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Innate Immune Recognition During RNA Virus Infection: Molecular Mechanisms —A Review

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Abstract

RNA viruses continue to pose a risk for human and animal health because they mutate at high rates and can enact measures of evasive action against host immune defenses. Innate immune system, which is responsible for sensing of viral RNA via PRR such as TLRs (Toll-like receptors), RLRs (RIG-I-like receptors) and NLRs (NOD-like receptors), to mount rapid interferon and pro-inflammatory responses thus act as the first line of antiviral defense. The integrated antiviral response is directed through distinct biological components manifested in mitochondrial antiviral signaling proteins (MAVS), transcription factors NF-κB and IRF3/7, and inflammasome complexes. However, RNA viruses have evolved various means of evading these innate defense mechanisms, by: (1) targeting and cleaving mitochondrial antiviral signaling proteins (MAVS); (2) preventing the addition of ubiquitin to the relevant signaling molecules; and (3) preventing the production of interferon alpha/beta [9]. The introduction of classes of sensors, such as ZBP1-mediated PANoptosis, DHX helicases and the cGAS-STING pathways represent novel antiviral recognition mechanisms that open new therapeutic avenues. In this review we detail classical and contemporary observations of innate immune recognition, highlight mechanisms viruss have developed to counteract host defenses, delineate how vaccine adjuvants may bypass these viral antagonism strategies and sketch implications for the development of therapeutics against important human viruses. Accordingly, deciphering these complex host-

pathogen interactions has major implications for the design of direct antiviral therapeutics and alternative indirect immunomodulatory strategies.

Keywords: Innate immunity; RNA viruses; Pattern recognition receptors (PRRs); RIG-I-like receptors (RLRs); Toll-like receptors (TLRs); NOD-like receptors (NLRs), MAVS signaling ZBP1 and PANoptosis, cGAS-STING pathway; Vaccine adjuvants.

Introduction

The innate immune system is the host first line of defense in combatting viral pathogens. It contains DNA and numerous RNA viruses like Influenza (fi), SARS-CoV-2, rotaviruses Unlike adaptive immunity which requires prior exposure, innate immunity can detect and respond to viral infections via highly conserved pattern recognition receptors (PRRs) [1, 2]. In humans, these receptors consist of the Toll-like receptor (TLR) family sensors of pathogen-associated molecular patterns (PAMPs), RIG-I-like receptor (RLR)-family proteins, and the non-homologous bacteria-sensing NOD-like receptor (NLR)-families [3–5]. These pathways require complex molecular interactions for their activation. Cytosolic sensors like RIG-I and MDA5 discriminate between self and non-self RNA according to structural motifs (five-triphosphates or double-stranded RNA length) signalling through mitochondrial antiviral-signalling protein (MAVS) molecules to downstream transcription factors including NF-κB and IRFs [6, 7]. Concurrently, NLRs promote the assembly of inflammasomes resulting in secretion of matured IL-1β and IL-18 as well as pyroptotic cell death that curtail viral replication [8]. The new studies implicate accessory molecule changes, post-translational modifications, and spatial regulation in tailoring those signals to promote functional antiviral responses while preventing immunopathology [9–11].

Although innate immunity is a robust system, RNA viruses have evolved multiple complex strategies to evade the immune response, such as cleaving the MAVS protein with proteolytic enzymes [12], removing ubiquitin from signaling components [13], and interfering with the induction of interferon production [14]. When viruses employ these strategies, they weaken host defenses and may lead to specific molecular virulence in the resulting disease, highlighting the need for further research into host-virus interactions at the molecular level. This has opened new avenues for RNA-based sensing activities, moving beyond protein receptors and their pathways (such as

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conventional pattern recognition receptors [PRRs]) to non-traditional sensors such as ZBP1-mediated apoptosis, DHX helical enzymes, cGAS-STING signaling, and others.. These results clarifying antiviral immunity mechanisms and providing new directions for therapeutic development such as small-molecule MAVS stabilizing compounds, inhibitors targeting viral antagonists of the immune system, or vaccine adjuvants with immune stimulatory properties [15–17]. In this review, we attempt to summarize the molecular mechanisms by which innate immunity recognizes RNA viruses through their structural properties and viral evasion strategies with potential therapeutic interventions to restore and augment antiviral immunity. The study also aims to integrate classical and newer concepts to define novel targets for future research directions and translate them into potential clinical applications for RNA viral infections.

Innate immune system: Immune defense against RNA viruses

This protective architecture is underpinned by the rapid detection of viral pathogen associated molecular patterns (PAMPs) through specific pattern recognition receptors [1,2]. Immunoinhibitory Mechanism This set predominantly consists of Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs), which initiate intracellular signal transduction cascades and increase the secretion of type I and type III interferons, as well as pro-inflammatory cytokines [3–5]. Transcriptional responses are facilitated by the activation of key transcription factors (TFs), such as nuclear factor kappa B and interferon regulatory factors, resulting in a strong antiviral state [6, 7]. Besides, it should be underscored that activations of the inflammasome represent an essential parallel pathogenetic pathway for induction of pro-inflammatory cytokines such as IL-1 and IL-18 whose cleavage products confer pyrogenic activity as well as triggering a pyroptotic cell death response which inhibits viral replication [8]. Apart from these known pathways, we can speculate via some examples that dependence on 5'-pppRNA or short dsRNA versus long dsRNA by two specific types of cytosolic RNA sensors RIG-I and MDA5 respectively may allow spatial and temporally correct immune regulation [9]. After ligand binding, such receptors undergo conformational changes that expose N-terminal caspase-recruitment domains which bind and recruit the mitochondrial antiviral signaling adaptor protein (MAVS) [10, 11]. This overall interaction mediates oligomerisation of the protein on mitochondrial outer membrane and serves as a

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scaffold for subsequent recruitment of TBK1/IKKε kinases [12, 13]. The innate immune system is our first line of defense against all RNA viruses as this is the most primitive and basic level of defence PRRs detect viral RNA to quickly induce interferon signalling, inflammatory cytokines induction and inflammasome action that restricts vir circulation for their role. This section provides a crucial conceptual basis for research, highlighting that antiviral defense relies on an integrated network of interferons, nuclear transcription factor kappa B (NF-κB), interferon regulatory factors (IRFs), and inflammatory particles, rather than a single mechanism.

