Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER THREE

Nucleic Acid Induced Interferon and Inflammasome Responses in Regulating Host Defense to Gastrointestinal Viruses

Hanne Dubois[*,†,‡], **Geert van Loo**[†,§], **Andy Wullaert**[*,†,‡,1]
[*]Department of Internal Medicine, Ghent University, Ghent, Belgium
[†]VIB-UGent Center for Inflammation Research, VIB, Ghent, Belgium
[‡]Ghent Gut Inflammation Group (GGIG), Ghent University, Ghent, Belgium
[§]Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium
[1]Corresponding author: e-mail address: andy.wullaert@ugent.be

Contents

1. The Viral Dimension of the Gut Microbiome 138
2. The Gastrointestinal Virome in Regulating Host Health 140
3. Gastrointestinal Viral Infections 143
   3.1 Rotavirus 144
   3.2 Norovirus 144
   3.3 Reovirus 145
   3.4 Astrovirus 145
   3.5 Other Gastrointestinal Infectious Viruses 145
4. General Principles in Antiviral IFN and Inflammasome Responses 146
5. Cytosolic Viral Nucleic Acid Receptors Inducing IFN and Inflammasome Responses 148
   5.1 Viral RNA Recognition by DExD/H Helicases 148
   5.2 DexD/H Helicase: NLR Collaborations in Responding to Gastrointestinal Viruses 151
   5.3 Cytosolic Viral DNA Receptors Leading to IFN and Inflammasome Responses 158
6. Concluding Remarks 159
Acknowledgments 161
References 161
Further Reading 171

Abstract

The gut bacterial and fungal communities residing in the gastrointestinal tract have undisputed far-reaching effects in regulating host health. In the meantime, however, metagenomic sequencing efforts are revealing enteric viruses as the most abundant

International Review of Cell and Molecular Biology, Volume 345
ISSN 1937-6448
https://doi.org/10.1016/bs.ircmb.2018.08.003

dimension of the intestinal gut ecosystem, and the first gut virome-wide association studies showed that inflammatory bowel disease as well as type 1 diabetes could be linked to the presence or absence of particular viral inhabitants in the intestine. In line with the genetic component of these human diseases, mouse model studies demonstrated how beneficial functions of a resident virus can switch to detrimental inflammatory effects in a genetically predisposed host. Such viral-induced intestinal immune disturbances are also recapitulated by several gastrointestinal infectious viruses such as rotavirus and human norovirus. This wide range of viral effects on intestinal immunity emphasizes the need for understanding the innate immune responses to gastrointestinal viruses. Numerous nucleic acid sensors such as DexD/H helicases and AIM2 serve as cytosolic viral guardians to induce antiviral interferon and/or pro-inflammatory inflammasome responses. In both cases, pioneering examples are emerging in which RNA helicases cooperate with particular Nod-like receptors to trigger these cellular responses to enteric viruses. Here we summarize the reported beneficial versus detrimental effects of enteric viruses in the intestinal immune system, and we zoom in on the mechanisms through which sensing of nucleic acids from these enteric viruses trigger interferon and inflammasome responses.

1. THE VIRAL DIMENSION OF THE GUT MICROBIOME

A vast number of studies over the last decade demonstrated that the phylogenetic composition of the gut microbiome as well as its collective metabolic functional output crucially impact on host health. Next-generation sequencing revolutions enabling the 16S DNA based identification of enteric bacteria sparked numerous microbiome-wide studies that correlated particular bacterial composition shifts termed dysbiosis with human disease. The presence of specific bacteria with presumed pathobiont characteristics and/or the absence of specific bacterial species with suspected beneficial effects such as the production of short-chain fatty acids have both been linked to a wide range of human immune, metabolic and neurodegenerative diseases as well as to cancer and its resilience to immunotherapy (Gilbert et al., 2016; Gopalakrishnan et al., 2018)

As this now undisputed role of enteric bacteria in modulating host health was being established, deep sequencing of the internal-transcribed-spacer (ITS) regions of fungal ribosomal genes exposed the enteric mycobiome as a second dimension of the gut microbiome (Nash et al., 2017). Recent studies indicated that also many fungi residing in our gastrointestinal tract affect host health. For instance, following depletion of the resident gut bacteria, commensal fungi could functionally substitute for these microbiota and as such protected the host from increased susceptibility to colitis and

influenza infection (Jiang et al., 2017). In addition, changes in the gastrointestinal fungi composition were recently shown to result in severe colitis in mice (Leonardi et al., 2018), demonstrating that—as shown on multiple occasions for commensal gut bacteria—also fungal dysbiosis can be linked to disease development in the host.

Although the above and also numerous other studies firmly established how a sophisticated interplay between the human host and the bacterial and fungal ecosystems inhabiting its intestines is continuously balancing host health and disease, the gut virome represents a third dimension of the gut microbiome that may very well outnumber the gastrointestinal bacteria and fungi and for which the effects on host health are only beginning to emerge. Indeed, apart from bacteria and fungi, human feces contains $>10^9$ viral particles per gram. This hidden part of our microbiota includes viruses infecting each domain of life (Bacteria, Archaea and Eukarya). The latter include the human host itself, in which enteric viruses can produce acute-, persistent- or latent-like infections and in which certain viruses can integrate into the host genome (Cadwell, 2015; Carding et al., 2017; Virgin, 2014).

In recent years, metagenomic fecal DNA sequencing studies started to systematically uncover the enormous complexity of the gut virome. While many viral sequences retrieved from intestinal contents cannot be taxonomically assigned and thus represent as yet uncharacterized viruses, it is clear from the mapped viral sequences that bacteriophages are by far the predominant component of the viral microbiome dimension (Carding et al., 2017; Manrique et al., 2016; Minot et al., 2013). Illustrative of the mass abundance of bacteriophages in the intestinal ecosystem, a single *Bacteroidetes*-infecting phage family was recently characterized for which the founding phage on its own represented up to 22% of all reads in the human gut metagenome project (Dutilh et al., 2014; Yutin et al., 2018). However, despite their massive abundance, thus far no host immune responses have been identified that are specifically directed toward gastrointestinal bacteriophages. Therefore, this review will focus on pattern recognition receptor (PRR) initiated responses directed at the eukaryotic viruses residing in the intestines.

Although the number of eukaryotic viruses present in the gut are fewer than bacteriophages (Minot et al., 2013; Reyes et al., 2010), they could be detected in metagenomics studies as well as by PCR-based fecal shedding analyses in healthy individuals. For instance, viruses from the *Picobirnaviridae, Adenoviridae, Anelloviridae* and *Astroviridae* families and species such as *bocavirus, rotavirus, enterovirus* and *sapovirus* were present in the microbiome

of healthy children (Kapusinszky et al., 2012; Zhao et al., 2017). These observations demonstrate that intestinal colonization with eukaryotic viruses, some of which known to have pathogenic potential, can be tolerated without apparent symptomatic disease and thus may be considered "commensal" gastrointestinal viruses. Similarly, specific murine norovirus (MNV) strains were found to persistently infect the intestines of wild-type mice without causing pathology (Baldridge et al., 2016). However, host genetic deficiencies in anti-viral interferon (IFN) responses or in the autophagy machinery turned this virus-host relationship sour, as in these cases MNV could cause lethality or increased susceptibility to intestinal inflammation, respectively (Cadwell et al., 2010; Karst, 2003). These genetic studies in mice elegantly demonstrated that although lifelong asymptomatic viral presence within the gastrointestinal immune system is possible, it requires tight control by the mucosal immune system. Therefore, continuous monitoring of the gut virome by means of PRR signaling induced cytokine and IFN responses is essential for maintaining intestinal immune homeostasis, while also being responsible for protecting the host against occasional intestinal invasions by true pathogenic viruses. PRR-mediating sensing of gastrointestinal viruses leading to cytokine and IFN responses will therefore form the focus of this review.

2. THE GASTROINTESTINAL VIROME IN REGULATING HOST HEALTH

As observed for the other gut microbiota dimensions, the gut virome comprises core components shared among multiple individuals (Carding et al., 2017; Manrique et al., 2016; Reyes et al., 2010), but significant inter-individual differences exist and gut virome diversity is influenced by age as well as by environmental factors such as diet composition (Lim et al., 2015; Minot et al., 2011; Reyes et al., 2015). Owing to their abundance, it is clear that the potential influence of such alterations in the gut virome composition on host health cannot be underestimated. Indeed, large metagenomics efforts have shown that the gut virome composition of human inflammatory bowel disease (IBD) and type 1 diabetes (T1D) patients differs from healthy individuals (Norman et al., 2015; Zhao et al., 2017). As opposed to a decreasing richness of the bacterial microbiota typically observed in IBD patients, both Crohn's disease (CD) and ulcerative colitis (UC) patients displayed an increased richness in their fecal virome when compared to healthy individuals (Norman et al., 2015). While this

increased viral richness was associated mainly with elevated numbers of the *Caudovirales* bacteriophages, Manrique et al. subsequently found that the fecal virome communities of these CD and UC patients harbored reduced numbers of the core bacteriophages commonly found in healthy subjects (Manrique et al., 2016). Although the exact viruses involved remain to be identified, these observations suggest that IBD development may be associated with the loss of particular core bacteriophages with beneficial functions for intestinal health, allowing a bloom in other bacteriophages that result in the observed increased virome richness in IBD patients. In contrast to the richer gut virome observed in IBD patients, the intestinal viromes of individuals developing T1D were found to be less diverse than the ones from healthy controls, with the latter harboring significantly more viruses of the *Circoviridae* family (Zhao et al., 2017). Together, these large virome-wide association studies thus highlighted the possibility that particular viruses in the gastrointestinal tract, such as *Circoviridae* in T1D, may exert beneficial functions for preserving host health. However, as many of the host PRR responses to bacteriophages and also several other enteric viruses remain to be identified, it is currently not clear how the observed correlations between skewed gut virome compositions and human disease development could be linked with altered innate immune responses to these intestinal viruses.

Nevertheless, several animal model studies have illustrated how particular enteric viruses can offer benefits for host health. For instance, a landmark study in mice showed that MNV mono-colonization of germfree (GF) or antibiotics (Abx)-treated mice reverted the gastrointestinal architectural and immune defects normally associated with depletion of commensal bacteria (Kernbauer et al., 2014). Indeed, MNV colonization restored small intestinal crypt-villus morphologies, increased lymphocyte numbers and functioning with regards to IFNγ and IgA production, reverted the type 2 versus type 3 innate lymphoid cell (ILC) balances, and restored Paneth cell functioning in these mice (Kernbauer et al., 2014). MNV colonization could thus functionally replace the gut homeostatic effects of the resident commensal bacteria, and was able to do so without causing disease or overt inflammation in the host. Moreover, beyond basal gastrointestinal immune homeostasis, MNV inoculation also protected Abx-treated mice against immune disturbances such as caused by *Citrobacter rodentium* infection or caused by dextran sodium sulfate (DSS)-induced tissue damage. Although the precise mechanisms of action require further investigation, experiments in mice lacking the IFNα receptor 1 (IFNAR1) showed that type I IFN

signaling was needed for the beneficial effects of MNV and thus indicate the importance of PRR-based responses in mediating its effects on the host (Kernbauer et al., 2014). The observation that MNV colonization could protect the host from subsequent gastrointestinal *C. rodentium* infection was reminiscent of previous studies showing protective effects of viral infections against future challenges. For instance, mice latently infected with the gammaherpesvirus 68 or murine cytomegalovirus (mCMV) were protected against bacterial infection with either *Listeria monocytogenes* or *Yersinia pestis* (Barton et al., 2007). These mouse model studies provided the proof of concept that resident individual viruses can exert beneficial effects for the host immune system both in homeostasis and upon infectious challenges.

Support for a beneficial role of the overall community of gut resident viruses in intestinal homeostasis was provided by Yang et al., who showed that depleting the gut virome through administrating an antiviral drug cocktail increased the sensitivity of mice to DSS-induced colitis (Yang et al., 2016). Administration of an inactivated rotavirus or combined triggering of Toll-like receptor (TLR)3 and TLR7 attenuated DSS-induced colitis, suggesting that viral RNA sensing through TLR3/7 may represent the molecular mode of action by which enteric viruses prevent excessive intestinal inflammation. In line with this notion as well as with the reported requirement for type I IFN signaling in the beneficial functions of MNV (Kernbauer et al., 2014), plasmacytoid dendritic cells (DCs) isolated from DSS-inflamed colons produced IFNβ upon combined TLR3/7 stimulation (Yang et al., 2016). Supported by several other studies showing protective effects of type I IFNs in the induction of DSS-induced acute colitis (Katakura et al., 2005; Rauch et al., 2014; Sainathan et al., 2012; Vijay-Kumar et al., 2007), these findings suggested that the resident gut virome prevents colitis through TLR3/7-induced type I IFN production. Interestingly, the combination of antiviral drugs used in the Yang et al. study decreased the overall viral load in the intestine but increased the level of bacteriophage *Caudovirales*, similar to the observations in human IBD patients (Norman et al., 2015). Moreover, IBD patients bearing combined mutations in the *Tlr3* and *Tlr7* genes had higher hospitalization rates, suggesting that also in humans viral RNA triggering of these PRRs may be protective (Yang et al., 2016).

