antiviral response. The type I interferon (IFN) system plays a major role in antiviral innate immunity (Samuel 2001; Stetson and Medzhitov 2006). Upon viral infection, type I IFN is secreted in body fluid and expands IFN response signals, resulting in the activation of various enzymes that prevent viral replication. In addition to antiviral activity, type I IFN has been known to exert various biological effects such as cell cycle regulation, differentiation, and immune modulation. Furthermore, innate immune responses lead to the activation of specific cells with antigen-presenting functions to facilitate the initiation of adaptive immunity.

The triggering of the IFN system is the activation of IFN genes. Since the initial discovery of type I IFN, the activation mechanism of the type I IFN genes has been a major focus of many researchers. Although several double-stranded (ds) RNA-binding proteins such as protein kinase-activated by RNA (PKR) have been attributed to the detection of replicating viral RNA, gene knockout studies do not support its role (Yang et al. 1995). Recent functional analyses revealed that TLRs function as pathogen receptors including those of viral origin (Takeda and Akira 2005). TLR3 has been identified as a receptor for exogenous dsRNA (Alexopoulou et al. 2001); however, TLR3-deficient cells can still activate type I IFN genes (Diebold et al. 2003; Yoneyama et al. 2004), suggesting the existence of other receptor(s). Screening of an expression cDNA library identified RIG-I as an essential receptor for virus-derived dsRNA (Yoneyama et al. 2004). In this article, we describe the recently identified function of the RIG-I family of RNA helicases in innate immune reactions to infecting viruses.

2
## The Role of TLR and RIG-I Family Helicases in Viral Infection

2.1
TLR Detects Extracellular Pathogen-Associated Molecular Patterns

Toll was first identified as a transmembrane receptor regulating insect morphogenesis (Hashimoto et al. 1988). Toll mutation also results in increased sensitivity to fungi in *Drosophila* (Lemaitre et al. 1996), leading to the identification of mammalian Toll-like receptors (TLRs) as sensing receptors of various pathogen-associated molecular patterns (PAMPs) (Medzhitov et al. 1997). Ten members of human TLRs are expressed in a tissue-specific manner and many are expressed in dendritic cells (DCs) and macrophages (Takeda and Akira 2005). Although each TLR detects a distinct set of PAMPs, a common extracellular leucine-rich repeat (LRR) motif is responsible for sensing. When LRR

