al., 2005)
P2RX7 (purinergic receptor P2X, ligand-gated ion channel, 7)	Splicing variant generates a protein lacking ligand binding and promotes cervical cancer proliferation	(Feng et al., 2006b)

<i>A. Apoptosis</i>		
Name	Function	Reference
PPARG (peroxisome proliferator-activated receptor gamma)	Alternative splicing generates a protein lacking ligand binding domain that promotes tumorigenesis	(Sabatino et al., 2005)
PRLR (Prolactin receptor)	Short isoform downregulates long isoform and prevents growth of breast cancer cells	(Tan and Walker, 2010)
PUF60 (poly-U binding splicing factor 60KDa)	Exon 2 contributes to c-myc repression and cancer progression	(Matsushita et al., 2006)
RUNX1 (runt-related transcription factor 1) RUNX1T1 (runt-related transcription factor 1; translocated to, 1 (cyclin D-related))	Exon induces leukemogenesis	(Yan et al., 2006)
TNFSF13B (tumor necrosis factor (ligand) superfamily, member 13b)	Exon 3 has proliferative activity	(Gavin et al., 2005)
VCAN (versican)	Alternative splice isoforms contain CS (chondroitin sulfate) beta or alpha domain and enhance or inhibit cell proliferation, respectively	(Sheng et al., 2005)
VEGFA (vascular endothelial growth factor A)	Alternative splicing gives rise to a shorter isoform that induces cell proliferation	(Herve et al., 2005)
<i>D. Angiogenesis</i>		
Name	Function	Reference
BIRC5 (baculoviral IAP repeat containing 5)	Exon 3 modulates angiogenesis	(Caldas et al., 2007)
F3 (coagulation factor III (thromboplastin, tissue factor))	Splicing variant codes for a different C-terminus protein, which enhances angiogenesis	(van den Berg et al., 2009)
VASH1 (vasohibin 1)	Alternative splicing isoform generates a shorter protein with anti-angiogenic effect	(Kern et al., 2008)
<i>E. Dominant effect on cellular functions</i>		
Name	Function	Reference
CHEK2 (checkpoint kinase 2)	Heterodimerization of splice variants decrease wild-type activity	(Berge et al., 2010)
EMR2 (egf-like module containing, mucin-like, hormone receptor-like 2)	An 11-amino acid deletion in exon 12 inhibits wild-type protein	(Davies et al., 2007)
Gipr (gastric inhibitory polypeptide receptor) Mus musculus	Intron retention generates a truncated protein with a dominant negative effect	(Harada et al., 2008a)
OLR1 (oxidized low density lipoprotein (lectin-like) receptor 1)	Splicing isoform with different C-terminus interacts with the full-length OLR1 and inhibits its binding activity	(Biocca et al., 2008)
Robo3 (roundabout, axon guidance receptor, homolog 3 (Drosophila) Mus musculus)	Two isoforms, generated by differential intron retention, have opposite functions in regulating commissural axon guidance	(Chen et al., 2008)
SLAH1 (seven in absentia homolog 1 (Drosophila))	A partial deletion of exon 2 generates a truncated protein and inhibits the full-length isoform	(Mei et al., 2007)
<i>F. Nervous system</i>		
Name	Function	Reference
Birc5 (baculoviral IAP repeat-containing protein 5) Mus musculus	Alternative splicing isoforms are expressed differently after mouse sciatic nerve injury	(Amiri et al., 2009)

<i>A. Apoptosis</i>		
Name	Function	Reference
CadN (cadherin-N)	Exon is involved in photoreceptor neuron development	(Nem et al., 2005)
DNM3 (dynamain 3)	Exon leads to aberrant synaptogenesis	(Gray et al., 2005)
fru (fruitless)	Different transcripts lead to sex-specific aggressiveness and dominance	(Vrontou et al., 2006)
Lrp8 (low density lipoprotein receptor-related protein 8, apolipoprotein e receptor)	Exon has neuron protective function	(Beffert et al., 2006)
Myh10 (myosin, heavy chain 10, non-muscle)	Two alternative splice isoforms regulate mouse brain development	(Ma et al., 2006)
Ncam1 (neural cell adhesion molecule 1)	The Ncam-Vase (variable alternative splice exon) isoform is responsible for the changing of structural plasticity of hippocampus and poor learning performance	(Qin et al., 2005)
NLGN1 (neuroligin 1)	Splice variant generates a shorter protein, which induces rapid presynaptic differentiation	(Lee et al., 2010b)
Pedh1 (protocadherin 1)	Alternative splicing isoform levels regulate learning and memory functions in the brain	(Fukuda et al., 2008)
<i>G. Miscellaneous</i>		
Name	Function	Reference
CCKBR (cholecystokinin B receptor)	Intron 4 retention encodes an additional 69 a.a. within the third intracellular loop domain, resulting in plasma membrane dissociation and rapid resensitization	(Chao et al., 2005)
CXCR3 (chemokine (C-X-C motif) receptor 3)	Splice variants activate different signaling pathways	(Datta et al., 2006)
Dnm2 (dynamain 2)	Different splicing variants of DNM2 display different effectiveness at rescuing p75 export from the TGN	(Liu et al., 2008)
FGF8 (fibroblast growth factor 8 (androgen-induced))	An alternative 3' splice site generates a longer protein and induces mesoderm formation	(Fleicher et al., 2006)
KCNMA1 (potassium large conductance calcium-activated channel, subfamily M, alpha member 1)	Exon insert is responsible for sensitivity of hypoxia	(McCartney et al., 2005)
MAD2L1 (Mad2, mitotic arrest deficient-like 1)	Expression of inefficient splice isoform result in decreased expression of efficient isoform	(Yin et al., 2006)
MAPKAP1 (mitogen-activated protein kinase associated protein 1)	Different splicing isoforms regulated the TORC2 (mammalian target of rapamycin complex 2) signaling	(Frias et al., 2006)
Mhc (Myosin heavy chain)	Alternative splicing of exon 15 correlates with different muscle physiological properties	(Suggs et al., 2007)
Mhc (Myosin heavy chain)	Exon 7 plays an important role in establishing fiber speed and flight performance	(Swank et al., 2006)
MYH11 (myosin, heavy chain 11, smooth muscle)	Exon encoding seven amino acids regulates contractive properties of myosin heavy chain	(Low et al., 2006)
MYO1B (myosin 1B)	Alternative splicing of the LCBD (light-chain binding domain) results in proteins with increased range of force sensitivities	(Laakso et al., 2010)

<i>A. Apoptosis</i>		
Name	Function	Reference
Nos1 (nitric oxide synthase 1 (neuronal) Mus musculus)	Alternatively spliced form controls erectile activity	(Hurt et al., 2006)
POU5F1 (POU class 5 homeobox 1)	Alternative splicing N-terminus isoform is crucial for totipotent cells	(Cauffman et al., 2006)
PYCARD (PYD and CARD domain containing)	Exon 2 skipping in PGR (proline and glycine-rich) domain may affect the structure of the protein and its activation	(Matsushita et al., 2009a)
Slc12a1 (solute carrier family 12 (sodium/potassium/chloride transporters), member 1) Mus musculus	Exon controls part of macula densa signaling	(Oppermann et al., 2006)
SNAP25 (synaptosomal-associated protein, 25kDa)	Isoforms regulate exocytotic burst and membrane secretion	(Nagy et al., 2005)
TBXA2R (thromboxane A2 receptor)	Two C-terminus spliced isoforms could heterodimerize and auto-regulate the gene expression	(Sasaki et al., 2006)
TPM1 (tropomyosin 1 (alpha))	Three alternatively spliced exons alter the folding of tropomyosin	(Kremneva et al., 2006)
TREX2 (three prime repair exonuclease 2)	No differences between two spliced isoforms	(Chen et al., 2007)

