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Type-I interferon-mediated Akt/mTORC2 signaling regulates autophagy and inflammasome activation in mouse liver injury/sepsis model

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Background: Sepsis is a clinical syndrome due to dysregulated systemic immune response to infection and tissue injury that causes life-threatening multiple organ failure. In murine model of sepsis and hepatic inflammatory injury induced by infection with *Ehrlichia*, an obligate intracellular bacteria targeting liver that compromises the immune system, we have shown that type I interferon (IFN-I) signaling triggered liver injury, excessive inflammation, and impaired bacterial clearance. We and others have also showed that *Ehrlichia* exploits autophagy proteins for their own survival and replication. This study was designed to investigate the role of IFN-I signaling in the regulation of autophagy and inflammatory responses in immune and non-immune cells such as macrophages and hepatocytes, respectively, during sepsis.

Results: In this study, we found that IFN-I signaling promotes autophagy and activates non-canonical inflammasome pathway mediated by caspase 11 in primary murine macrophages and hepatocytes. Enhancement of autophagy in hepatocytes and macrophages via IFN-I stimulation or rapamycin treatment increased bacterial replication. Conversely, inhibition of autophagy in macrophages using type III Phosphatidylinositol 3-kinases (PI-3K) inhibitor (3-MA) or blocking IFN-I receptor (IFNAR) signaling attenuated autophagy, abrogated caspase 11 activation, and decreased intracellular bacteria. These data suggest that IFN-I signaling impair anti-bacterial immunity via induction of autophagy. Further, IFN-I signaling also induced secretion of several chemokines and growth factors (e.g. MIP1alpha, MCP-1, RANTES, KC, GM-CSF and VEGF) by hepatocytes that are known to promote excessive infiltration of immune and inflammatory cells into the liver. Finally, microarray analysis identified mTORC2, rapamycin-insensitive companion of mTOR, and WNT, elevated in sepsis, signaling components to be enhanced in IFN-I stimulated and infected hepatocytes, which may play a role in IFN-mediated enhancement of autophagy and inflammation.

Conclusions: Together, our novel findings identify the IFN-I-mediated Akt/autophagy axis as a key regulator of innate inflammatory response in the mouse liver cells. By identifying molecular mechanisms of IFN-I-mediated Akt/autophagy/mTORC2 signaling during sepsis, our study provides a rationale for therapeutic approaches to manage inflammation and liver injury during sepsis.

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