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Prion degradation pathways: Potential for therapeutic intervention

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ABSTRACT

Prion diseases are fatal neurodegenerative disorders. Pathology is closely linked to the misfolding of native cellular PrP^{C} into the disease-associated form PrP^{Sc} that accumulates in the brain as disease progresses. Although treatments have yet to be developed, strategies aimed at stimulating the degradation of PrP^{Sc} have shown efficacy in experimental models of prion disease. Here, we describe the cellular pathways that mediate PrP^{Sc} degradation and review possible targets for therapeutic intervention. This article is part of a Special Issue entitled 'Neuronal Protein'.

Contents

1. Introduction

Prion diseases are thought to be caused by the misfolding of native cellular prion protein (PrP^{C}) into a β-sheet rich aggregation prone form (PrP^{Sc}). Their pathogenesis is associated with the build-up of PrP^{Sc} in the brains of affected individuals (Prusiner, 1998). As a result, prion diseases are included in a group of neurodegenerative disorders termed the proteinopathies, alongside Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) (Soto, 2003). The abnormal protein aggregates which accumulate in these disorders are thought to result in a toxic gain of function that ultimately leads to cell death and disease pathogenesis. Debate about the nature of these toxic effects is ongoing (Lindquist and Kelly, 2011); however, recent evidence has emerged implicating impaired protein homeostasis (proteostasis) as a major cause of toxicity common to these disorders (Hetz and Mollereau, 2014; Lindquist and Kelly, 2011). To function efficiently, cells must maintain protein content (proteome) in an active state. This presents a significant challenge given the inherently unstable nature of many proteins under physiological conditions. Proteostasis is defined as the balance between the protein degradation and synthesis needed to remove and replace denatured proteins, respectively. Almost 1400 proteins (~14% of the proteome) regulate proteostasis in mammalian cells, as part of a tightly co-ordinated proteostasis network (Kim et al., 2013; Powers et al., 2009).

Protein translation is regulated by a series of initiation and elongation factors. One of the key regulators is eIF2α (Walter and Ron, 2011) which is targeted by a number of signal transduction pathways

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known to control protein synthesis (Clemens, 2004; Deng et al., 2002; Harding et al., 1999). Phosphorylation of eIF2α inhibits its activity and suppresses global protein synthesis (Walter and Ron, 2011). This pathway forms a key arm of the unfolded protein response (UPR), which is activated during conditions of cellular stress. The UPR has been shown to be particularly significant in prion pathology (Hetz and Mollereau, 2014; Moreno et al., 2012).

Once translated, proteins are scrutinised for correct folding by multiple quality control pathways. In the cytosol, the hsp70/hsp40 chaperone system (Kim et al., 2013) surveys proteins for exposed hydrophobic regions found in misfolded proteins. If attempts at refolding fail, misfolded proteins are targeted for degradation. For secretory or membrane proteins which are translocated directly into the endoplasmic reticulum (ER) during synthesis (cotranslational translocation), specialised quality control systems operate within the ER lumen (ERQC). Here, the situation is more complex than in the cytosol due to the additional need to monitor signal peptide removal, N-linked glycosylation, and disulphide bond formation (Braakman and Hebert, 2013). Since the ER lumen lacks degradation machinery, misfolded proteins must be retro-translocated to the cytosol for degradation as part of the ER-associated degradation (ERAD) pathway. Irreversibly aggregated ER proteins are subject to ERQC and targeted for lysosomal degradation via autophagic pathways (Araki and Nagata, 2011). In addition to ERAD and ERQC pathways, it is likely that protein quality control systems in other cellular compartments also contribute to the clearance of misfolded proteins. An important example is the Golgi quality control (Golgi QC) pathway which directs misfolded proteins from the Golgi directly to lysosomes for degradation (Anelli and Sitia, 2008; Arvan et al., 2002).

Misfolded, damaged or aggregated mature proteins are subject to similar quality control mechanisms as those synthesised de novo (Hipp et al., 2014). Protein aggregates accumulate in cells when levels of misfolded proteins overwhelm the quality control systems. This can arise in conditions of cell stress, mutant protein expression or prion infection. Different classes of protein inclusions have been described depending on their cellular location, stability and protein content. They are thought to play a protective role by sequestering potentially harmful misfolded proteins from the cellular milieu (Sontag et al., 2014). Various systems have evolved to deal with these deposits. Hsp70, Hsp40 and Hsp100 chaperones act in concert to solubilise aggregates, allowing refolding or degradation (Kim et al., 2013). Insoluble aggregates are directly targeted for degradation by binding to adaptor proteins, such as p62 and NBR1 (Bjorkoy et al., 2005; Kirkin et al., 2009; Pankiv et al., 2007). The eventual fate of terminally misfolded or aggregated proteins is degradation. There are two main degradation pathways: the ubiquitin-proteasome system (UPS) and lysosomal proteolysis (including autophagic pathways). These systems are particularly important in neurons whose complex architecture, long lifespan and inability to divide (and thereby dilute the load of damaged proteins), make them particularly vulnerable to proteotoxic stress.

