Autophagy

Autophagy (or autophagocytosis) (from the Greek auto-, “self” and phagein, “to eat”), is the basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components.

Autophagy is an important cellular catabolic process that functions to maintain homeostasis by degrading excessive or unnecessary proteins and dysfunctional cellular organelles in living cells.

Autophagy is a process of self-cannibalization. Cells capture their own cytoplasm and organelles and consume them in lysosomes. The resulting breakdown products are inputs to cellular metabolism, through which they are used to generate energy and to build new proteins and membranes. Autophagy preserves the health of cells and tissues by replacing outdated and damaged cellular components with fresh ones. In starvation, it provides an internal source of nutrients for energy generation and, thus, survival. A powerful promoter of metabolic homeostasis at both the cellular and whole-animal levels, autophagy prevents degenerative diseases. It does have a downside, however–cancer cells exploit it to survive in nutrient-poor tumors [1)].

Unlike every other organ in the body, the brain parenchyma lacks a traditional lymphatic system to drain fluids and central nervous system (CNS) antigens. It was historically assumed that all brain wastes were removed by endogenous processing, such as phagocytosis and autophagy, while excess fluids drained directly into the blood. However, the twin discoveries of the glial-lymphatic (glymphatic) system and meningeal lymphatics have transformed our understanding of brain waste clearance. The glymphatic system describes the movement of fluids through the subarachnoid space (SAS), the influx along periarterial spaces into the brain parenchyma, and the ultimate efflux back into the SAS along perivenous spaces where it comes into direct contact with the meningeal lymphatics. The dura mater of the meninges contains a bona fide lymphatic network that can drain CSF that has entered the dura. Together, these pathways provide insights into the clearance of molecules and fluids from the brain, and show that the CNS is physically connected to the adaptive immune system. [2)]

Injury mechanism and treatment of blast traumatic brain injury has not made a breakthrough so far. Previous reports demonstrate autophagy is involved in regulating the pathophysiological process after traumatic brain injury. Therefore, a study explored whether autophagy was activated after blast traumatic brain injury. A total of 108 mice were divided randomly into six groups: 6 h, 1 d, 3 d, 7 d, 14 d after bTBI groups and sham group. The protein levels of anti-microtubule associated protein 1 light chain 3B (LC3B, hereafter referred to as LC3), beclin1, and p62 were detected using western blot. Moreover, HO-1 and Nrf2 were localized using histologic staining. Immunofluorescence of LC3 and immunohistochemistry of beclin1 were performed. The autophagy-related ultrastructure was observed by TEM. LC3-II and beclin1 reached their peak on day 3 after bTBI, while p62 showed a continuous downward trend. Immunofluorescence and immunohistochemistry also confirmed that the expression levels of LC3 and beclin1 were the highest at 3 days after bTBI. Autophagic vesicles containing lysosomes or digestive residual structures were observed then. Autophagy was induced in the frontal lobe tissues of bTBI mice induced by moderate-intensity explosion, with a peak at 3d and a gradual decline thereafter [3)]

Autophagy could promote tumor growth in specific cancer types. Tumor intrinsic PD1 or PD-L1 could both increase autophagy through ATG13 interaction [4].

The effects of autophagy on neuronal damage can be positive or detrimental negative. By establishing a model of fetal rat cortical neuron hydraulic shock injury, dipotassium bisperoxo (picolinoto) oxovanadate (V) [bpv(pic)] was used to inhibit PTEN at different time points post-injury and autophagy level after neuronal injury was assessed. Neurons were divided into several intervention groups according to the time point at which bpv(pic) was used to inhibit autophagy, normal neurons, and injured neurons were set as two control groups. The growth of neurons in each group was assessed through immunofluorescence staining. Expression of the autophagy-related proteins LC3-II and LC3-I was analyzed by western blot. Expression of PTEN, mTOR and Beclin-1 was detected by RT-PCR. The number of autophagosomes in the normal group, injury control group and 24 h, 36 h intervention groups were assessed by an electron microscope. We found that autophagy was enhanced after neuronal injury and that the levels of LC3-II was significantly reduced by bpv (pic) intervention. The growth of the injury control groups was worse than normal groups, while improved through bpv(pic) intervention at 24 h and 30 h after injured. Western blot analysis showed that the LC3-II and LC3-II/LC3-I ratios of cells increased post-injury, and autophagy induction was evident by electron microscopy. These effects were confirmed by RT-PCR analysis. Taken together, these data suggest that autophagy is activated after injury in neurons while can be inhibited by bpv(pic) administration and then promote the repair of injured neurons [5].

Many studies have provided compelling evidence that autophagy is involved in brain tumor recurrence and chemotherapy and radiotherapy resistance. Gliomas, as the primary central nervous system (CNS) tumors, are characterized by rapid, aggressive growth and recurrence and have a poor prognosis and bleak outlook even with modern multimodality strategies involving maximal surgical resection, radiotherapy and alkylating agent-based chemotherapy. Autophagy-associated signaling pathways, such as the extracellular signal-regulated kinase1/2 (ERK1/2) pathway, class I phosphatidylinositol 3-phosphate kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway and nuclear factor kappa-B (NF-κB) pathway, act as tumor suppressors or protect tumor cells against chemotherapy/radiotherapy-induced cytotoxicity in gliomagenesis. Through these pathways, both lethal autophagy and protective autophagy play crucial roles in tumor initiation, chemoresistance and glioma stem cell differentiation. Moreover, lethal autophagy and protective autophagy have been identified as novel therapeutic targets in glioma according to the mechanisms described above [6]

Autophagy is a tightly-regulated catabolic process of cellular self-digestion by which cellular components are targeted to lysosomes for their degradation. Key functions of autophagy are to provide energy and metabolic precursors under conditions of starvation and to alleviate stress by removal of damaged proteins and organelles, which are deleterious for cell survival. Therefore, autophagy appears to serve as a pro-survival stress response in most settings. However, the role of autophagy in modulating cell death is highly dependent on the cellular context and its extent. There is an increasing evidence for cell death by autophagy, in particular in developmental cell death in lower organisms and in autophagic cancer cell death induced by novel cancer drugs. The death-promoting and -executing mechanisms involved in the different paradigms of autophagic cell death (ACD) are

very diverse and complex, but a draft scenario of the key molecular targets involved in ACD is beginning to emerge [7].

Autophagy plays a critical role in spinal cord injury (SCI), including traumatic spinal cord injury (TSCI) and ischemia-reperfusion spinal cord injury (IRSCI).

However, while the understanding of mechanisms underlying autophagy in SCI has progressed, there remain several controversial points: (1) temporal pattern results of autophagic activation after SCI are not consistent across studies; (2) effect of accumulation of autophagosomes due to the blockade or enhancement of autophagic flux is uncertain; (3) overall effect of enhanced autophagy remains undefined, with both beneficial and detrimental outcomes reported in SCI literature. In this review, the temporal pattern of autophagic activation, autophagic flux, autophagic cell death, relationship between autophagy and apoptosis, and pharmacological intervention of autophagy in TSCI (contusion injury, compression injury and hemisection injury) and IRSCI are discussed. Types of SCI and severity appear to contribute to differences in outcomes regarding temporal pattern, flux, and function of autophagy. With future development of specific strategies on autophagy intervention, autophagy may play an important role in improving functional recovery in patients with SCI [8].

Intracranial aneurysm formation and rupture might be related to autophagy and immune responses, which possibly accounts for proteolytic degradation of vessel wall connective tissues and cytoskeleton components [9].

Autophagy-related genes

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Chaperone-mediated autophagy

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