Table 2

Transcription factors

<i>A. Change in Transactivation domain</i>		
Name	Function	Reference
GLI2 (GLI family zinc finger 2)	Premature stop codons in repressor domain results in higher transactivation activity	(Speck et al., 2006)
Hsf (heat shock factor) Drosophila melanogaster	Heat/cold stress changes transactivation and dimerization domains, resulting in different transcriptional activity	(Fujikake et al., 2005)
MEF2C (myocyte enhancer factor 2C)	Skipping of a domain increases the transactivation properties	(Zhu et al., 2005)
MYB (v-myb myeloblastosis viral oncogene homolog)	Modulation of transcriptional activities through at least six alternative exons, different splicing regulation in lymphoma and during hematopoietic differentiation	(O'Rourke and Ness, 2008)
NFKBIZ (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta)	Skipping of an exon in the central part of the transactivation domain generates isoforms not able to transactivate	(Motoyama et al., 2005)
NR1I2 (nuclear receptor subfamily 1, group I, member 2)	Skipping of 37 nt in the ligand binding domain generates dominant negative isoform that no longer transactivates	(Lin et al., 2009b)
POU1F1 (POU class 1 homeobox 1) Ovis aries	Insertion in transactivation domain reduces transactivation	(Bastos et al., 2006)
Ppfp19 (pre-mRNA-processing factor 19) Mus musculus	Exon inclusion generates an isoform that represses a transcription activator	(Urano et al., 2006)
RBM14 (RNA binding motif protein 14)	Modulates transactivation activity through different C terminus	(Iwasaki et al., 2005)
Sim2 (single-minded homolog 2 (Drosophila)) Mus musculus	Change in a repressive domain leads to transactivation	(Metz et al., 2006)
THRB (thyroid hormone receptor, beta)	Increased binding to a transcriptional co-activator after thyroid hormone binding	(Wan et al., 2005)
ZFPM2 (zinc finger protein, multitype 2)	Regulation of a repression motif in a tissue specific way, variant can no longer perform cofactor-mediated transactivation	(Dale et al., 2007)
ZNF318 (zinc-finger protein 318)	Usage of zinc-finger motif changes a repressor to a transactivator	(Tao et al., 2006)
<i>B. DNA-binding</i>		
Name	Function	Reference
Dmrt1 (doublesex and mab-3 related transcription factor 1) Mus musculus	DM domain (zinc finger-like DNA-binding domain), variant acts dominant negative	(Lu et al., 2007)
ESRRG (estrogen-related receptor gamma)	Loss of a part of the DNA-binding domain and transactivation properties	(Kojo et al., 2006)
FOXP2 (forkhead box P2)	Loss of DNA-binding domain leads to dominant negative form due to sequestration	(Vernes and Fisher, 2009)
hth (Homothorax) Drosophila melanogaster	Change in DNA-binding domain	(Noro et al., 2006)
PAX3 (paired box 3) PAX7 (paired box 7)	Isoforms have different affinity to DNA, resulting in different transcriptional activity	(Du et al., 2005)

<i>A. Change in Transactivation domain</i>		
Name	Function	Reference
PAX6 (paired box 6)	Change in DNA-binding domains	(Azuma et al., 2005)
REL (v-rel reticuloendotheliosis viral oncogene homolog (avian))	Exon 9 encodes for an inhibitory domain, its deletion increases DNA-binding activity	(Leeman et al., 2008)
SMAD2 (SMAD family member 2)	Change in DNA-binding activity	(Dunn et al., 2005)
Taf1 (TATA-binding protein-associated factor 1) Drosophila melanogaster	Change in DNA-binding domain	(Meicalf and Wassarman, 2006)
TCF712 (transcription factor 7-like 2 (T-cell specific, HMG-box))	Change in C clamp DNA recognition motif creates isoforms with different transactivation domains	(Weise et al., 2010)
TECP2 (transcription factor CP2)	Change in DNA-binding domain	(Kang et al., 2005)
THRA (thyroid hormone receptor, alpha)	Deletion of hinge domain abolishes DNA-binding and causes sequestration of active full-length form in the cytosol	(Casas et al., 2006)
ZGFAT (zinc finger, CCCH-type with G patch domain)	Loss of Zn-finger domain abolishes DNA-binding and creates dominant negative form	(Yu et al., 2010)
<i>C. Loss of regulation: Dominant negative forms/constitutively active</i>		
Name	Function	Reference
FOXO4 (forkhead box O4)	Dominant negative activity due to N-terminal changes	(Lee et al., 2008)
NR1I3 (nuclear receptor subfamily 1, group I, member 3) Sus scrofa	Dominant negative effect due to altered ligand binding domain	(Gray et al., 2009)
POU1F1 (POU class 1 homeobox 1)	Insertion into transactivation domain generates dominant negative isoform	(Jonsen et al., 2009)
PTCH1 (patched 1)	Alternative exon usage inserts premature stop codon. Factors truncated due to premature stop codon and act as dominant negative	(Uchikawa et al., 2006)
SREBP1 (sterol regulatory element binding transcription factor 1)	Premature stop codon abolishes transmembrane domain and generates constitutively active isoform	(Harada et al., 2008b)
TP53 (tumor protein p53)	Dominant negative form due to partial of core domain	(Garcia-Alai et al., 2008)
<i>D. Change in nuclear receptors/ligand binding</i>		
Name	Function	Reference
carm1 (coactivator-associated arginine methyltransferase 1) Xenopus laevis	Alternative usage exon 14 generates isoforms with opposite effects on ligand-mediated transcription	(Matsuda et al., 2007)
NCOR2 (nuclear receptor corepressor 2)	Alternative splicing generates two isoforms with different affinities for nuclear receptors	(Goodson et al., 2005)
NR1H3 (nuclear receptor subfamily 1, group H, member 3)	Exon encodes part of the ligand binding domain and its skipping abolishes receptor activity	(Chen et al., 2005b)
Nr112 (nuclear receptor subfamily 1, group I, member 2) Mus musculus	Loss of 41 aa adjacent to ligand binding pocket represses function of full-length form	(Matic et al., 2010)

<i>A. Change in Transactivation domain</i>		
Name	Function	Reference
THRβ (thyroid hormone receptor, beta)	Stop codon in ligand binding domain creates inactive receptor/transcription factor	(Tagami et al., 2010)
<i>E. Change in intracellular localization</i>		
Name	Function	Reference
ESRRB (estrogen-related receptor beta)	Change in F-domain that alters nuclear localization and ligand binding	(Zhou et al., 2006)
ESRRB (estrogen-related receptor beta)	Alternative sequence at the C-terminus influence intra-nuclear mobility and activation of reporter genes	(Bombail et al., 2010)
Grt2i (general transcription factor II-1) Mus musculus	On/off switch after change in localization due to cell stimulation	(Hakre et al., 2006)
NOSTRIN (nitric oxide synthase trafficker)	Truncated isoform has nuclear rather than cytoplasmic localization and negatively regulates transcription of its own gene	(Wiesenthal et al., 2009)
<i>F. Different interaction with proteins of transcriptional machinery</i>		
Name	Function	Reference
BRD8 (bromodomain containing 8)	Splicing regulates protein interaction motif that determines binding to different receptors	(Hosoya et al., 2008)
CARM1 (coactivator-associated arginine methyltransferase 1)	Isoform of the transcriptional co-activator CARM1 with different C-terminus associates with UIC and affects 5' splice site selection	(Ohkura et al., 2005)
IKBKKG (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma)	Change in coiled-coil domain needed for protein-protein interaction results in ligand response change	(Hai et al., 2006)
POU1F1 (POU class 1 homeobox 1)	Homodimerization of splice variants decreases their efficiency as transcriptional activators	(Sporici et al., 2005)
TAF4B (TAF4b RNA polymerase II, TATA box binding protein (TBP)-associated factor, 105kDa)	Loss of entire TFIIID-associating domain through generation of a stop codon	(Wu et al., 2005)
TBX5 (T-box 5)	Premature stop codon generates different C-terminus with altered ability to bind to co-factors	(Georges et al., 2008)
thraa (thyroid hormone receptor, alpha) Danio rerio	Alternative C-terminus (F-domain) modulates interaction with co-activator	(Takayama et al., 2008)
<i>G. NcRNA</i>		
Name	Function	Reference
DLX6-AS1 (DLX6 antisense RNA 1 (non-protein coding))	Alternative splice form of non-coding RNA activates by binding to dlx-2	(Feng et al., 2006a)
NR1H2 (nuclear receptor subfamily 1, group H, member 2)	Intronic sequence inserted into pre-mRNA generates RNA co-activator of receptor produced from the same gene, variant acts as RNA, not protein	(Hashimoto et al., 2009a)
<i>H. Miscellaneous</i>		
Name	Function	Reference
CREM (cAMP responsive element modulator)	CREM isoforms encode either transcriptional activators or repressors. Deregulation of activator isoforms can lead to male infertility	(Blocher et al., 2005)

<i>A. Change in Transactivation domain</i>		
Name	Function	Reference
GPR56 (G protein-coupled receptor 56)	Splice variants of the receptor activate transcription factors	(Kim et al., 2010a)
Myod1 (myogenic differentiation 1) Danio rerio	Alternative exon present in chromatin modifying domain	(Fernandes et al., 2007)
NCOA1 (nuclear receptor coactivator 1)	Different alternative splicing in C-terminus region leads to different receptor- and ligand-specific effects	(Meijer et al., 2005)
ncor2 (nuclear receptor corepressor 2) Xenopus laevis	Loss of CoRNR box changes co-repressor activity	(Malartre et al., 2006)
NR4A2 (nuclear receptor subfamily 4, group A, member 2)	The frame shift generates new C-terminus that reduces transcriptional activity	(Michelhaugh et al., 2005)
PPARGC1A (peroxisome proliferator-activated receptor gamma, co-activator 1 alpha)	Protein is a co-activator of a nuclear receptor. In absence of the ligand, the interaction with the receptor is lower for the alternatively spliced, truncated form	(Zhang et al., 2009)
SRA1 (steroid receptor RNA activator 1)	Alternative splicing variants SRC-1a co-activates transcription from single GREs, whereas SRC-1e co-activates the transcription with multiple response elements containing promoters	(Meijer et al., 2005)
SRF (serum response factor (c-fos serum response element-binding transcription factor))	Isoform auto-represses by binding to its own promoter	(Zhang et al., 2007b)
TNIP1 (TNFAIP3 interacting protein 1)	Changes transcriptional activation	(Shiote et al., 2006)

