The influence of microbiota-derived metabolites on viral infections

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Abstract

Intestinal microbiota have profound effects on viral infections locally and systemically. While they can directly influence enteric virus infections, there is also an increasing appreciation for the role of microbiota-derived metabolites in regulating virus infections. Because metabolites diffuse across the intestinal epithelium and enter circulation, they can influence host response to pathogens at extraintestinal sites. In this review, we summarize the effects of three types of microbiota-derived metabolites on virus infections. While short-chain fatty acids serve to regulate the extent of inflammation associated with viral infections, the flavonoid desaminotyrosine and bile acids generally regulate interferon responses. A common theme that emerges is that microbiota-derived metabolites can have proviral and antiviral effects depending on the virus in question. Understanding the molecular mechanisms by which microbiota-derived metabolites impact viral infections and the highly conditional nature of these responses should pave the way to developing novel rational antivirals.

Introduction

Gut microbiota are a vast population of microorganisms residing in the gastrointestinal tract that play a central role in maintaining metabolic and immune homeostasis. In recent years, it has become widely appreciated that these microbial communities enhance enteric viral infections through a multitude of direct and indirect mechanisms [1]. For example, bacterial surface glycans bound by an enteric virus can promote virion stabilization [2], host cell attachment and receptor binding [2,3], immune skewing in a proviral manner [4,5], and viral recombination [6]. Yet recent work in the murine norovirus (MNV) model system reveals a more nuanced situation where gut microbiota have opposing regional effects on an enteric virus, inhibiting proximal gut infection while simultaneously promoting distal gut infection [7•]. Moreover, gut microbiota also influence viral infections at extraintestinal sites where they generally have inhibitory effects instead of promoting ones [8-11]. Accumulating evidence indicates that inhibition of viral infections at local and distal sites results from microbial metabolite-mediated signaling events in contrast to the stimulatory effects of

microbial constituents (e.g. LPS). The focus of this review will be the mechanisms by which microbiota-derived metabolites modulate antiviral immune responses *in vivo*. Understanding the molecular details of these events could pave the way to developing novel rational antivirals.

Gut microbiota-derived metabolites

It is well-established that gut microbiota shape the development and function of the host immune system. For example, host recognition of bacterial ligands via pattern recognition receptors contributes to immune homeostasis [12]. In addition, microbiota-derived metabolites continuously interact with metabolite-specific receptors and regulate immune responses [13]. Microbial metabolites segregate into three broad categories: (1) metabolites produced from dietary components, (2) metabolites derived from the host and modified by microbes, and (3) metabolites produced *de novo* by gut bacteria [13]. Metabolites from all three categories are produced in the gut lumen and can diffuse across the intestinal epithelium and enter circulation to access extraintestinal tissues throughout the body. Expression of metabolite-specific receptors is generally broad, enabling these small molecules to shape activities in many cell populations. Herein we will summarize the effects of microbiota-derived metabolites on viral infections as we currently understand them. These interactions are likely complex and nuanced for several reasons. First, their production is influenced by the environment of the gut lumen with a cyclical relationship between metabolite levels and environmental conditions. Second, metabolite-mediated signaling events serve to fine-tune activating and inhibitory immune responses shaped by the local microenvironment. This review is intended to serve as a framework for dissecting these nuanced interactions as they pertain to influencing viral infections as we anticipate many new examples will be uncovered in the future. The conditional nature of these responses could result in seemingly contradictory findings across research labs so it will be important for the field to recognize and report key variables regulating these effects. We will focus on the most well-characterized examples of microbiota-derived metabolites that regulate viral infections, specifically short-chain fatty acids (SCFAs), flavonoids, and bile acids.

Short-chain fatty acids

One category of dietary-derived metabolites with established effects on viral infections are SCFAs like acetate, butyrate, and propionate which are produced during bacterial fermentation of undigested carbohydrates. They are generally considered to be anti-inflammatory due to their ability to inhibit histone deacetylases (HDACs) and their activation of G protein-coupled receptors GPR41/FFAR3 and GPR43/FFAR2 [14,15]. SCFAs can regulate viruses *in vitro*. For example, the HDAC inhibitory activity of butyrate has been linked to reactivation of latent HIV-1 and Epstein-Barr virus (EBV) in cell culture models [16,17]. Butyrate has also recently been shown to suppress expression of IFN-stimulated genes (ISGs) *in vitro*, leading to increased susceptibility of cells to infection by a range of IFN-sensitive viruses [18•] whereas SCFAs had no effect on SARS-CoV-2 replication in cultured intestinal biopsies [19].

