[S1-4]

Toll-Like Receptors as Pattern Recognition Receptors of Microbial Lipids

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Toll-like receptors (TLRs) are sentinels of defense system against invading microbial pathogens to mount immune and inflammatory responses (1, 2). The activation of TLRs and downstream signaling pathways leads to the expression of proinflammatory cytokines and type I IFN genes (3, 4). TLRs can also be activated by non-microbial endogenous molecules leading to induction of aseptic inflammation (5). Deregulated activation of TLRs is implicated in the cascade of events leading to many inflammatory and immune diseases including atherosclerosis, diabetes, rheumatoid arthritis, and cancer (6, 7).

LPS (TLR4 agonist) and bacterial lipopeptides (TLR2 agonist) are known to require saturated fatty acids acylated for their agonistic activity (8). Our results demonstrated that saturated fatty acid induced, while polyunsaturated fatty acid (DHA) suppressed, NFkappaB activation and target gene expression including cyclooxygenase-2 (COX-2) in macrophages (9). Similarly, the expression of co-stimulatory molecules (CD40, CD80, and CD86), MHC class II, and cytokines (IL-12p70), was reciprocally regulated by saturated fatty acid and DHA in bone marrow-derived dendritic cells (DCs) (10). Saturated fatty acid-induced expression of a CD86 promoter-reporter gene was suppressed by the dominant-negative mutants of TLR4 and its downstream signaling components. Consistently, DCs treated with saturated fatty acid showed increased T cell activation capacity, whereas DHA inhibited T cell activation induced by LPS-treated DCs. These reciprocal effects were dependent on differential modulation of TLRs by different types of fatty acids. Saturated fatty acid activated TLR2 dimers with TLR1 or TLR6 as well as TLR4, whereas DHA inhibited the activation of various TLRs tested (11, 12). DHA suppressed NFkappaB activation and COX-2 expression induced by constitutively active TLR4, but not by MyD88 or downstream signaling components suggesting that the molecular targets of DHA are the proximal events upstream of MyD88 leading to TLR activation.

Together, our results demonstrate that the reciprocal modulation of both innate and adaptive immune responses by saturated and polyunsaturated fatty acid is mediated at least in part through TLRs. These

results present novel mechanisms by which lipids derived from bacteria modulate innate and inflammatory signaling pathways and target gene expression. These further suggest that the modulation of TLR activity may provide new opportunities to develop effective therapeutics for chronic diseases by modifying immune and inflammatory responses in beneficial ways.

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