Table 3

Change in protein localization due to alternative splicing

A. Change between nucleus and cytosol		
Name	Function	Reference
ATN1 (atrophin 1)	Different splice site acceptor causes two variants: the form with a glutamine residue is nuclear and the GLN-excluded is cytosolic	(Tadokoro et al., 2005)
Axin7 (ataxin 7) Mus musculus	Alternative exon 12b increases cytosolic localization	(Strom et al., 2005)
BSSX (brain-specific homeobox)	Alternatively spliced variant moves from the nucleus to the cytoplasm	(Chu and Ohtoshi, 2007)
CAMK2A (calcium/calmodulin-dependent protein kinase II alpha)	Exon encodes an NLS and locates the protein into the nucleus	(O'Leary et al., 2006)
CCND1 (Cyclin D1)	Exon 4 deletion causes nuclear retention	(Leveque et al., 2007)
FOXP2 (forkhead box P2)	Inclusion of an alternative exon generates proteins that leave the nucleus and aggregate in the cytosol	(Vernes et al., 2006)
GLI1 (GLI family zinc finger 1)	Full-length form is nuclear, N-terminal alternative splicing leads to cytosolic accumulation	(Shimokawa et al., 2008)
HNRNPA2B1 (heterogeneous nuclear ribonucleoprotein A2/B1)	The inclusion of exon 2 and exon 9 generates a predominantly nuclear form, skipping of the exons generates cytosolic forms	(Han et al., 2010)
ILF3 (interleukin enhancer binding factor 3, 90kDa)	Different C-termini isoforms: the long form is nuclear and the short form is cytoplasmatic	(Parrott et al., 2005)
ING4 (inhibitor of growth family, member 4)	Isoform V1 is predominantly nuclear, isoform V2 and V4 accumulate more in the cytosol, but are also nuclear	(Unoki et al., 2006)
Lpin1 (lipin 1) Mus musculus	Exon 7 skipping isoform moves from the nucleus to the cytoplasm	(Peterfy et al., 2005)
Mif (Myelodysplasia/myeloid leukemia factor) Drosophila melanogaster	Splicing creates two variants with different C-termini. One is nuclear, one is both nuclear and cytosolic	(Martin-Lannerec et al., 2006)
Orc1 (origin recognition complex, subunit 1) Mus musculus	The short variant lacking part of exon 5 is retained in the cytosol. The full-length form is nuclear	(Miyake et al., 2005)
RBFOX1 (RNA binding protein, fox-1 homolog (C. elegans) 1)	Skipping of exon creates a nuclear isoform	(Lee et al., 2009)
SEPHS1 (selenophosphate synthetase 1)	One variant is localized at both the plasma and the nuclear membrane and the others are in the cytoplasm	(Kim et al., 2010b)
Smox (spermine oxidase) Mus musculus	Exon 6a encodes a nuclear signal domain; skipping causes a cytosolic localization	(Bianchi et al., 2005)
TRIM21 (tripartite motif containing 21)	Exon 4 skipping leads to isoform that is present in both the nucleus and the cytosol	(Wada et al., 2006)
UZAFIL4 (U2 small nuclear RNA auxiliary factor 1-like 4)	Variant lacking a nuclear localization signal is localized in the cytoplasm. The full-length isoform displays nucleo-cytoplasmic shuttling	(Heyd et al., 2008)
UBP1 (upstream binding protein 1 (LBP-1a))	Alternative exon contains a NLS (nuclear localization signal) that localizes isoform into the nucleus. The isoform with the skipped exon is cytosolic	(Sato et al., 2005)
ZNF268 (zinc finger protein 268)	Gene regulated by multiple cassette exons. One splice variant lacking two cassette exons is predominantly nuclear, whereas other splice variants are mainly cytosolic	(Shao et al., 2006)

<i>A. Change between nucleus and cytosol</i>		
Name	Function	Reference
ZNF415 (zinc finger protein 415)	Splicing events create five forms. Only the form lacking KRAB (Krüppel-associated box) A box is nuclear	(Cheng et al., 2006)
<i>B. Change in membrane association</i>		
Name	Function	Reference
Aqp4 (aquaporin 4) <i>Rattus norvegicus</i>	Lack of exon 2 causes intracellular localization, protein does not transport water. Exon 2 inclusion generates a membrane bound form that transports water	(Moe et al., 2008)
CA9 (carbonic anhydrase IX)	Exon skipping generates a truncated protein that accumulates in the cytosol and competes with the full-length protein for the regulation of the extracellular pH	(Malentacchi et al., 2009)
CADM1 (cell adhesion molecule 1)	Generation of a shorter soluble form (sCADM1)	(Hagiyaama et al., 2009)
CD40 (CD40 molecule, TNF receptor superfamily member 5)	Skipping of exon 5 and/or exon 6 generates a soluble isoform that can have antagonistic effects	(Eshel et al., 2008)
CD55 (CD55 molecule, decay accelerating factor for complement (Cromer blood group))	Intron 7 retention generates a membrane-bound variant	(Osuka et al., 2006)
Chr2 (corticotropin releasing hormone receptor 2) <i>Mus musculus</i>	The full-length protein is membrane-bound. Exon 6 skipping generates a soluble form	(Chen et al., 2005a)
CSF2RA (colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage))	Exon in juxtamembrane domain increases solubility of protein and decreases cell surface localization	(Pelley et al., 2007)
ECE1 (endothelin converting enzyme 1)	Exon 3 encodes a transmembrane domain. Exon skipping generates a cytosolic variant	(Meidan et al., 2005)
FLT1 (fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor))	Alternative splicing gives rise to two proteins: the shortest is soluble, the longest is transmembrane	(Thomas et al., 2007)
FRMD3 (FERM domain containing 3)	Exon 5 skipping creates a soluble isoform	(Seo et al., 2009b)
HPN (hepsin)	Exon encodes a transmembrane domain and causes cytosolic retention when skipped	(Li et al., 2005)
HRAS (v-Ha-ras Harvey rat sarcoma viral oncogene homolog)	Different C-termini variants, one variant is nuclear and cytoplasmic, the second variant is associated with the CTaSmα membrane	(Jeong et al., 2006)
HTR7 (5-hydroxytryptamine (serotonin) receptor 7, adenylylate cyclase-coupled)	C-terminal isoforms have different internalization behavior upon agonist presence	(Guthrie et al., 2005)
IL13RA2 (interleukin 13 receptor, alpha 2)	Exon 10 encodes a transmembrane domain, its skipping creates a soluble form	(Tabata et al., 2006)
IL17RD (interleukin 17 receptor D)	Alternative splicing generates two N-termini isoforms; the longer form is localized in the membrane, the shorter in the cytoplasm	(Rong et al., 2007)
IL6R (interleukin 6 receptor)	Exon skipping creates a cytoplasmic form of the receptor	(Chalaris et al., 2011)
LST1 (leukocyte specific transcript 1)	Exon 3 produces a membrane-bound form when present and a soluble form when absent	(Mulcahy et al., 2006)
MET (met proto-oncogene (hepatocyte growth factor receptor))	The splice variant lacks the transmembrane domain and acts as a dominant negative form	(Tiran et al., 2008)
OSMR (oncostatin M receptor)	The full-length form is membrane bound. A splice variant lacking part of exon 8 is soluble	(Diveu et al., 2006)
PROCR (protein C receptor, endothelial)	Loss of transmembrane domain creates a soluble receptor isoform that remains cytosolic	(Molina et al., 2008)

