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The Role of a Novel DEAD-Box Containing Protein in NLRP3 Inflammasome Activation

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Abstract : The inflammasome is a protein complex that modulates caspase-1 activity, resulting in proteolytic cleavage of proinflammatory cytokines such as IL-1β and IL-18, into their bioactive forms. It has been shown that the inflammasomes play a crucial role in the clearance of pathogenic infection and tissue repair. However, dysregulated inflammasome activation contributes to a wide range of human diseases such as cancers and auto-inflammatory diseases. Yet, regulation of NLRP3 inflammasome activation remains largely unknown. We discovered a novel DEAD box protein, whose biological function has not been reported, not only negatively regulates NLRP3 inflammasome activation by interfering NLRP3 inflammasome assembly and cellular localization but also mitigate pyroptosis upon pathogen evasion. The DEAD-box protein is the first DEAD-box protein gets involved in modulation of the inflammasome activation. In our study, we found that caspase-1 activation and mature IL-1β production were largely enhanced upon LPS challenge in the DEAD box-containing protein- deleted THP-1 macrophages and bone marrow-derived macrophages (BMDMs). In addition, this DEAD box-containing protein migrates from the nucleus to the cytoplasm upon LPS stimulation, which is required for its inhibitory role in NLRP3 inflammasome activation. The DEAD box-containing protein specifically interacted with the LRR motif of NLRP3 via its DEAD domain. Furthermore, due to the crucial role of the NLRP3 LRR domain in the recruitment of NLRP3 to mitochondria and binding to its adaptor ASC, we found that the interaction of NLRP3 and ASC was downregulated in the presence of the DEAD box-containing protein. In addition to the mechanical study, we also found that this DEAD box protein protects host cells from inflammasome-triggered cell death in response to broad-ranging pathogens such as Candida albicans, Streptococcus pneumoniae, etc., involved in nosocomial infections and severe fever shock. Collectively, our results suggest that this novel DEAD box molecule might be a key therapeutic strategy for various infectious diseases.

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