Review

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Autophagy in Huntington disease and huntingtin in autophagy

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Autophagy is an important biological process that is essential for the removal of damaged organelles and toxic or aggregated proteins by delivering them to the lysosome for degradation. Consequently, autophagy has become a primary target for the treatment of neurodegenerative diseases that involve aggregating proteins. In Huntington disease (HD), an expansion of the polyglutamine (polyQ) tract in the N-terminus of the huntingtin (HTT) protein leads to protein aggregation. However, HD is unique among the neurodegenerative proteinopathies in that autophagy is not only dysfunctional but wild type (wt) HTT also appears to play several roles in regulating the dynamics of autophagy. Herein, we attempt to integrate the recently described novel roles of wtHTT and altered autophagy in HD.

Huntington disease

HD is a devastating neurological disease that is characterized by loss of motor control and cognitive ability and, ultimately, death. The area of the brain most affected by the disease is the striatum, which plays a key role in initiating and controlling movements of the body, limbs and eyes [1]. HD is an autosomal dominant disease caused by a CAG expansion that encodes a polyQ repeat at the N-terminus of HTT [2]. Many factors have been implicated in HD including alterations in calcium handling, IGF signaling, vesicle transport, endoplasmic reticulum (ER) maintenance, and autophagy. The polyQ tract promotes the formation of toxic oligomers and aggregates, although it is still under debate whether these large aggregates are toxic or not [3]. As in Parkinson disease (PD), aggregates may act as sinks for aggregating proteins while the intermediate oligomers are toxic [3].

An expansion of the polyQ tract in HTT to greater than 36Q causes disease, and the greater the number of tandem repeats, the younger the age of onset. Ultimately, HD leads to death typically within 10–20 years after the appearance of the first diagnosable symptoms, with an average age of onset of about 35–40 years, although juvenile cases have been detected as early as 5 years of age. Currently, there is no disease-modifying therapy available for people suffering from HD.

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The vast majority of HD patients are heterozygous for the HTT mutation (mHTT), and therefore have a functional copy of wtHTT. HTT is essential for embryonic development, and adult-onset loss of total HTT leads to neurodegeneration, indicating an essential role in neuronal health [4–7]. While many efforts have been made to understand and develop novel therapeutics to promote pathways that can clear mHTT and its aggregates, it may be important to do so selectively without interfering with wtHTT levels.

We describe here the importance of protein clearance in neurodegenerative diseases with a focus on HD. This review addresses the emerging role and cyclical nature of HTT degradation, and potential regulation, of autophagy.

Protein clearance in neurodegeneration

The cell has two main pathways for clearance and removal of toxic proteins that are distinct, but linked; autophagy and the ubiquitin protein system (UPS)/unfolded protein response (UPR) [3]. Autophagy is divided into three main types based on how the cargo is delivered to the lysosome – microautophagy, chaperone-mediated autophagy (CMA); and macroautophagy.

Microautophagy involves the translocation of cytoplasmic materials into the lysosome by direct engulfment by the lysosomal membrane. The molecular components that participate in this autophagic process in mammals remain unknown [8].

In CMA, individual soluble proteins that contain a KFERQ-like motif are specifically selected by chaperone proteins, unfolded, and translocated across the lysosomal membrane [9]. Internalization of substrate proteins by this pathway is attained through the coordinated function of chaperones on both sides of the lysosomal membrane and by a membrane protein (the lysosome-associated membrane protein type 2A or LAMP-2A) that acts both as a receptor and as an essential component of the translocation complex [8].

Macroautophagy, hereafter referred to as autophagy, was first described as a bulk clearance mechanism that is activated during starvation and consists of three main stages: autophagosome formation, maturation, and fusion with lysosomes [10] (Figure 1A). During autophagosome formation, an isolation membrane forms that can engulf portions of cytoplasm containing proteins and whole organelles [10]. Once formed, these autophagosomes are transported along microtubules to finally fuse with lysosomes

