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Alternative Splicing and Alzheimer's Disease

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Abstract

Alzheimer's disease is a neurodegenerative process whose origin is unknown. It has been associated with this process at least two important proteins: the first is the β -amyloid forming amyloid plaques and the second protein is Tau, which has been determined to precipitates inside the neuron because hyperphosphorylation, causing instability in the axon. Tau microtubule-associated protein (MAP) is essential for the development of neuronal cell polarity. Tau protein is preferentially localized in the axons, whereas MAP2, another neuronal specific microtubule-associated protein, is localized in the somatodendritic domain. Previous studies have demonstrated that the localization of these proteins depends, at least in part, on messenger RNA (mRNA) subcellular localization, that is, Tau mRNA into the axon and MAP2 mRNA into the dendrite. Tau protein has an essential role in the pathology of Alzheimer's disease, and hyperphosphorylated Tau promotes destabilization of microtubules. Tau alternative splicing generates six isoforms in the adult human brain due to the inclusion or exclusion of exons 2, 3, and 10. The failure in the splicing process of exon 10 generates a tauopathy, which can be carried out by the amyloid peptide; however, the splicing of other exons is less studied. The impact of amyloid peptide on the alternative splicing of exons 2, 3, and 6 caused formed cell processes to retract in differentiated cells and altered the expression of exons 2/3 in cell culture. Expression of exon 6 was repressed under β -amyloid treatment. The molecular mechanism for this amyloid-Tau interaction remains to be determined, but may have potential implications for the understanding of the underlying neuropathological processes in Alzheimer's disease.

Keywords: Alzheimer, Tau, APP, PSEN1, PSEN2, alternative splicing

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative condition characterized by progressive loss of memory, orientation, sanity, and language. AD is a slow evolving disorder of multigenic nature with an average duration between 8 and 12 years. During the disease onset, symptoms are overlooked generally for the first 2 or 3 years. There are few hereditary cases (genetic or familial AD) resulting from autosomal dominant inheritance of chromosomal alterations. This condition is the most common type of dementia, and it is globally recognized as one of the leading causes of morbidity and mortality among the advanced age population. In 2004, approximately 44 million cases of dementia were diagnosed worldwide and the number of cases in 2050 is estimated to be 135 million [1].

In AD, there is neuron loss and two typical alterations appear: the neuritic plaque produced by the β -amyloid ($A\beta$) and the neurofibrillary tangle that contains the hyperphosphorylated Tau protein as the main component.

Neuritic plaques are sphere-like structures in which the major component is the β -amyloid ($A\beta$) protein. The latter is generated by proteolytic cleavage of a larger protein, β APP ($A\beta$ precursor protein), and the neurofibrillar tangle, an intracellular damage affecting pyramidal neurons [2].

When the disease is diagnosed, its pathology has progressed several years [3]. Cerebral changes underlying AD probably develop 20–30 years before the first symptoms appear.

AD diagnosis combines psychological and imaging tests as well as the exclusion of neurologic disorders [4].

The pathological processes frequently linked to AD are as follows: aging, amyloid deposition, neurofibrillar degeneration, synaptic loss, inflammation, loss of vascular integrity, and neuron loss [5].

The development of tangles and plaques leads to neuron death. Tangles are mainly located at the entorhinal cortex, hippocampus, parahippocampal gyrus, amygdala, and frontal, temporal, parietal, and occipital cortices and some subcortical nuclei projected toward these regions [6].

Tangles are composed by paired helical filaments (PHF), in which the latter are gathered in helices. Neuritic plaques are microscopic foci of extracellular amyloid depositions associated with axon and neurite damage. They are found in large amounts at the limbic and association cortex [7].

At the neuritic plaques, it is observed an abnormal extracellular accumulation of the $A\beta$ peptide, comprised by 40 or 42 amino acids ($A\beta$ 40 and $A\beta$ 42) [8]. Dystrophic neurites are located both within and surrounding the amyloid depositions, and they are distinguished by structural abnormalities including lysosomes, mitochondria, and PHF.