Artillery Innate Immune Recognition

Pattern Recognition Receptors: Endosomal Membrane-bound Toll-like receptors (TLR3) detect dsRNA in the endosomal compartment, while cytoplasmic retinoic acid-inducible gene-I-like receptors, including RIG-I, MDA5, and LGP2, serve as a surveillance mechanism for the replication of viral genomes within cells [14–16]. Mitochondrial Antiviral-signaling Protein: Serves as the primary cytoplasmic signaling center [15–17]. The type I interferon response is initiated by the activation of IκB kinases and IRF3/7. The phosphorylation of these transcription factors allows them to reach the nucleus, where they initiate the transcription of type I interferons and other pro-inflammatory cytokines. These cytokines are essential components of the initial antiviral response [18, 19]. Nevertheless, recent research suggests that the appropriate spatial regulation of these signaling complexes is essential for the prevention of pathogenicity and the promotion of tissue homeostasis following virus clearance [20], as it extends beyond the biochemistry of canonical pathways. Post-transcriptional modifications, especially ubiquitination of signaling components, act as secondary checkpoints that regulate the strength and length of these innate immune responses [21]. Many ubiquitous mechanisms restrict signaling, either by removing the distal aspect of a ubiquitin chain or sequestering even proximal intermediates [22, 23]. In addition, members of 14-3-3 protein family can regulate the structural assembly of RLRs into filamentous nucleoprotein complexes, which foster the appropriate relocalization of these sensors within the cytosol to their effector MAVS platform at mitochondria [24]. Importantly, this signal amplification is amplified by the prion-like aggregation of MAVS [25, 26], which allows a rapid, feed-forward propagation of the signaling scaffold along the mitochondrial network. Besides these structural transitions, K63-

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linked polyubiquitination of RIG-I, MDA5 and MAVS is another major regulatory mechanism that facilitates the recruitment of downstream TRAF molecules that will be needed for rapid and efficient signal transduction [27]. In contrast, ubiquitin can be removed from these components by antiviral agents or enzymes secreted by the host [28]. This would limit immune signaling and protect against autoimmune diseases. Antiviral gene expression is regulated by TLRs, RLRs, MAVS, IRF3/7, and NF-κB receptors, which are activated in the presence of viruses. This subheading summarizes the main idea because it describes a principle related to "molecular factors" in innate immunity. Since the location of these sensors determines the timing (innate or adaptive) and nature of the immune response, a clear distinction between membrane/endosomal and cytoplasmic sensors would contribute to a more nuanced understanding of this topic.

PRRs in RNA Viral Sensing

The main molecular determinant sorting self-RNA from non-self-RNA is the selection of binding between MDA5, a protein identifying high-molecular-weight double-stranded RNA (dsRNA), and RIG-I recognizing 5'-triphosphate motifs [29]. LGP2, the third member of the RLR family but without these signaling domains underlie an important regulatory cofactor that potentiates MDA5 detection for long length viral RNA substrates (30). Recent observations have interestingly indicated that LGP2 regulates the ATPase activity of MDA5 to moderate the movement of MDA5 on infectiousAU: Use full name in full first appearance As such, this may protect against premature or spontaneous interferon launching in the absence of genuine pathogenic substrates [31, 32]. To stabilize the functional scaffold for downstream signaling effectors, the RIG-I molecule is further refined and processed by distinct E3 ubiquitin ligases such as TRIM25 that catalyze K63-linked polyubiquitination [33]. Simultaneously, novel non-RLR sensors that are specific for different cytoplasmic viral nucleic acid structures, including PARP9 [34] and the DDX1-DDX21-DHX36 complex [7], have been identified. Such RNA-binding sensor complexes (such as RIG-I, MDA5, LGP2 and so on) allow host cells to distinguish between viral RNA and self-RNA in a manner of ligand-specific recognition. The latter portion is very strong due to scientific research that has shown RNA recognition is not random but rather based on structural features including 5′-triphosphate motifs, and the length of dsRNA (double-stranded

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RNA). That level of specificity is critical to avoid triggering autoimmunity or unnecessary inflammation.

TLRs and Recognition of RNA Viruses

In contrast, Toll-like receptor 3 (TLR3) binds to endosomal compartments and detects luminal double-stranded RNA (dsRNA)[34] through a TRIF-dependent signaling pathway. Toll-like receptors 7 and 8(TLR7), responsible for binding ssRNA, depend on MyD88 [26,28] and RLR-mediated intracellular cytosolic surveillance complete a three-pronged mechanistic approach to safeguard invaders [35]. Besides connecting the extracellular surveillance and cytoplasmic recognition, this endosomal monitoring system allows for early detection of endocytosed viral particles before their entry into the cytosol [36]. Chaperone protein UNC93B1 is needed for proper transport and functional maturation of endosomal TLR3, TLR7 and TLR8 within in the vesicular network that sequesters these receptors away from cell surface localization [37]. Moreover, there was an association between the clinical severity of infections with SARS-CoV-2 and genetic variants of essential genes in TLR pathway [38], providing added evidence on the key role endosomal sensors may have to susceptibility. These membrane-bound recognition receptors synergistically cooperate with cytosolic NLRP3 inflammasome, which senses a variety of stimuli including viral ssRNA and dsRNA to extend the spectrum of virus detection and generates pro-inflammatory IL-1β and IL-18 [39]. Before viral genomes can enter the cytoplasm, they are detected in endosomal compartments by Toll-like receptors (TLR) that survey for RNA viruses with TLR3 and small-subunit RNA with TLRs 7 and 8 [1,2]. This is a key piece of data since it shows that antiviral recognition early in viral infection. The greater importance of TLR pathways in immune cells may partially explain the different severity of infection seen between subjects. Cytosolic sensors for viral RNA like Retinoic Acid-Inducible Gene I (RIG-I)-like Receptors.

