1. ABSTRACT

Precise removal of introns from metazoan precursor mRNAs is critical for gene expression. Nevertheless, alternative splicing provides a means for higher eukaryotes to increase genomic complexity and proteome diversity and to regulate certain cellular functions. The presence of rare U12-type pre-mRNA introns in eukaryotic genomes further complicates splicing events. In this review, we discuss the mechanism of U12-type intron splicing with emphasis on how the U12 spliceosome selects alternative splice sites in various U12-type intron–containing pre-mRNAs. Moreover, we propose possible roles for U12-type introns in a wide range of gene regulation through splicing regulation.

2. GENE EXPRESSION REGULATED BY PRE-MRNA SPlicing

2.1. Effects of alternative splicing on gene expression

It has been estimated that there exist ~25,000 protein-coding genes in the human genome, a number similar to that of Arabidopsis thaliana and only two times that of Drosophila melanogaster (1-3). This rather surprising fact suggests that gene number may not correlate with organismal complexity. Indeed, metazoans use several mechanisms—including post-transcriptional and post-translational modifications—to enhance the diversity of protein products encoded by a limited number of genes. These mechanisms can also tailor proteomes in individual cell types or throughout cell differentiation. The vast
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The majority of the human precursor mRNAs (pre-mRNAs) undergo splicing-catalyzed splicing that allows exon ligation with concurrent intron release. Alternative splicing of pre-mRNAs from single genes of higher eukaryotes can generate mRNA isoforms that may encode proteins having different amino acid sequences and perhaps biological functions. It has been reported that more than 74% of human multi-exon genes undergo alternative splicing and that each gene generates an average of six mRNA isoforms (4-6). Therefore, alternative splicing appears to be a major mechanism to increase proteome diversity in higher eukaryotes (7, 8).

Alternative splicing in concert with other post-transcriptional events also provides a means by which cells regulate mRNA expression level. Aberrant and even programmed alternative splicing may induce premature termination codons within the coding region that can trigger subsequent mRNA degradation via nonsense-mediated mRNA decay (NMD). An estimate has suggested that ~40% of alternatively spliced transcripts acquire a stop codon and that more than half of such transcripts may be targeted for NMD (9). Moreover, alternative splicing can occur within untranslated regions (UTRs) of mRNAs. UTRs may contain cis-elements that control mRNA stability, transport or translation. Therefore, alternative splicing may also impact the fate of mRNAs by modulating post-splicing events (10, 11).

2.2. Regulation of alternative splicing

Regulation of alternative splicing involves a complex array of cis-elements of pre-mRNAs and various combinations of trans-acting factors (7, 12, 13). Cis-elements can act as splicing enhancers or silencers, or they can play a dual role depending on the binding of trans-acting factors. Multiple cis-elements may exist to fine tune the splicing patterns in different cell/tissue types or at different developmental stages. However, these cis-elements are somewhat divergent in sequence, and their interactions with corresponding splicing factors are generally weak (14). Nevertheless, these features may have some advantages such as to increase the capacity of cis-elements to bind different trans-acting factors and to provide a basis for exchanging binding factors in quick response to cellular signals (15, 16).

In general, trans-acting regulatory factors include two major types of RNA-binding proteins, namely serine/arginine dipeptide-rich (SR) proteins and heterogeneous ribonucleoproteins (hnRNPs) (14, 17, 18). These splicing factors may directly or indirectly associate with corresponding cis-elements and may collaborate with or antagonize each other to generate specific splicing patterns. An optimal balance among the levels/activities of trans-acting factors is critical for appropriate gene expression (19-24). For example, the dynamic balance between the muscleblind family members and their antagonizing trans-acting splicing factors, including polypyrimidine tract binding (PTB) protein and CUG-BP and ETR-like factors (CELFs), can determine the splicing pattern of several specific mRNAs during heart development (25).