<i>A. Change between nucleus and cytosol</i>		
Name	Function	Reference
RGS5 (regulator of G-protein signaling 5)	Skipping of exon 2 and 3 generates an exclusively cytosolic form. The full-length form is also membrane bound	(Liang et al., 2005)
SLC6A2 (solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2)	Exon 15 causes expression at the cell surface, when exon is skipped the protein moves in the intracellular compartment	(Sogawa et al., 2007)
SYT8 (synaptotagmin VIII)	Exon 6 encodes a transmembrane domain and produces a cytosolic variant when skipped	(Monterrat et al., 2006)
TMEFF2 (transmembrane protein with EGF-like and two follistatin-like domains 2)	The full-length form is a membrane protein. The truncated variant is cytosolic	(Quayle and Sadar, 2006)
USH2A (Usher syndrome 2A (autosomal recessive, mild))	Long isoforms encode transmembrane regions and are associated with the membrane, whereas shorter isoforms are cytosolic and the exon usage is cell-type specific	(Adato et al., 2005)
<i>C. Change between nucleus and membrane</i>		
Name	Function	Reference
DLG1 (discs, large homolog 1 (Drosophila))	Exon insertion 2 (I2) variant localizes in the nucleus, exon insertion 3 (I3) variant localizes to the membrane	(Roberts et al., 2007)
ERBB4 (v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian))	Exon inclusion generates a protein that less efficiently translocates from the plasma membrane to the nucleus	(Sundvall et al., 2007)
STX1B (syntaxin 1B)	Loss of a C-terminal transmembrane region creates a nuclear isoform	(Pereira et al., 2008)
<i>D. Creation of secreted forms</i>		
Name	Function	Reference
CD209 (CD209 molecule)	Exon 3 encodes a transmembrane domain, its skipping leads to a form that is cytoplasmatic rather than secreted	(Martinez et al., 2005)
CFHR4 (complement factor H-related 4)	The splice variant is a truncated protein and is secreted	(Jozsi et al., 2005)
CXCL16 (chemokine (C-X-C motif) ligand 16)	Variant lacking transmembrane and cytoplasmic domains is a secreted protein	(van der Voort et al., 2010)
EPOR (erythropoietin receptor)	Intron retention generates a shorter protein isoform that circulates in the blood and inhibits the function of full-length erythropoietin receptor located on the erythroblast's membrane	(Khankin et al., 2010)
ERBB3 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian))	Variants lacking TM domain are secreted proteins that still promote growth	(Lin et al., 2008)
FGFR3 (fibroblast growth factor receptor 3)	A variant lacking exon 8 to 10 is secreted	(Tomlinson et al., 2005)
FLT1 (fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor))	Secreted form functions as an inhibitor for full-length FLT1 receptor	(Thomas et al., 2010)
IL15 (interleukin 15) Mus musculus	A shorter variant lacking hydrophobic domain is not secreted and retained in the cytosol	(Nishimura et al., 2005)
IL27RA (interleukin 27 receptor, alpha)	Soluble isoform only encodes the extracellular region of the full-length receptor, but can functionally substitute the full-length receptor	(Hashimoto et al., 2009b)
LILRB1 (leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 1)	Soluble isoforms lacking transmembrane and cytoplasmic domains function as negative dominant regulators to full-length receptors	(Jones et al., 2009)

<i>A. Change between nucleus and cytosol</i>		
Name	Function	Reference
Nel12 (NEL-like 2 (chicken) Rattus norvegicus)	Exon 3 encodes part of the secretion signal and its skipping leads to a variant that is not secreted	(Hwang et al., 2007)
Rxfp1 (relaxin/insulin-like family peptide receptor 1) Mus musculus	Exon 4 inclusion generates a truncated isoform that is secreted; the full-length form is membrane bound	(Scott et al., 2005)
SEL1L (sel-1 suppressor of lin-12-like (C. elegans))	Exon skipping creates isoforms that are no longer in the endoplasmic reticulum, but are secreted	(Cattaneo et al., 2009)
TNFRSF1B (tumor necrosis factor receptor superfamily, member 1B)	Skipping of two alternative exons leads to a soluble TNFRSF1B receptor that is associated with greater insulin sensitivity	(Fernandez-Real et al., 2006)
<i>E. Different internal membranes</i>		
Name	Function	Reference
CLDN10 (claudin 10)	Among the six variants, exon 4 inclusion generates isoforms localized in the cytoplasmic membrane, while exon 4 excluded isoforms are retained in the endoplasmic reticulum	(Gunzel et al., 2009)
ENOX2 (ecto-NOX disulfide-thiol exchanger 2)	The full-length variant is retained in internal membranes, the exon 4 skipped form into the plasma membrane	(Tang et al., 2007)
GDNF (glial cell derived neurotrophic factor)	Shorter transcript lacking the pro-domain region is localized mostly in vesicles, while the full-length transcripts primarily in the Golgi complex	(Lonka-Nevalaita et al., 2010)
GLG1 (golgi glycoprotein 1)	Splicing produces two C-terminal variants localizing either at the Golgi apparatus or the cell surface	(Ahn et al., 2005)
Grik3 (glutamate receptor, ionotropic, kainate 3) Mus musculus	Splicing generates two C-termini, one is expressed at the plasma membrane and one is retained in the endoplasmic reticulum	(Jaskolski et al., 2005)
LHCGR (luteinizing hormone/choriogonadotropin receptor)	The splicing variant lacking exon 9 does not localize at the cell surface and is degraded in the lysosome	(Minegishi et al., 2007)
Lhcgr (luteinizing hormone/choriogonadotropin receptor) Rattus norvegicus	The full-length is a transmembrane receptor; Exon 11 skipping generates an isoform retained in the endoplasmic reticulum	(Apaja et al., 2006)
MOG (myelin oligodendrocyte glycoprotein)	Exon 7 and 8 target proteins to cell surface, exon 10 inclusion variant is in the endoplasmic reticulum	(Boyle et al., 2007)
minaD (neither inactivation nor afterpotential D) Drosophila melanogaster	The long form is localized at the cell surface, exon skipping generates forms found in the intracellular membrane	(Voolstra et al., 2006)
NPSR1 (neuropeptide S receptor 1)	Truncated isoforms caused by exon skipping are found in intracellular membranes, the full-length form is at the cell surface	(Vendelin et al., 2005)
Ntsr2 (neurotensin receptor 2) Rattus norvegicus	The full-length form is at the cell surface; a variant lacking two transmembrane domains is in intracellular membranes	(Perron et al., 2005)
SLC18A1 (solute carrier family 18 (vesicular monoamine), member 1)	The full-length form localizes to the membrane of secretory vesicles. Exon skipping generates a variant localized in the endoplasmic reticulum	(Essand et al., 2005)
SLC22A5 (solute carrier family 22 (organic cation/carnitine transporter), member 5)	Intron retention in the first extracellular loop causes retention of the protein in the endoplasmic reticulum	(Maekawa et al., 2007)

<i>A. Change between nucleus and cytosol</i>		
Name	Function	Reference
SLC30A2 (solute carrier family 30 (zinc transporter), member 2)	The shorter isoform is localized in the cytoplasmic membrane and the longer isoform is primarily localized in the endosomal compartment	(Lopez and Kelleher, 2009)
SLC30A5 (solute carrier family 30 (zinc transporter), member 5)	The short isoform is localized in the plasma membrane, the long isoform in the Golgi system	(Jackson et al., 2007)
<i>F. Mitochondria and other cell parts</i>		
Name	Function	Reference
CCKBR (cholecystokinin B receptor)	Insertion in the third intracellular loop mainly causes intracellular localization of the receptor and decreases its amount on the plasma membrane	(Chao et al., 2005)
CS (citrate synthase)	Exon encodes mitochondrial localization signal	(Cheng et al., 2009)
CYP24A1 (cytochrome P450, family 24, subfamily A, polypeptide 1)	Alternative splicing produces a truncated protein that lacks the mitochondrial signal domain and is inactive	(Ren et al., 2005)
MOBP (myelin-associated oligodendrocyte basic protein)	Skipping of exon 3 leads to a mitochondrial form; the full-length variant is nuclear. In a different splicing event, the long isoform is targeted to the nucleus, the short isoform generated through an alternative 5' splice site locates to the mitochondria	(Montague et al., 2005)
NUDT1 (nudix (nucleoside diphosphate linked moiety X)-type motif 1)	SNP in exon 2 reduces mitochondrial translocation efficiency	(Sakai et al., 2006)
NUDT6 (nudix (nucleoside diphosphate linked moiety X)-type motif 6)	Isoforms containing the mitochondrial targeting sequence are mitochondrial, others are nuclear and cytosolic	(Zhang et al., 2008)
PIF1 (PIF1 5'-to-3' DNA helicase homolog (S. cerevisiae))	Exon in the C-terminus region directs protein from the nucleus into the mitochondria	(Futami et al., 2007)
SIRT3 (sirtuin 3)	The long isoform with mitochondrial localization sequence is predominantly located in mitochondria, while the shorter isoform lacking that sequence has lower mitochondrial expression	(Bao et al., 2010)
XPNPEP3 (X-prolyl aminopeptidase (aminopeptidase P) 3, putative)	Exon 3 encodes a stop codon and produces a cytosolic variant. The exon 3 skipped form is mitochondrial	(Ersahin et al., 2005)
<i>G. Miscellaneous</i>		
Name	Function	Reference
CD6 (CD6 molecule)	Exon 5 skipping in the third SRCR (scavenger receptor cysteine-rich) domain causes a failure to localize in the immunological synapse	(Castro et al., 2007)
CRHR1 (corticotropin releasing hormone receptor 1)	CRHR1 splicing isoforms change localization and activity of the main isoform CRHR1 α	(Zmijewski and Slominski, 2009)
CRHR2 (corticotropin releasing hormone receptor 2)	Variant lacking a transmembrane region is subject to degradation	(Evans and Seasholtz, 2009)
CTNS (cystinosis, lysosomal cystine transporter)	Full-length isoform is in lysosomes; Exon skipping deletes lysosomal targeting signal and creates an isoform localized in the plasma membrane, in lysosomes and in other cytosolic structures	(Taranta et al., 2008)
ERBB4 (v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian))	Cytoplasmic domain differs in the four variants. Depending on exon usage, some variants are in endosomal vesicles and subject to endocytosis	(Sundvall et al., 2008)