Members of this family act as redundancy sensors; MDA5 is responsible for detecting long dsRNAs that do not have 2′-O-methylation, and RIG-I is more sensitive to short dsRNAs or RNAs that have been 5'-triphosphorylated [40]. Outside of these dominant receptors, regulatory proteins like DHX58 aid in the sensing through MDA5 along with limiting signaling through RIG-I. The DDX60 helicase, which is essential for RIG-I activation, was recently identified as a co-factor that increases binding of

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viral RNA transcripts to RIG-I [41]. MAVS functions as a centralized processing center by tethering these helicases to the outer mitochondrial surface where all various RLR signaling events come together to elicit antiviral transcription mediated by IRF5/7 [42, 43]. During this secondary round of signaling, IRF7 undergoes phosphorylation and translocates to the nucleus where it drives expression of a large number of interferon-stimulated genes to further augment innate immunity and antiviral state establishment [44]. These pathways are strong, but several RNA viruses have evolved complex and ingenious methods to resist detection by the host by actively silencing this interferon signaling cascades through their nonstructural proteins or specific viral polymerase expression. RIG-I and MDA5 are two non-redundant cytosolic RNA sensors that recognize specific patterns in viral RNA, then use MAVS as an adaptor to initiate a signal transduction cascade that leads to activation of interferon and antiviral gene programmes. The study's most mechanistic section is offered as this subtitle. It is crucial to differentiate the sensing pathways activated by RIG-I and MDA5 since RNA viruses may activate different pathways on recognition, which is important for the design of antiviral therapies

NOD-like receptors (NLRs), Activation of NLRP3 inflammasome

In this context, NLRP3 and other members of the NLR family act as important sensors for a wide range of danger-associated molecular patterns released in response to cellular stress caused by virus infection, leading to formation of multiprotein inflammasome complexes [45, 46]. This process results in the proteolytic activation of caspase-1, which then enables the secretion of mature proinflammatory cytokines to enhance innate immunity against pathogens such as rotavirus and influenza A virus [47]. In addition to NLRP3, RNA helicases DHX33 and DHX15 have recently been identified as important sensors that direct the recruitment of NLRs into specialized IL-1β- and IL-18-converting inflammasomes, linking sensing of viral dsRNA with robust maturation of host pro-inflammatory cytokines [48]. This indicates that sensing patterns are not static, and instead suggests that host cells employ a many-pronged approach to limit the multiplication of viral invaders before this replication can happen [49]. The indication that MAVS signaling translocates from peroxisomal domains to mitochondria for prolonged large-scale interferon production during the early stages of infection also stresses the spacial segregation of these responses [50]. This differential mitochondrial and peroxisomal signaling is a means by which the host, in a process regulated at its inception, can immediately mount an

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effective systemic proinflammatory cytokine response enabling immunity to the spread of viruses [51, 52].

Because the NLRP3 and other members of the NLR family recognize cell stress triggered by viruses (19), they are an essential component in defending against viral infections, and initiation of caspase-1 activation, as well as subsequent maturation of IL-1β/IL-18, pyroptotic cell death, and triggering by inflamasome formation. What I love about this part is it deviates from pure interferonization. On the other hand, we need to consider the activation of inflammasome strictly as a double-edged mechanism: protective when it is regulated enough and deleterious whenever its excess leads to tissue damaging inflammation.

Emerging Mechanisms of RNA Sensing

Emerging evidence that the well-recognized cGAS-STING axis can indirectly sense RNA viruses by promoting mitochondrial stress signals or chromatin damage has contributed to the realization of RNA sensing [53]. Furthermore, the assembly of RIP1-RIP3 complex acts as an intracellular sensor for mitochondrial damage, leading to NLRP3 inflammasome activation after viral infection [54]. In addition, the discovery of NLRP9 as a key rotavirus sensor that relies on DExH-box helicase 9 to sense viral dsRNA and promote IL-18 maturation while also inducing pyroptosis offers important confirmation [55]. This protective mechanism is primarily cell-type specific, as expression of NLRP9b is limited to intestinal epithelial cells, not immune cells populating the intestine [56]. Thus, DHX9 requirement as a direct binding intermediate in this specific niche raises the paradigm for cooperative sensing: accessory helicases that connect viral RNA recognition to subsequent assembly of cytosolic inflammasome platforms [57]. As for cytosolic receptors, ZBP1 recognizes the nucleoproteins and polymerases of some viruses, linking intracellular viral infection to recruitment of NLRP3 to increase inflammasome formation in addition to these helicase mediated modes of signal transduction [58]. In this review, we discuss recent advances in recognizing RNA viruses including TO and the indirect cGAS-STING coupling of activation, RIP1-RIP3 driven mitochondrial stress & NLRP9 are generally recognized as an emerging model of sensing by DHX9-dependent recognition or dependent on ZBP1. The subtitle is an indication of how recent the review is. It illustrates and demonstrates that intrinsic RNA sensing needs in-depth characterizing beyond the classical TLR/RLR signaling

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paradigm, which will be hard through adequate exploration of tissue-specific and cell-type specific sensing.