2. Ubiquitin–proteasome system

As the principal route of protein degradation in mammalian cells, the UPS represents a major protection against misfolded proteins. Proteins are marked for proteasomal degradation by covalent conjugation of ubiquitin (Ub) in a sequential reaction involving three enzymes: ubiquitin activating enzymes (E1), ubiquitin conjugating enzymes (E2) and ubiquitin ligases (E3) that recognise and transfer ubiquitin to an internal lysine residue on substrate proteins. In humans, there are two E1 molecules, a greater diversity of E2s, and several hundred E3s (Lee et al., 2011). Thus, E3 ubiquitin ligases provide the mechanisms of substrate specificity in proteasomal degradation. Following initial substrate ubiquitination further Ub molecules are added sequentially to the first via one of seven internal lysine residues. In addition to canonical lysine 48 linkages, lysine 11 and 29 linkages have been shown to target proteins for proteasomal degradation, with a chain of four molecules considered the minimum efficient signal (degron) for recognition by the 26S proteasome (Dantuma and Bott, 2014; McKinnon and Tabrizi, 2014). This large (2.5 MDa) multi-subunit complex consists of a barrel-shaped 20S catalytic core responsible for proteolytic activity (Groll et al., 2000) and the 19S regulatory particle, which is important for the recognition, unfolding, and translocation of ubiquitinated substrates into the 20S core particle (Bedford et al., 2010). Mutations in different components of the UPS have been identified in clinical cases of HD, AD and PD (Kitada et al., 1998; van Leeuwen et al., 2006). Furthermore, experimental knockout of proteasome subunits in mice has been shown to result in progressive neurodegeneration, clearly demonstrating the importance of proteasome catalytic activity to neuronal proteostasis and survival (Bedford et al., 2008; Tashiro et al., 2012). Ageing has also been linked with a reduction in UPS activity, a factor that may contribute to the late onset of many neurodegenerative diseases (Gamerdinger et al., 2009; Tydlacka et al., 2008; Zhou et al., 2003).

Although implicated in the clearance of many disease-associated proteins (Bhat et al., 2014; Goold et al., 2013; Li et al., 2010), proteasomal degradation may be restricted to soluble misfolded proteins or smaller oligomeric forms that can be unfolded to allow entry into the 20S catalytic chamber. For larger, more insoluble aggregates, the catalytic chamber may remain inaccessible, preventing their effective degradation (Qin et al., 2003; Scotter et al., 2014). Indeed, many oligomeric and aggregated forms of disease-associated proteins have been shown to inhibit proteasome activity, both in reconstituted systems using purified components, as well as in cultured cells and in vivo models (Andre and Tabrizi, 2012; Deriziotis et al., 2011; Hong et al., 2014; Kristiansen et al., 2007). In the context of UPS impairment, an upregulation of autophagy has been described, which may facilitate the clearance of larger aggregates (Korolchuk et al., 2010). This is a good example of the crosstalk and close interplay thought to exist between the two degradatory systems (Hao et al., 2013; Nedelsky et al., 2008).

3. Lysosomal degradation/autophagy

Lysosomes represent the major catabolic compartment in eukaryotic cells. A wide range of enzymatic activities are confined within the lysosomal limiting membrane. These include many classes of proteolytic enzymes (Appelqvist et al., 2013). Several routes deliver cell constituents to lysosomes including endolysosomal pathways mediated by the ESCORT machinery, as well as ERQC and Golgi QC pathways and autophagic pathways (Saftig and Klumperman, 2009). These systems are interlinked and crosstalk between them ensures the efficient removal of obsolete cellular components (Nixon, 2013).

Autophagy is a highly conserved system for the degradation of cytosolic macromolecules and organelles. Several pathways have been described with the most important for neuronal proteostasis being macroautophagy (Jimenez-Sanchez et al., 2012; Nixon, 2013; Yao et al., 2013). This is a process whereby cytosolic contents are engulfed in a double membrane-bound structure, called an autophagosome, which later fuses with lysosomes to enable degradation to take place. The process begins with formation of a crescent shaped isolation membrane (phagophore). The isolation membrane then extends around a region of cytoplasm or selected substrate. Subsequent closure of the inner and outer bilayers of the isolation membrane forms the autophagosome, which later fuses with a lysosome to yield an autolysosome (Rubinsztein et al., 2012). The mammalian target for rapamycin complex (mTORC) is an important negative regulator of autophagy whose activity is influenced by multiple signalling pathways (Rubinsztein et al., 2012). However, mTORC-independent pathways have also been described that involve Beclin 1 and the PI3K vps34 (Sarkar et al., 2005; Williams et al., 2008).

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