3. DISEASES CAUSED BY MISREGULATION OF SPLICING

3.1. Genetic effects

Genetic mutations in cis-elements of pre-mRNAs or alterations of trans-acting factors may result in misregulation of pre-mRNA splicing and thereby generate aberrant splicing products, leading to clinical manifestations (26-29). At least 15% of point mutations at intron-exon junctions cause splicing defects leading to genetic diseases (30). However, mutations within regulatory cis-elements may also affect splice site selection or exon utilization, indicating that the impact of genetic mutations on diseases in the above analysis is underestimated (31, 32). The autosomal recessive disorder spinal muscular atrophy (SMA) is representative of splicing defects primarily resulting from an exonic silent mutation. SMA is caused by mutations or deletion of the survival motor neuron 1 (SMN1) gene (33). However, the duplicate of human SMN1, SMN2, fails to produce sufficient amounts of full-length functional SMN protein and thus cannot fully compensate for the loss of SMN1 (34). SMN2 differs from SMN1 only by a few nucleotide changes; the silent mutation at position 6 of SMN2 exon 7 is responsible for exon 7 skipping in most SMN2 transcripts, thus yielding the exon 7-truncated protein (35-37). This nucleotide change may likely destroy a splicing enhancer or create a splicing silencer in SMN2, thus reducing the efficiency of exon 7 inclusion (38, 39). In addition, several lines of evidence including the case of SMN indicate that cis-elements involving secondary structure formation may regulate alternative splicing (34). Moreover, a type of genetic diversity called single nucleotide polymorphism (SNP) can occur in pre-mRNA cis-elements, causing cell dysfunction and modulate the extent of disease. One such example is the alternative splicing of the Wilms tumor suppressor (WT1) gene in Frasier syndrome. WT1 mRNA isoforms are produced by differential use of the two closely located 5' splice sites downstream of exon 9 (40). A downstream 5' splice site mutation in Frasier syndrome individuals shifts splicing towards the upstream 5' splice site, and thus alters the ratio of the mRNA isoforms, which leads to pathogenic effects. This observation indicates that maintenance of an appropriate isoform ratio is important for cell function (41, 42).

Moreover, single nucleotide polymorphisms (SNPs), a type of genetic diversity, in pre-mRNA cis-elements may cause differences in splicing efficiency or accuracy between alleles and individuals. Thus, SNPs can also cause variations in the ratio of mRNA isoforms and thereby influence the penetrance, process or severity of human diseases (26). Numerous cases support this view; for example, splicing variations caused by SNPs in the neural cell adhesion molecule (NCAM) and neuregulin-1 receptor ErbB4 genes have been implicated in neuronal disorders such as schizophrenia (43, 44). It is also widely accepted that inter-individual differences in splicing patterns can impact drug efficacy, and thus modulation of pre-mRNA splicing may have potential pharmacological values (45).
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3.2. Trans-acting effects

Many lines of evidence have suggested that trans-acting splicing factors contribute to the onset or progression of human diseases, such as cancer and sporadic neurological diseases including Alzheimer’s disease, frontotemporal dementia and amyotrophic lateral sclerosis. Indeed, aberrant splicing patterns of specific genes have been observed in several of these diseases (28, 46-51). However, lack of somatic mutations in known disease susceptibility genes suggests that modifications of splicing factors are responsible for the pathogenesis of certain acquired diseases (52-54). It is well established that cellular signaling profoundly affects the control of alternative splicing by modulating post-translational modifications—primarily phosphorylation—of splicing regulatory factors (55, 56). Such modifications can determine the abundance, localization or activity of individual factors and hence modulate the ratios of cooperative vs. antagonistic factors. Evidence has indicated that altered expression or phosphorylation levels of serine/arginine dipeptide-rich proteins (SR proteins) correlates with various splicing patterns of CD44 during breast cancer tumorigenesis (57). It is likely that signaling pathway perturbation in cancerous cells causes alterations in covalent modifications/respecification of splicing regulatory factors and ultimately leads to changes in splicing patterns. Thus, cis- and trans-regulatory factors of pre-mRNA splicing can act together as genetic modifiers, and changes in either may cause cellular dysfunction and contribute to pathogenesis (58).

