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Review

Autophagy for the quality control of adult hippocampal neural stem cells

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ABSTRACT

Autophagy plays an important role in neurodegeneration, as well as in normal brain development and function. Recent studies have also implicated autophagy in the regulation of stemness and neurogenesis in neural stem cells (NSCs). However, little is known regarding the roles of autophagy in NSC biology. It has been shown that in addition to cytoprotective roles of autophagy, pro-death autophagy, or 'autophagic cell death (ACD),' regulates the quantity of adult NSCs. A tight regulation of survival and death of NSCs residing in the neurogenic niches through programmed cell death (PCD) is critical for maintenance of adult neurogenesis. ACD plays a primary role in the death of adult hippocampal neural stem (HCN) cells following insulin withdrawal. Despite the normal apoptotic capability of HCN cells, they are committed to death by autophagy following insulin withdrawal, suggesting the existence of a unique regulatory program that controls the mode of cell death. We propose that dual roles of autophagy for maintenance of NSC pluripotency, as well as for elimination of defective NSCs, may serve as a combined NSC quality control mechanism.

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Contents

1. Introduction

Neurodegenerative diseases are characterized by progressive loss of neurons through programmed cell death (PCD) at specific anatomical and functional units (Vila and Przedborski, 2003). Lockshin and Williams defined PCD as strictly controlled cell death mechanisms regulated by various intracellular and extracellular signals (Ellis et al., 1991; Lockshin and Williams, 1965). PCD can be classified into three types according to morphological and biological characteristics; apoptosis, autophagic cell death (ACD), and necrosis (Chung and Yu, 2013; Clarke, 1990). For several decades, research regarding the molecular mechanisms of PCD in neuronal cell death has focused on identifying the pivotal signaling targets

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for therapeutic purposes. However, the PCD of NSCs remains under-studied.

Neural stem cells (NSCs), multipotent stem cells present in neurogenic niches in the brain, maintain the capacity for self-renewal, as well as for the proliferation and differentiation into neural lineage cell types (Doetsch, 2003; Temple, 2001). The discovery of the presence of multipotent NSCs in the adult mammalian brain has generated a high level of interest in both the scientific community and the public as well, based on their immediate appeal as potential therapeutic sources for the treatment of many inexorable neurodegenerative diseases. However, the results have been disappointing and dissatisfactory to date. Clearly, the neurodegeneration process affects exogenously added or endogenous NSCs residing in the neurogenic niches (Cicchetti et al., 2009). Various cellular events including neuroinflammation, deprivation of neurotrophic factors, alteration of cellular metabolism, and loss of cell–cell interaction in the stem cell niches occur in the degenerating brain areas, leading to perturbation of cellular homeostasis and the ultimate death of NSCs (Kwon, 2002; Sleeper et al., 2002).

Cellular homeostasis of NSCs will be critical in all aspects of stem cell functions. Examples of such functions include proliferation, self-renewal, multipotency, neurogenesis, and migration and incorporation into the neural circuits for regeneration. Autophagy is a vital lysosomal catabolic process for the degradation of a variety of cellular constituents including damaged or old proteins and organelles, and intracellular or extracellular pathogens (Gutierrez et al., 2004; Nakagawa et al., 2004; Shintani and Klionsky, 2004). As a basic cellular response to stress, we can infer the critical role of autophagy in the cellular homeostasis of NSCs. However, while our understanding of autophagy and related signaling mechanisms in the regulation of cellular functions and disease processes is fast improving, the role of autophagy in NSC biology remains to be elucidated. In this review, we will provide an overview of the key aspects of PCD and more closely examine the interplay between PCD and autophagy in the regulation of both homeostasis and function in NSCs. It is important to note that in stark contrast to the generally conceived cytoprotective role of autophagy, the pro-death role of autophagy in adult hippocampal neural stem (HCN) cells will be presented as well.

2. Principles and key molecules of PCD

The molecular process and causality of PCD in the CNS have been central topics of research in the past decades. For neurons, PCD is a fail-safe program that eliminates surplus populations to improve the efficiency of information processing or cellular metabolism (Williams and Herrup, 1988). PCD also counterbalances the continuous generation of new neurons by adult neurogenesis. Although proper maintenance of the functional pool of NSCs by PCD is necessary, diminished generation or accelerated death of NSCs hinders neurogenesis. We briefly highlight core regulatory molecules and biochemical pathways of apoptosis, macroautophagy, and necrosis in Section 2.

