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Platelets regulate innate immunity in autoinflammatory diseases and cancer

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The interleukin (IL)-1 family of pro-inflammatory cytokines are the most potent pyrogens in the body, and their excessive production can cause several auto- inflammatory syndromes, or contribute to a range of inflammatory and metabolic disorders. Furthermore, IL-1β is an important driver of tumor development and metastasis. The recent success of the first and largest randomized trial of the therapeutic monoclonal IL-1β antibody Canakinumab in human beings provided evidence that IL-1 is associated with increased incidence of fatal lung cancer. The expression of the key members of the IL-1 family, such as IL-1β and IL-18, is regulated at both the transcriptional and post-transcriptional levels. IL-1β and IL-18 are produced as inactive precursors, which require activation of caspase-1 by the inflammasomes for their maturation and release by from cells, occasionally at the cost of caspase-1-mediated cell death. We have recently discovered that inflammasomes are released into the extracellular space where they remain active after the demise of activated cells, and that extracellular inflammasomes can amplify inflammation by sustaining extracellular production of IL-1β. However, the sources of extracellular pro-IL-1β are not known. Recent advances in platelet proteomics have revealed that these non-nucleated cells are able to produce their own cytokines, including soluble IL-1β and membrane-bound IL-1α, and are able to significantly magnify IL-1 production by immune cells. As platelets outnumber leukocytes by several folds, they could potentially be the major source of extracellular inflammasomes in the body, or be a major producer of IL-1 precursors that are cleaved by extracellular inflammasomes released from dying immune cells. In this study, we investigated the mechanism(s) by which platelets produce IL-1, and the specific contribution of platelet- derived IL-1 to sterile inflammation, or host resistance to infection. We believe that a deeper understanding of platelet-IL-1 and their interaction with immune cells during sterile inflammation, or infection might help to uncover new targets for immune therapies.