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Contribution of Multivesicular Bodies to the Prion-Like Propagation of Lesions in Alzheimer's Disease

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1. Introduction

Alzheimer's disease (AD) is a chronic developing dementing disease characterized by coexistence of two types of lesions, the parenchymal amyloid deposits and the intraneuronal neurofibrillary tangles. Amyloid deposits are composed of amyloid-beta peptides that derive from sequential cleavages of its precursor named amyloid protein precursor (APP). Neurofibrillary tangles (NFT) results from intraneuronal aggregation of abnormally modified microtubule-associated Tau proteins. A synergistic relationship between the two lesions may trigger the progression of the disease. Thus, starting in the entorhinal cortex and slowly progressing through temporal, frontal, parietal and occipital cortex, the progression of NFT is well correlated with clinical expression of the disease. However, little is known about the mechanism underlying spatiotemporal propagation of these lesions ultimately leading to the disease. A growing number of studies suggest a prion-like diffusion of amyloid deposits and NFT, which could even be extrapolate to several other neurodegenerative diseases. In the present chapter, we will develop the current hypotheses regarding the molecular and cellular mechanisms driving the development and spreading of Alzheimer's disease lesions involving multivesicular bodies.

2. Alzheimer's disease

Alzheimer's disease is a slow and progressive disease affecting the brain and characterized by the loss of superior cognitive functions leading to dementia and death. Two neuropathological brain lesions are found in the brain tissue and their presence is instrumental for providing a definite diagnosis of the disease, as firstly described by Alois Alzheimer (Alzheimer, 1911). Amyloid deposits are amorphous parenchymal deposits of β -sheet ordered proteinaceous material. Amyloid deposition is observed with aging, in Alzheimer's disease, Down's syndrome, Dementia with Lewy bodies and vascular

dementia, all of which are aged-related neurodegenerative disorders. The major constituent of amyloid deposits is a small peptide of 39 to 43 amino acid residues, named A β for amyloid-beta peptide (Glenner and Wong, 1984), which derives from multiple and sequential cleavages of a larger precursor, named amyloid precursor protein (APP).

2.1 APP structure and metabolism

The amyloid precursor protein APP is encoded by a single *APP* gene located on the long arm of chromosome 21 at position 21q11.2 (Kang *et al.*, 1987; Goldgaber *et al.*, 1987). The gene spans more than 170kb and is constituted of 19 exons (Yoshikai *et al.*, 1990). Alternative splicing generates seven isoforms but there is a single neuronal isoform in human adult brain that is composed of 695 amino acids (Konig *et al.*, 1991). APP is a transmembrane protein with a large extra membrane domain, a transmembrane domain, and a short cytosolic tail composed of 59 amino acids (Fig. 1). The exact role of APP remains elusive but many functions have been proposed, for example APP was suggested to be instrumental to iron cellular homeostasis (Duce *et al.*, 2010), to regulate intracellular transport, to be a cell surface receptor, and some fragments derived from the cleavage of APP are suggested to be neuroprotective or to promote axon outgrowth (Chasseigneaux *et al.*, 2011) whereas others are related to an ancestral immunological mechanism of defense and would have antibacterial peptide property (Soscia *et al.*, 2010). However, the full spectrum of APP functions remains to be elucidated.

2.2 APP cleavage by secretases and amyloid production

Proteolytic cleavage of APP brings into play sequential events involving first the liberation of its ectodomain either by α - or β -secretase activities. These cleavages generate carboxy-terminal fragments remaining anchored to the plasma membrane and they shed extracellular soluble fragments, both of which are playing a role in axon outgrowth *in vitro* (Chasseigneaux *et al.*, 2011). The first cleavage to occur is mediated by α -secretase. This cleavage generates a soluble APP fragment α (sAPP α) and a carboxy-terminal α fragment composed of 83 amino acids (named C83 or CTF α). This cleavage takes place within the sequence of A β peptide thus precluding its formation. This pathway is therefore referred to as the non-amyloidogenic pathway. The α -secretase activity is carried by metalloproteases called ADAMs (for A Disintegrin And Metalloprotease). Several ADAM proteases with an α -secretase activity have been identified, including ADAM-17 or TACE (EC 3.4.24.86, peptidase family M12) (Buxbaum *et al.*, 1998), ADAM-10 (EC 3.4.24.81, peptidase family M12) (Lammich *et al.*, 1999; Lopez-Perez *et al.*, 2001), and ADAM-9 (EC 3.4.24.-) (Hotoda *et al.*, 2002; Koike *et al.*, 1999).

Alternatively to α -secretase, APP can be processed by β -secretase which can cleave at the first amino-terminal amino acid residue starting A β peptide sequence or at position 11, referred to as β' -cleavage. This β -cleavage generates a soluble fragment sAPP β and a CTF comprised of 99 amino acids (C99 or CTF β). This pathway is referred to as the amyloidogenic pathway. The protease responsible for both β - and β' -cleavage has been identified as BACE-1 (for β -site APP cleaving enzyme-1) (Memapsin 2, EC 3.4.23.46, peptidase family A1) (Hussain *et al.*, 1999; Lin *et al.*, 2000; Sinha *et al.*, 1999; Vassar *et al.*, 1999; Yan *et al.*, 1999). All APP-CTFs (CTF α , β' and β) can subsequently be cleaved at the juxtamembrane region by the γ -secretase. However, ectodomain cleavage of APP is mandatory to intramembrane γ -secretase proteolysis of APP-CTFs.