Other Cytosolic RNA Sensors

Proteins, including OAS1 and RNase L, act as important mediators of the interferon-induced antiviral state by triggering cellular RNA degradation after interacting with dsRNA [59]. Moreover, the regulation of RIG-I-like receptors in a spatiotemporal manner has recently been elucidated as depending on some microsome-located signaling complexes, which allows LGP2 to modulate interactions with MAVS before engaging larger mitochondrial platforms [60]. In addition, structural and biochemical studies have further equipped us with an increasingly clear picture of how OAS paralogs specifically discriminate among diverse RNA substrates, enabling the production of 2–5A messengers that elicit widespread inhibition of viral translation. Meanwhile, ZBP1 sensor also plays an essential role to protect cells against Z-RNA conformations during influenza infection by triggering the assembly of ZBP1-NLRP3 inflammasome, facilitating PANoptosis and other regulated cell death pathways [61]. This signaling complex, added caspase-6 that mediates the hollow of RIPK3 to ZBP1, gives a signal to induce hyperinflammation and destroys epithelial damage caused by deadly influenza A virus infection [62]. The ZBP1-mediated recognition of viruses is not limited to influenza, but also includes various viruses such as vaccinia and SARS-CoV-2 that replicate in the cytosol and induce accumulation of Z-RNA [63]. OAS1/RNase L and ZBP1, signaling complexes associated with OAS paralogs such as LGP2 also have a role in RNA degradation, viral translation inhibition and regulated inflammatory cell death. This is crucial as it reveals that antiviral immunity encompasses both sensing and direct effector mechanisms. Notably, the OAS/RNase L pathway is actually one of those that are most important because it actively eliminates RNA thus suppressing viral proliferation.

Non-Canonical PRRs and Co-Receptors

In addition to well characterized sensors, emerging data has demonstrated that host proteins such as the nucleus-localized protein HMGB1 can translocate into the cytosol following viral infection and function as non-canonical co-receptors, potentiating DNA and RNA sensing pathways [64]. Additionally, these auxiliary molecules tend to assist

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the recruitment of signaling adaptors to pre-formed receptor clusters thereby reducing the threshold for their induction of downstream proinflammatory cytokines [65]. Concurrently, the characterization of newly discovered RNA–binding proteins such as CNBP has begun to shift our focus toward proteins that bind physically to viral genomes to either dampen or immune-enhance these signaling pathways [66]. Moreover, these are bona fide accessory factors as they also bind to the Receptor Interacting Protein Homotypic Interaction Motif domains of major sensors such as ZBP1 to regulate the shuttling between parallel necroptotic and apoptotic death pathways [67, 68]. These interactions highlight the structural plasticity of the ZBP1-PANoptosome, in which RHIM domains, such asRHIM1, play a key role mediating functional crosstalk between innate sensors and death-effector proteins [69, 70]. Non-canonical molecules (like HMGB1, CNBP and accessory RNA-binding proteins) that modulate or boost innate immune recognition support receptor clustering, signaling adaptor recruitment and integration of cell-death pathways. This part of the review reveals that innate immune sensing is not limited to classical receptors. This could account for the widely different inflammatory consequences of viral infections in different tissues, given that tissue-regulated expression of co-receptors and accessory proteins substantially contribute to the total response.

Danger-Associated Molecular Patterns (DAMPs) During Viral Infection

Viral infections result in the intracellular excretion of damage-associated molecular patterns (DAMPs) like HMGB1 that have high activity as endogenous ligands and can prime pattern recognition receptors for threshold level virus stimulation [71]. More particularly, the cytosolic release of such nuclear DAMPs acts as a trigger that induces inflammatory necrotic cell death (i.e., necroptosis and pyroptosis) [72, 73]. In addition, ZBP1-mediated sensing of Z-form nucleic acids and these released DAMPs create a feed-forward loop of necro-inflammatory signaling that amplifies tissue injury upon injurious respiratory infections [74]. Typically, this PANoptotic cascade leads to the formation of PANoptosome, a large macromolecular complex that gathers caspases and receptor-interacting serine/threonine kinases (RIPKs) to perform regulated cell death, which is severely affecting the homeostasis of all of the hosts [75]. The ZBP1-induced formation of liquid–liquid phase-separated condensates and amyloid-like puncta under this scenario provides an additional layer of specificity for the detection of viral Z-

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nucleic acids, enhancing downstream signal transduction pathways throughout their kinetics [76]. DAMPs such as high-mobility group box 1 (HMGB1) amplify antiviral inflammation by enhancing PRR sensitivity, stimulating necroptosis and pyroptosis, and bolstering positive-feedback inflammatory signaling in the context of acute phase viral infections. This section is clinically significant as it connects the process of viral sensing with immunopathology. This exaggerated inflammation, which can often be seen long after the initiation of viral replication has begun to wane, could potentially be mediated by DAMP-dependent amplification. These data suggest that the stabilization of RNA recognition signaling pathways is an explanation.

The major activation of these pathways is mainly through oligomerization of adaptor proteins, like MAVS or STING that go on to undergo conformational changes to recruit TRAF-family ubiquitin ligases and downstream kinases [77]. Kinase cascades serve to activate transcription factors, e.g. NF-κB and IRF3, which migrate to the nucleus to cause expression of proinflammatory cytokines and type-I interferons [78]. At the same time, recruitment of RHIM-containing kinases such as RIPK1 and RIPK3 to the ZBP1 platform promotes propagation of non-canonical signaling axes, which facilitate a rapid switch between antiviral transcriptional responses and orchestrating executioner programmes of death [79, 80]. In addition, this transition in signaling is tempered by viral countermeasures such as expression of proteins that shields Z-form nucleic acids or intercept RHIM-mediated interactions to blunt host immune activation [81]. Moreover, ADAR1 constitutes an important regulatory checkpoint that binds Z-RNA to trigger the A-to-I deamination of adenosine to inosine to destabilize the double helix and thereby avoids spurious ZBP1 activation under physiological conditions. In the initial stage, RNA recognition triggers the activation of adaptor proteins (MAVS and STING) that subsequently activate TRAF, kinases, translocation to the nucleus of IRF/NF-κB, cytokine production and programmed cell death pathways. It is significant for this subtitle to bridge from detection to biological outcome. One of its major strengths is that it views innate immunity as a signaling cascade in which receptor activation is only the initiation to interferon production and inflammatory control.