4. PRESENCE OF U12-TYPE INTRONS AND THEIR SPlicing MECHANISM

4.1. A minor class of introns: U12-type introns

The vast majority of pre-mRNA introns belong to the U2 type. Another type of the intron, namely U12-type intron, also exists in representative eukaryotic organisms, except for some lineages such as Caenorhabditis elegans, Saccharomyces cerevisiae and Schizosaccharomyces pombe (59-63). U12 type-introns occur with a very low frequency; the human genome has the highest number (~700) among all species examined (61, 62).

U2- and U12-type introns differ between each other primarily in the 5’ splice site and branch site consensus sequences (59). Although the terminal dinucleotides of pre-mRNA introns in general follow the GT-AG rule, approximately one-third of U12-type introns contain the termini AT-AC. The U2- and U12-introns may have arisen from two different self-splicing group II introns in separate lineages and merged in a eukaryote progenitor upon lineage fusion (59, 64). As compared to U2-type introns, U12-type introns are more conserved at their 5’ splice sites and branch site sequences but appear to be spliced with less accuracy and at a slower rate (65, 66). Therefore, during evolution these disadvantages may have driven U12-type introns to convert gradually to U2-type introns.

4.2. The splicing mechanism of U12-type intron–containing pre-mRNAs

The U2- and U12-type introns are removed by distinct spliceosomes (67, 68). Except for the U5 small nuclear ribonucleoparticle (snRNP), the four other snRNPs differ between these two spliceosomes. The U1, U2, and U4/U6 snRNPs in the U2 spliceosome are replaced by their low-abundance functional analogs U11, U12, and U4atac/U6atac in the U12 spliceosome (69, 70). Interestingly, the respective snRNA analogs have highly similar secondary structures despite with little sequence identity, and, moreover, they make very similar RNA-RNA interaction frameworks in individual spliceosomes (68).

The most conserved part between the two sets of snRNAs in the spliceosome is the intramolecular stem-loop of U6 and U6atac, which is believed to be located near or at the catalytic center (71, 72). Thus, this striking conservation suggests that the mechanism of splicing is very similar between the U2 and U12 spliceosomes (73).

In addition, the two spliceosomes share a large number of protein factors, most of which are components of the U4/U6.U5 tri-snRNP and its U12-type counterpart (74). However, the U12 spliceosome–specific proteins are primarily associated with the U11 and U12 snRNPs, suggesting that the two types of spliceosomes have distinct features particularly in splice site recognition (75). Indeed, the U11 and U12 snRNPs form a functional di-snRNP through protein-protein and protein-snRNA interactions (76). Therefore, this di-snRNP complex may simultaneously recognize the 5’ splice site and the branch site elements via base pairing with the pre-mRNA (77). Moreover, the U12 snRNP may transiently interact with the sequence immediately upstream of the 5’ splice site early during spliceosome assembly (78). Thus, these features in splice site recognition may be unique to U12-type intron splicing.

Despite the similarities and differences between the two spliceosomes, each spliceosome can only catalyze the removal of its cognate introns, primarily because splice site recognition involves specific base pairing between the snRNAs and pre-mRNAs. Here, we propose that the U11 and U12 snRNPs act as a unit to speciy U12-type splice sites and thereby prevent unintended splicing of U12-introns by the abundant U2 spliceosome. This view is supported by results obtained from mutational analysis of U12-type introns in several human genes (79-81). Mutations of the U12-type 5’ splice site induce aberrant splicing primarily mediated by the U2 spliceosome instead of the U12 spliceosome (Figure 1), suggesting that the U12 spliceosome functions only when the cognate 5’ splice site can be properly recognized. Moreover, the U11-5’ splice site interaction may aid the U12 partner to locate the branch site in U12-type introns and hence define the 3’ splice site for splicing.