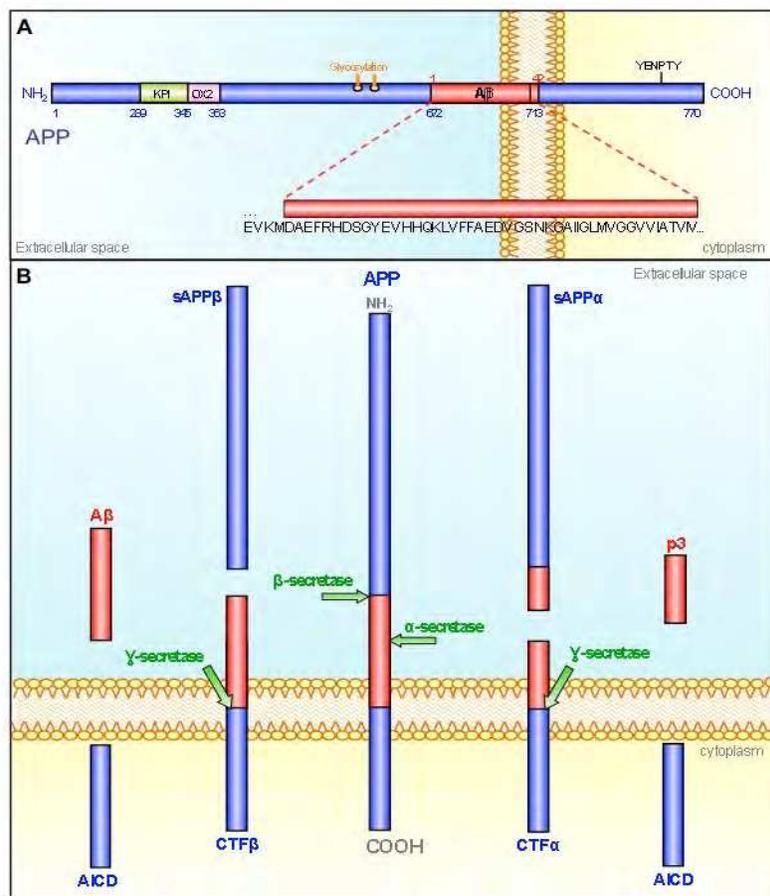


Fig. 1. Amyloid protein precursor structure and metabolism. (A) Schematic representation of APP structure. (B) APP processing by secretase activities. α - and β -secretase activities cleave APP in its extracellular domain to release respectively a soluble fragment sAPP α or sAPP β in the extracellular space and generate carboxy-terminal fragments CTF α or CTF β . These CTFs can subsequently be processed by γ -secretase to generate AICD and A β or p3.

The APP intracellular domain (AICD) is released from both CTF α and CTF β . The γ -secretase cleavage of CTF β represents the last step for A β production. The γ -secretase is a multiprotein complex composed of at least four proteins which are necessary and sufficient to form an active enzymatic complex (Edbauer *et al.*, 2003; Kimberly *et al.*, 2003; Takasugi *et al.*, 2003) which is composed of Presenilin (PS) (EC 3.4.23.-) (De Strooper *et al.*, 1998; Zhang *et al.*, 2000), Nicastrin (Esler *et al.*, 2002; Yu *et al.*, 2000), Aph-1 and Pen-2 (Bammens *et al.*, 2011; Francis *et al.*, 2002; Goutte *et al.*, 2002; Lee *et al.*, 2002; Steiner *et al.*, 2002; for review see Jorissen *et al.*, 2010). APP is not the unique γ -secretase substrate. This aspartyl protease belongs to the family of intramembrane-cleaving proteases, which also comprises the signal-peptide peptidases family of proteases (for review see Wolfe, 2010). Yet, more than 60 substrates of the γ -secretase have been characterized including APP (Jorissen *et al.*, 2010). Targeting the γ -secretase for drugs development that repress A β production is especially challenging due in part to the substrate-polyspecificity of this protease (For review see De Strooper *et al.*, 2010). However, recent data has shown that Gleevec/Imatinib, a tyrosine kinase inhibitor anti-cancer drug, could repress A β production without affecting γ -secretase cleavages of other substrates such as Notch (Netzer *et al.*, 2003; He *et al.*, 2010). Noteworthy,

A β production and release is repressed by Gleevec but AICD, which is released also from γ -secretase cleavage of APP-CTFs, is not repressed. Thus, two products that are supposedly generated by a same γ -secretase protease can be oppositely regulated; one is reduced the other is increased. However, A β is generated only from CTF β whereas AICD can be released from several APP-CTFs as for other γ -secretase substrates. This mechanism is also observed with alkalinizing drugs such as chloroquine, bafilomycin A1 and NH₄Cl (Schrader-Fischer and Paganetti, 1996; Vingtdeux *et al.*, 2007; Eisele *et al.*, 2007), also referred to as lysomotropic drugs. Although, alkalinizing drugs are known modifiers of intracellular and intravesicular pH, the molecular mechanism lowering A β production without modifying other γ -secretase substrate cleavages remain elusive. A mechanism has recently been proposed for Imatinib/Gleevec. Gleevec may repress the regulating function of a novel modulator of γ -secretase protease activity named GSAP (Gamma-Secretase Activating Protein) (He *et al.*, 2010). The substrate recognition of APP-CTFs is enhanced by GASP and consequently increases the production of A β . Gleevec represses GASP association to the γ -secretase complex leading to a selective lowering of A β production but not AICD or other γ -secretase substrates.

2.3 Cell localization of secretase activities and lysosome contribution

The α - and β -secretases are sheddases that release the extracellular domain of APP as well as several others type I transmembrane proteins. The cleavage and localization of enzyme activity is supposed to occur at the plasma membrane or in early endosomes. As for instance, BACE-1 resides within endosomes and APP endocytosis is a prerequisite for cleavage of APP by BACE1 and generation of A β (Ehehalt *et al.*, 2003; Vassar *et al.*, 1999; Walter *et al.*, 2001). BACE-1 optimal protease activity necessitates an acidic pH and acidification of endosome occurs during the route of endosomes to fuse with lysosomes where BACE1 is degraded (Koh *et al.*, 2005). Cleavage of APP-CTFs by γ -secretase can occur at several places in the cell (e.g. plasma membrane, endosomes...). Discrepancies exist regarding the cell localization of γ -secretase byproducts. Several APP metabolites including APP, APP-CTFs, A β and AICD have been shown to accumulate in multivesicular bodies following treatment of cells with alkalinizing drugs (Verbeek *et al.* 2002; Vingtdeux *et al.*, 2007). Interestingly and similarly to Gleevec, these alkalinizing drugs such as chloroquine, ammonium chloride, bafilomycin A1, block A β production without affecting AICD generation (Vingtdeux *et al.*, 2007). AICD can be released outside the cell and also inside the cell, reach the nucleus (Goodger *et al.*, 2009) where AICD may regulate gene expression (Pardossi-Piquard *et al.*, 2005). Interestingly, intracellular AICD may be generated from APP-CTFs produced from β -secretase (Belyaev *et al.*, 2010). However, further investigation is needed to determine whether there is one or several AICD and what is the function of AICD. For instance, BACE1 cleavage of APP and AICD derived from β CTF may contribute to learning, memory and neuronal plasticity (Ma *et al.*, 2007).

