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Innate Immune Evasion by Human Respiratory RNA Viruses

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Abstract
The impact of respiratory virus infections on the health of children and adults can be very significant. Yet, in contrast to most other childhood infections as well as other viral and bacterial diseases, prophylactic vaccines or effective antiviral treatments against viral respiratory infections are either still not available, or provide only limited protection. Given the widespread prevalence, a general lack of natural sterilizing immunity, and/or high morbidity and lethality rates of diseases caused by influenza, respiratory syncytial virus, coronaviruses, and rhinoviruses, this difficult situation is a genuine societal challenge. A thorough understanding of the virus-host interactions during these respiratory infections will most probably be pivotal to ultimately meet these challenges. This review attempts to provide a comparative overview of the knowledge about an important part of the interaction between respiratory viruses and their host: the arms race between host innate immunity and viral innate immune evasion. Many, if not all, viruses, including the respiratory viruses listed above, suppress innate immune responses to gain a window of opportunity for efficient virus replication and setting-up of the infection. The consequences for the host's immune response are that it is often incomplete, delayed or diminished, or displays overly strong induction (after the delay) that may cause tissue damage. The affected innate immune response also impacts subsequent adaptive responses, and therefore viral innate immune evasion often undermines fully protective immunity. In this review, innate immune responses relevant for respiratory viruses with an RNA genome will briefly be summarized, and viral innate immune evasion based on shielding viral RNA species away from cellular innate immune sensors will be discussed from different angles. Subsequently, viral enzymatic activities that suppress innate immune responses will be discussed, including activities causing host shut-off and manipulation of stress granule formation. Furthermore, viral protease-mediated immune evasion and viral manipulation of the ubiquitin system will be addressed. Finally, perspectives for use of the reviewed knowledge for the development of novel antiviral strategies will be sketched.

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Introduction

The epithelium of the lungs is the largest surface in the human body that is in contact with our environment. Huge amounts of air and aerosols pass these cells each day, whereby the lung tissue, as well as the rest of the respiratory tract is probably almost constantly exposed to viruses and bacteria present in the inhaled air. An elaborate machinery is therefore present at this large surface to defend this tissue against invading pathogens, including mechanical barriers such as a mucus layer. The first line of defense at the entire length of the tract from the nasopharynx to the alveolar membrane is formed by the innate immune system [1, 2]. In this review, the focus will be on the selection of common viruses that invade the lungs: coronaviruses (CoVs), rhinoviruses, respiratory syncytial virus (RSV), and influenza, which all have an RNA genome. This latter feature is of importance to the set of cellular innate immune sensors that recognize these viruses when they enter the cells of the respiratory tract, and the subsequent downstream signaling cascades that are triggered as a result. A myriad of different cell types such as alveolar macrophages, airway epithelial cells, innate lymphoid cells, and dendritic cells (DCs) have a major role in this first defense, while in these and other cells of the respiratory tract the sensing, and several subsequent specific molecular intra- and intercellular signaling cascades ensure the establishment of the so- called antiviral state in the lungs. This state can inhibit the development of a productive infection with each of these invading viruses, thereby preventing or at least mitigating illness, before adaptive immunity kicks in to completely clear these viruses from the lungs.

Importantly, as a countermeasure against these elaborate defense mechanisms, invading respiratory viruses evolve activities that either circumvent or suppress the innate immune responses to create a window of opportunity for efficient virus replication, thereby often causing disease. Ultimately, the balance between the efficacy of the combined innate and adaptive responses on the host's side, and the virulence and its capacity to evade the host's immune responses on the virus' side, together dictate the disease outcome.

This review will focus on the evasion of the innate immune system by the array of respiratory viruses as introduced above, to highlight this important aspect of the virus-host interaction that may provide us with possible opportunities for exploration of novel antiviral strategies against these important viruses. Particular viral activities will be highlighted and different viruses compared, but the information discussed will not be complete. I therefore apologize to any authors who miss discussion of their interesting work in this review. To facilitate comparison between the respiratory viruses described here, known and arguably important innate immune evasion strategies are listed, and for each strategy it is discussed how each virus group exploits its own mechanism. Innate immune evasion obviously links to the innate immune responses that are known to be elicited by respiratory and other (RNA) viruses, and while this will be elaborated to a limited extent below, they have also been reviewed comprehensively in recent reviews by others [2–17].

Importance and Composition of Innate Immune Responses against Respiratory Virus Infections

Arguably, the innate immune system is more important in early life, when the adaptive functions are still underdeveloped [14]. Yet, the young infant is probably exposed to as many incoming pathogens as older children and adults are, so the innate immune system plays a very important role in the protection from respiratory infection in young children. The fact that respiratory infections are one of the leading causes of mortality in children under 5 years of age [18, 19] suggests that the interactions of the (innate) immune responses in the infant respiratory tract with incoming pathogens is indeed a delicate one, and the balance between severe illness and overcoming an infection may be relatively easily tipping towards the dangerous side. That the innate immune response plays an important role in defense against respiratory infections in early life may be further illustrated by the fact that severe RSV infections in children are linked with polymorphisms in genes encoding innate immune factors (reviewed in [14, 20]). Also later in life, the innate immune system plays an important role in the response against respiratory viruses (reviewed in [1]), and in the lungs these first responses against incoming viruses are governed primarily by alveolar and interstitial macrophages, DCs, airway epithelial cells, innate lymphocytes, and neutrophils.

The innate immune response signaling cascade starts with the recognition of pathogen-associated molecular patterns by pattern recognition receptors (PRRs). For RNA viruses in the lungs, the Toll-like receptors (TLRs) 3, 7 and 8, which are expressed on several of the mentioned cell types, are important PRRs. Also, intracellular cytosolic PRRs such as MDA5 and RIG-I, which are present in virtually any cell type including those of the lung,

have been shown to be relevant for respiratory infections, as will be elaborated below. Each of these mentioned receptors, or sensors, recognize forms of RNA (e.g., 5′ triphosphate RNA, double-stranded RNA [dsRNA]) that are produced by (respiratory) RNA viruses during their infection process, and which are distinguishable from the RNA species that are normally present in the cells (such as capped mRNA in the cytosol). In this way, the innate immune system senses foreign material that is possibly pathogenic, and this triggers downstream signaling to ultimately induce transcription factors in the nucleus which in turn stimulate expression of types I and III interferons (IFNs) and other proinflammatory cytokines. A second round of autocrine and paracrine signaling subsequently ensures that infected, and the surrounding uninfected cells, express a myriad of interferon stimulated genes (ISGs) that establish a so-called antiviral state. This state quite efficiently inhibits further spread of the infection, and simultaneously triggers further adaptive responses that in most cases eventually will clear the virus from the infected individual. During all these signal transduction pathways, regulation of activation and inhibition of signal transduction in the cascades is governed in a strict manner by phosphorylation events as well as ubiquitination of different linkage types (K48, K63, K27, etc.) on numerous factors in the pathways (reviewed in [21]). These events critically regulate the downstream signaling to ensure a sufficiently strong, but not overly explosive triggering of innate immune responses, and a timely downregulation of these responses to protect the individual from damaging immunopathology.

Recently, it has become clear that particular type III IFNs (IL-28/29), or IFN lambdas, which were discovered in 2003 [22, 23], play a prominent role in defense of epithelial surfaces such as that in the lung (reviewed in [3, 5, 24]). They bind to a distinct heterodimeric receptor consisting of IFNLR1 and IL10RB (as opposed to type I IFN that binds to IFNAR1/2), but seem to trigger downstream signaling that is very similar to the type I IFN-induced pathways, and are also induced by the same PRRs as those triggering type I IFNs. However, whereas type I IFNs are made by many different cell types, IFN lambdas are primarily expressed by epithelial cells and DCs. Recent literature suggests that despite the clear similarities between the types I and III IFN signaling pathways, the type III IFN machinery seems especially equipped to protect epithelial surfaces from pathogenic attacks, and forms the primary local defense upon invasion of low doses of viruses and bacteria. When this first activation of the type III IFN machinery is insufficient due to higher doses of pathogens coming in, the more systemic type I IFN machinery forms the second line of defense over broader areas of the tissue (reviewed in [24]). Additionally, it seems that type III IFN does not trigger inflammation as much as type I IFN, and this probably indicates an important unique aspect of the type III IFN induction, which may have a role in the protection of, for example, the lung epithelial tissue from immunopathology [25].

Recently, it has become clear that the strict distinction between innate and adaptive responses that has been the general view for a long time is probably not accurate. In the respiratory tract, several of the newly identified cell types and mechanisms that integrate aspects from both branches of human immunity are now thought to be very important for the defense against respiratory infections. Natural killer T cells, mucosal-associated invariant T cells, and neutrophils, for example, each form a bridge between the innate and adaptive machineries and play very important roles during the clearance of respiratory viruses (reviewed in [1, 6, 10]). Aspects of immunological memory, which were thought to be only present in the adaptive immune system, have now clearly been shown to play a role in the innate immune response as well, also that induced by viruses, and was named "trained innate immunity" [9]. The general idea about the mechanism governing this is that epigenetic changes on innate immune factor genes in specialized immune cells such as macrophages are made after the activation of the innate immune response. This then positively influences the response upon a subsequent pathogen encounter, just as in the adaptive immune system [26]. Recently, it also became clear that after respiratory (bacterial) infections this mechanism indeed has a role, and strikingly, signaling from adaptive (CD8+ T cell responses) "back" to innate immune systems (alveolar macrophages) via IFN-gamma plays a role in generating epigenetically triggered innate immune memory to protect from re-infection [27, 28].

Besides these different responses, most of which are IFN-mediated, small non-coding (micro, circular, ...) RNAs, RNAi, and IFN-independent antiviral responses can be regarded as part of the innate immune response package as well [29–31]. An emerging hot topic is also the interplay of innate immune response with cellular metabolism, so-called immunometabolism, which likely is quite relevant for respiratory viral infections [4, 32, 33]. The general idea is that immune cells such as macrophages and DCs adapt the choice for the use of their metabolic systems to an immune-activated situation that requires increased amounts of energy. This resembles "the Warburg effect", as described in tumor cells, and after

pathogen sensing innate immune response thus triggers changes in the cell's metabolism from oxidative phosphorylation to glycolysis, thereby optimizing the cell's metabolism for the new situation [34]. Since the new insights mentioned above have generally not yet, or only to a limited extent, been investigated in the context of viral evasion, this will not be further elaborated in the subsequent sections for the selected respiratory viruses.