<i>A. Change between nucleus and cytosol</i>		
Name	Function	Reference
FMNL1 (formin-like 1)	Intron retention interrupts C-terminal diaphanous auto-regulatory domain. This isoform is localized on cell membrane	(Han et al., 2009)
ING4 (inhibitor of growth family, member 4)	Variant containing a NoLS (nucleolar localization signal) localized in the tandem splice sites translocate from nucleus to nucleolus	(Tsai et al., 2008)
MAPK3 (mitogen-activated protein kinase 3)	Alternatively spliced isoform lacks cytosolic retention domain and localizes to the Golgi apparatus	(Shaul and Seger, 2006)
NOXO1 (NADPH oxidase organizer 1)	Different splice site in exon 3 gives rise to four proteins; two are within the intracellular membrane, one in the plasma membrane and the last in the nucleus	(Ueyama et al., 2007)
RXF1 (relaxin/insulin-like family peptide receptor 1)	Alternative splicing produces different isoforms. One is localized at the cell surface, one is cytoplasmic and the third is secreted	(Muda et al., 2005)
SLC1A2 (solute carrier family 1 (glial high affinity glutamate transporter), member 2)	Exon 9 skipped isoform lacks endoplasmic reticulum translocation motif and is not functional	(Lauriat et al., 2007)
SLC35A2 (solute carrier family 35 (UDP-galactose transporter), member A2)	One form is in the Golgi system and a second form in the endoplasmic reticulum	(Kabuss et al., 2005)
svr (silver) Drosophila melanogaster	Alternative splicing generates different isoforms; the short variants are secreted; the long form with exon 8 is at the cell surface; the longest is found in the Golgi complex	(Kalinina et al., 2006)
TGME49_000320 (hypoxanthine-xanthine-guanine phosphoribosyltransferase) <i>Toxoplasma gondii</i>	Skipping generates a short cytosolic variant whereas the full-length protein is in the inner membrane complex	(Chaudhary et al., 2005)
WHSC1 (Wolf-Hirschhorn syndrome candidate 1)	Variants localized in the nucleus but not in the nucleoli	(Keats et al., 2005)

Table 4

Change of enzymatic properties due to alternative splicing

A. Loss of enzymatic activity		
Name	Function	Reference
Acsbg1 (acyl-CoA synthetase bubblegum family member 1) Rattus norvegicus	The alternative exon 8 is essential for the fatty acyl-CoA synthetase activity of GR-LACS	(Li et al., 2006)
AGRN (agrin)	An eight amino acid insert at the B-side is necessary for the enzymatic activity	(Scotton et al., 2006)
CES2 (carboxylesterase 2)	Alternative splicing in exon 10 results in an enzymatically inactive protein	(Schiel et al., 2007)
Cism (Cathepsin M) Mus musculus and Rattus norvegicus	Aberrant splicing of exon 7 leads to catalytically inactive isoforms	(Bode et al., 2005)
Entpd2 (ectonucleoside triphosphate diphosphohydrolase 2) Rattus norvegicus	Different in cellular distribution, catalytic properties and regulation by protein kinases	(Wang et al., 2005a)
FMR1 (fragile × mental retardation 1)	Reduction in methylation activity	(Dolzhanakaya et al., 2006)
Grk6 (G-protein-coupled receptor kinase 6) Mus musculus	C-terminus is required for the catalytic activity and contains three auto-regulatory elements	(Vatter et al., 2005)
hps (heparanase) Xenopus laevis	Skipping of cassette exon generates catalytic inactive form	(Bertolesi et al., 2008)
IDE (insulin-degrading enzyme)	Isoform with an exon 15b has inefficient proteolytic activity	(Farris et al., 2005)
IRAK1 (interleukin-1 (IL-1) receptor-associated kinase 1)	Alternative exon necessary for kinase activity	(Rao et al., 2005)
LPIN1 (lipin 1)	Alpha isoform has the highest turnover number, followed by the beta and gamma isoforms	(Han and Carman, 2010)
mhc (Myosin heavy chain) Drosophila melanogaster	Alternatively spliced exon 7 domain modulates myosin ATPase activity	(Miller et al., 2005)
MTHFD1L (methyltetrahydrofolate dehydrogenase (NADP+-dependent) 1-like)	Short isoform lacking exon 8 is soluble and enzymatically inactive	(Prasanna and Appling, 2009)
NOS3 (nitric oxide synthase 3 (endothelial cell))	Novel 3' splice sites within intron 13 given three splice variants of NOS3 resulting truncated proteins lacking enzyme activity	(Lorenz et al., 2007)
PIP5K1A (phosphatidylinositol-4-phosphate 5-kinase, type I, alpha)	Different kinase activity that regulates exocytosis	(Wang et al., 2005c)
PIP5K1B (phosphatidylinositol-4-phosphate 5-kinase, type I, beta)	Beta isoform has lower kinase activity and does not prime exocytosis	(Wang et al., 2005c)
PTGS1 (prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase))	Isoform lacking the last 111 nucleotides of exon 9 cannot be detected as protein. The recombinant protein is catalytically inactive	(Schneider et al., 2005)
SAT1 (spermidine/spermine N1-acetyltransferase 1)	Hypoxia and iron-deficiency promote inclusion of 110 nucleotides of intron 3 leading to a truncated isoform lacking catalytic activity	(Kim et al., 2005a)
TAZ (tafazzin)	The isoform lacking exon 5 has transacylase activity	(Xu et al., 2009)
TMLHE (trimethyllysine hydroxylase, epsilon)	TMLHE-b isoform lacking the last 90 amino acids at the C-terminal end is inactive	(Monfregola et al., 2005)
TPH2 (tryptophan hydroxylase 2)	TPH2B variant has a higher activity than TPH2B in which part of intron 3 is retained	(Grohmann et al., 2010)
Trhd (thyrotropin-releasing hormone degrading enzyme) Rattus norvegicus	Alternatively spliced isoform lacking part of the C-terminal domain is enzymatically inactive	(Chavez-Gutierrez et al., 2005)

<i>A. Loss of enzymatic activity</i>		
Name	Function	Reference
Tssk6 (testis-specific serine kinase 5) Mus musculus	Insertion of 10 amino acid residues in region V1b results in inactive splice variants	(Wei et al., 2007)
<i>B. Generation of constitutively active variants</i>		
Name	Function	Reference
Mst1r (macrophage stimulating 1 receptor (c-met-related tyrosine kinase) Mus musculus	Exon deletion is responsible for constitutive kinase activation	(Wei et al., 2005)
Pak3 (p21 protein (Cdc42/Rac)-activated kinase 3) Mus musculus	Alternative exons are inserted into the catalytic domain and make the kinase constitutively active	(Kreis et al., 2008)
<i>C. Dominant negative effects</i>		
Name	Function	Reference
ENTPD3 (Nucleoside triphosphate diphosphohydrolase 3 (NTPDase3))	Alternative exon of NTPDase3 (nucleoside triphosphate diphosphohydrolase 3) is necessary for activity, the presence of the inactive variant downregulates the activity of the active variant	(Crawford et al., 2007)
UGT1A (UDP glucuronosyltransferase 1 family, polypeptide A complex locus)	The inactive isoform inhibits the UGT1A-mediated glucuronidation from acting as a dominant-negative repressor	(Bellemare et al., 2010)
<i>D. Miscellaneous</i>		
ACSL5 (acyl-CoA synthetase long-chain family member 5)	Splice variant lacking exon 20 is inactive at highly alkaline pH	(Gassler et al., 2007)
ACSL6 (acyl-CoA synthetase long-chain family member 6)	Specific fatty acid gate-domain residues are essential for activity. Isoform lacking the domain is inactive, isoforms containing different motifs have different activity	(Soupeine et al., 2010)
CETP (cholesteryl ester transfer protein, plasma)	Alternative exons create less efficiently secreted variants	(Lira et al., 2008)
FYN (FYN oncogene related to SRC, FGR, YES)	Inclusion of either exon 7A or 7B changes the SH3-dependent interaction and tyrosine phosphorylation of Sam68. It affects the auto-inhibition of FYN	(Brignatz et al., 2009)
PRKDC (protein kinase, DNA-activated, catalytic polypeptide)	Splice variant II and III are conserved and expressed predominantly in non-dividing cells	(Convery et al., 2005)
PTGER3 (prostaglandin E receptor 3 (subtype EP3))	Prostaglandin-E2 mediated phosphorylation of ERK1/2 by PTGER3 isoform II and III involves activation of Galpha(i)/PI3K/PKC/Src and EGFR-dependent pathway. ERK 1/2 phosphorylation by isoform Ia is minimal and involves activation of Galpha(i)/Src and EGFR-dependent pathway	(Israel and Regan, 2009)
RAC1 (ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1))	Exon encodes a 19-a.a. insertion that leads to decreased GTPase activity and reduced affinity to GDP	(Orlichenko et al.)
TNFRSF1B (tumor necrosis factor receptor superfamily, member 1B)	Skipping of two alternative exons leads to a soluble TNFRSF1B receptor associated with greater insulin sensitivity	(Fernandez-Real et al., 2006)

