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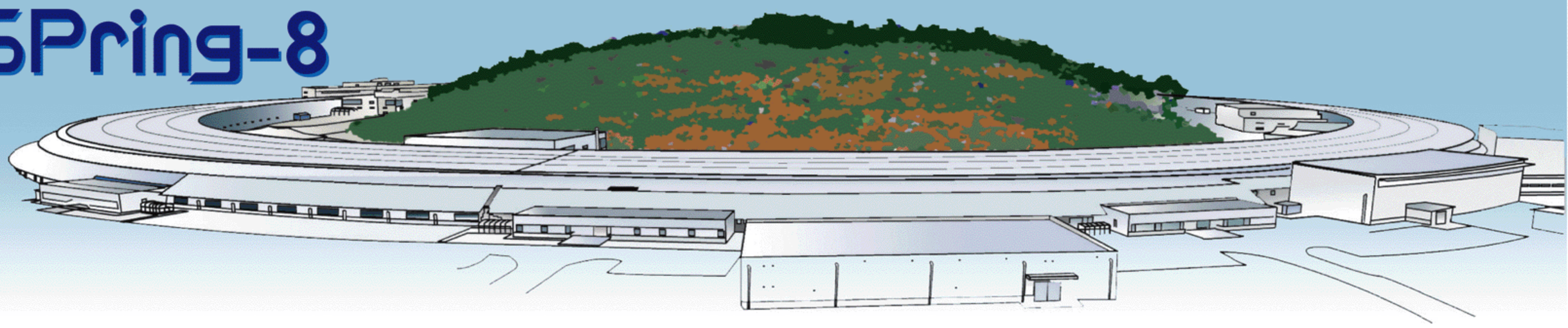

Elucidation of Mechanism of Ligand Recognition and Activity of Signaling by Nucleic Acid Sensor Toll-Like Receptor 8 (TLR8) in Innate Immunity

A research group consisting of Toshiyuki Shimizu (professor), Umeharu Ohto (assistant professor), and Hiromi Tanji (graduate student) of the Graduate School of Pharmaceutical Sciences, the University of Tokyo, and Kensuke Miyake (professor) and Takuma Shibata (specially appointed assistant professor) of the Institute of Medical Science, the University of Tokyo, clarified the detailed crystal structure of TLR8, which detects viral invasion and activates the immune system, for the first time in the world.

The innate immune system is inherent in our bodies as the defense system against pathogens such as bacteria and viruses, and receptor groups such as Toll-like receptors (TLRs) play a role in perceiving the pathogens. TLR8, the structure of which was clarified in the present research, and TLR7 are receptors that recognize virus-derived single-stranded RNA, and induce inflammation and the antiviral response. It is known that TLR7/8 are also activated by synthetic low-molecular-weight compounds, and such compounds activating or inhibiting TLR7/8 are actually used as antiviral agents and drugs for cancer treatment. However, the specific mechanism of how TLR7/8 is activated by RNA or low-molecular-weight compounds to perform intracellularly signaling remains unclear and, without understanding the ligand binding site or the mechanism of ligand recognition, it has been difficult to draw up guidelines for drug design.

The research group clarified the crystal structures of unliganded and ligand-induced activated human TLR8. It was demonstrated that both unliganded and ligand-induced activated human TLR8s exist as dimers, and that upon ligand binding, the TLR8 dimer is reorganized in such a way that the two C termini of TLR8 come in proximity to each other. This is considered to activate intracellular signaling. The detailed mechanism of ligand recognition was also clarified.

The achievements of this research are expected to contribute to the development of antiviral agents and cancer immunostimulators with TLR8 as a target.

Reference: "Structural Reorganization of the Toll-like Receptor 8 Dimer Induced by Agonistic Ligands"
Hiromi Tanji, Umeharu Ohto, Takuma Shibata, Kensuke Miyake, Toshiyuki Shimizu
Science **339** (6126) 1426-1429.