Innate Immune Evasion by Respiratory Viruses

Shielding Away the Dangerous Goods in the Replication Organelle

Viruses with an RNA genome, such as the respiratory viruses highlighted in this review, produce several RNA species during viral replication, which are normally absent in uninfected cells. For example, dsRNA and RNA with a 5′-triphosphate are commonly produced by RNA viruses during replication, but since the host cells do not normally copy RNA from RNA templates, these intermediate RNA species are recognized by the innate immune sensors discussed above as foreign, resulting in antiviral effector activation. To be able to set up a productive infection in the cell, these viruses therefore need to circumvent and/or suppress these intracellular innate antiviral responses. An obvious primary strategy would be to shield away the replication intermediates with their dangerous, recognizable features, from the innate immune sensors roaming the cytosol. Indeed, the viruses that have a +RNA genome, which replicate exclusively in the cytosol such as the CoVs and rhinoviruses that invade the lungs, generally modify intracellular membranes elaborately to form headquarters of viral RNA replication, also called "replication organelles" (ROs; CoVs), "replication factories," "double membrane vesicles" (DMVs; CoVs, enteroviruses), "invaginations," or other (reviewed in [35–37]). Also, the negative-stranded RSV genome and its replication enzymes are found associated with cytosolic occluded structures, in that case named inclusion bodies [38, 39]. Expression of a selection of specific hydrophobic viral proteins can usually mimic the formation of these structures, for example, nsp3 and nsp4 of CoVs [40], the N and P proteins of RSV [41], and 2B,2C and 3A proteins of enterovirus (polio; [42]). All these structures, while divers in morphology and contents, seem to concentrate the viral replication machinery, intermediates and products inside membrane-bound vesicles or invaginations, seemingly unreachable for the innate immune sensors of the cytosol. It is interesting to note that very little is known about the details of interaction of viral replication organelles with the innate immune system. While the protective function of such organelles in the context of innate immune sensing is assumed by many researchers, hardly any reports present investigation, let alone proof, of this concept. A report by Al-Mulla and co-workers showed that in CoV mutants that produced only half the number of ROs during infection or in which the structures were smaller, replication as well as fitness of these viruses was in fact unaffected or even higher than for wt viruses. This was also true in cultures of primary host cells, which presumably have a fully functional intracellular innate immune system [43]. Their results indicated that there is no strict correlation between the number of replication organelles and the replication rate of these viruses. It is not clear, however, whether (part of) the viral replication takes place outside the replication organelles in these mutant virus infections, and whether replication organelles do, or do not, protect viral replication from innate immune attack therefore remains elusive after all. Importantly, virtually all research investigating the role and structure of viral ROs was performed in cell cultures, and little is known about their presence or numbers during infections in animal models or real hosts. Investigation of the latter will, therefore, be pivotal for the true understanding of viral ROs and their role in protection from innate immune responses.

Attack of the Replication Organelles by the Innate Immune System

Besides the question whether the replication organelles protect from innate immune sensors that recognize viral RNA, it is also largely unclear whether the innate immune system possesses sensors or effectors that target viral replication organelles themselves. After all, all +RNA viruses produce membranous replication organelles, and since they are probably indeed supporting viral replication, recognizing and attacking them would provide an efficient way for the innate immune system to inhibit viral infection. Our recent research revealed that the type I IFN signaling cascade, which is utterly relevant for defense against +RNA viruses, indeed includes effectors that influence the integrity of ROs induced by equine arteritis virus, a +RNA arterivirus and a distant relative of the CoVs [44]. However, it is not yet clear which type I IFN-inducible factors are responsible. Some recent reports (reviewed in [45–47]) suggest that intracellular membrane modifications such as viral ROs can be recognized and targeted by guanylate-binding proteins (GBPs), a family of dynamin-related large GTPases, of which

MxA is a member. MxA is a well-known human type I and III interferon-inducible factor that inhibits influenza virus infections [48]. Although the exact mechanism of inhibition is still not clear for several of the viruses inhibited by Mx proteins, Mx GTPase family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins could target the ROs [48]. Since influenza replicates in the nucleus (see also below), the idea is that MxA attacks influenza while its products are in the cytosol. Several reports indicate that GBPs other than the Mx proteins act against human +RNA viruses such as hepatitis C virus, classical swine fever virus, and dengue virus, which are all members of the flavivirus family, possibly by attacking their ROs. In pigs, GBPs inhibit porcine reproductive and respiratory syndrome virus (an arterivirus, distantly related to the CoVs). In mice, encephalomyocarditis virus and murine norovirus, which are both +RNA viruses, are suppressed by interferon (-gamma)-induced GBPs [45]. For murine norovirus, it has now become clear that GBPs are indeed targeted to viral ROs and that this depends on part of the autophagy machinery, namely the LC3 conjugation system [49]. Lipidated LC3 associates with viral ROs, and while this does not depend on IFN-gamma induction it is clearly stimulated by it. The authors of this paper also mention in their discussion that similar mechanisms can be shown for encephalomyocarditis virus, suggesting that at least several +RNA virus induced ROs can be targeted by the innate immune system via GBPs [49]. Ultimately, the idea is that once GBPs associate with the viral RO membranes, they cause disruption and/or modification of these structures, resulting in less efficient viral replication [49, 50]. Mechanistically, this effect on viral replication could link to the viral RNA species and intermediates becoming exposed upon disruption of RO membranes by GBPs to the cytosolic innate immune RNA sensors such as RIG-I and MDA5, which subsequently triggers antiviral innate and adaptive immune responses to suppress further replication. Further research is needed to confirm such a hypothesis.

Interestingly, while CoVs, rhinoviruses, and RSV replicate in the cytosol of respiratory epithelial cells and shield their replicating RNAs as discussed above, influenza virus apparently takes another route, and as the only known exception to the rule this RNA virus replicates in the nucleus. RNA sensors like the RIG-I-like sensors or TLRs were thought to be absent there, and therefore replication inside the nucleus may have been an alternative solution to avoid innate immune recognition of viral RNA intermediates during replication. However, recent data indicated that RIG-I can be active in the nucleus against influenza RNA [51]. The viral genome, packaged in nucleocapsid proteins and bearing a panhandle- and 5′-triphosphate structure is recognized by RIG-I, presumably in the cytosol while on its way to the nucleus, or when being incorporated into new virus particles [52–54]. The recognition by RIG-I is the major trigger to the production of type I IFN during influenza infection, while also TLR3 plays a role [55]. Additionally, the cell has evolved multiple ways to attack influenza replication, for example, by GBPs that are localized in the nucleus and the cytosol [56].

In summary, the formation of membranous headquarters may be a major strategy for respiratory viruses to avoid innate immune recognition of viral nucleic acid products in the cytosol. Whether the cell can in turn recognize and attack these structures is still relatively unknown, along with viral countermeasures against these attacks. This kind of interactions illustrates the arms race between the cellular immune responses and viral evasion, which due to continuous evolution often has multiple levels.

Further Tricks for Circumventing Viral RNA Recognition

Protection of the 5′ Terminus of Viral RNAs

Apparently, the shielding of viral replication products by ROs is not a watertight system, and to further avoid recognition of their foreign RNA species, respiratory viruses have evolved several means of directly modifying these RNAs to avoid recognition by the innate immune RNA sensors. Adding a cap-structure or a mimic of this structure to the 5′-end is an effective way, since in this way the cell's own mRNAs are protected from recognition by the innate immune sensors. The respiratory viruses discussed here use quite diverse methods to achieve this kind of protection from recognition, concomitantly making sure their mRNAs can be properly recognized by the translation machinery of the cell, which they "chose" to utilize.

The rhinoviruses are members of the picornavirus family, and these use a specialized, virally encoded cap-mimicking peptide, called VPg, and attach this to the viral RNA 5′ end to protect it from recognition by the innate RNA sensors [57, 58]. These viruses indeed do not need a cap structure for translation of their RNAs, since they use cap-independent internal ribosomal entry site-mediated translation [59, 60]. Influenza viruses steal mRNA cap-structures from host mRNAs in the nucleus during transcription in a process called "cap-snatching," in

which the viral nucleoprotein plays a major role [61]. RSV and CoVs provide their mRNAs with cap-structures themselves, using enzymatic functions in their polymerase complexes. Interestingly, RSV RNAs have cap-structures that contain a 7-methyl guanosine; however, these caps are devoid of 2'-O-methylation [62]. Both methylations are part of the canonical cap-structures on cellular mRNAs, but why this is necessary was actually unknown. A more recent report in which CoVs and their cap-structures were studied indicated that the latter viruses make sure to add 2'-O methylation to their cap-structures using a dedicated viral enzyme called nsp16. This turned out to be important to avoid recognition by the MDA5 sensor and subsequent triggering of innate immune responses [63, 64]. RSV apparently does not need this 2'-O-methylation on its caps, and this may be explained by the observation that this virus is able to sequester MDA5 (and innate immune adapter MAVS) into its inclusion bodies (the RSV replication headquarters as discussed above) using association with its N protein, to avoid MDA5-dependent recognition of viral RNA species and subsequent innate immune response [38].

Viral Endoribonuclease Activity

Yet another activity provides additional means of avoiding recognition, and that is viral endoribonuclease activity. CoVs encode endonuclease activity in one of their non-structural proteins, and recent reports indicated that this is instrumental to avoid recognition by the MDA5, protein kinase R (PKR), and OAS/RNAse L machineries [65, 66]. The latter 2 systems recognize and destroy foreign RNA in the cytosol independently of the RIG-I-like sensors to remove microbial products. Though it may be counter-intuitive for an RNA virus to express an RNAse, the virus apparently destroys its own RNA at certain locations or in certain stages of the infection to avoid the triggering of the RNA sensing and virus-destroying machineries.

Influenza also encodes one or more endoribonucleases, the primary one in the PA protein, which is part of the viral polymerase complex together with the PB-1 and PB-2 subunits. The PA endonuclease is responsible for cleaving the host mRNAs for cap-snatching during transcription of the influenza RNA [67, 68], another mechanism of innate immune evasion that was discussed above. Additionally, many influenza strains express shorter forms of this protein encoded by the same gene, overlapping with PA at the N-terminal region, but with an alternative or truncated C-terminal region, added through a ribosomal frame shift or by natural truncation, respectively [69]. These alternative products of the PA gene from segment 3 of the influenza genome are called PA-X or PAXdeltaC20, which were discovered recently to also have an endonuclease activity. These were shown to have a role in innate immune evasion, although the truncated PAXdeltaC20 seems to have very low endonuclease activity [70]. The immune modulation by these alternative PA proteins is thought to be achieved by stimulating host shut-off, another innate immune evasion strategy further discussed below, whereby host cell mRNAs are destroyed to suppress the expression of host proteins, including those involved in the activation of the innate antiviral state. Interestingly though, PA-X was shown to cleave dsRNA quite efficiently [70], which may not be very relevant for host shut-off, as the cell does not really produce dsRNA. Whether PA-X also degrades viral dsRNA species to prevent recognition by cytosolic RNA sensors is not entirely clear, but mutant viruses in which this PA-X protein was expressed in significantly lower amounts elicited higher levels of innate immune response; for example, IFN-beta production was much higher in these infections [71]. This indeed suggests that PA-X, besides having a role in the degradation of cellular mRNAs, may also degrade viral RNA to prevent recognition by innate immune sensors and activation of innate immune responses, similar to what was shown for the CoVs. To my knowledge, an endoribonuclease has not been identified in the RSV genome, so this virus may use alternative innate immune evasion strategies, as discussed elsewhere in this review. The same counts for the rhinoviruses.

Besides the replication organelles, the viral 5′ end RNA capping/protection mechanisms, and the viral endonucleases, other ways of shielding RNA from innate immune sensors or protecting it from degradation are exploited by respiratory viruses. Influenza non-structural protein NS1, for which many different innate immune evasion strategies have been described, binds and sequesters viral RNA to protect it from being sensed by RIG-I, and this also protects from the activation of PKR and OAS/RNAse L-mediated viral RNA degradation [72–74].

