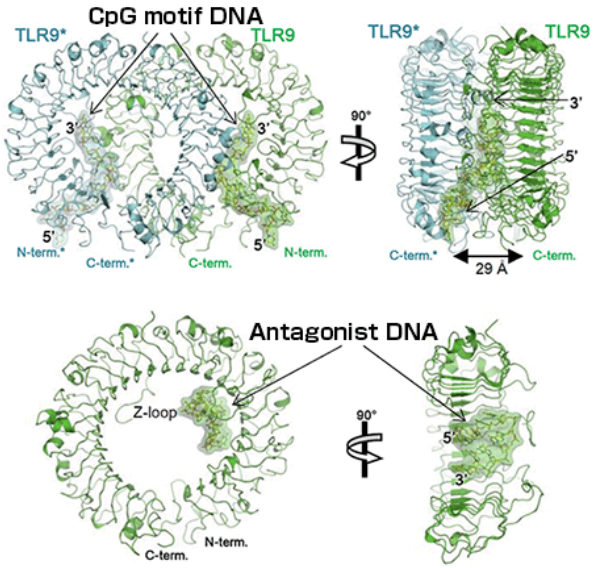
Clarification of Recognition Mechanism of Pathogenic Invasion

The crystal structure of TLR9, which recognizes pathogenic invasion and induces innate immune responses, was clarified in detail for the first time in the world. This was achieved by a research group led by Toshiyuki Shimizu (professor) and Umeharu Ohto (instructor) of the Graduate School of Pharmaceutical Sciences, the University of Tokyo.

The human body has an innate immune system that protects it from infection by pathogens such as bacteria and viruses. The protein Toll-like receptor (TLR) plays a prominent role in this system. TLR functions upon its activation by molecules from pathogens and dimerization. TLR9, a type of TLR whose crystal structure was clarified in this study, stimulates the production of interferon upon recognition of a pathogenic DNA sequence (CpG motif*). Although TLR9 has attracted attention as a target in the discovery of antiviral and antiallergy drugs, the mechanism of the TLR9 recognition of a pathogenic DNA sequence by TLR9 has not been clarified in detail.

The research group clarified the crystal structure of three forms of TLR9, namely, TLR9 not bound to a pathogenic DNA sequence, TLR9 bound to a pathogenic DNA sequence, and TLR9 bound to a DNA sequence that inhibits the function of TLR9. As a result, they found that TLR9 and the pathogenic DNA sequence bind to each other at a stoichiometric ratio of 2:2 and form an activated dimer (Fig.1, top). This DNA sequence was recognized by its binding to the groove in the N-terminus of TLR9. On the other hand, TLR9 and the DNA sequence that inhibits the function of TLR9 bind to each other at a stoichiometric ratio of 1:1 and do not form a dimer. This DNA sequence binds to the inner surface of the TLR9 horseshoe-like structure in the form of a compact loop (Fig.1, bottom). BL41XU at SPring-8 was used to obtain crystallographic data in making this achievement.

These findings will contribute to the design of antiviral drugs, antiallergy drugs, and vaccines in the future.



(Top) Binding mode between TLR9 and DNA sequence containing CpG motif.

(Bottom) Binding mode between TLR9 and antagonist DNA sequence. One of the TLR9 molecules forming a dimer is indicated in green and the other in blue. The CpG motif has an elongated structure and binds to the TLR9 dimer at two sites (2:2 complex). The antagonist DNA binds to the inner surface of the TLR9 horseshoe-like structure in the form of a loop (1:1 complex).

* CpG motif: A DNA sequence containing phosphodiester-linked cytosine and guanine. The CpG motif is often methylated in mammals, but it is unmethylated in bacteria and viruses. The unmethylated CpG motif strongly activates TLR9 and induces various immune responses.