ELSEVIER

The many faces of autophagy dysfunction in Huntington's disease: from mechanism to therapy

Constanza J. Cortes[1,2,3,4,5,6] and Albert R. La Spada[1,2,3,4,5,6,7]

[1] Department of Pediatrics, University of California, San Diego, La Jolla, CA 92093, USA
[2] Department of Cellular & Molecular Medicine, University of California, San Diego, La Jolla, CA 92093, USA
[3] Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093, USA
[4] Division of Biological Sciences, University of California, San Diego, La Jolla, CA 92093, USA
[5] Institute for Genomic Medicine, University of California, San Diego, La Jolla, CA 92093, USA
[6] Sanford Consortium for Regenerative Medicine, University of California, San Diego, La Jolla, CA 92093, USA
[7] Rady Children's Hospital, San Diego, CA 92123, USA

Autophagy is the cellular process by which proteins, macromolecules, and organelles are targeted to and degraded by the lysosome. Given that neurodegenerative diseases involve the production of misfolded proteins that cannot be degraded by the protein quality-control systems of the cell, the autophagy pathway is now the focus of intense scrutiny, because autophagy is primarily responsible for maintaining normal cellular proteostasis in the central nervous system (CNS). Huntington's disease (HD) is an inherited CAG–polyglutamine repeat disorder, resulting from the production and accumulation of misfolded huntingtin (Htt) protein. HD shares key features with common neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) and, thus, belongs to a large class of disorders known as neurodegenerative proteinopathies. Multiple independent lines of research have documented alterations in autophagy function in HD, and numerous studies have demonstrated a potential role for autophagy modulation as a therapeutic intervention. In this review, we consider the evidence for autophagy dysfunction in HD, and delineate different targets and mechanistic pathways that might account for the autophagy abnormalities detected in HD. We assess the utility of autophagy modulation as a treatment modality in HD, and suggest guidelines and caveats for future therapy development directed at the autophagy pathway in HD and related disorders.

As postmitotic nondividing cells, neurons are susceptible to the accumulation of damaged proteins and organelles. Their complex, polarized cellular architecture and their inability to dilute insults by cell division render them particularly sensitive to the accumulation of toxic protein aggregates and defective organelles [1]. Thus, neuronal survival depends heavily on maintaining protein quality control by efficient degradation mechanisms. Autophagy, an evolutionarily conserved lysosomal degradation pathway, is active in neurons and functions to eliminate these toxic components, which are hallmarks of neurodegenerative diseases, including AD, PD and HD.

Corresponding author: La Spada, A.R. (alaspada@ucsd.edu)

Three types of mammalian autophagy have been described: microautophagy, chaperone-mediated autophagy (CMA) and macroautophagy. The different autophagy pathways have been classified based upon the manner of cargo delivery to lysosomes, but they all culminate in cargo degradation by this organelle. Briefly, during microautophagy, the lysosomal membrane itself invaginates into the lysosomal lumen, and cargo is quickly degraded by lysosomal hydrolases. This type of autophagy is poorly understood, and its role in neurons remains unclear. During CMA, cargo is directly bound by cytosolic chaperones, and then recognized and imported into the lysosomal lumen by a receptor on the lysosomal membrane. Conversely, macroautophagy requires the formation of a double membrane-bound vesicle, the autophagosome, to isolate

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.02.014

Please cite this article in press as: C.J. Cortes, The many faces of autophagy dysfunction in Huntington's disease: from mechanistic pathways to therapeutic opportunities, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.02.014

cargo and, after autophagosome maturation, the autophagosomes fuse with lysosomes for degradation. The importance of basal neuronal macroautophagy was demonstrated by conditional knockout of key autophagy genes autophagy protein 5 and 7 (*Atg5* and *Atg7*), which, in the absence of any additional proteotoxic stress, resulted in neurodegeneration and the accumulation of ubiquitin-positive inclusions, which similar to what is typically observed in neurodegenerative disease [2,3].

All three types of autophagy can coexist in the same cell, and alterations in both macroautophagy and CMA have been described in many neurological disorders. Indeed, despite completely different etiologies, many neurodegenerative disorders share the common pathological finding of autophagic vacuole (AV) accumulation in degenerating neurons. Evidence now indicates that this increase in AVs is not principally the result of increased autophagy pathway activity, but rather reflects a decrease in autophagy flux; that is, the process of autophagosome maturation culminating in lysosomal fusion. Indeed, neurons are particularly sensitive to autophagy–lysosome pathway perturbations, as reflected by the high frequency of neurological disorders caused by mutations targeting the endolysosomal network [1]. Furthermore, certain disease gene mutations that cause neurodegenerative disorders [e.g. encoding presenilin-1, huntingtin, α-synuclein, parkin, Leucine-rich repeat kinase 2 (LRRK2) and dynein] directly impact proper autophagy progression at different steps [1]. This suggests that, although autophagy has powerful neuroprotective abilities, because it promotes the degradation of toxic proteins [2,3], the autophagy pathway itself might be a direct target of disease proteins in the CNS. In this review, we discuss current understanding of autophagy dysfunction in HD and the therapeutic potential for autophagy modulation in this complicated disorder and other related diseases.

