NLRP3 INFLAMMASOME-MEDIATED IL-1β PRODUCTION BY LPS IN DIFFERENT PHENOTYPES OF HUMAN MACROPHAGES

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Introduction: IL-1β is a "master" cytokine that has an indispensable role in orchestrating effective innate and adaptive immune responses. Due to its critical function, NLRP3 inflammasome-mediated IL-1β production requires distinct signals. Some of these signals induce the expression of the inactive pro-IL-1β through the activation of signaling pathways. Other signals, such as the activation of ATP-sensing P2X7 receptor trigger the processing of pro- IL-1β to mature IL-1β. Among the most important sources of the IL-1β are the activated macrophages (MFs). However depending on the tissue environment, monocytes differentiate into alternative MF subpopulations and it is clear that the actual IL-1β production by a particular cell is strongly depends on the cell type and its characteristic intra- and extracellular modulators. We aimed to study the molecular mechanisms of IL-1β production and secretion by LPS-activated human MFs which were polarized in different ways.

Methods: Macrophages were generated from human peripheral blood in the presence of granulocyte-macrophage colony stimulating factor (GM–CSF) or macrophage colony stimulating factor (M-CSF) which indicate the immuno-stimulatory (GM-MF) or the tissue repair (M-MF) functions of the cells.

Results: Our results show that though both types of LPS-activated MFs secrete IL-1β in the presence of ATP, 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. The IL-1β secretion in the presence of ATP depends on the P2X7 receptor, which is expressed in both MF types. The differential ability of M-MFs to release mature IL-1β is associated with early increased expression of NLRP3 and pro-IL-1β as well as enhanced LPS-induced early activation of the key signal transduction pathways. Using IL-10 neutralizing antibody we show that the notable amounts of IL-10 anti-inflammatory cytokine produced by M-MF has substantial role in the decrease of IL-1β.

Summary: Our results indicate that while LPS-activated GM-MFs secrete robust IL-1β contributing to activate certain immune responses against microbial stimuli, the "anti-inflammatory" M-MFs also release substantial amounts of mature IL-1β, but only in the early phase of stimulation and it is rapidly down-regulated which may correlate with their anti-inflammatory characteristics.