Structure Watch

VIRAL RNA: A PERFECT FIT FOR IFIT

Members of the interferon-induced protein with tetratricopeptide repeats (IFIT) family have important antiviral activities. Most IFIT functions involve disruptive protein–protein interactions, which are mediated by the interaction of their tetratricopeptide repeats (TPRs) with other host factors — they block the initiation of translation in this manner. Recently, it was found that IFITs directly recognize viral RNAs bearing a 5′-triphosphate group (PPP-RNA) and form large multiprotein complexes that promote viral clearance. As many viruses, but not mammals, generate PPP-RNAs, this provides a mechanism by which the host can distinguish between self and non-self RNAs. Abbas *et al.* have now generated crystal structures of human IFIT5 and of human IFIT5 complexed to PPP-RNA; these structures provide insight into how IFITs recognize viral PPP-RNAs. They show that the TPRs of IFIT5 are arranged in an atypical manner to form a deep, narrow pocket that is lined with positively charged residues. This pocket enables IFIT5 to bind single-stranded PPP-RNAs in a non-sequence-specific manner that requires a 5′-overhang of approximately three nucleotides. However, the pocket is too narrow for double-stranded PPP-RNAs.

ORIGINAL RESEARCH PAPER Abbas, Y. M. *et al.* Structural basis for viral 5′-PPP-RNA recognition by human IFIT proteins. *Nature* **494**, 60–64 (2013)

MAKING AND BREAKING MDA5 FILAMENTS

MDA5 is a RIG-I-like receptor that senses cytoplasmic viral RNA and induces antiviral responses via the adaptor protein MAVS. A recent study provides the structural basis for how MDA5 recognizes double-stranded RNA (dsRNA) and activates MAVS. Wu *et al.* generated crystal structures to show that MDA5 binds dsRNA as a monomer, with a domain organization similar to that previously shown for RNA-bound RIG-I. Whereas RIG-I has been shown to form an O-ring structure that caps the end of dsRNA, Wu *et al.* found that MDA5 forms a C-ring structure that binds to the internal duplex structure of dsRNA. Further analyses showed that MDA5 monomers stack along the dsRNA stem in a head-to-tail arrangement to form filaments. The tandem caspase-associated recruitment domains (CARDs) of MDA5, which are important for its signalling, are localized on the outside of the MDA5 filaments. Modelling studies suggested that the concentration of the tandem CARDs at 'patches' along MDA5 filaments promotes their oligomerization into elongated structures that activate MAVS. The findings by Wu *et al.* also suggest that, in addition to RNA binding, ATP hydrolysis is required for MAVS activation by MDA5. Indeed, a separate study found that viruses can target the ATP-hydrolysis domain of MDA5 to block its antiviral activity. Motz *et al.* determined the crystal structure of the ATP-hydrolysis domain of MDA5 in complex with the V protein of parainfluenza virus 5. They found that the V protein unfolds the ATP-hydrolysis domain of MDA5 and prevents RNA-bound MDA5 from forming filaments.

ORIGINAL RESEARCH PAPERS Wu, B. *et al.* Structural basis for dsRNA recognition, filament formation, and antiviral signal formation by MDA5. *Cell* **152**, 276–289 (2013) | Motz, C. *et al.* Paramyxovirus V proteins disrupt the fold of the RNA sensor MDA5 to inhibit antiviral signaling. *Science* **339**, 690–693 (2013)