Although the above human observational and mouse experimental studies clearly indicate that particular members of the gut virome may help in maintaining intestinal immune homeostasis, it should be noted that there

is only a fine line between the beneficial functions of a given virus and the potential detrimental outcomes of its presence. For instance, in mice with decreased expression levels of the autophagy executer *Atg16l1*, for which mutations in humans predispose to CD development, MNV colonization increased host sensitivity to DSS colitis (Cadwell et al., 2008, 2010). In addition, while remaining asymptomatic in wild-type mice, MNV colonization worsened intestinal inflammation in IL-10-deficient mice (Basic et al., 2014). As opposed to its beneficial role in maturing the intestinal immune system of wild-type mice (Kernbauer et al., 2014), these MNV studies illustrate how the host genetic status profoundly impacts on the response of the intestinal immune system to a gastrointestinal virus. Moreover, while gut virome depletion revealed an overall colitis preventing effect of the resident enteric viruses (Yang et al., 2016), mice with a latent mCMV infection developed more severe DSS colitis than control mice (Onyeagocha et al., 2009), illustrating the delicate balance between the either beneficial or detrimental effects of the intestinal viral ecosystem on the host.

Taken together, all of the above observations show that intestinal health depends on complex interactions between enteric viruses, host genetics, the mucosal immune system and other yet unidentified pathways. This complex host-viral cross talk emphasizes the need for better understanding of the innate immune mechanisms recognizing and responding to enteric viruses, which will be discussed further in this review.

3. GASTROINTESTINAL VIRAL INFECTIONS

In contrast to the above described potential beneficial actions of gastrointestinal viruses for host health, several enteric viruses can elicit acute gastroenteritis. Enteric viruses are mostly transmitted via the fecal-oral transmission route, and their shedding in the stool can continue for a long time after the gastroenteritis symptoms resolved. Depending on the conditions of infection, viral gastroenteritis patients can suffer from abdominal pain, vomiting, nausea and diarrhea potentially leading to serious dehydration. However, in some cases viral gastroenteritis remains asymptomatic or evolves into a chronic infection. The latter implies continuous viral shedding in the stool, which creates a reservoir for future outbreaks of newly developed pathogenic strains (Doerflinger et al., 2017; Graves, 2013; Shortland et al., 2014). Viral gastroenteritis pathologies normally are self-limiting and generally resolve within 14 days, but they can turn life-threatening for immunocompromised patients and for infants in developing countries

(Mcclarren et al., 2011). In fact, the World Health Organization (WHO) reported diarrheal diseases as the second leading cause of death worldwide in children under 5 years of age, estimated to kill more than half a million of these children each year (World Health Organization, 2017). Due to difficulties in their detection, the role for enteric viruses in eliciting diarrheal diseases was underestimated for a long time. However, after Kapikian identified in 1972 for the first time viral particles in the stool of a patient with diarrhea (Kapikian et al., 1972), many enteric viruses capable of causing diarrheal disease were described (Bartsch et al., 2016; Bok and Green, 2012; Tsolenyanu et al., 2014), of which the most common ones are introduced below.

3.1 Rotavirus

Rotavirus is a non-enveloped, double-stranded (ds)RNA virus of the *Reoviridae* family causing intestinal disease mainly in children. Rotavirus infection symptoms generally last up to 4 days and are represented in vomiting, diarrhea and low grade fever. Rotavirus infects and replicates in small intestinal epithelial cells, after which subsequent transcytosis into the lamina propria via the M cells can potentially lead to systemic spread and in some cases may evoke extra-intestinal disease manifestations (Blutt et al., 2003; Rivero-Calle et al., 2016). However, induction of an intestinal anti-rotavirus IgA response eventually clears the infection and induces protective immunity (Blutt and Conner, 2013; Blutt et al., 2012). Rotavirus is the only enteric virus for which (since 2006) two vaccines are available that in the meantime have been licensed by >100 countries worldwide. Given that in 2013 rotavirus infections were estimated to have caused 215,000 deaths in children below 5 years, routine use of the rotavirus vaccines is highly recommended by the WHO (Tate et al., 2009, 2012, 2016).

3.2 Norovirus

Human noroviruses (NoV) are non-enveloped single-stranded (ss)RNA viruses of the *Caliciviridae* family classified in six genogroups, of which genogroups I, II and IV are the ones infecting humans (Kroneman et al., 2013; Lopman et al., 2004). In comparison to other enteric viruses, NoV causes a shorter period of diarrhea, but it is often accompanied by abdominal pain, headache and vomiting. Human NoV infection is the most common non-bacterial cause of gastroenteritis as well as the most common cause of food-borne gastroenteritis worldwide, accounting for an estimated 684

million cases per year. Norovirus infections also cause >200,000 deaths annually, mostly affecting children in developing countries below 5 years of age (Lopman et al., 2016). Despite this huge global health and socio-economic impact, no vaccines or specific treatments for NoV infection are currently available.

3.3 Reovirus

Next to rotavirus, reovirus is another *Reoviridae* member of which particular strains can infect the gastrointestinal tract (Tai et al., 2005). Enteric infection with the dsRNA reovirus normally does not provoke pathology in humans or adult mice, but infecting mice with this seemingly innocuous virus was found to trigger inflammatory responses to dietary antigens causing loss of oral tolerance in a manner that at least partially relied on type I IFN responses (Bouziat et al., 2017). Therefore, despite not classifying as a typical gastro-enteritis causative agent, it is interesting to include the mechanisms underlying host IFN responses to reovirus in this review.

3.4 Astrovirus

Astroviruses are positive-sense ssRNA viruses belonging to the *Astroviridae* family (Monroe et al., 1993). After rotavirus, astrovirus is thought to be the second most common instigator of viral gastroenteritis in children (De Benedictis et al., 2011). Although the mechanisms of astrovirus-induced intestinal pathogenesis have not been fully elucidated, a capsid protein was suggested to act as an enterotoxin that damages the intestinal epithelium and as such to provoke diarrhea (Cortez et al., 2017). However, while astroviruses were shown to induce type I IFN production (Marvin et al., 2016), the viral ligands nor the host receptors initiating this antiviral response have been identified.

3.5 Other Gastrointestinal Infectious Viruses

Besides the above well-known instigators of viral gastroenteritis, other opportunistic viruses in some cases are capable of infecting the gastrointestinal tract and inducing pathology. For instance, *Coronaviridae* have long been considered solely as causative agents of common colds, but an outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) in China revealed diarrhea in up to 38% of the infected patients, presumably caused by toxins secreted during viral replication in enterocytes (Hui et al., 2004; Rota et al., 2003). However, SARS-CoV gastroenteritis incidence is rather

low and no mortality has been reported (Ding et al., 2004; Guan et al., 2004; Hon et al., 2003; Wang and Chang, 2004). In addition, immunosuppressed patients can suffer from atypical viral gastroenteritis caused by viruses that normally do not infect a healthy gastrointestinal tract such as human Cytomegalovirus, Epstein-Barr virus, Enterovirus and Coxsackievirus (Li et al., 2009; Ryan et al., 2012; Tapparel et al., 2013; Weber et al., 1999; Yuen et al., 1998).

4. GENERAL PRINCIPLES IN ANTIVIRAL IFN AND INFLAMMASOME RESPONSES

The above described collection of gastrointestinal viruses with diverse effects on the host mucosal immune system, ranging from beneficial actions in immune maturation and homeostasis to deleterious effects potentially causing lethal diarrhea, imply the need for sophisticated host viral recognition systems that in some cases sustain the symbiotic relationship but in other cases initiate immediate antiviral responses to clear the infection. Antiviral immune responses are initiated by germline encoded PRRs that scan the cytosolic and endosomal environments for viral pathogen-associated molecular patterns (PAMPs). The obligate intracellular viral infectious life cycle including genome replication, protein production and virion assembly implies the cytosolic presence of viral nucleic acids as well as proteins as potential PRR triggers. Although endosomal presence of viral nucleic acids is detected by TLR3, TLR7/8 and TLR9 (Lester and Li, 2014), in this review we will mainly focus on PRR-induced signaling pathways induced by viral ssRNA, dsRNA and dsDNA molecules residing in the cytosol. Several cytosolic PRRs have evolved to discriminate non-self viral nucleic acids from host nucleic acids in order to maintain tolerance to the latter (Diebold et al., 2006; Haas et al., 2008; Rutz et al., 2004) While discriminating viral DNA from host DNA is based mainly on their cytosolic versus nuclear presence, cytosolic non-self RNA sensors can detect a wide range of specific molecular patterns that are absent in host RNA and that have been reviewed elsewhere (Chow et al., 2018). Together, coordinated intracellular signaling pathways collectively initiated by these viral nucleic acid receptors will result in the activation of the NF-κB transcription factor leading to production of multiple pro-inflammatory mediators, as well as in an antiviral response characterized by the production of type I as well as type III IFNs (Schlee and Hartmann, 2016; Teijaro, 2016; Zanoni et al., 2017).

The type I IFNs are defined as IFNs that signal through the IFNAR complex, and comprise several IFNα subtypes, IFNβ, IFN-δ, IFN-ε, IFN-κ, IFN-ω, IFN-τ and IFN-ζ. Among type I IFNs, mainly IFNα/β are known to play key roles in limiting viral replication and spread. Autocrine and paracrine IFNα/β signaling will trigger a JAK/STAT signaling cascade leading to STAT1/2 phosphorylation and hetero-dimerization. These STAT heterodimers translocate to the nucleus to induce the expression of numerous interferon stimulated genes (ISG) that aid in restricting viral replication, inhibit protein synthesis and prime neighboring cells for a viral attack (Kisseleva et al., 2002; Wang et al., 2017b). In addition, antiviral IFNα/β signaling can induce apoptosis, thereby destroying the viral replicative niche (Balachandran et al., 2000; Mattei et al., 2010).

Type III IFNs (IFNλ) exert antiviral effects analogous to the ones exerted by IFNα/β owing to the similar JAK/STAT signal transduction pathway and IFN response gene expression they can induce upon binding their cellular receptor. However, type III IFNs (in humans comprising IFNλ1, IFNλ2, IFNλ3 and IFNλ4; while in mice only IFNλ2 and IFNλ3 are active) do not bind the IFNAR but instead signal through a receptor complex composed of the IL-10Rβ subunit and the specific IFNλ receptor 1 (IFNλR1) subunit. Binding to the latter defines type III IFNs. As the expression pattern of the IFNλR1 subunit is mainly restricted to epithelial cells, IFNλ is particularly important in responding to gastrointestinal antiviral responses, as it was shown to control the persistent character of several enteric viruses (Ingle et al., 2018; Lee and Baldridge, 2017).

Besides inducing these antiviral IFN responses, in some cases viral nucleic acid receptors induce signaling toward activation of host inflammasomes, mostly in cooperation with cytosolic Nod-like receptor (NLR) family members (Lupfer and Kanneganti, 2013; Man et al., 2017). The inflammasome is a multi-protein complex in which activation of its catalytic subunit caspase-1 mediates maturation and secretion of IL-1β and IL-18 cytokines (Dubois et al., 2016). While IL-1β exerts a broad diversity of functions within the innate immune response including lymphocyte activation and leukocyte transmigration, IL-18 is important for orchestrating the ensuing adaptive immune response by promoting IFNγ production (Dinarello, 2009). In addition, inflammasome activation can provoke a lytic form of cell death termed pyroptosis through cleavage of its Gasdermin D (GSDMD) substrate that forms pores in the cellular membrane (Aglietti et al., 2016; Ding et al., 2016; Zhang et al., 2017). Apart from eliminating the replicative niche of intracellularly-replicating pathogens such as

viruses, the lytic nature of pyroptotic cells also invokes extracellular release of danger-associated molecular patterns (DAMPs) such as IL-1α and HMGB1 that assist in coordinating inflammatory responses (Aachoui et al., 2013; Casson et al., 2013; Lamkanfi et al., 2010).