In terms of *in vivo* effects of SCFAs on virus infections, there is evidence that they can be both antiviral and proviral depending on the virus in question. For example, butyrate provides protection against influenza virus disease in mice by reducing the infiltration of neutrophils into the airways where they contribute to tissue damage [20] (Figure 1): Reduced neutrophil recruitment was linked to butyrate-mediated activation of FFAR3 on bone marrow cells, leading to the differentiation of monocytes predisposed to become alternatively activated macrophages (AAMs) in the lung instead of inflammatory macrophages. AAMs produce less neutrophil chemoattractant CXCL1 than inflammatory macrophages. Butyrate treatment also enhanced the CD8 T cell response to influenza virus, specifically by accelerating their metabolism and effector function [20]. These functional changes in CD8 T cells were partially FFAR3-dependent although the underlying mechanism is unclear.

While butyrate and a high fiber diet served to blunt the inflammatory response during influenza virus infection of mice and thereby reduce disease, they exacerbated the inflammatory arthropathy caused by chikungunya virus (CHIKV) infection in a mouse model [21] (Figure 1): Both a high-fiber diet and butyrate supplementation of drinking water resulted in increased foot swelling in CHIKV-infected mice compared to controls in spite of comparable virus titers. This phenotype correlated with an increase in edema and neutrophil inflammation at the peak of arthritis although mechanisms underlying these pathologies were not determined. RNAseq-based analysis of mice fed a high fiber diet uncovered a reduced signature of resolution phase macrophages which function to prevent further neutrophil infiltration and initiate tissue repair, suggesting impaired resolution of inflammation under high-fiber conditions.

These two *in vivo* studies highlight the conditional nature of microbial metabolite-mediated responses: While the SCFA butyrate dampens inflammatory disease during influenza virus infection, it exacerbates immunopathologic levels of inflammation during CHIKV infection. They also underscore the immunoregulatory activity of metabolites that can only be dissected using *in vivo* model systems.

Flavonoids

Plant-derived polyphenol compounds, or flavonoids, can be processed by commensal bacteria to a variety of bioactive metabolites. One flavonoid degradation product, DAT, has been shown to augment the type I IFN response in the lung and protect mice from influenza virus infection [22]. Extending earlier work demonstrating that gut microbiota provide protection from severe influenza virus infections in mice [9,10], Steed *et al.* demonstrated that oral DAT supplementation was sufficient to protect antibiotic-treated mice from severe influenza virus disease [22]. This protection was dependent on type I IFN signaling since no protection was observed in DAT-supplemented *Ifnar*$^{-/-}$ mice. As reported for butyrate-mediated protection of mice from influenza virus disease, DAT treatment reduced tissue damage and apoptosis in the lungs of infected mice although no differences in virus titers were detected. Two lines of evidence suggest that DAT priming of the IFN response before viral infection is important for its protective effect in this model system: First, DAT treatment increased expression of multiple ISGs in the lungs even in

the absence of exogenous viral infection. Second, DAT pretreatment for one week before viral infection was sufficient to protect animals while posttreatment for two days after viral infection actually exacerbated viral disease. Clodronate treatment of mice abolished DAT-mediated protection to influenza virus disease, suggesting that DAT primes phagocytes to confer this protection. DAT-mediated enhancement of ISG expression was maintained in *Mavs*^{−/−} bone marrow-derived macrophages (BMDMs) but was not observed in *Stat1*^{−/−} BMDMs, demonstrating a role in type I IFN signaling in contrast to induction.

Bile acids

The mammalian host converts cholesterol to the primary bile acids chenodeoxycholic acid (CDCA) and cholic acid (CA) in the liver where they are conjugated with taurine or glycine. Primary conjugated bile acids are stored in the gall bladder until ingestion of a meal, at which time they are released into the gut lumen to aid in digestion. Here they encounter commensal bacteria which deconjugate and dehydroxylate them to the secondary bile acids lithocholic acid (LCA) and deoxycholic acid (DCA) and various other modified forms. Approximately 95% of bile acids are reabsorbed in the distal ileum and transported back to the liver via enterohepatic circulation while only 5% are shed in the feces. Numerous bile acid receptors (BARs) sense bile acid pools and control a tight feedback mechanism to regulate the amounts of various bile acids within the liver and the intestine. These include nuclear receptors like farnesoid X receptor (FXR) and surface-expressed receptors like the G protein-coupled receptor TGR5, each of which interacts differently with various bile acids [23].

