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A role for autophagy in Huntington's disease

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Abstract

The lysosome-mediated degradation pathway known as macroautophagy is the most versatile means through which cells can eliminate and recycle unwanted materials. Through both selective and non-selective means, macroautophagy can degrade a wide range of cargoes from bulk cytosol to organelles and aggregated proteins. Although studies of disorders such as Parkinson's disease and Amyotrophic Lateral Sclerosis suggest that autophagic and lysosomal dysfunction directly contributes to disease, this had not been the case for the polyglutamine disorder Huntington's disease (HD), for which there was little indication of a disruption in the autophagic-lysosomal system. This supported the possibility of targeting autophagy as a much needed therapeutic approach to combat this disease. Possibly challenging this view, however, are a recent set of studies suggesting that the protein affected in Huntington's disease, huntingtin, might mechanistically contribute to macroautophagy. In this review, we will explore how autophagy might impact or be impacted by HD pathogenesis, and whether a therapeutic approach centering on autophagy may be possible for this yet incurable disease.

Introduction

Huntington's disease is an autosomal-dominantly inherited neurodegenerative disease characterized by cognitive dysfunction, psychiatric disturbances and severe motor dysfunction (Sturrock and Leavitt 2010). The primary site of neurodegeneration is the medium spiny neurons of the caudate putamen, which worsens in a dorsomedial to ventrolateral direction, whereas the interneurons of the region are largely spared (Vonsattel, Keller et al. 2011)). As the severity of pathology worsens, the affected regions broaden to include regions of the cortex, cerebellum, thalamus and white matter (Vonsattel, Keller et al. 2011). The age of onset is typically midlife, and the duration of the disease can extend through decades (Sturrock and Leavitt 2010, Vonsattel, Keller et al. 2011).

In a landmark study of reverse genetics in 1998, the genetic cause of HD was identified as a trinucleotide repeat expansion mutation of cysteine, adenine, and guanine (CAG) in the coding region of the ubiquitously expressed gene now known as the *HD* gene (HDCRG

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1993). At the protein level, the mutation leads to the production of abnormally long tracts of polyglutamine (polyQ) repeats near the N-terminus of the *HD* gene product, huntingtin (Htt) (Gusella, MacDonald et al. 1993, Hoogeveen, Willemsen et al. 1993, Li, Schilling et al. 1993). One of the most marked features of the mutant protein is its propensity to accumulate and aggregate (Perutz, Johnson et al. 1994, Scherzinger, Lurz et al. 1997, Bauerlein, Saha et al. 2017) and to form the intranuclear and intracytoplasmic neuronal inclusions which are now considered a pathological hallmark of the disease (Roizin, Stellar et al. 1979, Davies, Turmaine et al. 1997, DiFiglia, Sapp et al. 1997, Gutekunst, Li et al. 1999). Given that the rediscovery of protein aggregation in this disease was due to the creation of the first HD mouse model, the R6/2 model (Mangiarini, Sathasivam et al. 1996, Davies, Turmaine et al. 1997, DiFiglia, Sapp et al. 1997), much of what we understand about HD is based on experimental model systems, and validation in patient material is limited (Vonsattel 2008, Cepeda, Cummings et al. 2010). A recent study using neurons generated from human HD fibroblasts however suggests that mechanistic validation using endogenously expressed mutant Htt might soon be forth coming (Victor, Richner et al. 2018).

