High mobility group box 1 mediates caspase-11-dependent lethality in sepsis

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Lv Ben (吕奔) at the Department of Hematology and Key Laboratory of Non-resolving Inflammation and Cancer of Hunan Province, The 3rd Xiangya Hospital, Central South University, recently reported that High Mobility Group Box 1 Mediates Caspase-11-Dependent Lethality in Sepsis in *Immunity* (2018, 49: 740—753), and this study was commented in "HMGB1: LPS Delivery Vehicle for Caspase-11-Mediated Pyroptosis" in *Immunity* (2018, 49: 582—584).

Caspase-11, a cytosolic endotoxin (lipopolysaccharide: LPS) receptor, mediates pyroptosis, a lytic form of cell death. Caspase-11-dependent pyroptosis mediates lethality in endotoxemia, but it is unclear how LPS is delivered into the cytosol for the activation of caspase-11. Prof. Lv's team discovered that hepatocyte-released high mobility group box 1 (HMGB1) was required for caspase-11-dependent pyroptosis and lethality in endotoxemia and bacterial sepsis. Mechanistically, hepatocyte-released HMGB1 bound LPS and targeted its internalization into the lysosomes of macrophages and endothelial cells via the receptor for advanced glycation end-products (RAGE). Subsequently, HMGB1 permeabilized the phospholipid bilayer in the acidic environment of lysosomes. This resulted in LPS leakage into the cytosol and caspase-11 activation. Depletion of hepatocyte HMGB1, inhibition of hepatocyte HMGB1 release, neutralizing extracellular HMGB1, or RAGE deficiency prevented caspase-11-dependent pyroptosis and death in endotoxemia and bacterial sepsis. These findings indicate that HMGB1 interacts with LPS to mediate caspase-11-dependent pyroptosis in lethal sepsis.

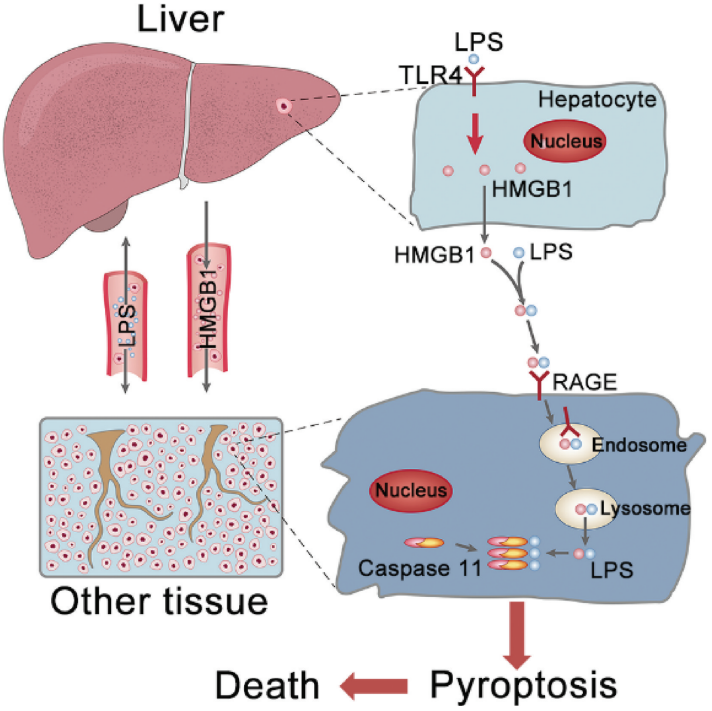

Figure Hepatocytereleased HMGB1 mediates caspase-11- dependent pyroptosis and lethality in sepsis by delivering extracellular LPS into the cytosol of macrophages and endothelial cells, where LPS activates caspase-11.