

# RIG-I like receptors

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## Abstract

RIG-I (retinoic-acid inducible gene 1, also known as DDX58) is the best characterized receptor within the RIG-I like receptor (RLR) family. Together with MDA5 (melanoma differentiation-associated 5) and LGP2 (laboratory of genetics and physiology 2), this family of cytoplasmic pattern recognition receptors (PRRs) are sentinels for intracellular viral RNA that is a product of viral infection. The RLR receptors provide frontline defence against viral infections in most tissues.

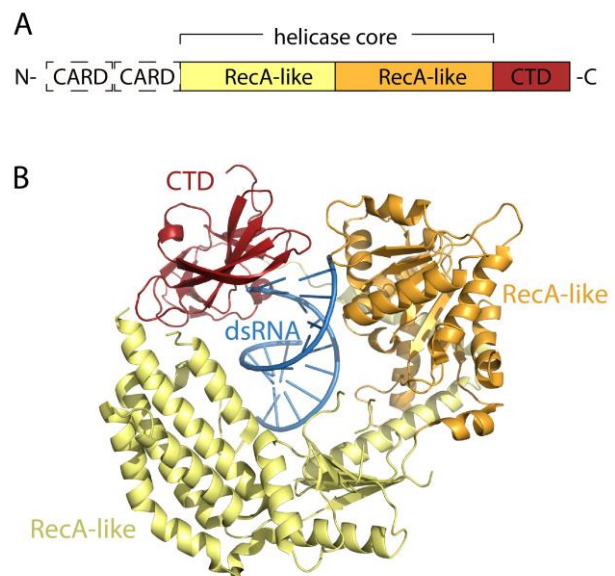
## RLR ligands

The RIG-I receptor prefers to bind short (<2000 bp) single- or double-stranded RNA carrying an uncapped 5' triphosphate and additional motifs such as poly-uridine rich RNA motifs.<sup>[1][2]</sup> RIG-I triggers an immune response to RNA viruses from various families including the paramyxoviruses (e.g. measles), rhabdoviruses (e.g. vesicular stomatitis virus) and orthomyxoviruses (e.g. influenza A).<sup>[3][4][5][6][7]</sup> MDA5 ligands are poorly characterized, but the preference is for long double-stranded RNA (>2000 bp), such as the replicative form of picornavirus RNA that is found in picornavirus-infected cells.<sup>[8][9]</sup> LGP2 binds to blunt-ended double-stranded RNA of variable length,<sup>[10][11]</sup> and also to RNA-bound MDA5 to regulate filament formation.<sup>[12]</sup> The latter is linked to LGP2's recognition of picornaviruses (e.g. encephalomyocarditis virus), as per MDA5.<sup>[13]</sup>

## Structural features of the RLR receptors

The RLR receptors are members of the DEAD-box helicase family (despite containing a DExD/H motif, rather than the DEAD motif characteristic of the family) and share a common domain architecture. All contain a catalytic helicase core made up of two RecA-like domains (Figure 1A). The catalytic helicase core contains at least

9 highly conserved sequence motifs that coordinate ATP and RNA binding and the hydrolysis of ATP to unwind RNA. A C-terminal domain (CTD) follows the helicase core and this domain also binds viral RNA (Figure 1A, 1B). Distinct RNA-binding loops within the CTD of the three RLRs dictate the type of RNA that they can bind.<sup>[14]</sup> In addition to the helicase core and CTD, RIG-I and MDA5 have two N-terminal CARD (caspase active recruitment domains) that are essential to the initiation of downstream signaling (Figure 1A). LGP2 is dissimilar to both RIG-I and MDA5 as it lacks the CARD signaling domains and instead is implicated as a positive and negative regulator of RIG-I and MDA5.<sup>[15][16][17][18][19][20][21]</sup>



**Figure 1** | RIG-I domain architecture. (A) Schematic representation of full-length RIG-I. (B) X-ray crystal structure of RNA-bound RIG-I (PDB: 2YKG), excluding the CARD domains.

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## Activation of RLR signaling

In uninfected cells that are absent of viral RNA RIG-I exists in an inactive conformation in which the CARD domains are masked due to their interaction with the CTD.<sup>[22]</sup> Upon binding RNA, RIG-I changes into a conformation in which the CARD domains are exposed and 'available' for signaling. Conversely, the MDA5 CARDS are unhindered in the absence of viral RNA.<sup>[23]</sup> As a safeguard for RLR activation, the exposed RIG-I and MDA5 CARDS can undergo **post-translational modifications** (e.g. **ubiquitination**, **phosphorylation**) that either positively or negatively regulate downstream signaling.