The presence of the polyQ expansion at the NH3-terminus of Htt, as well as the fact that Htt can be proteolyzed to shorter fragments (Goldberg, Nicholson et al. 1996, Kim, Yi et al. 2001, Mende-Mueller, Toneff et al. 2001, Lunkes, Lindenberg et al. 2002, Graham, Deng et al. 2006, Landles, Sathasivam et al. 2010, Bhat, Yan et al. 2014) raised question as to what form of the protein was preferentially accumulating: A short NH3-terminal fragment of the Htt protein (of which there are several possible lengths); the complete 348 kDa protein with the polyQ expansion; or a combination of both. Although it is clear from single cell-based systems to *in vivo* models such as flies and mice that the kinetics of aggregation is significantly affected by the length of the Htt protein itself, it is difficult to know how relevant these differences might be in a disease that onsets mid-life and lasts for decades. To further complicate matters, more recent studies using Htt fragment- and full length- models suggest that the trinucleotide repeat mutation might also be problematic at the level of RNA, leading to the production and accumulation of proteins containing dipeptide repeats (Banez-Coronel, Ayhan et al. 2015), alternative splicing (Neueder and Bates 2018), as well as to the creation of RNA foci (Rudnicki, Pletnikova et al. 2008, de Mezer, Wojciechowska et al. 2011, Krzyzosiak, Sobczak et al. 2012, Jain and Vale 2017).

HD and Htt

Expression of Htt is essential for life, and elimination of *HD* gene expression results in embryonic lethality between days embryonic (E) 8.5 to 9.5 in mice (Duyao, Ambrose et al. 1993, Nasir, Floresco et al. 1995, Zeitlin, Liu et al. 1995). Subsequent genetic studies eliminating *HD* gene expression postnatally found that the loss of Htt can have consequences both within and outside of the brain, even when expression is eliminated in the adult (Dragatsis, Levine et al. 2000, Wang, Liu et al. 2016, Dietrich, Johnson et al. 2017). Although the vast majority of patients with HD are heterozygous for the expansion mutation, rare cases in which patients are homozygous for the mutation revealed that solely a loss of Htt function is unlikely to be the cause of HD (Wexler, Young et al. 1987, Myers, Leavitt et al. 1989). Moreover, there is little indication that the symptoms of disease are dependent on dosage of either the mutant or the normal allele, and homozygous patients are not more

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affected than heterozygous individuals (Wexler, Young et al. 1987, Myers, Leavitt et al. 1989). Taken together, the genetic studies in mice and humans indicate that HD pathogenesis cannot be ascribed to a pure loss of Htt function.

Nonetheless, given how the expanded polyQ stretch can affect protein-protein interactions, and the solubility of Htt, a partial loss of function due to the polyQ mutation cannot be excluded (Liu and Zeitlin 2017), and might exacerbate, possibly in a cell type specific manner, mutant Htt toxicity. Htt is a large, neuronally enriched 350 kDa protein predominated by HEAT motifs, indicative of its role as a scaffold protein (Guo, Bin et al. 2018), and has been implicated in a broad range of functions from transcriptional regulation, nucleo-cytoplasmic shuttling, mitochondrial dynamics, vesicle trafficking, synaptic function, and anti-apoptotic activity (reviewed in (Harjes and Wanker 2003, Schulte and Littleton 2011, Reddy and Shirendeb 2012, Saudou and Humbert 2016)). Additionally, studies have shown Htt to be an integrator of transport along the cellular cytoskeleton through its roles in endocytosis, endosomal motility, and axonal transport and can regulate trafficking and transport dynamics within a cell (Gauthier, Charrin et al. 2004, Gunawardena and Goldstein 2005, Her and Goldstein 2008, Caviston and Holzbaur 2009, Power, Srinivasan et al. 2012, Liot, Zala et al. 2013, Zala, Hinckelmann et al. 2013, Wong and Holzbaur 2014). Importantly, reports have also shown huntingtin and the huntingtin-associated protein 1 (HAP1) to be involved in axonal transport through interactions with both the anterograde and retrograde transport machinery (Engelender, Sharp et al. 1997, Li, Gutekunst et al. 1998, McGuire, Rong et al. 2006, Caviston, Ross et al. 2007, Wong and Holzbaur 2014). Although Htt is reported to associate with components of both motor complexes the exact role of Htt in axonal transport is unclear, but recent studies in *D. melanogaster* suggests that dHtt acts locally at cargo interaction sites to regulate processivity (Weiss and Littleton 2016).