In addition to regulating bile acid metabolism, BAR signaling can have profound effects on immune responses [23,24] including those elicited by viral infections (Figure 2). Bile acids have long been recognized to have proviral activity. For example, it was first reported in 1994 that high serum bile acid concentrations correlated with resistance of hepatitis C virus (HCV) patients to IFN-α treatment [25]. Bile acid treatment of HCV replicon-bearing cells increased viral replication and decreased the antiviral activity of IFN in a FXR-dependent manner, suggesting that bile acid engagement of FXR negatively regulates the IFN signaling pathway [26]. Likewise, bile acids promote replication of porcine enteric calicivirus *in vitro*, a proviral effect that was associated with reduced STAT-1 phosphorylation [27]. Bile acids also promote replication of human noroviruses and sapoviruses *in vitro* [28,29]. A recent study proposed a model for bile acid-mediated enhancement of human norovirus infection *in vitro* in which bile acids increase endosomal/lysosomal acidification, activating the sphingomyelinase ASM which in turn converts sphingomyelin to ceramide in host membranes; ceramide-rich microdomains could result in clustering of a surface protein that serves as the human norovirus receptor [28]. For murine noroviruses, VP1 capsid protein binding to bile salts induces a major conformational change in the virion that both increases receptor binding and infectivity [30,31] as well as blocking antibody recognition [32•]. Overall, bile acids can promote viral infections in a variety of ways ranging from suppressing antiviral immune responses to directly enhancing viral binding to host receptors.

In apparent contradiction to the studies described above, bile acids can also trigger antiviral responses. For example, bile acids reduce replication of murine cytomegalovirus (MCMV)

in primary hepatocytes [33]. Interestingly, this phenotype displayed cell type specificity since MCMV replication in murine fibroblasts was unaffected by bile acid treatment. Similar to the proviral effects of bile acids, their antiviral activity has been linked to engagement of specific BARs: Bile acids and FXR agonists can reduce rotavirus replication *in vitro* and virus shedding *in vivo* [34]. Furthermore, *Fxr*$^{-/-}$ mice infected with lymphocytic choriomeningitis virus (LCMV) had higher viral loads and reduced type I IFN gene expression in their livers compared to wild-type controls [35]. TGR5 has also been linked to promotion of type I IFN responses. Xiong *et al.* discovered that TGR5 is an ISG since its expression was enhanced in response to viral infection and exogenous IFN-β treatment in a STAT1-dependent manner [36]. Moreover, TGR5 overexpression in macrophages inhibited replication of a variety of viruses including vesicular stomatitis virus (VSV), New-castle disease virus, and herpes simplex virus 1 (HSV-1) while bile acid or TGR5 agonist treatment potentiated IFN expression and blocked viral replication [36,37]. Mechanistically, two studies have reported that TGR5 promotes IRF3 phosphorylation although Xiong *et al.* discovered a key role for AKT in TGR5-dependent IRF3 activation [36] while Hu *et al.* discovered a key role for the nonreceptor tyrosine kinase SRC and downstream phosphorylation of multiple signaling components in the IFN induction pathway, including RIG-1, MAVS, STING, TBK1, and IRF3 [37]. The *in vivo* relevance of TGR5-mediated IFN enhancement has been demonstrated by reduced serum IFN-β and IFN-α levels, increased viral loads and reduced survival in *Tgr5*$^{-/-}$ mice infected with EMCV, VSV, or HSV-1 compared to wild-type controls [36,37]. Furthermore, injection of wild-type, but not *Tgr5*$^{-/-}$, mice with the bile acid CDCA was sufficient to increase serum IFN-β, reduce viral loads, and increase survival following HSV-1 infection [37]. Collectively, these studies reveal a key role for the BAR TGR5 in potentiating type I IFN responses during viral infections.

A general theme emerges from this collective body of work that bile acid engagement of BARs can regulate type I IFN responses to either promote or inhibit a range of enteric and hepatic viruses. Several recent studies provide additional context to the relationship between bile acids, IFN, and viral infections. First, Grau *et al.* discovered that bile acids can promote type III IFN expression and that this response is necessary for the control of murine norovirus infection the proximal small intestine [7•]: Antibiotic treatment (which dramatically reduces levels of unconjugated and secondary bile acids in the intestine due to the depletion of bile acid-biotransforming bacteria) and type III IFN deficiency both resulted in significantly increased viral titers in the proximal small intestine of infected mice. Control of viral infection could be rescued by reconstitution of antibiotic-treated mice with *Clostridium scindens*, a bacteria with potent bile-acid biotransforming activity, or by oral supplementation with bile acids. Importantly, bile acid supplementation failed to reduce virus titers in *Ifnlr1*$^{-/-}$ mice, providing a direct link between bile acids and type III IFN (unpublished results). Furthermore, bile acid treatment of cells enhanced type III IFN expression in response to poly(I:C) or murine norovirus infection [7•]. Although the mechanism by which bile acids prime type III IFN remains unresolved, type I and type III induction and signaling pathways are largely overlapping so it would not be surprising if bile acid regulation occurs in a similar manner. Second, Winkler *et al.* revealed that bile acids can mediate effects on viruses outside of the intestine and liver by demonstrating