Alternative exons that encode protein domains

Table 5

Name	Function	Reference
AAK1 (AP2 associated kinase 1)	Variant encodes clathrin-binding domain	(Henderson and Conner, 2007)
CD55 (CD55 molecule, decay accelerating factor for complement (Cromer-blood group))	Alternative splicing generates either a protein with a GPI anchor or with a transmembrane domain	(Mizuno et al., 2007)
Cd80 (CD80 molecule) Mus musculus	Exon encodes for IgV (immunoglobulin-like domains) and acts as a negative regulator	(Bugeon et al., 2006)
dglk-1 (Diacylglycerol Kinase) Caenorhabditis elegans	Alternative splicing generates two new forms with the kinase domain and part of the PH (pleckstrin homology) domain	(Jose and Koelle, 2005)
DYRK4 (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 4)	Exon encodes nuclear localization domain	(Papadopoulos et al., 2011)
ERBB2IP (erbb2 interacting protein)	Variant lacks the SID (SMAD-interacting domain) and loses its ability to inhibit TGFβ (transforming growth factor beta)	(Dai et al., 2007)
FGFR1 (fibroblast growth factor receptor 1)	Exon encodes one immunoglobulin domain that increases cellular proliferation in high density cultures	(Zhang et al., 2006)
matn1 (matrilin 1, cartilage matrix protein) Danio rerio	Exon encodes a threonine/serine domain	(Ko et al., 2005)
MUC1 (mucin 1, cell surface associated)	Exons encode mucin domain	(Levitin et al., 2005)
NOD2 (nucleotide-binding oligomerization domain containing 2)	Alternative splicing produces a new variant that lacks a LRR (Leucine-rich repeat) domain	(Leung et al., 2007)
RPGRIP1 (retinitis pigmentosa GTPase regulator interacting protein 1)	Alternative stop codon deletes C2 and RID (Rho GTPase inactivation domain)	(Lu and Ferreira, 2005)
Syne2 (spectrin repeat containing, nuclear envelope 2) Mus musculus	Exon codes for an actin-binding domain. Its skipping causes thickening of epidermis	(Luke et al., 2008)
TNFRSF13B (tumor necrosis factor receptor superfamily, member 13B)	Exon encodes a CRD (cysteine-rich domain)	(Hymowitz et al., 2005)

Table 6

Protein binding regulated by alternative splicing

<i>A. Binding being regulated by individual domains</i>		
Name	Function	Reference
ADAM15 (ADAM metallopeptidase domain 15)	Exons encode different putative SH3 domain binding sites, causing selective binding to SH3-containing proteins	(Kleino et al., 2009)
CACNA1D (calcium channel, voltage-dependent, L-type, alpha 1D subunit)	Exon encodes a SH3 and a class I PDZ-binding domain that binds Shank proteins	(Olson et al., 2005)
CADPS2 (Ca ⁺⁺ -dependent secretion activator 2)	Exon 3 encodes a dynactin 1-binding domain and affects axonal CADPS2 protein distribution	(Sadakata et al., 2007)
Col4a3bp (collagen, type IV, alpha 3 (Goodpasture antigen) binding protein) Danio rerio	Splicing isoform produces a protein missing a serine-rich domain. The splicing isoform overexpression doesn't rescue the knockdown phenotype	(Granero-Molto et al., 2008)
FMR1 (fragile × mental retardation 1)	Exon 15 encodes C-terminal G-R rich domain that can reduce methylation by PRMTs	(Dolzhanakaya et al., 2006)
FRMD3 (FERM domain containing 3)	Alternative exon 5, encoding a peptide in the FERM domain of protein 4.1R, is necessary for plasma membrane targeting	(Seo et al., 2009a)
Hph (HIF prolyl hydroxylase) Drosophila melanogaster	Alternative splicing gives rise to an isoform missing a MYND-type (myeloid, Nervy and DEAF-1) zinc finger domain, which is upregulated in adult stages	(Acevedo et al., 2010)
ITSN1 (intersectin 1 (SH3 domain protein))	Exon 20 encodes five a.a. in the first SH3A (SH3 domain) and changes the binding properties of the SH3 domain	(Tsyba et al., 2008)
LDB2 (LIM domain binding 2)	Exon encodes LID (lim interaction domain) and regulates protein interactions	(Tran et al., 2006)
MAPT (microtubule-associated protein tau)	Exon includes microtubule binding site, its skipping weakens binding	(Levy et al., 2005)
MAPT (microtubule-associated protein tau)	Alternative exon weakens the binding of the SH3 domain of fyn	(Bhaskar et al., 2005)
MYO1B (myosin IB)	Exon encodes IQ motifs that regulate interaction with calmodulin	(Lin et al., 2005)
Pde1a (phosphodiesterase 1A, calmodulin-dependent) Mus musculus	The new variant lacks the first calmodulin-binding domain, but not the second	(Vasta et al., 2005)
POU3F2 (POU class 3 homeobox 2)	Exon encodes beta domain that blocks the interaction between Pit-1 and CBP	(Sporici et al., 2005)
PPARG (peroxisome proliferator-activated receptor gamma)	Deletion of the ligand binding domain	(Sabatino et al., 2005)
SH2D2A (SH2 domain containing 2A)	Exon encodes four tyrosines that interact with a SH2 domain of Lck	(Granum et al., 2006)
TNFRSF13B (tumor necrosis factor receptor superfamily, member 13B)	Alternative splicing controls cysteine rich domain, which controls affinity to APRIL and BAFF ligands	(Hymowitz et al., 2005)
<i>B. Binding to individual proteins</i>		
Name	Function	Reference
ABI1 (abl-interactor 1)	Splicing isoforms of Abi1 have different relative affinities for activated Rac1 in Wave 2 complex, thus regulating macrophocytosis	(Dubielecka et al.)

<i>A. Binding being regulated by individual domains</i>		
Name	Function	Reference
AMOT (angiominin)	Exons encode a N-terminal extension, which mediates the interaction between AMOT and membrane associated guanylate kinase MAGI-1	(Bratt et al., 2005)
BIN1 (bridging integrator 1)	The tumor-specific Bin 1 with exon 12A inclusion inhibits Bin 1 binding to c-Myc	(Pineda-Lucena et al., 2005)
BRAF (v-raf murine sarcoma viral oncogene homolog B1)	The presence of an alternative exon 8b increases the binding of the B-Raf N terminus to a MEK kinase	(Hmitou et al., 2007)
CXCL12 (chemokine (C-X-C motif) ligand 12)	The splicing variant CXCL12 gamma displays higher binding affinity to heparane sulfate expressed at the cell surface	(Laguri et al., 2007)
DSG1 (desmoglein 1)	Retained intron encodes a specific peptide sequence that binds to D β cat1 *0102	(Mouquet et al., 2006)
ID1 (inhibitor of DNA binding 1, dominant negative helix-loop-helix protein)	Different affinity to CASK (calcium/calmodulin-dependent serine protein kinase (MAGUK family))	(Qi et al., 2005)
KIF1B (kinesin family member 1B)	Splicing variants show different affinity for microtubules and have different motor activities	(Matsushita et al., 2009b)
MAPT (microtubule-associated protein tau)	Tau isoforms 6D/6P, due to exon 6 alternative splicing, remain soluble and inhibit polymerization of hTau40	(Lapointe et al., 2009)
MYO5A (myosin VA (heavy chain 12, myosin))	Exon B constitutes an essential part of the DYNLL2 binding site. A brain-specific isoform in which exon B is skipped can no longer interact with DYNLL2	(Wagner et al., 2006)
MYO5A (myosin VA (heavy chain 12, myosin))	Alternative exon B that encodes three residues is essential for DLC2 binding	(Hodi et al., 2006)
NRXN1 (neurexin 1)	Only the neurexins lacking an insert in exon can bind to LRRTM2 as ligands	(Ko et al., 2009)
OCRL (oculocerebrorenal syndrome of Lowe)	Splicing alters the clathrin binding properties	(Choudhury et al., 2009)
PLCB1 (phospholipase C, beta 1 (phosphoinositide-specific))	Alternative splicing variant PLCbeta1b, but not PLCbeta1a, associates with Galphaq and inhibits PLC in responses to alpha ₁ -adrenergic receptor activation	(Grubb et al., 2008)
PNRC1 (proline-rich nuclear receptor coactivator 1)	Alternative 3' splice sites of exon 1 creates splicing variant RNRC1c with an increased affinity to NRs (nuclear receptors) and PNRC1f with no binding ability to NRs	(Wang et al., 2008)
RGS8 (regulator of G-protein signaling 8)	The shorter isoform of RGS8 has lower binding strength to mACjRs	(Itoh et al., 2006)
VCAM1 (vascular cell adhesion molecule 1)	Exons encode the Ig-like domain 4 of VCAM1. The 6D isoform, lacking domain four, has a higher affinity to to integrin alpha4beta1	(Woodside et al., 2006)
<i>C. Binding to ligands</i>		
Name	Function	Reference
ADCYAPIR1 (adenylate cyclase activating polypeptide 1 (pituitary) receptor type I)	Alternative splicing generates PAC1 isoforms with diversity in ligand specificity, binding affinity and downstream signaling	(Ushiyama et al.)
EDNRA (endothelin receptor type A)	Splicing changes affinity to receptor antagonist BQ123	(Chester et al., 2007)
EPM2A (epilepsy, progressive myoclonus type 2A, Lafora disease (laforin))	Different binding ability to glycogen and affinity to Malin	(Dubey and Ganesh, 2008)
H2AFY (H2A histone family, member Y)	Alternative splicing regulates the interaction between mH2A and NAD metabolites OAADPR and ADPR	(Kustatscher et al., 2005)
HRH3 (histamine receptor H3)	Splicing variants have different affinity and potency for H3R agonists	(Bongers et al., 2007)

