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Trafficking and degradation pathways in pathogenic conversion of prions and prion-like proteins in neurodegenerative diseases

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ABSTRACT

Several neurodegenerative diseases such as transmissible spongiform encephalopathies, Alzheimer's and Parkinson's diseases are caused by the conversion of cellular proteins to a pathogenic conformer. Despite differences in the primary structure and subcellular localization of these proteins, which include the prion protein, α-synuclein and amyloid precursor protein (APP), striking similarity has been observed in their ability to seed and convert naïve protein molecules as well as transfer between cells. This review aims to cover what is known about the intracellular trafficking of these proteins as well as their degradation mechanisms and highlight similarities in their movement through the endocytic pathway that could contribute to the pathogenic conversion and seeding of these proteins which underlies the basis of these diseases.

1. Introduction

Transmissible spongiform encephalopathies (TSEs) are caused by the conformational change of the ubiquitous cellular prion protein PrP^{C} to its pathogenic form PrP^{Sc} (Colby and Prusiner, 2011). This conformer recruits native PrP^{C} molecules and induces their conversion to PrP^{Sc}, resulting in oligomers or higher order structures of pathogenic protein aggregate which can seed the conversion of more protein molecules (Lee and Eisenberg, 2003). While TSEs have been regarded as uncommon in being transmissible between organisms and across species, striking evidence indicates that a large number of neurodegenerative diseases share with prions the common feature of being amyloidogenic, thus involving the conversion of specific cellular proteins to a stable misfolded conformer which forms ordered β-sheet rich aggregates that result either directly or indirectly in neurotoxicity and inexorable neurodegeneration. These include the age-related diseases Alzheimer's (AD) and Parkinsons (PD), which are caused by misfolding of tau and amyloid β; α-synuclein; and huntingtin, respectively. Different models have been proposed to describe the seeding process (Aguzzi and Calella, 2009) which is important in formulating common principles that may be applied to other neurodegenerative diseases caused by aggregating proteins. Indeed, evidence has accumulated that these proteins are "prion-like" and are capable of seeding the conversion of native conformer molecules as prions do (Brundin et al., 2010; Kane et al., 2000; Luk et al., 2009). Evidence of transmissibility across cells of different species or in grafts is also documented (Angot et al., 2012; Kordower et al., 2008; Morales et al., 2012). Certainly some common feature or tendency of these proteins may provide the impetus for their seeding and template-mediated conversion of native molecules and it seems likely that there must be cellular conditions that help promote their tendency to initial conversion and propagation (Jucker and Walker, 2013). The intracellular localization and trafficking of these proteins may provide clues to how the conversion is triggered, as the locale wherein protein conversion occurs may contain certain conditions or factors that promote conversion or seeding (Marijanovic et al., 2009). Additionally, alterations in the normal composition of the microenvironment surrounding the protein, such as abnormalities or defects in trafficking or degradation may contribute to the initial conversion. In the present article we briefly review what is known of the role of intracellular trafficking in conversion and seeding, and discuss a possible biophysical basis for conversion specifically focusing on defects in protein degradation in providing conditions for these processes in prion and prion-like diseases.

2. Intracellular trafficking in conversion and seeding

Proteins and lipids that are synthesized by the cell have to be targeted to their correct location for functional homeostasis (Mellman

Abbreviations: PrPC, cellular prion protein; PrPSc, scrapie conformer; DRM, detergent resistant membranes; GPI-AP, glycosylphosphatidylinositol-anchored proteins; ERC, endosomal recycling compartment; ERAD, endoplasmic reticulum associated-proteasomal degradation; RML, Rocky Mountain Laboratory.

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and Nelson, 2008) and alterations in trafficking are often noted in neurodegenerative diseases. There are several studies to suggest that compartments in the endo-exocytic pathway serve as conversion or seeding points for both prions and prion-like proteins despite their differences in subcellular localization and structure and may be involved in their intercellular transfer as well (reviewed in Costanzo and Zurzolo, 2013).