detects a pathogen, a signal is generated in the cytoplasm, which is mediated by the cytoplasmic domain of the receptor. TLR activation results in the production of various cytokines, leading to the activation of innate immune responses (as described in this volume by Severa and Fitzgerald). Upon TLR activation, macrophages and DCs differentiate into antigen-presenting cells initiating antigen-specific acquired immunity. Viral infection is sensed by three TLRs: TLR3 (Alexopoulou et al. 2001), TLR7/8 (Diebold et al. 2004; Heil et al. 2004; Lund et al. 2004), and TLR9 (Hemmi et al. 2000; Krug et al. 2004; Lund et al. 2003), which are mostly expressed on the endosomal membrane (Fig. 1). Double-stranded RNA (dsRNA), single-stranded RNA, and unmethylated CpG DNA are detected by TLR3, TLR7/8, and TLR9, respectively (Fig. 2). This subset of TLRs activates transcription factors including NF-κB, IRF-3, and
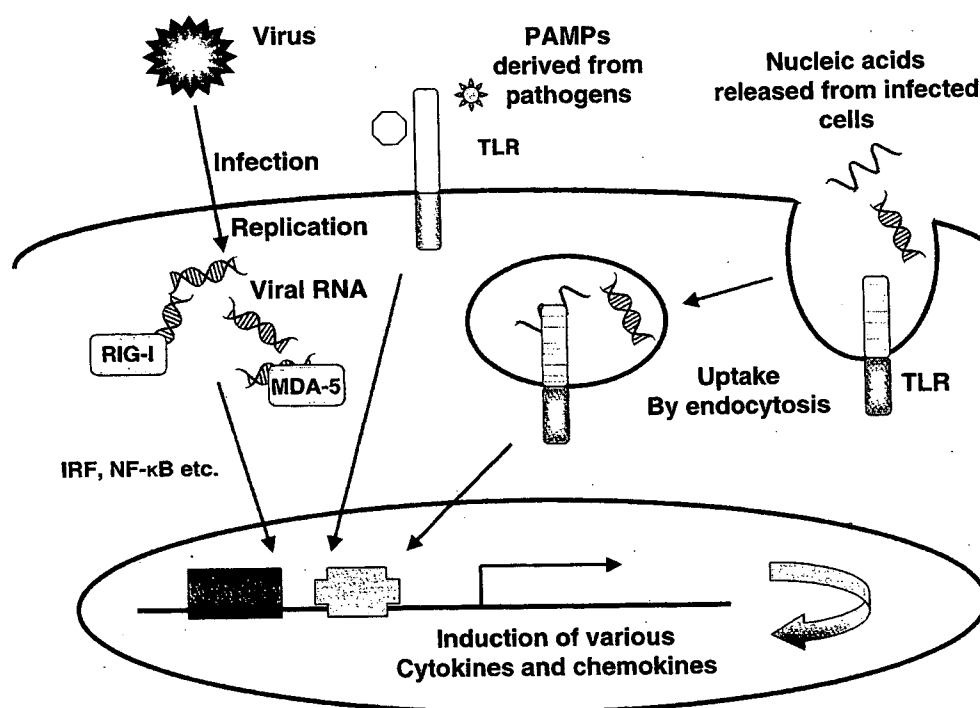
Fig. 1 Recognition of PAMPs by TLR and RIG-I family helicases. Transmembrane receptor TLR is expressed on the plasma or endosomal membranes and senses extracellular PAMPs. RIG-I family helicases detect viral RNA in the cytoplasm. Activation of these receptors transduces signals resulting in overlapping, but in a different set of target genes, including cytokines and chemokines
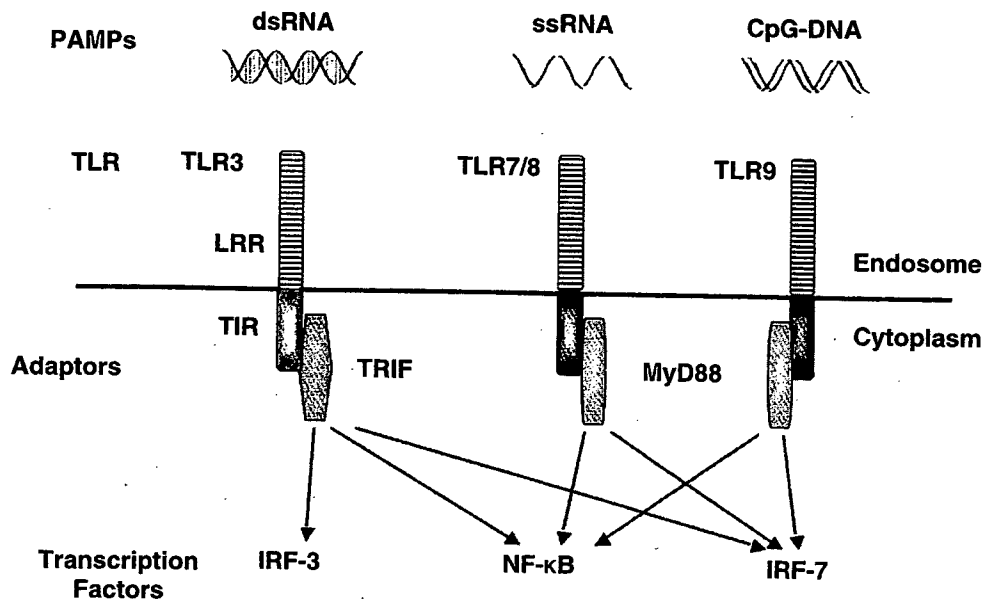
Fig. 2 Recognition of viral nucleic acids by different TLRs. TLR3, TLR7/8, and TLR9 detect dsRNA, ssRNA, and unmethylated CpG DNA. MyD88 adaptor is indispensable for signaling by TLR7/8 and 9, whereas another adaptor TRIF is essential for TLR-3 signaling
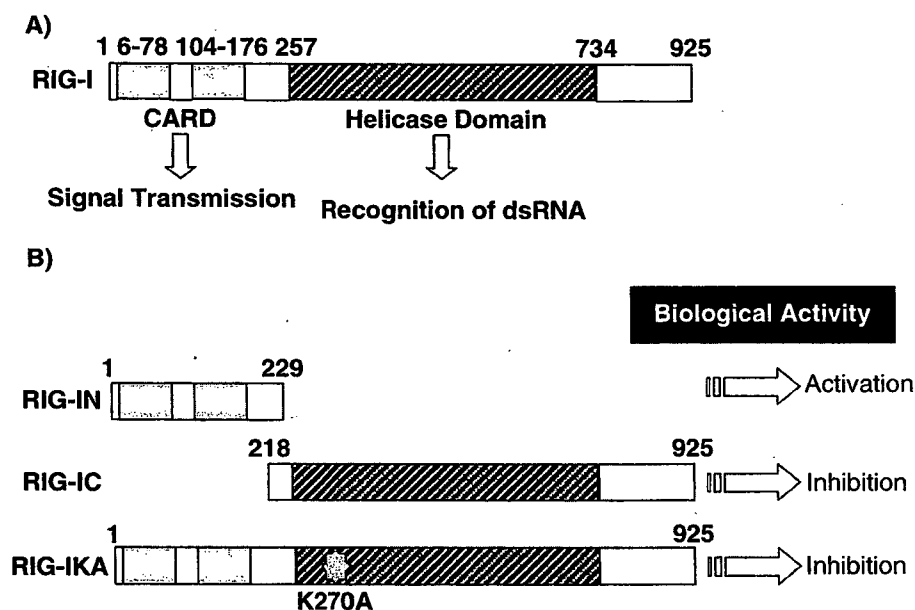
IRF-7 through common and distinct cytoplasmic adaptor molecules (Takeda and Akira 2005).

2.2
Cytoplasmic Receptor, RIG-I Helicase Family

Since dsRNA such as polyI:polyC is known to induce IFN synthesis, it is generally accepted that dsRNA is the major viral product responsible for the activation of innate immune responses. TLR3 was first shown to confer responsiveness to exogenously added polyI:polyC in HEK293T cells (Alexopoulou et al. 2001), and is thus hypothesized to function as a physiological sensor of replicating viruses. However, TLR-3-deficient cells are still responsive to viral infection or poly I:poly C transfection (Yoneyama et al. 2004), suggesting an alternative cytoplasmic sensor.

Functional screening identified human RIG-I as putative positive regulator of IFN genes (Yoneyama et al. 2004). RIG-I is a putative RNA helicase containing two repeats of caspase recruitment domain (CARD) at the N-terminal region and a DExH/D box helicase homology region at its C-terminal region (Fig. 3). RIG-I exhibits specific binding activity to dsRNA. Overexpression of

A)

1 6-78 104-176 257 734 925
RIG-I

CARD Helicase Domain

⇩ ⇩

Signal Transmission Recognition of dsRNA

B)

Biological Activity

1 229
RIG-IN ⟶ Activation

218 925
RIG-IC ⟶ Inhibition

1 925
RIG-IKA ⟶ Inhibition
K270A

Fig. 3 A, B Structure–function relationship of RIG-I. A Structure of RIG-I. B Biological activity of RIG -I mutants

RIG-I in cultured cells did not significantly activate the IFN promoter; however, overexpression of the N-terminal region containing two CARD repeats alone constitutively activated the IFN promoter. This suggests that CARD is essential and sufficient for signaling, and is under negative regulation by the C-terminal region. Full-length RIG-I is present as an inactive form; however, it can be activated by viral infection or transfection of dsRNA. This supports the speculation that inhibition of CARD by the C-terminal region is reversed by dsRNA. Interestingly, RIG-I lacking CARD acts as a dominant-negative inhibitor of virus-induced activation of IFN-β promoter. Furthermore, K270A mutant, which has disrupted ATP binding motif within the conserved helicase domain, also functions as a dominant inhibitor. These observations suggest that, in addition to dsRNA binding, ATP hydrolysis is necessary for the induced unmasking of CARD.