Thus, alongside inducing antiviral IFN responses aimed at limiting viral dissemination, activating the inflammasome is an important cellular response to cytosolic viral nucleic acids that promotes inflammatory reactions. Moreover, IFN and inflammasome pathways are intimately linked. For instance, transcription of caspase-11 is controlled by type I IFN signaling (Rathinam et al., 2012), suggesting that anti-viral IFN responses could prime neighboring cells for executing non-canonical inflammasome activation in response to Gram-negative bacteria. Conversely, several studies have shown that type I IFNs can also downregulate inflammasome responses. For instance, type I IFNs were shown to reduce Nlrp3 inflammasome mediated production of mature IL-1β. This could in part be explained through type I IFNs activating STAT1, which in turn lead to production of IL-10 that decreased pro-IL-1β levels in an autocrine manner (Guarda et al., 2011). In addition to these IL-10 dependent effects, type I IFNs were also shown to induce the production of 25-hydroxycholesterol (25-HC) that inhibits inflammasome-mediated inflammatory responses both in the priming and in the activation stages. Indeed, on the one hand 25-HC was reported to restrain pro-IL-1β expression on the transcriptional level (Reboldi et al., 2014), while on the other hand it was also reported to maintain mitochondrial integrity and as such to prevent the cytosolic release of mitochondrial DNA that could otherwise activate the absent in melanoma 2 (AIM2) inflammasome (Dang et al., 2017). Therefore, it is clear that the concerted actions of type I IFNs and inflammasome responses induced by gastrointestinal viruses could influence mucosal immunity in multiple autocrine and paracrine ways. Below, we will outline the several classes of viral nucleic acid recognizing PRRs and highlight in more detail the ones that have been implicated in IFN and inflammasome responses to gastrointestinal viruses.

5. CYTOSOLIC VIRAL NUCLEIC ACID RECEPTORS INDUCING IFN AND INFLAMMASOME RESPONSES

5.1 Viral RNA Recognition by DExD/H Helicases

Cytosolic viral ssRNA and dsRNA molecules are recognized by particular members of a large family of DexD/H-box containing helicases, among which RIG-I-like receptors (RLRs) have been best characterized

(Hornung et al., 2006; Kato et al., 2006; Yoneyama et al., 2015). Members of the DexD/H helicase protein family all share a conserved DexD/H motif. This motif varies between DEAD and DEAH amino acid sequences, which defines the DDX and DHX helicases, respectively. Regardless, although the DEAD-box containing helicases have a preference for ATP, all DexD/H helicases can bind RNA structures to induce conformational changes upon ATP/NTP hydrolysis. This confers many of these proteins host RNA household functions such as in aiding RNA transcription, editing, splicing, export, translation, and turnover, as well as in ribosome biogenesis. However, some DexD/H helicases have evolved to recognize non-self RNA. The best known example is retinoic acid-inducible gene (RIG)-I, encoded by the *Ddx58* gene, which is the prototypical member of the RLRs (Chow et al., 2018; Fullam and Schroder, 2013; Linder, 2006).

5.1.1 RIG-I-Like Receptors (RLRs)

The RLRs are DexD/H helicases that stably bind cytosolic viral ssRNA or dsRNA to induce production of antiviral IFNs and pro-inflammatory cytokines. Members of this family include RIG-I, melanoma differentiation-associated gene 5 (MDA-5) and laboratory of genetics and physiology 2 (LGP2) (Cui et al., 2001; Kang et al., 2002; Yoneyama et al., 2004). Both RIG-I and MDA-5 contain an RNA-binding DExD/H helicase domain and two N-terminal caspase-recruitment domains (CARDs), which serve for interacting with the signaling adaptor protein mitochondrial anti-viral signaling (MAVS) (Andrejeva et al., 2004; Seth et al., 2005; Yoneyama et al., 2004). As it lacks CARDs, LGP2 does not have signaling capacities like RIG-I and MDA-5, but rather functions as an accessory protein that can regulate RLR signaling either positively or negatively (Komuro and Horvath, 2006; Venkataraman et al., 2007; Yoneyama et al., 2005). RIG-I or MDA-5 mediated binding of viral RNA initiates CARD-CARD interactions between the respective RLR and MAVS. The latter then propagates a signaling cascade culminating in phosphorylation of IFN responsive factor (IRF)3 and IRF7, which translocate to the nucleus for inducing transcription of IRF responsive genes. In addition, RLR-induced MAVS signaling will also lead to NF-κB activation to induce transcription of several pro-inflammatory genes (Reikine et al., 2014). RIG-I and MDA-5 together enable broad-range antiviral responses because they recognize different RNA structures. Although the exact ranges and structural underpinnings of the differential viral RNA recognition modes by these RLRs are not entirely clear yet and have been reviewed elsewhere (Chow et al., 2018),

in general RIG-I was reported to bind short dsRNA stretches as well as ssRNA bearing 5′ di- or tri-phosphate ends, while MDA-5 prefers binding to long dsRNA sequences (Goubau et al., 2014; Hornung et al., 2006; Kato et al., 2006, 2008).

5.1.2 Other DExD/H Helicases Involved in Cytosolic Viral RNA Recognition

Apart from the above RLRs, several other DexD/H helicases were suggested to directly recognize viral RNA and to initiate cellular anti-viral responses (Fullam and Schroder, 2013). For instance, the DDX1-DDX21-DHX36 protein complex was reported to bind reovirus and influenza dsRNA via the helicase domain of DDX1, after which DDX21 and DHX36 enabled interaction with the TRIF adaptor protein to initiate downstream signaling (Zhang et al., 2011a). Other reports proposed also DDX3 to be capable of directly sensing viral RNA in the cytosol, although some observations indicated that this RNA helicase could be involved as a more general scaffold in RLR-mediated antiviral signaling cascades. For instance, DDX3 was shown to interact with RNA molecules from diverse viral origins suggesting its role as an RNA sensor (Gringhuis et al., 2017), but it was also reported to mediate RIG-I-induced signaling by promoting the assembly of MAVS signaling complexes (Gu et al., 2017), rendering it hard to discriminate whether DDX3 functions as a RIG-I-independent viral RNA sensor or as a signal transducer. Finally, although a function for DDX60 has been proposed as an upstream RNA sensor facilitating RIG-I-induced signaling (Oshiumi et al., 2015), these findings were later questioned by DDX60-deficient cells and mice that did not show impaired IFN responses to a wide variety of viral RNA triggers (Goubau et al., 2015). While it is thus clear that the individual roles of multiple non-RLR DexD/H helicases in viral RNA induced responses require additional investigational efforts, we will further highlight the functions of three particular DexD/H helicases—DHX9, DHX15 and DHX33—that were suggested to collaborate with distinct cytosolic NLRs in order to mount IFN or inflammasome responses to gastrointestinal viruses (summarized in Fig. 1). However, it should be mentioned that for each of these three cases also TLRs or "classical" RLRs have been suggested to participate in sensing viral nucleic acids, as summarized in Table 1. Therefore, a certain level of redundancy and/or cell type specificity can be envisaged in recognizing and responding to gastrointestinal viruses.

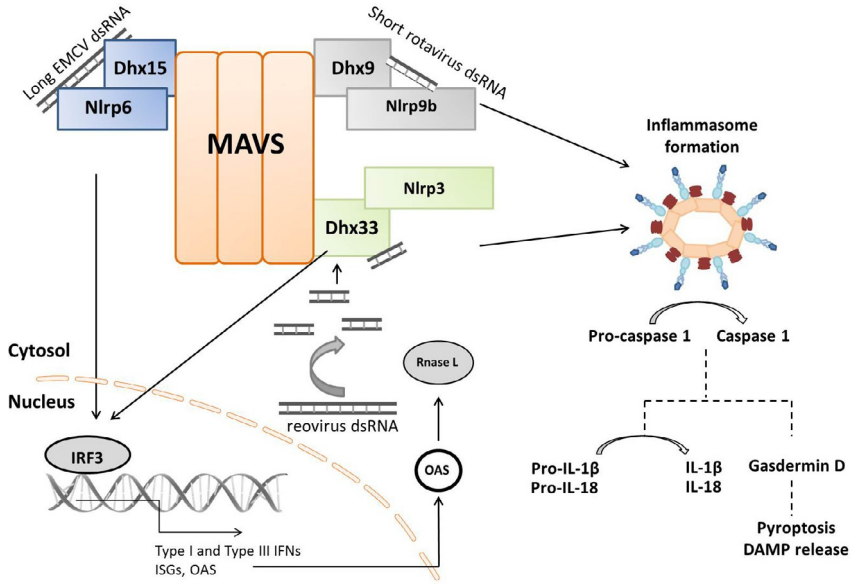

Fig. 1 Scheme of DExD/H helicase—NLR collaborations in cytosolic viral dsRNA induced IFN and inflammasome responses to gastrointestinal viruses. Dhx15-Nlrp6 complex formation enables recognition of EMCV long dsRNA stretches, upon which interaction with MAVS initiates downstream signaling toward IRF3-mediated IFN responses. Conversely, the Dhx9-Nlrp9b and Dhx33-Nlrp3 complexes facilitate dsRNA-induced inflammasome activation. Dhx9-Nlrp9b complex formation facilitates recognition of short dsRNA molecules from rotavirus infection, leading to inflammasome activation. Dhx33 recognizes short dsRNA cleavage products generated by OAS-activated RNase L. Dhx33 is then able to initiate signaling toward IFN responses in an NLR-independent manner by interacting with MAVS, while Dhx33 interaction with Nlrp3 is required to activate the inflammasome. See text for further details.

5.2 DexD/H Helicase: NLR Collaborations in Responding to Gastrointestinal Viruses

5.2.1 Dhx9-Nlrp9b Mediated Inflammasome Responses to Rotavirus Infection

The acute but transient nature of rotavirus-induced gastroenteritis suggests that specific innate immune responses are capable of rapidly controlling the infection. Initial studies on host responses to rotavirus infection focused on the role of TLRs. Administration of rotavirus dsRNA to mice resulted in small intestinal inflammation in a manner dependent on the endosomal dsRNA sensor TLR3 (Zhou et al., 2007). TLR3-deficient mice were subsequently found to be hyper-susceptible to rotavirus infection at adult age but not in the neonatal stage of life (Pott et al., 2012). Although this

Table 1 Overview of Potential Redundancies and/or Cell Type Specificities of Host Receptors Initiating Viral RNA Signaling in Response to Gastrointestinal Rotavirus, Norovirus and Reovirus Infections

Enteric Virus	Nucleic Acid PAMP	Host PRR	Host Adaptors and Downstream Effect	Human/Mouse Cell Type or Model System in Which the Response Was Demonstrated	References
Rotavirus	Endosomal dsRNA	TLR3	TRIF, type I IFNs	Adult mouse IECs	Zhou et al. (2007) and Pott et al. (2012)
	Cytosolic dsRNA	RIG-I, MDA-5	MAVS, type I IFNs	Human transformed IECs, $MAVS^{-/-}$ mice	Broquet et al. (2011)
	Cytosolic short dsRNA stretches	Dhx9	Nlrp9b, ASC, inflammasome	Adult mouse IECs	Zhu et al. (2017)
Murine Norovirus	Cytosolic dsRNA	MDA-5	MAVS, type I IFN and cytokine responses	Mouse bone marrow derived DCs	McCartney et al. (2008)
	Cytosolic long dsRNA stretches	Dhx15, suggested based on ECMV studies	Suggested Nlrp6—MAVS—type I IFN response based on ECMV studies	Higher MNV loads in $Nlrp6^{-/-}$ mice upon oral infection	Wang et al. (2015b)

Reovirus	Cytosolic dsRNA (suggested to be RNAse L-processed based on influenza dsRNA studies)	DHX33	NLRP3, ASC, inflammasome	Human THP-1 macrophages, human primary monocyte-derived macrophages	Mitoma et al. (2013) and Chakrabarti et al. (2015)
	Cytosolic dsRNA	Dhx33	MAVS, type I IFNs	Murine splenic DC cell line D2SC, mouse bone marrow derived DCs, and mouse embryonic fibroblasts	Liu et al. (2014)
	Cytosolic dsRNA	RIG-I and MDA-5	MAVS, type I IFNs	Mouse bone marrow derived cDCs and mouse embryonic fibroblasts	Kato et al. (2008)
	Cytosolic dsRNA	RIG-I	MAVS, type I IFNs	Human 293 T cells	Holm et al. (2007)
	Cytosolic dsRNA	DDX1/ DDX21/ DHX36	TRIF, type I IFNs and TNF	Murine splenic DC cell line D2SC	Zhang et al. (2011a)

observation showing a crucial role for TLR3 specifically in adulthood suggested that instead RLR sensing of rotavirus RNA could be essential at neonatal stages, another study also using adult mice showed that abrogating RLR signaling by deleting MAVS rendered mice unable to induce antiviral IFN responses leading to increased rotavirus burdens in these MAVS-deficient mice (Broquet et al., 2011). Together, these studies suggested non-redundant protective roles for TLR3- and RLR-mediated IFN responses in murine rotavirus infection.

