1. Introduction

The pathology of Alzheimer Disease (AD) has been intensely studied in the last 20 years (Duyckaerts et al., 2009) because it is a progressive neurodegenerative disorder that causes dementia in approximately 10% of individuals older than 65 years (Hampel et al., 2010). AD occurs gradually; starting with the so called mild cognitive impairment (MCI) recognized by mild memory disturbances and noticed difficulties in performing more demanding cognitive tasks. With disease progression the decline in memory and cognition become more expressed and are accompanied by changes in personality and behaviour. In later stages of the disease loss of speech and movement is followed by total disability and finally death. A person with AD lives on average eight years after the onset of symptoms (Zerovnik, 2010). Actual studies are focused in many strategies for markers of susceptibility, early diagnostic, understanding of molecular mechanism, effective treatment and preventing strategies. According to Duyckaerts and coworkers (2009) AD could be divided in three broad chapters: lesions related to abnormal accumulation of proteins, those that are due to neural losses and finally those that are due to the reactive processes. According to abnormal accumulations proteins, AD is characterized by the presence of two types of neuropathological hallmarks: neurofibrillary tangles (NFTs) and neuritic plaques (NP). NFTs are intraneuronal aggregates of abnormally modified Tau (phosphorylated at non physiological sites, truncation, etc). NP are extracellular and mainly composed of amyloid β-peptide (AB) deposits (Martin et al., 2011). The most of the cases of AD are reported as “sporadic” pathway, because we still do not know what could be the factors that lead to this disease. Many hypotheses has been proposed, including immune system participation (Solomon & Frenkel, 2010), pathogens (Miklossy, 2011), oxidative stress responses, and more. At the end, in patients we can always find NFTs and NP in several regions of the brain.
About these lesions, Braak and Braak (1991) established a relationship between the appearance of NP and NFTs with cognitive decline in post-mortem studies (Braak & Braak, 1991).

At the moment, AD can be diagnosed conclusively only post-mortem. However, advances in neuroimaging by magnetic resonance imaging (MRI) and by positron electron tomography (PET) allow researchers to see accumulation of amyloid plaques and NFTs in the living brain. In such a way, the course of the disease at various time points can be followed and an early diagnosis obtained. One, in principle, could even monitor the development/progression of the disease (Zerovnik, 2010). Several evidences demonstrate that under the formation of these lesions, are implicated in an important manner, conformational changes for Tau and amyloid β-peptide. Understanding the process at the molecular level is important for toxic aggregates could be stopped from forming or, alternatively, their removal could be accelerated. Antibodies directed against a common structural epitope shared by the prefibrillar oligomers could serve such a role. Common structural characteristics of amyloid fibrils are: predominantly β-sheet secondary structure, detected by specific dyes, and binding and a characteristic pattern seen by X-ray diffraction. By electron microscopy amyloigenic fibrils also are visualized allowing morphological studies (Zerovnik, 2010). In this chapter we focus on the importance of changes in conformation of both proteins during abnormal aggregation associated to AD.

2. Amyloid β

A growing body of evidence suggests that altered processing of amyloid precursor protein (APP) is one of the early events in the pathogenesis of AD. APP is a transmembrane glycoprotein of type 1 from 120 to 200 kD which are ubiquitously expressed, but are most abundant in the brain (Selkoe, 1994). The APP gene is located on the long arm of chromosome 21 in humans (Kang 1987) and contains 18 exons (figure 1A) through alternative splicing of exons 7, 8 and 15 are generated 8 isoforms that have pattern cell specific expression and are designated by the number of amino acids they contain. The size of the isoforms can vary from 563 to 770 amino acids (Coulson et al., 2000). In central nervous system express only 4 isoforms: PPA695, PPA714, PPA751 and PPA770, PPA695 of which is the most abundant isoform in neurons, while that PPA751 and PPA770 isoforms are expressed mainly in glial cells (Yoshikai et al., 1990; Zheng & Koo, 2006). Only isoforms PPA695, PPA751 and PPA770 contains the sequence encoding the amyloid-β (AB) peptide (Golde et al., 1990; Kang et al., 1987). The full-length APP (APP 770) consists of 18 exons, where exon 17 resembles the membrane spanning domain. APP 695 lacking both, exon 7 and exon 8 is primarily expressed by neurons and is the most abundant APP transcript in the brain (Neve 1988). APP 751 (lacking exon 8), APP 714 (lacking exon 7) and APP 770 were first identified in peripheral organs but are also expressed in brain glial cells. Other alternatively generated splice variants of APP involving exon 15 were recently discovered in peripheral leucocytes and in microglial cells and therefore denoted as leukocyte-derived APP (L-APP) (Konig et al., 1992). The AB fragment is part of exon 16 and 17 (figure 1B) and begins 99 amino acid residues from the carboxy terminus and extends 12-15 residues into the hydrophobic membrane domain (Estus et al., 1992). The APP protein is composed of three regions: a large extracellular domain in the N-terminal region that forms a globular structure, a transmembrane region, which contains part of the AB sequence, and a small...
cytoplasmic domain laregion C-terminal (figure 1B). The overall structure includes the position of a heparin binding domain, metal binding domains, sites of phosphorylation and glycosylation. Two of the isoforms (APP 751 and APP 770) have a domain Kunitz-type protease inhibitor (KPI) and a signal peptide (De Strooper, 2010).