2.4 Neurofibrillary tangles and microtubule-associated Tau

Neurofibrillary tangles are characterized by intraneuronal accumulation of fibrillar material named paired helical filaments. Abnormally modified Tau proteins are the major components of this filamentous material. Tau proteins belong to the family of microtubule-associated proteins. A single gene, named *MAPT* located at position 17q21 encoded for several isoforms resulting from alternative splicing of exons 2, 3 and 10 in the human adult

brain. Thus, they are six isoforms, half of which contains the exon-10 encoding sequence, two-third are having the exon 2 whereas the exon 3 is found in one-third of Tau isoforms. In the human brain, Tau proteins constitute a family of six isoforms (six mRNAs) that range from 352 to 441 amino acids. Their molecular weight ranges from 45 to 65 kDa when resolved on polyacrylamide gel electrophoresis in presence of sodium dodecyl sulfate (SDS-PAGE). The Tau isoforms differ from each other by the presence of either three (3R) or four repeat-regions (4R) in the carboxy-terminal (C-terminal) part of the molecule and the absence or presence of one or two inserts (29 or 58 amino acids) in the amino-terminal (N-terminal) part (Goedert *et al.*, 1989a; Goedert *et al.*, 1989b; Andreadis *et al.*, 1992). Each of these isoforms is likely to have particular physiological roles since they are differentially expressed during development. For instance, only one Tau isoform, characterized by 3R and no N-terminal inserts, is present during fetal stages, while the six isoforms (with one or two N-terminal inserts and 3 or 4R) are expressed during adulthood (Goedert and Jakes, 1990; Kosik *et al.*, 1989). Exons 2 and 3 are alternatively spliced in the brain whereas included in muscle (Leroy *et al.*, 2006). Thus, Tau isoforms are likely to have specific functions related to absence or presence of regions encoded by cassette exons 2, 3 and 10. Furthermore, the six Tau isoforms are not equally expressed in neurons. For example, Tau mRNAs containing exon 10 are not found in granular cells of the dentate gyrus (Goedert *et al.*, 1989a). Thus, Tau isoforms are differentially distributed in neuronal subpopulations.

Tau proteins bind microtubules through repetitive regions in their C-terminal part. These repetitive regions are the repeat domains (R1-R4) encoded by exons 9-12 (Lee *et al.*, 1989). The three (3R) or four copies (4R) are made of a highly conserved 18-amino acid repeat (Goedert *et al.*, 1989b, Himmler, 1989, Lee *et al.*, 1988, Lee *et al.*, 1989) separated from each other by less conserved 13- or 14-amino acid inter-repeat domains. Tau proteins are known to act as promoter of tubulin polymerization *in vitro*, and are involved in axonal transport (Brandt and Lee, 1993; Cleveland *et al.*, 1977a; Weingarten *et al.*, 1975). They have been shown to increase the rate of microtubule polymerization, and to inhibit the rate of depolymerization (Drechsel *et al.*, 1992). The 18-amino acid repeats bind to microtubules through a flexible array of distributed weak sites (Butner and Kirschner, 1991, Lee *et al.*, 1989). It has been demonstrated that adult Tau isoforms with 4R (R1-R4) are more efficient at promoting microtubule assembly than the fetal isoform with 3R (R1, R3-R4) (Butner and Kirschner, 1991; Goedert and Jakes, 1990; Gustke *et al.*, 1994). Interestingly, the most potent part to induce microtubule polymerization is the inter-region between repeats 1 and 2 (R1-R2 inter-region) and more specifically peptide 274KVQIINKK281 within this sequence. This R1-R2 inter-region is unique to 4R Tau (since it occurs between exons 9 and 10), adult-specific and responsible for differences in the binding affinities between 3R and 4R Tau (Goode and Feinstein, 1994). Recent evidence supports a role for the microtubule-binding domain in the modulation of the phosphorylation state of Tau proteins. A direct and competitive binding has been demonstrated between residues 224-236 (according to the numbering of the longest isoform) and microtubules on one hand, and residues 224-236 and protein phosphatase 2A (PP2A) on the other hand (Sontag *et al.*, 1999). As a consequence, microtubules could inhibit PP2A activity by competing for binding to Tau at the microtubule-binding domains. The lysine residue 280 is crucial for microtubule-binding of 4R Tau. This lysine is mutated in genetic form of FTDP-17 and promotes Tau aggregation *in vitro* and *in vivo* (Fischer *et al.*, 2007; Eckermann *et al.*, 2007). Much more recently, acetylation of Tau has been shown to regulate microtubule-binding of Tau (Min *et al.*, 2010; Cohen *et al.*, 2011). Histone acetyl transferase P300 or CREB-binding protein (CBP) and

deacetylase SIRT1 or HDAC6 likely regulate the acetylation of Tau (Min *et al.*, 2010; Cohen *et al.*, 2011). Moreover, Tau-acetylation is suggested to promote Tau aggregation and is observed in animal models, Alzheimer's disease and brain tissues of patients with Tauopathies, at the exception of Pick's disease where Pick bodies are negative for acetylated lys-280 as well as phosphorylation at ser-262 (Cohen *et al.*, 2011; Sergeant *et al.*, 1997; Probst *et al.*, 1996). However, due to selective aggregation of 3R Tau in Pick's disease (Delacourte *et al.*, 1996; Sergeant *et al.*, 1997), acetylation of 3R Tau on another lysine residue cannot be precluded.

Besides its major microtubule-binding, -stabilizing, paralleled-ordering functions, Tau also has other functions. Tau proteins bind to spectrin and actin filaments (Carlier *et al.*, 1984, Correas *et al.*, 1990, Henriquez *et al.*, 1995, Selden and Pollard, 1983). Through these interactions, Tau proteins may allow microtubules to interconnect with other cytoskeletal components such as neurofilaments (Miyata *et al.*, 1986; Andreadis *et al.*, 1995) and may restrict the flexibility of the microtubules (Matus, 1990). There is also evidence that Tau proteins interact with cytoplasmic organelles. Such interactions may allow for binding between microtubules and mitochondria (Jung *et al.*, 1993). The Tau N-terminal projection domain also permits interactions with neural plasma membrane (Brandt *et al.*, 1995). Thus, Tau may act as a mediator between microtubules and plasma membrane. This interaction has been defined as involving a binding between the proline-rich sequence in the N-terminal part of Tau proteins and the SH3 domains of Src-family non-receptor tyrosine kinases, such as Fyn. Studies have determined that human Tau Tyr18 and Tyr29 are phosphorylated by the Src family tyrosine kinase Fyn (Lee *et al.*, 2004; Williamson *et al.*, 2002). The same proline-rich region of Tau proteins is likely involved in the interaction with phospholipase C- γ (PLC- γ) isozymes (Jenkins and Johnson, 1998; Hwang *et al.*, 1996). Hwang and colleagues have demonstrated in vitro that Tau proteins complex specifically with the SH3 domain of PLC- γ , and enhance its activity in the presence of unsaturated fatty acids such as arachidonic acid. These results suggest that in cells that express Tau proteins, receptors coupled to cytosolic phospholipase A2 may activate PLC- γ indirectly, in the absence of the usual tyrosine phosphorylation, through the hydrolysis of phosphatidylcholine to generate arachidonic acid (Jenkins and Johnson, 1998; Hwang *et al.*, 1996). Altogether, these data indicate that Tau proteins may also play a role in the signal transduction pathway involving PLC- γ (for review see Rhee, 2001). In line with this idea, recent data demonstrate that Tau is necessary for glutamatergic signaling (Ittner *et al.*, 2010).