Recent data hint at the importance of protecting the 3′ ends of viral RNAs as well, besides the 5′ ends, as it was shown that Tut4 and Tut7, 2 cellular terminal uridylyltransferases, can add one or 2 uridines to the 3′ ends of polyadenylated influenza mRNAs, as well as RNAs of several other viruses, to target these RNAs for degradation by cellular machineries [75–77]. Additionally, a recent report indicated that cytosolic coronaviral mRNAs are targeted by the cellular nonsense-mediated decay pathway, a pathway that detects aberrant translation termination

features such as premature termination codons in mRNA, resulting in the degradation of these mRNAs [78]. In the case of CoV, the viral N protein plays a role in counteracting this latter effect [79], presumably by packaging the viral RNAs, thereby protecting them from degradation. All these data suggest that viruses likely evolved escape mechanisms to avoid all these different cellular mechanisms for RNA degradation to be able to set-up a productive infection in this hostile environment, however, the details of several of these mechanisms for the respiratory viruses discussed here are still unknown.

Active Suppression of Innate Immune Signaling Routes by Respiratory Viruses

Host Shut-Off

General host shut-off, that is viruses halting cellular protein expression, is an effective way to actively suppress all cellular innate immune responses against the virus, and simultaneously provide the virus with the full capacity of the cellular translation machinery for their own use. Besides using viral endoribonucleases PA-X and derivatives to attack cellular mRNAs, as has been briefly discussed for influenza viruses above, the viral polymerase complex and the viral "immune evasion" NS1 each also contribute importantly to host shut-off during influenza infection. Since the polymerase complex takes care of cap-snatching, it will leave considerable amounts of cellular mRNAs without a cap, and this in fact triggers the degradation of these molecules by cellular machineries such as Xrn2 exonuclease, diminishing the general cellular mRNAs available for translation. Additionally, the interactions of viral polymerase complex with the cellular translation machinery cause degradation of Pol II, thereby inhibiting cellular mRNA production and translation [80]. In 1998, Nemerof et al. discovered the role of influenza encoded NS1 in host shut-off [81]. NS1 interacts with an essential component of the 3′ end processing machinery of cellular pre-mRNAs, CPSF30, whereby 3′-end cleavage and polyadenylation of cellular mRNAs is inhibited, thereby contributing to host shut-off. In the past decades, details of the molecular mechanism in which NS1 influences host shut-off have been investigated, and it is also clear that these mechanisms can be strain-specific [72, 80].

Like influenza viruses, CoVs such as SARS-CoV and MERS-CoV also use a combination of ways to achieve host shut-off both at the transcriptional and the translational levels. Nsp1, the most 5′-terminal subunit of the replicate polyprotein of these viruses, was shown to cause host shut-off by binding to cellular factors of the translation machinery thereby preventing translation of host mRNAs. SARS-CoV nsp1 binds the 40S subunit of ribosomes to halt translation [82–85], however, for the MERS-CoV encoded nsp1 the mechanism of halting translation of cellular mRNA seems a bit different [86]. One of the differences is that MERS-CoV encoded nsp1 distinguishes between cellular mRNAs produced in the nucleus, and viral mRNAs in the cytosol, and the translation of the latter is not inhibited by MERS-CoV nsp1. In this way, specificity towards disrupting cellular mRNA translation is achieved [86]. This is different from SARS-CoV nsp1, which inhibits all mRNA translations. Additionally, the nsp1 protein of both viruses causes host mRNA degradation, however, not through intrinsic endoribonuclease activity of nsp1 itself but by activating the cellular mRNA degradation machinery and its exonuclease Xrn1 [82, 83, 86, 87].

Rhinoviruses, like poliovirus and other enteroviruses, cleave translation initiation factor elF4G to shut down cap-dependent translation of cellular mRNAs. This does not interfere with the translation of viral mRNAs since these viruses depend on internal ribosomal entry site-mediated translation (see above). The 2A protease of these viruses is responsible for this, by directly cleaving this factor [88, 89]. Recent work indicated that interaction of rhinovirus A encoded 2A protease with elF4E, another subunit of the cellular translation initiation complex, is required for the cleavage of elF4G during infection [90].

Finally, for RSV little is known about possible host shut-off mechanisms. A report by Bruce et al. [91] suggested that RSV specifically targets mRNA encoding surfactant protein A, an innate immune factor with an important role in the epithelial tissue of the lung, which directly binds to virus particles to cause their destruction by host defense mechanisms. During RSV infection, surfactant protein A mRNA translation efficiency seems inhibited, however, the mechanism for this effect has not been elucidated to date. An indirect way for viruses to manipulate host mRNA expression besides the classical host shut-off mechanisms discussed for the other respiratory viruses above, may be the induction of stress granules. In these structures, cellular mRNAs are accumulated upon induction of cellular stress responses that lead to inhibition of cellular translation. RSV, for example, seems to induce stress granules and this benefits its replication, as will be discussed in the next section.

Manipulation of Stress Granule Formation

Stress granules are structures in which, upon stress responses such as resulting from virus infections, the cell concentrates mRNAs that are produced but can no longer

be translated. The triggering of PKR, a viral RNA sensor, for example, causes phosphorylation of the eiF2alpha translation factor, which halts cellular translation thereby also affecting viral translation. The accumulation of untranslated mRNAs and stalled translation and pre-initiation complexes trigger the formation of stress granules. Recent insights suggest that stress granules may form a platform for innate immune responses, since the accumulation of (viral) RNA species there provides a pool of substrates for cellular sensors such as RIG-I and MDA5 [92–94]. Indeed, these sensors have been shown to be recruited to stress granules, supporting this view [94–96]. In the last decade, it has become clear that many viruses manipulate stress granule formation to benefit their replication, for example, RSV, as was also mentioned above. In the later stages of RSV infection in epithelial cells, stress granules are formed, and if expression of G3BP, a factor that is essential for stress granule formation, is knocked-down, replication of RSV is inhibited, suggesting a beneficial role for stress granules [97]. A subsequent report showed that PKR activation is required for the induction of stress granules by RSV, however, this is dispensable for viral replication [98]. Several other reports also show how RSV counteracts the formation of stress granules [99], suggesting a negative effect of stress granule formation on RSV infection. Up till today, it therefore remains unclear what the role of stress granules during RSV infection is exactly.

CoVs also manipulate stress granule formation. In collaboration with the group of Frank van Kuppeveld, our lab showed that MERS-CoV encoded 4a protein (translated from ORF4 in the virus) impedes dsRNA-mediated PKR activation, thereby preventing stress granule formation [100]. Protein 4a binds viral dsRNA, which is essential for its antagonistic function in PKR activation and stress granule formation, suggesting that 4a prevents recognition of viral RNA by PKR. Recombinant MERS-CoV in which ORF 4 (encoding 4a and 4b proteins) was removed, however, still suppressed stress granule formation in Vero cells, suggesting that 4a's activity is not the only way in which the virus inhibits stress granule formation [100]. Indeed, CoV nsp1 with its host-shut-off activities (see above) is a likely candidate viral protein that could play a role. A later report by Nakagawa et al. [101] however showed that the ORF4 MERS-CoV mutant virus did induce stress granules in another cell line (Hela/CD26), and also a virus mutant in which 4a alone was removed was not able to suppress SG formation in these cells. This suggests that the activity of 4a, and possibly other stress granule-inhibiting MERS-CoV proteins, may differ per cell line, or that cell lines differ in the activity of their antiviral pathways.

Influenza virus infection is also negatively influenced by the triggers that induce stress granule formation [102, 103]. Indeed, this virus also inhibits the formation of stress granules, and influenza virus encoded NS1 seems to play a major role in this [104]. This is not surprising given the role of NS1 in host-shut-off as well as in protecting the viral RNA from recognition by RNA sensors in the cell (see above), thereby preventing the activation of PKR and concomitant eiF2alpha phosphorylation and stress granule formation. Interestingly, this innate immune evasion activity of NS1 is counteracted by cellular protein NF90, which partly prevents the suppression of PKR triggered stress granule formation by NS1 by binding both PKR and NS1 [105]. Besides NS1, the influenza nucleoprotein NP and polymerase subunit PA-X help to prevent stress granule formation, due to their RNA protection and host-shut off functions, respectively [103].

For rhinoviruses, nothing is known about their capacity to manipulate stress granule formation, however, for other picornaviruses the 2A and L proteases have recently been shown to interfere by cleaving stress granule factors such as G3BP1 and G3BP2 [106–109]. A recent report showed that binding of eiF4GI translation factor to stress granule-inducing protein G3BP1 is essential for antiviral stress granule formation, and this interaction is disrupted by the 2A or L proteases of picornaviruses [110]. Given these data, it may be likely that rhinoviruses also affect stress granule formation using their proteases, which is further supported by data described in the next paragraph, but this needs to be investigated.

Respiratory Virus Proteases Cleaving Cellular (Innate Immune) Factors

Most, if not all, positive strand RNA viruses encode proteases, which they generally use to cleave their viral polyproteins into functional subunits during the viral life cycle. It has lately become apparent that these proteases often have side-functions that support immune evasion by these viruses.

Among the viruses discussed here, rhinoviruses and CoVs carry a positive strand RNA genome, and each of the members of these virus families encode at least 2 proteases.

Rhinoviruses use their 2A papain-like protease (PLpro) to effectively disable cap-dependent translation by cleaving eiF4G to induce host-shut off. This may well also prevent stress granule formation, however as mentioned, this has not been investigated for rhinoviruses yet. Addition-

ally, rhinovirus 2A protease cleaves nuclear pore proteins Nup62 and Nup98, while 3C protease seems to cleave Nup153 [111, 112]. These activities are thought to influence host immune response signaling for which cytosol-nucleus communication and trafficking is essential. It recently became clear that rhinovirus 2A protease activity also plays a role in targeting rhinovirus 3C protein to the nucleus [113, 114], however, it is not clear what 3C protease is doing there exactly [114, 115].

As discussed in the beginning of this review, the type I IFN antiviral pathway is very relevant for RNA virus infections, and an essential adaptor that enables downstream signaling in this pathway is IPS-1 (also called MAVS). This factor is cleaved by both 2A and 3C proteases of rhinovirus to halt type I IFN signal transduction [116]. Rhinovirus 3C protease can inhibit apoptotic cell death and activation of antiviral protein complexes by cleaving cellular apoptosis factor RIPK1 [117, 118].

CoV proteases also cleave cellular substrates to benefit the infection. The functions of PLpro of CoVs in manipulating the ubiquitin regulation of the innate immune system will be discussed later. The main, or 3C-like, protease of CoVs may have side-functions in cleaving innate immune factors as it was shown for 2 porcine CoVs that their main proteases cleave NEMO [119, 120], however, nothing is known yet in this respect for the human respiratory CoVs.

Manipulation of Ubiquitin and ISG15 Regulated Innate Immune Responses

The ubiquitin system is essential for the correct functioning of virtually all important cellular processes. The central molecule is ubiquitin, a small 76 amino acid protein that can be conjugated with its C-terminus to lysine residues in substrate proteins. Three classes of enzymes are needed for the conjugation: activating E1 enzyme, conjugating E2 enzyme, and an E3 ligase. Additional ubiquitins can be added to the first via one of 7 lysines in ubiquitin itself, yielding poly-ubiquitin chains. The signal that the ubiquitin chain gives depends on the linkage type(s) of the chain. K48 and K63-linked ubiquitin chains are best studied and are generally the cause of degradation or activation of the substrate, respectively. In antiviral innate immune signaling, ubiquitin is an important regulating factor, and ISG15, an interferon-induced ubiquitin-like molecule, is also an important factor in antiviral innate immunity. It is therefore not a surprise that a lot of viruses have evolved ways to manipulate the ubiquitin system and ubiquitin-like molecules such as ISG15, which they do in very diverse ways [121].