<i>A. Binding being regulated by individual domains</i>		
Name	Function	Reference
IGF1R (insulin-like growth factor 1 receptor)	Splicing variants of hybrid IR (insulin receptor) do not change the binding properties to insulin and IGF-I	(Slaaby et al., 2006)
INSR (insulin receptor)	Exon 11 modulates the time course of IRS-1 activation	(Deutsch et al., 2008b)
LEPR (leptin receptor) Gallus gallus	Exon 9 encodes leptin binding domain and modulates leptin action	(Liu and Sharp, 2007)
NTSR2 (neurotensin receptor 2)	Alternative exon introduces a stop codon that abolishes two of the transmembrane domains and the ligand binding	(Perron et al., 2005)
OPRM1 (opioid receptor, mu 1)	Variants loose binding to [(3)H]diprenorphine	(Choi et al., 2006)

Table 7

Change of channel protein properties

Name	Function	Reference
ANO1 (anoctamin 1, calcium activated chloride channel)	TMEM 16A splicing variants exhibit differences in voltage dependence and Ca ⁺⁺ sensitivity	(Ferrera et al., 2009)
CACNA1A (calcium channel, voltage-dependent, P/Q type, alpha 1A subunit)	Mutations of FHM-1 exhibit differential effects on voltage-dependent properties, on recovery from inactivation and on accumulation of inactivation during tonic and burst firing of Ca _v 2.1 splice variants	(Adams et al., 2009)
CACNA1B (calcium channel, voltage-dependent, N type, alpha 1B subunit)	Change in the channel opening time and expression density	(Daberrtrand et al., 2006)
CACNA1B (calcium channel, voltage-dependent, N type, alpha 1B subunit)	Exon 37a acts as a molecular switch that tailors the channels toward specific roles in pain	(Altier et al., 2007)
CACNA1C (calcium channel, voltage-dependent, L type, alpha 1C subunit)	Changes in the kinetics and voltage-dependence of inactivation, recovery from inactivation and rundown of the Ca ⁺⁺ current	(Tiwari et al., 2006)
CACNA1C (calcium channel, voltage-dependent, L type, alpha 1C subunit)	Exon 33 encodes part of the IVS3-S4 linker region of the Ca _v 1.2 calcium channel. Ca _v 1.2SM, lacking exon 33, displays hyperpolarized shifts for steady-state inactivation and is more sensitive to nifedipine inhibition	(Liao et al., 2007)
CACNA1D (calcium channel, voltage-dependent, L type, alpha 1D subunit)	The longer isoform of the Ca _v (V) 1.4 channel retunes channel affinity to apoCaM	(Liu et al.)
CACNA1H (calcium channel, voltage-dependent, T type, alpha 1H subunit)	Change in gating behavior, sensitivity to neuromodulation and interaction with extracellular matrix	(Zhong et al., 2006)
CACNA1H (calcium channel, voltage-dependent, T type, alpha 1H subunit)	Exon 25, encoding part of the III-IV linker of Ca _v 3.2, influences the voltage-dependence and kinetics of both activation and inactivation	(Cooper et al., 2008)
CACNB1 (calcium channel, voltage-dependent, beta 1 subunit)	The isoform of Ca _v beta1, lacking exons that encode the alpha-binding pocket, can modulate the gating behavior of L-type Ca ⁺⁺ channels	(Roszelle et al., 2008)
CACNB4 (calcium channel, voltage-dependent, beta 4 subunit)	Alternative splicing regulates cell-specific expression	(Vendel et al., 2006)
GABRB2 (gamma-aminobutyric acid (GABA) A receptor, beta 2)	Change in hyperpolarization	(Zhao et al., 2006)
GRIA1 (glutamate receptor, ionotropic, AMPA 1) GRIA2 (glutamate receptor, ionotropic, AMPA 2) GRIA3 (glutamate receptor, ionotropic, AMPA 3) GRIA4 (glutamate receptor, ionotropic, AMPA 4)	Change in resensitiation kinetics	(Schlesinger et al., 2005)
GRIA2 (glutamate receptor, ionotropic, AMPA 2)	Flip/flop splicing alters GluR2 assembly and endoplasmic reticulum secretion kinetics	(Deutsch et al., 2008c)
GRIN1 (glutamate receptor, ionotropic, N-methyl D-aspartate 1)	Change in inhibition by ethanol	(Jin and Woodward, 2006)
KCNMA1 (potassium large conductance calcium-activated channel, subfamily M, alpha member 1)	Skipping of exon that encodes an acidic cluster-like motif results in a dominant negative subunit that suppresses cell surface expression of BK channels	(Chen et al.)

Name	Function	Reference
KCNQ4 (potassium voltage-gated channel, KQT-like subfamily, member 4)	Exons encode different calmodulin binding domains of KCNQ4 channel, thus the channels can be modulated differentially by calmodulin	(Xu et al., 2007)
Oprm1 (opioid receptor, mu 1) Mus musculus	Exon 4 encodes the MOR1-derived recycling sequence. OPRM1 splicing variants lacking exon 4 recycle inefficiently after ligand-induced endocytosis	(Tanowitz et al., 2008)
PDK2 (pyruvate dehydrogenase kinase, isozyme 2)	The isoform with exon 7 skipping no longer interacts with polycystin-1	(Cooper et al., 2010)
RYR1 (ryanodine receptor 1 (skeletal))	The ASI(+)-splicing variant contributes to an inhibitory module in RYR1 that influences skeletal muscle EC coupling	(Kimura et al., 2009)
RYR2 (ryanodine receptor 2 (cardiac))	Splicing isoforms modulate intracellular Ca ⁺⁺ fluxes following caffeine exposure	(Deutsch et al., 2008a)
SLC1A3 (solute carrier family 1 (glial high affinity glutamate transporter), member 3)	Loss of glutamate uptake	(Vallejo-Illarramendi et al., 2005)
SLC8A2 (solute carrier family 8 (sodium/calcium exchanger), member 2)	The BD splicing variant of NCX, with a different Ca ⁺⁺ -binding site, displays no Ca ⁺⁺ binding	(Breukels and Vuister)

Table 8

Changes in RNA stability and function

Name	Function	Reference
CD247 (CD247 molecule)	When the retained intron in the 3' UTR is spliced out, the mRNA is less stable and the protein is less efficiently translated. The splicing out is seen more in patients with Systemic Lupus Erythematosus	(Chowdhury et al., 2005)
GLRX (glutaredoxin (dithioltransferase))	The alternative 3' end of the last exons changes stability of the mRNA when assayed with a luciferase reporter construct	(Park and Levine, 2005)
SLC11A2 (solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2)	The 3' UTR splicing variant of DMT1 lacking an IRE binds to Let-7D on its 3' UTR	(Andolfo et al., 2010)
SLC40A1 (solute carrier family 40 (iron-regulated transporter), member 1)	Alternative splicing changes the UTR and creates/abolishes an iron response element through cassette exons and alternative 3' splice sites and changes translation	(Cianetti et al., 2005)

Table 9

Other functions

<i>A. Influence on protein stability</i>		
Name	Function	Reference
ATXN3 (ataxin 3)	Splicing regulates the aggregation and degradation of protein isoforms	(Harris et al.)
IYD (iodotyrosine deiodinase)	Splicing regulates protein stability	(Gnidehou et al., 2006)
MAPT (microtubule-associated protein tau)	Tau isoforms 6D/6P, due to exon 6 alternative splicing, remain soluble and inhibit polymerization of hTau40	(Lapointe et al., 2009)
MIMP (migration and invasion inhibitory protein)	Exon 7 skipped isoform has a different C-terminus and is degraded	(Song et al., 2005)
<i>B. Alternative splicing of splicing factors</i>		
Name	Function	Reference
TIA1 (TIA1 cytotoxic granule-associated RNA binding protein)	Skipping of exon 5 generates a shorter isoform and increases splicing stimulatory activity	(Izquierdo and Valcarcel, 2007)
WT1 (Wilms tumor 1)	Insertion of a small exon abolishes the effect of WT1 on alternative splicing	(Markus et al., 2006)

