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Review

Candida albicans-enteric viral interactions—The prostaglandin E_2 connection and host immune responses

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SUMMARY

The human microbiome comprises trillions of microorganisms residing within different mucosal cavities and across the body surface. The gut microbiota modulates host susceptibility to viral infections in several ways, and microbial interkingdom interactions increase viral infectivity within the gut. *Candida albicans*, a frequently encountered fungal species in the gut, produces highly structured biofilms and eicosanoids such as prostaglandin E_2 (PGE_2), which aid in viral protection and replication. These biofilms encompass viruses and provide a shield from antiviral drugs or the immune system. PGE_2 is a key modulator of active inflammation with the potential to regulate interferon signaling upon microbial invasion or viral infections. In this review, we raise the perspective of gut interkingdom interactions involving *C. albicans* and enteric viruses, with a special focus on biofilms, PGE_2, and viral replication. Ultimately, we discuss the possible implications of *C. albicans*-enteric virus associations on host immune responses, particularly the interferon signaling pathway.

INTRODUCTION

Natural ecological systems contain highly diverse microbial communities.[1,2] The human body is such a system that comprises trillions of microorganisms residing within different mucosal cavities, including the vaginal mucosa, the oral mucosa, and the gastrointestinal tract (GIT) or the surface of the body.[3] The human microbiome, a collective term describing microorganisms (eukaryotes, bacteria, viruses, and archaea) inhabiting the human body, plays a significant role in health, disease, and overall homeostasis.[4,5] The GIT is by far the largest organ sheltering the human microbiome, harboring approximately 100 trillion microorganisms.[6–8] These microbes express more than 3 million genes capable of processing thousands of metabolites that may aid in systemic metabolism or modulate human host functions.[9,10] Some of these functions include the interaction with intestinal cells, production of essential micronutrients (e.g., vitamin K and B complexes), training of the immune system, prevention of pathogen colonization, enhancement of pathogen clearance, and protection from epithelial injury.[11–16] The majority of these microbes are concentrated in the colon and are comprised predominantly of highly diverse bacterial communities, which are complemented by archaea, eukaryotic microorganisms, and viruses (including bacteriophages) (Figure 1).[12]

The complexity and diversity of these microbial communities in the human gut, and their proximity within the same niche, allow for polymicrobial interactions across microbial domains. These interdomain interactions may be by direct or indirect contact involving physical or chemical components, resulting in microbial interdependence, antagonism, or competition. Importantly, these interactions can ultimately influence disease persistence and severity or even complicate therapy.[17–19] Most data involving gut microbial interactions focus on bacterial interactions with other domains, possibly due to their predominance in the gut and their propensity to cause severe disease. Gut bacteria have been reported to aid other gut colonizers in several ways, including evasion of host immune responses and modulation of cytokine signaling as well as attachment and replication of enteric viruses.[20–26] However, interactions between nonbacterial gut community members, especially between the mycobiome and virome, are largely lacking.

Candida albicans and enteric viruses are human pathogens that are of global health importance, causing high morbidity and mortality both in children and adults.[27–30] In this review, we provide a brief overview of the gut microbiome and diseases associated with its perturbation. Then, we discuss the different