In the human genome database, there are two other genes encoding RIG-I-related helicases, MDA5 and LGP2 (Yoneyama et al. 2005). MDA5 exhibits a similar domain structure as RIG-I, characteristic of two repeat CARDs and the helicase domain (Fig. 4). The third helicase LGP2 lacks CARD. Functional analyses of these helicases, using cell culture, revealed that MDA5 functions as a positive signaling regulator, similar to RIG-I. Recent studies using gene disruption of RIG-I and MDA5 revealed that these helicases detect different viruses (Gitlin et al. 2006; Kato et al. 2005, 2006). MDA5 was essential for detection of picorna virus infection,
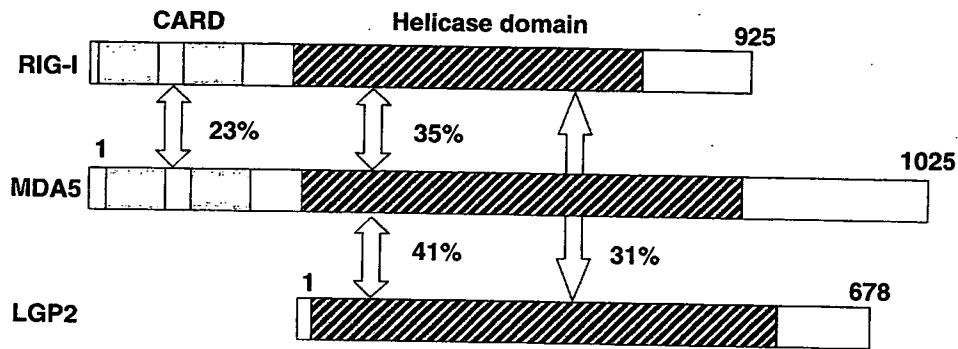
Fig. 4 Structure of RIG-I family helicases. Human and mouse RIG-I family consists of RIG-I, MDA5, and LGP2. Percentage indicates amino acid identity between corresponding domains

while RIG-I was critical for detection of other viruses types tested. Interestingly, this virus specificity likely reflects different RNA species generated by respective viruses. At present, the chemical basis of this difference is not known. Functional analyses of LGP2 in cell culture revealed that LGP2 dominantly inhibits the virus-induced activation of IFN genes (Rothenfusser et al. 2005; Yoneyama et al. 2005). Since LGP2 is transcriptionally induced by autocrine IFN, its function as a feedback negative regulator has been suggested.

3
Signaling Cascades of Antiviral Innate Responses

A comparison of signaling cascades initiated by the detection of dsRNA by TLR3 and RIG-I/MDA5 is illustrated in Fig. 5. TLR3 activation by dsRNA occurs in the endosome and the signal is transmitted through TRIF (Hoebe et al. 2003; Oshiumi et al. 2003; Yamamoto et al. 2002, 2003), TBK-1 (NAK, T2K)/IKKi (IKK-ε) kinases (Fitzgerald et al. 2003; Hemmi et al. 2004; McWhirter et al. 2004; Perry et al. 2004; Sharma et al. 2003). The latter kinases are responsible for a specific phosphorylation and activation of IRF-3. It was shown that TBK-1/IKKi kinases are under positive and negative regulation by NAP1 and SIKE, respectively (Huang et al. 2005; Sasai et al. 2005). RIG-I/MDA5 activates a novel adaptor IPS-1 (MAVS, Cardif, VISA) containing a single copy of CARD (Kawai et al. 2005; Kumar et al. 2006; Meylan et al. 2005; Seth et al. 2005; Sun et al. 2006; Xu et al. 2005). Interestingly, IPS-1 is anchored on the outer membrane of mitochondria via its C-terminal transmembrane domain (Seth et al. 2005). Although a mitochondrial association is critical for the signaling, its mechanism is elusive. IPS-1 apparently activates the
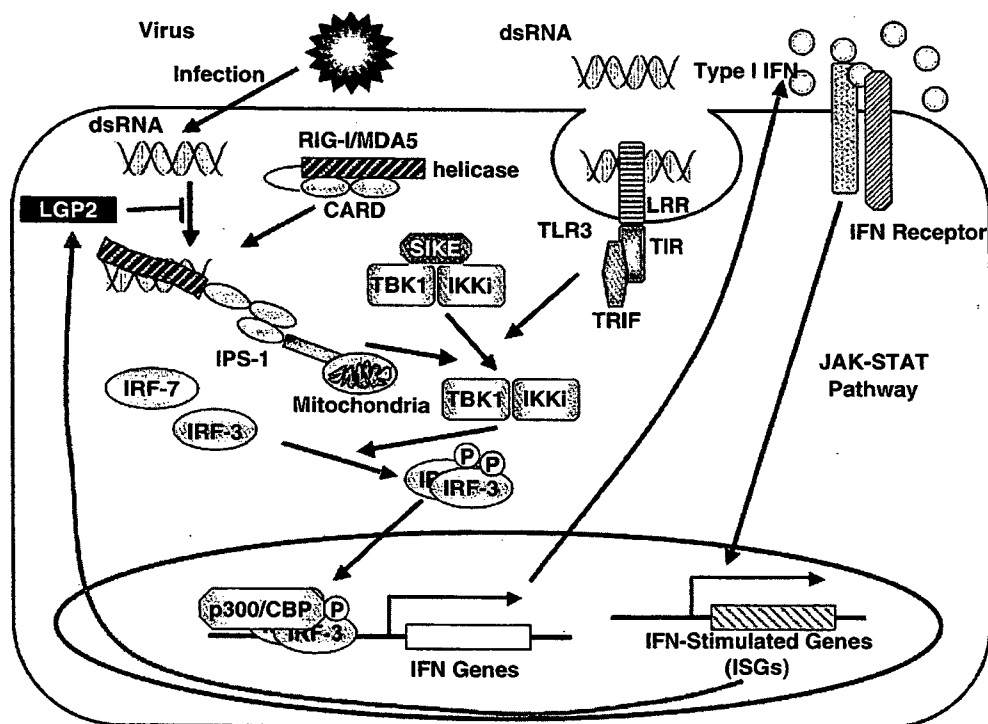
Fig. 5 Signaling cascade induced by dsRNA. TLR3 recognizes extracellular dsRNA in endosomes. Upon dsRNA binding, the cytoplasmic domain of TLR3 transmits a signal to an adaptor, TRIF. Cytoplasmic dsRNA is recognized by RIG-I and MDA5. CARD of these helicases interacts with an adaptor, IPS-1, which localizes on the outer membrane of mitochondria. Signals mediated by TRIF and IPS-1 activate common protein kinases TBK-1 and IKK-I, resulting in phosphorylation-mediated activation of transcription factor IRF-3. IRF-3, as a complex with co-activator CBP or p300, activates target genes including type I IFN genes. Secreted IFN activates secondary signals through IFN receptor and JAK-STAT pathway to activate ISGs