5. ALTERNATIVE SPlicING OF U12-TYPE INTRON–CONTAINING PRE-mRNAs

Increasing evidence indicates that U12-type intron–containing pre-mRNAs also undergo various types of alternative splicing. Although the regulation of U12-type intron splicing has not been extensively studied, several reports have indicated that this splicing can be activated by both SR proteins and exonic splicing enhancers, a scenario similar to that for U2-type introns (82-85). Moreover,
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**Figure 1.** Alternative 5' or 3' splice site selection of U12 intron–containing pre-mRNAs. Mutations of splice site signals in the U12-type intron of the human genes, LKB1/STK11, WDFY1 and P120, induce alternative 5' and/or 3' splice site utilization. Observed alternative splicing is mediated by either the U2 or the U12 spliceosome due to mutations at the 5' splice site (red), branch site (green), or 3' splice site (blue). Representative alternatively spliced patterns are shown for each case.

**Figure 2.** The “twintron” of the *Drosophila prospero* pre-mRNA. The U2-type intron (GU-AG termini) is located within the U12-type intron (AU-AC termini). The purine-rich splicing enhancer is located within the inner intron.

According to the “exon definition” model (86, 87), SR proteins may possibly function to bridge adjacent U12 and U2 spliceosomes during the splicing of U12-type intron pre-mRNAs. Perhaps SR proteins mediate communication between the two spliceosomes through direct contact with the 5' splice site and branch site of both types of introns (85). Finally, whether any other *trans*-acting regulatory factors also participate in U12-type intron splicing as well as how they modulate alternative splicing involving U12-type introns remains to be characterized.

5.1. An intron within an intron

The *Drosophila* gene *prospero* provides an unusual example of alternative splicing. The *prospero* pre-mRNA contains a “twintron”, in which a U2-type intron (with GU-AG termini) is located within a U12-type intron (AU-AC termini) (Figure 2). Removal of the U2- or U12-type intron generates two alternatively spliced isoforms. Interestingly, expression of individual isoforms predominates at different stages during embryogenesis, indicating that a developmentally regulated factor(s) is likely involved in splicing regulation (88). Moreover, a purine-rich enhancer sequence in the inner intron appears to be required for splicing of both types of intron (85). This finding suggests that a *cis*-element can function to regulate both types of spliceosome, and that the two types of spliceosomes may compete for a similar set of regulatory factors during twintron splicing.

5.2. Exon skipping

Because splice site recognition depends on spliceosome type, coexistence of two types of introns in a pre-mRNA may potentiate the diversity of alternatively spliced mRNAs. Evidence comes from the observation that a 5' splice site mutation in a U2-type intron of the mouse gene *Scn8a* leads to exclusion of two upstream exons, between which is a U12-type intron (89). In addition, several genes contain more than one U12-type intron (90). Among these genes, the DER1-like domain family members (*DERL2* and *DERL3*) and the xanthine dehydrogenase gene (XDH) harbor two successive U12-type introns. An Expressed Sequence Tag (EST) analysis (our unpublished data) revealed a number of exon-skipped or intron-retained DERL transcripts (Figure 3), indicating that alternative or aberrant splicing of U12-type introns occurs in some circumstances. This analysis also suggested that both types of spliceosomes can share a functional 3' splice site (Figure 3, isoform 4). Moreover, retention of
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Figure 3. Alternative splicing of the human DERL2/3 pre-mRNA. The organization of the human DERL2/DERL3 genes and their putative transcript patterns are illustrated. The data for the alternatively spliced transcripts were obtained from the EST database. The transcript patterns shown were obtained from the UCSC Genome Browser spliced EST database (http://genome.ucsc.edu).

U12-type intron(s) in mRNA isoforms suggests their lower splicing efficiency (Figure 3, isoforms 5, 6 and 7) and also supports a previous view that removal of U12-type introns may be a rate-limiting step during splicing (65, 66).