In brain tissue, APP can be processed in two ways: non-amyloidogenic and amyloidogenic pathway. In the non-amyloidogenic pathway, APP is first cleaved by α-secretase within the AB sequence, which releases the sAPPα ectodomain. Further processing of the resulting carboxyl terminal by γ-secretase results in the release of the p3 fragment and AICD (figure 1C) (Greenwald & Riek, 2010). The most prevalent area of research in AD studies the proteolytic generation of AB from APP. The β-secretase and γ-secretase cleave APP in the so-called amyloidogenic pathway β-secretase release the ectodomain sAPPβ, and the
remaining APP carboxy-terminal fragment (C99) is subsequently cleaved by the γ-secretase liberating the secreted AB peptide(s) and the APP intracellular domain (AICD) (figure 1C). The biological functions of sAPPβ, AB, and the AICD remain rather elusive, although AB release is associated with synaptic activity, depression excitatory synaptic transmission onto neurons. The production of AB occurs naturally inside the human brain, these fragment possesses and amphiphilic structure with hydrophilic N- and hydrophobic C- terminus, however the C-terminal end is variable ranging at least from 37 to 42 residues; the most studied forms are AB 1-40 and AB 1-42 that consist of 40 and 42 residues respectively (Fandrich et al., 2011). Under physiological conditions, the ratio of AB42 to AB40 is about 1:10. AB42 plays a critical role in the pathogenesis of AD since its aggregative ability and neurotoxicity are much greater than those of AB40 (De Strooper, 2010).

About APP function, the analysis sequence and structure indicate that the protein is organized into different domains, because it is believed that APP is important for functions as neuronal survival, synaptogenesis, cell adhesion, inhibition of clotting factors, inhibiting platelet activation and in the modulation of copper homeostasis (Chow et al., 2010; De Strooper, 2010). The precise function of various APP isoforms in the brain is still unknown. It has been suggested that APP plays a role in establishing or maintaining cell-cell contacts which is also consistent with preferential localization of APP at nerve terminals, because have been shown their interaction with extracellular matrix proteins and heparin sulfate proteoglycans through E1 and E2 regions of APP (Schubert et al., 1995; Small et al., 1999). The function of APP as a cell surface receptor has been proposed for the evidence of AB could bind to APP and also the similarities of their secondary structure with Notch receptor (Zheng & Koo, 2011). About the neuronal survival and synaptogenesis functions of APP the reports showed that APP expression is upregulated during neuronal maturation and differentiation, also induced after traumatic brain injury, these results are reinforced because the reduction of APP is associated with neuronal impairment (Hung et al., 1992; Leyssen et al., 2005). The APP can be phosphorylated at multiple sites resulted in several consequence such as localization to the growth cones and neuritis (Muresan & Muresan, 2005). Other contrasting activity of soluble APP is the cytotoxic properties of C99 fragment as result of β-secretase cleavage (Neve et al., 1996). Meanwhile, the functional properties of AB peptides have not been fully clarified to date, although numerous studies suggest that peptides have a number of neurotrophic and neurotoxic properties (Tycko, 2011). It is suggested that AB soluble plays an important role in neuronal growth, survival, and synaptic modulation, while the oligomers and fibrils have toxic properties (Kamenetz et al., 2003; Plant et al., 2003; Puzzo et al., 2008). Studies have shown that AB oligomers are able to induce increased cell death and apoptosis soluble or fibrillar forms, suggesting that the structural conformation peptide is important in determining its physiological action (Small et al., 2001).

2.1 Amyloid β structure and aggregation

Recent biophysical investigations using electron microscopy, Fourier Transform Infrared Resonance (FTIR) studies and Circular Dicroism (CD) spectroscopy showed that AB fibrils adopt a β-sheet structure (Serpell et al., 2000). However, a high-resolution structural analysis of AB fibrils has yet to be conducted since single crystal X-ray crystallography and solution nuclear magnetic resonance (NMR) cannot be applied to insoluble AB fibrils (Greenwald & Riek, 2010). AB peptides generated can exist as monomers, dimers and oligomers with
aggregation and eventually produce protofibrils fibrils, they acquire a conformation which β-pleated sheet. The AB peptide has a spontaneous tendency to oligomerization, forming toxic species which can even add intracellularly and therefore believed to play a role this fundamental neurotoxicity in AD (Klein et al., 2001; Murray et al., 2009). Recent experiments have established that the main structure adopted by these peptides depends on the environment. The monomers contain a amphipathic sequence that favors the α-helix structure in solution but preferred aqueous β-pleated structure (Greenwald &Riek, 2010).

The structures of β-sheets are parallel or anti-parallel alignments of two or more β-stranded peptides that are held together by inter-strand hydrogen bonds. The β-sheet is not an unusual structure with more than 30% of the secondary structure of all proteins. The structure consisting of strands aligned in parallel feature twelve-membered hydrogen bonded rings, while those with strands in anti-parallel arrays are characterized by alternating 10- and 14-membered H-bonded rings. Dihedral angles commonly found in parallel (φ = -119°, ψ = 113°) and anti-parallel (φ = -139°, ψ = 135°) β-sheets are closer to those of the fully extended single-strand conformation (φ = ψ = ±180°) than β-turns or α-helices. The β-sheet usually acts as a scaffold to stabilize protein architecture, but it is also an important recognition motif in some protein–protein and protein–DNA interactions that mediate biological processes and some notable diseases (Harrison et al., 2007; Jenkins &Pickersgill, 2001). The peptide self-assembly to AB fibrils is a widespread phenomenon in nature; these structures are associated with protein aggregation pathologies such as AD. Therefore the structural analysis of AB fibrils is one of the most promising ways of revealing the mechanism involved in this event. Investigations showed a conserved evolutionarily protein motifs. The description of a common cross-β structure consists of β-strand peptides aligned in either parallel or antiparallel orientations to provide β-sheet structures that ultimately laminate to form fibrillar architectures. This process is mediated by noncovalent forces such as hydrophobic and hydrogen bonding interactions. However, the contribution of these forces is poorly understood (Bemporad et al., 2006; Tycko, 2011). Other critical interactions in cross-β peptide self-assembly are aromatic π-π, frequent in aromatic amino acids in the core of amyloid sequences, because mutations or deletions cause the loss of the structure (Bowerman et al., 2011; Marshall et al., 2011). Fibrils of AB42 and AB10-35 show a strong dependence of pH on morphology observed; at pH 7.4 protofilaments of AB42 exist singly and in pairs, but protofilaments of AB10-35 exist in pairs only. Studies on NMR indicate a parallel β-sheet organization on AB42 fibrils, consistent with supramolecular structures of other fibrils of AB10-35 and AB40. Although, there is a disagreement in the results obtained for fibrils formed by AB10-35 and AB40 with parallel organization, while the observations in AB42 fibril showed an antiparallel β-sheet structure. The explanation is that amyloid fibrils do not have a universal supramolecular organization. Also the results obtained of electronic microscopy and diffraction support a tubular structure for AB fibrils (Antzutkin et al., 2002). Analysis of the amyloidogenic regions in fibril-forming proteins showed a high occurrence of the aromatic residues phenylalanine and tyrosine, which have a high propensity to stack the delocalized π-electron rings in a parallel manner. Studies with short peptides have confirmed that even two consecutive phenylalanine residues are sufficient to facilitate assembly into nanotube-like structures, and stacks of aromatic residues were observed in crystal structures (Nerelius et al., 2010).