2.5 The cortical brain spreading of neurofibrillary degeneration

With aging, neurofibrillary tangles are affecting the entorhinal cortex followed by the hippocampal formation. At this stage, no clear clinical symptoms are associated with the presence of these lesions and they are therefore considered as an aging-associated phenomenon. But this remains an open debate. Indeed, neuropathological as well as biochemical approaches show that Tau pathology of Alzheimer's disease spreads progressively, invariably, hierarchically, from the transentorhinal cortex to the whole neocortex, along cortico-cortical connections. The brain regions that are sequentially affected explain well the successive types of cognitive impairments that characterize the disease: amnesia following the entorhinal and hippocampal degeneration; aphasia, apraxia and agnosia with the involvement of the neocortex. Of course, amyloid and Tau pathology are present before the clinical symptoms, because neuronal plasticity is able to compensate at the first AD stages. Our studies show that Tau pathology is already distributed in the

hippocampal formation and the temporal cortex at the “pre-clinical” stage of AD (Delacourte *et al.*, 1999, 2002).

PHF-Tau pathology, visualized as a triplet of abnormal Tau proteins, was systematically present in variable amounts in the entorhinal and hippocampal regions of non-demented patients aged over 75 years. When Tau pathology was found in other brain areas, it was always along a stereotyped, sequential, hierarchical pathway. The progression was categorized into 10 stages according to the brain regions affected: transentorhinal cortex (S1), entorhinal (S2), hippocampus (S3), anterior temporal cortex (S4), inferior temporal cortex (S5), mid temporal cortex (S6), polymodal association areas (prefrontal, parietal inferior, temporal superior) (S7), unimodal areas (S8), primary motor (S9a) or sensory (S9b, S9c) areas, and all neocortical areas (S10). Up to stage 6, the disease could be asymptomatic. In all cases of our study, stage 7 individuals with two polymodal association areas affected by Tau pathology were cognitively impaired. Since the neuropathological observation of this stereotype cortical brain progression of Tau pathology (Braak and Braak, 1991; Duyckaerts *et al.*, 1997) is the question of how does neurofibrillary degeneration is selective toward neuronal subpopulations of cortical brain layers III and V (Hof *et al.*, 1990) and progressively propagates through brain structures.

3. Multivesicular bodies and exosomes

3.1 Multivesicular bodies

During endocytosis, some of the extracellular components, such as viruses, ligands or diffusible factors and, part of the plasma membrane proteins are internalized and are either recycled to the cell surface via early endosomes and recycling endosomes or will be address through a set of vesicular compartments: early endosomes, late endosomes and finally delivered to lysosomes for degradation (for review see Gruenberg, 2009). Late endosomes are also known as multivesicular endosomes or multivesicular bodies (MVBs) (Gruenberg and Stenmark, 2004; Raposo and Marks, 2007) and are prerequisite before degradation of internalized material by fusion with lysosomes. Multivesicular bodies are large vesicles of several hundred nanometers that are characterized by numerous smaller intraluminal vesicles (ILVs) formed by the inward budding of the endosome limiting membrane. The formation of these intraluminal vesicles requires sequential steps and the contribution of complex multi molecular machinery named ESCRT for Endosomal Sorting Complex Required for Transport. The ESCRT machinery is composed of four ESCRT complexes (0, I, II and III) acting sequentially to sort cargo and to form a coated subdomain on endosomes that forms the ILVs (Fig. 2). The Vps27/Hrs-Hse1/STAM complex (ESCRT-0) is first recruited to the endosomes by binding PI(3)P and ubiquitinated cargos. ESCRT-0 then recruits ESCRT-I (composed of Tsg101/Vps23-Vps28-Vps37) to the membrane, where ESCRT-I interacts with ubiquitinated cargos via its Vps23 subunit. Then, ESCRT-I recruits ESCRT-II complex (composed of Vps22/Eap30-Vps25/Eap25-Vps36/Eap45), which in turn initiates the oligomerization of ESCRT-III complex (composed of Vps2/CHMP2-Vps20/CHMP6-Vps24/CHMP3-Snf7/Vps32/CHMP4). Finally, ESCRT-III recruits supplementary factors like Bro1 and Vsp4 AAA ATPase. Bro1 will recruit a deubiquitination enzyme whereas Vps4 AAA ATPase will work to break apart ESCRT-III and other ESCRT complexes, resulting in their dissociation from the membrane. Evidences for alternative pathways for cargos sorting into MVBs are emerging, which are independent of the ESCRT machinery but seems to depend on lipid composition of raft-based micro domains. Proper

cholesterol levels in late endosomes generated by ORPs (oxysterol-binding protein-related proteins) are required for normal MVBs formation and MVB-mediated membrane protein degradation (Kobuna *et al.*, 2010).

