I
nate immunity is the first line of defense that is rapidly mobilized to detect pathogen-associated molecular patterns (PAMPs), using PAMP receptors such as scavenger receptors and toll-like receptors (TLRs). The TLR family is the best characterized group of innate receptors in terms of known ligands, downstream signaling pathways and functional relevance. There are 10 human TLR family members, each with distinct ligands and functional properties. All these receptors have a central role in linking pathogen recognition to induction of innate immunity, inflammation and adaptive immunity.

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TLRs recognize a bewildering range of microbial ligands, such as bacterial and fungal cell wall components, bacterial lipoproteins, highly conserved microbial proteins, and bacterial and viral nucleic acids. Recognition of microorganisms is linked to a cascade of events that promotes inflammation, activates innate immune responses and primes adaptive immune responses. Key to this central role in host defense is the expression of TLRs on antigen-presenting cells, especially macrophages and dendritic cells. When these cells encounter microorganisms or microbial products, TLR activation initiates signal transduction pathways that culminate in potent transcriptional responses. Recent studies have shown that TLR-associated signaling consists of 4 adaptor proteins, including myeloid differentiation factor 88 (MyD88), Toll-receptor-associated molecule (TRAM), and MYD88-adaptor-like/TLR-associated protein (MAL/TTRAP), and 3 primary kinases. The TLR consists of homodimers or heterodimers, as well as adaptor proteins (Figure). Ligands binding to TLRs initiate signals that involve many kinases, including nuclear factor (NF)-κB and signal transducer and activator of transcription 1 (STAT1), resulting in the induction of numerous cytokines and chemokines.

In addition to the induction of distinct signaling pathways, TLRs sample different compartments within cells. The TLRs involved in the recognition of nucleic acids (TLR3, TLR7, TLR8 and TLR9) are localized within endolysosomal com-

Figure. Toll-like receptor (TLR) consists of homodimers or heterodimers, as well as adaptor proteins, including myeloid differentiation factor 88 (MyD88), and Toll-receptor-associated molecule (TRAM). Ligands binding to TLRs initiate signals that involve many kinases, including nuclear factor (NF)-κB and signal transducer and activator of transcription 1 (STAT1), resulting in the induction of numerous cytokines and chemokines.

TNF, tumor necrosis factor; IL, interleukin.
Toll-Like Receptor 2 in AAA

Abdominal aortic aneurysm (AAA) is pathologically characterized by atherosclerosis of the intima or disruption or attenuation of the elastic media with various degrees of adventitial inflammatory infiltration. Chronic inflammation of the aortic wall and progressive degradation of extracellular matrix (ECM) proteins are involved in the development, progression, or rupture of AAA. Medial elastic fibers and interstitial collagens (types I and III) in the media and adventitia determine much of the structural integrity and stability of arteries. The histological features of AAA include chronic medial and adventitial inflammation with medial degeneration, including smooth muscle cell apoptosis and excessive loss of ECM, especially extensive elastin fragmentation. Increased turnover and loss of types I and III fibrillar collagens, as well as extensive elastolysis caused by increased collagenase, elastase, and especially matrix metalloproteinase (MMP) expression, probably underlie aortic dilation and rupture. Increased expression of MMPs has been demonstrated in human aneurysms. MMP-2 and MMP-9 are critical factors in AAA initiation and development.

Infectious agents, including Chlamydia (C.) pneumoniae, Helicobacter pylori and periodontal bacteria such as Porphyromonas (P.) gingivalis have been reported as pathogens in atherosclerosis. Interestingly, polymerase chain reaction (PCR) has detected C. pneumoniae DNA in the wall of the AAA in 14 of 40 (35%) cases of noninflammatory AAA >5 cm in diameter, suggesting that C. pneumonia infection may contribute to the pathogenesis and development of AAA. Periodontal bacteria, such as P. gingivalis, stimulate TLR-2. Recognition by TLRs induces an inflammatory reaction followed by MMP activation.

In this issue of the Journal, Aoyama et al show that TLR-2-deficient mice with P. gingivalis infection showed less development of AAA in comparison with wild-type (WT) mice. In addition, the levels of MMP-2 and MMP-9 in the abdominal aneurysmal samples from the WT mice were significantly higher than in those from TLR-2-deficient mice. These findings suggest that TLR2 plays a fundamental role in periodontal bacteria-accelerated AAA.

However, the authors did not detect P. gingivalis DNA by PCR in any sample. Therefore, the precise mechanism(s) by which periodontal infection accelerates the progression and development of AAA has not been demonstrated. Further studies of the role of periodontal pathogens on AAA development through TLR recognition are needed.

References