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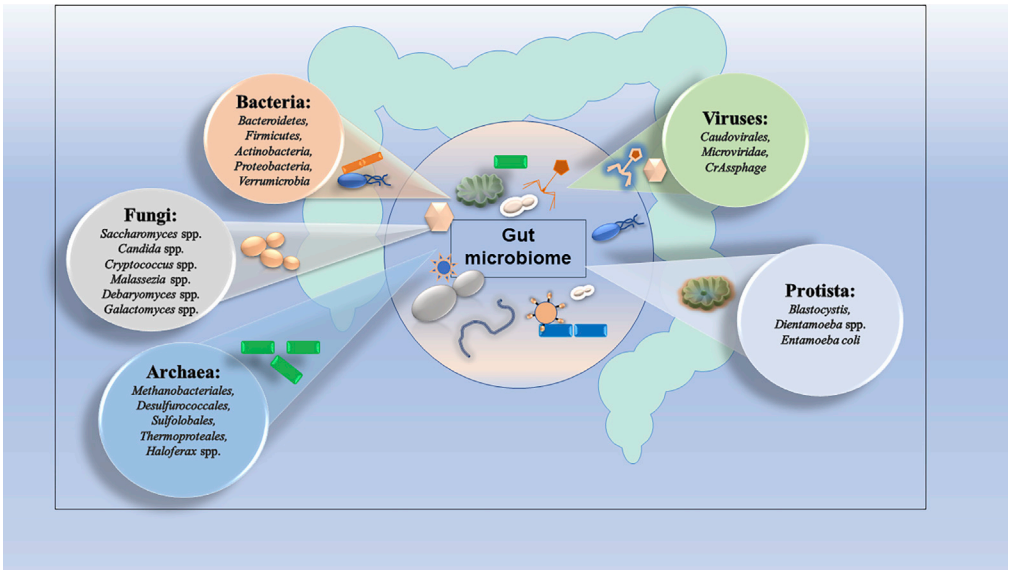

Figure 1. The taxonomic groups and species of the human gut microbiome

The gut microbiome is dominated by bacteria, while the main eukaryotic microorganisms are fungal species, especially *Candida* spp. The known number of viral types is likely to increase as gut virome studies increase.

determinants that influence *C. albicans'* gut commensalism and competitive fitness as a pathobiont. Also, we briefly highlight the gut virome, its diversity, and the role it plays in health and disease. Importantly, we discuss the reports on *C. albicans*-virus interactions and the limitations of the current literature, particularly regarding clinically relevant enteric pathogens. Then lastly, we provide the possible implications of *C. albicans*-enteric virus associations on host immune response, particularly the interferon (IFN) signaling pathway.

OVERVIEW OF THE GUT MICROBIOME

Generally, in healthy individuals, the intestinal bacterial species of the gut microbiome belong to the phyla *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrumicrobia*, with *Bacteroidetes* and *Firmicutes* being predominant.[11,31–34] However, intrapersonal gut bacteriome phyla distribution changes throughout a lifetime due to lifestyle and exposure to chemicals or antibiotics.[6,35,36] Alterations in bacterial communities (dysbiosis) due to environmental factors are associated with irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and colorectal cancer.[37,38] In contrast, the gut archaea are dominated by methanogenic organisms, mainly isolates from the *Methanobacteriales*, *Desulfurococcales*, *Sulfolobales*, *Thermoproteales*, *Nitrososphaerales*, and the halophilic archaeon, *Haloferax* massiliensis.[39–41] Methane-producing archaea have been associated with chronic constipation and IBD, as well as subgingival dental plaque and induction of the proinflammatory release of cytokines from monocytic cells.[42–47]

The gut microbiome also contains various Eukarya. Historically, protists and helminths within the gut microbiome have been regarded as parasites and as such were presumed to have pathogenic capabilities.[48] However, emerging evidence shows that gut protists, such as *Blastocystis,* are frequently encountered in healthy individuals.[49–52] In addition, the protist *Dientamoeba fragilis* shows prevalence in healthy individuals—although it may frequently be associated with illness.[48,53,54] Interestingly, helminths have been reported to downregulate host immune responses in the gut and modulate the response toward other pathogens or antigens, including allergens or vaccines.[55,56] For instance, helminths are associated with downregulation of Th1 immunological responses, which is known to be essential in regulating bacterial, viral, or protozoal infections.[57,58]

