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Filament assemblies in foreign nucleic acid sensors

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Helical filamentous assembly is ubiquitous in biology, but was only recently realized to be broadly employed in the innate immune system of vertebrates. Accumulating evidence suggests that the filamentous assemblies and helical oligomerization play important roles in detection of foreign nucleic acids and activation of the signaling pathways to produce antiviral and inflammatory mediators. In this review, we focus on the helical assemblies observed in the signaling pathways of RIG-I-like receptors (RLRs) and AIM2-like receptors (ALRs). We describe ligand-dependent oligomerization of receptor, receptor-dependent oligomerization of signaling adaptor molecules, and their functional implications and regulations.

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Introduction

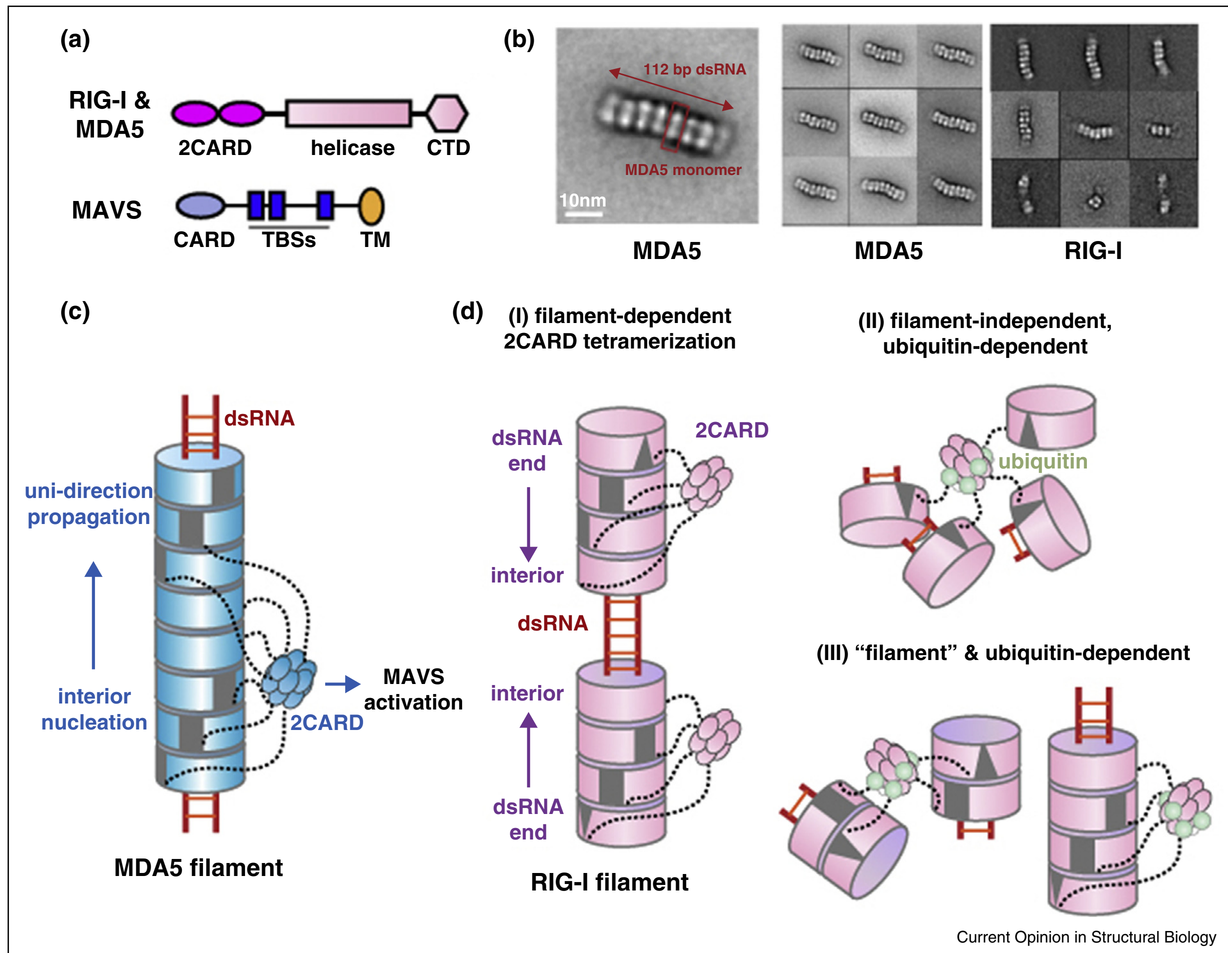
Pattern Recognition Receptors (PRRs) in the innate immune system serves as the front line of defense against pathogen infection. PRRs detect a broad range of pathogens by recognizing conserved molecular patterns (also known as Pathogen Associated Molecular Patterns, PAMPs), and activate the inflammatory innate immune response to restrict infection. These PAMPs include unique chemical structures of bacterial cell membrane or cell wall components, and certain features of viral nucleic acids, such as duplex structure of RNA and cytoplasmic location of DNA, that are rarely found in host nucleic acids. While their activities are often transient and restricted to the infected state, an increasing number of studies have shown that dysregulated function of PRRs can also lead to a variety of auto-inflammatory or chronic inflammatory diseases [1–3], and have led to the on-going efforts to therapeutically inhibit PRRs for the treatment of these immune disorders. Over the last decade or so, there has been a rapid progress in our understanding of the structures of PRRs in the ligand-free and ligand-bound states, and their interactions with downstream signaling adaptors, activators and regulators [4–9]. In doing so, one common observation made by many laboratories, including ourselves, is that PRRs and many molecules in the signaling pathway often aggregate *in vitro*, which has posed technical challenges in biochemical and structural characterization. The accumulating evidence, however, suggest that underlying the apparent aggregation phenomena are ordered structural assemblies, in particular helical assemblies, that are key to their functions.