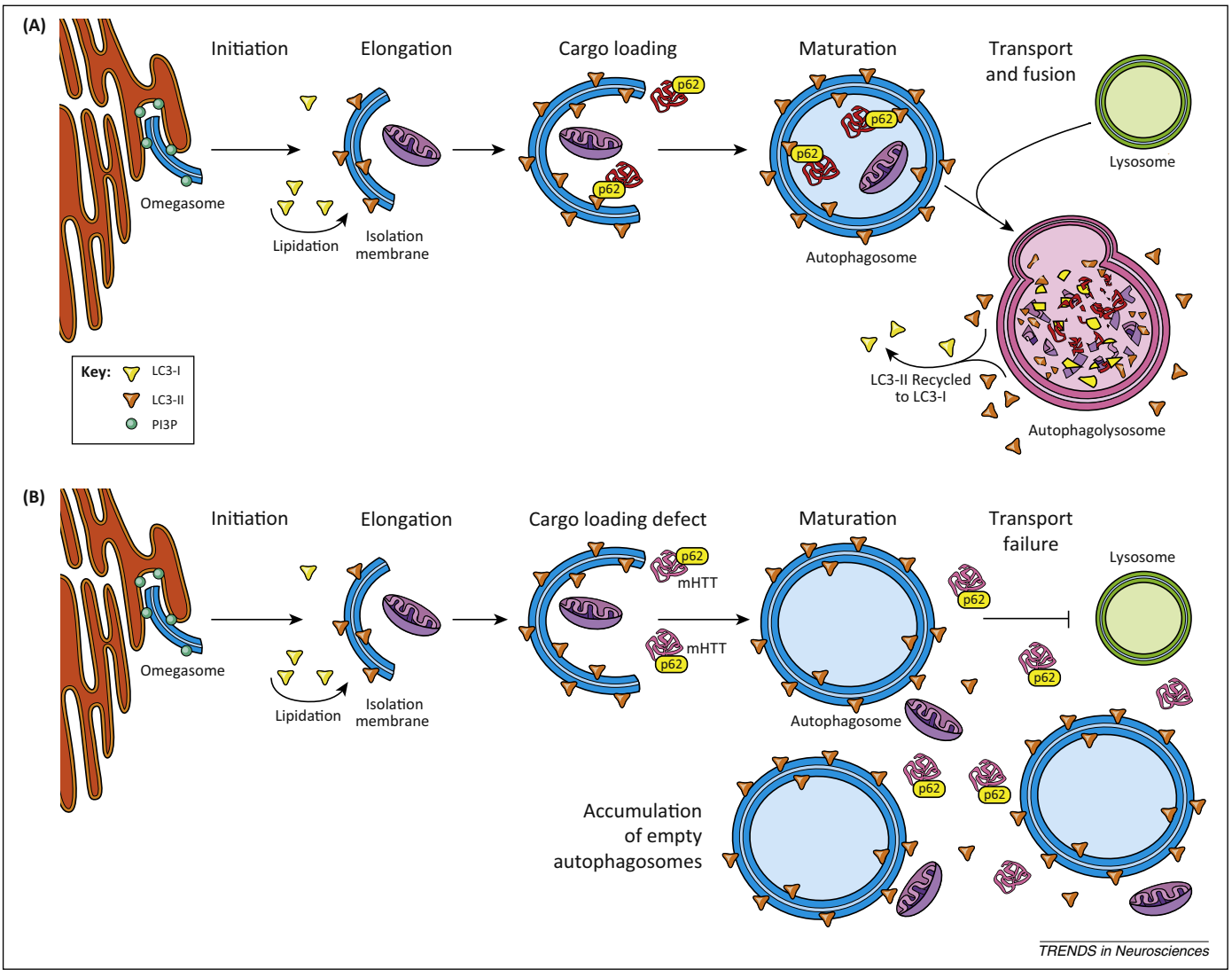

Figure 1. Autophagy is altered in Huntington disease (HD). **(A)** Autophagy involves the formation of double-membraned vesicles that incorporate damaged organelles and toxic or aggregated proteins, and fuse with the lysosome for degradation. **(B)** In HD it has been shown that autophagy is affected at several steps including a defect in cargo loading, trafficking of autophagosomes, and decreased fusion between autophagosomes and lysosomes leading to a build-up of toxic materials in the cytoplasm and empty autophagosomes.

leading to degradation of the autophagic cargo by lysosomal proteases [10]. Although autophagy was initially described as a bulk degradation mechanism, selective forms of autophagy have recently been identified that are specific for mitochondria, ribosomes, ER, or aggregated proteins such as mHTT; these are known as mitophagy [11], ribophagy [12], ERphagy [13], and aggrephagy [14,15], respectively.

The autophagy process can be regulated through the serine/threonine kinase mTOR, which suppresses autophagosome formation under nutrient-rich conditions, while its inhibition by starvation signals leads to increased autophagy [16]. Pharmacological inhibition of mTOR by drugs such as rapamycin can constitutively increase autophagic flux [16]. Additionally, mTOR-independent pathways have also been identified that can be modulated pharmacologically to alter autophagic flux. For example, autophagosome formation is upregulated by increased levels of beclin1, which is freed from its inhibitory interaction with Bcl-2 upon different types of cellular stress [17]. Furthermore, high intracellular calcium levels can inhibit autophagy through the activation of calpains and G-stimulatory protein α with a subsequent increase of cAMP levels [18].

The UPS is the second main form of protein degradation in mammalian cells, and its targets are marked for degradation through the attachment of ubiquitin. Typically, the UPS is responsible for the degradation of short-lived, soluble proteins, and cannot efficiently degrade bulky oligomeric and aggregated proteins such as mHTT [19]. HTT is subject to ubiquitination at amino acids K6, K9, and K15, which leads to its degradation and lowers the toxicity of mHTT [20–22]. However, this UPS-mediated degradation mechanism is thought to become impaired during the course of the disease, allowing mHTT to accumulate into insoluble, ubiquitin-containing aggregates *in vitro* and *in vivo* [23–25].

While ubiquitination can serve as a signal for degradation by the UPS, it has become apparent that it can fulfill a plethora of functions such as mediating protein transport