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Review

Proteostasis impairment in ALS

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ABSTRACT

In physiological conditions the maintenance of the cellular proteome is a prerequisite for optimal cell functioning and cell survival. Additionally, cells need to constantly sense and adapt to their changing environment and associated stressors. Cells achieve this via a set of molecular chaperones, protein clearance pathways as well as stress-associated signaling networks which work together to prevent protein misfolding, its aggregation and accumulation in subcellular compartments. These processes together form the proteostasis network which helps in maintaining cellular proteostasis. Imbalance or impairment in this processes is directly linked to ageing associated disorders such as diabetes, cancer, stroke, metabolic disorders, pulmonary fibrosis, inflammation and neurodegenerative diseases. In this review, we provide insights into the proteostasis process and how its failure governs neurodegenerative disorders with a special focus on Amyotrophic lateral sclerosis (ALS).

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Contents

1. Introduction

In order to be functional, proteins after synthesis need to be folded in a specific and unique three-dimensional tertiary structure. However, about 30% of the newly-synthetized proteins are misfolded and therefore require refolding (Schubert et al., 2000). Under normal conditions, cells have an efficient protein quality control machinery which is able to detect and handle misfolded proteins. This is accomplished by various chaperones such as heat shock proteins that recognize wrongly folded proteins, help in their refolding, prevent their aggregation and

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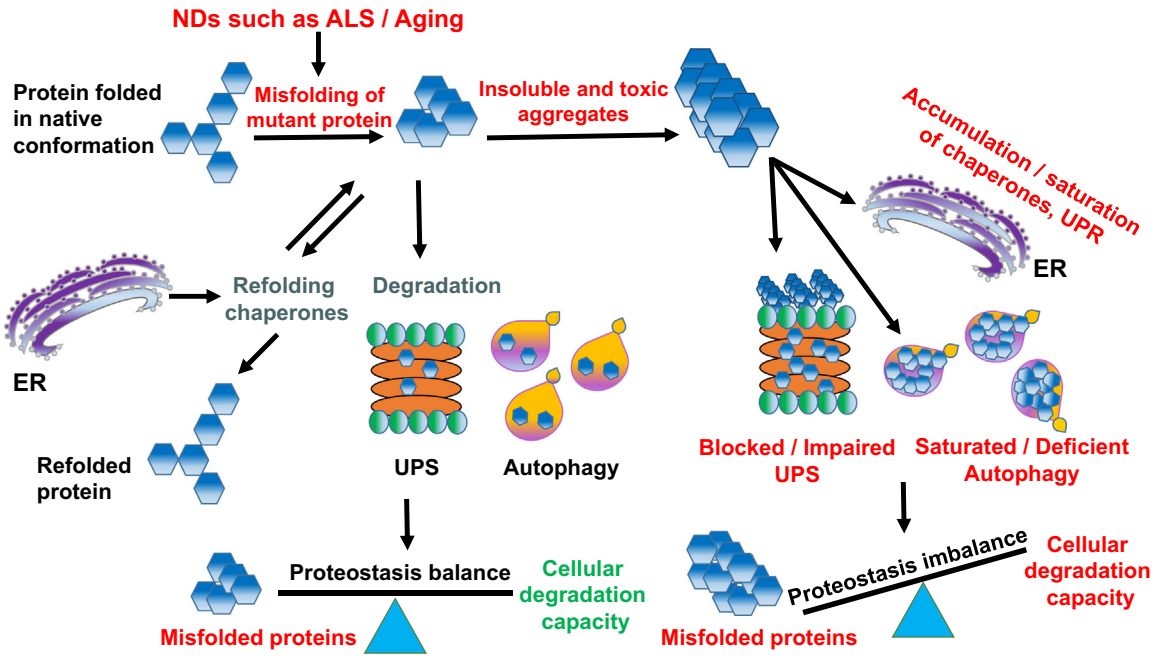

Fig. 1. Schematic depiction of normal cellular proteostasis and its impairment in neurodegenerative diseases (NDs).