IRF-3 kinases TBK-1/IKKi. Thus, RIG-I/MDA5 activates a distinct signaling cascade from TLR3 and the signal is converged at TBK-1/IKKi (Fig. 5).

4
Cell-Type-Specific Function of TLRs and the RIG-I Family

As mentioned earlier, TLR7/8 and TLR9 detect distinct viral PAMPs and activate signaling cascades, MyD88, IRAK1, and IRF-7 (Takeda and Akira 2005). So far, this signaling has been showed to be specific for plasmacytoid DCs (pDCs), which are responsible for the production of high levels of serum IFN-α (Fig. 6).
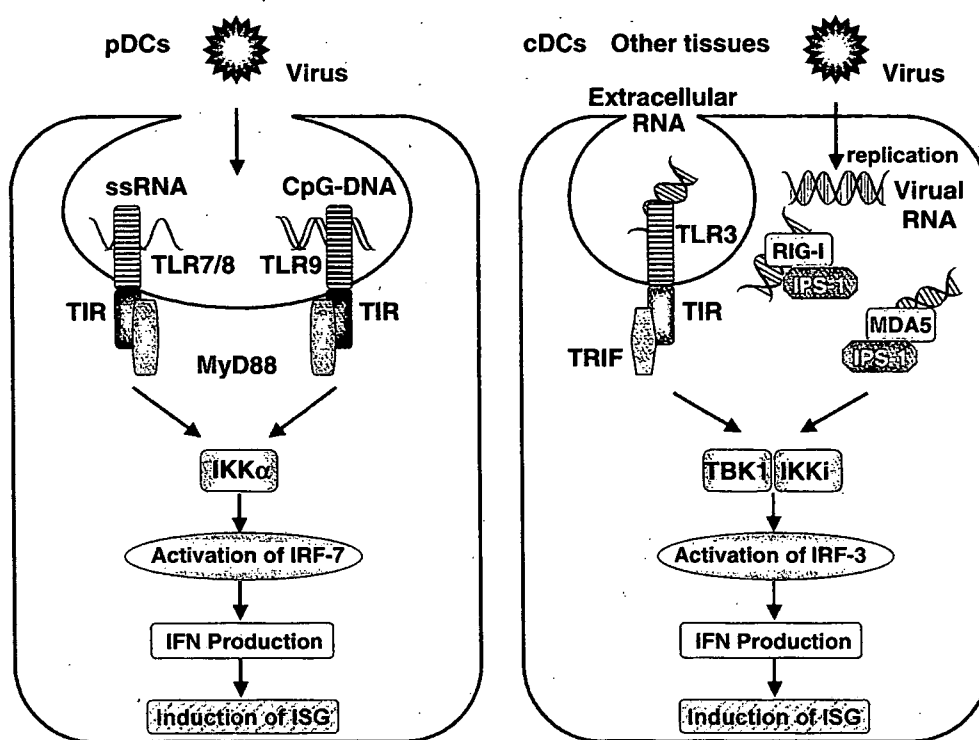
Fig. 6 Tissue-specific signaling cascade for IFN gene activation. Virus infection triggers a distinct signaling cascade in pDCs and other cell types including cDCs. TLR7/8 and TLR9 are specifically expressed in pDCs, whereas TLR3 is expressed in cDCs. IFN induction in pDC is dependent on MyD88, IKKα, and IRF-7, whereas these adaptors are dispensable in other cell types

pDCs and other cell types, including cDCs, use distinct pathways in a mutually exclusive manner to sense viral infections. As revealed by analysis using knockout mice, MyD88 but not RIG-I is essential in pDCs, and RIG-I but not MyD88 is critical in cDCs (Kato et al. 2005, 2006) (Fig. 6). The biological significance of TLR3 function in viral infection is not well established.

5
Viral Evasion Strategies for Antiviral Responses

With the elucidation of host antiviral response mechanisms, it has become evident that replication-competent viruses are equipped to counteract the antiviral mechanisms. It is well known that acutely infecting viruses, which undergo a lytic infection, selectively inhibit host macromolecular syntheses collectively

known as shut off. Apart from this nonspecific blockade, viruses encode inhibitory proteins, which target specific processes of the antiviral signaling.