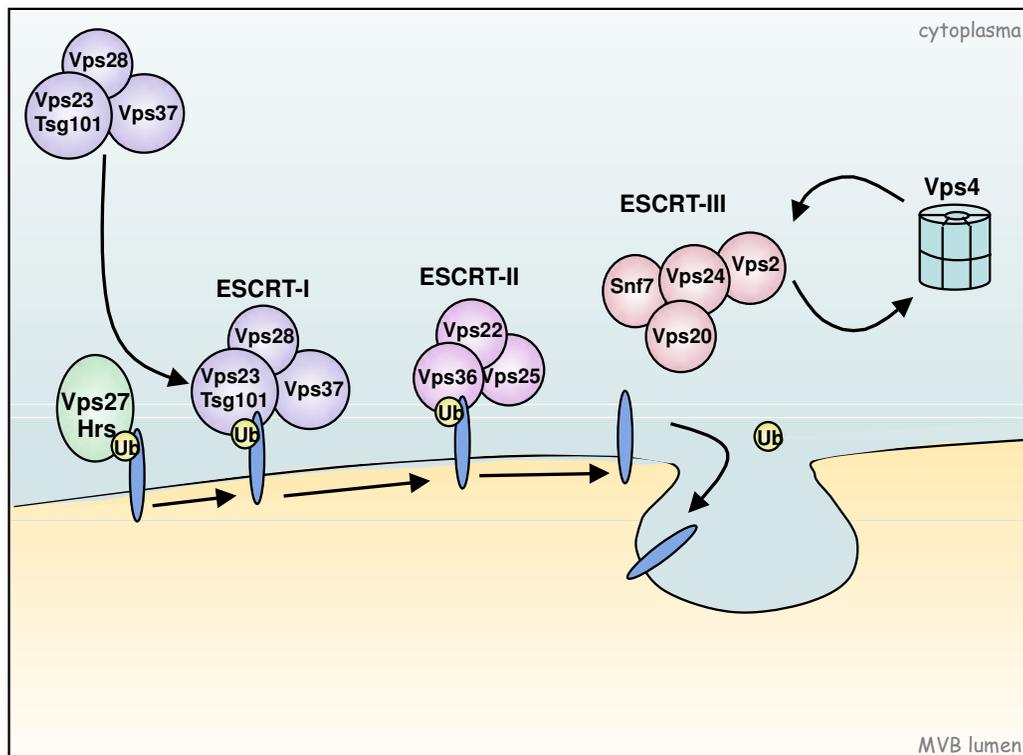


Fig. 2. Model for the ubiquitin-dependent sorting of proteins by the ESCRT machinery. The different ESCRT complexes act sequentially for the recognition and sorting of ubiquitinated transmembrane proteins into the internal vesicles of multivesicular bodies.

The phospholipid LBPA (lysobisphosphatidic acid) possessed the capacity to drive the formation of membrane invaginations within acidic liposomes. Alix controls this invagination process *in vitro* and the organization of LBPA-containing endosomes *in vivo* (Matsuo *et al.*, 2004). These micro domains also contain high concentrations of sphingolipids from which ceramide are formed. Ceramide induced the coalescence of small microdomains into larger domains, which promotes domain-induced budding. In addition ceramide cone-shaped structure might induce spontaneous negative curvature by creating an area difference between the membrane leaflets (Trajkovic *et al.*, 2008). Ubiquitination (Ub) is the main sorting signal for cargo entry into the vesicles that bud from the limiting membrane into the lumen of endosomes during the biogenesis of MVBs. A single Ub is sufficient to direct ILV targeting. Ub is recognized by an expanding cohort of endosomal proteins, which may act as Ub-sorting receptors responsible for binding and directing cargo toward ILVs like some ESCRT subunits, including Vps27/Hrs, Vps23/Tsg101 and Vps36/Eap45 (For review see: Piper and Katzmann, 2007). Many integral membrane proteins targeted for lysosomal degradation are ubiquitinated; however, non-ubiquitin sorting signals have also been described. Much less is known about non-Ub signals that sort proteins to ILVs; proteins which have been described to enter ILVs in an Ub-independent manner include Pmel17/Silver (Berson, 2003), TfR (Geminard, 2004), Nedd4 (Morita and Sundquist, 2004),

sna3 (McNatt, 2007; Oestreich 2007). Two motifs 'NTR' and 'PKD' located on the extracellular part of Pmel17 are responsible for its targeting into the internal vesicles of MVBs (Theos *et al.*, 2006) and COP9 signalosome (CSN)-associated protein CSN5 is involved in protein sorting into ILVs since siRNA of CSN5 causes a significant increase in both ubiquitinated and non-ubiquitinated proteins detected in exosomes (Liu *et al.*, 2009).

Genetic also supports the importance of functional MVB in neurological disease and frontotemporal dementia. Thus, the gene encoding the ESCRT-III subunit CHMP2B was found to be mutated in a form of frontotemporal dementia (Skibinski *et al.*, 2005) and amyotrophic lateral sclerosis (Cox *et al.*, 2010) suggesting that functional MVBs are required to prevent accumulation of abnormal proteins that can disrupt neural function and ultimately lead to neurodegeneration (Filimonenko *et al.*, 2007). Mutations in *CHMP2B* were first described in Danish and Belgian families but remain rare (Ghanim *et al.*, 2010). Mutations are supposed to lead to C-terminal truncation of CHMP2B. Brain tissue examination of patient with *CHMP2B* mutation showed enlarged vacuoles stained with a mannose-6-phosphate receptor antibody. The truncated protein impairs the fusion of endosome with lysosomes without obvious modification of protein sorting to MVB (Urwin *et al.*, 2010). Staining of tissue from Alzheimer disease patients with CHMP2B showed an accumulation of the protein in vesicular structures resembling GranuloVacuolar Degeneration (Yamazaki *et al.*, 2010; Funk *et al.*, 2011) suggestive of defective autophagic and endocytic pathways in Alzheimer disease. Thus, restoring or enhancing the lysosomal degradation and rates of autophagic protein turnover in a transgenic animal model of amyloid deposition can rescue the phenotype and decrease the amyloid burden (Yang *et al.*, 2011). Together, a defective function of the endocytic pathway including MVB, autophagy and lysosome may certainly contribute to the development of Alzheimer disease.

3.2 Exosomes

Alternatively to their fusion with lysosomes for degradation of their contents, MVBs have been described to fuse with the plasma membrane and release their content in the extracellular space, the ILVs contained in the MVBs when released are known as exosomes. Exosomes have a size ranging from 40 to 100 nm and can be secreted by many cell types including neuronal cells (Faure J *et al.*, 2006; Rajendran *et al.*, 2006; Vingtdeux *et al.*, 2007; Lachenal *et al.*, 2010). Exosomes are isolated from the media of cultured cells. However, purification of exosomes is not trivial since membrane fragments or cell debris can easily contaminate exosome preparation. Due to their small size, exosomes are obtained after filtration on 0.22 μm filters and by a series of centrifugation and sucrose gradient (Raposo *et al.*, 1996; Wubbolts *et al.*, 2003; Faure *et al.*, 2006; For review see Olver and Vidal, 2007). Further immunoisolation can be used (Wubbolts *et al.*, 2003). Several parameters should be evaluated to ascertain the purity of exosomes preparation. The first and likely most important characteristic is the observation of exosomes by transmission electron microscopy. Several proteins are also common to exosomes and described in exosomes preparation that originate from different sources (For review Vella *et al.*, 2008). Interestingly, several tetraspanins proteins are enriched in exosomes and may contribute to exosomes formation (De Gassart *et al.*, 2004; Wubbolts *et al.*, 2003). Tetraspanins are a growing family of transmembrane proteins with pleiotropic functions found associated with lipid-raft micro domains (for review Hemler *et al.*, 2005). Interestingly, tetraspanins CD81 and CD9, which are found in exosomes derived from B-cells (Wubblots *et al.*, 2003), are co-purified with the γ -secretase interactome. Absence of those tetraspanins induces a partial disruption of γ -

secretase activity or reduces γ -secretase substrate interaction (Wakabayashi *et al.*, 2009). Although detailed molecular mechanisms remain unknown, together those results further support the idea that MVB and most possibly exosomes are important cellular compartments for APP metabolism regulation and that several γ -secretase regulators may act at this level.

