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Role of autophagy in environmental neurotoxicity☆

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ABSTRACT

Human exposure to neurotoxic pollutants (e.g. metals, pesticides and other chemicals) is recognized as a key risk factor in the pathogenesis of neurodegenerative disorders. Emerging evidence indicates that an alteration in autophagic pathways may be correlated with the onset of the neurotoxicity resulting from chronic exposure to these pollutants. In fact, autophagy is a natural process that permits to preserving cell homeostasis, through the seizure and degradation of the cytosolic damaged elements. However, when an excessive level of intracellular damage is reached, the autophagic process may also induce cell death. A correct modulation of specific stages of autophagy is important to maintain the correct balance in the organism. In this review, we highlight the critical role that autophagy plays in neurotoxicity induced by the most common classes of environmental contaminants. The understanding of this mechanism may be helpful to discover a potential therapeutic strategy to reduce side effects induced by these compounds.

1. Introduction

The nervous system is the most complex and highly organized system of the human body for its structure and function. It plays an important role in coordinating the activities of other organ systems, in mediating communication with the environment, and in maintaining metabolic balance.

Thus, damage to the nervous system may produce severe consequences (National Research Council, 1992). Indeed, though the nervous system has several compensatory and adaptive mechanisms, it is vulnerable to toxic insult, due to its inability to regenerate after lethal damage and because of a number of intrinsic characteristics (e.g., its dependence upon aerobic metabolism, the presence of axonal transport, the process of neurotransmission) (Office of Technology Assessment, 1990; National Research Council, 1992). Moreover, the developing nervous system is more susceptible to neurotoxic chemicals. For this reason, several neurotoxicants are primarily developmental neurotoxicants, and show different toxicity during development and in adulthood (Giordano and Costa, 2012).

A large number of environmental contaminants are able to induce neurotoxicity, defined as any adverse effect on the central or peripheral nervous system. Depending on their chemical profile, time of exposure, and dose, the environmental contaminants may affect the nervous system both directly and indirectly (Cannon and Greenamyre, 2011; Manivannan et al., 2015; Wani et al., 2015). Indeed, neurotoxicity can also manifest as a consequence of damage to other organ, such as, for example, damage to hepatic or cardiovascular structures. In particular, pollutants may induce morphological changes (e.g. neuronopathy, axonopathy, myelinopathy, and other gliopathies) and neurochemical changes in humans (Genc et al., 2012; Wani et al., 2015). These effects are considered adverse, even if they are mild, transient or reversible: in fact, they lead to impaired function and structure of nervous system (Giordano and Costa, 2012). Several data suggest an association between the onset of neurologic impairment and exposures to environmental pollutant. More studies show that neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, may be correlated with exposure to environmental contaminant (Elbaz and Moisan, 2008; Lauer, 2010; Genc et al., 2012). Similarly, exposure to environmental neurotoxicants has also been associated with neurodevelopmental disorders (Giordano and Costa, 2012).

In this review, we examine the role of autophagy in pollutants-induced neurotoxicity. The understanding and decipherment of this mechanism may be helpful to identifying potential targets and novel strategies for neuroprotection against side effects induced by environmental contaminants.

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2. Autophagy

Autophagy is a well-conserved intracellular process resulting in the irreversible degradation of cellular constituents, which takes place in all eukaryotic cells. The term "autophagy" [self (auto)-eating (phagy)] was introduced by Christian de Duve in 1963, and the process was first identified in yeast cells under starvation condition (Klionsky, 2008). Since then, autophagy has been extensively studied, with the discover of 32 autophagy-related genes (ATGs), earlier identified in the *Saccharomyces cerevisiae* and in the *Pichia pastoris*, and later also in higher eukaryotes (Pyo et al., 2012; Orrenius et al., 2013).

Autophagy is characterized by the formation of vesicles (autophagosomes), able to fuse with lysosome (mammals) or vacuole (plant, fungi), where the degradation of damaged parts of cytoplasm occurs (Todde et al., 2009). The lysosomal hydrolases degrade the damaged material and convert it in monomeric units, useful for cell survival. This event can in some instances be preceded by an additional step in which the autophagosome initially merges with the endosomal vesicles and only subsequently with lysosomes (Glick et al., 2010). Autophagy occurs in almost all cell types and it is useful to maintain cellular homeostasis, allowing cellular differentiation, tissue remodelling, growth control, cell defence, and adaptation to adverse environments (Cuervo, 2004). Indeed, under conditions of cellular stress (e.g. oxidative stress and starvation), autophagy participates in cell survival, providing the cells with all the substances necessary for energy production (Rodolfo et al., 2016). Inhibition of autophagy caused by several factors accelerates cell death in mammals (Orrenius et al., 2013). For example, increasing age causes a progressive decline in the ability of the autophagic process to remove the damaged intracellular components (Cuervo et al., 2005). In contrast, dietary caloric restriction is able to stimulate autophagy (as indicated by an increase of autophagosomes) and to protect nerve cells, thereby improving learning and memory abilities (Dong et al., 2016). Sometimes, however, an increase in the number of autophagosomes may reflect a reduction in autophagosome turnover or the inability to remove the new autophagosome formation (Wong and Cuervo, 2010; Klionsky et al., 2016). However, autophagy may also be a double-edged sword, as in addition to a protective role, it may also contribute to cell death (Zhang et al., 2016). For this reason, autophagy can be defined as a type II programmed cell death (Bursch et al., 2000; Berry and Baehrecke, 2008), to distinguish it from apoptosis.