Htt is expressed ubiquitously across all cell types, but observed most highly in neurons especially in the neocortex, the cerebellar cortex, the striatum and the hippocampus (Li, Schilling et al. 1993, Fusco, Chen et al. 1999). It is distributed throughout the cell as a cytosolic protein as well as in the nucleus, axonal processes and at synapses, and in association with various organelles and structures including microtubules, clathrin-coated vesicles, caveolae, mitochondria and synaptosomes (DiFiglia, Sapp et al. 1995, Velier, Kim et al. 1998, BorrellPages, Zala et al. 2006, Reddy and Shirendeb 2012). Htt is expressed broadly early in development, and reaches its highest expression in the developing brain (Bhide, Day et al. 1996). Given its early expression and the breadth of functions in which it has been implicated, it is perhaps unsurprising that neurodevelopmental alterations have been reported recently in patients carrying this disease-causing mutation (Kerschbamer and Biagioli 2015, Lee, Conrad et al. 2018). Segregating whether these events are due to a partial loss-of-function of Htt or a mutation-dependent gain-of-function remains to be seen. Moreover, how and if these neurodevelopmental changes might influence HD onset and pathogenesis is unclear.

Selective degradation of aggregated protein by MA

The abnormal accumulation of the mutant htt protein (mHtt) gave rise to a question posed across all proteinopathies, which was whether the aggregated species of mHtt contributed to

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pathogenesis. Although large, visible intraneuronal inclusions are found in at most 10% of cortical, striatal and thalamic neurons in adult HD (Vonsattel, Keller et al. 2011), the distribution of smaller oligomeric species remains unclear. Interestingly, studies across HD mouse models suggest that abolishing expression of mutant Htt in symptomatic animals is sufficient to bring about therapeutic reversal, including significantly lowering levels of aggregation in the brain (Yamamoto, Lucas et al. 2000, Regulier, Trottier et al. 2003, Harper, Staber et al. 2005, DiFiglia, Sena-Esteves et al. 2007, Kordasiewicz, Stanek et al. 2012). These data indicated that adult neurons have the capacity to eliminate proteinaceous inclusions. Should the aggregated structures contribute to pathogenesis, then identification of how these inclusions are eliminated could lead to a therapeutic approach to combat HD and other proteinopathies.

Studies by several groups implicated the lysosome-mediated degradation pathway macroautophagy (MA) to play a critical role in aggregate-clearance (Johnston, Ward et al. 1998, Ravikumar, Duden et al. 2002, Iwata, Christianson et al. 2005, Iwata, Riley et al. 2005, Yamamoto, Cremona et al. 2006). MA is one of three autophagy pathways that traffics cytosolic cargoes for lysosomal degradation (review in (Kaushik and Cuervo 2012, Yamamoto and Yue 2014)). In MA, cargoes are captured into a transient organelle known as an autophagosome, a multilamellar structure formed through a coordinated effort of several proteins, including those known as the Autophagy-related genes (Atg) (Mizushima, Yoshimori et al. 2011). Although MA is not the exclusive pathway through which aggregated proteins might be eliminated (Juenemann, Schipper-Krom et al. 2013, Schipper-Krom, Juenemann et al. 2014, Hjerpe, Bett et al. 2016, Dikic 2017) its contribution is robust enough that the elimination of mutant Htt aggregates is often used as a primary screen to identify proteins involved in autophagic degradation (Bjorkoy, Lamark et al. 2005, Yamamoto, Cremona et al. 2006, Filimonenko, Stuffers et al. 2007, Filimonenko, Isakson et al. 2010, Korac, Schaeffer et al. 2013, Eenjes, Dragich et al. 2016, Wold, Lim et al. 2016).

