Nogo-B Controls Inflammation by Regulating Autophagy in Macrophage

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Objective—Autophagy, initiated from endoplasmic reticulum (ER), plays a housekeeping role that controls inflammatory response in cell. However, the precise mechanisms underlying this process are not yet fully understood. The ER is believed to be one of the major membrane sources and the scaffold for autophagosome formation. ER remodeling participates in autophagy initiation. Nogo-B is a ubiquitously expressed reticulon family protein that mainly localized to ER membrane. Nogo-B has been shown to regulate ER membrane remodeling and trafficking. Herein, we hypothesize that Nogo-B may have a critical role in balancing autophagy, inflammation and cell homeostasis. ***Approach and Results***— In this study, we have been able to show that genetic loss of Nogo-B (Nogo-B$^{-/-}$) protected against cecal ligation and puncture or lipopolysaccharide (LPS)-mediated sepsis in vivo. Nogo-B deficiency increased autophagic flux in the lung and, decreased proinflammatory cytokine, IL-1beta, production in Bronchoalveolar lavage fluid and blood *in vivo*. Macrophage specific Nogo-B deletion mice phenocopied the global Nogo-B$^{-/-}$ mice, suggests that Nogo-B in macrophage serves a critical role in controlling the process of sepsis. Furthermore, loss of Nogo-B in monocytes and macrophages enhanced starvation and LPS-induced autophagy and ameliorated IL-1β production, which was not due to the alteration of LPS-mediated NFκB signaling or MAPK signaling, but through enhanced inflammasome degradation, in vitro. Mechanistically, Nogo-B associates with Bcl2 and stables Bcl2:Beclin1 complex in ER and in turn negatively regulates autophagosome formation. ***Conclusions***— Taken together, our findings define a novel mechanism controlling autophagy by a ER membrane protein, Nogo-B. Nogo-B is a negative regulator of the autophagy initiation and, facilitates inflammation. The results from this study deepen our understanding on the mechanisms of autophagosome formation and its role in inflammation regulation.

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