In addition to IFNs, a later study pointed at a potentially important role for inflammasomes in preventing rotavirus infection, as intraperitoneal injection of mice with IL-18 prior to gastrointestinal rotavirus infection diminished subsequent fecal shedding of the virus (Zhang et al., 2014). Since IL-18 requires maturation by the inflammasome to obtain its biological activity, this study suggested that perhaps endogenous inflammasome activation by the virus could evoke host protective responses. This hypothesis was confirmed by Zhu et al., who showed that rotavirus infection in mice lacking the inflammasome components ASC or caspase-1 resulted in higher small intestinal viral titers and a higher diarrhea incidence (Zhu et al., 2017). The authors identified Nlrp9b as the NLR responsible for initiating rotavirus-induced inflammasome responses, as Nlrp9b$^{-/-}$ mice phenocopied the response of ASC- or caspase-1-deficient mice upon rotavirus infection. Moreover, consistent with the fact that rotavirus replicates in intestinal epithelial cells (IECs), also IEC-specific deletion of Nlrp9b or caspase-1 aggravated rotavirus gastroenteritis. Rotavirus dsRNA-induced Nlrp9b inflammasome activation resulted both in IL-18 release and in GSDMD-dependent pyroptosis. Interestingly, GSDMD-deficient mice but not IL-18-deficient mice displayed increased susceptibility to rotavirus infection when compared with wild-type mice (Zhu et al., 2017). This suggests that beyond inducing IL-18 release, Nlrp9b inflammasome activation limits intestinal rotavirus burdens by inducing pyroptosis, perhaps to destroy the viral intracellular replicative niche or to release additional DAMPs needed for augmenting host antiviral responses. Similar to the reported age-related increase in TLR3 expression (Pott et al., 2012), also intestinal expression levels of ASC and Nlrp9b increased as mice grew older (Zhu et al., 2017), suggesting that potentiating these two non-redundant modes of viral dsRNA recognition may explain how rotavirus susceptibility declines with age.

In order to identify the molecular mechanism by which Nlrp9b senses rotavirus presence in IECs, immunoprecipitation studies were performed

that revealed an interaction between the human NLRP9 and DHX9 proteins (Zhu et al., 2017). The latter was previously shown to act as an RNA-sensing DexD/H helicase during reovirus and influenza infection, after which it interacted with MAVS and as such mediated production of IFNs and cytokines (Zhang et al., 2011c). Aligning with this already reported DHX9 function, DHX9-NLRP9 complexes were found to bind short dsRNA stretches more efficiently than NLPR9 itself. In addition, primary IEC organoid cultures derived from $Dhx9^{-/-}$ mice were defective in rotavirus induced inflammasome responses and allowed higher rotavirus replication rates than wild-type organoids. Thus, this study provided an example of a DexD/H helicase—NLR collaboration, showing that Dhx9 assists in rotavirus dsRNA sensing allowing Nlrp9b to induce the assembly and activation of an inflammasome that restricts viral replication by triggering pyroptosis (see Fig. 1) (Zhu et al., 2017).

5.2.2 Dhx15-Nlrp6 Mediated IFN Responses to EMCV and MNV Infection

A second example of DexD/H helicase-assisted functioning of NLR-mediated antiviral immunity in the gut was provided by a study using an oral encephalomyocarditis virus (EMCV) infection model. Mice lacking the NLR family member Nlrp6 showed higher viral burdens in their intestines and increased mortality upon oral EMCV infection as compared to wild-type mice, indicating a role for Nlrp6 in limiting EMCV replication in the intestinal mucosa (Wang et al., 2015b). Oral EMCV infection of $Nlrp6^{-/-}$ mice was associated with lower intestinal IFN and ISG levels compared to wild-type mice, showing that Nlrp6 was crucially contributing to antiviral IFN responses in this model. Consistent with this suggested role of Nlrp6 in mediating IFN responses, co-immunoprecipitation experiments showed that Nlrp6 was able to interact with MAVS. Similar experiments then revealed the ATP-dependent RNA helicase Dhx15 as a direct binding partner of Nlrp6 (Wang et al., 2015b). As human DHX15 had previously been shown already to bind EMCV dsRNA (Mosallanejad et al., 2014), this suggested that Nlrp6 binding to this DexD/H helicase could increase their cumulative affinity for EMCV dsRNA. Indeed, similar to the above observations for the DHX9/NLRP9 complex, the interaction of Dhx15 and Nlrp6 resulted in improved dsRNA binding and facilitated complex formation with MAVS to induce IFN responses (see Fig. 1). However, in contrast to the preferential binding of DHX9/NLRP9 to short dsRNA, the Dhx15/Nlrp6 interaction resulted in a preference for binding high-molecular weight dsRNA (Wang et al., 2015b; Zhu et al., 2017).

Accordingly, unlike Nlrp6$^{-/-}$ mice, Nlrp9b$^{-/-}$ mice were not more sensitive to oral EMCV infection than wild-type mice (Zhu et al., 2017).

Interestingly, apart from EMCV, also MNV was described as subject to Nlrp6-dependent antiviral immune signaling. In the absence of Nlrp6, oral MNV infection resulted in higher fecal and intestinal epithelial MNV loads, suggesting a role for Nlrp6 in clearing this virus from the gut (Wang et al., 2015b). However, unlike for EMCV, no information was provided by Wang et al. on the role of Dhx15 in Nlrp6 responses to MNV, nor on the effects of Nlrp6 on MNV-induced IFN responses (Wang et al., 2015b). In fact, IFN responses to MNV were previously reported to depend entirely on MDA-5-mediated recognition of its dsRNA. Indeed, in contrast to wild-type as well as TLR3$^{-/-}$ DCs, MDA-5-deficient DCs did not mount cytokine or IFN responses to MNV infection (McCartney et al., 2008). This observation showing that MDA-5 is crucial for initiating MNV dsRNA-induced IFN responses seems contradictory with the suggested similar role for Nlrp6, although it should be noted that MDA-5 and Nlrp6 have differential expression patterns. Indeed, given its major expression in IECs, Nlrp6 might represent the intestinal epithelial sensor for MNV dsRNA, while MDA-5 could initiate MNV antiviral defense in immune cells. However, although human NoV can readily infect human IECs (Ettayebi et al., 2016), the preferred murine target cells of MNV are immune cells such as macrophages, DCs and B cells (Jones et al., 2014; Wobus et al., 2004). Only recently, a potential effect of MNV in IECs was discovered. After several studies consolidated a major role for IFNλ signaling in controlling the persistency of intestinal MNV colonization (Baldridge et al., 2015b, 2017), a particular persistent MNV-CR6 strain was found to dodge the intestinal antiviral effects of IFNλ in a tiny subpopulation of IECs, which it used as a reservoir to persist *in vivo* (Lee et al., 2017). These MNV-CR6-infected cells accounted for only 0.0003% of the IECs, and were recently identified by Wilen et al. as specialized intestinal epithelial Tuft cells (Wilen et al., 2018). Considering the mainly IEC-restricted Nlrp6 expression pattern, it is puzzling how Nlrp6 could exert its antiviral effects on MNV loads from these very rare Tuft cells. Since MNV infection of Tuft cells was linked to secretion of IL-4 and IL-25 (Wilen et al., 2018), it will be interesting to see whether the Nlrp6 effects acting in IECs could potentially restrict intestinal MNV replication through modulating the expression of such type 2 cytokines thereby indirectly affecting intestinal immune cells.

5.2.3 DHX33-Nlrp3 Mediated Inflammasome Responses to Reovirus

Similar to the above Dhx9-Nlrp9b and Dhx15-Nlrp6 cooperative antiviral responses, also the DexD/H RNA helicase DHX33 was reported to relay viral RNA signaling through a cytosolic NLR. Indeed, Mitoma et al. provided evidence that human DHX33 recognizes reovirus dsRNA leading to NLRP3 inflammasome activation (Mitoma et al., 2013). The NLRP3 inflammasome is well known as an innate immune effector triggered by a broad range of stimuli including enteric bacterial pathogens such as *Vibrio cholerae* and *C. rodentium* (Song-Zhao et al., 2014; Toma et al., 2010). However, reovirus was the first viral intestinal trigger suggested to activate the NLRP3 inflammasome through it dsRNA. Upon transfection of reoviral dsRNA in human macrophages, DHX33 was proposed to bind the reovirus dsRNA via its helicase domain, after which the DEAD domain of DHX33 directly interacts with the NACHT domain of NLRP3 leading to activation of the inflammasome. Knock-down of DHX33 expression abrogated this reovirus dsRNA induced NLRP3 inflammasome activation (Mitoma et al., 2013). Similar Dhx33 knock-down experiments in murine DCs and fibroblasts later suggested that Dhx33 also initiates MAVS-mediated but RIG-I- and MDA-5-independent IFN responses upon reovirus infection (Liu et al., 2014), arguing that also in mice Dhx33 could have a role in responding to reovirus infections. In contrast, also classical RLR pathways were described in reovirus infected murine cells, as deleting both RIG-I and MDA-5 prevented the induction of type I IFNs after reovirus infection of conventional DCs and upon transfection of reovirus genomic RNA in mouse embryonic fibroblasts (Kato et al., 2008). Furthermore, adding to the complexity of comparing reovirus responses in different murine or human cell types, knockdown experiments in human 293T cells showed that only RIG-I but not MDA-5 was responsible for inducing IFN responses to this virus (Holm et al., 2007). Moreover, as mentioned before, also a DDX1/DDX21/DHX36 complex was suggested already as a receptor recognizing reoviral dsRNA in murine DCs via both TRIF and MAVS (Zhang et al., 2011a). Although these observations illustrate the many potential redundancies and different cell type specific responses to this virus (Table 1), it is clear that DHX33 can contribute at least in some cases to host responses to reoviral dsRNA.

Although the exact mechanisms how DHX33 links viral dsRNA to both IFN and inflammasome signaling, an independent study on the role of the 2′,5′-oligoadenylate synthetase (OAS)-RNase L signaling cascade during

influenza infection suggested an additional layer of complexity in this response (see Fig. 1) (Chakrabarti et al., 2015). Upon viral infection, OAS is one of the antiviral ISGs expressed. This enzyme mediates synthesis of 2′,5′-linked oligonucleotides, which activate the host RNase L to cleave viral dsRNA into smaller fragments. DHX33 knock-down experiments in human macrophages suggested that DHX33 recognizes such RNase L generated influenza dsRNA cleavage products, thereby promoting its interaction with both MAVS and Nlrp3 (Banerjee, 2016; Chakrabarti et al., 2015). Thus, although genetic *in vivo* confirmation is still needed, the above *in vitro* DHX33 knock-down studies suggest that this DexD/H helicase performs a dual role in viral dsRNA-induced IFN responses and Nlrp3 inflammasome activation.

5.3 Cytosolic Viral DNA Receptors Leading to IFN and Inflammasome Responses

Intracellular viral DNA can be detected by several host DNA sensors. A central theme upon cytoplasmic DNA sensing is cyclic GMP-AMP synthase (cGAS)-mediated production of cGAMP, which can bind and activate stimulator of interferon gene (STING) as an essential signaling intermediate in antiviral IFN responses (Tao et al., 2016). Triggering of STING-mediated IFN responses have been suggested for several upstream cytosolic DNA sensors, among which the DexD/H helicase DDX41 (Zhang et al., 2011b), the IFNγ-inducible protein (IFI)16 (Unterholzner et al., 2010), and DNA-dependent activator of IFN regulatory factors (DAI, encoded by *Zbp1*) (Takaoka et al., 2007). In addition, multiple other STING-dependent as well as -independent DNA sensors have been proposed and were reviewed elsewhere (Xia et al., 2016). However, since to our knowledge these IFN response inducing intracellular DNA sensors have not been implicated yet in the response to gastrointestinal viruses, these PRRs are beyond the scope of this review.

In contrast, AIM2—a cytosolic dsDNA sensor that does not induce an IFN response but instead leads to inflammasome activation (Fernandes-Alnemri et al., 2009; Hornung et al., 2009)—was implicated in the host response to mCMV (Rathinam et al., 2010), of which the human CMV counterpart causes gastroenteritis in immunocompromised patients (Weber et al., 1999). Although mCMV was administered intraperitoneally in this study and intestinal immune responses were not studied, AIM2- as

well as ASC-deficient mice showed impaired IL-18 responses consistent with defective inflammasome activation upon mCMV infection (Rathinam et al., 2010). Insufficient systemic IL-18 levels in these AIM2- and ASC-deficient mice correlated with a lack of NK cell dependent IFNγ production and higher viral loads (Rathinam et al., 2010). This observations thus illustrates the *in vivo* requirement for AIM2-mediated mCMV dsDNA sensing to mount strong innate and adaptive immune responses for viral control, suggesting that perhaps impaired AIM2 responses contribute to the sensitivity of immunocompromised individuals to hCMV-induced gastroenteritis.

