HMGB1 (high mobility group box 1) is a multifunctional, ubiquitous protein located inside and outside cells that plays a critical role in various physiological and pathological processes including cell development, differentiation, inflammation, immunity, metastasis, metabolism, and death. Increasing evidence demonstrates that HMGB1-dependent autophagy promotes chemotherapy resistance, sustains tumor metabolism requirements and T cell survival, prevents polyglutamine aggregates and excitotoxicity, and protects against endotoxemia, bacterial infection, and ischemia-reperfusion injury in vitro or in vivo. In contrast, HMGB1 may not be required for autophagy in some organs such as the liver and heart. Understanding HMGB1-dependent and -independent autophagy in more detail will provide insight into the integrated stress response and guide HMGB1-based therapeutic intervention.

HMGB1-Dependent Autophagy

HMGB1 participates in the autophagy process at several levels (Fig. 1A). First, HMGB1 translocates to the cytoplasm following several autophagic stimuli (e.g., hydrogen peroxide, rapamycin, and starvation), which in turn promotes autophagy through direct interaction with BECN1 to dissociate it from BCL2 in immortalized mouse embryonic...
fibroblasts and cancer cells. Meanwhile, HMGB1 C23S and C45S mutants lose their ability to mediate autophagy, as they are unable to bind BECN1 and therefore cannot disrupt BCL2-BECN1 interactions. In addition, the HMGB1-BECN1 complex seems to be tightly controlled at the transcriptional, post-transcriptional, post-translational, and protein-protein interaction level. For example, ULK1 (unc-51 like autophagy activating kinase 1), MAPK (mitogen-activated protein kinase), and NACC1 (nucleus accumbens associated 1, BEN and BTB [POZ] domain containing) positively regulate HMGB1-mediated autophagy, whereas TP53, SNCA/α-synuclein, IFI30/gamma-interferon-inducible lysosomal thiol reductase, MIR34A, and MIR22 negatively regulate HMGB1-mediated autophagy. Second, HMGB1 induces autophagy and tumor growth through AGER/RAGE (advanced glycosylation end product-specific receptor), whereas oxidized HMGB1 induces apoptosis in cancer cells. HMGB1 released from cancer cells induces autophagy in the muscle, which sustains anaerobic energy production (namely the Warburg effect) during tumor growth in vitro and in vivo. These findings suggest that HMGB1 is an important mediator of systemic autophagic syndrome.

**HMGB1-Independent Autophagy**

HMGB1 global knockout mice die shortly after birth due to the downregulation of glucocorticoid receptor and subsequent hypoglycemia, suggesting a critical role for HMGB1 in sustaining life. We and others recently generated transgenic mice with conditional knockout (Fig. 1B) or knockin (Fig. 1C) of HMGB1 within the pancreas, liver, heart, and myeloid cells through a different strategy. All these mice were viable and had no significant defects such as glucose and energy metabolism defects under unstressed growth conditions. However, these mice have various, even opposite, phenotypes in response to different stressors. For example, knockout of HMGB1 in the pancreas (n = 18–25 mice per group), liver (n = 6 mice per group), and myeloid cells (n = 6–9 mice per group) make mice more sensitive to sterile inflammation (e.g., pancreatitis and liver ischemic reperfusion) and infection (e.g., lipopolysaccharide and *L. monocytogenes*), partly through downregulation of autophagy and upregulation of mitochondrial injury and nuclear catastrophe. Knockin of HMGB1 in the heart protects mice against myocardial infarction.
In contrast, a recent study from Robert Schwabe's lab indicates that HMGB1 is not required for mitochondrial function and autophagy in the liver. In this study, the authors crossed HMGB1 conditional liver knockout mice with GFP-LC3 mice and then starred these mice for 24 h (n = 3 mice per group). The expression patterns of GFP-LC3 puncta and GFP-LC3 cleavage were similar between these mice upon starvation, suggesting that an HMGB1-independent autophagy system exists in the liver. Although the exact mechanism of this phenotype is not clear, a major difference between Robert Schwabe's engineered HMGB1 mice and other groups is the tissue-level expression of HMGB1 after knockout. Mice with hepatocyte-specific deletion of Hmgb1 from Robert Schwabe's lab are not complete conditional knockout mice; the protein level of HMGB1 in the liver is decreased by about 70%. Thus, autophagy appears to correlate with HMGB1 protein level, and low HMGB1 levels may still maintain autophagy pathway activation. Moreover, the original GFP-LC3 mice study by Mizushima et al. demonstrated that the regulation of autophagy is tissue/organ-dependent and not restricted to a starvation response at 24 or 48 h.

Conclusions

It has become clear that HMGB1-dependent autophagy promotes chemotherapy resistance and T cell survival, prevents polyglutamine aggregates and excitoxicity, and protects against endotoxemia, bacterial infection, and ischemia-reperfusion injury. However, many questions remain unanswered regarding HMGB1-independent autophagy in the liver, including its tissue-specific role. HMGB1 dysfunction has been implicated in various forms of liver disease ranging from liver damage to fibrosis, as well as tumorigenesis. Extensive research is needed to determine the relationship between HMGB1, autophagy, and liver diseases. Of note, primary cells and cell lines have different baseline levels of autophagy as well as HMGB1 because transformed cell lines display different gene expression profiles. Understanding HMGB1-dependent and independent autophagy in more detail will provide insight into the integrated stress response and guide HMGB1-based therapeutic intervention in cancer and other diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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