Structural Basis of Conserved Flagellin-mediated TLR5 Stimulation

Wan Seok Song[1], Ye Ji Jeon[1], Byeol Namgung[1], Minsun Hong[2*], and Sung-il Yoon[1*]

[1]Division of Biomedical Convergence, College of Biomedical Science, Kangwon National University, Chuncheon 24341, Republic of Korea [2]Division of Biomedical Science and Technology, Yonsei University, Wonju 26493, Republic of Korea

The bacterial flagellum is a whip-like organelle, which extends from the cell membrane to the extracellular space and is involved in motility. The flagellar filament of bacteria assembles through the helical self-polymerization of flagellin protomers. In the host, flagellin is detected as a common molecular pattern of diverse bacteria by Toll-like receptor 5 (TLR5) and activates innate immune response. Here, we report that TLR5 interacts with various flagellins from the Gammaproteobacteria and Firmicutes groups with comparable binding affinity and, as a result, is activated by flagellins in similar potency. To reveal the structural mechanism used by TLR5 to recognize various flagellins, we have determined the crystal structure of a complex between TLR5 and flagellin. In the complex structure, TLR5 accommodates highly conserved flagellin residues using a cavity that is generated by the LRR9 loop of TLR5. Furthermore, our mutational study on flagellin showed that an arginine residue and its neighboring glutamate residue of flagellin play a key role in TLR5 interaction and activation. These results provide a structural basis of the conserved flagellin-mediated TLR5 activation mechanism.