After the discovery of a structural resemblance between SARS-CoV expressed PLpro and the cellular deubiquitinase HAUSP/USP7 [122], it soon became clear that CoV PLpros had intrinsic deubiquitinating activity and could potentially deconjugate cellular (or viral) substrates to disrupt ubiquitin-mediated signaling, as well as deconjugate ISG15 off its substrates [123]. It is still not clear which cellular and viral factors are deconjugated by PLpro during infection, but mutant MERS-CoV in which the deubiquitinating/de-ISG15ylating function of PLpro was removed clearly showed increased type I IFN innate immune responses (Knaap et al., unpublished results), indicating that PLpro's DUB activity has an important role in the suppression of innate immunity during infection. For PLpro from human common cold virus HCoV-NL63 it was shown, although only by over-expression experiments, that it can deubiquitinate Mdm2, the E3 ligase that mediates p53 ubiquitination and subsequent degradation, thereby possibly inhibiting apoptosis and innate immune signaling [124]. Similarly, SARS-CoV PLpro can deubiquitinate E3 ligase RCHY1 to stimulate ubiquitination of p53 by this ligase, and thus also potentially inhibit apoptosis [125].

For influenza, several different interactions with the ubiquitin system have been identified that critically influence the outcome of the infection [126]. Generally, the activation of the RIG-I – MAVS – irf3 signaling axis in type I IFN signaling, which is important for all viruses discussed in this review, is governed by ubiquitin linked through its lysine at position 63 (forming K63-linked chains). About a decade ago, influenza virus NS1 was shown to bind E3 ligase TRIM25, thereby interfering with K63-linked ubiquitination of RIG-I, and therefore uniquely inhibiting innate immune signaling in the type-I IFN pathway [127]. There has been a recent debate as to whether these chains are actually conjugated to RIG-I or other factors within the cascade or whether they are free ubiquitin chains that provide a scaffold for activating the aggregation of RIG-I and MAVS, which in turn enables downstream signaling [128]. Influenza B virus-encoded NS1 additionally inhibits ISG15 antiviral activity by binding the N-terminus of human ISG15 (and not mouse ISG15) [129]. Furthermore, and similar to what some of the CoV PLpro's may do (see above in this section), Influenza NS1 was recently shown to destabilize Mdm2 E3 ligase which somehow benefits the IAV infection. According to the authors, this is because Mdm2 seems to have a p53-independent antiviral function which is then alleviated [130]. This is, however, in contrast to what was mentioned for NL63 CoV, where PLpro seems to stabilize

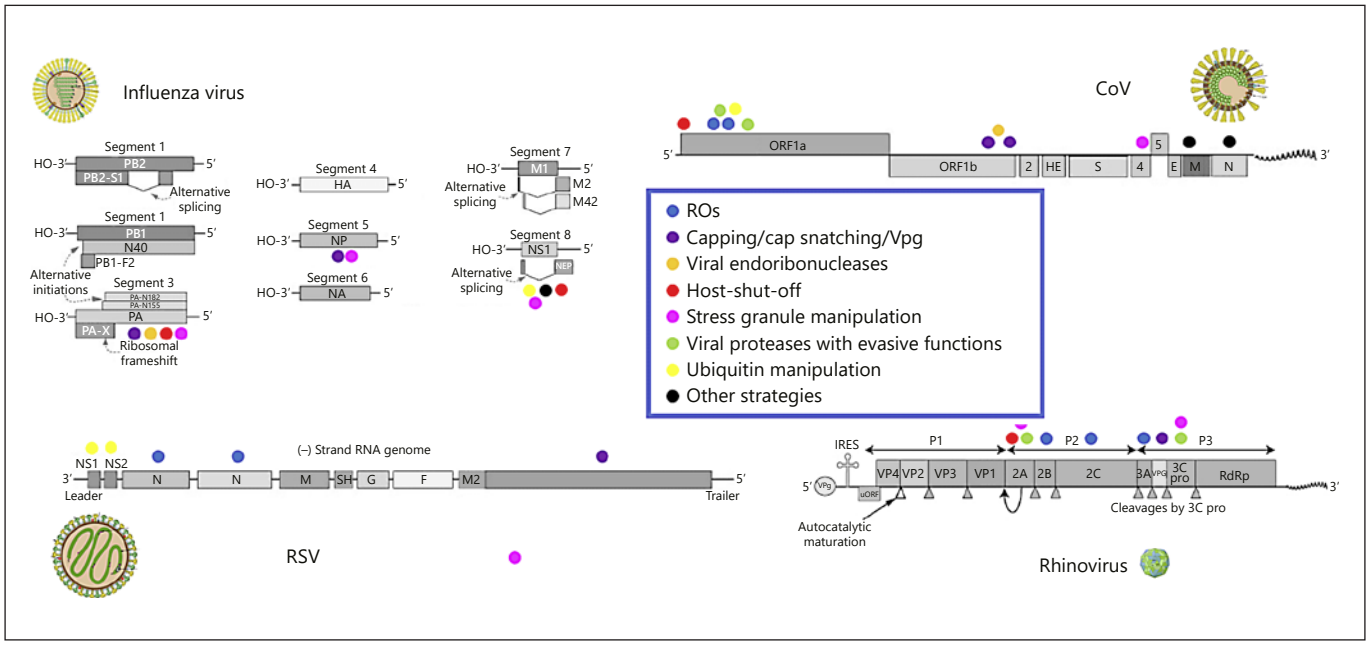

Fig. 1. Overview of respiratory viruses and major immune evasive activities as discussed in this review. The location in the viral genomes where immune evasive activities are encoded are indicated with colored spheres. If an activity was allocated to a virus, but the location on the genome is not known, the colored sphere was placed beside the name of the virus. Representations of viral genomes were adapted from ViralZone: www.expasy.org/viralzone, SIB Swiss Institute of Bioinformatics under the Creative Commons License. CoV, coronavirus; RSV, respiratory syncytial virus; ROs, replication organelles.

Mdm2 to also benefit infection [124]. Further research is needed to conclude whether these opposite effects indeed benefit the respective infections, or whether either of the results is incorrect. Finally, influenza NS1 was shown to mediate the upregulation of A20, a deubiquitinase with a role in the downregulation of RIG-I activation, to suppress the activation of RIG-I [131].

RSV also manipulates ubiquitin-mediated signaling, mainly directed by its non-structural proteins NS1 and NS2. Quite recently it was shown that RSV NS1 targets TRIM25 to suppress RIG-I ubiquitination, very similar to influenza's NS1's strategy [132]. This probably corroborates the importance of TRIM25-mediated ubiquitination in the innate immune signaling cascade. Earlier reports suggested that NS2 of RSV can direct proteasomal degradation of signal transducer and activator of transcription 2 (STAT2) in lung epithelial cells [133, 134]. STAT2 and STAT1 are transcription factors in the second round of innate immune signaling after binding of IFN to its receptor on the original, or surrounding cells. However, the mechanistic details of NS2's action has not become completely clear yet, although it has been claimed that NS2 somehow stimulates (K48-linked) ubiquitination of proteins, which can be alleviated again by a combination of mutations in NS2. These mutations when introduced into the virus prevent STAT2 from being degraded during infection, providing possibilities for novel vaccines [135].

Although it was reported that RSV infection in cell culture and in patients causes induction of ISG15 and that ISG15 conjugation to proteins has an antiviral effect [136], it is not clear whether RSV inhibits or evades ISG15 antiviral effects or not.

For rhinoviruses, it is unclear how it interacts with the cell's ubiquitin system. While picornavirus family member foot-and-mouth disease virus leader protease was shown to have deubiquitinating activity [137], neither 2A nor 3C protease from rhinovirus has been implicated in ubiquitin-regulated processes to date, and no other reports hinting at manipulation of the ubiquitin system by rhinoviruses have been published to my knowledge.

Conclusions and Discussion

The data summarized and discussed above illustrate that innate immune evasion is a major function of respiratory and other RNA viruses (Fig. 1), which probably

takes a significant volume of the genetic capacity of these viruses. This also implies that, given the restricted genetic space available to these viruses, the evasive functions must be pivotal for viruses to survive, otherwise they would likely not have evolved. Since each virus employs multiple different activities to suppress immune responses, and often evolved multifunctional proteins to do so, it remains difficult to acquire a complete picture of the immune evasive arsenal of a virus and how this is balanced with symptoms and disease outcome in different cell types or situations. Nevertheless, in-depth knowledge of this virus-host interaction creates important avenues for novel antiviral strategies, some of which have already been mentioned in the text above, and some more examples will be discussed in the next section.

Besides the major strategies for innate immune suppression by respiratory viruses discussed, several other mechanisms of innate immune evasion have been described for the 4 respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here. One example is the virus-encoded macrodomain. These domains have been identified in CoVs (and several other non-respiratory +RNA viruses) and have been shown to counteract IFN signaling with a yet unknown mechanism [138]. They are absent in influenza virus, rhinoviruses, and RSV, and therefore has not been discussed in this review. Many of these additional evasive activities have been comprehensively reviewed recently by others [13, 17, 72, 74, 99, 108, 123, 139–177]. Undoubtedly, yet other evasive activities are additionally still to be identified. The newly discovered aspects of human innate immunity, such as trained innate immunity and the integrated innate/adaptive cell types, as well as the links between innate immune responses and cellular metabolic changes, as discussed in the first part of this review, due to their recent discovery have not yet been studied extensively in the context of possible viral evasion strategies. This direction of course forms an obvious avenue for new research that should be undertaken, since it is likely that viruses also target these newly discovered mechanisms.

An important question is how exactly the viral innate immune evasive functions of respiratory viruses influence disease outcome and ultimate immune responses. It is noticeable that many of the viruses discussed here do not elicit a long-lasting immune protection after infection, and indeed rhino, corona, and RSV can re-infect individuals sometime after earlier infection, again causing symptoms (reviewed in [178, 179]), which is in sharp contrast to several other childhood-associated viral infections, where lifelong protection is achieved after generally experiencing only one episode of disease. It may well be that, besides their strong genetic variation, the innate immune evasive activities of the mentioned respiratory viruses play a role in this lack of eliciting protective immunity [180], and to possibly improve our options for effective antiviral strategies, it seems pivotal to further investigate this. For influenza the situation is slightly different, since this virus elicits protective immunity [172]; however, its genetic drift and shift causes new strains that are not, or inefficiently, recognized by existing influenza immunity which generally means that individuals will experience multiple influenza infections in the course of their lives. Besides contributing to the problem of limited immunological protection, viral innate immune evasion may also contribute to often reported immune over-reactions associated with respiratory infections, including cytokine storms, damaging inflammation, and other severe complications [181–184]. Some studies on SARS-CoV and MERS-CoV infections in patients suggest that the delayed innate immune response that is the result of temporary suppression by innate immune evasion, contributes to an exacerbated response [144]. How this works exactly is unclear to date.

Respiratory pathogens are associated with asthma. The exacerbation of asthma symptoms upon infection with rhinoviruses have been associated with defective types I and III IFN responses [185, 186]. In lung tissue, antiviral defenses may be further compromised by other mechanisms that impair these defenses such as Th2 cytokines IL-4 and IL-13 [187], and possibly high affinity IgE receptor expression and crosslinking [188]. However, suppressed antiviral innate immune response during virus-induced asthma exacerbations is likely also influenced by the innate immune evasive functions of respiratory viruses, as these activities contribute to more severe pathogenicity and slower virus clearance, likely stimulating asthmatic manifestations [182, 189]. Understanding (innate) immune evasion by respiratory viruses could, therefore, shed light on the possibilities for the prevention and cure of asthmatic complications associated with respiratory infections.

