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Assembly mechanism of foreign dsDNA-sensing inflammasomes

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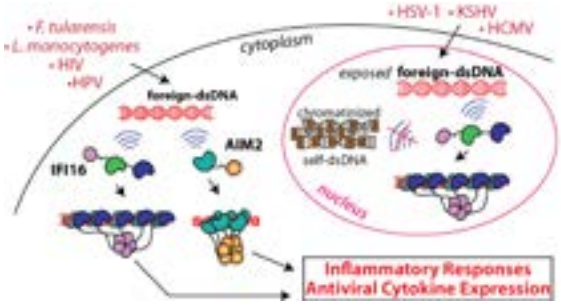
Absent-in-melanoma-2-like receptors (ALRs) detect foreign double-stranded (ds)DNA from invading pathogens and assemble into filamentous signaling platforms termed inflammasome. The ALR filaments play crucial roles in launching antiviral and inflammatory responses against many pathogens (e.g. HIV and HSV); however, persistent ALR complexes are also linked to autoimmune disorders (e.g. Sjogren's syndrome and lupus). Here, by combining solution assays, electron microscopy, and single-molecule methods, we investigate the filament assembly mechanisms of two prototypical ALRs, namely Interferon Gamma Inducible Protein 16 (IFI16) and (absent in melanoma 2) AIM2. (1) IFI16 detects foreign dsDNA both in the host nucleus and cytoplasm. We found that IFI16 uses dsDNA as a one-dimensional diffusion-scaffold to assemble into filaments. The dsDNA-binding HIN200 domains of IFI16 are responsible for tracking dsDNA, while its pyrin domain (PYD) is necessary for filament assembly. Importantly, nucleosomes represent barriers that prevent IFI16 from targeting host dsDNA by directly interfering with its assembly. This unique scanning-assisted assembly mechanism would allow IFI16 to distinguish self- from non-self-dsDNA in the nucleus. (2) AIM2 detects cytoplasmic dsDNA and assembles into an inflammasome. We found that the PYD of AIM2 (AIM2 PYD) drives both filament formation and dsDNA binding. As with IFI16, the size of exposed dsDNA acts a key regulator for the polymerization of AIM2. The helical symmetry of the upstream $AIM2^{PYD}$ filament is consistent with the filament assembled by the PYD of the downstream ASC adaptor, indicating that AIM2 acts as a structural template for polymerizing ASC. Together, our studies provide a unifying paradigm for how ALRs carry out foreign dsDNA-sensing pathways, where generating a structural template by coupling ligand-binding and oligomerization plays a key signal transduction mechanism.



Biography

Jungsan Sohn has his research focused on understanding the molecular mechanism by which human immune system engages invading pathogens. He received BS from University of Michigan, and PhD from Duke University. Upon completing his Post-doctoral training at MIT with Dr. Bob Sauer, he joined the faculty at Johns Hopkins in 2011.

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