Brain Pathology ISSN 1015-6305

MINI-SYMPOSIUM: Autophagy Dysregulation in Neuropathology
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Introduction

Since the late 1960s, neuropathologists have recognized structural changes related to alterations in autophagy and the lysosomal degradation system in multiple diseases of the nervous system. Indeed, these changes seemed so ubiquitous that for many years they were relegated to the bucket of "non-specific injury responses." With the advent of specific molecular tools to track and manipulate autophagy (4), it has become clear that perturbations in autophagy are frequently observed in diseases of the nervous system and muscle because of its essential physiological roles in these tissues (3, 5–7). Autophagy dysregulation has been described in neurons, myofibers, astrocytes, Schwann cells, oligodendrocytes and macrophage/microglia, sometimes with interactions that adversely affect neuron health. Moreover, autophagy dysregulation actively contributes to disease pathogenesis as highlighted in this Mini-Symposium. With the elucidation of specific mechanisms by which autophagy can be impaired, upregulated or dysregulated in diseases comes the promise of selective therapeutic interventions targeting autophagy.

Simply defined, autophagy refers to a group of processes by which proteins, lipids, organelles or other intracellular constituents are delivered into the lysosome for degradation. The process of macroautophagy involves *de novo* formation of membrane-bound organelles called autophagosomes, which envelope cytoplasm in general, or sequester specific organelles or protein aggregates. Although classically differentiated from endocytic and phagocytic mechanisms by virtue of the intracellular versus extracellular divide, these pathways intersect with and cross-regulate autophagosome maturation to autolysosomes. Microautophagy, which involves uptake of cytoplasm by direct invagination of lysosomal membranes, occurs in yeast and cells characterized by large lysosomes. An evolutionary latecomer, chaperone-mediated autophagy utilizes heat-shock proteins to recognize proteins with an amino acid signature for translocation through lysosomal protein pores. Macroautophagy, hereafter referred to as simply autophagy, is the most heavily studied of these in disease pathogenesis, and comprises the focus of this Mini-Symposium.

Neurons are particularly vulnerable to disruptions in autophagy, due in part to metabolic factors (2) and in part to their extremely polarized and specialized structure (1). As introduced in the article Autophagy in Dementias by Kragh *et al*, autophagy impairment may arise from deficits in inducing autophagy as well as in later stages of autophagosome maturation and lysosomal degradation. While induction relies upon correct signaling pathway integration to trigger specific covalent modifications of the membrane destined for autophagosome formation, maturation involves trafficking of completed autophagosomes along microtubules and fusion with lysosomes. Not surprisingly, dementias, which are characterized by degeneration of cortical and subcortical projection neurons, exhibit impaired autophagic clearance in Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia and HIV encephalitis.

Among the chronic neurodegenerative diseases, amyotrophic lateral sclerosis affects some of the longest projection neurons in the body—namely, the upper and lower motor neurons of the corticospinal tract that controls movement. The article Autophagy Dysregulation in Amyotrophic Lateral Sclerosis by Chen *et al* offers an in-depth review of cytoskeletal processes that are important for successful completion of autophagic degradation, and how these may be perturbed by the gene products linked to amyotrophic lateral sclerosis. These include superoxide dismutase, TDP-43, dynactin, ubiquilin 2, the endosomal sorting complex subunit CHMP2B and valosin-containing protein, the latter two of which are also implicated in frontotemporal dementias. Emerging possibilities include defective p62-related substrate sequestration, defective endosomal-multivesicular body maturation and microtubule transport.

In genetically encoded lysosomal myopathies, it has become increasingly clear that the pathogenesis of muscle weakness cannot be explained solely by the enzyme deficit, which is observed systemically. While there are several types of vacuolar myopathies, in which abnormal autophagolysosomal structures are prominent at the level of light microscopy, two are caused by mutations directly affecting lysosomal proteins: Pompe disease and Danon disease. The article Autophagy in Lysosomal Myopathies by Malicdan and Nishino reveals that the massive accumulation of autophagosomes itself may play pathogenic roles leading to symptoms or interfering with therapy. This involves destabilization of myofiber structure and impaired delivery of enzymes to the lysosome. Indeed, inhibiting autophagy induction has beneficial effects on the efficacy of enzyme replacement therapies, presumably by decreasing the levels of interfering autophagosomes.

Thus, while deficient autophagy activity impairs cellular quality control, resulting in accumulation of aggregated proteins, the induction of autophagy can also be detrimental to cells, particularly under pathological situations with reduced efficiency of autophagosome clearance. Conditions that create autophagic stress, defined as autophagy initiation that exceeds the cellular capacity for completion (1), may harm cells through multiple mechanisms. These include futile expenditure of energy and sequestration of proteins necessary for protein/vesicular transport (Malicdan and Nishino). Early autophagosomes also serve as reservoirs for pathogenic beta-amyloid production (9) and suppression of autophagy maturation by human immunodeficiency virus results in expansion of compartments beneficial for viral propagation (Kragh *et al*). At the other end of the spectrum, autophagy that proceeds to completion may be involved in muscle atrophy, retraction of axodendritic processes, mitochondrial clearance and may promote or mediate cell death (8).

In the final article Autophagy in Brain Tumors: A New Target for Therapeutic Intervention by Kaza *et al*, the double-edged role of autophagy is further highlighted in the context of developing therapies for gliomas. These neoplasms arise more commonly in astrocytes than oligodendroglia or ependymal cells, and often present as high-grade malignancies with very poor survival rates. On the one hand, autophagy proteins such as beclin 1 act as tumor suppressors, and may promote type II programmed cell death, a beneficial

feature for tumors that are resistant to apoptosis. On the other hand, autophagy promotes the survival of neoplastic cells under conditions of hypoxia and nutrient limitation. The role of autophagy in conventional chemotherapeutic and radiation therapies is discussed along with possibilities for combined therapies targeting either induction or completion of autophagy.

In summary, these articles provide a snapshot of four different neuropathological categories that illustrate the major current themes in autophagy research. It is important to keep in mind that autophagosomes are formed, undergo maturation to autolysosomes and the cargo degraded in a dynamic, continuous process. Insufficient autophagic turnover of substrates can result from deficits in autophagy induction, cargo targeting or the completion of lysosomal degradation. Induction of autophagy may have beneficial, detrimental or mixed effects depending upon whether or not there are downstream blockages, and on the overall catabolic-anabolic balance of the system. As more information is gained on the nature of autophagy disruption in diseases of the nervous system, future therapies may be designed that selectively manipulate specific aspects of this complex, dynamic and essential cellular quality control system.

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doi:10.1111/j.1750-3639.2011.00547.x