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Autophagy and polyglutamine diseases

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ABSTRACT

In polyglutamine diseases, an abnormally elongated polyglutamine tract results in protein misfolding and accumulation of intracellular aggregates. The length of the polyglutamine expansion correlates with the tendency of the mutant protein to aggregate, as well as with neuronal toxicity and earlier disease onset. Although currently there is no effective cure to prevent or slow down the progression of these neurodegenerative disorders, increasing the clearance of mutant proteins has been proposed as a potential therapeutic approach. The ubiquitin–proteasome system and autophagy are the two main degradative pathways responsible for eliminating misfolded and unnecessary proteins in the cell. We will review some of the studies that have proposed autophagy as a strategy to reduce the accumulation of polyglutamine-expanded protein aggregates and protect against mutant protein neurotoxicity. We will also discuss some of the currently known mechanisms that induce autophagy, which may be beneficial for the treatment of these and other neurodegenerative disorders.

Contents

1. Introduction . . . 68
2. Polyglutamine diseases . . . 68
   2.1. Genetics of CAG repeat disorders . . . 68
   2.2. Properties and toxicity of polyglutamine aggregates . . . 68
   2.3. Mechanisms for clearance of polyglutamine proteins: the UPS and autophagy . . . 69
3. Autophagy . . . 69
   3.1. Introduction . . . 69
   3.2. Autophagy machinery . . . 70
      3.2.1. Initiation . . . 70
      3.2.2. Elongation . . . 71
      3.2.3. Maturation . . . 71
   3.3. Signalling pathways regulating autophagy . . . 71
4. Autophagy and neurodegeneration . . . 72
5. Autophagy implications in polyglutamine disorders . . . 73
   5.1. Polyglutamine-expanded proteins are substrates for autophagy . . . 73
   5.2. Molecular forms of polyglutamine-expanded proteins that are autophagy substrates . . . 73
   5.3. Selective degradation of protein aggregates by autophagy . . . 74
   5.4. Consequences of polyglutamine expansions on autophagic activity . . . 74

Abbreviations: HD, Huntington's disease; SCA, spinocerebellar ataxia; DRPLA, Denatorubral-pallidoluysian atrophy; SBMA, spinal and bulbar muscular atropy; Htt, Huntingtin; UPS, ubiquitin–proteasome system; HDL-2, Huntington's disease-like 2; IBs, inclusion bodies; RNAi, RNA interference; Atg, autophagy-related genes; ER, endoplasmic reticulum; PI3K, phosphatidylinositol 3-kinase; JNK1, c-Jun N-terminal protein kinase 1; PE, phosphatidylethanolamine; SNAREs, soluble N-ethylmaleimide-sensitive factor attachment protein receptors; mTOR, mammalian target of rapamycin; PI-3-P, phosphatidylinositol-3-phosphate; ROS, reactive oxygen species; IP_3, inositol-1,4,5-triphosphate; IP_3R, IP_3 receptors; cAMP, cyclic AMP; IMPase, inositol monophosphatase; GSK3β, glycogen synthase kinase-3 β; I1R, imidazoline-1-receptor; SMERs, small molecule enhancers of rapamycin; SMIRs, small molecule inhibitors of rapamycin.

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6. Modulating autophagy to treat polyglutamine diseases . . . 75
6.1. mTOR-dependent autophagy inducers . . . 75
6.2. mTOR-independent autophagy inducers . . . 75
6.2.1. Regulating the phosphoinositol pathway . . . 75
6.2.2. Regulating the cAMP-Epac-PLC-ε pathway . . . 77
6.2.3. Regulating the Ca^{2+}-calpain-$G_{s\alpha}$ pathway . . . 77
6.2.4. Other mTOR-independent mechanisms . . . 78
6.3. Combination treatment approaches that induce autophagy . . . 78
6.4. Future therapeutic prospects . . . 78
Acknowledgements . . . 78
References . . . 78