These plaques are associated with microglia either contiguous or within the amyloid nucleus. The period of time for neuritic plaque development is unknown. Most of the fibrillar $A\beta$ located

at the neuritic plaques is the species ending in the amino acid 42 (A β 42), which is the slightly larger and hydrophobic form, prone to aggregation [9].

In AD, there is neurotransmitter deficiency at brain level. Dementia symptoms develop because the severe degeneration suffered by neurons that synthesize and liberate acetylcholine. The level and activities of the synthesizing and degrading enzymes, choline acetyltransferase and acetylcholinesterase, decrease at the limbic and cerebral cortex showing an associated loss of cholinergic cell bodies at the septal nucleus and the anterior forebrain cholinergic system [6].

Glutamatergic system is also deteriorated in AD. There are interactions between β -amyloid and glutamate at the synaptic function: the former has influence on the generation of the latter and glutamate levels may be modified by the peptide. Concentration changes of these two molecules may impact AD progression. Because hippocampus and cortex are fundamental for learning and memory, it is possible that glutamatergic neuron degeneration appears at early stages of AD [10].

The cerebral regions severely affected by AD are as follows: hippocampus, entorhinal cortex, amygdala, cerebral cortex, and some subcortical areas such as cholinergic neurons at the anterior forebrain, serotonergic neurons at the dorsal raphe, and noradrenergic neurons at the locus coeruleus [11].

Four main genes have been associated to Alzheimer's disease; all of them are processed by ribonucleic acid (RNA) alternative splicing.

2. RNA splicing

Ribonucleic acid (RNA) splicing is a mechanism used by eukaryotic cells in order to eliminate introns. These introns are non-coding RNA sequences, and therefore, they need to be removed by a ribonucleoprotein-rich structure termed the spliceosome complex. Thus, exon sequences are joined, producing a mature transcript that is available for migrating from the cell nucleus to the cytoplasm in order to be translated into a protein.

Splicing mechanism must be very accurate, as at least 50% of human genetic diseases are associated with mutations occurring in consensus sequences of splicing sites. These sequences consist on GU at the 5' intron and an AG sequence at 3'. Toward the 5' end of the intron, there is a pyrimidine-rich region (C U).

In order to carry out the splicing, the spliceosome complex needs to be assembled. The consensus sequences located at the exon-intron boundary are essential to bind the 5 ribonucleoproteins (snRNP) U1, U2, U4, U5, and U6 in such sequences in order to form the spliceosome. Several protein complexes constitute the spliceosome: the complex E (U1 binds to the GU sequence at the 5' site of an intron, SF1 binds to the intron branch point, U2AF1 binds to the 3' splicing site, and U2F2 binds to the polypyrimidine sequence), the complex A (U2 displaces SF1 and it binds to the branch point sequence), the complex B (U5, U4, and U6 form

a trimer that bind to U2 along with U5). U1 is released, U5 shifts from exon to intron, and U6 binds to the 5' splicing site). Complex C (U4 is released, and U6/U2 catalyze a transesterification to induce the binding of the 5'-end intron to the complex A, forming an intron lariat. U5 bind to the exon 3' splicing site, which is cleaved). Afterward, U2, U5, and U6 remain bound to the lariat forms and the 3' site is cleaved, whereas exons are ligated by means of ATP hydrolysis. Lariat forms are degraded, and the snRNP are recycled (**Figure 1**).

Alternative splicing generally is a mean by which a gene may generate a variety of messenger RNAs (mRNAs) with biological significance, that is coding for a protein. It has been estimated that at least 90% of all expressed genes are subjected to alternative splicing.

It has been identified at least six ways to generate alternative splicing: (a) exon exclusion or inclusion, (b) selecting one or more exons, (c) and (d) competition for the splicing site at a defined exon either in the 5' or 3' region, (e) retaining an intron, (f) multiple promoters, (g) multiple poly-A sites [12] (**Figure 2**). Exon and intron sequences may regulate the splicing site through enhancer or silencer sequences.

