

Damage-associated molecular pattern molecules [DAMPs], Autophagy, and Redox Regulate Immunity

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Abstract: OBJECTIVES - Our recent discovery of cytosolic HMGB1 as an inducer of autophagy and others of cytosolic p53 as an inhibitor of autophagy has placed these two molecules at the crux of metabolism. HMGB1 is a cytosolic activator of autophagy and associated with post-translational modifications of p53. HMGB1 serves as a damage-associated molecular pattern molecule [DAMP] interacting with the RAGE, TLR2, TLR4 or TLR9 central to sepsis, arthritis, myocardial and hepatic ischemia reperfusion, and cancer.

METHODS - Western blotting, imaging cytometry, automated measures of oxygen consumption/extracellular acidification, and confocal microscopy.

RESULTS - We identified a novel role for HMGB1 as a cytosolic factor promoting autophagy and mitophagy, enhancing aerobic glycolysis, rapid ATP generation, and limiting apoptosis. Autophagic stimuli promoted cytosolic and mitochondrial translocation and non-necrotic HMGB1 release, inhibited by PI3K/AKT inhibitors. HMGB1 knockouts had markedly diminished autophagy and enhanced apoptosis in response to stress. Colocalization of LC3-II and mitochondrial markers including HSP70 required pERK1/2 and Beclin 1 HMGB1-mediated translocation to the mitochondria. Cytosolic HMGB1 displaced BCL-2 by binding Beclin-1 promoting autophagy and limiting apoptosis. Oxidative phosphorylation, ATP generation, generation of ROS, and the number of mitochondria were profoundly diminished in cells lacking HMGB1. Exogenous reduced HMGB1 furthermore enhanced survival limiting ROS generation in epithelial tumors but required HMGB1 B-box activity to enhance survival whereas both the A-box and B-box were competent to enhance autophagy.

CONCLUSIONS - HMGB1 serves as a critical link, regulating metabolism, the response to stress, and cellular survival. This is perhaps best demonstrated in the setting of infectious diseases and cancer.

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