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-1 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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