Also it has been suggested that the amphiphilicity of the peptide plays a significant role in determining whether peptide strands within the fibril are parallel or anti-parallel. Parallel β-
sheets in proteins usually adjoin α-helices, suggesting that they are intrinsically less stable on their own than are anti-parallel β-sheets. The AB40 and AB10–35 peptides both have hydrophobic C-termini, and their reported assembly into parallel β-sheets allows the juxtaposition of the hydrophobic portions of the peptides, shielding them from aqueous solution. An anti-parallel disposition would be costly energetically because of the forced association of hydrophobic and hydrophilic regions. AB16–22 and AB34–42 both have a centrally located hydrophobic segment and thus no advantage of sequestration of hydrophobic regions provided by either a parallel or antiparallel arrangement. The anti-parallel β-sheet arrangements found for these two peptides may then be the result of favorable charge interactions between side chains or termini, or improved H-bonding (Harrison et al., 2007). A model proposed for this structure is a parallel β-helix consisting of an extended polypeptide chain wrapping around a cylindrical template, where adjacent strands of the helix are connected through H-bonds and is based on two key features of the polyglutamine diffraction data; the absence of a 10-Å reflection and the presence of a weak, low-angle reflection of 31 Å (Perutz et al., 2002).

The crucial region for the formation of crossed-β fibrils is found in 15-23 residues (QKLVFFAED) (figure 2A), substitution of Thr for Phe19 can abolish plaque-forming competence of the mutant peptide and that the mutant peptide was significantly less folded in aqueous buffer than the wild-type peptide. Further, the Phe19 in the AB antiparallel β-sheet is key in determining the properties of the fibril, because the observation that the Thr for Phe19 substitution lacks fibril-forming competence. Also the Lys16 in AB is positioned for electrostatic interaction with the charged sulfate groups of inducers of aggregation such as Congo Red (Carter & Chou, 1998). The KLVFFAED motif, a known amyloidogenic sequence of the AB, which contains positively and negatively charged residues (figure 2B) and has a high β-strand propensity (figure 2C). As mentioned above, minor alterations in sequence, such as replacement of Val or Phe with Leu or Ala, can abolish fibril formation and that the amyloidogenic properties of short peptides can be abolished by introduction of adjacent sequence motifs such as β-turns. These data indicate that both the amino acid sequence as such and its structural context affect the ability to form amyloid fibrils (Nerelius et al., 2010). In macromolecular level, aggregates are typically fibrillar in electron microscopy images generally with linear (figure 2D), unbranched fibrils of variable length. Each fibril is thought to consist of several protofilaments, the number being specific to the particular amyloid protein. Improved imaging of protofilaments has revealed that certain fibrils are clearly helical, with the protofilaments slowly twisting around each other. For Aβ34–42 fibrils, the twisted fibril “unwinds” under denaturing conditions and for Aβ40 at high pH, suggesting that these protofilaments are associated through both electrostatic and hydrophobic interactions (Fraser et al., 1992; Halverson et al., 1990). Amyloids are typically large (Megadalton) elongated structures with varying lengths and often varying ultrastructural appearances (Toyama & Weissman, 2011). Here we describe some of the most commonly used techniques employed in amyloid structure characterization. Electron microscopy and atomic force microscopy (AFM) are the two most widely used microscopy techniques employed in the study of amyloids. Both provide a nanometer-resolution perspective of the ultrastructural characteristics of amyloids. This includes amyloid fiber length and width, morphology such as curvature and persistence length, surface characteristics such as periodic twists, and higher-order assembly. Electron microscopy and AFM helped establish many of the common ultrastructural characteristics of amyloid fibers, such as the long, relatively straight and unbranched nature of the fibers; the typical fiber
width of 5–15 nm; the periodic twist often observed; and the conclusion that many amyloid fibers are made up of the bundling of thinner protofibrils. To better understand the higher-order assembly of amyloid fibers, scanning transmission electron microscopy (STEM) and tilted-beam transmission electron microscopy, both forms of electron microscopy, have provided data that describe the amount of mass-per-unit length (MPL) of amyloids. These data are particularly valuable in determining how many monomers make up a single layer of the fiber structure. AFM has also been used to determine the relative fiber rigidity by monitoring its propensity to bend. Electron microscopy and AFM both have the advantage of being single-fiber approaches, which are useful in visualizing structural heterogeneity within a single-fiber preparation (Chen et al., 2009; Shirahama & Cohen, 1965).

Fig. 2. Characteristics of Amyloid β. (A) Structure diagram and amino acid sequence of AB42. (B) Amino acid distribution histogram of AB42. (C) Proposed AB42 structure based on predicted β-strand propensities (Displayed in Jmol). (D) Electron Microscopy photograph of in vitro AB42 aggregates.