1. Introduction

Protein misfolding and subsequent aggregation are common features in many late-onset neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease and other tauopathies. The presence of these protein aggregates in brains of patients has been correlated with neuronal cell death and with earlier onset and increased symptom severity (Soto and Estrada, 2008). These disorders are commonly referred to as proteinopathies and include a group of conditions in which the aggregated proteins are encoded by genes containing trinucleotide repeat expansions. When this trinucleotide encodes the amino acid glutamine, it results in proteins with abnormally extended polyglutamine tracts and the disorders are hence termed poluglutamine disorders (Orr and Zoghbi, 2007). These expanded regions confer the protein the tendency to aggregate when the number of repeats exceeds a normal physiological number. Whether aggregated forms of these proteins and their intermediate forms represent toxic or protective species has been a matter of debate (Takahashi et al., 2010). However, the mutant proteins cause disease via a toxic gain-of-function mechanism, and it is generally accepted that degradation of polyglutamine-containing proteins would be a beneficial therapeutic approach for the treatment of these diseases. Two main degradative pathways are responsible for clearance of misfolded and unnecessary proteins in the cell: the ubiquitin–proteasome system (UPS) and autophagy (Rubinsztein, 2006). While oligomierised forms of proteins are inefficiently degraded by the proteasome, they can be targeted for degradation by autophagy, a lysosomal degradative pathway. In this review, we will focus on the role of autophagy in polyglutamine disorders, mainly Huntington's disease, the most prevalent of these conditions. We will review some of the increasing number of studies showing the potential benefit of upregulating autophagy for reducing the presence of these protein aggregates and therefore for the treatment of these and, other aggregate-prone protein disorders. We will also discuss different pharmacological approaches that, through autophagy stimulation, provide protection in polyglutamine neurodegenerative disorders.

2. Polyglutamine diseases

2.1. Genetics of CAG repeat disorders

Polyglutamine diseases consist of a group of ten autosomal dominant neurodegenerative disorders, which include Huntington's disease (HD), dentatorubral-pollidoluysian atrophy (DRPLA), spinal and bulbal muscular atrophy (SBMA), several types of spinocerebellar ataxias (SCAs), and the more recently proposed Huntington's disease-like 2 (HDL-2) (Orr and Zoghbi, 2007; Wilburn et al., 2011). Despite the large spectrum of neurological, psychiatric and motor symptoms present in these conditions, they all lead to chronic, slow progressive diseases affecting the central nervous system, for which no cure is available to date.

These disorders share a common genetic etiology, in which genes contain a repetitive DNA sequence consisting of the trinucleotide CAG, coding for the amino acid glutamine. This CAG rich region is unstable and tends to expand from one generation to the next (La Spada et al., 1994). As a consequence, the resulting protein contains an abnormal extension of polyglutamines that leads to individuals developing the disease when the repeats exceed a certain number. The threshold differs between diseases and is usually around 40 glutamines (Semaka et al., 2006; Langbehn et al., 2010). However, in the case of SCA6, an expansion between 18 and 33 glutamines in the CACNA1A gene, which encodes the alpha1A subunit of the P/Q-type voltage-gated calcium channel, is sufficient to cause the disease (Riess et al., 1997). Although in all known polyglutamine disorders there is a direct correlation between the severity of the disease and the polyglutamine length, the molecular and cellular mechanisms underlying the pathology are not fully understood (Orr, 2001). Moreover, the population of target neurons and the symptoms differ from one disease to the other, indicating that the nature of the affected protein as well as other genetic factors contribute to the progression of the disease and specificity (Gatchel and Zoghbi, 2005).

Proteins involved in CAG repeat disorders have crucial cellular activities, and are involved in different functions such as transcription, signalling or transport. And it is therefore possible that some aspects of the disease phenotype arise from a loss-of-function of the wild-type protein. However, mice heterozygous for Htt deletion do not mimic HD pathology, similar to the lack of evidence of ataxia or neurodegeneration in ataxin-1-null mice (Duyao et al., 1995; Zeitlin et al., 1995; Matilla et al., 1998). In contrast, experimental evidence suggests that that these diseases result mainly from a gain-of-function of the protein carrying a CAG expansion. Transgenic expression of the first exon or the full length Htt protein with an expanded polyglutamine produces pathological and phenotypic features of HD (Mangiarini et al., 1996; Hodgson et al., 1999). Moreover, a mouse model ectopically expressing a polyglutamine repeat presented a neurotoxic phenotype, characteristic of polyglutamine disorders, as well as the presence of intraneuronal protein aggregates (Ordway et al., 1997), suggesting that the polyglutamine repeat itself is sufficient to render neuronal cell death. A recent study has suggested that any contribution of a loss-of-function mechanism to HD may be minimal. Transcriptional regulation was compared between cells expressing a polyglutamine-expanded Htt and Huntingtin-null cells, and there was no overlap in the genes regulated in each condition, suggesting that a loss of the wild-type Htt does not contribute to the pathology of HD (Jacobsen et al., 2011).

2.2. Properties and toxicity of polyglutamine aggregates

Similar to other proteinopathies, the presence of intraneuronal protein aggregates is a common feature in the brains of patients suffering from CAG repeat disorders. Although the polyglutamine tract is common to all of these disorders and is responsible for the