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Roles of autophagy in pathogenesis of lysosome storage disease and neuron death after hypoxic-ischemic brain injury

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We have shown that autophagy contributes to the accumulation of vacuolar structures in neurons obtained from CD-/- and CB-/-CL-/- mice, murine models for neuronal ceroid lipofuscinoses (NCLs). In these mutant mice, abnormal vacuolar structures accumulating in neurons of the brains resemble autophagosomes/autolysosomes (Koike et al. 2000; NAkanishi et al. 2001; Koike et al. 2003; Koike et al. 2005). An increased conversion of the molecular form of LC3 was demonstrated for autophagosome formation, from LC3-I, a cytosolic form, to LC3-II. The membrane-bound LC3-II form predominated in both cathepsin D-deficient and cathepsins B and L-deficient mouse brains, while LC3 signals accumulated in granular structures located in neuronal perikarya and axons of these mutant brains and were localized to the membranes of autophagosomes, evidenced by immunofluorescence microscopy and freeze-fracture-replica immunoelectron microscopy (Koike et al. 2005). Moreover, like cathepsin D-deficient neurons, autofluorescence and subunit c of mitochondrial ATP synthase accumulated in cathepsins B and L-deficient neurons, indicating that not only cathepsin D-deficient but also cathepsins B and L-deficient mice could be animal models for neuronal ceroid-lipofuscinosis/Batten disease (Koike et al. 2005). These data strongly argue for a major involvement of autophagy in the pathogenesis of Batten disease/lysosomal storage disorders. Until recently, it remains largely unknown what signaling is essential for autophagosome formation. Interestingly, in the conditional Atg7-knock-out mice where autophagy is absent specifically in the liver or brain, numerous ubiquitinated aggregates are detected in the cytosol of hepatocytes, suggesting that protein ubiquitination may serve as a signal to the autophagic process (Komatsu et al. 2005; 2006). We therefore examined the immunohisto/cytochemical localization of ubiquitin and LC3, and found that in our NCL model mice, positive signals for ubiquitin and LC3 were co-localized on the membranes of granular structures in the neuronal perikarya. From these results it is likely that protein ubiquitination may be involved in signaling for autophagosome formation in NCLs. It has been shown that the lysosomal system including autophagy is activated in the CA1 pyramidal neurons of gerbil hippocampus after brief forebrain ischemia (Nitatori et al. 1995). The mechanism underlying neuronal death in hypoxia and ischemia brain injury is excitotoxicity, while the cell death mode associated with ischemic brain injury still remains controversial. We examined neuron death in the CA1 pyramidal layer of the hippocampus in young mice after hypoxic-ischemic (H-I) brain injury and found that the activation of caspase-3 occurred within 24 hr after H-I injury, while TUNEL-positive neurons appearing abundantly at 3 days after H-I insult were negative for caspase-3 but positive for LC3. These lines of data indicate that autophagy may play an important role in neuron death in the CA1 region after H-I brain injury. Thus autophagy that plays an essential role in the metabolism of mammalian cells is largely associated with pathogenesis of neurodegenerative diseases.

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