Fiber X-ray diffraction was one of the first structural techniques that provided a substantial clue to the overall fold of amyloid fibers. In this method, fibrous samples are bombarded with X-ray radiation, and diffraction patterns result from interference patterns from any regularly spaced structural features present in the fibers. As alluded to above, this technique established the cross-β diffraction pattern interpreted as β-sheets parallel to the fiber axis, with β-strands perpendicular. It has also aided in testing the validity of particular model structures. Here, a theoretical X-ray fiber diffraction pattern is calculated on the basis of a
particular model and then is compared to an actual diffraction pattern (Makin et al., 2005). FTIR and CD are absorptive spectroscopic techniques that measure nonsymmetrical or chiral molecular systems in bulk, FTIR spectroscopy measuring molecular bond vibrational frequencies and CD the differential absorption of left versus right circular polarized light. Both of these properties are highly sensitive to secondary structure, and therefore, deconvoluted FTIR and CD spectrum provide accurate estimations of the contribution of β-sheets, α-helices, and loops to the overall structure (Berthomieu & Hienerwadel, 2009; Ranjbar & Gill, 2009). Cryoelectron Microscopy: is a technique that positions itself as a capable alternative to conventional X-ray crystallography and solution NMR in amyloid structure determination. Unlike X-ray crystallography, proteins of interest need not be in a crystalline form for cryoelectron microscopy; rather, structural data can be acquired on single particles. Furthermore, amyloid preparations do not need to be labeled with stable isotopes, is the case with NMR, nor do they even need to be highly pure preparations. This is particularly advantageous owing to the inherent heterogeneous nature of the amyloid conformation (Mizuno et al., 2011). X-Ray Crystallography: although the large and heterogeneous nature of amyloid fibers would seem to be incompatible with X-ray crystallography, Eisenberg and colleagues have been able to acquire adequate diffraction data from microcrystals of short peptides (6–7 residues) that formed amyloid-like structures. Based on X-ray crystallography showed that structures bore strong resemblance to many existing models of amyloid fibers, suggesting they may in fact represent the structure of the amyloid fold. Since this initial study, multiple amyloidogenic peptides have been successfully crystallized and their structures solved (Nelson et al., 2005; Wiltzius et al., 2009).

AB early aggregates also can showed a globular appearance that further organize into beaded chains, globular annular “doughnut” shaped assemblies eventually giving mature protofilaments and fibrils. Pre-fibrilar aggregates may interact with reconstituted phospholipid membranes and with cell membranes where they form aspecific channels (pores) disrupting cellular homeostasis (figure 5). The latter possible mechanism of toxicity is similar to that displayed by antimicrobial peptides, pore-forming eukaryotic proteins and bacterial toxins and newly synthesised cyclic peptide antibiotics (Stefani & Dobson, 2003).

The cell membrane could be a nucleating center for amyloid aggregation. The evidence showed that AB species are tight binding to GM1 ganglioside (GM1), in the brain showing early pathological changes of AD. The ganglioside-bound AB (GAB) possessed unique characteristics, including its altered immunoreactivity, which suggests its distinct conformation from native AB, and its strong potency to accelerate Aβ assembly into fibrils. The hypothesis is that AB adopts an altered conformation following interaction with GM1, leading to the generation of GAB, and then GAB acts as an endogenous seed for Alzheimer amyloid in the brain. GAB is favorably generated in the unique ganglioside-enriched (clustered), raft-like microdomains; moreover, amyloid fibrils formed in the presence of gangliosides are neurotoxic. Probably the ganglioside binding is the initial and common step in the development of a part of human misfolding-type amyloidoses, including AD (Matsuzaki et al., 2010). Recent reports supports that soluble oligomers of AB may be the key neurotoxic species associated with the progression of AD and that the process of AB aggregation may drive this event. Recent data obtained in our laboratory suggest that the presence of soluble oligomers in rat hippocampus promotes localized mechanism of inflammatory responses (unpublished data). Is also reported that soluble oligomers of AB and Tau accumulate in the lipid rafts of brains from AD patients through an as yet unknown
mechanism. In cell culture models the exogenously applied AB in the form of oligomers can be trafficked on the neuronal membrane and accumulate in lipid rafts. The oligomers induced dynamic alterations in lipid raft protein composition were found to facilitate this movement. There is a clear association between AB accumulation and redistribution on the neuronal membrane and alterations in the protein composition of lipid rafts. Also the reports showed that fyn is a key protein on AB redistribution and accumulation in lipid rafts as and mediating the cell death induced by the AB oligomers and defines a mechanism by which oligomers of AB and Tau accumulate in lipid rafts (Williamson et al., 2008).

