Regulatory aspects of innate immune responses

av

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Abstract

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Activation of innate immunity is regulated by a variety of signaling molecules within the immune cells. The present thesis was aimed to improve our understanding of innate signaling mechanism and their possible use as bio-indicators of exposure and disease. The first part of the thesis deals with the involvement of TOM1L1 (Target of Myb1 like 1) in innate immune signaling and regulation of inflammatory cytokines in immune cells (study I and II). The initial event of T-cells activation depend on the recruitment of Src family kinases Fyn and Lck, leading to interleukine-2 (IL-2) production in T cells. Understanding the regulatory aspects of IL-2 induction in T-cells is of importance as IL-2 is a key regulator for T-cell proliferation and survival. Interaction screening indicated the ability of TOM1L1 protein to interact with Fyn, and Lck, that is important for IL-2 production in Jurkat T-cells. TOM1L1 silencing decreased the levels of CD3/CD28 dependent induction of IL-2 in Jurkat T-cells, and LPS dependent induction of TNF-α in THP-1. Furthermore, overexpression of TOM1L1 in Jurkat T-cells causes an increase of STAT3 expression. This was accompanied by an increase in the levels of IL-1β dependent induction of IL-6 and TNF-α in THP-1 cells. These results indicate that TOM1L11 participate in regulation of innate immune response. The second part of the thesis deals with development of innate immune signaling responses used as a diagnosis tools for disease and exposure (study III and IV). Inflammatory diseases are associated with innate immune reactions. In response to inflammation, the immune cells release inflammatory cytokines such as IL-1-β, IL-2, IL-6, IL-10, TNF-α and CXCL8. These cytokines are regulated by stress related kinases include MAP kinase proteins such as ERK1-2, JNK, and MAPK p38, through activation of transcription factors AP-1, ATF-2, and NF-AT. In a clinical study, it was observed that activated MAPK p38 has a potential role in the regulation of IL-10 expression in intermittent claudication. However, expression of IL-10 and MAPK p38 was opposed in stable angina group. Therefore, targeting MAPK p38 in inflammatory disease such as cardiovascular diseases, diabetes, and rheumatoid arthritis might be useful in development of treatment strategies. Innate immune reactions can also be used to monitor stress related inflammatory responses following environmental exposure of immune cells. Inflammatory responses of exposure were studied by *in vitro* exposure to waters from sewage treatment works and recipient waters. The analysis shows that exposure to inland waters can result in activated immune responses and that these responses are both site dependent and vary over time.

Keywords: Innate immunity, TOM1L1, inflammatory responses.