Saccharomyces, *Malassezia,* and *Candida* have been reported as the most abundant fungal genera in the gut of healthy individuals, although *Saccharomyces* spp. and *Malassezia* spp. can also be associated with food and skin colonization, respectively.[59,60] Interestingly, other fungal genera such as *Cryptococcus*, *Aspergillus*, *Trichosporon*, *Cladosporium*, *Debaryomyces*, and *Galactomyces* have been

identified, but the general composition of gut mycobiome becomes unstable over time relative to bacteria spp.[61–63] Of note, *Candida* spp. are generally regarded as GIT colonizers, and of these, *C. albicans* is the most frequently encountered species.[59] Yeast colonizers have been demonstrated to colonize the human gut as early as the first month after birth.[64,65]

The neonatal gut is also colonized by viruses within the first month.[66] The human gut virome comprises approximately 10^8–10^9 viral particles and is generally dominated by bacteriophages that appear as early as two days after birth.[66–68] The identified portion of the gut virome suggests that bacteriophages are from the dsDNA order, *Caudovirales* (tailed phages), or the ssDNA *Microviridae* (spherical) family, with CrAssphages (part of tailed phages) representing 90% of the gut virome of ~50% of individuals.[69] Metagenomic sequencing data of eukaryotic viruses in the gut indicate that the commonly encountered RNA viruses belong to the families *Caliciviridae*, *Sedoreoviridae*, and *Picornaviridae*.[70] The eukaryotic DNA viruses encountered belong to the families of *Parvoviridae* and *Anelloviridae*.[66,71] Plant viruses, such as Virgaviridae, are also often detected in infant fecal samples.[68,72]

CANDIDA ALBICANS: GUT COMMENSALISM AND COMPETITIVE FITNESS

It is estimated that the *Candida* genus consists of approximately 150 species, which mainly exist as unicellular yeasts but may demonstrate other morphological types, such as pseudohyphae or true hyphae.[73–76] A limited number of *Candida* spp. have been implicated in causing human disease, especially in immunocompromized individuals.[77–79] *Candida albicans* gut colonization begins as early as the first month after birth (10%–15% of infants), and at 4 months, up to 50% of infants are colonized.[64,65,80–82] Importantly, gut colonization and fitness of *C. albicans* are influenced by crucial parameters, including its genetic determinants, interaction with the gut microbiome, metabolic adaptation, and host-defense mechanisms (Figure 2A).[83] Several genetic determinants have been implicated in *C. albicans* gut commensalism and competitive fitness.[83] For instance, *SFU1*, a transcription factor regulating iron-uptake genes, has been shown to promote colonization and persistence in the gut (Figure 2A-i).[84] Another transcription factor, *WOR1*, an epigenetic regulator of white-to-opaque switching in *C. albicans*, induces the distinct GUT (gastrointestinally induced transition) cell type that is functionally adapted for GIT colonization and persistence.[85,86] In addition, a mutant deficient in *UME6*, a gene encoding for a master regulator (a Zn(II) 2Cys6 transcription factor) of filamentation (i.e. hyphal formation), exhibited enhanced colonization fitness relative to wild-type strains, while a mutant overexpressing *UME6* resulted in defective commensalism.[87] *Candida albicans* hyphal formation or filamentation is associated with virulence and tissue damage via active penetration or induced endocytosis.[81,88,89] Recently, Shao and colleagues showed that *UME6* primes protective Th17 immunity during *C. albicans* colonization to protect against invasive candidiasis.[90] Furthermore, mutant strains lacking genes *FLO8* and *EFG1*, which encode for transcription factors that regulate hyphal formation, virulence, and biofilm formation,[91,92] similarly outcompeted the wild-type strain in competitive fitness for gut colonization (Figure 2A-i).[86,93–95] Overall, these results show that *C. albicans* can prefer commensalism and gut adaptation within the host over a pathogenic lifestyle, and the yeast morphology is the preferred morphotype for gut colonization, while the hyphal morphology shows a detrimental effect on gut colonization and is mainly associated with tissue penetration and damage.[96,97] *Candida albicans* genetic determinants involved in gut colonization are not confined to transcription factors. Expression of *HOG1* (Figure 2A-i) (a gene encoding for a MAP kinase necessary for stress response and environmental adaptation) was shown to be essential for prolonged colonization of *C. albicans* in the mammalian gut.[92]