6. CONCLUDING REMARKS

The above outlined viral nucleic acid recognition systems and signaling pathways that can be triggered by enteric viruses illustrate the complexity of the coordinated cellular response to the presence of a viral guest in its cytosol. While many of the cytosolic DexD/H helicases need further investigation on their individual role in responding to non-self nucleic acids, it is already clear that many of them will couple to other PRR systems in order to fine-tune and diversify their actions. The outlined examples of the Dhx9/Nlrp9b, Dhx15/Nlrp6 and the even more complex RNase L/Dhx33/Nlrp3 viral RNA signaling complexes (see Fig. 1) nicely illustrate this notion. In the described DexD/H helicase—NLR collaborations it is interesting to note that Dhx9 and Dhx33 engage NLRs to activate inflammasomes, while Dhx15 instructs an NLR to induce IFN responses. Although it is tempting to speculate that interaction with particular DexD/H helicases could modulate NLR functions, these differences could also simply reflect inherently different functions of the respective NLR family members. For instance, while Nlrp6 was relaying Dhx15 EMCV dsRNA sensing to IFN responses, inflammasome responses upon EMCV infection were in fact reported to depend on MDA-5 mediated sensing of its dsRNA leading to Nlrp3 activation (Poeck et al., 2010). This illustrates how different NLRs can induce either IFN or inflammasome responses to a single virus, although one needs to bear in mind that also cell type specific functions of the respective NLRs remain possible. Finally, it deserves mentioning that although we focused on the already described viral RNA/DNA initiated responses, several enteric viruses including SARS-CoV, Enterovirus 71 and Coxsackievirus B3 were reported to

activate the Nlrp3 inflammasome upon host recognition of a viral-derived protein (Chen et al., 2017; Lei et al., 2017; Li et al., 2017; Nieto-Torres et al., 2015; Wang et al., 2015a, 2017a). Upon integrating also these viral protein induced signaling cascades the picture will appear even more complex.

Due to the multicellular organization of the gastrointestinal tract and the diversity of its inhabitants, an intense cross talk between the bacterial, fungal and viral dimensions of the microbiome as well as with the host ultimately determines intestinal homeostasis. For instance, prior antibiotics treatment leading to depletion of the gut microbiota was shown to decrease rotavirus, reovirus as well as MNV infectivity in mice (Jones et al., 2014; Kuss et al., 2011; Uchiyama et al., 2014). In the latter case, histo-blood group antigens derived from enteric bacteria were shown to act as stimulatory agents allowing MNV as well as human NoV to infect B cells (Jones et al., 2014). In addition, the resident gut bacterial community prevents persistent MNV colonization in mice by suppressing type III IFN responses (Baldridge et al., 2015b). These interactions demonstrate how the bacterial gut microbiota can affect host immune responses to a viral trigger both directly and indirectly. Moreover, given the vast amount of intestinal bacteriophages that depend on the presence of their specific bacterial hosts, there is no doubt that future research in this area will reveal additional ways by which alterations in the gut microbiota composition determine the composition of the gut virome and hence also host anti-viral responses.

With regards to viral-host interactions, the described beneficial effects of MNV colonization in wild-type GF intestines versus its detrimental effects in autophagy-defective or IL-10$^{-/-}$ mice illustrate how host genetics influence intestinal immune responses to resident viruses (Basic et al., 2014; Cadwell et al., 2010; Kernbauer et al., 2014). The altered gut virome compositions observed in CD, UC and T1D patients (Norman et al., 2015; Zhao et al., 2017) predict that many more of such disbalanced virus-host interaction may contribute to disease development. Indeed, similar to how failures in discriminating self versus non-self nucleic acids can provoke autoimmune diseases (Kato and Fujita, 2015), perhaps diseases such IBD and T1D derive from sustained responses to nucleic acids from pathogenic viruses, or from inappropriate responses to viral nucleic acids derived from the endogenous gut virome. In this respect, it is interesting to note that T1D is associated with gastrointestinal enterovirus infections and that a polymorphism in the *IFIH1* gene encoding MDA-5 was shown to be associated with the severity of enterovirus 70 gastrointestinal infection (Cinek et al., 2012;

Oikarinen et al., 2012). Moreover, the exact same *IFIH1* polymorphism also associates to T1D development, and the gut virome composition is associated with T1D development (Smyth et al., 2006; Zhao et al., 2017). Therefore, although cause and consequence are always difficult to discriminate, it is tempting to speculate that there could indeed be link between altered viral dsRNA induced MDA-5 responses, enteric viral presence and T1D development. Adding to this suspicion, the success of fecal transfers in IBD patients has recently been associated with the gut virome composition (Conceição-Neto et al., 2017; Zuo et al., 2018). While at the moment they are mere correlations, there is no doubt that these observations will spark many future efforts investigating the response of the intestinal immune system to "commensal" and infectious viral nucleic acids.

ACKNOWLEDGMENTS

Research in the A.W. lab is supported by the Odysseus Grant G.0C49.13 N, and the research Grants 3G.0447.18 and 3G.0448.18 from the Fund for Scientific Research-Flanders. We apologize for the studies that could not be cited due to space restrictions.

REFERENCES

Aachoui, Y., Leaf, I.A., Hagar, J.A., Fontana, M.F., Campos, C.G., Zak, D.E., Tan, M.H., Cotter, P.A., Vance, R.E., Aderem, A., Miao, E.A., 2013. Caspase-11 protects against bacteria that escape the vacuole. Science 339, 975–978.

Aglietti, R.A., Estevez, A., Gupta, A., Ramirez, M.G., Liu, P.S., Kayagaki, N., Ciferri, C., Dixit, V.M., Dueber, E.C., 2016. GsdmD p30 elicited by caspase-11 during pyroptosis forms pores in membranes. Proc. Natl. Acad. Sci. U.S.A. 113, 7858–7863.

Andrejeva, J., Childs, K.S., Young, D.F., Carlos, T.S., Stock, N., Goodbourn, S., Randall, R.E., 2004. The V proteins of paramyxoviruses bind the IFN-inducible RNA helicase, mda-5, and inhibit its activation of the IFN-beta promoter. Proc. Natl. Acad. Sci. U.S.A. 101, 17264–17269.

Balachandran, S., Roberts, P.C., Kipperman, T., Bhalla, K.N., Compans, R.W., Archer, D.R., Barber, G.N., 2000. Alpha/beta interferons potentiate virus-induced apoptosis through activation of the FADD/caspase-8 death signaling pathway. J. Virol. 74, 1513–1523.

Baldridge, M.T., Nice, T.J., McCune, B.T., Yokoyama, C.C., Kambal, A., Wheadon, M., Diamond, M.S., Ivanova, Y., Artyomov, M., Virgin, H.W., 2015b. Commensal microbes and interferon-lambda determine persistence of enteric murine norovirus infection. Science 347, 266–269.

Baldridge, M.T., Turula, H., Wobus, C.E., 2016. Norovirus regulation by host and microbe. Trends Mol. Med. 22, 1047–1059.

Baldridge, M.T., Lee, S., Brown, J.J., McAllister, N., Urbanek, K., Dermody, T.S., Nice, T.J., Virgin, H.W., 2017. Expression of Ifnlr1 on intestinal epithelial cells is critical to the antiviral effects of IFN-lambda against norovirus and reovirus. J. Virol. 91, 02079–16.

Banerjee, S., 2016. RNase L and the NLRP3-inflammasome: an old merchant in a new trade. Cytokine Growth Factor Rev. 29, 63–70.

Barton, E.S., White, D.W., Cathelyn, J.S., Brett-McClellan, K.A., Engle, M., Diamond, M.S., Miller, V.L., Virgin, H.W.T., 2007. Herpesvirus latency confers symbiotic protection from bacterial infection. Nature 447, 326–329.

Bartsch, S.M., Lopman, B.A., Ozawa, S., Hall, A.J., Lee, B.Y., 2016. Global economic burden of norovirus gastroenteritis. PLoS One 11, e0151219.

Basic, M., Keubler, L.M., Buettner, M., Achard, M., Breves, G., Schroder, B., Smoczek, A., Jorns, A., Wedekind, D., Zschemisch, N.H., Gunther, C., Neumann, D., Lienenklaus, S., Weiss, S., Hornef, M.W., Mahler, M., Bleich, A., 2014. Norovirus triggered microbiota-driven mucosal inflammation in interleukin 10-deficient mice. Inflamm. Bowel Dis. 20, 431–443.

Blutt, S.E., Conner, M.E., 2013. The gastrointestinal frontier: IgA and viruses. Front. Immunol. 4, 402.

Blutt, S.E., Kirkwood, C.D., Parreño, V., Warfield, K.L., Ciarlet, M., Estes, M.K., Bok, K., Bishop, R.F., Conner, M.E., 2003. Rotavirus antigenaemia and viraemia: a common event? Lancet 362, 1445–1449.

Blutt, S.E., Miller, A.D., Salmon, S.L., Metzger, D.W., Conner, M.E., 2012. IgA is important for clearance and critical for protection from rotavirus infection. Mucosal Immunol. 5, 712–719.

Bok, K., Green, K.Y., 2012. Norovirus gastroenteritis in immunocompromised patients. N. Engl. J. Med. 367, 2126–2132.

Bouziat, R., Hinterleitner, R., Brown, J.J., Stencel-Baerenwald, J.E., Ikizler, M., Mayassi, T., Meisel, M., Kim, S.M., Discepolo, V., Pruijssers, A.J., Ernest, J.D., Iskarpatyoti, J.A., Costes, L.M., Lawrence, I., Palanski, B.A., Varma, M., Zurenski, M.A., Khomandiak, S., McAllister, N., Aravamudhan, P., Boehme, K.W., Hu, F., Samsom, J.N., Reinecker, H.C., Kupfer, S.S., Guandalini, S., Semrad, C.E., Abadie, V., Khosla, C., Barreiro, L.B., Xavier, R.J., Ng, A., Dermody, T.S., Jabri, B., 2017. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. Science 356, 44–50.

Broquet, A.H., Hirata, Y., McAllister, C.S., Kagnoff, M.F., 2011. RIG-I/MDA5/MAVS are required to signal a protective IFN response in rotavirus-infected intestinal epithelium. J. Immunol. 186, 1618–1626.

Cadwell, K., 2015. The virome in host health and disease. Immunity 42, 805–813.

Cadwell, K., Liu, J.Y., Brown, S.L., Miyoshi, H., Loh, J., Lennerz, J.K., Kishi, C., Kc, W., Carrero, J.A., Hunt, S., Stone, C.D., Brunt, E.M., Xavier, R.J., Sleckman, B.P., Li, E., Mizushima, N., Stappenbeck, T.S., Virgin, H.W.T., 2008. A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature 456, 259–263.

Cadwell, K., Patel, K.K., Maloney, N.S., Liu, T.C., Ng, A.C., Storer, C.E., Head, R.D., Xavier, R., Stappenbeck, T.S., Virgin, H.W., 2010. Virus-plus-susceptibility gene interaction determines Crohn's disease gene Atg16L1 phenotypes in intestine. Cell 141, 1135–1145.

Carding, S.R., Davis, N., Hoyles, L., 2017. Review article: the human intestinal virome in health and disease. Aliment. Pharmacol. Ther. 46, 800–815.

Casson, C.N., Copenhaver, A.M., Zwack, E.E., Nguyen, H.T., Strowig, T., Javdan, B., Bradley, W.P., Fung, T.C., Flavell, R.A., Brodsky, I.E., Shin, S., 2013. Caspase-11 activation in response to bacterial secretion systems that access the host cytosol. PLoS Pathog. 9, e1003400.

Chakrabarti, A., Banerjee, S., Franchi, L., Loo, Y.M., Gale Jr., M., Nunez, G., Silverman, R.H., 2015. RNase L activates the NLRP3 inflammasome during viral infections. Cell Host Microbe 17, 466–477.

Chen, W., Foo, S.S., Zaid, A., Teng, T.S., Herrero, L.J., Wolf, S., Tharmarajah, K., Vu, L.D., Van Vreden, C., Taylor, A., Freitas, J.R., Li, R.W., Woodruff, T.M.,

Gordon, R., Ojcius, D.M., Nakaya, H.I., Kanneganti, T.D., O'neill, L.A.J., Robertson, A.A.B., King, N.J., Suhrbier, A., Cooper, M.A., Ng, L.F.P., Mahalingam, S., 2017. Specific inhibition of NLRP3 in chikungunya disease reveals a role for inflammasomes in alphavirus-induced inflammation. Nat. Microbiol. 2, 1435–1445.

Chow, K.T., Gale Jr., M., Loo, Y.-M., 2018. RIG-I and other RNA sensors in antiviral immunity. Annu. Rev. Immunol. 36, 667–694.

Cinek, O., Tapia, G., Witso, E., Kramna, L., Holkova, K., Rasmussen, T., Stene, L.C., Ronningen, K.S., 2012. Enterovirus RNA in peripheral blood may be associated with the variants of rs1990760, a common type 1 diabetes associated polymorphism in IFIH1. PLoS One 7, e48409.

Conceição-Neto, N., Deboutte, W., Dierckx, T., Machiels, K., Wang, J., Yinda, K.C., Maes, P., Van Ranst, M., Joossens, M., Raes, J., Vermeire, S., Matthijnssens, J., 2017. Low eukaryotic viral richness is associated with faecal microbiota transplantation success in patients with UC. Gut 67, 1558–1559.

Cortez, V., Meliopoulos, V.A., Karlsson, E.A., Hargest, V., Johnson, C., Schultz-Cherry, S., 2017. Astrovirus biology and pathogenesis. Annu. Rev. Virol. 4, 327–348.

Cui, Y., Li, M., Walton, K.D., Sun, K., Hanover, J.A., Furth, P.A., Hennighausen, L., 2001. The Stat3/5 locus encodes novel endoplasmic reticulum and helicase-like proteins that are preferentially expressed in normal and neoplastic mammary tissue. Genomics 78, 129–134.