Closing Remarks: Use of Knowledge on Viral Innate Immune Evasion Strategies for Development of Novel Vaccines and Antivirals

For particularly RSV and influenza, efforts to develop effective and long-lasting vaccines and antivirals have been relatively unsuccessful for decades [179, 190]. Many, if not all, of the problems that have caused the barriers that prevented this goal from being achieved probably

link to the viruses' capability to manipulate the host's immune responses, thereby breaking through pre-existing natural or vaccine inflicted immunity. Detailed knowledge on the mechanisms whereby these viruses deal with and modify the immune responses they encounter is therefore pivotal to genuinely advance this field. Some studies have focused on mapping the interactions of respiratory viruses, and their immune evasion proteins, with their host cells to find promising cell-based drug targets [191, 192], and this could be an effective way to developing novel vaccines and antiviral drugs.

Effective rhinovirus and CoV antivirals and vaccines have also been lacking, and for these viruses causing common colds, an additional hurdle is the cost-effectiveness of these medicines. The general symptoms of these virus infections are mild, and before the public is willing to buy specific and effective medicines against these infections, these should be relatively cheap. Given that these viruses are generally difficult to control due to factors of viral immune modulation, the more knowledge we gain on the link between virus infection and (innate) immune responses in the host, the higher the chance that we may be able to develop successful and cost-effective remedies. Although the impact of a common cold may not be high, the fact that these infections are extremely widespread in the human population makes controlling these viruses a desirable goal. The cost-effectiveness balance is also a factor for the CoVs causing severe infections, that is, SARS-CoV and MERS-CoV, since infections with these viruses are either not being reported any more (SARS-CoV), or are quite localized and relatively scarce (MERS-CoV). Still, since 35% of MERS-CoV-infected patients succumb to the infection, and the lingering threat of larger outbreaks is felt as long as the virus replicates in humans, WHO has been recommending the development of specific vaccines for both viruses. Recently, a number of efforts for MERS-CoV vaccines have reached the stage of clinical trials, and having these vaccines "on the shelf" will at least ease societal concerns of dangerous outbreaks with this lethal virus [193].

A more or less obvious way of exploiting a virus' innate immune evasive functions for the development of new vaccines is to remove one or more of these from the virus using reverse genetic technology. In this way, the virus may become attenuated and at the same time it may trigger better innate immune responses due to the lack of one or more of its evasive functions. This could yield effective modified live virus vaccines that are attenuated by design, and for influenza there has been many attempts at constructing vaccine viruses lacking (parts of) NS1 or containing mutated NS1. None of these have, however, reached the market yet [73, 150, 194]. In our own group, we have been exploring the removal of viral deubiquitination activity from the viral PLpro of MERS-CoV and are in the process of analyzing the effect on disease outcome and immune responses in a mouse model ([195] and unpublished results). The knowledge we gained about the innate immune evasive activity of viral deubiquitinases like MERS-CoV PLpro also prompted an innovative antiviral option encompassing the screening for high affinity ubiquitin sequence variants that actually block the entire activity of the viral protease and therefore form promising antiviral molecules [196].

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References

1 Martin TR, Frevert CW. Innate immunity in the lungs. Proc Am Thorac Soc. 2005;2(5):403–11.
2 Gasteiger G, D'Osualdo A, Schubert DA, Weber A, Bruscia EM, Hartl D. Cellular Innate Immunity: An Old Game with New Players. J Innate Immun. 2017;9(2):111–25.
3 Zhou JH, Wang YN, Chang QY, Ma P, Hu Y, Cao X. Type III Interferons in Viral Infection and Antiviral Immunity. Cell Physiol Biochem. 2018;51(1):173–85.
4 Zhang S, Carriere J, Lin X, Xie N, Feng P. Interplay between Cellular Metabolism and Cytokine Responses during Viral Infection. Viruses. 2018 Sep;10(10):10.
5 Wells AI, Coyne CB. Type III Interferons in Antiviral Defenses at Barrier Surfaces. Trends Immunol. 2018 Oct;39(10):848–58.
6 Trottein F, Paget C. Natural Killer T Cells and Mucosal-Associated Invariant T Cells in Lung Infections. Front Immunol. 2018 Aug;9:1750.
7 Supramaniam A, Lui H, Bellette BM, Rudd PA, Herrero LJ. How myeloid cells contribute to the pathogenesis of prominent emerging zoonotic diseases. J Gen Virol. 2018 Aug;99(8):953–69.

8 Said EA, Tremblay N, Al-Balushi MS, Al-Jabri AA, Lamarre D. Viruses Seen by Our Cells: The Role of Viral RNA Sensors. J Immunol Res. 2018 Apr;2018:9480497.
9 Rusek P, Wala M, Druszczyńska M, Fol M. Infectious Agents as Stimuli of Trained Innate Immunity. Int J Mol Sci. 2018 Feb;19(2):19.
10 Naumenko V, Turk M, Jenne CN, Kim SJ. Neutrophils in viral infection. Cell Tissue Res. 2018 Mar;371(3):505–16.
11 Meier-Stephenson V, Mrozowich T, Pham M, Patel TR. DEAD-box helicases: the Yin and Yang roles in viral infections. Biotechnol Genet Eng Rev. 2018 Apr;34(1):3–32.
12 Hammer Q, Rückert T, Romagnani C. Natural killer cell specificity for viral infections. Nat Immunol. 2018 Aug;19(8):800–8.
13 Okamoto M, Tsukamoto H, Kouwaki T, Seya T, Oshiumi H. Recognition of Viral RNA by Pattern Recognition Receptors in the Induction of Innate Immunity and Excessive Inflammation During Respiratory Viral Infections. Viral Immunol. 2017 Jul/Aug;30(6):408–20.
14 Lambert L, Culley FJ. Innate Immunity to Respiratory Infection in Early Life. Front Immunol. 2017 Nov;8:1570.
15 Hu MM, Shu HB. Multifaceted roles of TRIM38 in innate immune and inflammatory responses. Cell Mol Immunol. 2017 Apr;14(4):331–8.
16 Dagenais-Lussier X, Loucif H, Murira A, Laulhé X, Stäger S, Lamarre A, et al. Sustained IFN-I Expression during Established Persistent Viral Infection: A "Bad Seed" for Protective Immunity. Viruses. 2017 Dec;10(1):10.
17 Zinzula L, Tramontano E. Strategies of highly pathogenic RNA viruses to block dsRNA detection by RIG-I-like receptors: hide, mask, hit. Antiviral Res. 2013 Dec;100(3):615–35.
18 Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015 Jan;385(9966):430–40.
19 Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. Lancet. 2013 Apr;381(9875):1405–16.
20 Lambert L, Sagfors AM, Openshaw PJ, Culley FJ. Immunity to RSV in Early-Life. Front Immunol. 2014 Sep;5:466.
21 Davis ME, Gack MU. Ubiquitination in the antiviral immune response. Virology. 2015 May;479-480:52–65.
22 Kotenko SV, Gallagher G, Baurin VV, Lewis-Antes A, Shen M, Shah NK, et al. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nat Immunol. 2003 Jan;4(1):69–77.
23 Sheppard P, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol. 2003 Jan;4(1):63–8.
24 Andreakos E, Salagianni M, Galani IE, Koltsida O. Interferon-λs: Front-Line Guardians of Immunity and Homeostasis in the Respiratory Tract. Front Immunol. 2017 Sep;8:1232.
25 Galani IE, Triantafyllia V, Eleminiadou EE, Koltsida O, Stavropoulos A, Manioudaki M, et al. Interferon-λ Mediates Non-redundant Front-Line Antiviral Protection against Influenza Virus Infection without Compromising Host Fitness. Immunity. 2017;46:875–90.e6.
26 Netea MG, Joosten LA, Latz E, Mills KH, Natoli G, Stunnenberg HG, et al. Trained immunity: A program of innate immune memory in health and disease. Science. 2016 Apr;352(6284):aaf1098.
27 Yao Y, Jeyanathan M, Haddadi S, Barra NG, Vaseghi-Shanjani M, Damjanovic D, et al. Induction of Autonomous Memory Alveolar Macrophages Requires T Cell Help and Is Critical to Trained Immunity. Cell. 2018 Nov;175(6):1634–1650.e17.
28 Netea MG, Joosten LA. Trained Immunity and Local Innate Immune Memory in the Lung. Cell. 2018 Nov;175(6):1463–5.
29 Te Velthuis AJ, Long JC, Bauer DL, Fan RL, Yen HL, Sharps J, et al. Mini viral RNAs act as innate immune agonists during influenza virus infection. Nat Microbiol. 2018 Nov;3(11):1234–42.
30 Berkhout B. RNAi-mediated antiviral immunity in mammals. Curr Opin Virol. 2018 Oct;32:9–14.
31 Paludan SR. Innate Antiviral Defenses Independent of Inducible IFNα/β Production. Trends Immunol. 2016 Sep;37(9):588–96.
32 Cheng SC, Joosten LA, Netea MG. The interplay between central metabolism and innate immune responses. Cytokine Growth Factor Rev. 2014 Dec;25(6):707–13.
33 Cheng SC, Quintin J, Cramer RA, Shepardson KM, Saeed S, Kumar V, et al. mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. Science. 2014 Sep;345(6204):1250684.
34 Kelly B, O'Neill LA. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell Res. 2015 Jul;25(7):771–84.
35 Romero-Brey I, Bartenschlager R. Membranous replication factories induced by plus-strand RNA viruses. Viruses. 2014 Jul;6(7):2826–57.
36 den Boon JA, Ahlquist P. Organelle-like membrane compartmentalization of positive-strand RNA virus replication factories. Annu Rev Microbiol. 2010;64(1):241–56.
37 van der Hoeven B, Oudshoorn D, Koster AJ, Snijder EJ, Kikkert M, Bárcena M. Biogenesis and architecture of arterivirus replication organelles. Virus Res. 2016 Jul;220:70–90.
38 Lifland AW, Jung J, Alonas E, Zurla C, Crowe JE Jr, Santangelo PJ. Human respiratory syncytial virus nucleoprotein and inclusion bodies antagonize the innate immune response mediated by MDA5 and MAVS. J Virol. 2012 Aug;86(15):8245–58.
39 Collins PL, Fearns R, Graham BS. Respiratory syncytial virus: virology, reverse genetics, and pathogenesis of disease. Curr Top Microbiol Immunol. 2013;372:3–38.
40 Oudshoorn D, Rijs K, Limpens RW, Groen K, Koster AJ, Snijder EJ, et al. Expression and Cleavage of Middle East Respiratory Syndrome Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronaviral RNA Replication. MBio. 2017 Nov;8(6):8.
41 García J, García-Barreno B, Vivo A, Melero JA. Cytoplasmic inclusions of respiratory syncytial virus-infected cells: formation of inclusion bodies in transfected cells that coexpress the nucleoprotein, the phosphoprotein, and the 22K protein. Virology. 1993 Jul;195(1):243–7.
42 Suhy DA, Giddings TH Jr, Kirkegaard K. Remodeling the endoplasmic reticulum by poliovirus infection and by individual viral proteins: an autophagy-like origin for virus-induced vesicles. J Virol. 2000 Oct;74(19):8953–65.
43 Al-Mulla HM, Turrell L, Smith NM, Payne L, Baliji S, Züst R, et al. Competitive fitness in coronaviruses is not correlated with size or number of double-membrane vesicles under reduced-temperature growth conditions. MBio. 2014 Apr;5(2):e01107–13.
44 Oudshoorn D, van der Hoeven B, Limpens RW, Beugeling C, Snijder EJ, Bárcena M, et al. Antiviral Innate Immune Response Interferes with the Formation of Replication-Associated Membrane Structures Induced by a Positive-Strand RNA Virus. MBio. 2016 Dec;7(6):7.
45 Praefcke GJ. Regulation of innate immune functions by guanylate-binding proteins. Int J Med Microbiol. 2018 Jan;308(1):237–45.
46 Scutigliani EM, Kikkert M. Interaction of the innate immune system with positive-strand RNA virus replication organelles. Cytokine Growth Factor Rev. 2017 Oct;37:17–27.
47 Santos JC, Broz P. Sensing of invading pathogens by GBPs: at the crossroads between cell-autonomous and innate immunity. J Leukoc Biol. 2018 Oct;104(4):729–35.
48 Haller O, Staeheli P, Schwemmle M, Kochs G. Mx GTPases: dynamin-like antiviral machines of innate immunity. Trends Microbiol. 2015 Mar;23(3):154–63.
49 Biering SB, Choi J, Halstrom RA, Brown HM, Beatty WL, Lee S, et al. Viral Replication Complexes Are Targeted by LC3-Guided Interferon-Inducible GTPases. Cell Host Microbe. 2017 Jul;22(1):74–85.e7.
50 Choi J, Biering SB, Hwang S. Quo vadis? Interferon-inducible GTPases go to their target membranes via the LC3-conjugation system of autophagy. Small GTPases. 2017 Oct;8(4):199–207.
51 Liu G, Lu Y, Thulasi Raman SN, Xu F, Wu Q, Li Z, et al. Nuclear-resident RIG-I senses viral replication inducing antiviral immunity. Nat Commun. 2018 Aug;9(1):3199.