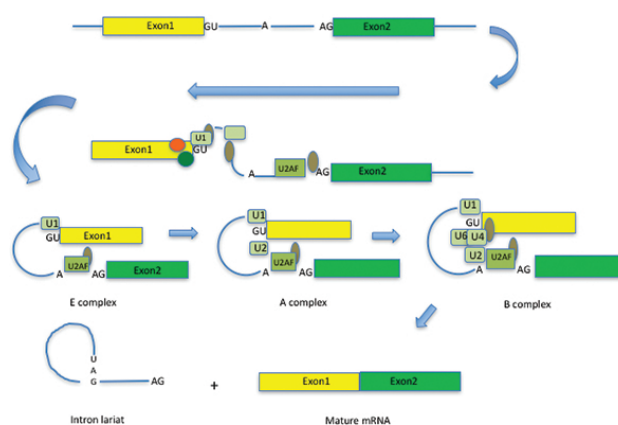


Figure 1. RNA splicing. Exon 1 flanked on its 3' end by the GU sequence and exon 2 on its 5' end by AG, with both target sites for the ribonucleoproteins and the assembled spliceosome complex. The spliceosome will cut the intron in the consensus sequences and will enable the joining of the exons, generating a mature RNA. Scheme taken from [49].

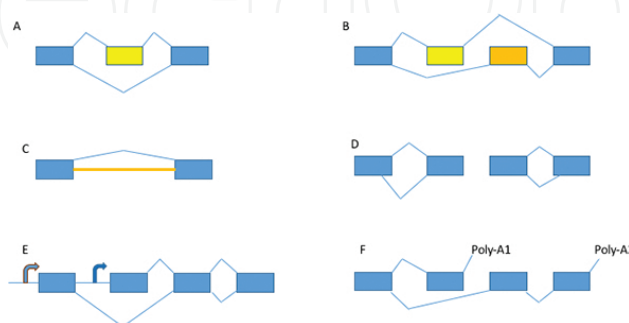


Figure 2. Forms of alternative splicing. (A) Exclusion or inclusion of exons, (B) selection of one or more exons, (C) intron retention, (D) competencies by the site of splicing in a particular exon in the region 5' or 3', (E) multiple promoters, (F) multiple poly-A sites.

3. The Tau gene and its alternative splicing

Tau is a cytoskeleton protein involved in neuron morphology and polarity. It possesses the ability to bind to microtubules in order to provide stability, and it maintains the neuron phenotype at the axon level [13].

It has been determined that Tau is located at the axon hillock, the axon and the growth cone, as its mRNA is transported to its translation site by a protein complex involving kinesin-3 as transporter and the HuD protein as mRNA stabilizer [14–16]. This is possible because Tau mRNA possesses in its 3'-UTR region a uracil-rich axon localization sequence [14, 17].

Tau protein is mainly constituted by two domains: the N-terminal whose function is to interact with the plasma membrane [18] and the C-terminal domain, in which the microtubule-binding region is coded [19].

The human Tau gene is located at chromosome 17 [20], it is formed by 16 exons, and it has a promoter region that confers it with neuron specificity [21].

This gene is transcribed into three RNAs of 2, 6, and 9 kb, which are differentially expressed in the central nervous system, depending on their maturity state and the neuron type [18]. Six Tau mRNA isoforms have been identified as consequence of alternative splicing, five of them in the adult central nervous system and one fetal isoform. These messenger RNAs code six proteins ranging from 352 to 441 amino acids (aa). The fetal isoform (352 aa) does not contain exons 2, 3, and 10. The adult form of 383 aa lacks exons 2 and 3; however, it includes exon 10. The 381 aa isoform includes exon 2 but not 10. The 410 aa isoform includes both exons 2 and 3; the 412 aa isoform includes exon 2 but not 10; the 441 aa isoform includes exons 2, 3, and 10 [22] (**Figure 3**).