HD: a polyglutamine repeat disorder belonging to a large family of neurodegenerative proteinopathies

HD is an autosomal dominant neurodegenerative disorder characterized by involuntary motor movement, cognitive decline and psychiatric illness. The disorder is relentlessly progressive, with a median age of disease onset of approximately 40 years, and leads to death 10–30 years after the initial presentation. HD is caused by a CAG trinucleotide repeat expansion (≥36 CAG repeats) that is located in the amino-terminal region of the Htt protein and encodes an abnormally long polyglutamine (polyQ) tract. Thus, HD is one of nine inherited neurodegenerative diseases known as CAG–polyQ repeat disorders, a category that also includes six spinocerebellar ataxias (SCA1, 2, 3, 6, 7 and 17), X-linked spinobulbar muscular atrophy (SBMA) and dentatorubral-pallidoluysian atrophy (DRPLA). One of the most striking pathological hallmarks of HD is the selective degeneration of the striatum and cortical neurons that project to the striatum. Within the HD striatum, the medium spiny neurons (MSNs) turn out to be exquisitely vulnerable. Despite this pattern of selective neuronal vulnerability, Htt protein is widely expressed and readily detected in most cell types, both within and outside of the CNS. This selective neurotoxicity in the face of widespread expression is a shared feature of all polyQ disorders.

Another feature common to polyQ disorders is the production of a disease protein that misfolds, cannot be degraded and accumulates as proteinaceous aggregates. These aggregates form in the nucleus and cytoplasm as intraneuronal inclusion bodies, and are enriched in the relevant aggregation-prone polyQ-expanded disease protein. HD inclusions mostly comprise amino-terminal fragments of polyQ-expanded Htt, and are found both in neuron nuclei and dystrophic neurites throughout the cortex and striatum of patients with HD [4,5]. The extent of these inclusions correlates with the length of the polyQ expansion, suggesting that they are a feature of HD pathology [5]. Inclusions are also enriched in ubiquitin and ubiquitinated-Htt, as well as with components of the ubiquitin proteasome system and with heat-shock protein chaperones [5].

Understanding the normal function of Htt is crucial for understanding its toxicity in the context of the polyQ expansion. Complete Htt knockout in mice is embryonic lethal, suggesting that it has a nonredundant function essential for life, with a crucial role in mouse embryonic brain development, as well as being crucial for the survival of adult neurons in the forebrain [6]. The finding that normal Htt function is essential for neuronal survival in the same brain regions that are also sensitive to polyQ-Htt toxicity suggests that a loss-of-function mechanism contributes to HD pathology. In agreement with this thesis, considerable work has shown that the polyQ expansion tract alters Htt protein folding, resulting in aberrant protein conformations, which are likely to impact Htt normal function significantly [7]. However, the dominant inheritance pattern of HD supports a gain-of-function model of polyQ-Htt toxicity. In support of this model, expression of either full-length or amino-terminal truncated forms of polyQ-Htt is sufficient to induce motor abnormalities and neurodegeneration in numerous animal models, yielding phenotypes that are reminiscent of what is observed in patients with HD. The precise nature of this gain-of-function toxicity is not known; however, transcriptional dysregulation, mitochondrial dysfunction and autophagy pathology are consistent features in HD animal models [8–11]. Thus, the HD disease mechanism is likely to be complex, and might involve a combination of gain-of-function proteotoxicity and a loss-of-function of endogenous Htt protein, stemming from aberrant protein–protein interactions caused by the polyQ expansion tract [7]. The presence of misfolded, aggregate-prone proteins in the CNS of patients with HD defines HD as a member of a large family of neurodegenerative proteinopathies, which includes AD, PD, amyotrophic lateral sclerosis, prion diseases, tauopathies and synucleinopathies.

HD: a disorder of impaired proteostasis

The finding that polyQ-Htt inclusions are positive for ubiquitin and ubiquitinated-Htt probably reflects a generalized deficiency in ubiquitin proteasome system (UPS)-mediated degradation of mutant Htt species [5]. Indeed, eukaryotic proteasomes cannot efficiently degrade long polyQ sequences, and recent work indicates that aberrant sequestration of key UPS components prevents delivery of misfolded proteins to the nuclear proteasome in HD and related disorders [12]. Failure of the UPS might lead to upregulation of autophagy via cross-talk between degradation pathways in the attempt by the cell to maintain normal proteostasis [13,14]. Whereas the proteasome has steric selectivity for its substrates and can only process those substrates that can be unfolded and passed through its core machinery, macroautophagy has no

Please cite this article in press as: C.J. Cortes, The many faces of autophagy dysfunction in Huntington's disease: from mechanistic pathways to therapeutic opportunities, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.02.014