MA can package cargoes in a selective manner through adaptor proteins that scaffold protein aggregates to the growing membrane of the autophagosome, a pathway known as aggrephagy (Yamamoto and Yue 2014, Dikic 2017, Gatica, Lahiri et al. 2018). There are several adaptor proteins including the autophagy receptor proteins p62/Sequestesome-1 (p62/sqstm1)(Shin 1998, Seibenhener, Babu et al. 2004, Bjorkoy, Lamark et al. 2005, Pankiv, Clausen et al. 2007), Near BRCA 1 (Nbr1) (Kirkin, Lamark et al. 2009, Lamark, Kirkin et al. 2009), and optineurin (Optn)(Korac, Schaeffer et al. 2013), in addition to the selectivity adaptor protein Autophagy Linked FYVE protein (Alfy)(Simonsen, Birkeland et al. 2004, Filimonenko, Isakson et al. 2010), that have been linked to autophagy-mediated clearance of aggregates. How or why multiple adaptor proteins are required for selective degradation is unclear. Genetic studies in mice, as well as a recent study in a recombinant system (Zaffagnini, Savova et al. 2018) indicate that the most well-studied adaptor protein, p62, acts to sequester and consolidate misfolded proteins and other cargoes preparing them for degradation through its ubiquitin binding domain and a self-interacting PB1 domain (Bjorkoy, Lamark et al. 2005, Pankiv, Clausen et al. 2007). p62, like all autophagy receptor proteins, contain a LIR domain giving it the ability to bind to the mammalian orthologues of the yeast protein, Atg8, which can be found in a cytosolic form or covalently attached to the autophagosome membrane (Pankiv, Clausen et al. 2007).

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Although the ability to bind to mammalian Atg8 orthologues such as Microtubule associated protein light chain 3B (LC3B) is modeled to be sufficient to bring the nascent autophagic membrane to the aggregate-structure (Rogov, Dotsch et al. 2014), other adaptor proteins such as Alfy appear necessary for the clearance of protein aggregates, including those containing mutant Htt (Filimonenko, Isakson et al. 2010). Alfy is a 380 kDa protein that has a series of protein-protein domains and a protein-lipid interaction domain in the C-terminus (Simonsen, Birkeland et al. 2004). Through these domains, Alfy can bind to the p62-positive inclusion (Clausen, Lamark et al. 2010) and the Atg5–12-16L complex (Filimonenko, Isakson et al. 2010), which acts as an E3-like protein that helps conjugate Atg8 proteins to the autophagosome membrane. In addition, the FYVE domain binds to a key lipid on the autophagosome membrane, phosphatidylinositol 3-monophosphate, and is speculated to stabilize the growing autophagosome membrane to the cargo (Simonsen, Birkeland et al. 2004, Filimonenko, Isakson et al. 2010). Although Alfy also has a LIR domain, unlike p62, Alfy interacts with a subset of Atg8 homologs, specifically the GABA-A receptor associated protein (GABARAP) family of proteins but not the LC3 family (Lystad, Ichimura et al. 2014). The physiologic significance of the differential interaction with the two different Atg8 families remains unclear.

A role for Alfy in the clearance of aggregated proteins first came to light in flies, in which the loss of expression of the *Drosophila* homolog, Blue cheese (Bchs), led to neurodegeneration and the accumulation of ubiquitinated proteins (Finley, Edeen et al. 2003). Studies in stable mammalian cell lines (Filimonenko, Isakson et al. 2010) and primary cells derived from mice (Dragich, Kuwajima et al. 2016) similarly found that the depletion or loss of Alfy expression could accelerate aggregate-accumulation. In addition, increasing Alfy expression diminishes aggregate-load in primary neurons, and protects against polyQ toxicity in a fly eye model (Filimonenko, Isakson et al. 2010). Subsequent studies confirmed that the diminished aggregate load is due to the ability of Alfy to eliminate preformed inclusions, rather than interfering with aggregate-formation (Eenjes, Dragich et al. 2016). Given how Alfy may play a rate-limiting role in aggregate-clearance, establishing how Alfy expression impacts protein accumulation in mouse models of HD will provide much needed insight into how aggregation might influence disease pathogenesis.