Little is known about the requirements and regulation of MVBs fusion with the plasma membrane and the release of exosomes outside cells. Recently, in primary neuronal culture cell, release of exosomes by neurons was shown to be regulated by glutamatergic signaling (Lachenal *et al.*, 2010). Calcium ionophores stimulate exosomes release in some cell types suggesting that intracellular calcium levels also play a role in plasma membrane fusions event. The Rab family of GTPase proteins seems to be required for exosomes release. Rab11, a well-known regulator of endosomal recycling, has been linked to the control of exosomes release in K562a cells (Savina *et al.*, 2005). Silencing of five other Rab proteins, Rab2b, Rab9a, Rab5a, Rab27a and Rab27b inhibited exosomes secretion. Rab27a and Rab27b function in MVBs docking to the plasma membrane (Ostrowski *et al.*, 2010). Inhibition of Rab35 function leads to intracellular accumulation of endosomal vesicles and impairs exosomes secretion possibly by controlling the docking/tethering of endocytic vesicles with the plasma membrane (Hsu *et al.*, 2010). MVBs fate can be affected by macroautophagy (hereafter referred to as autophagy). During autophagy, parts of the cytoplasm and organelles are encapsulated in double-membrane vacuoles called autophagosomes, which eventually fuse with lysosomes for degradation (for review see Levine *et al.*, 2011). Under conditions that stimulate autophagy, MVBs are diverted to autophagic pathway with subsequent inhibition in exosomes secretion (Fader *et al.*, 2008). With regards to Tau, the autophagy-lysosomal pathway contributes to the degradation of Tau (Wang *et al.*, 2009).

How exosomes are processed in recipient cells is not yet fully understood. Exosomes are able to be endocytosed into the endosomal system of recipient cells. Once internalized, exosomes could fuse with the limiting membrane of endosomes to deliver their cytoplasmic content into the host cell cytoplasm. It is also possible that exosomes could directly fuse with the plasma membrane. Although their exact function remains to be discovered, within the extracellular space and in biological fluids such as urine or serum, exosomes have been proposed to participate in different physiological and/or pathological processes such as neurodegenerative diseases (for review see Vella *et al.*, 2008). They could be responsible not only for protein and lipids exchange between cells, but also for mRNA and microRNAs exchange (Valadi *et al.*, 2007). Exosome release and content may be regulated by cellular stress. Thus DNA damage and activation of p53 induce the expression of protein that will be included inside exosomes (Yu *et al.*, 2006). Exosomes may mediate a signal of cellular damage or stress. In the central nervous system, exosomes are proposed to constitute an intercellular communication system (for review see Mathivanan *et al.*, 2011). AICD and several APP metabolites are found in exosomes derived from primary neuronal cultured cells (Vingtdeux *et al.*, 2007) (Fig. 3). L1 CAM that is also processed by γ -secretase (Riedle *et al.*, 2009) is recovered in exosomes (Lachenal *et al.*, 2011). Although speculative, if several intracellular domains of proteins processed by γ -secretase are internalized and secreted within exosomes, the fusion of those exosomes with surrounding cells may regulate gene expression by those intracellular domains and therefore constitute a cell communication system.

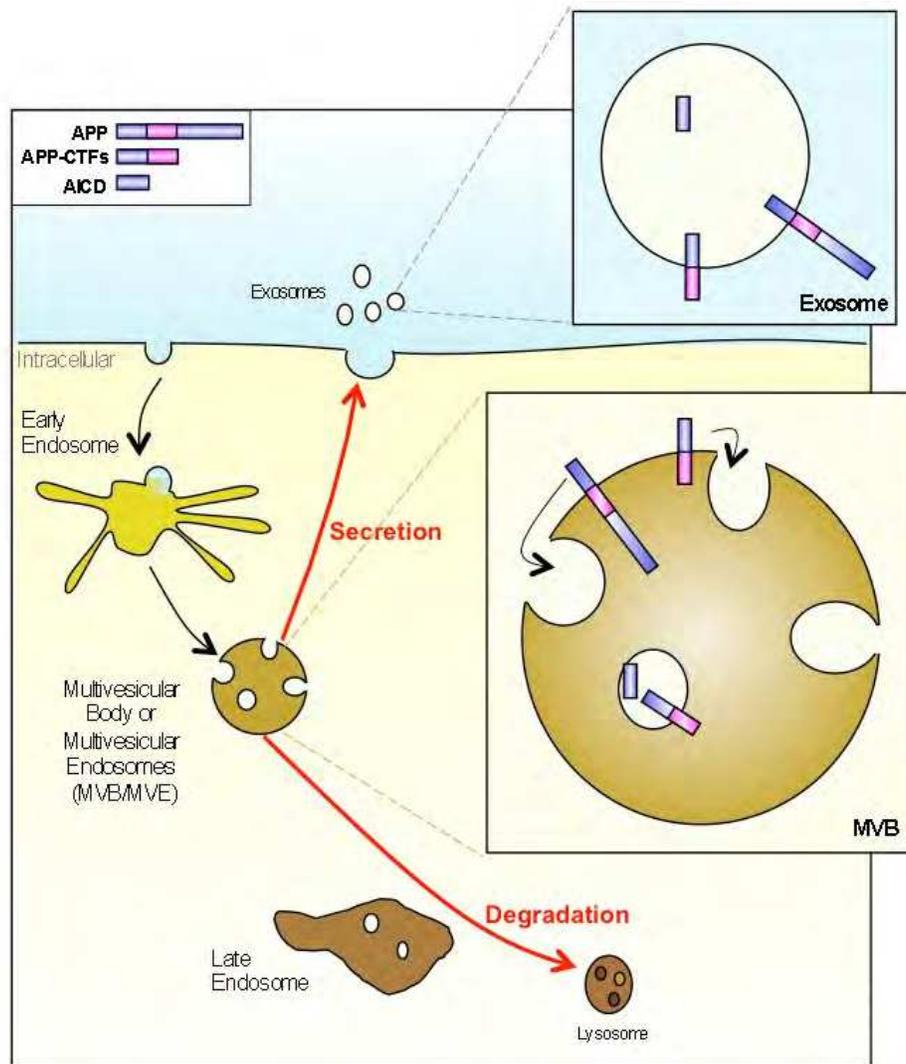


Fig. 3. APP and its metabolites are present in multivesicular bodies and exosomes. APP and APP-CTFs are internalized and directed into the internal vesicles of multivesicular bodies (MVB). At this point APP and its metabolites can either be degraded after the fusion of MVB with lysosomes or can be released in the extracellular space in association with exosomes consecutively to the fusion of MVB with the plasma membrane.