The switch of *C. albicans* to the GUT morphotype promotes a long-term metabolic adaptation to the gut environment as GUT cells express genes that support growth in the digestive tract compared to other morphotypes (e.g., white or opaque cells) (Figure 2A-ii).[86,92] These may include downregulation of genes essential for glucose acquisition and high-affinity iron-uptake genes or upregulation of genes critical in acquisition of N-acetylglucosamine and short-chain fatty acids. The metabolic plasticity of *C. albicans* is also critical for the successful colonization of the mammalian gut. This nutritional flexibility (Figure 2A-iii) enables the organism to utilize alternative carbon sources such as lactate, citrate, or glycerol in the mammalian gut where the preferred carbon source, glucose, is limited.[98] Intriguingly, the absence of ubiquitination sites in enzymes catalyzing alternative carbon source assimilation in *C. albicans* renders the organism catabolite-inactivation negative, as such, alternative carbon sources are still utilized even in the presence of glucose.[98,99] Mutant strains incapable of utilizing alternative carbon sources show less competitive fitness in mammalian gut colonization compared to wild-type cells.[98,100] In addition, *C. albicans* utilizes

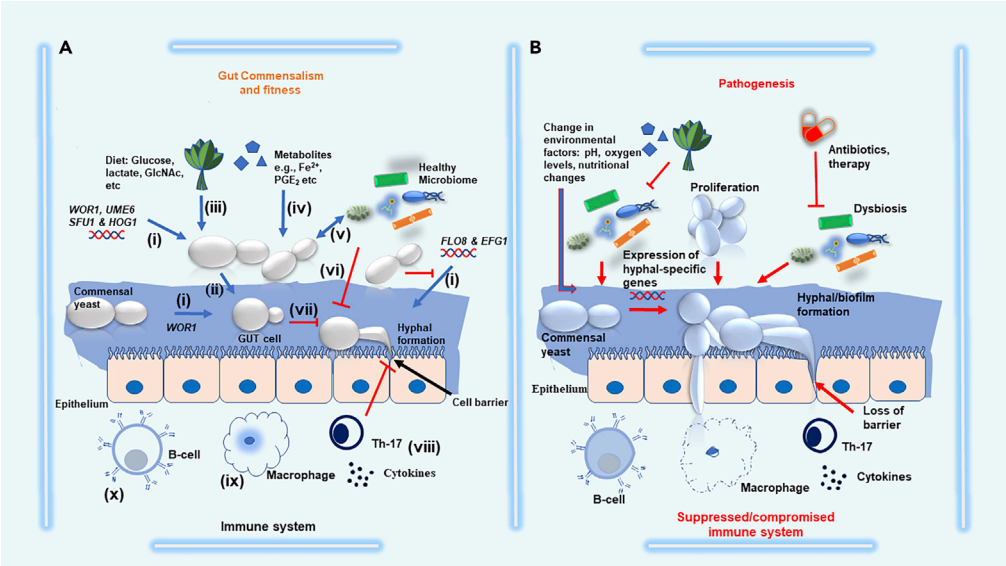

Figure 2. *Candida albicans* commensalism vs pathogenic state in the gut

(A) Gut commensalism and fitness (i, ii) *Candida albicans* genetic determinants regulating gut colonization. The commensal types adapted for GIT colonization (yeast-form or GUT morphotype) are maintained by regulating the expression of genes such as *WOR1* and *UME1* or downregulation of hyphal-specific genes (*FLO8* and *EFG1*).[86,93,94] (iii) A sufficient and nutritious diet provides the required nutrients like lactate for persistent colonization.[164] (iv) Host-derived metabolites like iron and PGE_2 promote gut fitness and survival, especially in nutrient-limited GIT.[102,103] (v, vi) A healthy microbiome mediates *C. albicans* colonization and increases resistance to the pathogenic state through stimulation of antifungal metabolites.[105] (vii) GUT morphotype provides adaptation for gut colonization, and no evidence of hyphal switch has been documented.[86] (viii - x) Host immunity and commensal yeast act as determinants in *C. albicans* gut colonization. Commensal *C. albicans* primes Th-17 $CD4^+$ T cells and IL-17 cytokines, and these protect against invasive candidiasis.[111] Gut resident mononuclear phagocytes (CX3CR1+) modulate fungal burden by activating antifungal receptors and antifungal responses.[112] Intestinal *C. albicans* can induce antifungal immunoglobulin-G (IgG) to protect against disseminated candidiasis.[114]