Nonetheless, it should be noted that studies affecting cargo adaptor proteins rather than autophagy directly can have unexpected results. For example, Nukina and colleagues found that the loss of p62 led to partial neuroprotection in two mouse models of HD (Kurosawa, Matsumoto et al. 2015), rather than potentially enhancing toxicity by slowing the ability of inclusion to form and be eliminated. Instead, the loss of p62 significantly diminished the number of nuclear inclusions, and augmented the number of cytosolic inclusions. These unexpected findings might in part be due to a specific feature of the models used; the R6/2 and HD109QG models, are aggressive, early onset models of HD, that demonstrate predominantly intranuclear accumulations of a short mutant Htt fragment. Given the ability of this short mutant Htt fragment to aggregate *in vitro* and in cell-based systems, it was often assumed that the polyQ expansion was sufficient to drive aggregation and accumulation, regardless of whether it was in a nuclear or cytoplasmic compartment. However, the work by Kurosawa *et al.* brought to light how the nuclear aggregation observed in these mice requires p62, whereas the cytosolic aggregation does not. These data suggest that the intranuclear

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sequestration of the exon1 Htt fragment by p62 is maladaptive, potentially preventing the turnover of the mutant Htt fragment by MA, and aggravate the intranuclear toxicity of the fragment mutant Htt. Thus the loss of p62 was partially protective, but only partial because the mutant Htt was still present and aggregating in the cytosol. Given that this study also shows how wholesale disruption of MA in the same HD mice (in the presence of p62) increases toxicity, this strongly suggest that ongoing MA might be continuing to confer protection regardless of the presence of p62. The potential role of other adaptor proteins working in the absence of p62, or the ability of non-adaptor mediated capture of aggregates by the autophagosome might explain this effect. These observations highlight the importance of studying different HD models simultaneously that express different Htt fragments to full length protein to fully understand how pathogenesis might evolve when augmenting or diminishing autophagic degradation.

Another consideration when examining the role of MA in HD requires our better understanding of how MA is utilized by the different cells of the CNS. Although the contribution of polyQ toxicity in glial cells cannot be disregarded (Myers, Vonsattel et al. 1991, Huang, Wei et al. 2015, Jin, Peng et al. 2015, Phillips, Joshi et al. 2016, Teo, Hong et al. 2016), how autophagy in these cells might be relevant remains uncertain because virtually nothing is known about MA in astrocytes, microglia or oligodendrocytes, especially in context of a disease. Even our understanding of MA in neurons, which represent one of the first cell types in which MA was described, is still in its early stages. An early study in cultured neurons by Hollenbeck (Hollenbeck 1993) suggested that autophagosomes could form in the distal axon tip and mature as it trafficked retrograde towards the soma. Recently, this study was elegantly revisited and expanded upon by Holzbaur and colleagues (Maday and Holzbaur 2012, Maday, Wallace et al. 2012, Maday and Holzbaur 2014, Maday and Holzbaur 2016), extending the observations from dorsal root ganglia neurons to hippocampal and cortical neurons. These studies together with observations made by Yue, Burke and others, highlight how that axon health (Komatsu, Wang et al. 2007), and axonal die-back in the presence of toxins (Cheng, Kim et al. 2011), are MAdependent. Moreover, the Holzbaur lab indicate that MA is not limited to axons, and MA might spatially be defined in a cargo-dependent manner (Wong and Holzbaur 2015, Maday and Holzbaur 2016). Given that mutant Htt deposits are observed throughout the neuron, and differently across neuronal subtypes, modulating MA might impact discrete aspects of HD pathogenesis such as the age-of-onset or rate-of-progression.

Autophagy: A direct link to HD?