3. Tau protein

Tau is a microtubule-associated protein (MAP) that is believed to stabilise microtubules and to promote microtubule assembly. Of the neuronal MAPs, it is one of the most abundant (Goedert & Spillantini, 2011). Tau protein is found in many animal species such as Caenorhabditis elegans, Drosophila, goldfish, bullfrog, rodents, bovines, goat, monkeys and humans (Buee et al., 2000). In humans, Tau is encoded by a single-copy gene located on chromosome 17q21.1 in humans (figure 3A). It produces three transcripts of 2, 6 and 9 kb which are differentially expressed in the nervous system, depending upon stage of neuronal maturation and neuron type. The 2 and 6 kb Tau mRNAs arise from utilization of two alternative polyadenylation sites separated by ~4 Kbp. So far, one promoter has been mapped for the Tau gene in both human and rat, located directly upstream of Tau exon -1. However, the 6 kb Tau transcript is responsive to NGF, whereas the 9 kb one is not. Also, the 6 and 9 kb transcripts are restricted to neuronal tissues, whereas the 2 kb Tau transcript is ubiquitous (Andreadis, 2005; Andreadis et al., 1996). Tau primary transcript contains 16 exons, but two of them (exons 4A and 8) are not present in mRNA in human brain. Exon 4A is present in peripheral nervous system not only in humans, also in bovine and rodent peripheral tissues. On the other hand, exon 8 has not been described in humans. Exon -1 is part of the promoter, transcribed but not translated, just like exon 14 (Buee et al., 2000). Exon 3 is never found without exon 2, and as exon 10, are present in an adult-specific manner (figure 1B), but their ratios differ in various central nervous system compartments (Andreadis, 2011; Takuma et al., 2003). All six possible product combinations of the 2/3/10 splicing events have been observed (figure 3B), indicating that separate factors govern their splicing (Andreadis, 2011). Alternative splicing of hinge-region exon 6 gives rise to Tau variants that lack the domain responsible of microtubule binding, and is mentioned that alters Tau function (Andreadis, 2011; Luo et al., 2004). Saitohin (STH), an intronless gene encoding an open reading frame of 128 amino acids, is located in the intron between exons 9 and 10 of the human Tau gene (Wang et al., 2011). Recently has been associated the existence of a polymorphic form with AD, but is still under research. In the 6 principal human Tau protein isoforms are present two domains (Figure 2C): the projection domain located in the amino-terminal and is composed of an acidic region and a proline rich region (PRR). The other domain is named microtubule binding domain (MTBD), which contain the C-termini per se, and a microtubule binding region (MTBR), conformed indeed by the presence from three (3R) to four repeats (4R) (Buee et al., 2000). They differ from each other by the presence or absence of 29- or 58-amino acid inserts located in the amino-terminal half and an additional 31-amino acid repeat in the carboxy-terminal half (Goedert & Spillantini, 2011). Tau is enriched in axons of growing and mature neurons and is critical for neuronal
function. Among its many roles, Tau promotes neurite outgrowth, organizes axonal microtubules (MTs) and is involved in kinesin-dependent axonal transport (Andreadis, 2011; Hirokawa et al., 1988; LaPointe et al., 2009). Additionally, the interaction of Tau with diverse structural and functional proteins suggests that Tau may play crucial roles not only in normal architecture but also in signal transduction of the neurons (Wang & Liu, 2008). The acidic sequences may be involved in cation binding and in iron binding site motif, also is

Fig. 3. Characteristics of human Tau protein. (A) Human Tau gene presents 14 exons and -1 is part of the Tau gene promoter: -1 and 14 can be transcribed but not translated; in human CNS are not normally expressed exons 4A, 6 and 8. In all isoforms are expressed exons 1, 4, 5, 7, 9, 11, 12 and 13. Exons 2, 3 and 10 can be excluded depending of Tau isoform. In exon 9 is codified the protein Saitohin. Exons are indicated by rectangles. Distances between exons are representative. (B) Tau isoforms expressed in human CNS, showing number of aminoacids and inserts that differ each of them. Functional protein domains are indicated by different colors (C) Domains contained in most of the isoforms of human Tau protein: the N-terminal is named projection domain and is subdivided in acidic domain and proline rich regions; also here is a PXXP motif for SH3 domain interactions. The C-terminal, also named microtubule binding domain (MTBD) contains the MTBR and the C-terminus per se; in 4R isoforms is present 2 sequences with β sheet structure tendency adjacent to the second and third repeats. P= phosphorylation sites; ≪= truncations sites.
proposed that the motif KKXK is involved in heparing binding (Ávila et al., 2002) and actin interaction (Zmuda & Rivas, 2000). In this regions is present various PPXXP or PXXP motifs which allow Tau protein to interacts with SH3 domains of diverse proteins such as Src family members like Fyn, Lck, Src (Lee, 2005; Lee et al., 1998; Scales et al., 2011) and others like PCL-γ (Hwang et al., 1996; Jenkins & Johnson, 1998). Is also mentioned that STH interacts with Tau and Abl and influences in Abl phosphorylation (Wang et al., 2011), but this phenomena needs further research.

The efficacy of Tau to binding MTs is influenced by the degree of phosphorylation and the exclusion/inclusion of exon 10. The affinity of Tau against MTs is weaker in 3R isoforms than 4R isoforms, perhaps leading to differential regulation of microtubule behaviour (Eckermann et al., 2007; Goode et al., 2000; Lu & Kosik, 2001). Another important factor influences Tau-MTs interaction: site-specific phosphorylation. This is due to the high frequency of phosphorylatable residues (45 S, 35 T and 5 Y in the largest isoform), combined with the open structure of Tau which renders it accessible to many kinases (Mandelkow et al., 2007). The majority of the phosphorylation sites are Serine or Threonine residues followed by Prolines (SP/TP motifs) that lie in the domains flanking the repeats and can be phosphorylated by several Proline-directed kinases and by neuronal kinases MARK (affecting the KXGS motifs within Tau’s repeat domain) (Eckermann et al., 2007; Trinczek et al., 1995). Among the kinases responsible for Tau phosphorylation are Glycogen Synthase Kinase 3β (Lin et al., 2007), cyclin-dependent kinase 5 (Cdk5), MT-affinity regulatory kinase, cAMP-dependent protein kinase (Johnson & Stothoff, 2004), dual-specificity tyrosine-phosphorylated and regulated kinase 1A, Tau– tubulin kinase 1, and calmodulin-dependent protein kinase 2 (Meraz-Ríos et al., 2010).

3.1 Tau conformational changes in physiological and pathological conditions

Tau is a highly flexible and extended protein, natively unfolded and with hydrophilic and basic character, highly soluble shown by sequence analysis and CD experiments (Eckermann et al., 2007; Shkumatov et al., 2011). Firstly was suggested that Tau in solution may be as much as 77% random coil and behave like “Gaussian coils” or “worm-like chains”, in which the direction of the polypeptide backbone chain varies in a more-or-less random fashion (Goode et al., 2000). However, a potential β-pleated region has been proposed for the microtubule binding region (Ávila et al., 2002). When Tau is attached to MTs, is suggested to assume an “L” conformation, meaning that MTBR interacts with the MTs and the N-termini is projected to cytosol, where can interacts with other proteins (Hirokawa et al., 1988; Mandelkow et al., 2007; Sillen et al., 2007).