(B) Pathogenesis A shift or alterations in these determinants (genetic, host metabolite, host immune system, and gut microbiome) that regulate *C. albicans'* gut commensalism may result in a pathogenic state involving a switch to hyphal and biofilm formation that is destructive to the gut epithelium. These include hyphal penetration to the epithelial barrier and translocation to other sites to cause systemic candidiasis (Reviewed in [83,164]).

N-acetylglucosamine (GlcNAc), a structural component of the bacterial cell wall, as a signal molecule for nutrient availability and to enhance the efficiency of nutrient utilization by activating GlcNAc-induced apoptosis in nutrient-limiting niches.[101] This nutritional suicide and adaptive behavior have been postulated to be essential in *C. albicans'* gut colonization and competitive advantage.[101] Importantly, *C. albicans'* iron regulation and acquisition determine colonization fitness and adaptation in the iron-rich gut (Figure 2A-iv). The double mutant strain for the iron permease gene (Δ/Δ*ftr1*) was shown to be outcompeted by wild-type cells in gut competitive fitness, demonstrating that iron acquisition is essential and promotes gut colonization.[102] Comparably, repression of high-affinity iron-acquisition genes promotes *C. albicans* gut colonization, while their upregulation is critical in iron-limited environments such as the bloodstream.[84] As such, *C. albicans* alternates iron-uptake mechanisms depending on iron availability in order to support gut colonization and fitness. Of note, *C. albicans* utilizes host-derived arachidonic acid (AA) to synthesize prostaglandin E_2 (PGE_2), a lipid inflammatory mediator initially associated with virulence, for colonization and competitive fitness in the gut (Figure 2A-iv).[103]

There is emerging evidence of healthy gut microbiota interactions and regulation of *C. albicans* commensalism in the gut (Figure 2A-v, vi). An intact and healthy microbiota prevents *C. albicans* colonization in a murine model, while microbial dysbiosis through antibiotic use increases susceptibility to yeast colonization.[104,105] In addition, antibiotic use in patients receiving hematopoietic stem cell transplantation or in ICU shows enriched intestinal *C. albicans* and *Candida* spp.[106,107] Also, recent reports have shown that bacterial gut colonizers can produce metabolites, such as short-chain fatty acids, that have direct antifungal

effects on the pathological morphologies (biofilm development, hyphae, and germ tube formation) of *C. albicans*.[108,109] Similarly, activation of epithelial-derived antimicrobial peptides (e.g., β-defensins) by gut microbiota facilitates resistance against *C. albicans* colonization.[104] Conversely, the presence of commensal *C. albicans* in the gut promotes the recolonization of bacterial populations, in particular, *Enterococcus faecalis* and *Bacteroidetes* following antibiotic treatment.[110]