52 Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. RIG-I-mediated antiviral responses to single-stranded RNA bearing 5′-phosphates. Science. 2006 Nov; 314(5801):997–1001.
53 Rehwinkel J, Tan CP, Goubau D, Schulz O, Pichlmair A, Bier K, et al. RIG-I detects viral genomic RNA during negative-strand RNA virus infection. Cell. 2010 Feb;140(3):397–408.
54 Weber M, Sediri H, Felgenhauer U, Binzen I, Bänfer S, Jacob R, et al. Influenza virus adaptation PB2-627K modulates nucleocapsid inhibition by the pathogen sensor RIG-I. Cell Host Microbe. 2015 Mar;17(3): 309–19.
55 Wu W, Zhang W, Duggan ES, Booth JL, Zou MH, Metcalf JP. RIG-I and TLR3 are both required for maximum interferon induction by influenza virus in human lung alveolar epithelial cells. Virology. 2015 Aug;482: 181–8.
56 Nordmann A, Wixler L, Boergeling Y, Wixler V, Ludwig S. A new splice variant of the human guanylate-binding protein 3 mediates anti-influenza activity through inhibition of viral transcription and replication. FASEB J. 2012 Mar;26(3):1290–300.
57 Flanegan JB, Petterson RF, Ambros V, Hewlett NJ, Baltimore D. Covalent linkage of a protein to a defined nucleotide sequence at the 5′-terminus of virion and replicative intermediate RNAs of poliovirus. Proc Natl Acad Sci USA. 1977 Mar;74(3):961–5.
58 Lee YF, Nomoto A, Detjen BM, Wimmer E. A protein covalently linked to poliovirus genome RNA. Proc Natl Acad Sci USA. 1977 Jan;74(1):59–63.
59 Pelletier J, Sonenberg N. Internal initiation of translation of eukaryotic mRNA directed by a sequence derived from poliovirus RNA. Nature. 1988 Jul;334(6180):320–5.
60 Jang SK, Kräusslich HG, Nicklin MJ, Duke GM, Palmenberg AC, Wimmer E. A segment of the 5′ nontranslated region of encephalomyocarditis virus RNA directs internal entry of ribosomes during in vitro translation. J Virol. 1988 Aug;62(8):2636–43.
61 De Vlugt C, Sikora D, Pelchat M. Insight into Influenza: A Virus Cap-Snatching. Viruses. 2018 Nov;10(11):10.
62 Barik S. The structure of the 5′ terminal cap of the respiratory syncytial virus mRNA. J Gen Virol. 1993 Mar;74(Pt 3):485–90.
63 Züst R, Cervantes-Barragan L, Habjan M, Maier R, Neuman BW, Ziebuhr J, et al. Ribose 2′-O-methylation provides a molecular signature for the distinction of self and non-self mRNA dependent on the RNA sensor Mda5. Nat Immunol. 2011 Feb;12(2):137–43.
64 Menachery VD, Eisfeld AJ, Schäfer A, Josset L, Sims AC, Proll S, et al. Pathogenic influenza viruses and coronaviruses utilize similar and contrasting approaches to control interferon-stimulated gene responses. MBio. 2014 May;5(3):e01174–14.
65 Kindler E, Gil-Cruz C, Spanier J, Li Y, Wilhelm J, Rabouw HH, et al. Early endonuclease-mediated evasion of RNA sensing ensures efficient coronavirus replication. PLoS Pathog. 2017 Feb;13(2):e1006195.
66 Deng X, Hackbart M, Mettelman RC, O'Brien A, Mielech AM, Yi G, et al. Coronavirus nonstructural protein 15 mediates evasion of dsRNA sensors and limits apoptosis in macrophages. Proc Natl Acad Sci USA. 2017 May; 114(21):E4251–60.
67 Dias A, Bouvier D, Crépin T, McCarthy AA, Hart DJ, Baudin F, et al. The cap-snatching endonuclease of influenza virus polymerase resides in the PA subunit. Nature. 2009 Apr; 458(7240):914–8.
68 Yuan P, Bartlam M, Lou Z, Chen S, Zhou J, He X, et al. Crystal structure of an avian influenza polymerase PA(N) reveals an endonuclease active site. Nature. 2009 Apr;458(7240): 909–13.
69 Jagger BW, Wise HM, Kash JC, Walters KA, Wills NM, Xiao YL, et al. An overlapping protein-coding region in influenza A virus segment 3 modulates the host response. Science. 2012 Jul;337(6091):199–204.
70 Bavagnoli L, Cucuzza S, Campanini G, Rovida F, Paolucci S, Baldanti F, et al. The novel influenza A virus protein PA-X and its naturally deleted variant show different enzymatic properties in comparison to the viral endonuclease PA. Nucleic Acids Res. 2015 Oct; 43(19):9405–17.
71 Hayashi T, MacDonald LA, Takimoto T. Influenza A Virus Protein PA-X Contributes to Viral Growth and Suppression of the Host Antiviral and Immune Responses. J Virol. 2015 Jun;89(12):6442–52.
72 Nogales A, Martinez-Sobrido L, Topham DJ, DeDiego ML. Modulation of Innate Immune Responses by the Influenza A NS1 and PA-X Proteins. Viruses. 2018 Dec;10(12): 10.
73 Wang BX, Fish EN. Interactions Between NS1 of Influenza A Viruses and Interferon-α/β: Determinants for Vaccine Development. J Interferon Cytokine Res. 2017 Aug;37(8):331–41.
74 Krug RM. Functions of the influenza A virus NS1 protein in antiviral defense. Curr Opin Virol. 2015 Jun;12:1–6.
75 Le Pen J, Jiang H, Di Domenico T, Kneuss E, Kosałka J, Leung C, et al. Terminal uridylyltransferases target RNA viruses as part of the innate immune system. Nat Struct Mol Biol. 2018 Sep;25(9):778–86.
76 Lim J, Ha M, Chang H, Kwon SC, Simanshu DK, Patel DJ, et al. Uridylation by TUT4 and TUT7 marks mRNA for degradation. Cell. 2014 Dec;159(6):1365–76.
77 Huo Y, Shen J, Wu H, Zhang C, Guo L, Yang J, et al. Widespread 3′-end uridylation in eukaryotic RNA viruses. Sci Rep. 2016 May;6(1): 25454.
78 Lloyd JP. The evolution and diversity of the nonsense-mediated mRNA decay pathway. F1000Res. 2018 Aug;7:1299.
79 Wada M, Lokugamage KG, Nakagawa K, Narayanan K, Makino S. Interplay between coronavirus, a cytoplasmic RNA virus, and nonsense-mediated mRNA decay pathway. Proc Natl Acad Sci USA. 2018 Oct;115(43):E10157–66.
80 Levene RE, Gaglia MM. Host Shutoff in Influenza A Virus: Many Means to an End. Viruses. 2018 Sep;10(9):10.
81 Nemeroff ME, Barabino SM, Li Y, Keller W, Krug RM. Influenza virus NS1 protein interacts with the cellular 30 kDa subunit of CPSF and inhibits 3'end formation of cellular pre-mRNAs. Mol Cell. 1998 Jun;1(7):991–1000.
82 Tanaka T, Kamitani W, DeDiego ML, Enjuanes L, Matsuura Y. Severe acute respiratory syndrome coronavirus nsp1 facilitates efficient propagation in cells through a specific translational shutoff of host mRNA. J Virol. 2012 Oct;86(20):11128–37.
83 Lokugamage KG, Narayanan K, Huang C, Makino S. Severe acute respiratory syndrome coronavirus protein nsp1 is a novel eukaryotic translation inhibitor that represses multiple steps of translation initiation. J Virol. 2012 Dec;86(24):13598–608.
84 Huang C, Lokugamage KG, Rozovics JM, Narayanan K, Semler BL, Makino S. SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage. PLoS Pathog. 2011 Dec; 7(12):e1002433.
85 Kamitani W, Huang C, Narayanan K, Lokugamage KG, Makino S. A two-pronged strategy to suppress host protein synthesis by SARS coronavirus Nsp1 protein. Nat Struct Mol Biol. 2009 Nov;16(11):1134–40.
86 Lokugamage KG, Narayanan K, Nakagawa K, Terasaki K, Ramirez SI, Tseng CT, et al. Middle East Respiratory Syndrome Coronavirus nsp1 Inhibits Host Gene Expression by Selectively Targeting mRNAs Transcribed in the Nucleus while Sparing mRNAs of Cytoplasmic Origin. J Virol. 2015 Nov;89(21):10970–81.
87 Gaglia MM, Covarrubias S, Wong W, Glaunsinger BA. A common strategy for host RNA degradation by divergent viruses. J Virol. 2012 Sep;86(17):9527–30.
88 Lamphear BJ, Yan R, Yang F, Waters D, Liebig HD, Klump H, et al. Mapping the cleavage site in protein synthesis initiation factor eIF-4 gamma of the 2A proteases from human Coxsackievirus and rhinovirus. J Biol Chem. 1993 Sep;268(26):19200–3.
89 Petersen JF, Cherney MM, Liebig HD, Skern T, Kuechler E, James MN. The structure of the 2A proteinase from a common cold virus: a proteinase responsible for the shut-off of host-cell protein synthesis. EMBO J. 1999 Oct;18(20):5463–75.
90 Aumayr M, Schrempf A, Üzülmez Ö, Olek KM, Skern T. Interaction of 2A proteinase of human rhinovirus genetic group A with eIF4E is required for eIF4G cleavage during infection. Virology. 2017 Nov;511:123–34.