provide aid to repair damaged proteins. In case all attempts to repair and correctly refold the proteins fails then these chaperones also actively mediate their removal. This protein quality control and the maintenance of proteome homeostasis; also termed as proteostasis is a fundamental process required to keep cells healthy and functional. As proteins are only slightly stable at physiological temperatures they are constantly exposed to the high probability of misfolding and therefore the process of cellular proteostasis is highly demanding (Hipp et al., 2014). Proteostasis deficits increase with age and have been shown to facilitate the development and progression of various diseases, including neurodegenerative diseases (NDs), (see Fig. 1), (Ciechanover and Brundin, 2003; Hartl et al., 2011; Hipp et al., 2014; Takalo et al., 2013).

The pathogenesis of NDs centrally involves abnormal accumulation and aggregation of specific misfolded proteins in distinct regions of the brain (Davies et al., 1997; Koo et al., 1999; Martindale et al., 1998; Takalo et al., 2013). For this reason, NDs are viewed as cerebral proteopathies, in which the accumulation of particular misfolded protein aggregates is a key causative factor (Frost and Diamond, 2010; Golde and Miller, 2009; Haass and Selkoe, 2007; Saxena and Caroni, 2011; Stoppini et al., 2004). Further, there is increasing evidence suggesting that genetic mutations or environmental factors can provoke or accelerate protein misfolding and aggregation in NDs (Takalo et al., 2013). Proteins that are known to be involved in NDs like Aβ, tau, α-synuclein and polyQ expanded proteins, possess few stable three-dimensional structures in physiological conditions and are prone to misfolding. It is well accepted that specific neuronal populations are selectively affected but how those misfolded proteins eventually disrupt particular cellular protein networks, thereby leading to selective neuronal vulnerability in NDs remains unresolved (Brignull et al., 2006; Saxena and Caroni, 2011).

In normal conditions a large majority of proteins are made up of structured and ordered domains which are connected together by flexible linkers. In contrast, NDs causing proteins such as α-synuclein, A-beta, Tau, and Polyglutamine expanded proteins are intrinsically disordered and largely unstable in physiological conditions. If misfolded these proteins expose beta sheets which are prone to aberrant interactions with other important protein complexes thereby deregulating multiple signaling pathways (Gidalevitz et al., 2006; Hartl et al., 2011; Hetz et al., 2015; Hipp et al., 2014; Roth and Balch, 2011). Moreover, these beta sheet-aggregates are largely resistant to proteolytic pathways and eventually lead to the formation of inclusion bodies or extracellular plaques. Importantly, each ND specific protein impairs a unique cellular signaling network, thereby contributing to proteostasis impairment and selective neuronal vulnerability in NDs. The identity and understanding of these signaling pathways whose impairment governs the well observed selective neuronal vulnerability is critical for the understanding of mechanisms associated with NDs.

Aging is considered to be a major risk factor for NDs (Cuanalo-Contreras et al., 2013; Kikis et al., 2010). It has been shown that insoluble proteins accumulate in all tissues during aging in different species (Cuanalo-Contreras et al., 2013; David et al., 2010; Kikis et al., 2010). What is not clear is whether the age-dependent accumulation of those insoluble proteins is the cause for cellular dysfunction leading to aging or a consequence of reduced proteostasis during aging (Cuanalo-Contreras et al., 2013). Using *Caenorhabditis elegans* as a model system for aging, several hundreds of proteins with diverse functions were shown to become highly insoluble with age and misfold (David et al., 2010; Reis-Rodrigues et al., 2012). Notably, small molecules against specific misfolded proteins restored protein homeostasis *in vivo* and increased life span, consistent with the relationship between protein aggregation and aging (Alavez et al., 2011; Alavez and Lithgow, 2012).

2. Protein quality control pathways

We first briefly describe the relevant pathways involved in proteostasis maintenance and later discuss how those pathways are perturbed in motoneurons in ALS and provide examples implicating proteostasis dysfunction in the etiology of ALS.