5.3. Selection of alternative 5' or 3' splice sites

A number of mutation studies have revealed clues as to how the U12 spliceosome selects splice sites. Several reports have shown that introduction of mutations in U12-type 5' splice sites can drive either type of spliceosome to use a suboptimal 5' splice site for splicing to the authentic or an alternative 3' splice site (80, 81, 91) (Figure 1). The U2 spliceosome acts dominantly in alternative splicing, likely due to its relative high abundance and low stringency with regard to 5' splice site recognition. Similar scenarios have been observed for mutations within either the branch site or 3' splice site elements (81) (Figure 1). Because most U12-type introns lack a characteristic pyrimidine tract, the branch site may dictate selection of the 3' splice site. Therefore, in the case of U12 spliceosome–activated alternative 3' splice site selection, the U12 snRNP may select a suboptimal branch site and activate a downstream AG as the 3' splice site. Nevertheless, as compared to the U12-type 5' splice site, recognition of the 3' splice site is less constrained (92). Moreover, as hypothesized above, the interaction between the U11 snRNP and 5' splice site may help the U12 snRNP to locate a branch site and thereby activate the use of a 3' splice site. Thus, while natural nucleotide alterations (mutations or SNPs) occur within a U12-type intron, a more complex splicing result may be obtained due to involvement of both types of spliceosomes (Figure 1).

5.4. U2-U12 hybrid introns

U2-U12 hybrid introns have been observed in several mitogen-activated protein kinase (MAPK) family members (81). The use of the hybrid intron strategy may provide a mechanism that drives mutually exclusive splicing to produce transcripts containing either one or the other of the exons flanking the hybrid intron (93). The two exons flanking the hybrid intron are never joined. This mechanism has its basis in the specificity of the two spliceosomes for their corresponding splice sites. In the human genome, four MAPKs, i.e. MAPK8/JNK1, MAPK9/JNK2, MAPK10/JNK3, and MAPK14/p38-alpha, contain a U2-U12 hybrid intron (Figure 4). The alternative exons in each gene share significant sequence similarity; however, the upstream exon shows higher conservation with its cognate exon in the hybrid intron-lacking MAPK members, suggesting that the downstream exon is a duplicate. Notably, the architecture of the hybrid intron differs between JNKS and p38-alpha (Figure 3). The hybrid intron of JNKS contains U12-type 5' and U2-type 3' splice sites whereas the opposite case holds for p38-alpha (Figure 4). Therefore, the U12-type intron is inevitably located downstream of the hybrid intron in JNKS but upstream of the hybrid in p38-alpha (Figure 4). Some of the JNK-like MAPK members of pufferfish (Fugu rubripes) and zebrafish (Danio rerio) harbor a U12-type intron but no hybrid intron (81). Therefore, the hybrid intron may have originated from a U12-type intron via DNA rearrangement, as mutually exclusive exons are generated due to an exon duplication event (93, 94).

As shown in Figure 4, inclusion of exon 6a in JNK2 is specific to neuronal cells, whereas exon 6b–containing transcripts can be expressed in almost any cell type (54, 95). We have recently reported that exon 6b inclusion is primarily attributed to the exceptionally long and highly C/U-rich polypyrimidine tract of the hybrid intron (81). Perhaps this element recruits a ubiquitous splicing activator(s) for exon 6b inclusion. On the other hand, the RNA binding protein Nova has been implicated as a neuron-specific activator to increase the expression of exon 6a-containing transcripts (95). Thus, it would be interesting to investigate whether Nova merely promotes exon 6a utilization or can also antagonize the activity of the pyrimidine element–binding factor(s). Moreover, it would
Figure 4. The U2-U12 hybrid intron in the MAPK family members. The illustration shows the gene organization of the JNK subfamily members JNK1, 2 and 3 (i.e., MAPK8, 9 and 10) and that of the p38-alpha (MAPK14). The hybrid intron is depicted in dashed lines; U12-type splice sites are indicated by short red lines. The transcript patterns shown were obtained from the EST database.

be valuable to understand how the splicing of the hybrid introns is regulated in other JNK/p38-alpha members.