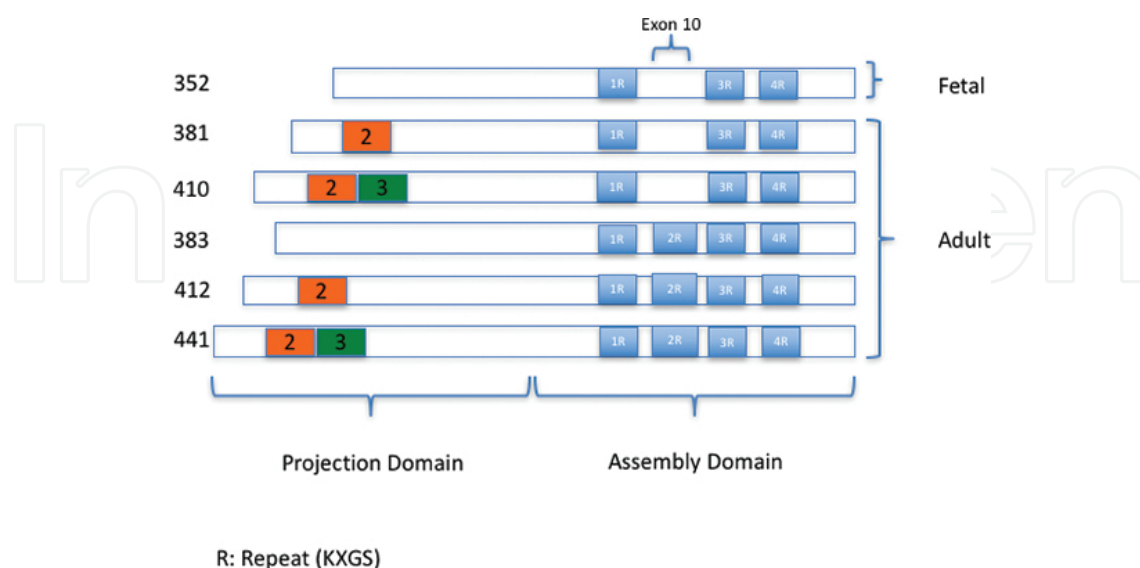


Figure 3. Tau isoforms, showing the different Tau proteins from the alternative splicing of exons 2, 3 and 10. Scheme taken from [49].

Tau alternative splicing occurs in exons 2, 3, and 10 and its form is of the (a) type that corresponds to exon exclusion or inclusion.

The studies conducted on Tau alternative splicing have been comprehensive, and most of them have been focused on exon 10.

Exon 10 displays a splicing pattern of inclusion and it is not present on fetal neurons. It is influenced by exon 9, which promotes its inclusion [18]. Exon 10 codes the second region of the (R) (KXGS) repeats in Tau. Alternative splicing generates Tau isoforms with 3 or 4 repeats that bind to microtubules. In mature brains, the level of 3R and 4R is similar. Exon 10 disruption is able and enough to cause neuron degeneration or taupathies [23].

Exon 10 is flanked by a long 13.6-kb intron and a short 3.8-kb intron, possessing a weak 5' splicing site, which is similar to that in 3'. This would allow the inclusion or not of exon 10 in order to generate proteins with or without it [24, 25].

Exon 2 alternative splicing has been less studied. However, the studies conducted in our laboratory show that when PC12 cells (rat pheochromocytoma) cultures are exposed to the $\beta 1 \rightarrow 42$ amyloid peptide; alternative splicing of exons 2 and 3 is affected, as immature forms of Tau mRNA are transcribed in mature PC12 cells (phenotype differentiated into neuron). We observed that processes in these cells begin to retract. In spite the mechanism is still unknown, the effect produced in these cells indicate that immature Tau forms cease to stabilize microtubules in these cells processes [26] (**Figure 4**). The inclusion of exons 2 and 3 promotes the shift from immature Tau forms to their mature counterparts, stabilizing microtubules.