Recently, studies in *Drosophilia* and mice implicated Htt to play a significant role in selective autophagy. Zeitlin and colleagues first found that the loss of the polyQ stretch, even in normal Htt appeared to enhance autophagic capacity in neurons (Zheng, Clabough et al. 2010). Although it was unclear why a simple deletion of the polyQ domain would lead to these observation, Steffan proposed in 2010 that Htt showed structural similarities to three yeast selective autophagy proteins Atg11, Atg23, and Vac8 in tandem (Steffan 2010). In a follow up study, Steffan and colleagues found common Htt interactions with an Atg11 binding partners, as well as the identification of a conserved motif of Htt that mediates some of these interactions (Ochaba, Lukacsovich et al. 2014). Additionally, they reported that the

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loss of Htt function in *Drosophila* and mouse CNS led to protein accumulation, which corresponded with an independent study indicating that depletion of Htt or its interactor, HAP1, impaired retrograde transport of autophagosomes containing non-degraded selective cargo, thereby leading to accumulation (Wong and Holzbaur 2014). Soon after, a collaborative effort by Zheng, Cuervo and colleagues similarly found that Htt functions as a scaffold for selective autophagy by promoting cargo recognition and autophagy initiation in both fly and mammalian cells, mediating the binding between p62 and the autophagy-initiating kinase, ULK1 (Rui, Xu et al. 2015), suggesting that a loss of autophagy regulation might contribute to HD pathogenesis (Gelman, Rawet-Slobodkin et al. 2015). Given that Htt has already been implicated to play a role in endocytosis (DiFiglia, Sapp et al. 1995, Velier, Kim et al. 1998) and in trafficking of cargoes from mitochondria to different vesicle populations, (Reddy and Shirendeb 2012, White, Anderson et al. 2015), including autophagosomes (Wong and Holzbaur 2014), an involvement of Htt in autophagy might be unsurprising. Nonetheless the question remains as to what extent the polyQ mutation impacts Htt function in this regard in patients. The mutation lengths often used in the experimental paradigms far exceed the typical adult onset repeat length of 44, and the impact of these shorter repeat lengths are of little study. Moreover, even mice and cells with transgenic overexpression of mutant Htt with greater than one hundred polyQ, or homozygous knock-in mice with greater polyQ lengths do not exhibit gross alterations in autophagic function, and the clearance of aggregates by autophagy can still occur (Heng, Duong et al. 2010, Baldo, Soylu et al. 2013, Eenjes, Dragich et al. 2016). This would suggest, that although Htt function might be a critical player in autophagy and vesicle trafficking overall, it is likely that despite the presence of the polyQ mutation, there is still sufficient Htt function to drive these events. Moreover, these observations also suggest that therapeutic interventions overcoming the losses due to the HD mutation might be possible.

Autophagy and HD: A therapeutic approach?

The activation of autophagy has been a sought after approach for a wide array of disorders with adult onset neurodegenerative diseases only representing a small subset. However, this has been particularly challenging especially in cells of the CNS for different reasons. For example, although starvation and the subsequent inhibition of the serine/threonine mTOR is the first identified means to activate MA (and led to the discovery of autophagy), it is widely accepted that MA can occur despite mTOR activation, such as by modulating the Vps34-Beclin1 kinase complex(Yamamoto, Cremona et al. 2006, Johnson, Melia et al. 2012, Sarkar 2013, Manzoni, Mamais et al. 2016). In addition, to what extent autophagy induction is achieved via mTOR inhibition in neurons is unclear (Du, Hickey et al. 2009, Alirezaei, Kemball et al. 2010, Dubinsky, Dastidar et al. 2014, Tang, Gudsnuk et al. 2014, Maday and Holzbaur 2016). Taken together, how MA is most effectively activated in the adult brain remains uncertain.