Prion diseases: The cellular prion protein PrP^C is an ubiquitously expressed glycosylphosphatidylinositol-anchored protein (GPI-AP) which shares remarkable conservation across species (Aguzzi and Calella, 2009). It is targeted to the outer leaflet of the plasma membrane and while its actual function is unclear, many roles have been proposed for it including myelination maintenance, synaptic function and signaling (Bremer et al., 2010; Pradines et al., 2013; Prado et al., 2004). PrP^C synthesis starts on the surface of the endoplasmic reticulum where it is translocated into the ER lumen and is attached by its C-terminus to the pre-formed GPI anchor. Upon GPI-anchoring, PrP^C becomes associated with cholesterol enriched fractions or detergent-resistant membranes (DRMs), in the endoplasmic reticulum (ER), which appears to be necessary for both its correct folding and further axonal trafficking in neurons (Galvan et al., 2005; Sarnataro et al., 2004). It then continues along the secretory pathway, through the Golgi and is delivered to the plasma membrane, experiencing many post-translational modifications to both the protein and the anchor, including glycosylation and acyl chain remodeling (Fujita and Kinoshita, 2010; Orlean and Menon, 2007). In hippocampal neurons it is transported in vesicles along axons driven by the molecular motors kinesin-1C and cytoplasmic dynein (Encalada et al., 2011). At the plasma membrane PrP^C appears to be enriched in lipid domains (rafts) of specific lipid and protein composition, that differ from domains occupied by other GPI-APs like Thy-1, containing significantly higher levels of unsaturated long fatty acyl chains and hexosylceramides (Brügger et al., 2004). The specific composition of these rafts, especially with regards to cholesterol, appears to be important for conversion, since cholesterol depletion decreased PrP^{Sc} accumulation and increasing sphingolipid levels enhanced conversion (Naslavsky et al., 1999; Taraboulos et al., 1995). From the plasma membrane PrP^C can be internalized both via clathrin, dynamin- and lipid raft-dependent mechanisms (Lainé et al., 2001; Magalhães et al., 2002; Sarnataro et al., 2009; Shyng et al., 1994; Sunyach et al., 2003) and enter the endocytic pathway where it may be targeted toward late endosomes and lysosomes for degradation (the endo-lysosomal pathway) or be recycled back to the surface through the endocytic recycling compartment (Campana et al., 2005; Prado et al., 2004). While PrP^C is largely distributed evenly over the plasma membrane except for the small fraction being recycled through the endocytic pathway, during prion infection PrP^{Sc} forms punctate aggregates that appear to be predominantly intracellular and can be found concentrated along the endocytic pathway in early endosomes, the recycling compartment and late endosomes/lysosomes (Jeffrey et al., 2000; Marijanovic et al., 2009). However, μm-long PrP^{Sc} aggregates have also been noted on the plasma membrane in the form of "strings" and branching webs formed by the strings (Rouvinski et al., 2014). The internalization and endocytic recycling of PrP appears to be significant for conversion. While reports using tagged convertible PrP^C demonstrates that PrP^{Sc} conversion occurs on the cell surface within minutes to hours of exogenously added prion-infected brain homogenate (Goold et al., 2011, 2013), in many studies PrP^{Sc} aggregates are observed to accumulate or reside along the endocytic pathway, and by increasing retrograde transport of PrP^C into the endocytic pathway, PrP^{Sc} conversion is enhanced (Béranger et al., 2002; Yamasaki et al., 2012). Finally, by selectively blocking transport to and from different endocytic compartments, the endosomal recycling compartment (ERC) has been identified as a prominent site of intracellular conversion (Marijanovic et al., 2009). Additionally, PrP^{Sc} strings found on the cell surface are composed of both full-length PrP^{Sc} and PrP27-30, the C2-like fragment believed to be the result of cleavage by acid proteases in endosomal compartments (Rouvinski et al., 2014). Thus some proportion of surface PrP^{Sc} may be a product of intracellular conversion and recycling and the endocytic pathway provides locales for conversion of infectious prion.

Interestingly, during prion infection there is delayed post-Golgi trafficking and reduced surface expression of PrP but also of other raft-associated membrane proteins such as Thy-1 and the insulin receptor in 22L- and RML prion-infected mouse brains, suggesting that prion infection impairs normal post-Golgi trafficking of certain proteins (Uchiyama et al., 2013). The raft-association of these proteins suggests involvement of cholesterol in regulating traffic and indeed prion infections upregulate cholesterol production and cholesterol depletion slowed down PrP^C internalization (Bach et al., 2009; Sarnataro et al., 2009). Recently our lab has shown that U18666A treatment, which diverts cholesterol to late endosomes, resulted in impaired trafficking of PrP from early endosomes to the ERC, a site of conversion (Marijanovic et al., 2009). We postulate that this might be due to cholesterol-driven trafficking of the protein. As the retention of other GPI-anchored proteins within the ERC has been shown to be cholesterol-dependent (Mayor et al., 1998) together with the findings (see below) that tamoxifen also induces cholesterol redistribution from ERC and early endosomes to lysosomes while rerouting PrP^C to lysosomes, these data suggest that cholesterol may regulate PrP trafficking and thereby its conversion (Marzo et al., 2013; Browman and Zurzolo, 2013).

Alzheimer's disease: The primary protein aggregates in AD are the intracellular neurofibrillary tau tangles (NFTs) and the extracellular plaques of amyloid β (Aβ) fragments created by the cleavage of the amyloid precursor protein APP (Rajendran and Annaert, 2012). APP is targeted to the plasma membrane where it may be enzymatically cleaved in two distinct pathways known as the non-amyloidogenic and the amyloidogenic pathways. The non-amyloidogenic processing by α-secretase, results in the extracellular release of soluble N-terminal sAPPα, and a membrane-bound C-terminal fragment (CTF), which is further processed by the γ-secretase complex to yield the p3 fragment (Rajendran and Annaert, 2012). The amyloidogenic pathway starts when the initial cleavage is mediated by β-secretase, which cleaves at a different position, resulting in the release of sAPPβ and a CTF-β that is then cleaved by γ-secretase, yielding either a 40-(Aβ40) or 42-amino acid long (Aβ42) peptide herein collectively referred to simply as Aβ.

Both the endocytic and autophagic–lysosome pathways have been reported to be important in AD models for progression of pathogenicity as in the case of prionopathies (Cirrito et al., 2008). Though APP is plasma-membrane localized and Aβ plaque formation occurs extracellularly, there is a body of evidence suggesting that, as for prion, APP processing and Aβ production is mediated by endocytic recycling. Firstly, studies show that blocking APP internalization could decrease Aβ production, suggesting that endocytosis is involved in the production of the toxic peptide (Koo and Squazzo, 1994; Carey et al., 2005). Additionally, Aβ localization and production has been demonstrated within the trans-Golgi, lysosomes and multivesicular bodies as well as cytosol (Cataldo et al., 2004; Langui et al., 2004; Yu et al., 2005; Zheng et al., 2012) thus cementing the idea that the endosomal/secretory pathway could be a major source of the toxic peptides. The β-secretase enzyme, which has maximum activity at low pH, is localized together with APP in both endosomes and lysosomes, and both β- and γ-secretase activity, as well as Aβ, are found in lysosome and autophagic vacuole fractions (Kinoshita et al., 2003; Pasternak et al., 2003; Yu et al., 2004) adding weight to this idea. Depletion of

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