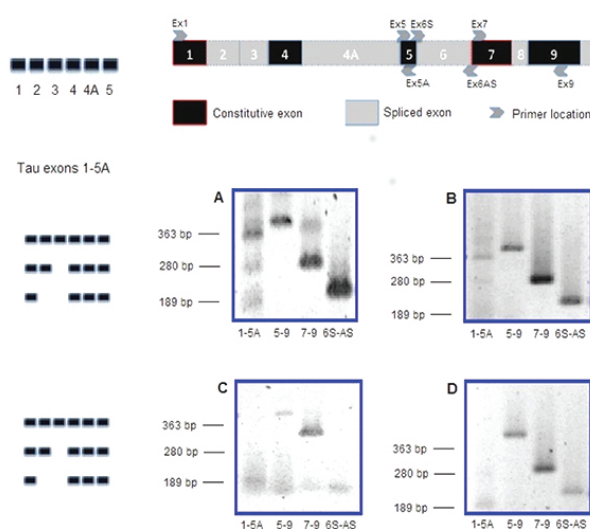


Figure 4. Tau exons 1–9 (modified from [50]), the primers Ex1 and Ex5A, amplify from exons 1 to 5. The exons 2 and 3 are amplified by (Ex1/Ex5A), the exon 6 is amplified by (Ex5/Ex9, Ex6S/Ex6AS) and exon 8 by (Ex7/Ex9). (A) Untreated undifferentiated cells and (B) NGF-induced differentiated PC12 cells; and from PC12 cells exposed to $A\beta(1-42)$ peptide in (C) undifferentiated cells and (D) NGF-induced differentiated cells. Differentiation inhibits fetal tau expression. $A\beta$ exposure promotes exclusion of exons 2/3 in undifferentiated and differentiated cells, and exclusion of exon 6 in undifferentiated cells. Scheme taken from [26].

It has been demonstrated that immature Tau forms are similar to those found on PHF [27], suggesting that exclusion of exons 2 and 3 induced by amyloid peptide in AD may destabilize neurites, and thus, the cells would lose their polarity.

Currently, splicing regulation has been studied with microRNAs (miRNAs), which are regulators of genetic expression [28]. miRNAs are short RNA molecules that bind to transcripts in order to repress and regulate expression. A miRNA deregulation was found on hippocampus and the prefrontal cortex. It was ascertained that miR-132-3-p was the most affected in this disease. miR-132-3-p downregulation in neurons was inversely proportional to the occurrence of hyperphosphorylated Tau [29], and it is linked to the splicing of exon 10 [30].

The inclusion of exon 10 is inhibited by the constitutive factors ASF/SF2, SRp55, SRp75, and SWAP [31].

Exon 2 regulation has been determined by inclusion and exclusion of exons 2 and 3, and it has been determined that exon 3 never appears without exon 2 [32].

4. Amyloid precursor protein (APP) gene

APP is one of the three members of a small gene family coding type I membrane proteins possessing an extracellular domain and a small cytoplasmic region. Only APP contains the sequence coding the A β domain. APP human gene is located at chromosome 21, which is involved in autosomal dominant inheritance in some families affected by early Alzheimer's disease. This gene contains 18 exons, and it is more than 170 kb long [33]. More than 25 mutations have been identified to cause the familial type of AD. All of these mutations substitute amino acids near or within the A β domain [34]. A β is derived from APP by proteolytic cleavage due to an alternative splicing process (generating three isoforms composed by 695, 751, and 770 residues, respectively) [35], of exons 7, 8, and 15 (**Figure 5**). The APP form without the residues coded by exon 15 is called L-APP, and this isoform is found in most tissues [36]. The APP695 isoform is predominantly expressed in neurons, whereas

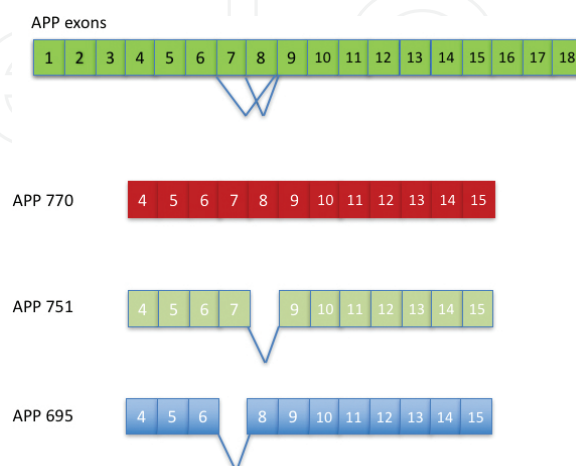


Figure 5. APP isoforms, showing the different APP proteins from alternative splicing of exons 7 and 8.