Aside from the molecular basis of autophagy in the CNS, global activation of autophagy would by definition extend to organs beyond the brain and spinal cord. Thus, even though the focus of neurodegenerative diseases such as HD is the brain, one must consider the importance of other organs such as striated muscle. Muscle wasting is a significantly devastating aspect of the disease, and ultimately contributes to the demise of HD patients

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(Mielcarek and Isalan 2015). Sandri and colleagues have found that the role for MA in muscle wasting is complex, and that although MA is activated during catabolic conditions, it is also essential to maintain muscle mass (Masiero, Agatea et al. 2009, Bonaldo and Sandri 2013, Schiaffino, Dyar et al. 2013). Whereas there is still much to be learned about why patients lose muscle mass in HD, augmenting MA systemically by using approaches that mimic catabolic conditions might have devastating effects on patients.

Experimentally however, many of the mouse models of HD do not appear to manifest the cachexic symptoms, and thus the impact of mTOR inhibitors and other compounds that might lead to mTOR inhibition such as rapamycin, CC1–779, glucose and glucose-6-phosphate can be examined for their impact on the proteinopathy, and all have been shown to enhance the clearance of mutant huntingtin fragments, reduces formation of aggregate-prone proteins and is protective against cytotoxicity in cell, Drosophila and mouse models of HD (Ravikumar, Duden et al. 2002, Berger, Ravikumar et al. 2006). A key question remains, however, whether these observations are solely due to the activation of MA, or whether mTOR inhibition decreased translation of the exogenously expressed mutant Htt protein. Potential mTOR-independent activators of MA, primarily driven through modulators of intracellular calcium have also been identified to enhance mutant Htt clearance, primarily in cell- and *Drosophila*-based models of HD. (Sarkar, Floto et al. 2005, Criollo, Maiuri et al. 2007, Zhang, Yu et al. 2007, Williams, Sarkar et al. 2008). How calcium might influence MA is complex, as it can both increase and decrease MA, depending on the source of the intracellular calcium (Johnson, Melia et al. 2012). In mouse models, therapeutic benefit likely through the activation of AMPK has been shown to be evoked by trehalose and metformin in the R6/2 mouse model (Tanaka, Machida et al. 2004, Ma, Buescher et al. 2007, Sarkar, Davies et al. 2007), and in the N171–82Q mouse model (Jiang, Wei et al. 2015).

Although the number of studies have been limited, no obvious deficits in the expression of the core MA machinery has been reported in HD patient samples (Hodges, Strand et al. 2006, Kuhn, Thu et al. 2011), suggesting that if MA in brains can be selectively activated, the possibility for potential therapeutic intervention exists. Interestingly, Luthi-Carter and colleagues found that in the caudate nucleus of patient samples, levels of the adaptor proteins Alfy and Optn were significantly decreased, suggesting that the selective turnover of aggregated proteins and mitochondria might selectively diminished. Thus, enhancing cargo recognition by these adaptor proteins, possibly via posttranslational modifications, might be a way through which this can be overcome. Finally, studies in animal models suggest that MA regulation through the Beclin1Vps34 complex might be diminished (Mealer, Murray et al. 2014). Nonetheless, MA capacity might be positively impacted by increasing that activity of transcription factor EM (TFEB), which transcriptionally regulates lysosomal degradation(Sardiello 2016), which has shown promise in mouse models (Tsunemi, Ashe et al. 2012). Ultimately, targeting the upregulation of autophagy as a therapeutic strategy has some promise, but rather than global activation of a status of metabolic stress, other means such as through activation of cargo adaptors might be beneficial. However, it is clear that much research still must be performed before the development of beneficial therapies may be created.

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Conclusion

Although a powerful means to establish whether aggregated proteins might contribute to pathogenesis, the recent implication that Htt itself might be necessary for selective MA brings to question how effective autophagy might be harnessed for therapeutic benefit. The uncovering of Htt as a potential modulator of autophagy specifically highlights how much we are still learning about this fascinating pathway. Given that the vast majority of patients are heterozygous for the mutation gives rise to a key question, to what extent are Htt levels rate limiting for autophagy. Moreover, Htt's already implicated roles in vesicle trafficking, and how that relates to its proposed role in selective autophagy remains to be uncovered. On-going studies examining how modulating autophagic processes on HD pathogenesis in mouse models, might give insight into these question. Nonetheless, it is clear that working with experimental models alone will not suffice, and a back and forth between patient materials, with relevant polyQ lengths, will be essential to fully define how much a loss of function of Htt is contributing to disease. Taken together, there is still significant work to be done to establish the importance of MA as both a contributor and savior against this devastating disease.