91 Bruce SR, Atkins CL, Colasurdo GN, Alcorn JL. Respiratory syncytial virus infection alters surfactant protein A expression in human pulmonary epithelial cells by reducing translation efficiency. Am J Physiol Lung Cell Mol Physiol. 2009 Oct;297(4):L559–67.
92 Kim SS, Sze L, Liu C, Lam KP. The stress granule protein G3BP1 binds viral dsRNA and RIG-I to enhance IFN-β response. J Biol Chem. 2019 Apr;294(16):6430–38.
93 McCormick C, Khaperskyy DA. Translation inhibition and stress granules in the antiviral immune response. Nat Rev Immunol. 2017 Oct;17(10):647–60.
94 Onomoto K, Jogi M, Yoo JS, Narita R, Morimoto S, Takemura A, et al. Critical role of an antiviral stress granule containing RIG-I and PKR in viral detection and innate immunity. PLoS One. 2012;7(8): e43031.
95 Sánchez-Aparicio MT, Ayllón J, Leo-Macias A, Wolff T, García-Sastre A. Subcellular Localizations of RIG-I, TRIM25, and MAVS Complexes. J Virol. 2017 Jan;91(2):91.
96 Oh SW, Onomoto K, Wakimoto M, Onoguchi K, Ishidate F, Fujiwara T, et al. Leader-Containing Uncapped Viral Transcript Activates RIG-I in Antiviral Stress Granules. PLoS Pathog. 2016 Feb;12(2):e1005444.
97 Lindquist ME, Lifland AW, Utley TJ, Santangelo PJ, Crowe JE Jr. Respiratory syncytial virus induces host RNA stress granules to facilitate viral replication. J Virol. 2010 Dec;84(23):12274–84.
98 Lindquist ME, Mainou BA, Dermody TS, Crowe JE Jr. Activation of protein kinase R is required for induction of stress granules by respiratory syncytial virus but dispensable for viral replication. Virology. 2011 Apr;413(1):103–10.
99 Cervantes-Ortiz SL, Zamorano Cuervo N, Grandvaux N. Respiratory Syncytial Virus and Cellular Stress Responses: Impact on Replication and Physiopathology. Viruses. 2016 May;8(5):8.
100 Rabouw HH, Langereis MA, Knaap RC, Dalebout TJ, Canton J, Sola I, et al. Middle East Respiratory Coronavirus Accessory Protein 4a Inhibits PKR-Mediated Antiviral Stress Responses. PLoS Pathog. 2016 Oct; 12(10):e1005982.
101 Nakagawa K, Narayanan K, Wada M, Makino S. Inhibition of Stress Granule Formation by Middle East Respiratory Syndrome Coronavirus 4a Accessory Protein Facilitates Viral Translation, Leading to Efficient Virus Replication. J Virol. 2018 Sep;92(20):92.
102 Slaine PD, Kleer M, Smith NK, Khaperskyy DA, McCormick C. Stress Granule-Inducing Eukaryotic Translation Initiation Factor 4A Inhibitors Block Influenza A Virus Replication. Viruses. 2017 Dec;9(12):9.
103 Khaperskyy DA, Emara MM, Johnston BP, Anderson P, Hatchette TF, McCormick C. Influenza a virus host shutoff disables antiviral stress-induced translation arrest. PLoS Pathog. 2014 Jul;10(7):e1004217.
104 Khaperskyy DA, Hatchette TF, McCormick C. Influenza A virus inhibits cytoplasmic stress granule formation. FASEB J. 2012 Apr;26(4):1629–39.
105 Li T, Li X, Zhu W, Wang H, Mei L, Wu S, et al. NF90 is a novel influenza A virus NS1-interacting protein that antagonizes the inhibitory role of NS1 on PKR phosphorylation. FEBS Lett. 2016 Aug;590(16):2797–810.
106 Visser LJ, Medina GN, Rabouw HH, de Groot RJ, Langereis MA, de Los Santos T, et al. Foot-and-Mouth Disease Virus Leader Protease Cleaves G3BP1 and G3BP2 and Inhibits Stress Granule Formation. J Virol. 2019 Jan;93(2):93.
107 Yang X, Hu Z, Fan S, Zhang Q, Zhong Y, Guo D, et al. Picornavirus 2A protease regulates stress granule formation to facilitate viral translation. PLoS Pathog. 2018 Feb; 14(2):e1006901.
108 Feng Q, Langereis MA, van Kuppeveld FJ. Induction and suppression of innate antiviral responses by picornaviruses. Cytokine Growth Factor Rev. 2014 Oct;25(5): 577–85.
109 White JP, Cardenas AM, Marissen WE, Lloyd RE. Inhibition of cytoplasmic mRNA stress granule formation by a viral proteinase. Cell Host Microbe. 2007 Nov;2(5):295–305.
110 Yang X, Hu Z, Zhang Q, Fan S, Zhong Y, Guo D, et al. SG formation relies on eIF4GI-G3BP interaction which is targeted by picornavirus stress antagonists. Cell Discov. 2019 Jan;5(1):1.
111 Watters K, Palmenberg AC. Differential processing of nuclear pore complex proteins by rhinovirus 2A proteases from different species and serotypes. J Virol. 2011 Oct; 85(20):10874–83.
112 Walker EJ, Younessi P, Fulcher AJ, McCuaig R, Thomas BJ, Bardin PG, et al. Rhinovirus 3C protease facilitates specific nucleoporin cleavage and mislocalisation of nuclear proteins in infected host cells. PLoS One. 2013 Aug;8(8):e71316.
113 Walker E, Jensen L, Croft S, Wei K, Fulcher AJ, Jans DA, et al. Rhinovirus 16 2A Protease Affects Nuclear Localization of 3CD during Infection. J Virol. 2016 Nov;90(24):11032–42.
114 Ghildyal R, Jordan B, Li D, Dagher H, Bardin PG, Gern JE, et al. Rhinovirus 3C protease can localize in the nucleus and alter active and passive nucleocytoplasmic transport. J Virol. 2009 Jul;83(14):7349–52.
115 Amineva SP, Aminev AG, Palmenberg AC, Gern JE. Rhinovirus 3C protease precursors 3CD and 3CD' localize to the nuclei of infected cells. J Gen Virol. 2004 Oct;85(Pt 10): 2969–79.
116 Drahos J, Racaniello VR. Cleavage of IPS-1 in cells infected with human rhinovirus. J Virol. 2009 Nov;83(22):11581–7.
117 Lötzerich M, Roulin PS, Boucke K, Witte R, Georgiev O, Greber UF. Rhinovirus 3C protease suppresses apoptosis and triggers caspase-independent cell death. Cell Death Dis. 2018 Feb;9(3):272.
118 Croft SN, Walker EJ, Ghildyal R. Human Rhinovirus 3C protease cleaves RIPK1, concurrent with caspase 8 activation. Sci Rep. 2018 Jan;8(1):1569.
119 Zhu X, Fang L, Wang D, Yang Y, Chen J, Ye X, et al. Porcine deltacoronavirus nsp5 inhibits interferon-β production through the cleavage of NEMO. Virology. 2017 Feb;502: 33–8.
120 Wang D, Fang L, Shi Y, Zhang H, Gao L, Peng G, et al. Porcine Epidemic Diarrhea Virus 3C-Like Protease Regulates Its Interferon Antagonism by Cleaving NEMO. J Virol. 2015 Dec;90(4):2090–101.
121 Heaton SM, Borg NA, Dixit VM. Ubiquitin in the activation and attenuation of innate antiviral immunity. J Exp Med. 2016 Jan; 213(1):1–13.
122 Sulea T, Lindner HA, Purisima EO, Ménard R. Deubiquitination, a new function of the severe acute respiratory syndrome coronavirus papain-like protease? J Virol. 2005 Apr; 79(7):4550–1.
123 Mielech AM, Chen Y, Mesecar AD, Baker SC. Nidovirus papain-like proteases: multifunctional enzymes with protease, deubiquitinating and deISGylating activities. Virus Res. 2014 Dec;194:184–90.
124 Yuan L, Chen Z, Song S, Wang S, Tian C, Xing G, et al. p53 degradation by a coronavirus papain-like protease suppresses type I interferon signaling. J Biol Chem. 2015 Jan; 290(5):3172–82.
125 Ma-Lauer Y, Carbajo-Lozoya J, Hein MY, Müller MA, Deng W, Lei J, et al. p53 down-regulates SARS coronavirus replication and is targeted by the SARS-unique domain and PLpro via E3 ubiquitin ligase RCHY1. Proc Natl Acad Sci USA. 2016 Aug;113(35):E5192–201.
126 Rudnicka A, Yamauchi Y. Ubiquitin in Influenza Virus Entry and Innate Immunity. Viruses. 2016 Oct;8(10):8.
127 Gack MU, Albrecht RA, Urano T, Inn KS, Huang IC, Carnero E, et al. Influenza A virus NS1 targets the ubiquitin ligase TRIM25 to evade recognition by the host viral RNA sensor RIG-I. Cell Host Microbe. 2009 May; 5(5):439–49.
128 Okamoto M, Kouwaki T, Fukushima Y, Oshiumi H. Regulation of RIG-I Activation by K63-Linked Polyubiquitination. Front Immunol. 2018 Jan;8:1942.
129 Versteeg GA, Hale BG, van Boheemen S, Wolff T, Lenschow DJ, García-Sastre A. Species-specific antagonism of host ISGylation by the influenza B virus NS1 protein. J Virol. 2010 May;84(10):5423–30.
130 Pizzorno A, Dubois J, Machado D, Cartet G, Traversier A, Julien T, et al. Influenza A viruses alter the stability and antiviral contribution of host E3-ubiquitin ligase Mdm2 during the time-course of infection. Sci Rep. 2018 Feb;8(1):3746.