APP751 is expressed in all tissues and it includes exon 7, codifying a domain similar to that of the Kunitz protease inhibitor [37].

In neurons, APP is found on terminal vesicles in axons and it can be transported in an anterograde or retrograde manner [38]. Other brain cells also express APP and release variable amounts of A β , including astrocytes and microglia.

APP may be subjected to proteolytic cleavage during and after its transit through the secretory pathway. The first of them is carried out by the α -secretase enzyme resulting in the release of a large and soluble ectodomain fragment (α -APP) [39] in the extracellular space, while retaining a 83-residue C-terminal fragment (CTF) in the membrane. Alternatively, some APP molecules that were not cleaved by α -secretase may be processed by the activity of an enzyme named β -secretase, generating a β -APP ectodomain that retains one residue from the 99 CTF [6].

The main β -secretase in neurons is a transmembrane aspartyl protease named BACE1, predominantly located at the transgolgi network (TGN) and also in endosomes [40]. The cleavage mediated by BACE1 generates the N-terminal fragment of A β . The high level of neuronal BACE1 expression preferably targets APP to the amyloidogenic processing pathway in the brain [34]. A β is constitutively released from cells expressing APP in normal conditions. The cleavage generated by β -secretase is followed by a constitutive trim at the C-terminal of the A β region, and it is carried out by the activity of γ -secretase. Simultaneously, a peptide fragment designated as p3 is produced from the sequential activity of both α - and γ -secretases [6]. A substantial amount of α -APP is generated by γ -secretase that acts on the inserted APP in plasma membrane.

The A β 40 and A β 42 fragments are generated to a large extent during APP internalization and endosomal processing. Most of the A β generated within the cell is destined for secretion.

APP has autocrine and paracrine functions during growth regulation. It has been best characterized as trophic as it has been demonstrated that it stimulates neurite growth. This phenotype is compatible with its increased expression during neuron maturation [41, 42].

5. PSEN 1 and PSEN 2

Presenilins (PSEN) are an important part of the γ -secretase enzyme activity, and they are responsible for the proteolytic cleavage of APP. γ -secretase is a multimeric complex of PSEN1 or PSEN2, nicastrin, and APH1. All mutations in PSEN1 increase APP cleaving activity by γ -secretase, which generates the A β 42 fragment. The PSEN1 gene is located in chromosome 14 and that of PSEN2 in chromosome 1, both of them are approximately 60% similar [43]. Regarding the gene's structure, it has been demonstrated that the first 4 exons contain untranslated regions, and exons 1 and 2 possess alternative transcription sites. The function of these sites is still unclear. The first ATG is located in exon 4, and its 12 bp is used as an alternative splicing donor site. Exon 9 is subjected to alternative splicing in leukocytes but not in other tissues. Most of the expressed transcripts are polyadenylated after the TAG stop codon

in exon 13 [44]. A PSEN 2 variant has been shown to lack exon 5, which has been detected on individuals with sporadic Alzheimer's disease [45].

Several mutations on the PSEN genes are responsible for early familial Alzheimer's disease. The loss of exons 3 and 4 of PSEN demonstrates that transcripts are efficiently translated as truncated proteins at their N-terminal; however, this does not affect their function as amyloid fragment generators [46].

A PSEN2 variant that does not possess exon 5 has been reported to increase the generation of the A β 40 y 42 fragments [47].

6. Conclusion

Currently, there is no cure for Alzheimer's disease and the research conducted nowadays in order to fully understand this condition is relevant. Nevertheless, its underlying causes have not yet been determined.

The mechanism of the disease is not fully understood, and the conducted studies have shown that proteins such as Tau, APP, and both presenilins are highly important for developing the disease.

Through artificial intelligence studies, it has been demonstrated that more than 70 genes are associated to these proteins [48], rendering this disease extremely complex.

Alternative splicing is key in order to generate the appropriate proteins that do not affect neuron functioning; thus, the individual may carry a healthy life.

Final note

We seek the most current literature on the subject, and the database used was the PubMed for the development of this chapter.

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