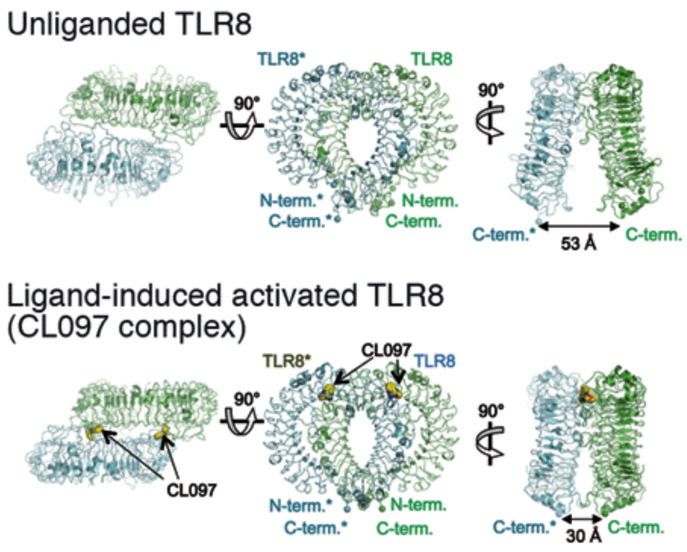

Fig. 1 Crystal structure of TLR8 dimer
(Upper figure) Unliganded TLR8. (Lower figure) Ligand-induced activated TLR8 (CL097 complex). One of the TLR8 molecules forming the dimer is colored green and the other is colored blue. The ligands bind to the dimer at two sites. The liganded TLR8 has the two C termini brought in proximity to each other.

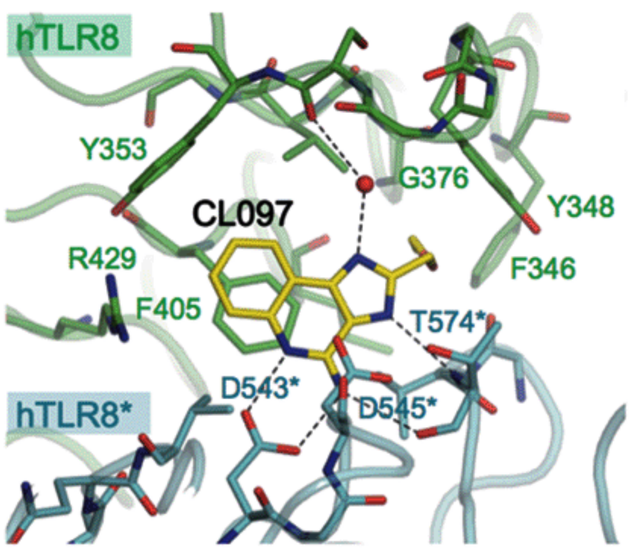

Fig. 2 Enlarged view of ligand-binding site of TLR8
The CL097 complex is shown. The ligand (yellow) is bound between the two molecules (shown in green and blue) of TLR8. Hydrogen bonding is shown with a dotted line. CL075 and R848 complexes are also bound in nearly the same mode.

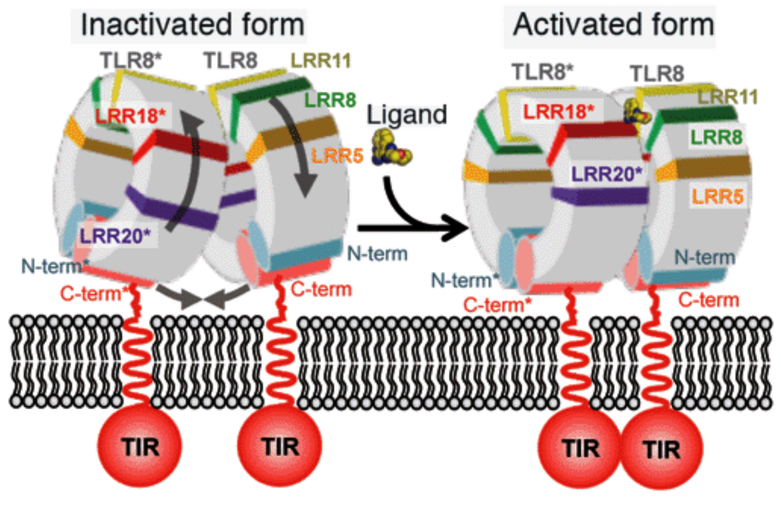

Fig. 3 Model of the activation mechanism of TLR8 upon ligand binding
It is considered that, upon ligand binding, the C termini of TLR8 come in proximity to each other within the intracellular Toll/interleukin-1 receptor (TIR) domain and that intracellular signaling is thereby activated.