131 Feng W, Sun X, Shi N, Zhang M, Guan Z, Duan M. Influenza a virus NS1 protein induced A20 contributes to viral replication by suppressing interferon-induced antiviral response. Biochem Biophys Res Commun. 2017 Jan;482(4):1107–13.
132 Ban J, Lee NR, Lee NJ, Lee JK, Quan FS, Inn KS. Human Respiratory Syncytial Virus NS 1 Targets TRIM25 to Suppress RIG-I Ubiquitination and Subsequent RIG-I-Mediated Antiviral Signaling. Viruses. 2018 Dec; 10(12):10.
133 Ramaswamy M, Shi L, Monick MM, Hunninghake GW, Look DC. Specific inhibition of type I interferon signal transduction by respiratory syncytial virus. Am J Respir Cell Mol Biol. 2004 Jun;30(6):893–900.
134 Ramaswamy M, Shi L, Varga SM, Barik S, Behlke MA, Look DC. Respiratory syncytial virus nonstructural protein 2 specifically inhibits type I interferon signal transduction. Virology. 2006 Jan;344(2):328–39.
135 Whelan JN, Tran KC, van Rossum DB, Teng MN. Identification of Respiratory Syncytial Virus Nonstructural Protein 2 Residues Essential for Exploitation of the Host Ubiquitin System and Inhibition of Innate Immune Responses. J Virol. 2016 Jun;90(14):6453–63.
136 González-Sanz R, Mata M, Bermejo-Martín J, Álvarez A, Cortijo J, Melero JA, et al. ISG15 Is Upregulated in Respiratory Syncytial Virus Infection and Reduces Virus Growth through Protein ISGylation. J Virol. 2016 Jan;90(7):3428–38.
137 Wang D, Fang L, Li P, Sun L, Fan J, Zhang Q, et al. The leader proteinase of foot-and-mouth disease virus negatively regulates the type I interferon pathway by acting as a viral deubiquitinase. J Virol. 2011 Apr;85(8): 3758–66.
138 Fehr AR, Jankevicius G, Ahel I, Perlman S. Viral Macrodomains: Unique Mediators of Viral Replication and Pathogenesis. Trends Microbiol. 2018 Jul;26(7):598–610.
139 Shokri S, Mahmoudvand S, Taherkhani R, Farshadpour F. Modulation of the immune response by Middle East respiratory syndrome coronavirus. J Cell Physiol. 2019 Mar; 234(3):2143–51.
140 Schulz KS, Mossman KL. Viral Evasion Strategies in Type I IFN Signaling - A Summary of Recent Developments. Front Immunol. 2016 Nov;7:498.
141 Lei X, Xiao X, Wang J. Innate Immunity Evasion by Enteroviruses: Insights into Virus-Host Interaction. Viruses. 2016 Jan;8(1):8.
142 Chatterjee S, Basler CF, Amarasinghe GK, Leung DW. Molecular Mechanisms of Innate Immune Inhibition by Non-Segmented Negative-Sense RNA Viruses. J Mol Biol. 2016 Aug;428(17):3467–82.
143 Ma DY, Suthar MS. Mechanisms of innate immune evasion in re-emerging RNA viruses. Curr Opin Virol. 2015 Jun;12:26–37.
144 Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. J Pathol. 2015 Jan;235(2):185–95.
145 Guo H, Kumar P, Malarkannan S. Evasion of natural killer cells by influenza virus. J Leukoc Biol. 2011 Feb;89(2):189–94.
146 Hale BG, Albrecht RA, García-Sastre A. Innate immune evasion strategies of influenza viruses. Future Microbiol. 2010 Jan;5(1):23–41.
147 Weber M, Weber F. Segmented negative-strand RNA viruses and RIG-I: divide (your genome) and rule. Curr Opin Microbiol. 2014 Aug;20:96–102.
148 Onomoto K, Yoneyama M, Fung G, Kato H, Fujita T. Antiviral innate immunity and stress granule responses. Trends Immunol. 2014 Sep;35(9):420–8.
149 Menachery VD, Debbink K, Baric RS. Coronavirus non-structural protein 16: evasion, attenuation, and possible treatments. Virus Res. 2014 Dec;194:191–9.
150 Marc D. Influenza virus non-structural protein NS1: interferon antagonism and beyond. J Gen Virol. 2014 Dec;95(Pt 12):2594–611.
151 DeDiego ML, Nieto-Torres JL, Jimenez-Guardeño JM, Regla-Nava JA, Castaño-Rodriguez C, Fernandez-Delgado R, et al. Coronavirus virulence genes with main focus on SARS-CoV envelope gene. Virus Res. 2014 Dec;194:124–37.
152 Nicholls JM. The battle between influenza and the innate immune response in the human respiratory tract. Infect Chemother. 2013 Mar;45(1):11–21.
153 Harris KG, Coyne CB. Enter at your own risk: how enteroviruses navigate the dangerous world of pattern recognition receptor signaling. Cytokine. 2013 Sep;63(3):230–6.
154 van de Sandt CE, Kreijtz JH, Rimmelzwaan GF. Evasion of influenza A viruses from innate and adaptive immune responses. Viruses. 2012 Sep;4(9):1438–76.
155 Oshiumi H, Matsumoto M, Seya T. Ubiquitin-mediated modulation of the cytoplasmic viral RNA sensor RIG-I. J Biochem. 2012 Jan;151(1):5–11.
156 Munir M. TRIM proteins: another class of viral victims. Sci Signal. 2010 Apr;3(118):jc2.
157 Fleming SB. Viral Inhibition of the IFN-Induced JAK/STAT Signalling Pathway: Development of Live Attenuated Vaccines by Mutation of Viral-Encoded IFN-Antagonists. Vaccines (Basel). 2016 Jun;4(3):4.
158 Chan YK, Gack MU. Viral evasion of intracellular DNA and RNA sensing. Nat Rev Microbiol. 2016 Jun;14(6):360–73.
159 Rossi GA, Silvestri M, Colin AA. Respiratory syncytial virus infection of airway cells: role of microRNAs. Pediatr Pulmonol. 2015 Jul; 50(7):727–32.
160 Narayanan K, Ramirez SI, Lokugamage KG, Makino S. Coronavirus nonstructural protein 1: common and distinct functions in the regulation of host and viral gene expression. Virus Res. 2015 Apr;202:89–100.
161 Goraya MU, Wang S, Munir M, Chen JL. Induction of innate immunity and its perturbation by influenza viruses. Protein Cell. 2015 Oct;6(10):712–21.
162 Dash P, Thomas PG. Host detection and the stealthy phenotype in influenza virus infection. Curr Top Microbiol Immunol. 2015; 386:121–47.
163 Báez-Santos YM, St John SE, Mesecar AD. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antiviral Res. 2015 Mar;115:21–38.
164 Balistreri G, Bognanni C, Mühlemann O. Virus Escape and Manipulation of Cellular Nonsense-Mediated mRNA Decay. Viruses. 2017 Jan;9(1):9.
165 Agrawal P, Nawadkar R, Ojha H, Kumar J, Sahu A. Complement Evasion Strategies of Viruses: an Overview. Front Microbiol. 2017 Jun;8:1117.
166 Wong LY, Lui PY, Jin DY. A molecular arms race between host innate antiviral response and emerging human coronaviruses. Virol Sin. 2016 Feb;31(1):12–23.
167 Weber-Gerlach M, Weber F. To Conquer the Host, Influenza Virus Is Packing It In: Interferon-Antagonistic Strategies beyond NS1. J Virol. 2016 Sep;90(19):8389–94.
168 Liu Y, Olagnier D, Lin R. Host and Viral Modulation of RIG-I-Mediated Antiviral Immunity. Front Immunol. 2017 Jan;7: 662.
169 Kindler E, Thiel V, Weber F. Interaction of SARS and MERS Coronaviruses with the Antiviral Interferon Response. Adv Virus Res. 2016;96:219–43.
170 Unterholzner L, Almine JF. Camouflage and interception: how pathogens evade detection by intracellular nucleic acid sensors. Immunology. 2019 Mar;156(3):217–27.
171 Lei J, Kusov Y, Hilgenfeld R. Nsp3 of coronaviruses: structures and functions of a large multi-domain protein. Antiviral Res. 2018 Jan;149:58–74.
172 Ascough S, Paterson S, Chiu C. Induction and Subversion of Human Protective Immunity: Contrasting Influenza and Respiratory Syncytial Virus. Front Immunol. 2018 Mar;9:323.
173 Sun Y, López CB. The innate immune response to RSV: advances in our understanding of critical viral and host factors. Vaccine. 2017 Jan;35(3):481–8.
174 Rodríguez Pulido M, Sáiz M. Molecular Mechanisms of Foot-and-Mouth Disease Virus Targeting the Host Antiviral Response. Front Cell Infect Microbiol. 2017 Jun;7:252.
175 Plant EP, Ilyushina NA, Sheikh F, Donnelly RP, Ye Z. Influenza virus NS1 protein mutations at position 171 impact innate interferon responses by respiratory epithelial cells. Virus Res. 2017 Aug;240:81–6.
176 Canedo-Marroquín G, Acevedo-Acevedo O, Rey-Jurado E, Saavedra JM, Lay MK, Bueno SM, et al. Modulation of Host Immunity by Human Respiratory Syncytial Virus Virulence Factors: A Synergic Inhibition of Both Innate and Adaptive Immunity. Front Cell Infect Microbiol. 2017 Aug;7:367.

177 Wimmer P, Schreiner S. Viral Mimicry to Usurp Ubiquitin and SUMO Host Pathways. Viruses. 2015 Aug;7(9):4854–72.
178 van der Hoek L. Human coronaviruses: what do they cause? Antivir Ther. 2007;12(4 Pt B):651–8.
179 Collins PL, Melero JA. Progress in understanding and controlling respiratory syncytial virus: still crazy after all these years. Virus Res. 2011 Dec;162(1-2):80–99.
180 Farrag MA, Almajhdi FN. Human Respiratory Syncytial Virus: Role of Innate Immunity in Clearance and Disease Progression. Viral Immunol. 2016 Jan-Feb;29(1):11–26.
181 Bohmwald K, Espinoza JA, Becerra D, Rivera K, Lay MK, Bueno SM, et al. Inflammatory damage on respiratory and nervous systems due to hRSV infection. Curr Opin Immunol. 2015 Oct;36:14–21.
182 Grainge CL, Davies DE. Epithelial injury and repair in airways diseases. Chest. 2013 Dec;144(6):1906–12.
183 Vandini S, Calamelli E, Faldella G, Lanari M. Immune and inflammatory response in bronchiolitis due to respiratory Syncytial Virus and Rhinovirus infections in infants. Paediatr Respir Rev. 2017 Sep;24:60–4.
184 Newton AH, Cardani A, Braciale TJ. The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. Semin Immunopathol. 2016 Jul;38(4):471–82.
185 Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PA, Bartlett NW, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nat Med. 2006 Sep;12(9):1023–6.
186 Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med. 2005 Mar;201(6):937–47.
187 Contoli M, Ito K, Padovani A, Poletti D, Marku B, Edwards MR, et al. Th2 cytokines impair innate immune responses to rhinovirus in respiratory epithelial cells. Allergy. 2015 Aug;70(8):910–20.
188 Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. J Allergy Clin Immunol. 2012 Aug;130(2):489–95.
189 Tay H, Wark PA, Bartlett NW. Advances in the treatment of virus-induced asthma. Expert Rev Respir Med. 2016 Jun;10(6):629–41.
190 Glanville N, Johnston SL. Challenges in developing a cross-serotype rhinovirus vaccine. Curr Opin Virol. 2015 Apr;11:83–8.
191 Smith SB, Dampier W, Tozeren A, Brown JR, Magid-Slav M. Identification of common biological pathways and drug targets across multiple respiratory viruses based on human host gene expression analysis. PLoS One. 2012;7(3):e33174.
192 Pichlmair A, Kandasamy K, Alvisi G, Mulhern O, Sacco R, Habjan M, et al. Viral immune modulators perturb the human molecular network by common and unique strategies. Nature. 2012 Jul;487(7408):486–90.
193 Schindewolf C, Menachery VD. Middle East Respiratory Syndrome Vaccine Candidates: cautious Optimism. Viruses. 2019 Jan;11(1):11.
194 Hsu AC. Influenza Virus: A Master Tactician in Innate Immune Evasion and Novel Therapeutic Interventions. Front Immunol. 2018 Apr;9:743.
195 Bailey-Elkin BA, Knaap RC, Johnson GG, Dalebout TJ, Ninaber DK, van Kasteren PB, et al. Crystal structure of the Middle East respiratory syndrome coronavirus (MERS-CoV) papain-like protease bound to ubiquitin facilitates targeted disruption of deubiquitinating activity to demonstrate its role in innate immune suppression. J Biol Chem. 2014 Dec;289(50):34667–82.
196 Zhang W, Bailey-Elkin BA, Knaap RC, Khare B, Dalebout TJ, Johnson GG, et al. Potent and selective inhibition of pathogenic viruses by engineered ubiquitin variants. PLoS Pathog. 2017 May;13(5):e1006372.