Dang, E.V., McDonald, J.G., Russell, D.W., Cyster, J.G., 2017. Oxysterol restraint of cholesterol synthesis prevents AIM2 inflammasome activation. Cell 171, 1057–1071.e11.

De Benedictis, P., Schultz-Cherry, S., Burnham, A., Cattoli, G., 2011. Astrovirus infections in humans and animals—molecular biology, genetic diversity, and interspecies transmissions. Infect. Genet. Evol. 11, 1529–1544.

Diebold, S.S., Massacrier, C., Akira, S., Paturel, C., Morel, Y., Reis E Sousa, C., 2006. Nucleic acid agonists for Toll-like receptor 7 are defined by the presence of uridine ribonucleotides. Eur. J. Immunol. 36, 3256–3267.

Dinarello, C.A., 2009. Immunological and inflammatory functions of the interleukin-1 family. Annu. Rev. Immunol. 27, 519–550.

Ding, Y., He, L., Zhang, Q., Huang, Z., Che, X., Hou, J., Wang, H., Shen, H., Qiu, L., Li, Z., Geng, J., Cai, J., Han, H., Li, X., Kang, W., Weng, D., Liang, P., Jiang, S., 2004. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J. Pathol. 203, 622–630.

Ding, J., Wang, K., Liu, W., She, Y., Sun, Q., Shi, J., Sun, H., Wang, D.C., Shao, F., 2016. Pore-forming activity and structural autoinhibition of the gasdermin family. Nature 535, 111–116.

Doerflinger, S.Y., Weichert, S., Koromyslova, A., Chan, M., Schwerk, C., Adam, R., Jennewein, S., Hansman, G.S., Schroten, H., 2017. Human norovirus evolution in a chronically infected host. mSphere 2, 00352–16.

Dubois, H., Wullaert, A., Lamkanfi, M., 2016. General strategies in inflammasome biology. Curr. Top. Microbiol. Immunol. 397, 1–22.

Dutilh, B.E., Cassman, N., McNair, K., Sanchez, S.E., Silva, G.G., Boling, L., Barr, J.J., Speth, D.R., Seguritan, V., Aziz, R.K., Felts, B., Dinsdale, E.A., Mokili, J.L., Edwards, R.A., 2014. A highly abundant bacteriophage discovered in the unknown sequences of human faecal metagenomes. Nat. Commun. 5, 4498.

Ettayebi, K., Crawford, S.E., Murakami, K., Broughman, J.R., Karandikar, U., Tenge, V.R., Neill, F.H., Blutt, S.E., Zeng, X.-L., Qu, L., Kou, B., Opekun, A.R., Burrin, D., Graham, D.Y., Ramani, S., Atmar, R.L., Estes, M.K., 2016. Replication of human noroviruses in stem cell-derived human enteroids. Science 353, 1387–1393.

Fernandes-Alnemri, T., Yu, J.W., Datta, P., Wu, J., Alnemri, E.S., 2009. AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. Nature 458, 509–513.
Fullam, A., Schroder, M., 2013. DExD/H-box RNA helicases as mediators of anti-viral innate immunity and essential host factors for viral replication. Biochim. Biophys. Acta 1829, 854–865.
Gilbert, J.A., Quinn, R.A., Debelius, J., Xu, Z.Z., Morton, J., Garg, N., Jansson, J.K., Dorrestein, P.C., Knight, R., 2016. Microbiome-wide association studies link dynamic microbial consortia to disease. Nature 535, 94–103.
Gopalakrishnan, V., Helmink, B.A., Spencer, C.N., Reuben, A., Wargo, J.A., 2018. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. Cancer Cell 33, 570–580.
Goubau, D., Schlee, M., Deddouche, S., Pruijssers, A.J., Zillinger, T., Goldeck, M., Schuberth, C., Van Der Veen, A.G., Fujimura, T., Rehwinkel, J., Iskarpatyoti, J.A., Barchet, W., Ludwig, J., Dermody, T.S., Hartmann, G., Reis, E.S.C., 2014. Antiviral immunity via Rig-I-mediated recognition of RNA bearing 5′-diphosphates. Nature 514, 372–375.
Goubau, D., Van Der Veen, A.G., Chakravarty, P., Lin, R., Rogers, N., Rehwinkel, J., Deddouche, S., Rosewell, I., Hiscott, J., Reis, E.S.C., 2015. Mouse superkiller-2-like helicase DDX60 is dispensable for type I IFN induction and immunity to multiple viruses. Eur. J. Immunol. 45, 3386–3403.
Graves, N.S., 2013. Acute gastroenteritis. Prim. Care 40, 727–741.
Gringhuis, S.I., Hertoghs, N., Kaptein, T.M., Zijlstra-Willems, E.M., Sarrami-Forooshani, R., Sprokholt, J.K., Van Teijlingen, N.H., Kootstra, N.A., Booiman, T., Van Dort, K.A., Ribeiro, C.M., Drewniak, A., Geijtenbeek, T.B., 2017. HIV-1 blocks the signaling adaptor MAVS to evade antiviral host defense after sensing of abortive HIV-1 RNA by the host helicase DDX3. Nat. Immunol. 18, 225–235.
Gu, L., Fullam, A., McCormack, N., Hohn, Y., Schroder, M., 2017. DDX3 directly regulates TRAF3 ubiquitination and acts as a scaffold to co-ordinate assembly of signalling complexes downstream from MAVS. Biochem. J. 474, 571–587.
Guan, Y., Peiris, J.S.M., Zheng, B., Poon, L.L.M., Chan, K.H., Zeng, F.Y., Chan, C.W.M., Chan, M.N., Chen, J.D., Chow, K.Y.C., Hon, C.C., Hui, K.H., Li, J., Li, V.Y.Y., Wang, Y., Leung, S.W., Yuen, K.Y., Leung, F.C., 2004. Molecular epidemiology of the novel coronavirus that causes severe acute respiratory syndrome. Lancet 363, 99–104.
Guarda, G., Braun, M., Staehli, F., Tardivel, A., Mattmann, C., Forster, I., Farlik, M., Decker, T., Du Pasquier, R.A., Romero, P., Tschopp, J., 2011. Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity 34, 213–223.
Haas, T., Metzger, J., Schmitz, F., Heit, A., Muller, T., Latz, E., Wagner, H., 2008. The DNA sugar backbone 2′ deoxyribose determines toll-like receptor 9 activation. Immunity 28, 315–323.
Holm, G.H., Zurney, J., Tumilasci, V., Leveille, S., Danthi, P., Hiscott, J., Sherry, B., Dermody, T.S., 2007. Retinoic acid-inducible gene-I and interferon-beta promoter stimulator-1 augment proapoptotic responses following mammalian reovirus infection via interferon regulatory factor-3. J. Biol. Chem. 282, 21953–21961.
Hon, K.L.E., Leung, C.W., Cheng, W.T.F., Chan, P.K.S., Chu, W.C.W., Kwan, Y.W., Li, A.M., Fong, N.C., Ng, P.C., Chiu, M.C., Li, C.K., Tam, J.S., Fok, T.F., 2003. Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet 361, 1701–1703.
Hornung, V., Ellegast, J., Kim, S., Brzozka, K., Jung, A., Kato, H., Poeck, H., Akira, S., Conzelmann, K.K., Schlee, M., Endres, S., Hartmann, G., 2006. 5′-Triphosphate RNA is the ligand for RIG-I. Science 314, 994–997.

Hornung, V., Ablasser, A., Charrel-Dennis, M., Bauernfeind, F., Horvath, G., Caffrey, D.R., Latz, E., Fitzgerald, K.A., 2009. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. Nature 458, 514–518.
Hui, D.S., Chan, M.C., Wu, A.K., Ng, P.C., 2004. Severe acute respiratory syndrome (SARS): epidemiology and clinical features. Postgrad. Med. J. 80, 373–381.
Ingle, H., Peterson, S.T., Baldridge, M.T., 2018. Distinct effects of type I and III interferons on enteric viruses. Viruses 10, 46.
Jiang, T.T., Shao, T.Y., Ang, W.X.G., Kinder, J.M., Turner, L.H., Pham, G., Whitt, J., Alenghat, T., Way, S.S., 2017. Commensal fungi recapitulate the protective benefits of intestinal bacteria. Cell Host Microbe 22, 809–816.e4.
Jones, M.K., Watanabe, M., Zhu, S., Graves, C.L., Keyes, L.R., Grau, K.R., Gonzalez-Hernandez, M.B., Iovine, N.M., Wobus, C.E., Vinje, J., Tibbetts, S.A., Wallet, S.M., Karst, S.M., 2014. Enteric bacteria promote human and mouse norovirus infection of B cells. Science 346, 755–759.
Kang, D.C., Gopalkrishnan, R.V., Wu, Q., Jankowsky, E., Pyle, A.M., Fisher, P.B., 2002. mda-5: an interferon-inducible putative RNA helicase with double-stranded RNA-dependent ATPase activity and melanoma growth-suppressive properties. Proc. Natl. Acad. Sci. U.S.A. 99, 637–642.
Kapikian, A.Z., Wyatt, R.G., Dolin, R., Thornhill, T.S., Kalica, A.R., Chanock, R.M., 1972. Visualization by immune electron microscopy of a 27-nm particle associated with acute infectious nonbacterial gastroenteritis. J. Virol. 10, 1075–1081.
Kapusinszky, B., Minor, P., Delwart, E., 2012. Nearly constant shedding of diverse enteric viruses by two healthy infants. J. Clin. Microbiol. 50, 3427–3434.
Karst, S.M.E.A., 2003. Stat1-dependent innate immunity to a Norwalk-like virus. Science 299, 1575–1578.
Katakura, K., Lee, J., Rachmilewitz, D., Li, G., Eckmann, L., Raz, E., 2005. Toll-like receptor 9-induced type I IFN protects mice from experimental colitis. J. Clin. Invest. 115, 695–702.
Kato, H., Fujita, T., 2015. RIG-I-like receptors and autoimmune diseases. Curr. Opin. Immunol. 37, 40–45.
Kato, H., Takeuchi, O., Sato, S., Yoneyama, M., Yamamoto, M., Matsui, K., Uematsu, S., Jung, A., Kawai, T., Ishii, K.J., Yamaguchi, O., Otsu, K., Tsujimura, T., Koh, C.S., Reis E Sousa, C., Matsuura, Y., Fujita, T., Akira, S., 2006. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. Nature 441, 101–105.
Kato, H., Takeuchi, O., Mikamo-Satoh, E., Hirai, R., Kawai, T., Matsushita, K., Hiiragi, A., Dermody, T.S., Fujita, T., Akira, S., 2008. Length-dependent recognition of double-stranded ribonucleic acids by retinoic acid-inducible gene-I and melanoma differentiation-associated gene 5. J. Exp. Med. 205, 1601–1610.
Kernbauer, E., Ding, Y., Cadwell, K., 2014. An enteric virus can replace the beneficial function of commensal bacteria. Nature 516, 94–98.
Kisseleva, T., Bhattacharya, S., Braunstein, J., Schindler, C.W., 2002. Signaling through the JAK/STAT pathway, recent advances and future challenges. Gene 285, 1–24.
Komuro, A., Horvath, C.M., 2006. RNA- and virus-independent inhibition of antiviral signaling by RNA helicase LGP2. J. Virol. 80, 12332–12342.
Kroneman, A., Vega, E., Vennema, H., Vinje, J., White, P.A., Hansman, G., Green, K., Martella, V., Katayama, K., Koopmans, M., 2013. Proposal for a unified norovirus nomenclature and genotyping. Arch. Virol. 158, 2059–2068.
Kuss, S.K., Best, G.T., Etheredge, C.A., Pruijssers, A.J., Frierson, J.M., Hooper, L.V., Dermody, T.S., Pfeiffer, J.K., 2011. Intestinal microbiota promote enteric virus replication and systemic pathogenesis. Science 334, 249–252.