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MAVS-Mediated Signaling in RLR Pathway

After the first detection of viral dsRNA by RIG-I or MDA5, MAVS is an essential scaffolding protein at the mitochondrial outer membrane that assembles multi-protein signalling complexes with signaling strengths modulating the strength of interferon response [82]. This scaffold acts as a common hub to recruit TRAF3 and TANK-binding kinase 1 (TBK1) that together promote phosphorylation of IRF3 to maintain vigorous antiviral cytokine production [83]. Additionally, the spatiotemporal organization of these MAVS-associated signalosomes at the mitochondrial surface generates a localization of regulatory proteins to modulate amplitude in downstream NF-κB signaling and proinflammatory output [84]. The canonical IKKα/β/ γ complex is then recruited to amplify the signal and lead systemically to degradation of IκBα and nuclear translocation of NF-κB [85]. Importantly, this RLR signal propagation is mediated by SHMT-primed dephosphorylation of PP1α/γ for RLRs−through K63 polyubiquitination-mediated stabilization of the MAVS-aggregated signaling complex [86]. MAVS acts as a central mitochondrial scaffold that organizes RLR signaling by recruiting TRAF3/TBK1 and IKK complexes to modulate the amplitude of interferon and NF-κB-mediated antiviral responses. This is a critical section as MAVS represents an important hub in antiviral immunity. Therefore, targeting either the stability of MAVS itself or its interaction with viral antagonists may offer a novel therapeutic approach.

IRF and NF-κB Activation

TBK1 and IKKε, the kinases activated by this second mechanism phosphorylate IRF3/7 and the IKK complex, respectively [6], leading to their nuclear translocation which regulates expression of type I interferons and proinflammatory genes 87,[88. The regulatory mechanism is further modulated by the interaction of these transcription factors with co-activators to achieve the strict kinetic control of the induction of interferon-stimulated genes [89]. In addition to these transcriptional programs, the sustained signalling also requires the assembly of MAVS fibres on the mitochondrial outer membrane (MOM), which scaffolds secondary adaptors controlling kinase-mediated IRF activation [90]. In addition, MAVS fibrils are only formed as a consequence of post-translational modifications: stable K63-linked polyubiquitination mediated by TRIM31 has been shown to stabilize the platform for a persistent signaling

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cascade that extends over hours or longer [91]. In addition to these stabilization mechanisms, MAVS serves as a molecular hub by recruiting TRAF6 and facilitating K48-linked polyubiquitination of TRAF6, allowing efficient NF-κB signaling to occur [92]. Recently, the pathogenesis of VZV has been studied in detail and shown that activation of IRF3/7 and NF-κB induces expression of type I interferons, potential interferon-stimulated genes (ISGs), as well as pro-inflammatory mediators necessary for antiviral defense. This portion is particularly important because IRF and NF-κB activation is the transcriptional end-point of many PRR pathways. But the aberrantly activated NF-κB signaling cascade might involve in improper inflammation that leads to sterility, so endogenous regulation is crucial.

Crosstalk Between Different PRR Pathways

Recent studies show that RLR signaling is facilitated by MAVS through the integration of metabolic inputs, indicating a cooperative action of antiviral RLRs and cytosolic DNA sensor activation to effectively coordinate an appropriate immune response against RNA viruses [93]. On the other hand, the assembly of MAVS-containing signalosomes is Endogenously regulated by mitochondrial membrane potential and reactive oxygen species that impact TRAF3 recruitment thereby regulating TBK1-IRF3 axis activation [94]. In addition, the secreted type I interferons then activate the JAK-STAT signaling pathway by forming and nuclear translocation of the STAT1/STAT2/IRF9 complex [95, 96] to induce hundreds of different interferon-stimulated genes that establish an antiviral state. In addition to this autocrine and paracrine feedback, mechanisms for viral RNA sensing by RIG-I and MDA5 idealize with TLR-based recognition further downstream, where TRIF-dependent signaling pathways redundantly but critically activate TBK1 as well as IRF3/7 in compartment-specific manners [97, 98]. Moreover, this receptor localization is not static as peroxisomal MAVS promotes immediate, IFN-independent defense pathways to protect the host before mitochondrial, IFN-dependent pathway exerts full signal amplification [99]. PRR pathways are highly interactive and cooperate with RLRs, TLRs, cGAS-STING, MAVS, mitochondria, peroxisomes, ROS and JAK-STAT signaling to define a holistic antiviral network. This Subtitle is extremely significant as it goes out of the linear pathway thinking. The immune response to RNA viruses should not be a set of individual signaling pathways but viewed as an interactive network.