4. Prion-like propagation of amyloid and Tau pathology

Besides being a potential system of intercellular communication, exosomes are also known to be instrumental to the dissemination of pathogens, whether those are viruses or proteinaceous pathogens. The first pathological protein described associated with exosomes was the prion protein (PrP) (Fevrier *et al.*, 2004; Alais *et al.*, 2008). Prions diseases are fatal neurodegenerative disorders. They are associated with the conversion of the cellular prion protein (PrP^c) into the scrapie PrP (PrP^{Sc}), an abnormal conformational state that tends to form amyloid deposits in brain tissue leading to dementia. Into its misfolded conformation the PrP^{Sc} is thought to be infectious (For review see Aguzzi and Rajendran, 2009). Recent findings revealed an unexpected role for exosomes in vehiculation of prions: exosomes from prion-infected neuronal cells have been demonstrated to be efficient initiators of prion

propagation in uninfected recipient cells and, more importantly, to produce prion disease when inoculated into mice.

4.1 Amyloid propagation

Exosomal release instead of lysosomal processing might be of advantage to cells that have poor degradative capacities. In the context of AD, exosomes secretion could be a way to dispose of unwanted proteins. Indeed, maturation of autophagolysosomes and their retrograde transport are impeded in AD. The underlying mechanism behind the hypothesis that neurodegeneration in AD is triggered by proteins spread, cell-to-cell, throughout brain areas could be the shipping of toxic agents such as A β or Tau by exosomes. What at the beginning would be beneficial (to bypass a degradation system which is overwhelmed) could become the reason why there is propagation of the disease thorough the brain. A β peptides are released by cells in association with exosomes (Rajendra *et al.*, 2006) and interestingly, exosomal proteins such as Alix and flotillin-1 were observed around neuritic plaques, a lesion found in brains from AD patients (Rajendran *et al.*, 2006) suggesting that exosomes-associated A β could be involved in plaque formation. MVBs are an intracellular compartment where internalized A β can grow into fibrils thereby MVBs may also contribute to amyloid plaque formation (Friedrich *et al.*, 2010). Overall these results suggest that exosomes could play a role in the pathogenesis of AD.

4.2 Tau pathology propagation

The stereotype propagation scheme of neurofibrillary degeneration in AD is evidenced by neuropathological examination as well as biochemical analyses but until recently, hypotheses and experiments trying to address this question remained elusive. Neurofibrillary degeneration is following cortico-cortical connections therefore suggesting a loss of neurotrophic factor or a diffusible factor responsible for a cascade of molecular events leading to Tau aggregation and neuronal death. However, what is this propagating factor? What if Tau itself wouldn't be the "missing link"? Thus, recent data suggest that neurofibrillary degeneration cortical spreading could follow a transmissible prion-like process. In fact, aggregates of PHF-Tau were purified from a transgenic mice model of neurofibrillary degeneration. Intracranial injection of this preparation was done in a different mouse model, which overexpresses human Tau protein but does not display Tau pathology. Following the injection, development of a Tau pathology was observed. This pathology progressed from the injection site to neighboring brain structures, suggestive of a propagating mechanism (Clavaguera *et al.*, 2010). However, results show that PHF-Tau are sufficient to promote the transformation of normal human Tau into "pathological Tau" leading to the formation of neurofibrillary degeneration, the prototypical neuropathological lesion of Alzheimer disease. However, how an extracellular transmissible agent could reach the intracellular compartment to transform the normal protein remains an open question. Very recently, Frost and collaborators have shown using a cell-based system that extracellular Tau aggregates are internalized inside cells and promote the mis-folding and fibrillization of Tau (Frost *et al.*, 2009). Internalization of preformed Tau fibrils is facilitated by the use of a lipid-based protein delivery system (BioPorter®) and is likely mediated by endocytosis (Guo *et al.*, 2011). Moreover, in addition to transmissibility of Tau-fibril conformation, the internalized preformed fibrils reduce microtubule-stabilization suggesting a loss-of-function of normal Tau in infected cells. Although, the mechanisms of

Tau fibrils diffusion remain elusive *in vitro* and *in vivo* arguments strongly support the notion of prion-like transmissibility of Tau-PHF in Alzheimer's disease and possibly in other Tauopathies. There are some evidences suggesting that Tau may be secreted and secretion of Tau may differ depending of Tau isoform. Thus, Tau isoforms with exon 2 encoding sequence are likely not secreted and this exon 2 sequence is therefore suggested to repress Tau secretion (Kim *et al.*, 2010). However, it is not known how Tau is secreted, exosomes? Preliminary study suggests that Tau is not in the exosomes derived from primary embryonic neuronal culture cells (Fauré *et al.*, 2006). Further work is therefore needed to determine how Tau is secreted and by which cell-based mechanism. A good example of such a dilemma is fibroblast growth factor 2 that is a secreted growth factor without any signal peptide and that is also found in cell nucleus following its interaction with its cognate receptors (Meunier *et al.*, 2009). Tau is likely secreted and is also located into the nucleus following stress conditions (Sultan *et al.*, 2011). Tau secretion, as for Tau nuclear localization, may depend upon yet undefined conditions and therefore, contributions of MVB-exosomes pathways or autophagy-lysosomal pathways (Wang *et al.*, 2009) remain completely open. Recent data strongly suggest that both pathways are possibly interconnected (Sahu *et al.*, 2010). With regards to Tau, the degradation systems may bring insights for the potential routing of Tau to MVB-exosomes or autophagy lysosome pathway. In NFT or more generally in aggregates, Tau is found ubiquitinated, thus suggesting that Tau may be processed by the proteasome (David *et al.*, 2002). Ubiquitin-independent degradation system, such as the caspase or calpain cleavage of Tau have also been described (Berry *et al.*, 2003; Carrettiero *et al.*, 2009; Delobel *et al.*, 2005; Ding *et al.*, 2006; Ferreira *et al.*, 2011) The autophagy-lysosomal pathway contributes to the degradation of Tau via the chaperone-mediated autophagy (CMA) (Wang *et al.*, 2009; for review see Wang *et al.*, 2010). The CMA is a lysosome-mediated degradation system of cytosolic protein (for review see Arias *et al.*, 2010). This system implies the recognition of substrates by a complex of chaperones and translocation of substrates inside lysosomes for further degradation. The CMA malfunction has been connected to the development of several neurodegenerative diseases including Parkinson disease and Alzheimer Disease (Arias *et al.*, 2010). Although speculative and purely hypothetic, through the use of CMA, aggregates of proteins or even oligomers could reach the lysosome and due to their low sensitivity to degradation (e.g. Tau aggregates), the fusion of lysosome with other vesicular structures such as MVB could finally lead to the release of aggregates outside the cell and contribute to their propagation following neuronal connections. Alternatively, proteins such as Tau would normally be addressed to lysosome by the CMA system but a defective lysosome could be the place where oligomers are generated and thereafter route to MVB/exosome pathway. However, further work is definitely needed to get insights into these mechanisms.