V proteins of paramyxoviruses bind to MDA5 and inhibit its signaling (Andrejeva et al. 2004; Yoneyama et al. 2005). V protein of Sendai virus specifically binds to MDA5 but neither interaction nor blockade was observed with RIG-I; however, in light of the fact that paramyxoviruses are specifically detected by RIG-I, as evidenced by RIG-I knockout mice, its physiological relevance is controversial.

Hepatitis C virus (HCV) is known to be poorly adaptable to tissue culture for replication. One reason is its high sensitivity to IFN-mediated reaction: HCV replication requires host cell mutations that inactivate RIG-I signaling (Sumpter et al. 2005). HCV encodes a protein complex, NS3/4A, which acts as RNA helicase and protease. NS3/4A protease cleaves IPS-1 at its cytoplasmic domain, thus releasing it from mitochondria (Lin et al. 2006; Loo et al. 2006; Meylan et al. 2005). As IPS-1 is an essential adaptor for both RIG-I and MDA5 signaling and its association with mitochondria is obligatory, this cleavage completely blocks RIG-I/MDA5 signaling. Indeed, IPS-1 mutation at the cleavage motif or NS3/4A protease inhibitor restores the activation cascade stimulating the IFN genes.

NS1 protein of influenza A virus has been implicated in the inhibition of IFN gene activation. Using influenza A virus with NS1 mutation and RIG-I knockout mice, it was shown that NS1 blocks the signaling cascade triggered by RIG-I (Kato et al. 2006). NS1 is a dsRNA binding protein, thus sequestration of RIG-I from its ligand is one mechanism; however, the dsRNA-binding-deficient mutant of NS1 remains inhibitory (Donelan et al. 2003), suggesting multiple actions of this protein.

Ebola virus VP35 protein is another dsRNA binding protein inhibiting RIG-I-mediated signaling (Cardenas et al. 2006). Like NS1 of influenza A virus, VP35 may have dual inhibitory functions: in addition to dsRNA sequestration, it may be inhibiting steps downstream of IPS-1 and IRF-3 kinases.

Since RIG-I and MDA5 are IFN-inducible and positive feedback is an important trait of the system, inhibition of IFN action, including IFN-R, by the JAK-STAT pathway remotely inhibits RIG-I and MDA5. In this regard, viral proteins that target IFN action are also inhibitory for IFN production.

6
Ligands for RIG-I and MDA5

In vitro binding studies revealed that RIG-I exhibits a specific binding activity to dsRNA, such as poly I:C, poly A:U, 5' or 3' non-coding genomic RNA of HCV synthesized in vitro, but not to poly A, tRNA, single-stranded region of HCV genomic RNA and dsDNA (Sumpter et al. 2005; Yoneyama et al. 2004).

MDA5 exhibits a much weaker binding activity to poly I:C. Inconsistent with the in vitro binding, functional analysis using knockout mice and cells deficient in either RIG-I or MDA5 revealed that dsRNA produced by in vitro transcription and poly I:C are specifically detected by RIG-I and MDA5, respectively (Kato et al. 2006). Furthermore, the RNA viruses tested were classified into two groups; picorna viruses (including EMCV) are specifically sensed by MDA5 and other viruses (including VSV, influenza virus and Sendai virus) by RIG-I. The specificity arises from different classes of RNA structure, as suggested by the results that RNA extracted from VSV and EMCV viral particles activated RIG-I and MDA5, respectively. This result includes noteworthy facts: VSV genomic RNA is unlikely to be highly double-stranded; under certain circumstances, viral replication may not be necessary to activate RIG-I. For dsRNA recognition, one report suggests the importance of end structure for selective activation of IFN genes or RNA interference (Marques et al. 2006). The search and elucidation for true ligands present in virus-infected cells for RIG-I and MDA5 is absolutely necessary to further our understanding of how self and non-self is recognized at the RNA level. At present there is no reasonable explanation to satisfy all these observations.

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炎症と免疫

別　刷

細胞内ウイルスセンサーによる
インターフェロン誘導機構

小野口和英*　　米山光俊*　　藤田尚志*

われわれの免疫機構は自然免疫と獲得免疫の2つに大別されるが，インターフェロンはこの両方を調節する蛋白質として機能している．ウイルス感染の場合，われわれの免疫系は細胞外あるいは細胞質で感染を認識してⅠ型インターフェロンを産生する．RIG-Ⅰファミリーは細胞質で感染を認識する細胞内レセプターであり，ウイルス由来のRNAを認識することで活性化する．RIG-ⅠファミリーにはRIG-Ⅰ，MDA5，LGP2の3種類の蛋白質があり，それぞれ別々の機能を担っている．最近，このRIG-Ⅰファミリーの制御機構が徐々に解明され，インターフェロン誘導機構の詳細が明らかとなってきた．

はじめに

Ⅰ型インターフェロン(以下インターフェロン)はわれわれの免疫機構を調節する重要な蛋白質であり，抗ウイルス作用や抗癌作用をもつことから，今日の医療現場に欠かせない治療薬として使用されている．インターフェロンはウイルスや細菌の感染により特異的かつ一過的に発現することが知られており，インターフェロン遺伝子発現のON/OFFの差が明確だったことから，インターフェロン誘導機構の研究は他の遺伝子に先駆けておこなわれてきた．1980年代に入ってから，遺伝子や蛋白質レベルでの解析により，転写にかかわる因子についての研究が精力的になされてきた[1]．そして近年，ウイルスや細菌の感染を認識するレセプターについての全体像が徐々に明らかとなってきている．ウイルス感染を認識するレセプターには細胞外の病原体を認識するToll-like receptor(TLR)ファミリーと，細胞内の病原体を認識するretinoic acid inducible gene(RIG)-Ⅰファミリーがあり，どちらもインターフェロンやその他のサイトカイン遺伝子を誘導するシグナルを惹起する[2][3]．