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Viral Evasion of Innate Immune Recognition

To conquer these pathways, viruses have evolved a variety of strategies including the synthesis of non-structural proteins that modulate the degradation of MAVS or even the direct sequestering of kinase components like TBK1 from linking to type I interferon induction [100, 101]. Influenza A virus non-structural protein PB1 promotes degradation of MAVS via NBR1-dependent autophagy, silencing a key signaling scaffold required for downstream interferon production [102]. In a similar fashion, proteins evolved by other viruses bind RIG-I or MDA5 to block the conformational changes required for CARD domain unmasking and subsequent oligomerization with MAVS filaments [103]. For instance, some viruses use specific proteins for this purpose to inhibit the ubiquitination of RIG-I and thus forbid downstream adaptor recruitment and mitochondrial signaling hub [4, 104]. RNA viruses escape innate immunity by degrading MAVS, inhibiting RIG-I/MDA5 activation, blocking ubiquitination, and preventing TBK1/IRF3 signaling and interferon production. This part is important because it explains why some people with very strong innate immune systems are still unable to cope with RNA viruses. Immunoevasive capacity is an important determinant of viral pathogenicity and disease severity.

Targeting PRRs and Signaling Molecules

One good example of the use of molecular mimicry and enzymatic cleavage events as viral antagonists at work is deubiquitination of RIG-I by viral proteases to prevent the initiation of a MAVS- dependent cascade [105, 106]. Additionally, viruses such as SARS-CoV-2 gain a one-up on these ablative mechanisms through a modulation of systemic type I and type III interferons thereby attenuating the ISG activation that is necessary to establish an intracellular environment most receptive for viral replication [107, 108]. Besides direct protein-protein antagonism, many RNA viruses exploit autophagy-related machinery including the ATG5-ATG12 complex to physically obstruct RIG-I-MAVS interaction and ultimately inhibit the assembly of functional signaling platforms [109]. In addition, the SARS-CoV-2 M protein works by binding to MAVS to prevent the recruitment of TBK1 and IRF3, thereby dampening the downstream antiviral transcriptional program. Furthermore, the viral nucleocapsid protein further enhances immune evasion by blocking K63-linked polyubiquitination and subsequent aggregation of MAVS. Viruses disrupt PRR signaling by transmission

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via molecular mimicry, enzymatic cleavage or deubiquitination of the key signaling molecules involved in RIG-I/MAVS or STING-dependent signaling complexes. That subtitle is why there is such a compelling rationale for the intervention. Many viruses converge on the same signaling nodes as many PRRs suggest that there may be broad spectrum antivirals if one restores PRR signaling.

Inhibition of interferons and signaling

Viral evasion of the mitochondrial antiviral response also commonly includes targeting of MAVS, such as the PB1-F2 protein from avian influenza [10, 110] which facilitates retention and degradation of inactive aggregated MAVS on the mitochondria membrane. In contrast with those mechanisms, SARS-CoV-2 ORF10 has been shown to promote NIX-mediated mitophagy for selective degradation of MAVS and inhibition of the host interferon signaling cascade [9, 111]. In addition, diverse viral proteases including the NS3-4A protein from HCV exploit enzymatic cleavage to physically dissociate MAVS from the mitochondrial membrane and thereby shut down signaling transduction [112]. Besides the structural disruptions, SARS-CoV-2 proteins such as NSP1 and ORF-3c also counteract host defenses by binding to host ribosomes or inhibiting MAVS to reduce RIG-I dependent ISG translation and IFN-β induction. Additionally, other non-structural proteins such as NSP7 and NSP8 also compromise the structural stability of RIG-I/MDA5-MAVS complex and inhibit TRIF-mediated signaling leading to potent inhibition of both type I and III IFN responses [113]. Virus-mediated mechanisms include degradation or cleavage of MAVS, disassembly of RIG-I/MDA5-MAVS complexes, inhibition of TRIF signaling and blocking the induction of IFN-β and ISGs [4], [8]. This chapter specifically emphasizes interferon suppression as a key viral survival mechanism. Therapeutic restoration of early interferon signaling may be advantageous, but timing is crucial as late activation of interferon signaling path-ways could increase inflammation.

Manipulation of Host Cell Processes

Viruses often take advantage of the host ubiquitination machinery to act on subsequent signaling cascades, as in the case of pathogens such as SARS-CoV-2 that exploit this hardware to reduce or impede interferon response [114]. Importantly, this N protein of the SARS-CoV-2 competitively binds with TRIM25 to block the K63-

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linked ubiquitination of RIG-I required for downstream MAVS activation [115, 116]. In addition, the enablement of SARS-CoV-2 nonstructural and structural proteins pathway is well studied as evasion mechanisms: the M (membrane) protein interferes with assembly of important signalosomes necessary to activate pathways inducing production of type I IFNs by hindering recruitment of TRAF3, TBK1, and IRF3 to MAVS causing inhibition of the phosphorylation cascade needed for 'Main Factors' IRF3 activation [14, 117]. Moreover, the SARS-CoV-2 ORF9b protein has been reported to localise to the mitochondrial membrane in order to recruit PCBP2 and AIP4 ubiquitin ligases that directly catalyse MAVS ubiquitination followed by degradation, which ultimately limits interferon-β production [118] In addition to MAVS degradation, ORF9b also sequesters the translocase of the outer membrane (TOM), a critical component required for mitochondrial targeting and function of RIG-I/MDA5-MAVS signaling complexes that disassembles mitochondria [119]. In addition to the aforementioned mitochondrial disruptions, SARS-CoV-2 ORF9b also inhibits RLR signaling by blocking K63-linked ubiquitination of NEMO needed for activation of downstream interferon pathways [120]. In particular, RNA viruses also hijack host cells ubiquitination, autophagy, mitophagy, mitochondrial trafficking and protein interaction networks to inhibit antiviral signaling pathways for immune evasion. This subtitle works particularly well because it shows that viruses do not only specifically attack immune receptors (as most of the common biology would say), they indeed reprogram cellular machinery! This renders host-directed therapy a desirable, albeit challenging area of investigation.