In this review, we will focus on the helical assemblies observed in the signaling pathways of RIG-I-like receptors (RLRs) and AIM2-like receptors (ALRs). We will describe ligand-dependent oligomerization of receptor, receptor-dependent oligomerization of signaling adaptor molecules, and their functional implications and regulations. We will also describe our speculation and perspectives about the common occurrence of the helical oligomers or filamentous assemblies in innate immune signaling. Due to the space limitation, we will not discuss Toll-like receptors and other helical assemblies in cell death as outstanding reviews are available elsewhere [7•,10].

RIG-I-like receptors (RLRs): RIG-I and MDA5

RIG-I and MDA5 are non-membrane bound, soluble receptors that recognize viral double-stranded RNAs (dsRNAs) and activate antiviral immune response by stimulating transcriptional up-regulation of type I interferons [11]. RIG-I and MDA5 share a high sequence similarity and the same domain architecture, consisting of the N-terminal tandem caspase activation and recruitment domain (2CARD), central DExD/H box motif helicase domain and zinc-binding C-terminal domain (CTD). As with many proteins with similar helicase domains, RIG-I and MDA5 appear to lack the duplex unwinding activity [12•] (unpublished data for MDA5) although there is a conflicting report on RIG-I [13]. 2CARD mediates signal activation by interacting with the downstream signaling adaptor molecule, MAVS, while the helicase domain and CTD are responsible for RNA recognition (Figure 1A). Despite the shared domain organization and the downstream signaling pathway, RIG-I and MDA5 play non-redundant functions by recognizing largely distinct types of viral RNAs [14,15]. MDA5 recognizes long (>∼1 kb) dsRNA that are produced in the form of replication intermediates of picornaviruses and other positive strand viruses [16–18]. In contrast, RIG-I

Figure 1



dsRNA-dependent oligomerization of RIG-I and MDA5.

(A) Domain organization of RIG-I, MDA5 and MAVS. CTD refers to the C-terminal domain. TBS and TM refer to the TRAF-binding site and transmembrane domain, respectively.

(B) The electron micrographs of MDA5 filament and RIG-I filament formed on 112 bp dsRNA. The images were adapted from [26••] and [32••].

(C) A schematic of the filament assembly process of MDA5. The MDA5 filament nucleates on the dsRNA interior and unidirectionally propagates to the dsRNA end. Filament formation brings 2CARDs of nearby MDA5 molecules into close proximity and promotes 2CARD oligomerization, which is a pre-requisite for activation of MAVS.

(D) Schematics of the filament-dependent and ubiquitin-dependent oligomerization of RIG-I 2CARD. (I) On >40 bp dsRNA, RIG-I forms a signaling-competent filament that assembles from the dsRNA end and propagates to the dsRNA interior. Within this filament, 2CARD oligomerization can occur independent of K63-Ub$_n$ through the proximity-induced mechanism as with MDA5. (II) On short dsRNA (<20 bp), only a single RIG-I molecule can bind per RNA molecule, and thus 2CARD oligomerization exclusively depends on K63-Ub$_n$. (III) In general, the two mechanisms synergize to obtain stable tetramerization of 2CARD and robust signal activation.

recognizes relatively short duplex RNA or hairpin structure with the 5′ tri-phosphate or di-phosphate, as a sign of the lack of 5′-processing that normally occurs in cellular RNAs [19–24]. These RNAs are often formed from defective interfering particles or genomic single-stranded RNA of both positive and negative strand viruses [19–24].

dsRNA-triggered receptor oligomerization of MDA5

Recognition of viral dsRNAs by MDA5 involves helical filament assembly of the RNA-binding domain (helicase-CTD), which in turn triggers the second step of oligomerization by 2CARD [25]. Upon dsRNA binding, the helicase-CTD cooperatively assembles into a filament that extends along the length of dsRNA [26••,27••] •] (Figure 1B). This filament formation is required for high affinity interaction with dsRNA as binding of a monomeric MDA5 is inefficient [28•]. The MDA5 filament nucleates on a dsRNA interior with no obvious sequence preference, and propagates to the RNA termini [28•] (Figure 1C). A combination of crystallography, electron microscopy and protein-protein crosslinking studies provided a detailed model of the MDA5 filament:

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