On the other hand, is suggested by fluorescence resonance energy transfer (FRET), electron paramagnetic resonance (EPR) and small-angle X-ray scattering that Tau can adopt a global hairpin (paperclip) structure in solution (when is not attached to MTs) (Jeganathan et al., 2008a; Mandelkow et al., 2007; Mylonas et al., 2008). From a structural perspective, the folding of the N- and C-domains over the repeat domain would be expected to protect against aggregation, and indeed Tau forms aggregates more readily when the non-repeat domains are cleaved off (Mylonas et al., 2008). The conversion of certain soluble peptides and proteins into insoluble filaments or misfolded amyloid proteins is believed to be the central event in the etiology of a majority of neurodegenerative diseases (Nonaka et al.,
Tau protein is not the exception. Despite its random coil appearance in solution, Tau assembles into well-defined fibres, the Paired Helical Filaments (PHFs) (von Bergen et al., 2000). The appearance of conformational changes in Tau as early alterations in AD neuropathology has been eloquently confirmed in several studies (Ávila et al., 2002). Even when is reported that α-helix structures are present in PHFs (Sadqi et al., 2002), the β-sheet structure seems to be the major structure involved in Tau aggregation. Two hexapeptides, VQJINK and VQJVYK which are respectively located at the beginning of the second and third MTBR are prominent in generating β-sheet structures during Tau aggregation process (Martin et al., 2011). These hexapeptides structure are well characterized by several methodologies, like FTIR, AFM and CD (Chaudhary et al., 2009). Another reports mention that proline is frequently involved in a β-turn by reason of its restricted ζ angle and that the Pro-Gly motif is favored to make a Type II β-turn and the SPXX motif is known to stabilize β-turns, independent of X. Also is predicted that Tau contains 54 β-turns involving about 35% the protein sequence (Goux, 2002). For the conformational studies, Goux (2002) mentions that is important to consider factors as temperature or solvent-induced changes in Tau to the cis-trans proline distribution of isomers, resulting in a change in protein conformation, also mentioned by other authors for the two hexapeptides mentioned before (Chaudhary et al., 2009; Goux, 2002).

As a general view for aggregation studies, conformational changes have been studied by the use of aggregations inducers or punctual mutations in the MTBR. The other manner is by promoting post-translational modifications in Tau molecule, such as phosphorylations or truncations or by the analysis of PHFs. In the presence of pro-aggregatory factors as polyanions, stimuli the assembly of full lenght Tau, 3R or 4R, and when mutations forms associated to other Tauopathies seem to be a faster process of filament formation. In both are reported the presence of β-sheet enriched structures (Friedhoff et al., 2000). The β-strands usually run perpendicular to the helix axis forming a cross-β motif. By in vitro assays, is suggested that β-sheet structures might be stabilized by the presence of salt bridges or by hydrogen bonds, which promote forming a continuous β-sheet extending along the axis (Berriman et al., 2003; Jeganathan et al., 2008b). Such structures can be stained with certain dyes such as Congo red (CR), Thioflavine S (TS) or Thiazine Red (TR) which are thought to interact with the repeating β strands (Glenner et al., 1972; Luna-Muñoz et al., 2008; Zilka et al., 2006). Planar aromatic dyes as CR, TR, and TS also are capable of inducing Tau fibrillization in vitro. In our group we developed a cellular model to study the particularities of these dyes at in vivo Tau aggregation. The SH-SY5Y cells were incubated with each dye and our results showed that three dyes gave rise to aggregates of Tau with different morphological characteristics. This method can be used to test related drugs with inhibitory potential for Tau abnormal polymerization (Lira-De León et al, unpublished data).

Alternatively, Tau can indeed adopt distinct conformations has been observed in sequential phosphorylation reactions. This theory is supported by biophysical evidence showing that Tau paracrystals become longer and stiffer following phosphorylation, suggesting a conformational change of the protein upon phosphorylation; specifically NMR and CD evidence shows that a Tau peptide undergoes a conformational change following phosphorylation at Thr231 and Ser235 (Goux, 2002). Moreover, where the AD-specific phosphoepitope of antibody AT-100 in the proline-rich region can only be generated by a sequential phosphorylation of Tau first by GSK-3β (at Thr212) and then by PKA (at Ser214),
indicating that pre-phosphorylation at certain sites can alter the conformation such that other phosphorylation reactions are no longer possible (Friedhoff et al., 2000). Tau abnormal phosphorylation at specific sites are strongly associated to other post-translational modifications such endogenous proteolysis or truncation. This abnormal process is defined as a protein cutting that could also promote aberrant aggregation (Ávila et al., 2004) In the case of Tau molecule, the lost of any of its C- and N-extremes leads to a change of properties of the molecule. The lost of the N-terminal has been proposed as an early event in Tau aggregation process because of the capability of this extreme of inhibit Tau oligomerization in vitro (Ghoshal et al., 2002; Horowitz et al., 2006) On the other hand, C-terminal proteolysis is strongly correlated with neuropathological lesions and cognitive impairment (García-Sierra et al., 2001; Meraz-Ríos et al., 2010). Latest years many reports have demonstrated the relationship between site-specific phosphorylation at sites Ser199, Ser202, Thr205, Thr212, Ser214, located in proline-rich region, and Ser396 and Ser 404, located near C-termini. These impact in conformation of Tau, and perhaps expose sites for further specific proteolysis in Asp421 and Glu391 (Fischer et al., 2009; Jeganathan et al., 2008a; Luna-Muñoz et al., 2007; Mondragon-Rodriguez et al., 2008). Specific Tau-phosphorylation also alters microtubule-binding capacity and increase rate of filament nucleation (Chang et al., 2011; Fischer et al., 2009). With this issue, is proposed the sequential relationship between phosphorylation→ conformational change→ truncation, which can be repeated until Tau protein lost their N- and C-termini, exposing a minimal resistance protease region named PHF-core (Binder et al., 2005; García-Sierra et al., 2008; Wischik et al., 1985; Wischik et al., 1996). The dense core of PHFs is compound of the repeat region of the Tau protein, forming a fuzzy coat beside the filament with N- and C-termini of the protein(Skrabana et al., 2004).