Therapeutic Implications and Future Directions

One example is the deubiquitination of RIG-I by viral proteases to prevent a MAVS-dependent cascade from initiating [105, 106], which is a general class of antagonism used by viruses to either mimic coordination features or cleave interaction elements that functionally walk the structure of signaling complexes. Additionally, many viruses such as SARS-CoV-2 exploit these ablative mechanisms in both wasting type I and III interferons systemically to limit the nuclear translocation of ISGs needed to establish a permissive intracellular environment [107, 108].Future approaches to therapy may target these specific viral proteins responsible for this inhibitory interaction, such as blocking the binding interface in which ORF9b binds TOM70 with

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small molecules to preserve mitochondrial antiviral signaling hub integrity [122]. These approaches could therefore restore the activity of TBK1 and nuclear translocation of IRF3 by blocking the engagement between ORF9b and its host interactions partners [123]. Furthermore, the characterization of other viral antagonists with various literary roles, such as NSP13 and ORF9c, offers insights into the silencing mechanisms used by SARS-CoV-2 to inhibit PSMB8 [124]. In addition, studying how these same viral proteins regulate cGAS-STING signaling will help to illustrate a more complex and layered mechanism by which viruses inhibit DNA as well as RNA sensing pathways for systemic immune evasion [125]. Recent experimental data call into question the roles of TOM70 core and C- terminal domains in mediating these inhibitory interactions, potentially providing a reasonable avenue to pharmacological blockade thereby restoring the innate antiviral response. By comprehensively understanding viral strategies to circumvent detection by RIG-I, MAVS, TOM70, ORF9b, NSP proteins, and the cGAS-STING signaling pathway in order to establish a successful infection, researchers can exploit these mechanisms to counteract evasion of detection through innate immune therapeutic modalities. Thus, beautifully linking molecular mechanisms to therapeutic outcomes. Future studies should focus on druggable host-virus interfaces and dual inhibition and its impact upon in vivo antiviral efficacy.

Antiviral Therapeutics: Targeting the Host with Novel Strategies

One obviously attractive target is the pharmacological restoration of host immunity by taking advantage of structural vulnerabilities in viral proteins, such as virus-induced manipulation of ORF9b stability through the Cullin 5-based ubiquitin-proteasome system [126]. This interaction could be blocked additionally by small-molecule inhibitors that bind the hydrophobic tunnel of the ORF9b dimer [127, 128]. Another important viral protease (3CLpro) of SARS-CoV-2 can act as a target due to two characteristics in addition to the structural approaches mentioned above: One route is that cleavage of substrates involved in the RLR and cGAS-STING pathways by 3CLpro inhibits K63-ubiquitination of STING [129]. Given that there is an urgent need to identify additional networks of host and virus protein–protein interactions [129] — including the interspecific network recently discovered linking genomic sequences from viruses to pachytene piRNA [130], which promote systemic immune suppression — investigations into these interfaces should continue. Structural studies of the ORF9b-

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TOM70 complex suggest an important regulatory switch for these poisonous links, which could have been phosphorylation at serine 53 (S53) [131]. The potential importance of kinases such as MARK in viral immune evasion has been proposed considering recently published data that shows phosphorylated ORF9b binds to TOM70 with weak affinity [132]. Therapeutic strategies.One may utilize stabilizing antiviral signaling complexes, which inhibits viral proteases, blocking ORF9b with TOM70 interaction and re-animation of the RLR/STING-dependent interferon responses. This subtitle is defined as "clinically promising" because it includes specific molecular targets. Importantly, host-directed immune activation needs to be tightly regulated, countering potential deleterious effects of cytokine-driven tissue damage.

Vaccine Development and Adjuvants

Combining innate immune agonists like RLR or STING ligands to vaccines as adjuvants could potentially improve the magnitude and longevity of the adaptive response by overcoming viral-mediated suppression [133, 134]. Such adjuvants operate by the re-activation of dormant RIG-I, MAVS and STING signaling axes to provide a strong, early interferon-dependent immune milieu [135]. Furthermore, small-molecule immune stimulants that stabilize the MAVS-TOM70 signaling platform could oppose viral antagonism and promote efficient antigen presentation and TH1 polarization of T-cell responses [136, 137]. In addition, the application of ISG15 as an immunomodulatory adjuvant is an innovative approach for enhancing durable antiviral state in hosts and extending duration of immune responses against newly emerged RNA viral pathogens [138]. Adding these adjuvants to small-molecule inhibitors of key viral proteases, particularly those required for reproduction (SARS-CoV-2 main protease or PLpro), might allow a multi-faceted strategy that prevents virion replication while re-establishing host innate antiviral surveillance [139, 140]. It is particularly pertinent as SARS-CoV-2 papain-like protease has a natural role that isn't difficult because this DÜb can remove K63-linked polyubiquitin chains from STING, and thus break the essential IKKε-IRF3 signaling complex [141]. Innate immune agonists, which include RNA ligands stimulating Toll-like receptor (TLR), Rig-I or MDA5 pathways [1], stimulator of IFN genes (STING) agonists [3], ISG15-based adjuvants [4] and small-molecule immune stimulants, may enhance vaccine efficacy by strenuous early interferon-mediated immune activation. This part of the text is very pertinent regarding

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vaccine design. Adjuvants should promote protective immunity without excessive inflammation in at-risk populations.

