



Endoplasmatic reticulum turnover and outcome of sepsis

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Abstract

Autophagy is an evolutionarily conserved strategy to respond to organelle damage. Stress events associated with infection, such as “pathogen-associated molecular pattern” receptor signaling, hypoxia and redox changes, as well as protein unfolding are well known triggers to induce autophagy limiting the development of tissue injury and subsequent organ dysfunction. Damaged organelles, including ER are captured by the isolation membrane. The resulting autophagosome then fuses with lysosomes, initiating degradation and recycling. Consequently, autophagy and its manipulation by pathogens may modulate host resistance primarily via tissue damage control, and disease tolerance in the context of infection. The few experimental data available so far suggest beneficial effect via a mechanism involving components of the unfolded protein as well as autophagy damage response, e.g. the autophagy protein microtubule-associated protein 1 light chain-3B (LC3B) and the autophagy-related protein 7 (Atg7) primarily implying a role in mitophagy. Thus, mitophagy (and autophagy in general) might provide tissue damage control in parenchymal tissues conferring disease tolerance to sepsis, i.e. infection associated with an inappropriate host response characterized by organ dysfunction.

Members of the reticulon protein family, i.e. FAM134, that act as ER-resident receptors binding autophagy modifiers such as LC3B have recently been shown to facilitate ‘ER-phagy’. FAM134B facilitated ER-phagy reflects a central housekeeping mechanism and its lack leads to sensory neuropathy. The FAM134 family of proteins consists of 3 isoforms with different tissue-specific expression patterns but their role under inflammatory stress conditions remains unknown. We hypothesize that these proteins differentially modulate tissue-specific stress responses upon life-threatening infections ultimately protecting against development of, or propagating resolution from multi-organ dysfunction associated with sepsis.