FUNCTIONAL DIFFERENCES IN NLRP3 INFLAMMASOME ACTIVATION IN LPS-ACTIVATED HUMAN MONOCYTE-DERIVED MACROPHAGE POPULATIONS

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Introduction: IL-1β pro-inflammatory cytokine has indispensable role in orchestrating innate and adaptive immune responses via regulating processes like T cell polarization, cell death, tissue repair and inflammation. One of the main sources of IL-1β production is the activated macrophages (MFs). Depending on the tissue environment MFs differentiate to morphologically and functionally different populations. We aimed to investigate the molecular mechanisms of Nlrp3 inflammasome activation and subsequent IL-1β secretion of different human macrophages in response to LPS and ATP stimulation.
Methods: Macrophages were generated from human peripheral blood in the presence of granulocyte-macrophage colony stimulating factor or macrophage colony stimulating factor which mimic immuno-stimulatory (GM-MF) or tissue repair (M-MF) functions, respectively. M-MFs and GM-MFs were stimulated with ultrapure LPS in the presence or absence of ATP. Cytokine production was measured by ELISA, expression of inflammasome components and induction of signaling pathways were measured by Western blot, enzyme activity was measure using fluorescent substrates, ATP production was measured with luminescent method.
Results: Our results show that though both types of LPS-activated MFs secrete IL-1β, in the case of M-MFs IL-1β is released rapidly and only for a short time period, while IL-1β secretion by GM-MFs is sustained. We found striking differences in Nlrp3 and caspase-1 expression, also in caspase-1 activation. We measured substantial differences in the activation of signaling pathways, as well as in the effect of IL-10 neutralizing antibody, and in the expression of IL-1Ra and that of the ecto-ATPases on Nlrp3 inflammasome activation.
Conclusion: Due to intensive studies, the general mechanism of Nlrp3 inflammasome activation is well characterized, nevertheless our results demonstrate that the actual inflammasome activation and IL-1β secretion is substantially determined by the molecular characteristics of a given cell.
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