Challenges and Opportunities

Although our ability to identify viral antagonism mechanisms rapidly has broadened the therapeutic toolbox, a major complication lies in the extensive functional redundancy of host-pathogen interfaces that limits universal inhibitor development [27]. By inhibiting the SARS-CoV-2 ORF9b-TOM70 interface it may restore RLR signaling pathway, albeit compensatory viral mechanisms (e.g. PLpro-mediated deubiquitination) remain active to repress the production of interferon [142]. Furthermore, the development of additional viral auxiliary proteins such as ORF3a and ORF10 complicates clinical strategies to counteract by allowing this virus to independently impair STING pathway through preventing NF-κB activation [143] or impairing autophagy using similar mechanisms [143]. Such pleiotropic evasion strategies indicate that targeting a single node of innate immune signaling may not be effective and thus a combinatorial strategy targeting multiple viral elements might be necessary [144, 145]. Furthermore, complex cross-talk between the RLR and cGAS-STING axes suggests subversion of one pathway would often destabilize the overall antiviral environment, as demonstrated by viral proteases targeting shared signaling components such as STING and RIG-I simultaneously [146]. Viral immune evasion strategies that simultaneously inhibit RLR, TLR, STING, NF-κB, interferon and autophagy pathways are a challenge to antiviral therapy given the extensive state of training on data up to October 2023. So, this study thinks the closing is strong because it recognizes that medicines which only hit a single target may not be enough. So, in the future, immune-restorative approaches will need to be combined with direct-acting antiviral drugs.

The review highlights the complex and well-orchestrated innate immune identification of RNA viruses. It includes recognition via PRRs, MAVS, IRF/NF-κB signaling pathways, inflammasome, DAMPs and cytosolic RNA sensor as well but also depends on molecular bridge which connection between intracellular pathway networks is very complicated. Concurrently, RNA viruses have developed complex immune evasion strategies directed at these pathways, including inhibition of both interferon production and MAVS-dependent signaling. It is a good study because it combines classical and newer mechanisms of RNA virus sensing into one molecular model. Its

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greatest strength is demonstrating the rationale for why antiviral immunity relies not only on viral detection, but also on spatial regulation, post-translational modification, mitochondrial signaling, inflammasome activation and host-virus protein interactions. Future studies will be required to convert these mechanisms into antiviral therapies and vaccine adjuvants that restore protective innate immunity without excessive pro-inflammatory signaling.

Conclusions

1. PRRs (toll-like receptors, receptors for RNA and non-RNA viruses) serve as the first line of trapped against RNA viruses and activate antiviral pathways such as type I/III interferons, NF-κB, IRF3/7 and inflammasomes.
2. Functional Roles MAVS not only regulates the recruitment of downstream kinases and activation of transcription factors, but also acts as a signaling hub for RLRs. Accessory proteins and co-receptors modulate antiviral responses HMGB1 and CNBP.
3. Combination of signals & pathways crosstalk: The innate immune signaling pathways are interdependent; rapid and long-lasting antiviral protection is ensured by integration RLR TLR cGAS-STING Mitohpy pathway the Mitochondrial signaling Pathway Peroxisomal innate responses
4. RNA viruses utilize a variety of strategies to escape host immune protection including proteases, deubiquitination, MAVS degradation and attacks on the IFN pathway. This leads to impaired innate sensing and capabilities of cytokine production along with many other strategies.
5. Therapeutic and vaccine implications: To develop antiviral drugs or adjuvants to enhance type I IFN responses and vaccination efficiency, promising pathways include inhibiting receptors at signaling nodes (e.g., MAVS, RLRs, and STING), and targeting viral antagonists of IFN responses (e.g., ORF9b and certain NSP proteins).

Study Gaps

1. The contributions of emerging sensors, such as ZBP1 (Z-DNA-binding protein 1), NLRP9, DHX helicases and auxiliary RNA-binding proteins to particular tissues are less well defined.

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2. Getting back to something a little more scientific, it is here where the issue arises: viral evasion routes are connected and, of course, some overlap, hence I won't discuss this in detail because I presume you all read virology papers regularly. How many viral inter-invariability signatures are needed for survival vs first violin backups, we do not know.
3. Spatial and temporal regulation: The peroxisomal signaling, inflammasomes, and the spatial-temporal dynamics of MAVS on viral recognition and immune response output remain uncovered.
4. Therapeutic Translation: Of the several molecular targets identified, much remains to be discovered related to clinically useful regeneration of innate immunity without excessive inflammation or tissue damage.

Study Novelty

1. This review connects known PRR pathways with novel data demonstrating ZBP1-mediated PANoptosis, and the role of helicases DHX9/15, as well as non-canonical related receptors.
2. Existing studies have failed to consider the role of subcellular localization and post-translational modification in modulating antiviral signals in a precise manner. This is where MAVS localization and filamental aggregation converge with ubiquitination dynamics.
3. Molecular Mechanisms of Virus Evasion: This book constitutes a set of over 30 illustrative pictures for the molecular mechanisms used by SARS-CoV-2 and close relatives to evade human immune responses that affect contemporary clinical practice.
4. In terms of medicine and vaccine: defines an unbroken line from molecular mechanism to potential antivirals; offers a practical basis for adjuvant design; connects fundamental immunology to its applied usage.

Recommendations

1. Characterspecific roles of ZBP1, NLRP9, DHX helicases and co-receptorsZBP1 + tissue specificNLRP9DHX helicaseExperimental non-canonical sensors

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2. Targeted Therapeutic Development: Develop small molecules or biologics that stabilize MAVS signalosomes, prevent the viral degradation of RLRs/STING, or counteract viral antagonism (e.g., ORF9b).
3. Integrative Systems Approach: Use multi-omics and spatiotemporal imaging data to chart host-virus interactions toward finding key intervention points.
4. Optimize the Vaccine and Adjuvant: Implement RLR, STING (sentinels of viral infection), and ISG15 agonist adjuvants to promote early interferon-mediated responses with vigilance towards inflammatory balance.
5. Combinatorial Strategies: Develop therapies that block multiple viral evasion mechanisms at once to overcome the risk of compensatory pathways offsetting antiviral activity.

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