According to in vitro assays, this PHF-core is able to promote Tau aggregation (Campos-Peña et al., 2009; Wischik et al., 1996).

Considering these data, is important to use diverse strategies for the study of this phenomena. For elucidated this issue is used conformational-specific antibodies. The Alz-50 and MC-1, two conformational sensitive antibodies, have been demonstrated to recognize a pathological conformation of Tau molecule in NFTs (Jicha et al., 1997; Lin et al., 2007). Either antibody recognizes the N-termini nearby C-termini, determinate by fluorescence lifetime imaging and other techniques (Hyman et al., 2005). Even these antibodies recognize a region in the N-termini (7-9) and C-termini (312-342), both conserved in all Tau human isoforms, in tissue they have a distinct pattern of signal (Jicha et al., 1997). In AD brain, MC1 stains “pretangle neurons”, and its immunopositivity is indicative of very early neuronal pathological changes. Alz50 stains both pretangle neurons, as well as early-formed paired-helical filaments (Nogalska et al., 2011). Moreover, a number of studies have proposed that the phosphorylation modification at S-P or T-P motifs in Tau might cause Tau conformational change and the cis-trans isomerisation, made by the prolyl-peptide isomerise Pin-1, might regulate Tau function. This association is dependent on a folding of the Tau molecule, this bend occurring locally in the vicinity of Thr231-P motif, and actually recognized by TG3 antibody (Friedhoff et al., 2000; Lin et al., 2007; Luna-Muñoz et al., 2005; Weaver et al., 2000). The antibody Tau-66 is another conformational-associated antibody, recognizing residues between 155-244 and 305-314. This antibody recognizes NFT, and also cytoplasmic points on some non-fibrillary neurons, mostly associated to truncated N- and C-termini (García-Sierra et al., 2003). During this study, they suggest there is a progression from Alz-50 to Tau-66 conformation during NFTs evolution. Related to this, Goux based on PHFs extraction and CD assays, mention that Tau has a structure containing 31-37% helix,
15-20% β-sheet, 20-23% turn, and 26-29% unordered structure (Goux, 2002), perhaps influencing in this "specific-antibody" conformation. It was also mentioned by Barghorn and co-workers that for aggregation issues, Tau must adopt a specific conformation that allows a subsequent fibril formation (Barghorn & Mandelkow, 2002). Recent studies use mAb423 antibody, which recognize truncated Tau in Glu391, as a tool for structural studies directed to the PHF core (from 297-391 of 441 isoform), allowing to estimate the enrichment of β-sheet structures (Sevcik et al., 2007; Skrabana et al., 2010; Wischik et al., 1985). In this aim, antibodies have probe been an important tool for recognize conformational changes in Tau during aggregation events.

3.2 Impact of Tau conformational change during aggregation process

Partially folded or misfolded states often tend to aggregate because these forms typically expose hydrophobic amino acid residues and regions of unstructured polypeptide backbone, features that are largely buried in the native state. Like intramolecular folding, aggregation, i.e., the association of two or more non-native protein molecules, is driven by hydrophobic forces and predominantly results in the formation of amorphous structures that lack long range order. Although the toxic principle operating in the age-of-onset diseases is far from being understood, a consensus is emerging that oligomeric, soluble states of the respective disease protein are the primary cytotoxic species (Vabulas et al., 2010). Tau proteins fibrillize efficiently in vitro into β-pleated sheet structures with biochemical and biophysical properties of amyloid fibrils (figure 4A-B), but they do so only in the presence of negatively charged cofactors such as heparin, RNA, or DNA. The kinetic profile of Tau fibrillation in vitro generally resembles that of other amyloid proteins, when is important an increase of β-sheet structures (figure 4C), with a lag phase during which time nucleating units are believed to be formed followed by rapid fibril growth (Congdon et al., 2008; Matthes et al., 2011; von Bergen et al., 2000; Xu et al., 2010). Covalently linked dimers can be formed by disulfide cross-linking and by electronic microscopy it seems as rod-like particles (Friedhoff et al., 2000). The dimers of Tau molecules become subunits of filaments, forming protomers, adopting the parallel, in register cross-β-sheet structure typical of amyloid aggregates. On the basis of morphology and mass-per-unit length measurements, mature Tau filaments (PHFs) consist of two protofilaments wound around each other (Congdon et al., 2008). This has led to several proposed "nucleation-elongation" models of Tau fibril assembly (figure 5). In the classic equilibrium nucleation-elongation model elaborated for linear polymer formation, assembly-competent monomer is in rapid equilibrium with a thermodynamically unstable species termed the nucleus, in Tau case, probably the PHF-core (figure 4D). Once assembly-competent conformations are adopted (Weaver et al., 2000), the rate-limiting step in the reaction becomes dimerization, with subsequent aggregate growth occurring through monomer addition. When the critical nucleus cluster size is reached, subsequent additions to the nascent filament end are energetically favorable, and elongation proceeds efficiently (figure 5). This pathway leads to peaked distributions of filament lengths early in the reaction time series followed by slow relaxation toward exponential distributions at equilibrium. Finally, aggregation rates can be limited by secondary nucleation events, which occur on existing aggregates (Congdon et al., 2008). In addition, an alternative linear colloidal aggregation model has been proposed for Tau in which the protein forms colloidal spheres that serve as nucleation units that, through charge-dipole and dipole-dipole interactions, go on to form linear fibers (Xu et al., 2010). Either pathway seems that adoption of assembly competent conformations, perhaps
associated with enriched β-sheet content, can be driven by small diffusible ligands in a process that approximates homogeneous nucleation (Congdon et al., 2008).