Table 10

Bioinformatic resources for alternative splicing

A. General Databases					
Databases	Notes	Species	URL	Reference	
AccView	Computationally generated from cDNA alignment onto genome (annotations include alternative splicing variants)	Human, Mouse, Rat, Arabidopsis, C. Elegans	http://www.ncbi.nlm.nih.gov/IEB/Research/Aceembly/	(Thierry-Mieg and Thierry-Mieg, 2006)	
AS-ALPS	Computationally generated (predict protein structural changes due to alternative splicing)	Human, Mouse, Fly, C. Elegans, Arabidopsis, O. Sativa, Swiss-Prot	http://as-alps.nagahama-i-bio.ac.jp or http://genomework.nig.ac.jp/as-alps/	(Shionyu et al., 2009)	
ASAP II	Alternative splicing annotation and intergenome comparison for 15 species (human, mouse, rat, western clawed frog, chicken, cow, dog, C. elegans, ciona, zebrafish, fruit fly, fugu, yellow fever mosquito, honeybee and African malaria mosquito)	15 Species	http://bioinfo.mbi.ucla.edu/ASAP2/	(Kim et al., 2007b)	
ASMD	Computationally generated alternative splicing information using mutation data	Human	http://mco321125.meduohio.edu/~jbechtel/asmd/1.1/	(Bechtel et al., 2008a)	
ASPicDB	Computationally generated	Human, Arabidopsis	http://www.caspar.it/ASPicDB	(Castrignano et al., 2006)	

<i>A. General Databases</i>					
Databases	Notes	Species	URL	Reference	
AVATAR	Computationally generated by mapping ESTs and mRNAs to the whole human genome	Human	http://avatar.iecs.fcu.edu.tw/	(Hsu et al., 2005)	
FAST DB	Computationally generated from EST and mRNA	Human And Mouse	http://www.fast-db.com/	(de la Grange et al., 2007) (Lerivray et al., 2006)	
H-DBAS	Human-transcriptome database for alternative splicing (based on H-invitational full-length cDNAs)	Human And Mouse	http://h-invitational.jp/h-dbas/	(Takeda et al., 2007) (Takeda et al., 2010)	
SCNIA infobase	Manually generated from literature and updated with computational calculations	Human	http://www.scn1a.info/	(Lossin, 2009)	
Splice Browser	Computationally generated using high-throughput RNA sequencing and microarray profiling (identified novel splicing events including developmental regulated AS)	C. Elegans	http://splicebrowse.ccb.utoronto.ca/	(Ramani et al., 2011)	
<i>B. Specialized Databases</i>					
Databases	Notes	Species	URL	Reference	
ProSAS	Protein structure based analysis	Human, Mouse, Rat, Chimpanzee	http://www2.bio.ifi.lmu.de/ProSAS/	(Birzele et al., 2008)	

<i>A. General Databases</i>					
Databases	Notes	Species	URL	Reference	
RegRNA	Interactive Web server for identifying sequence and structure homologs of regulatory RNAs (motifs gathered from literature and databases)	Human, Mouse, Rat	http://regma.mbc.nctu.edu.tw/	(Huang et al., 2006a)	
snoRNP DB	Computationally generated from NCBI (a collection of 8994 snoRNA sequences and 589 snoRNA-associated protein sequences, both confirmed and putative)	Many species from Bacteria, Archaea and Eukaryotes	http://evolweathome.com/snoRNA/snoRNA.php	(Ellis et al., 2010)	
SpliceInfo	Collection of occurrences of exon skipping, 5'-alternative splicing, 3'-alternative splicing and intron retention; prediction tool for secondary structure; identify regulatory motifs	Human	http://spliceinfo.mbc.nctu.edu.tw/	(Huang et al., 2005a)	
ssSNPTargetB	Genome-wide splice site SNPs database	Human and Mouse	http://variome.kobic.re.kr/ssSNPTarget/	(Yang et al., 2009)	
TassDB	Tandem Splice Site DataBase (2 different versions: TassDB1 and TassDB2)	Human, Mouse, Rat, Dog, Chicken, Zebrafish, Drosophila, C. Elegans	http://www.tassdb.info/	(Hiller et al., 2007) (Sinha et al., 2010)	

<i>A. General Databases</i>				
Databases	Notes	Species	URL	Reference
UMD	Universal Mutation Databases with tools to calculate consensus values for potential splice sites and splicing enhancers	Human	http://www.umd.be/	(Beroud et al., 2005)
UTRdb	5' and 3' UTR variants and UTR Site motifs including ones generated from alternative splicing	Human, Mouse and other species	http://utrdb.ba.itb.cnr.it/	(Grillo et al., 2010)
<i>C. Software tools</i>				
Software Tools	Notes	Species	URL	Reference
Free Web-based Tools				
ASePCR	RE-PCR emulator compatible with RefSeq, Ensembl, ECgene, AceView and GenBank (allows search for alternative splicing patterns of orthologous genes of different species)	Human, Mouse, Rat, Chicken	http://s47.rna.kr/ASePCR/	(Kim et al., 2005b)
ASTALAVISTA	Improved visualization tool for complex alternative splicing events (can be used for whole transcriptome data from GENCODE, REFSEQ,	Many Species from Bacteria, Archaea and Eukaryotes	http://genome.crg.es/astalavista/	(Foissac and Sammeth, 2007)

A. General Databases					
Databases	Notes	Species	URL	Reference	
AUGUSTUS	Tool for eukaryotic gene prediction including alternative splicing using a Generalized Hidden Markov Model (can be locally installed)	Human, Fly, Arabidopsis, C. Cinereus (Fungus)	http://bioinf.uni-greifswald.de/augustus/	(Stanke et al., 2006c) (Stanke et al., 2006a) (Stanke et al., 2006b)	
Simap	Webserver for prediction of splicing factor binding sites in genomic data	Human (Other Eukaryotes accepted but not considered for evolutionary conservation)	http://sfmap.technion.ac.il/	(Paz et al., 2010)	
Skippy	Splicing assessment tool; scores human exon variants for exon-skipping events; identifies potential splice-affecting genome variants	Human	http://research.nhgri.nih.gov/skipky/index.shtml	(Woolfe et al., 2010)	
SpliceCenter	Computational/analysis tools for RT-PCR primer/probe sets, RNAi effectors, microarrays and protein-targeting technologies	Human	http://projects.insilico.us/SpliceCenter/SpliceOverview.jsp	(Ryan et al., 2008)	
SpliceMiner	Web interface for querying Evidence Viewer Database (filters splice variants from NCBI) and for mapping probes for splice variants; used for microarray analysis	Human, Mouse, Rat, Fruit Fly, C. Elegans, Cow, Zebrafish, Asian Rice, Arabidopsis	http://projects.insilico.us/SpliceMiner/intro.jsp	(Kahn et al., 2007)	
Open Source Programs (Local Installation)					

<i>A. General Databases</i>					
Databases	Notes	Species	URL	Reference	
ExAlt	Predict alternatively spliced exons using a non-expression based statistical method	Drosophila	http://www.cbcb.umd.edu/software/exalt/	(Allen and Salzberg, 2006)	
MARS	Extension to Twinscan (uses pairwise informant sequences from mouse, rat, dog, opossum, chicken and frog genome to predict alternatively spliced transcripts de novo)	Human, Mouse, Rat, Dog, Opossum, Chicken, Frog	http://www.ebi.ac.uk/~flicek/MARS/	(Flicek and Brent, 2006)	
SNPSplicer	Utility for screening SNPs for effects on alternative splicing	Human	http://www.ikmb.uni-kiel.de/snpspicer/	(ElSharawy et al., 2006)	
Splign	Computationally generated (improved) method for co-aligning EST to genome)	Human	http://www.ncbi.nlm.nih.gov/sutils/splign/splign.cgi	(Kapustin et al., 2008)	
Proprietary Software					
AspAlt	Alternative splicing and alternative transcription annotations and provide inter-database comparisons among Ensembl, RefSeq and Ace View (Genome International)	46 Eukaryotes	http://www.genome.com/products-1/integrated-genomics-resources-products-integrated-genomics-resources-igr-asfalt	(Bhasi et al., 2009)	
EuSplice	Analysis tool for alternative	Eukaryotes	http://www.genome.com/products-1/integrated-genomics-resources/eusplce	(Bhasi et al., 2007)	

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<i>A. General Databases</i>				
Databases	Notes	Species	URL	Reference
	splicing events with data mining and graphics capabilities for inter-genomic comparison (Genome International)			