2.1. Apoptosis

The term apoptosis has been coined to describe cells undergoing distinguishable changes (including chromatin condensation, nuclear fragmentation, and cytoplasmic condensation) in both ultrastructural and biochemical events (Kerr et al., 1972). Mitochondria play a central regulatory role in sensing, adapting, and generating apoptotic signals in both intrinsic and extrinsic apoptosis (Galluzzi et al., 2012a).

In the mitochondrial pathway of intrinsic apoptosis, anti-apoptotic proteins (Bcl-2, Bcl-X_L, Mcl-1, and A1) and pro-apoptotic proteins (Bax, Bak, Bik, Bid, Bim, and Noxa) regulate cell fate (Hardwick and Soane, 2013; Huang and Strasser, 2000). At the mitochondrial outer membrane (MOM), Bax and Bak form protein-permeable pores that are large enough to release apoptogenic proteins, such as cytochrome c, Smac/Diablo, and AIF, into the cytosol (Bleicken et al., 2013). Subsequently, the released cytochrome c initiates the formation of the multimeric apoptosome complex (comprised of APAF-1, cytochrome c, and procaspase 9), followed by processing procaspase 9 and triggering of downstream caspase cascade activation (Gorman et al., 2000; Zou et al., 1999). Regulation of the multi-level apoptotic signaling pathway is best demonstrated through interaction studies of Bcl-2 proteins and Bax. Bax or Bak activation is a term connoting manifold processes of redistribution of cytosolic and monomeric Bax or Bak to mitochondria, conformational change, and oligomerization (Gavathiotis et al., 2008). Recently, the results of crystal structure studies demonstrated that an executer BH3 molecule, tBid, binds to the Bax α2 helix and disengages N-terminal α5 from C-terminal α6, thereby making Bax available to form oligomers at the MOM (Czabotar et al., 2013). Conversely, Bax oligomerization after insertion into the MOM can be prevented by Bcl-2 proteins (Mikhailov et al., 2001). In fact, overexpression of the pro-survival protein Bcl-X_L in *bcl-x*$^{-/-}$ mouse embryonic fibroblasts prevents cell death when constitutively active Bax is introduced (Fletcher et al., 2008).

Extrinsic apoptosis is a death receptor-mediated type of apoptosis that is induced by ligands, such as tumor necrosis factor α (TNFα), Fas/CD95, and TNF-related apoptosis-inducing ligand (TRAIL) (Galluzzi et al., 2012b). Receptor activation recruits procaspase 8 to the membrane-associated death inducing signaling complex (DISC) complex for proteolytic activation into a mature form (Chang et al., 2003). Activation of caspase 8 cleaves the N-terminal portion of Bid, and the subsequent translocation of the truncated Bid (tBid) to mitochondria induces release of cytochrome c in Fas- or TNFα-induced apoptosis (Li et al., 1998).

2.2. Necrosis

Cells challenged with death ligands suffer necrosis in a programmed manner rather than apoptosis when caspase activation is inhibited or when the intracellular ATP concentration is not sufficient to facilitate apoptosis (Kawahara et al., 1998; Leist et al., 1997). Upon receiving a necrotic signal, receptor interacting protein kinase (RIP)-1 and -3 form a hetero-oligomeric amyloidal signaling complex, denoted as the 'necrosome,' which is required for the kinase activities of RIP1/RIP3 (Li et al., 2012; Wallach et al., 2011). RIP1/3 kinase activation leads to mitochondrial permeability transition pore opening, resulting in dysfunctional mitochondrial respiratory function. As a consequence, ATP depletion leads to a metabolic failure, breakdown of the plasma membrane, and subsequently, intense inflammation in vivo (Dorn, 2013). Whether necrosis is a consequence of inflammation or a direct cause of inflammation is difficult to determine at present (Wallach et al., 2011).

2.3. Autophagy

Autophagy is a physiological process that catabolizes cytoplasmic materials including long-lived proteins and dysfunctional organelles in order to provide cells with new building materials and energy via autophagosomes and lysosomes (De Duve and Wattiaux, 1966; Yang and Klionsky, 2010b). More than 36 autophagy-related (Atg) genes that regulate autophagy have been identified, most of which are conserved in yeast and mammals (Klionsky et al., 2011). Early autophagosome formation requires