2.1. Mechanisms of autophagy

The three major forms of autophagy described in mammalian cells are macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) (Mizushima and Komatsu, 2011; Boya et al., 2013). They differ primarily for the mechanisms used to degrade altered organelles (He and Klionsky, 2009) (Fig. 1). Macro- and microautophagy occur in all eukaryotes (mammals, plants and fungi), while CMA is only described in mammals. Although these processes may occur at the same time in the same organism, generally the activation of a type of autophagy depends principally from the inducers, and by environmental conditions (Todde et al., 2009).

The predominant form of autophagy, macroautophagy, is characterized by the sequestration of cytosolic faulty elements in a double membrane structure (autophagosome), where degradation occurs. The membrane of the autophagosome merges with the lysosome membrane with consequently formation of the autophagolysosome and destruction of macromolecular cargo by the lysosomal hydrolases. Subsequently, the membrane of the vesicle is rapidly degraded and the monomeric units can be recycled for energy production and/or other biosynthetic reactions (Yang and Klionsky, 2010; Wong et al., 2011) (Fig. 1). Several proteins, called Atg proteins, are involved in the macroautophagic process. These proteins form multi-molecule complexes, such as the Beclin 1-VPS34 class III phosphoinositide 3-kinase (PI3K) complex, and the Atg5-Atg12-Atg16 and Atg8/LC3 conjugation systems, which are able to regulate phagosome formation (Boya et al., 2013; Feng et al., 2014). In particular, Beclin 1, the mammalian orthologue of yeast Atg6, has an important role in autophagic pathways. Indeed, it interacts with several cofactors (Atg14L, UVRAG, Bif-1, Rubicon, Ambra1, HMGB1, nPIST, VMP1, SLAM, IP3R, PINK and survivin) to regulate the lipid kinase Vps-34 protein and promote formation of Beclin 1-Vps34-Vps15 core complexes, inducing autophagy (Kang et al., 2011).

Another major form of autophagy is microautophagy. The term indicates a non-selective lysosomal degradative process present in mammalian cells. Indeed, microautophagy induces the elimination of small portions of cytoplasmatic elements that are wrapped directly from the lysosomal membrane without requiring the formation of autophagic vacuoles. In this way, microautophagy contributes to maintain cellular homeostasis (Mijaljica et al., 2011) (Fig. 1).

These two processes are the most frequent catabolic events involved in the degradation of the functional organelles, such as the endoplasmic reticulum (reticulophagy), and ribosomes (ribophagy) (Orrenius et al., 2013). An additional, well-studied type of autophagy is mitophagy, which degrades damaged or excessive mitochondria (Ding and Yin, 2012; Ashrafi and Schwarz, 2013) (Fig. 2). The process may be both selective and non-selective. However, in mammalian cells, mitochondrial elimination seems to occur more by macroautophagy than microautophagy (Tolkovsky, 2009). Whilst lack of mitophagy seems to be deleterious, understanding the interplay between autophagy, mitochondrial performance, and cell pathology is a much-needed area of research. Mitophagy is also necessary for production of cellular energy, calcium homeostasis, redox signaling, and apoptotic signaling (Zhang, 2015). Moreover, mitophagy is used by cells as a response to hypoxia; through this process, cells are able to limit production of reactive oxygen species, reducing mitochondrial mass (Tracy and Macleod, 2007). There are three different variants of mitophagy (Fig. 2). Type 1 mitophagy (which occurs during nutrient deprivation) is characterized by the formation of phagophore, that sequesters mitochondria and generated mitophagosome. After that, the mitophagosome fuses with lysosomes, and the hydrolytic enzymes induce the degradation of the mitochondrion. Type 2 mitophagy is induced when mitochondria are subject to injury by photodamage or other injurious stresses, and mitochondrial depolarization occurs. The vesicles fuse with the depolarized mitochondrion, and form a mitophagosome, that is processed as in Type 1 mitophagy. A third form of mitochondria degradation (micromitophagy) consists in the formation of mitochondria-derived vesicles containing oxidized mitochondrial proteins. These transit first in multivesicular bodies and then in lysosomes. The internalization of mitochondria-derived vesicles by invagination of the surface of multivesicular bodies followed by vesicle scission into the lumen (Soubannier et al., 2012a,b; Lemasters, 2014; Sun et al., 2015) (Fig. 2).

The last autophagic process, CMA, is a multistep process in which cytosolic faulty proteins are degraded in lysosomes. Defective proteins are selectively targeted by chaperones and brought to lysosomes. In contact with the membrane, they bind to lysosomal receptors and this connection permits the translocation of the proteins into the lumen, where the proteins are digested. Through this process CMA, like macroautophagy and microautophagy,