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Autophagy and apoptosis dysfunction in neurodegenerative disorders

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ABSTRACT

Autophagy and apoptosis are basic physiologic processes contributing to the maintenance of cellular homeostasis. Autophagy encompasses pathways that target long-lived cytosolic proteins and damaged organelles. It involves a sequential set of events including double membrane formation, elongation, vesicle maturation and finally delivery of the targeted materials to the lysosome. Apoptotic cell death is best described through its morphology. It is characterized by cell rounding, membrane blebbing, cytoskeletal collapse, cytoplasmic condensation, and fragmentation, nuclear pyknosis, chromatin condensation/fragmentation, and formation of membrane-enveloped apoptotic bodies, that are rapidly phagocytosed by macrophages or neighboring cells. Neurodegenerative disorders are becoming increasingly prevalent, especially in the Western societies, with larger percentage of members living to an older age. They have to be seen not only as a health problem, but since they are care-intensive, they also carry a significant economic burden. Deregulation of autophagy plays a pivotal role in the etiology and/or progress of many of these diseases. Herein, we briefly review the latest findings that indicate the involvement of autophagy in neurodegenerative diseases. We provide a brief introduction to autophagy and apoptosis pathways focusing on the role of mitochondria and lysosomes. We then briefly highlight pathophysiology of common neurodegenerative disorders like Alzheimer's diseases, Parkinson's disease, Huntington's disease and Amyotrophic lateral sclerosis. Then, we describe functions of autophagy and

Abbreviations: AMBRA, activating molecule in Beclin-1-regulated autophagy; AD, Alzheimer's diseases; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Aβ, amyloid-beta; α-syn, alpha-synuclein; ALS, amyotrophic lateral sclerosis; APP, amyloid beta precursor protein; AMPK, AMP-activated protein kinase; Apo-E, apolipo-protein E; AIF, apoptosis-inducing factor; ATG, autphagy related genes; LC3, autophagosome-associated light chain 3; BDNF, brain-derived neurotrophic factor; CMA, chaperon-mediated autophagy; ER, endoplasmic reticulum; ESCRT, endosomal sorting complexes required for transport; HEK293, human embryonic kidney 293 cells; HD, Huntington's disease; Htt, Huntingtin protein; HIP-1, Huntingtin interacting protein; InsP(6)Ks, inositol hexakisphosphate kinases; LAMP, lysosomal associated membrane proteins; MAP15, microtubule-associated protein 15; LRPPRC, mitochondrion-associated leucine-rich PPR-motif containing protein; mPTP, mitochondrial permeability transition pore; mTOR, mammalian target of rapamycin; mHtt, mutant Huntingtin protein; NMDA, *N*-methyl-D-aspartate; NCCD, nomenclature committee on cell death; PD, Parkinson's disease; PON 1–3, paraxonase enzymes; pQ, poly-glutamine; PCD, programmed cell death; PINK-1, PTEN-induced putative kinase 1; RCAN-1, regulator of calcineurin-1; RUBICON, RUN domain and cysteine rich domain containing; TDP-43-kDa, TAR DNA-binding protein 43 kDa; p53, tumor protein 53; UPS, ubiquitin-proteasome system; UVRAG, ultra-violet radiation resistance-associated gene; VCP, valosin-containing protein; XBP-1, X-box binding protein-1.

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apoptosis in brain homeostasis, especially in the context of the aforementioned disorders. Finally, we discuss different ways that autophagy and apoptosis modulation may be employed for therapeutic intervention during the maintenance of neurodegenerative disorders.

Contents

1. Introduction

In proteopathies, certain proteins become structurally abnormal, accumulate in cells and tissues, and disrupt their function (Luheshi et al., 2008). Proteopathies include diverse neurodegenerative disorders such as Alzheimer's diseases (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic lateral sclerosis (ALS) in which abnormally assembled proteins appear to play a central role (Xilouri and Stefanis, 2010). Abnormal or misfolded proteins, when aggregated in cytoplasmic, nuclear and extracellular inclusions cause organelle damage and synaptic dysfunction in the nervous system (Walker and LeVine, 2000). Two elimination pathways are currently known for damaged cellular components. Both of them control the quality of cellular components and maintain cell homeostasis. These are, the ubiquitin-proteasome system (UPS) that degrades short-lived proteins in the cytoplasm and nucleus, and the autophagy-lysosome pathway (ALP) which digests long-lived proteins and abnormal organelles just in the cytoplasm (Nijholt et al., 2011). The proper function and balance in the action of these two systems are especially important in neurons and other long-lived cells. Hence, their dysfunction contributes to pathogeneses of neurodegenerative diseases (Ciechanover, 2005; Rubinsztein, 2006).

Besides autophagy disturbances, deregulation of apoptosis is associated with a long list of pathologies, including neurodegenerative disorders (Agostini et al., 2011). After multi-cellular organisms reach adulthood, apoptotic processes remove old and damaged cells to maintain tissue homeostasis without harming adjacent cells (Hellwig et al., 2011). With the exception of post-mitotic cells such as differentiated neurons and muscle cells, which are usually highly apoptosis-resistant, the majority of other cells in the body is regularly renewed, particularly within epithelia, endothelia and the blood (Hellwig et al., 2011). Hence, recent reports have emphasized the importance of apoptosis in proteopathies diseases (Agostini et al., 2011; Hellwig et al., 2011).

Below, we briefly introduce autophagy and apoptosis pathways focusing on the role of mitochondria and lysosomes in both pathways, followed by autophagy and apoptosis function in brain homeostasis. Furthermore, some of the most common neurodegenerative diseases will be described, then, we explain characteristic