S01-5 Structural basis for Toll-like receptor sensing pathogen infection

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Toll-like receptors (TLRs) are a family of pattern-recognition receptors that recognize pathogen components and initiate subsequent immune responses. Although nucleic acids are one of the principal TLR ligands, they are not inherently pathogen-specific and, thus, carry the risk of triggering autoimmunity.

We determined crystal structures of TLR7 and TLR8, both of which recognize ssRNA. TLR7 and TLR8 harbor two ligand-binding sites, the first and second sites. The first site is used for nucleoside and is essential for activation in both TLR7 and TLR8. The second site is an ssRNA-binding site, but the site of TLR7 is spatially distinct from that of TLR8. TLR7 and TLR8 exhibited the preference for guanosine and uridine, respectively, and its binding affinity is synergistically activated by the binding of ssRNA to the second site. The structural and biochemical works indicate that TLR7 and TLR8 are dual receptors of oligoribonucleotides and nucleosides derived from RNA-degradation products.

TLR7 and TLR8 require Z-loop cleavage for activation. We demonstrated that proteolytic degradation of the Z-loop is a prerequisite for receptor dimerization and activation.

The requirement of RNA processing and Z-loop cleavage for activation strongly suggests the multiple unique regulatory mechanisms aimed at preventing accidental activation of nucleic acid-sensing TLRs.