Pathologic Tau fibrils show diverse morphologies in diseased brains, where transmission electron microscopy (TEM) images typically reveal PHFs in AD NFTs or neuropil threads, although straight filaments (SFs) and twisted ribbons (TRs) are also seen (Xu et al., 2010). Those protofibrils seem to be wound around one another exposing a crossover repeat of ~80 nm, a maximal width of ~22 nm, and a narrow waist of ~12 nm. The twisted appearance is variable as follows: ~10% of Tau fibrils are straight filaments (Wegmann et al., 2010). Additional morphologic variants of Tau fibrils have been observed in other Tauopathies such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick’s disease, and FTDP-17 syndromes. It seems that in these pathologies the crossover repeat is ~160 nm. Likewise, Tau fibrils reassembled in vitro can display a variable twist between filaments assembled from different variants of Tau proteins (e.g., different splicing variants) or even within a given filament (Wegmann et al., 2010). In the cellular environment protein expression, protein folding, and protein degradation are highly regulated processes. Protein

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Fig. 4. Characteristics of PHF-core. (A) Structure diagram and amino acid sequence of PHF core (Tau441). Although Tau presents a secondary random coil structure, the R2 and R3 of MTBD showed a motif with regional trend to β-sheet structure. (B) Amino acid distribution histogram of PHF core; they are partially hydrophobic; (C) Proposed core structure based on predicted β-strand propensities (Displayed in Jmol). (D) Electron Microscopy photograph of Tau aggregates induced by the presence of the PHF core.
over-expression can lead to protein aggregation, which also is a regulated process. The molecular machines, from the microtubular transport system which assists protein folding and prevents aggregation, to the ubiquitin proteasome system and autophagic vacuoles, which degrade normal and aggregated proteins all work in concert. In a healthy cell they can maintain the equilibrium between synthesis, folding, function and degradation (Zerovnik, 2010). Recent evidence suggests that proteins that are able to constrain the structural freedom of Tau are essential for Tau processing and participate in its accumulation. Interactions of Tau with a specific family of proteins termed cis-trans peptidyl-prolyl isomerases (PPIases) has already revealed the importance of this protein family to regulate Tau phosphorylation cycles and its overall stability (Koren et al., 2011). Pin-1 is demonstrated to interact with Tau through Thr231-P, promoting a conformational change that allows the action of phosphatase PP2A over Tau (Bulbarelli et al., 2009). Recent findings suggest that FKBP51 has a similar activity to Pin1; however, unlike Pin1, FKBP51 coordinates with Hsp90 to isomerize Tau. It also cooperates with distinct protein phosphatases that may also be novel participants in Tau biology. Recently is also suggested the participation of another isomerases like cyclophilin family, but is under research (Koren et al., 2011). In this matter chaperones, specially Hsp90, also can be necessary to maintain Tau in a non-aggregated state, a consequence that may ultimately be deleterious for the brain under pathological conditions (Koren et al., 2009).

The phenomena are not stopped there. The accumulation and propagation of amyloidogenic proteins like Tau are believed to occur through nucleation-dependent polymerization and propagate in an extracellular manner. Tau may be released to the extracellular space upon neuron degeneration, where it could be toxic to other neurons (Ávila, 2010; Gómez-Ramos et al., 2006). This suggests that high molecular weight protein aggregates or amyloid seeds shed from one cell may easily be propagated to others (e.g. neurons or glial cells) under pathological conditions (e.g. alteration in membrane permeability due to aging or virus infection, impairment of membrane function as a result of physical interaction or abnormal membrane depolarization) that favor intracellular deposition of protein fibrils (Nonaka et al., 2010). Further investigation about this must be done. Until now, there is still an incomplete understanding of the sequence of events leading to Tau fibrillization, and it is unclear how the different structural variants of Tau fibrils arise or if these variants (PHFs, SFs, TRs) are interconvertible (Xu et al., 2010). And as a recent issue, the importance of extracellular misfolded Tau during aggregation issues and cellular components such as plasma membrane or mislocalization (Campos-Peña et al., 2009; Lira-De León, 2009), need more investigations. With this last purpose, in cell-models we noticed the enrichment of β-sheet structures in cells expressing PHF-core with a signal promoting the localization of it into Plasma membrane associated to presence of 441-Tau (Campos-Peña et al., 2009). Further investigation in this aim needs complementary studies.

4. Conclusion

Structural studies of amyloidogenic fibrils are crucial. The insolubility and stability of fibrils makes difficult to work with by conventional methods. The research has concentrated on the use of peptides for structural studies, but the information obtained is complex for the different conditions used in the assembly of amyloidogenic fibrils in Tau or AB proteins. There is a minimum sequence with amino acids partially hidrofobic that trend to form a β-sheet structure, this region nucleating amyloidogenic fibril formation and is extremely insoluble.
Analysis of the amyloidogenic regions showed a high occurrence of the aromatic residues phenylalanine and tyrosine, which have a high propensity to stack the delocalized π-electron rings. Studies with short peptides have confirmed that even two consecutive phenylalanine residues are sufficient to facilitate assembly into nanotube-like structures. Protofibrils have been identified which appear to be fibrillar precursors to amyloidogenic fibril formation, and these are preceded by the appearance of small oligomers of Tau and AB. Whether these small intermediates interact directly to form protofibrils and then these elongate to form the fully formed fibril (figure 5). This process can be favored by interaction with membranes rich in negative charged surface, whereas the hydrophobic interior strengthens electrostatic secondary interactions and favors monomer recruitment with increase of local concentration, resulting in aggregate nucleation and membrane disassembly. Developing techniques for directly visualizing amyloidogenic fibrils at high resolution is promising solution to answer many key questions remain to be addressed. Elucidating these questions will undoubtedly reveal novel insights into diseases pathogenesis.

Fig. 5. Common fibrillization pathway of amyloid-β and Tau protein. Under physiological conditions, both proteins adopt a basal conformation (1), but when this is altered, they can adopt a pro-aggregatory conformation (enriched in β-sheet structures). This abnormal conformation (2) allows the formation of dimers and the beginning of a nucleation phase (3). Continuous recruitment of pro-aggregatory forms lead to an elongation phase (4); which finally ends in the formations of fibrils or pores (5).

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