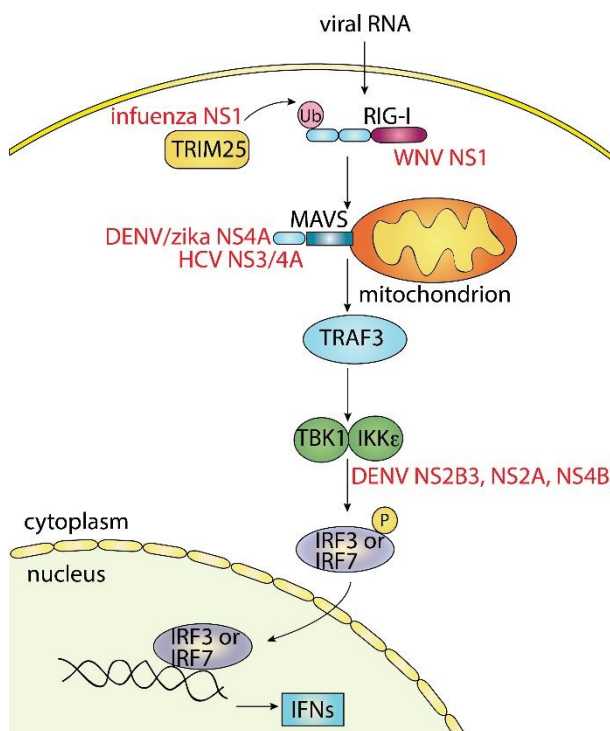
## RIG-I antiviral signaling

In the activated state the exposed RIG-I CARD domains interact with the CARD domains of **MAVS** (mitochondrial antiviral signaling protein, also known as IPS-1, VISA or Cardif) which sits on the outer surface of the **mitochondria** (Figure 2). This binding event is essential to signaling as it causes MAVS to form large functional aggregates in which **TRAF3** (TNF receptor-associated factor 3) and subsequently the **IKK $\epsilon$ /TBK1** (I-kappa-B kinase-epsilon/TANK-binding kinase 1) complex are recruited. The IKK $\epsilon$ /TBK1 complex leads to the activation of the **transcription factors** **interferon regulatory factor**

3 (IRF3) and **IRF7** which induce **type I** (including **IFN $\alpha$**  and **IFN $\beta$** ) and **type III interferons** (IFN) (Figure 2). The type I IFNs bind type I IFN receptors on the surface of the cell that produced them, and also other cell types that express the receptor, to activate **JAK-STAT** (Janus kinase/signal transducers and activators of transcription) signaling. This leads to the induction of hundreds of **interferon stimulated genes** (ISGs) that amplify the IFN response. Overall this causes the death of infected cells, the protection of surrounding cells and the activation of the antigen-specific antiviral immune response. Collectively this coordinated antiviral immune response controls the viral infection.

## Regulation of RLR signalling

As prolonged IFN production is linked to human disease RLR signaling must be tightly regulated. One of various ways that this is achieved is by post-translationally modifying, or tagging, host RLR signaling proteins with phosphate (known as **phosphorylation**) or **ubiquitin** (known as **ubiquitination**). These tags can also be removed, which adds an additional regulatory layer to RLR signaling. These **post-translational modifications**, and their removal, are prevalent in RLR signaling and even regulate the RIG-I receptor itself. Most famously the RIG-I CARD domain is phosphorylated by **protein kinase C- $\alpha$**  (PKC- $\alpha$ ) and PKC- $\beta$  in the resting state to negatively regulate signaling.<sup>[24][25][26]</sup> Upon viral infection RIG-I is **dephosphorylated** by **PP1 $\alpha$**  and **PP1 $\gamma$** ,<sup>[27]</sup> permitting the ubiquitination of the RIG-I CARD domain by the E3 ligase **TRIM25** to activate the RLR-mediated antiviral immune response.<sup>[28]</sup> Given post-translational modifications are so pertinent to the activation of RLR signaling, it is not surprising that they are directly, or indirectly, targeted by viruses such as influenza A<sup>[29]</sup> and measles,<sup>[30]</sup> respectively, to suppress signaling (Figure 2).



**Figure 2** | Schematic of RLR signaling. Ub denotes **ubiquitination**, P denotes **phosphorylation**.

## Viral hijacking of RLR signaling

Viruses have evolved ways to subvert RLR signaling to enhance their survival. For example, **influenza A virus** and **West Nile virus** (WNV) use their NS1 (nonstructural protein 1) proteins to block RIG-I ubiquitination by TRIM25, or cause RIG-I degradation, respectively, which in turn inhibits IFN production (Figure 2).<sup>[29][31]</sup> This outcome is also achieved by the **hepatitis C** (HCV) NS3/4A protein by cleaving a part of MAVS (Figure 2),<sup>[32]</sup> and the **foot-and-mouth disease virus** (FMDV) leader protease (Lpro) which cleaves LGP2.<sup>[33]</sup> Likewise, **den-gue virus** (DENV) uses its NS2B3, NS2A and NS4B pro-



teins to bind IKKε and prevent IRF3 phosphorylation<sup>[34][35]</sup> and its NS4A protein, as per the zika virus, to bind MAVS to block RLR receptor binding.<sup>[36][37]</sup> Another prominent example is that of the paramyxovirus V proteins, which directly bind various RLR or downstream signaling proteins including MDA5, LGP2, and STAT,<sup>[38][39][40]</sup> or proteins such as PP1α and PP1γ<sup>[30]</sup> that negatively regulate RLR signaling (Figure 2).

## Summary

The RLR receptors are cytoplasmic PRRs that provide frontline defence against prominent viral infections such as influenza A and measles. RLR signaling produces proinflammatory cytokines and type I and type III interferons (IFN) and orchestrates the induction of ISGs via the JAK-STAT signalling pathway to establish an antiviral state that controls infection. The RLR signaling cascade is heavily regulated by post-translational modifications. Viral proteins also target proteins within the cascade to enhance virus survival.

## Additional information

### Competing interests

The author has no competing interests

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