本稿では，このうちRIG-Ⅰファミリーについて取り上げる．

1．RIG-Ⅰファミリー

インターフェロンは自然免疫だけでなく，獲得免疫の調節にも深くかかわっていることが知られている．とくに樹状細胞(DC)などの免疫細胞は自然免疫・獲得免疫の両方で機能している．pDCはウイルスの感染などで大量のインターフェロンを産生するが，そこではおもにTLRが感染を認識し，インターフェロン産生を誘導している[2][3]．

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1 925
RIG-I

23%　　　35%　　31%
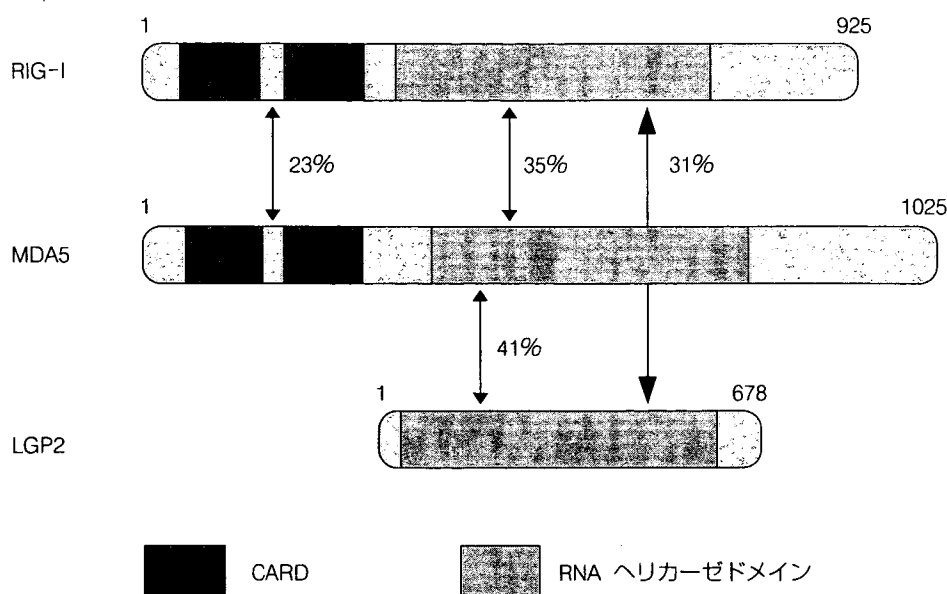
1 1025
MDA5

41%

1 678
LGP2

■ CARD　　▓ RNA ヘリカーゼドメイン

図 1. RIG-I ファミリーの構造
RIG-I ファミリーは共通して C 末端側に RNA ヘリカーゼドメインを
もち，さらに RIG-I および MDA 5 は N 末端側に caspase recruitment
domain(CARD)を 2 個もつ．数字(%)はそれぞれのドメイン間のアミ
ノ酸の相同性を示す．

しかしながら，TLR はこのような一部の免疫系の細胞にしか発現しておらず，さらに TLR による認識は細胞の表面，あるいはエンドサイトーシスによって細胞内部に取り込まれた膜構造内，つまり細胞外でしか起こらない．しかし，ウイルス感染は免疫細胞以外でも起こり，さらに感染した細胞内でウイルスは増殖している．このような TLR が存在しないところでは，別のファミリーである RIG-I ファミリーがウイルス感染を認識している[3]~[5]．RIG-I ファミリーはほとんどの細胞で発現していることから，より広くウイルス感染に応答した免疫誘導に関与していると考えられている．

RIG-I ファミリーには RIG-I，MDA 5，LGP 2 の 3 種類の蛋白質があり，どれも共通して RNA ヘリカーゼドメインをもっている(図1)．通常われわれの体内には比較的長い二重鎖 RNA は存在しないが，ウイルスに感染するとウイルス増殖の過程において細胞質内に二重鎖 RNA が産生される．RIG-I/MDA 5 はこの RNA をヘリカーゼドメインで認識することで活性化し，インターフェロン誘導シグナルを起こすと考えられている．RIG-I/MDA 5 にさらに特徴的なのが N 末側に存在する caspase recruitment domain(CARD)様の構造である．CARD ははじめはアポトーシスを引き起こす caspase ファミリーのドメインとして同定された．たとえば，Apaf-1 と caspase-9 は CARD 同士で会合することによって，アポトーシスを誘導する[6]．しかし RIG-I/MDA 5 の CARD の場合，caspase にみられる CARD とのホモロジーは低く，caspase とはまったく別の分子と結合することが明らかとなっている(後述)．このことからおのおのの CARD には特異性があり，選択的に下流の分子にシグナルを伝えていると考えられる．

RIG-I ファミリーのうち RIG-I および MDA 5 はどちらも正の制御因子として機能することによりインターフェロンシグナルを誘導するが，ノックアウトマウスの解析からそれぞれが認識する RNA ウイルスの種類が異なることが明らかとなった[5][7]．RIG-I はパラミクソウイルスやフ

ラビウイルスを認識するが，MDA 5 はピコルナウイルスを特異的に認識している．最近，RIG-Ⅰは 5'triphosphate 構造をもつ一本鎖 RNA も認識することができ，必ずしも二重鎖 RNA である必要はないということが報告された[8)9)]．RIG-Ⅰが認識できないピコルナウイルスは RNA の 5' 末端にウイルス蛋白質が特異的に結合していることが知られており[10)]，この蛋白質があるために RIG-Ⅰはピコルナウイルス RNA を認識できないのではないかと考えられる．これらのことから，RIG-Ⅰ/MDA 5 の認識するウイルスの違いは RNA の構造に起因しており，MDA 5 もまた別の RNA 構造を認識していると思われる．

