論文の内容の要旨

論文題目　Understanding Toll-like receptor 11 ligand recognition
（Toll-like receptor 11 リガンド認識機構の解明）

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Toll-like receptors (TLRs) recognize microbial molecules termed pathogen-associated molecular patterns (PAMPs) by interacting with them in the extracellular compartment or within endosomes. Following interaction with their ligands, TLRs initiate signal transduction cascades leading to activation of immune cells and antimicrobial defense.

TLRs are type I transmembrane proteins that possess an N-terminal ectodomain (ECD) containing leucine-rich-repeat (LRR) motifs for ligand interaction, a single transmembrane domain, and a C-terminal cytoplasmic signaling domain. There are 13 TLRs in mammalian species and each TLR recognizes specific ligands. TLR11 is known to recognize both *Toxoplasma gondii* (*T.gondii*) profilin (TPRF) and flagellin (FliC) from *Salmonella* typhimurium.

Flagellin is a bacterial protein that forms flagella, the structure that promotes bacterial chemotaxis and invasion in host tissues. Recognition of flagellin by the mammalian host is an important event in mounting immune responses to flagellated bacteria. However the consequence of flagellin recognition on infection is complex. For example, although TLR5, a known flagellin receptor, recognizes and responds to *Salmonella* flagellin and induces proinflammatory cytokines, TLR5-deficient mice show enhanced resistance against oral *Salmonella* infection. In addition to infectious diseases, the immune response to flagellin has also been implicated in autoimmune disease. Flagellin is an immunodominant antigen in murine colitis and human Crohn's disease. Finally, as the best characterized protein PAMP, flagellin is also being actively investigated for use as a vaccine adjuvant.

T.gondii is a protozoan apicomplexan parasite that can infect all mammals. In humans, infection primarily occurs through the ingestion of infected foods. In healthy adults, the immune system controls *T.gondii* and maintains it in a quiescent state. However, *T. gondii* causes severe neurological disease in immunocompromised individuals as well as when transmitted in utero.

TLR11 recognizes the unconventional apicomplexan actin-binding protein profilin, which regulates parasite motility and host cell invasion. Studies of TLR11 function in *T.gondii* infection have reinforced the importance of parasite recognition and T helper 1 cells (Th1) response in *T. gondii* clearance in murine models.

Although TLR11 is not expressed in humans, investigation of TLR11 informs our understanding of the human immune response against bacterial and apicomplexan pathogens carrying these two PAMPs because TLR11 regulates immune responses that are shared with other TLRs. In addition, TLR11-deficient mice are susceptible to human pathogens carrying these two PAMPs and may, therefore, serve as an animal model to examine corresponding human infectious diseases. Furthermore, the established ability of TLR11 to recognize two distinct protein PAMPs provides a unique opportunity to further our understanding of recognition of protein PAMPs by pattern recognition receptors. However, it is first necessary to understand the mechanism of ligand recognition by TLR11. Here I demonstrate that a single TLR is capable of recognizing two distinct PAMPs through highly divergent mechanisms.