Lamkanfi, M., Sarkar, A., Vande Walle, L., Vitari, A.C., Amer, A.O., Wewers, M.D., Tracey, K.J., Kanneganti, T.D., Dixit, V.M., 2010. Inflammasome-dependent release of the alarmin HMGB1 in endotoxemia. J. Immunol. 185, 4385–4392.
Lee, S., Baldridge, M.T., 2017. Interferon-lambda: a potent regulator of intestinal viral infections. Front. Immunol. 8, 749.
Lee, S., Wilen, C.B., Orvedahl, A., McCune, B.T., Kim, K.W., Orchard, R.C., Peterson, S.T., Nice, T.J., Baldridge, M.T., Virgin, H.W., 2017. Norovirus cell tropism is determined by combinatorial action of a viral non-structural protein and host cytokine. Cell Host Microbe 22, 449–459.
Lei, X., Zhang, Z., Xiao, X., Qi, J., He, B., Wang, J., 2017. Enterovirus 71 inhibits pyroptosis through cleavage of gasdermin D. J. Virol. 91, e01069–17.
Leonardi, I., Li, X., Semon, A., Li, D., Doron, I., Putzel, G., Bar, A., Prieto, D., Rescigno, M., McGovern, D.P.B., Pla, J., Iliev, I.D., 2018. CX3CR1^{+} mononuclear phagocytes control immunity to intestinal fungi. Science 359, 232–236.
Lester, S.N., Li, K., 2014. Toll-like receptors in antiviral innate immunity. J. Mol. Biol. 426, 1246–1264.
Li, L., Victoria, J., Kapoor, A., Blinkova, O., Wang, C., Babrzadeh, F., Mason, C.J., Pandey, P., Triki, H., Bahri, O., Oderinde, B.S., Baba, M.M., Bukbuk, D.N., Besser, J.M., Bartkus, J.M., Delwart, E.L., 2009. A novel picornavirus associated with gastroenteritis. J. Virol. 83, 12002–12006.
Li, Z., Wang, H., Chen, Y., Niu, J., Guo, Q., Leng, Q., Huang, Z., Deng, Z., Meng, G., 2017. Interleukin-18 protects mice from enterovirus 71 infection. Cytokine 96, 132–137.
Lim, E.S., Zhou, Y., Zhao, G., Bauer, I.K., Droit, L., Ndao, I.M., Warner, B.B., Tarr, P.I., Wang, D., Holtz, L.R., 2015. Early life dynamics of the human gut virome and bacterial microbiome in infants. Nat. Med. 21, 1228–1234.
Linder, P., 2006. Dead-box proteins: a family affair—active and passive players in RNP-remodeling. Nucleic Acids Res. 34, 4168–4180.
Liu, Y., Lu, N., Yuan, B., Weng, L., Wang, F., Liu, Y.J., Zhang, Z., 2014. The interaction between the helicase DHX33 and IPS-1 as a novel pathway to sense double-stranded RNA and RNA viruses in myeloid dendritic cells. Cell. Mol. Immunol. 11, 49–57.
Lopman, B.A., Reacher, M.H., Vipond, I.B., Sarangi, J., Brown, D.W.G., 2004. Clinical manifestation of norovirus gastroenteritis in health care settings. Clin. Infect. Dis. 39, 318–324.
Lopman, B.A., Steele, D., Kirkwood, C.D., Parashar, U.D., 2016. The vast and varied global burden of norovirus: prospects for prevention and control. PLoS Med. 13, e1001999.
Lupfer, C., Kanneganti, T.-D., 2013. The expanding role of NLRs in antiviral immunity. Immunol. Rev. 255, 13–24.
Man, S.M., Karki, R., Kanneganti, T.D., 2017. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol. Rev. 277, 61–75.
Manrique, P., Bolduc, B., Walk, S.T., Van Der Oost, J., De Vos, W.M., Young, M.J., 2016. Healthy human gut phageome. Proc. Natl. Acad. Sci. U.S.A. 113, 10400–10405.
Marvin, S.A., Huerta, C.T., Sharp, B., Freiden, P., Cline, T.D., Schultz-Cherry, S., 2016. Type I interferon response limits astrovirus replication and protects against increased barrier permeability in vitro and in vivo. J. Virol. 90, 1988–1996.
Mattei, F., Schiavoni, G., Tough, D.F., 2010. Regulation of immune cell homeostasis by type I interferons. Cytokine Growth Factor Rev. 21, 227–236.
McCartney, S.A., Thackray, L.B., Gitlin, L., Gilfillan, S., Virgin, H.W., Colonna, M., 2008. MDA-5 recognition of a murine norovirus. PLoS Pathog. 4, e1000108.
Mcclarren, R.L., Lynch, B., Nyayapati, N., 2011. Acute infectious diarrhea. Prim. Care 38, 539–564. ix.

Minot, S., Sinha, R., Chen, J., Li, H., Keilbaugh, S.A., Wu, G.D., Lewis, J.D., Bushman, F.D., 2011. The human gut virome: inter-individual variation and dynamic response to diet. Genome Res. 21, 1616–1625.
Minot, S., Bryson, A., Chehoud, C., Wu, G.D., Lewis, J.D., Bushman, F.D., 2013. Rapid evolution of the human gut virome. Proc. Natl. Acad. Sci. U.S.A. 110, 12450–12455.
Mitoma, H., Hanabuchi, S., Kim, T., Bao, M., Zhang, Z., Sugimoto, N., Liu, Y.J., 2013. The DHX33 RNA helicase senses cytosolic RNA and activates the NLRP3 inflammasome. Immunity 39, 123–135.
Monroe, S.S., Jiang, B., Stine, S.E., Koopmans, M., Glass, R.I., 1993. Subgenomic RNA sequence of human astrovirus supports classification of Astroviridae as a new family of RNA viruses. J. Virol. 67, 3611–3614.
Mosallanejad, K., Sekine, Y., Ishikura-Kinoshita, S., Kumagai, K., Nagano, T., Matsuzawa, A., Takeda, K., Naguro, I., Ichijo, H., 2014. The DEAH-box RNA helicase DHX15 activates NF-kappaB and MAPK signaling downstream of MAVS during antiviral responses. Sci. Signal. 7, ra40.
Nash, A.K., Auchtung, T.A., Wong, M.C., Smith, D.P., Gesell, J.R., Ross, M.C., Stewart, C.J., Metcalf, G.A., Muzny, D.M., Gibbs, R.A., Ajami, N.J., Petrosino, J.F., 2017. The gut mycobiome of the Human Microbiome Project healthy cohort. Microbiome 5, 153.
Nieto-Torres, J.L., Verdia-Baguena, C., Jimenez-Guardeno, J.M., Regla-Nava, J.A., Castano-Rodriguez, C., Fernandez-Delgado, R., Torres, J., Aguilella, V.M., Enjuanes, L., 2015. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. Virology 485, 330–339.
Norman, J.M., Handley, S.A., Baldridge, M.T., Droit, L., Liu, C.Y., Keller, B.C., Kambal, A., Monaco, C.L., Zhao, G., Fleshner, P., Stappenbeck, T.S., McGovern, D.P., Keshavarzian, A., Mutlu, E.A., Sauk, J., Gevers, D., Xavier, R.J., Wang, D., Parkes, M., Virgin, H.W., 2015. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell 160, 447–460.
Oikarinen, M., Tauriainen, S., Oikarinen, S., Honkanen, T., Collin, P., Rantala, I., MÄki, M., Kaukinen, K., HyÖty, H., 2012. Type 1 diabetes is associated with enterovirus infection in gut mucosa. Diabetes 61, 687–691.
Onyeagocha, C., Hossain, M.S., Kumar, A., Jones, R.M., Roback, J., Gewirtz, A.T., 2009. Latent cytomegalovirus infection exacerbates experimental colitis. Am. J. Pathol. 175, 2034–2042.
Oshiumi, H., Miyashita, M., Okamoto, M., Morioka, Y., Okabe, M., Matsumoto, M., Seya, T., 2015. DDX60 is involved in RIG-I-dependent and independent antiviral responses, and its function is attenuated by virus-induced EGFR activation. Cell Rep. 11, 1193–1207.
Poeck, H., Bscheider, M., Gross, O., Finger, K., Roth, S., Rebsamen, M., Hannesschlager, N., Schlee, M., Rothenfusser, S., Barchet, W., Kato, H., Akira, S., Inoue, S., Endres, S., Peschel, C., Hartmann, G., Hornung, V., Ruland, J., 2010. Recognition of RNA virus by RIG-I results in activation of CARD9 and inflammasome signaling for interleukin 1 beta production. Nat. Immunol. 11, 63–69.
Pott, J., Stockinger, S., Torow, N., Smoczek, A., Lindner, C., Mcinerney, G., Backhed, F., Baumann, U., Pabst, O., Bleich, A., Hornef, M.W., 2012. Age-dependent TLR3 expression of the intestinal epithelium contributes to rotavirus susceptibility. PLoS Pathog. 8, e1002670.
Rathinam, V.A., Jiang, Z., Waggoner, S.N., Sharma, S., Cole, L.E., Waggoner, L., Vanaja, S.K., Monks, B.G., Ganesan, S., Latz, E., Hornung, V., Vogel, S.N., Szomolanyi-Tsuda, E., Fitzgerald, K.A., 2010. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. Nat. Immunol. 11, 395–402.

Rathinam, V.A., Vanaja, S.K., Waggoner, L., Sokolovska, A., Becker, C., Stuart, L.M., Leong, J.M., Fitzgerald, K.A., 2012. TRIF licenses caspase-11-dependent NLRP3 inflammasome activation by gram-negative bacteria. Cell 150, 606–619.

Rauch, I., Hainzl, E., Rosebrock, F., Heider, S., Schwab, C., Berry, D., Stoiber, D., Wagner, M., Schleper, C., Loy, A., Urich, T., Muller, M., Strobl, B., Kenner, L., Decker, T., 2014. Type I interferons have opposing effects during the emergence and recovery phases of colitis. Eur. J. Immunol. 44, 2749–2760.

Reboldi, A., Dang, E.V., McDonald, J.G., Liang, G., Russell, D.W., Cyster, J.G., 2014. Inflammation. 25-hydroxycholesterol suppresses interleukin-1-driven inflammation downstream of type I interferon. Science 345, 679–684.

Reikine, S., Nguyen, J.B., Modis, Y., 2014. Pattern recognition and signaling mechanisms of RIG-I and MDA5. Front. Immunol. 5, 342.

Reyes, A., Haynes, M., Hanson, N., Angly, F.E., Heath, A.C., Rohwer, F., Gordon, J.I., 2010. Viruses in the faecal microbiota of monozygotic twins and their mothers. Nature 466, 334–338.

Reyes, A., Blanton, L.V., Cao, S., Zhao, G., Manary, M., Trehan, I., Smith, M.I., Wang, D., Virgin, H.W., Rohwer, F., Gordon, J.I., 2015. Gut DNA viromes of Malawian twins discordant for severe acute malnutrition. Proc. Natl. Acad. Sci. U.S.A. 112, 11941–11946.

Rivero-Calle, I., Gomez-Rial, J., Martinon-Torres, F., 2016. Systemic features of rotavirus infection. J. Infect. 72 (Suppl), S98–S105.

Rota, P.A., Oberste, M.S., Monroe, S.S., Nix, W.A., Campagnoli, R., Icenogle, J.P., PeÑaranda, S., Bankamp, B., Maher, K., Chen, M.-H., Tong, S., Tamin, A., Lowe, L., Frace, M., Derisi, J.L., Chen, Q., Wang, D., Erdman, D.D., Peret, T.C.T., Burns, C., Ksiazek, T.G., Rollin, P.E., Sanchez, A., Liffick, S., Holloway, B., Limor, J., Mccaustland, K., Olsen-Rasmussen, M., Fouchier, R., GÜnther, S., Osterhaus, A.D.M.E., Drosten, C., Pallansch, M.A., Anderson, L.J., Bellini, W.J., 2003. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science 300, 1394–1399.

Rutz, M., Metzger, J., Gellert, T., Luppa, P., Lipford, G.B., Wagner, H., Bauer, S., 2004. Toll-like receptor 9 binds single-stranded CpG-DNA in a sequence- and pH-dependent manner. Eur. J. Immunol. 34, 2541–2550.

Ryan, J.L., Shen, Y.J., Morgan, D.R., Thorne, L.B., Kenney, S.C., Dominguez, R.L., Gulley, M.L., 2012. Epstein-Barr virus infection is common in inflamed gastrointestinal mucosa. Dig. Dis. Sci. 57, 1887–1898.

Sainathan, S.K., Bishnupuri, K.S., Aden, K., Luo, Q., Houchen, C.W., Anant, S., Dieckgraefe, B.K., 2012. Toll-like receptor-7 ligand Imiquimod induces type I interferon and antimicrobial peptides to ameliorate dextran sodium sulfate-induced acute colitis. Inflamm. Bowel Dis. 18, 955–967.

Schlee, M., Hartmann, G., 2016. Discriminating self from non-self in nucleic acid sensing. Nat. Rev. Immunol. 16, 566–580.

Seth, R.B., Sun, L., Ea, C.K., Chen, Z.J., 2005. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF 3. Cell 122, 669–682.

Shortland, A., Chettle, J., Archer, J., Wood, K., Bailey, D., Goodfellow, I., Blacklaws, B.A., Heeney, J.L., 2014. Pathology caused by persistent murine norovirus infection. J. Gen. Virol. 95, 413–422.

Smyth, D.J., Cooper, J.D., Bailey, R., Field, S., Burren, O., Smink, L.J., Guja, C., Ionescu-Tirgoviste, C., Widmer, B., Dunger, D.B., Savage, D.A., Walker, N.M., Clayton, D.G., Todd, J.A., 2006. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. Nat. Genet. 38, 617.

Song-Zhao, G.X., Srinivasan, N., Pott, J., Baban, D., Frankel, G., Maloy, K.J., 2014. Nlrp3 activation in the intestinal epithelium protects against a mucosal pathogen. Mucosal Immunol. 7, 763–774.

