Autocrine-acting BLT2-linked cascade contributes to septic inflammation

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Sepsis is triggered by bacterial infection, with the most lethal form (endotoxic shock) being caused by lipopolysaccharide (LPS) released from the replicating Gram-negative bacteria into the circulation, where it is recognized by various innate immune cells including macrophages. The interaction of LPS with macrophages triggers the production of various proinflammatory cytokines including IL-6 and thereby contributes to the pathogenesis of sepsis. The production of IL-6 is a hallmark of sepsis, with high levels of this cytokine in individuals with septic mortality. IL-6 is thus a potential marker for the severity of systemic bacterial infection. Despite the central role of IL-6 production in sepsis, however, the signaling mechanisms responsible for triggering IL-6 production by LPS in macrophages have still remained unclear. We have now shown that LPS-induced IL-6 synthesis in macrophages is significantly contributed by an autocrine-/paracrine-acting BLT2-linked cascade. Consistent with this role for BLT2 in LPS signaling to IL-6 production, we found that the abundance of BLT2 mRNA in mouse lung tissue was increased in response to i.p. administration of LPS, and that treatment with the BLT2 inhibitor markedly ameliorated septic lung inflammation and mortality associated with LPS-induced sepsis.

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Modulation of macrophage’ response to pro-inflammatory cytokines by Taenia infection and its antigens

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It has been largely appreciated that helminth infections modulate the immune response of their hosts, but mechanisms involved in such modulation are not entirely known. Macrophages and dendritic cells appear to be consistently affected during these types of infections and are common target cells for helminth-derived molecules. Here we found that macrophages obtained from chronically Taenia crassiceps-infected mice, displayed an impaired response to TNF-α, IFN-γ but not to IL-4 neither IL-6, measured through the phosphorylation of NF-kB, STAT1, STAT6 and STAT3, respectively. At the same time, such macrophages expressed high levels of SOCS3. Interestingly, exposure of naïve murine macrophages to excreted/secreted products from T. crassiceps (TcES) similarly interfered with the signaling of these cytokines. Moreover, macrophages exposed to TcES expressed high levels of SOCS3 as well as phosphatase SHP1. Strikingly, inhibition of phosphatases abrogated the impaired IFN-γ-signaling induced by TcES. Together these data demonstrate a new mechanism by which helminth derived products target intracellular pathways to block macrophage response to inflammatory cytokines.

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