The Modulation of Toll-Like Receptors: A New Gate to Control Chronic Inflammatory Diseases

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Toll-like receptors (TLRs) provide critical signals to induce innate immune responses in antigen presenting cells such as macrophages by recognizing invading microbial pathogens. The activation of TLRs triggers the activation of two major downstream signaling pathways, MyD88-dependent and –independent pathways, leading to the activation of NF-kappaB and IRF3 and the expression of proinflammatory cytokines and type I IFN genes. The activation of macrophages is also an important step in the cascade of events leading to many inflammatory diseases including atherosclerosis, diabetes, rheumatoid arthritis, and cancer. Results from our studies demonstrated that n-3 polyunsaturated fatty acids, DHA and EPA rich in fish oil, inhibit agonist-induced TLR activation and COX-2 expression whereas saturated fatty acids activate TLRs in macrophages. The target of inhibition by DHA is TLR itself or the proximal events leading to TLR activation, but not the downstream signaling molecules. We also demonstrated that resveratrol, a phytoalexin abundant in grapes, inhibits NF-kappaB activation and COX-2 expression induced by TLR3 and TLR4 activation. Our results demonstrated that resveratrol specifically inhibits TRIF signaling in the TLR3 and TLR4 pathway by targeting TBK1 and RIP1 in TRIF complex. These results represent novel mechanisms by which pharmacological or dietary factors modulate inflammatory signaling pathways and gene expression. Deregulated activation of TLRs can lead to the development of severe systemic inflammation including septic shock with high mortality. Moreover, recent evidence suggests the involvement of TLRs in various chronic inflammatory diseases. Therefore, identifying new pharmacological or dietary factors which modulate TLR-mediated signaling pathways and target gene expression would provide new opportunity to manage the deregulation of TLR-mediated inflammatory responses leading to acute and chronic inflammatory diseases.