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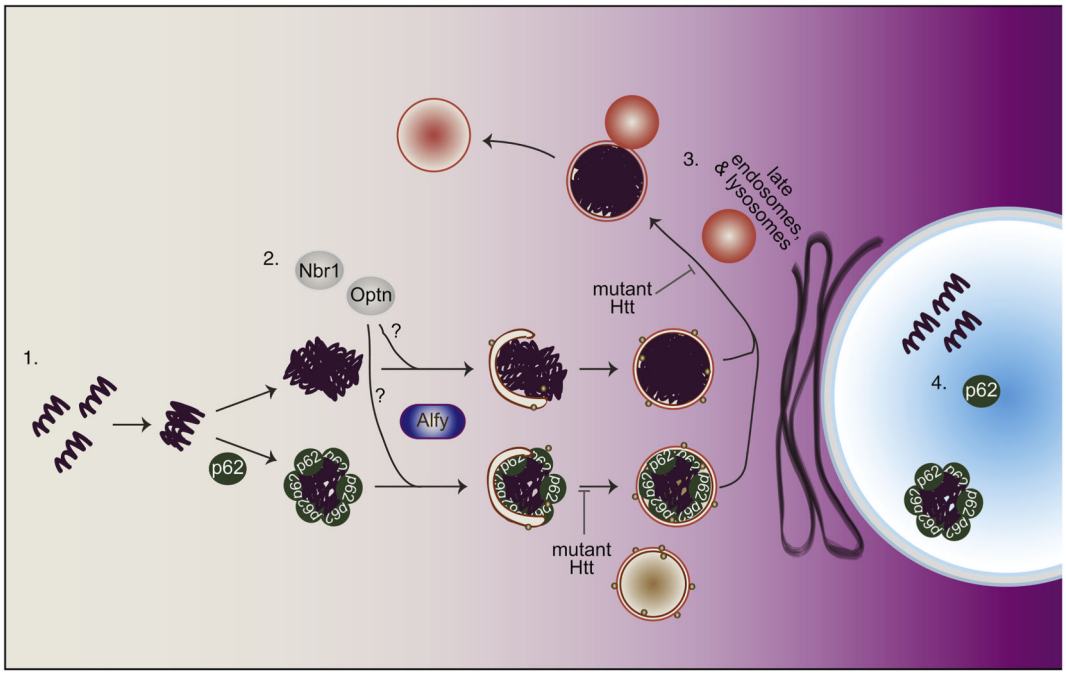

Figure 1.

Schematic summary of macroautophagy (MA) in relation to Huntington's disease (HD). 1. In the cytosol, mutant Htt oligomerizes then form aggregates in p62-dependent and –independent manner. 2. Targeting p62-positive, and possibly p62-negative aggregated proteins are then targeted to the autophagosome-membrane, with the help of the selectivity adaptor protein Alfy. Other autophagy receptors implicated in the turnover of aggregates include Optn and Nbr1, but whether then are involved together or separately remains unclear. Mutant Htt may impede cargo capture leading to the formation of empty autophagosomes, although the mechanism through which this occurs is uncertain. 3. Upon autophagosome formation, the autophagosome matures and acidifies by fusing into the endolysosomal system. Mutant Htt may impede autophagosome maturation, by disrupting retrograde trafficking of the autophagosome back into the soma. 4. In the nucleus, mutant Htt can also accumulates. This accumulation and aggregation, at least of a Htt fragment encoded by *exon 1* of the *HD* gene, appears to require the presence of p62.