5. How to explain the selective patterns of neurodegeneration in Tauopathies?

Conceptually, how could we imagine that prion-like spreading of misfolded proteins could reproducibly cause selective patterns of neurodegeneration and skipping nearby "less vulnerable" neuronal targets. That's certainly a major fundamental question to address, which to date remains with no clear answer even in prion disease. Why is the brain affected in prion diseases and no other organs? Why in this scheme of spatiotemporal spreading and propagation of lesions in Alzheimer disease and other tauopathies only selective neuronal

subpopulations are affected. As for instance, affected neurons in Alzheimer disease essentially belong to the cholinergic system. One possibility would be that selectivity of propagation could follow neuronal circuitry through synaptic transmission. This is possible if exosomes are preferentially released at the synaptic junction, as suggested by Smalheiser (2007). They are strong evidences that exosomes are produced and secreted by neurons (Lachenal *et al.*, 2011). However, the demonstration derives from *in vitro* experiments using primary neuronal embryonic culture cells. Study of exosomes in tissue yet remains highly challenging. Consequently, little if not nothing is known about the cell localization of exosomes release and their propensity of diffusion *in vivo*. They are therefore other possibilities, such as the tunneling nanotubes (for review see Goedert *et al.*, 2010). Tunneling nanotubes are fine membrane channels that have recently been described in mammalian cells for communication between cells but also for cell-to-cell propagation of misfolded prion proteins (for review see Gerdes *et al.*, 2007; Gousset *et al.*, 2009). These tunneling nanotubes could also propagate other transmissible misfolded proteins but the question of selectivity of transmission remains however open. Coming back to exosomes and now considering that exosomes release and secretion is controlled and localized to pre- or post-synaptic locations then several hypotheses can be postulated. In both pre- and post-synaptic situations propagation through exosomes would be closely dependent upon neuronal connections, as far as the diffusion of exosomes is following a paracrine or "juxtacrine" rule of diffusion (Mathivanan *et al.*, 2010). Thus, only interconnected neurons would disseminate toxic species via exosomes. We can also imagine that exosomes originating from different type of neurons (e.g. cholinergic, GABAergic, glutamatergic...) and may contain specific membrane associated biomarkers. Intercellular communication mediated by exosomes may result from passive fusion of exosome membrane with the plasma membrane of the targeted cell or may use a ligand receptor system. In line with the latter system, the selectivity of intercellular communication could result from specific interaction between ligand and receptor. They are several examples that could illustrate a selectivity of propagation of exosomes using this ligand receptor selectivity. For instance, protocadherin is a cluster of 52 cadherin-like genes with a singular organization. The amino-terminal region of protocadherins is encoded by three sets of separate exons arranged in three clusters (alpha, beta and gamma). N-terminal encoding exons are spliced with one of three carboxy-terminal encoding exons. Alternative splicing generates an extraordinary diversity of protocadherin isoforms suggested to confer selective and specific intermolecular membrane-associated protein interactions (Wu *et al.*, 2000; Wang *et al.*, 2002). The second example is DSCAM, the *Drosophila* homolog of human Down syndrome cell adhesion molecule that belongs to the axonal guidance receptor family. Alternative splicing of DSCAM can generate as many as 38016 mRNA isoforms and therefore lead to expression of huge protein diversity (Schmucker *et al.*, 2000). More interestingly, one DSCAM protein isoform binds exactly to the same isoform but not a slightly different one, making the binding of DSCAM isoforms very stringent (Wojtowicz *et al.*, 2004). As for DSCAM, the selectivity of transmission pattern could be mediated following an axonal guidance-like system. In a very simplified view, axonal guidance is driven by equilibrium between attractive and repulsive signals through specific signaling pathways, allowing axonal growth and connection to its specific neuronal target (for review see Bashaw and Klein, 2011). Thus exosomes release from one type of cell will be attracted by its target cell and repulsed by surrounding cells. Altogether, examples provide could contribute to neuronal communication and propagation of misfolded proteins along specific identified neuronal circuitries. Although, all these hypotheses could be

envisioned a better knowledge of the metabolism of exosomes in vitro and in vivo is necessary to address this problematic.

6. Conclusion

Among pathophysiological mechanisms of neurodegenerative diseases leading to intra or extracellular protein aggregates, a consensual mechanism support a common mechanism of prion-like propagation of mis-folded proteins. However, when this mechanism implies the propagation from cell-to-cell, cellular pathways incriminate remains poorly understood. A growing body of evidences suggests that the endocytic - multivesicular and exosomes pathways may be instrumental to this process. Much is known about the routing of proteins through those recycling or degradative pathway but much less is known about the contribution of those systems to the development of neurodegenerative diseases. However, this MBV-exosome system can be diverted from its physiological function as for instance to produce human immunodeficiency viral particles (Nguyen *et al.*, 2003; for review see Gould *et al.*, 2003). Following this hypothesis, the autophagy-lysosome and/or MVB-exosome pathways could also be diverted to deliver and propagate toxic oligomers or aggregates in neurodegenerative disease such as Alzheimer's disease. Blocking intracellular inclusion of those toxic species to this secretory pathway could also represent a potential therapeutic approach of neurodegenerative diseases such as Amyloidopathies, Tauopathies, Synucleopathies, all of which are sharing a "prion-like" propagation of toxic mis-folded proteins.

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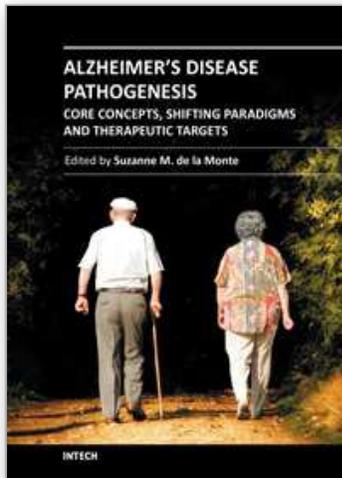
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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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