bile acid-mediated inhibition of circulating Chikungunya virus (CHIKV) [38•]: Similar to findings of Grau *et al.* for murine norovirus, CHIKV titers were higher in antibiotic-treated mice than in controls and this phenotype could be rescued by colonization with *C. scindens* or oral bile acid supplementation. Reduced viral titers in the serum of *C. scindens*-colonized or bile acid-supplemented mice was associated with increased type I IFN levels and was dependent on STAT-1 and MyD88. Third, highlighting the conditional nature of the effect of microbiota-derived metabolites on viral infections, Grau *et al.* revealed that bile acids play regionally opposing roles during murine norovirus infection of the intestinal tract [7•]: While bile acids prime type III IFN to inhibit infection of the proximal small intestine, they instead enhance murine norovirus infection of distal regions of the gut likely by promoting viral binding to the host receptor CD300lf [30]. It will be fascinating to unravel the regional nature of these interactions.

Conclusions

Over the past decade it has been clearly established that intestinal microbiota have profound effects on viral infections, both locally along the intestinal tract and systemically. While commensal bacteria in the gut lumen can directly influence enteric virus infections in a multitude of ways, there is also an increasing appreciation for the role of microbiota-derived metabolites in regulating virus infections. Because metabolites diffuse across the intestinal epithelium and enter circulation, they can influence host response to pathogens at extraintestinal sites. In this review, we summarize the effects of three types of microbiota-derived metabolites — short-chain fatty acids (SCFAs), flavonoids, and bile acids — on virus infections. While SCFAs serve to regulate the extent of inflammation associated with viral infections, the flavonoid desaminotyrosine and bile acids commonly regulate interferon responses. A common theme that emerges is that individual microbiota-derived metabolites can have proviral and antiviral effects depending on the model system and virus in question. Understanding the molecular mechanisms by which microbiota-derived metabolites impact viral infections and the highly conditional nature of these responses should pave the way to developing novel rational antivirals.

Acknowledgement

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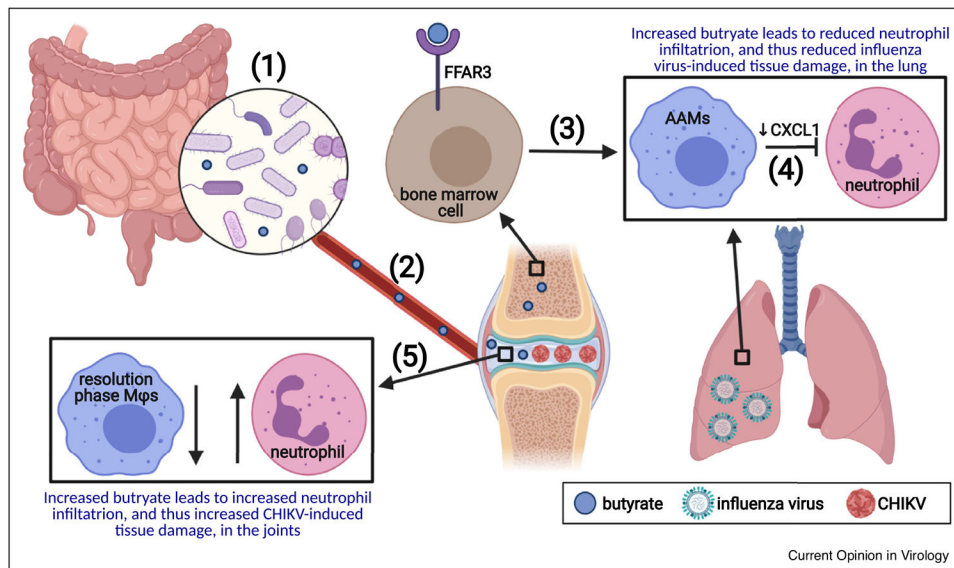
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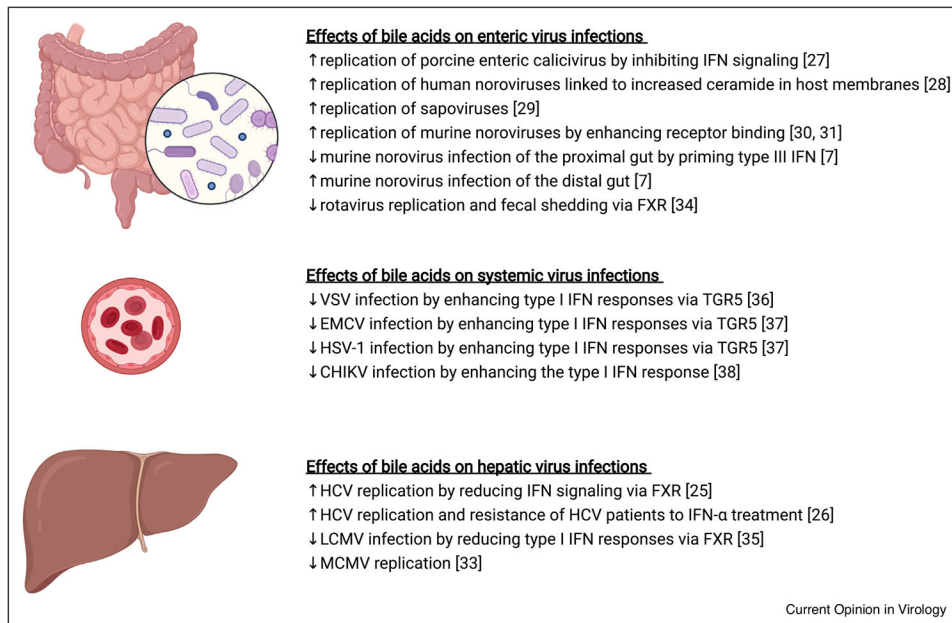
Figure 1.

