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Regulation of HMGB1 in Hepatocytes by MyD88 and Type-I interferon (IFN-I) During *Ehrlichia*-induced acute liver injury.

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Background: Liver is the major target organ in Human Monocytic ehrlichiosis (HME), an undifferentiated febrile illness that is life-threatening and caused by intracellular bacterial pathogen, *Ehrlichia,* that target liver and infect macrophages, hepatocytes and endothelial cells. Severe Hepatic inflammation is the common cause of acute liver injury following systemic infection with *Ehrlichia*. Our previous studies have shown that Myeloid differentiation primary response gene 88 (MYD88) and type I IFN (IFN-I) promotes excessive inflammation and liver damage following fatal *Ehrlichia* infection. In this study, we explored the role of the MyD88 and IFN-I in liver inflammation.

Results: In this study, we provide evidence to support that high mobility group box 1 (HMGB1), a chromosomal protein and damage-associated molecular patterns (DAMPs), plays a role in the regulation of innate responses and autophagy during *Ehrlichia* infection. Wild-type (WT) mice infected with virulent *Ehrlichia* develop sepsis and liver injury marked by excessive systemic production of pro-inflammatory cytokines and chemokines as well as HMGB1. To determine the cellular source of HMGB1 and regulatory mechanisms, we infected hepatocytes (HC) from WT and MYD88$^{-/-}$ knockout mice with virulent *Ehrlichia*. To mimic paracrine effect of IFN-I cytokines produced by immune cells on HC response to *Ehrlichia* infection, we cultured infected HC in the presence or absence of IFN-β (100 IU/mL). Our data indicate that *in-vitro* infected HC produces low levels of IFN-beta compared to uninfected cells. Exogenous stimulation of infected HC with IFN-β induced elevated expression and cytoplasmic translocation of HMGB1 in WT-HC. This was associated with increased autophagy and higher expression of IL-23R, IFNAR, and heightened JAK/STAT signaling. Importantly, the effect of high dose IFN-I on autophagy and HMGB1 was MYD88-dependent. Interestingly, infection of MYD88$^{-/-}$ HC with *Ehrlichia*, in the absence of exogenous IFN-β, enhanced autophagy induction and cytosolic translocation of HMGB1, suggesting that MYD88 negatively regulate HMGB1 and autophagy in HC in the absence of the paracrine effect of IFN-β.

Conclusion: Together, our data suggest that autophagy regulation and HMGB1 response in hepatocytes during *Ehrlichia*-induced sepsis is controlled by the strength of IFN-I signaling and dependent on interplay between MYD88 and IFN-I pathways.

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