一方，LGP 2 は RIG-Ⅰや MDA 5 と異なり，インターフェロン誘導シグナルの抑制にはたらいている[11)]．図 1 に示すとおり，LGP 2 には CARD がなく RNA ヘリカーゼドメインだけの構造をとっている．LGP 2 は二重鎖 RNA に対して高い親和性をもち，二重鎖 RNA を奪うことで RIG-Ⅰ/MDA 5 の活性化を抑制していると考えられる．RIG-Ⅰファミリーはインターフェロンによって発現量が増えるインターフェロン誘導遺伝子でもあり，インターフェロンによってはじめは RIG-Ⅰ/MDA 5 の発現量が増え，インターフェロン誘導シグナルの正のフィードバックが起こる．しかし，LGP 2 の発現量がある一定を超えると LGP 2 による抑制効果が現れ，インターフェロン遺伝子の発現量が減少し，シグナルの沈静化へとつながっていくと考えられている．

2．RIG-Ⅰファミリーから下流のシグナル

RIG-Ⅰと MDA 5 からのシグナルは下流に位置する IPS-1（別名 MAVS/VISA/Cardif）へと伝えられ，さらにインターフェロン遺伝子の転写因子である IRF-3 や IRF-7，NF-κB へとシグナルが伝わることで，インターフェロンが発現する（図 2）[12)~15)]．転写因子についての詳細は他稿に譲るが，ここでは IPS-1 に着目したい．IPS-1 にも

N 末側に CARD が存在し，この CARD を介して活性化された RIG-Ⅰおよび MDA 5 と直接結合している．IPS-1 は他にも TRAF 3 や TRAF 6，FADD などとも結合し，大きな複合体を形成していると考えられている[12)14)~16)]．しかし IRF ファミリーの活性化キナーゼである TBK 1/IKK-i が IPS-1 に結合するかどうかについては議論が分かれており，IPS-1 から下流のシグナルについての詳細は明らかとなっていない．興味深いことに IPS-1 はミトコンドリアの外膜に存在する膜蛋白質であり[13)]，この局在が機能に重要であることが示されている．ミトコンドリアのインターフェロン誘導における役割が注目されている．

3．ウイルスによるインターフェロン誘導シグナルの抑制

われわれの体はウイルス感染を認識し，さまざまな方法で増殖の抑制や排除をおこなうが，ウイルスもわれわれの免疫系を撹乱させる手段をもち，有利に増殖をおこなおうとしている．RIG-Ⅰファミリーを介したインターフェロン誘導機構もこの例に漏れず，ウイルスによるシグナル抑制が報告されている（図 3）．たとえばパラミクソウイルスのもつ V プロテインは MDA 5 に結合し，インターフェロン誘導シグナルを抑制している[17)]．V プロテインは RIG-Ⅰを介したシグナルには影響を与えないことから[11)]，MDA 5 特異的に機能していると思われる．しかしながら，先ほど述べたようにパラミクソウイルスを認識するのは RIG-Ⅰであり，なぜ MDA 5 を抑制するのかについてはよくわかっていない．

V プロテインの他にもインターフェロン誘導シグナルを抑制する蛋白質として，C 型肝炎ウイルスがもつ NS 3/4 A が知られている[18)]．はじめは RIG-Ⅰ/MDA 5 を介したシグナルを特異的に抑制することが報告され，その後 IPS-1 が NS 3/4 A のターゲット分子であることが明らかとなった[15)19)20)]．NS 3/4 A はヘリカーゼ活性とプロテ
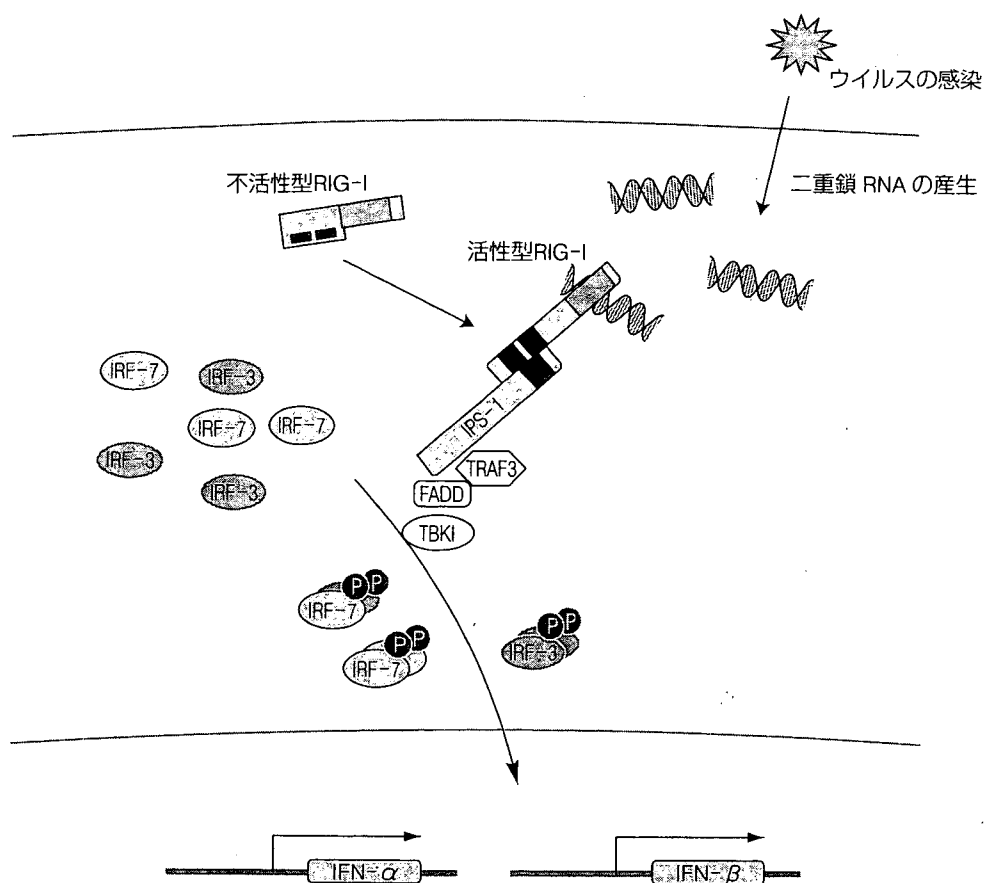
図 2. RIG-Ⅰ のシグナル機構
　通常不活性化状態で細胞質に存在する RIG-Ⅰ は二重鎖 RNA と結合することにより，RNA ヘリカーゼドメインによる ATPase 活性のエネルギーを得て，立体構造を変化させ CARD を露出する．活性型 RIG-Ⅰ は IPS-1 と相互作用し，下流へとシグナルを伝え，最終的に転写因子である IRF-3 および IRF-7 が活性化することでインターフェロン遺伝子が転写される．

