Structural mechanism for autoinhibition of a NOD-like receptor

With the strong support from the National Natural Science Foundation of China, the research group led by Prof. Chai Jijie reported the crystal structure and autoinhibition mechanism of a member of NOD-like receptors (NLRs) in *Science* (**2013**, 341(6142): 172—175).

The innate immune system of any multi-cellular organism is its first line of defense against invading microorganisms, which recognize and eliminate most pathogens quickly. The recognition of pathogens relies on a large collection of germ-line encoded receptors, termed pattern recognition receptors (PRRs), which recognize the unique and highly conserved features of pathogens called pathogen associated molecular patterns (PAMPs). NLRs are a large family of PRRs involved in sensing the cytoplasmic environment inside cells. NLRC4 (NOD-like receptor containing CARD 4), one member of NLRs, recognizes the cytosolic flagellin and the rod protein of type III secretion system. In the resting state, NLRC4 is believed to be autoinhibited, though structural evidence for this is lacking. Once sensing PAMPs, NLRC4 is activated and oligomerizes into multi-protein signaling complexes termed inflammasomes, activating the inflammation and other immune reactions. The mechanisms underlying NLR autoinhibition and activation, and PAMP recognition remain poorly defined.

In this study, Prof. Chai and colleagues reported the crystal structure of mouse NLRC4 at 3.2 Å (Figure A). The structure shows that an inactive and monomeric form of NLRC4 is bound by ADP. The ADP-mediated interaction between the central nucleotide-binding domain (NBD) and the winged-helix domain (WHD) is critical for structuring the closed conformation of NLRC4. The helical domain (HD2) repressively contacts a functionally important α-helix of the NBD that is involved in oligomerization of other STANDs. Presented to a spatial position required for oligomerization of the NBD, the C-terminal leucine-rich repeats (LRRs) further sequester NLRC4 in a monomeric state. Supporting the structural observations, NLRC4 variants with the ADP-mediated NBD-WHD, NBD-HD2 or NBD-LRRs interactions disrupted are constitutively active. Together these data reveal the NBD-organized cooperative autoinhibition of NLRC4 and provide insight into its activation (Figure B). The structure of NLRC4 can act as a model for understanding other members of the NLR proteins.

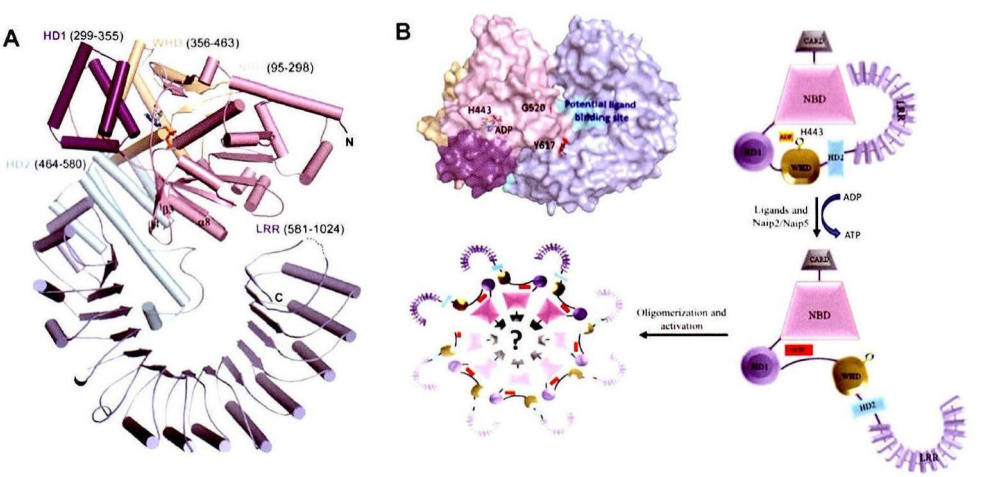

Figure **A** The overall structure of mNLRC4△CARD is shown in cartoon. The structural domains and their boundaries are labeled. **B** A model on ligand-induced activation of mNLRC4.

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