The SCFA butyrate has opposing effects on inflammatory disease associated with influenza virus infection of the lung and CHIKV infection of joints.

(1) Gut microbes produce SCFAs including butyrate through fermentation of undigested carbohydrates in the intestinal lumen. (2) SCFAs enter circulation, reaching a wide range of peripheral tissues including bone and joints. (3) Butyrate promotes differentiation of bone marrow cells into monocytes predisposed to become tissue repair AAMs in a FFAR3-dependent process. (4) During influenza virus infection of the lung, mice fed a high fiber diet or supplemented with butyrate contain a higher proportion of AAMs in the lung macrophage population, resulting in reduced levels of the neutrophil chemoattractant CXCL1 and hence reduced tissue damage resulting from neutrophilia. (5) Conversely, mice fed a high fiber diet or supplemented with butyrate develop more severe inflammatory arthropathy during CHIKV infection, correlating with a reduced signature of resolution phase macrophages (Mfs) which function to prevent neutrophil infiltration and initiate tissue repair. Created with BioRender.com.

Effects of bile acids on enteric virus infections
↑replication of porcine enteric calicivirus by inhibiting IFN signaling [27]
↑replication of human noroviruses linked to increased ceramide in host membranes [28]
↑replication of sapoviruses [29]
↑replication of murine noroviruses by enhancing receptor binding [30, 31]
↓murine norovirus infection of the proximal gut by priming type III IFN [7]
↑murine norovirus infection of the distal gut [7]
↓rotavirus replication and fecal shedding via FXR [34]

Effects of bile acids on systemic virus infections
↓VSV infection by enhancing type I IFN responses via TGR5 [36]
↓EMCV infection by enhancing type I IFN responses via TGR5 [37]
↓HSV-1 infection by enhancing type I IFN responses via TGR5 [37]
↓CHIKV infection by enhancing the type I IFN response [38]

Effects of bile acids on hepatic virus infections
↑HCV replication by reducing IFN signaling via FXR [25]
↑HCV replication and resistance of HCV patients to IFN-α treatment [26]
↓LCMV infection by reducing type I IFN responses via FXR [35]
↓MCMV replication [33]

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Figure 2.
Bile acids have opposing effects on virus infections in local and systemic sites. Numerous studies have reported a role for bile acids in promoting and inhibiting viral infections, as summarized here. In general, bile acids regulate viral infections by either promoting or inhibiting IFN responses. Yet additional mechanisms are emerging, including enhancement of virus-receptor binding (e.g. murine norovirus) and increased ceramide-rich microdomains in host membranes which could cause clustering of the viral receptor (e.g. human norovirus). Created with BioRender.com.