アーゼ活性をもつ蛋白質であるが，そのプロテアーゼ活性が IPS-1 の C 末側を切断する．IPS-1 の C 末側には膜貫通ドメインがあり，NS 3/4 A による切断を受けた IPS-1 はこの膜貫通ドメインを欠くために，ミトコンドリア膜から放出される．このことが下流へのシグナルをブロックしていると考えられる．

　このほかにも詳細なメカニズムはわからないが，インフルエンザウイルスの NS 1 やエボラウイルスがもつ VP 35 も RIG-Ⅰ からのシグナルを抑制することが報告されている[21)22)]．さまざまなウイルスが RIG-Ⅰ からのシグナルを抑制する機能をもっていることは，RIG-Ⅰ によるインターフェロ

ン誘導機構がいかに重要かを物語っている．

おわりに

　感染における細胞内レセプターに関する研究ははじまったばかりであるが，その多様性を示すデータが報告されている．最近，細胞質内に B 型 DNA が存在するとインターフェロン遺伝子を誘導することが報告された[23)]．このことは B 型 DNA を認識する細胞内レセプターの存在を示唆しているが，興味深いことに，B 型 DNA による活性化シグナルには，TBK 1, IKK-i や IRF ファミリーが必要であり，下流では RIG-Ⅰ と同様のシグナルを伝達することが示唆されている[24)]．今後
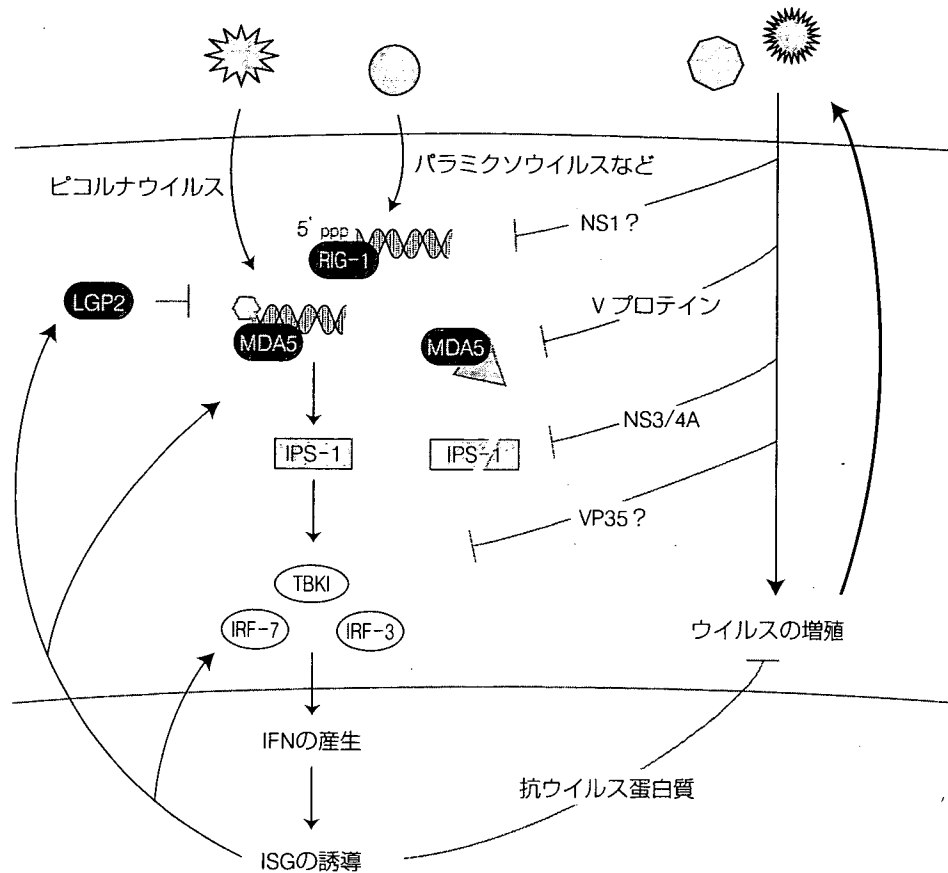
図 3. インターフェロンシステムとウイルスによるシグナルの抑制
ウイルス感染によって RIG-Ⅰ/MDA 5 を介したインターフェロン誘導シ
グナルが起こると，インターフェロン誘導遺伝子 (ISG) の発現が増え，抗ウ
イルス作用をもつ蛋白質によってウイルスの増殖が抑制される．さらに
RIG-Ⅰ/MDA 5 や IRF-7 の発現も増え，インターフェロンシグナルの正
のフィードバックが起こる．しかし，過度のインターフェロンは細胞にダ
メージを与えるため，LGP 2 がその沈静化に作用している．一方，ウイル
スのなかにはインターフェロン誘導シグナルを阻害する蛋白質をもつ種が
いる．最終的にはこれらのバランスによって，ウイルス増殖の進行具合が
決まると考えられている．

は細胞内レセプターと免疫の関係を明らかにする
ことで，新しい治療法へと応用されることが期待
される．

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蛋白質 核酸 酵素

PROTEIN, NUCLEIC ACID AND ENZYME

別 刷