Tai, J.H., Williams, J.V., Edwards, K.M., Wright, P.F., Crowe, J.J.E., Dermody, T.S., 2005. Prevalence of reovirus-specific antibodies in young children in Nashville, Tennessee. J. Infect. Dis. 191, 1221–1224.

Takaoka, A., Wang, Z., Choi, M.K., Yanai, H., Negishi, H., Ban, T., Lu, Y., Miyagishi, M., Kodama, T., Honda, K., Ohba, Y., Taniguchi, T., 2007. DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. Nature 448, 501–505.

Tao, J., Zhou, X., Jiang, Z., 2016. cGAS-cGAMP-STING: the three musketeers of cytosolic DNA sensing and signaling. IUBMB Life 68, 858–870.

Tapparel, C., Siegrist, F., Petty, T.J., Kaiser, L., 2013. Picornavirus and enterovirus diversity with associated human diseases. Infect. Genet. Evol. 14, 282–293.

Tate, J.E., Rheingans, R.D., O'Reilly, C.E., Obonyo, B., Burton, D.C., Tornheim, J.A., Adazu, K., Jaron, P., Ochieng, B., Kerin, T., Calhoun, L., Hamel, M., Laserson, K., Breiman, R.F., Feikin, D.R., Mintz, E.D., Widdowson, M.A., 2009. Rotavirus disease burden and impact and cost-effectiveness of a rotavirus vaccination program in Kenya. J. Infect. Dis. 200 (Suppl. 1), S76–S84.

Tate, J.E., Burton, A.H., Boschi-Pinto, C., Steele, A.D., Duque, J., Parashar, U.D., 2012. 2008 Estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect. Dis. 12, 136–141.

Tate, J.E., Burton, A.H., Boschi-Pinto, C., Parashar, U.D., World Health Organization-Coordinated Global Rotavirus Surveillance, N, 2016. Global, regional, and national estimates of rotavirus mortality in children <5 years of age, 2000–2013. Clin. Infect. Dis. 62 (Suppl. 2), S96–S105.

Teijaro, J.R., 2016. Pleiotropic roles of type 1 interferons in antiviral immune responses. In: ALT, F.W. (Ed.), Advances in Immunology. Academic Press. Chapter 5.

Toma, C., Higa, N., Koizumi, Y., Nakasone, N., Ogura, Y., McCoy, A.J., Franchi, L., Uematsu, S., Sagara, J., Taniguchi, S., Tsutsui, H., Akira, S., Tschopp, J., Nunez, G., Suzuki, T., 2010. Pathogenic vibrio activate NLRP3 inflammasome via cytotoxins and Tlr/nucleotide-binding oligomerization domain-mediated NF-kappa B signaling. J. Immunol. 184, 5287–5297.

Tsolenyanu, E., Seheri, M., Dagnra, A., Djadou, E., Tigossou, S., Nyaga, M., Adjeoda, E., Armah, G., Mwenda, J.M., Atakouma, Y., 2014. Surveillance for rotavirus gastroenteritis in children less than 5 years of age in Togo. Pediatr. Infect. Dis. J. 33 (Suppl. 1), S14–S18.

Uchiyama, R., Chassaing, B., Zhang, B., Gewirtz, A.T., 2014. Antibiotic treatment suppresses rotavirus infection and enhances specific humoral immunity. J. Infect. Dis. 210, 171–182.

Unterholzner, L., Keating, S.E., Baran, M., Horan, K.A., Jensen, S.B., Sharma, S., Sirois, C.M., Jin, T., Latz, E., Xiao, T.S., Fitzgerald, K.A., Paludan, S.R., Bowie, A.G., 2010. IFI16 is an innate immune sensor for intracellular DNA. Nat. Immunol. 11, 997–1004.

Venkataraman, T., Valdes, M., Elsby, R., Kakuta, S., Caceres, G., Saijo, S., Iwakura, Y., Barber, G.N., 2007. Loss of DExD/H box RNA helicase LGP2 manifests disparate antiviral responses. J. Immunol. 178, 6444–6455.

Vijay-Kumar, M., Wu, H., Aitken, J., Kolachala, V.L., Neish, A.S., Sitaraman, S.V., Gewirtz, A.T., 2007. Activation of toll-like receptor 3 protects against DSS-induced acute colitis. Inflamm. Bowel Dis. 13, 856–864.

Virgin, H.W., 2014. The virome in mammalian physiology and disease. Cell 157, 142–150.

Wang, J.T., Chang, S.C., 2004. Severe acute respiratory syndrome. Curr. Opin. Infect. Dis. 17, 143–148.
Wang, H., Lei, X., Xiao, X., Yang, C., Lu, W., Huang, Z., Leng, Q., Jin, Q., HE, B., Meng, G., Wang, J., 2015a. Reciprocal regulation between enterovirus 71 and the NLRP3 inflammasome. Cell Rep. 12, 42–48.
Wang, P., Zhu, S., Yang, L., Cui, S., Pan, W., Jackson, R., Zheng, Y., Rongvaux, A., Sun, Q., Yang, G., Gao, S., Lin, R., You, F., Flavell, R., Fikrig, E., 2015b. Nlrp6 regulates intestinal antiviral innate immunity. Science 350, 826–830.
Wang, W., Xiao, F., Wan, P., Pan, P., Zhang, Y., Liu, F., Wu, K., Liu, Y., Wu, J., 2017a. EV71 3D protein binds with NLRP3 and enhances the assembly of inflammasome complex. PLoS Pathog. 13, e1006123.
Wang, W., Xu, L., SU, J., Peppelenbosch, M.P., Pan, Q., 2017b. Transcriptional regulation of antiviral interferon-stimulated genes. Trends Microbiol. 25, 573–584.
Weber, R., Ledergerber, B., Zbinden, R., et al., 1999. Enteric infections and diarrhea in human immunodeficiency virus-infected persons: prospective community-based cohort study. Arch. Intern. Med. 159, 1473–1480.
Wilen, C.B., Lee, S., Hsieh, L.L., Orchard, R.C., Desai, C., Hykes, B.L., Mcallaster, M.R., Balce, D.R., Feehley, T., Brestoff, J.R., Hickey, C.A., Yokoyama, C.C., Wang, Y.-T., Macduff, D.A., Kreamalmayer, D., Howitt, M.R., Neil, J.A., Cadwell, K., Allen, P.M., Handley, S.A., Van Lookeren Campagne, M., Baldridge, M.T., Virgin, H.W., 2018. Tropism for tuft cells determines immune promotion of norovirus pathogenesis. Science 360, 204–208.
Wobus, C.E., Karst, S.M., Thackray, L.B., Chang, K.O., Sosnovtsev, S.V., Belliot, G., Krug, A., Mackenzie, J.M., Green, K.Y., Virgin, H.W., 2004. Replication of Norovirus in cell culture reveals a tropism for dendritic cells and macrophages. PLoS Biol. 2, e432.
World Health Organization, 2017. Diarrhoeal Disease. [Online]. Accessed 2 May 2017.
Xia, P., Wang, S., Gao, P., Gao, G., Fan, Z., 2016. DNA sensor cGAS-mediated immune recognition. Protein Cell 7, 777–791.
Yang, J.Y., Kim, M.S., Kim, E., Cheon, J.H., Lee, Y.S., Kim, Y., Lee, S.H., Seo, S.U., Shin, S.H., Choi, S.S., Kim, B., Chang, S.Y., Ko, H.J., Bae, J.W., Kweon, M.N., 2016. Enteric viruses ameliorate gut inflammation via Toll-like receptor 3 and Toll-like receptor 7-mediated interferon-beta production. Immunity 44, 889–900.
Yoneyama, M., Kikuchi, M., Natsukawa, T., Shinobu, N., Imaizumi, T., Miyagishi, M., Taira, K., Akira, S., Fujita, T., 2004. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat. Immunol. 5, 730–737.
Yoneyama, M., Kikuchi, M., Matsumoto, K., Imaizumi, T., Miyagishi, M., Taira, K., Foy, E., Loo, Y.M., Gale, M., Akira, S., Yonehara, S., Kato, A., Fujita, T., 2005. Shared and unique functions of the DexD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. J. Immunol. 175, 2851–2858.
Yoneyama, M., Onomoto, K., Jogi, M., Akaboshi, T., Fujita, T., 2015. Viral RNA detection by RIG-I-like receptors. Curr. Opin. Immunol. 32, 48–53.
Yuen, K.Y., Woo, P.C., Liang, R.H., Chiu, E.K., Chen, F.F., Wong, S.S., Lau, Y.L., Ha, S.Y., Peiris, J.S., Siau, H., Chan, T.K., 1998. Clinical significance of alimentary tract microbes in bone marrow transplant recipients. Diagn. Microbiol. Infect. Dis. 30, 75–81.
Yutin, N., Makarova, K.S., Gussow, A.B., Krupovic, M., Segall, A., Edwards, R.A., Koonin, E.V., 2018. Discovery of an expansive bacteriophage family that includes the most abundant viruses from the human gut. Nat. Microbiol. 3, 38–46.
Zanoni, I., Granucci, F., Broggi, A., 2017. Interferon (IFN)-lambda takes the helm: immunomodulatory roles of type III IFNs. Front. Immunol. 8, 1661.

Zhang, Z., Kim, T., Bao, M., Facchinetti, V., Jung, S.Y., Ghaffari, A.A., Qin, J., Cheng, G., Liu, Y.J., 2011a. DDX1, DDX21, and DHX36 helicases form a complex with the adaptor molecule TRIF to sense dsRNA in dendritic cells. Immunity 34, 866–878.

Zhang, Z., Yuan, B., Bao, M., Lu, N., Kim, T., Liu, Y.J., 2011b. The helicase DDX41 senses intracellular DNA mediated by the adaptor STING in dendritic cells. Nat. Immunol. 12, 959–965.

Zhang, Z., Yuan, B., Lu, N., Facchinetti, V., Liu, Y.J., 2011c. DHX9 pairs with IPS-1 to sense double-stranded RNA in myeloid dendritic cells. J. Immunol. 187, 4501–4508.

Zhang, B., Chassaing, B., Shi, Z., Uchiyama, R., Zhang, Z., Denning, T.L., Crawford, S.E., Pruijssers, A.J., Iskarpatyoti, J.A., Estes, M.K., Dermody, T.S., Ouyang, W., Williams, I.R., Vijay-Kumar, M., Gewirtz, A.T., 2014. Viral infection. Prevention and cure of rotavirus infection via TLR5/Nlrc4-mediated production of Il-22 and IL-18. Science 346, 861–865.

Zhang, Y., Chen, X., Gueydan, C., Han, J., 2017. Plasma membrane changes during programmed cell deaths. Cell Res. 28, 9–21.

Zhao, G., Vatanen, T., Droit, L., Park, A., Kostic, A.D., Poon, T.W., Vlamakis, H., Siljander, H., Härkönen, T., Hämäläinen, A.-M., Peet, A., Tillmann, V., Ilonen, J., Wang, D., Knip, M., Xavier, R.J., Virgin, H.W., 2017. Intestinal virome changes precede autoimmunity in type I diabetes-susceptible children. Proc. Natl. Acad. Sci. U.S.A. 114, E6166–E6175.

Zhou, R., Wei, H., Sun, R., Tian, Z., 2007. Recognition of double-stranded RNA by TLR3 induces severe small intestinal injury in mice. J. Immunol. 178, 4548–4556.

Zhu, S., Ding, S., Wang, P., Wei, Z., Pan, W., Palm, N.W., Yang, Y., Yu, H., Li, H.B., Wang, G., Lei, X., de Zoete, M.R., Zhao, J., Zheng, Y., Chen, H., Zhao, Y., Jurado, K.A., Feng, N., Shan, L., Kluger, Y., Lu, J., Abraham, C., Fikrig, E., Greenberg, H.B., Flavell, R.A., 2017. Nlrp9b inflammasome restricts rotavirus infection in intestinal epithelial cells. Nature 546, 667–670.

Zuo, T., Wong, S.H., Lam, K., Lui, R., Cheung, K., Tang, W., Ching, J.Y.L., Chan, P.K.S., Chan, M.C.W., Wu, J.C.Y., Chan, F.K.L., Yu, J., Sung, J.J.Y., Ng, S.C., 2018. Bacteriophage transfer during faecal microbiota transplantation in *Clostridium difficile* infection is associated with treatment outcome. Gut 67, 634–643.

FURTHER READING

World Health Organization, 2009. Meeting of the immunization Strategic Advisory Group of Experts. April 2009—conclusions and recommendations. Wkly. Epidemiol. Rec. 84, 220–236.

Baldridge, M.T., Nice, T.J., McCune, B.T., Yokoyama, C.C., Kambal, A., Wheadon, M., Diamond, M.S., Ivanova, Y., Artyomov, M., Virgin, H.W., 2015a. Commensal microbes and interferon-lambda determine persistence of enteric murine norovirus infection. Science 347, 266–269.