6. POSSIBLE REGULATORY ROLES FOR U12-TYPE INTRONS

U12-type introns are found in several gene families, such as solute transporters, MAPKs, and importin-beta, likely due to gene duplication events during evolution (81). Moreover, it has been noted that U12-type introns prevail in some functionally but not genetically related genes, such as those implicated in Ras-Raf and phosphoinositol signaling pathways and in mRNA and protein metabolism (59, 81, 90). Of particular interest is a set of both constitutive and regulatory splicing factors as well as proteins involved in mRNA decay (90). Previous studies have shown that U12-type intron splicing is likely rate-limiting and is less tolerant to splice site and branch site variations as compared with U2-type introns (65, 80, 81). Perhaps through control of U12-type intron splicing, the expression of their host genes can be regulated. It is known that splicing factors can regulate the splicing of their own pre-mRNAs to generate specific alternative isoforms or modulate the expression level (23, 93, 96-99). Therefore, it is interesting to speculate whether the RNA processing factors whose genes host a U12-type intron can autoregulate their own expression by controlling the rate or accuracy of U12 intron splicing. A recent report shows that alternative splicing of SRp38 activated by an ultraconserved cis-element results in unproductive expression due to inclusion of a premature termination codon (99). Meanwhile, such alternative splicing prevents the use of an authentic U12-type 5’ splice site but activates a cryptic U2-type site. Therefore, control of U12-type intron splicing is possibly a means by which the level of a set of splicing factors is regulated. Moreover, several genes involved in metabolism or regulation of splicing factors also host a U12-type intron; these genes encode transportins and SR protein kinases, which are involved in nuclear transport and phosphorylation of certain splicing regulators, respectively (81). Certainly, a change in expression pattern of any of these RNA processing factors would be expected to have a considerable impact on global gene expression at the level of alternative splicing regulation.

In general, the position of U12-type introns is conserved among members of a gene family due to gene duplication. An exception is the importin-beta paralogs, several of which contain one or two U12-type introns. Intriguingly, the position as well as the length of these U12-type introns varies highly among these paralogs (Table 1). Variable intron position suggests vigorous intron gain and shuffling during evolution but cannot exclude the possibility of intron loss. We presume that the presence of U12-type introns provides a means by which at least several importin-beta proteins control their expression and/or activity; such a benefit(s) may have driven importin-beta genes to acquire and maintain U12-type introns.

7. CONCLUSIONS AND PERSPECTIVES

The discovery of U12-type introns over the past dozen years has brought us insights into intron evolution and the mechanism(s) of splicing. Nevertheless, our knowledge of U12-type intron splicing and its regulation still remains at the periphery. The bioinformatic and experimental results discussed above shed light on how the U12 spliceosome recognizes splice sites in various cases of U12-type intron alternative splicing. However, questions remain as to how the U12 spliceosome competes with the more abundant U2 spliceosome to define the splice sites, particularly in the context of pre-mRNA sequences with many degenerate splice site signals, and how trans-acting factors coordinate the two types of spliceosomes for splicing of U12-type intron–containing pre-mRNAs.

The U12-type spliceosome is less tolerant to mutations within splice site signals. Thus, as compared with U2-type intron splicing, U12-type splicing may be prone to alternative splicing particularly when genetic variations occur within such sites. Consequently, alteration
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Table 1. U12-type introns in human importin-beta family members. The list shows the position and the length of the hybrid intron and total exon number of each importin-beta paralogous gene.

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Intron position</th>
<th>Exon number</th>
<th>Intron length</th>
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<tbody>
<tr>
<td>IPO4</td>
<td>26</td>
<td>30</td>
<td>110</td>
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<tr>
<td>IPO4</td>
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in splicing patterns can influence cell functions. Moreover, because a set of RNA processing factors is encoded by U12 intron–containing genes, we propose that U12-type intron splicing may regulate the expression of these proteins and subsequently amplify its effect to the expression of a wide range of other genes. Thus, U12-type introns may have a significant impact on genomic and physiological diversity, and such aspects must be tested in future studies.

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