Host immunity and commensal yeast morphological type can act as determinants in *C. albicans'* gut colonization (Figure 2-viii - x). Commensal *C. albicans* primes Th-17 $CD4^+$ T cells and IL-17 cytokines, and these protect against invasive candidiasis.[111] Gut-resident mononuclear phagocytes (CX_3CR1^+) modulate fungal burden by activating antifungal receptors and antifungal responses.[112] The CX_3CR1^+ gut-resident phagocytes express antifungal c-type lectins (e.g., dectin-1 or dectin-2) on their cell surfaces to facilitate intake and phagocytosis of opportunistic fungal pathogens such as *C. albicans*.[112,113] Moreover, this recognition process further activates cytokines that promote Th-17 antifungal responses and mediates the recruitment of neutrophils to the intestines to impede proliferation of *C. albicans*.[113] Intestinal *C. albicans* can induce antifungal immunoglobulin-G (IgG) to protect against disseminated candidiasis.[114] Of note, predisposing factors that negatively affect the determinants maintaining the commensal state may result in a switch to a pathogenic state and translocation into the bloodstream resulting in systemic candidiasis (Figure 2B).

THE GUT VIROME, ENTERIC VIRUSES, AND ASSOCIATION WITH THE HUMAN HOST

Viruses are the most widely distributed and abundant of the biological entities on earth.[66] Viruses play a vital ecological role and are associated with multiple dynamics in microbial diversity or biogeochemical cycles due to their presence in various ecosystems.[115] The human body harbors an extensive number of viruses (collectively termed the virome) residing at different anatomical sites, and the diversity of these viral populations differs vastly across these various sites.[116] Although studies on the human virome are reasonably limited and still emerging, the gut virome has in recent years received much attention due to its association with diseases such as IBD, type 1 diabetes, and colorectal cancer.[117–121] It is widely accepted that the human GIT hosts the majority of the human virome, consisting of both eukaryotic DNA and RNA viruses as well as bacteriophages, with an estimated 10^8–10^9 viral particles per gram of fecal matter.[66] Recent studies showed that neonates are devoid of detectable viral particles shortly after birth, but colonization increases within a month to approximately 10^9 particles per gram of sample.[116,122] Interestingly, these studies report that neonatal viral colonization happens in a distinctive stepwise form as prophages are dominant in the first month, but around four months after birth, viruses replicating within humans become predominant and persist into adulthood.[122] Of note, some of the viruses identified in stool samples, particularly in infants, are known to be human pathogens but exist latently without causing any gastrointestinal symptoms.[68,123] The bacteriophages from the order *Caudovirales* and *Microviridae* (spherical) are predominant, and these bacteriophages directly modulate microbiome populations by killing bacterial hosts during lytic infections but also integrate into bacterial genomes, which may ultimately affect the microbiome and host's physiology.[66,124] A DNA bacteriophage termed crAssphage (cross-assembly phage) has been identified in 50%–77% of the human population worldwide, and it is clustered within individuals, cities, and countries.[69,125–127] Other viruses identified from the human fecal virome are from the *Anelloviridae*, *Virgaviridae*, *Picornaviridae*, *Astroviridae*, *Herpesviridae*, *Sedoreoviridae*, and *Caliciviridae* families (Table 1).[128] Intriguingly, recent reports demonstrate SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) replication in the intestinal tissue, with the viral RNA being detected in rectal swabs and fecal samples 7 months after diagnosis.[129,130] The SARS-CoV-2 infection of intestinal enterocytes is attributed to the receptor protein angiotensin-converting enzyme 2 (ACE2), which is highly expressed in intestinal cells and binds SARS-CoV-2 spike proteins.[131,132] Of note, SARS-CoV-2 gut infection is directly associated with microbial dysbiosis, especially with the concurrent alteration of bacterial populations.[133] However, the impact of SARS-CoV-2 on fungal and viral populations still needs investigation.

Viruses from *Picornaviridae* (e.g., coxsackievirus, poliovirus), *Astroviridae* (e.g., astrovirus), *Caliciviridae* (e.g., norovirus), *Adenoviridae* (e.g., adenovirus), and *Sedoreoviridae* (e.g., rotavirus [RV]) families are transmitted via the fecal-oral route.[134] These human enteric viruses cause serious illnesses in humans, including children under five years (Table 1),[134,135] which include acute gastroenteritis (AGE), a condition defined as the inflammation of the mucous membranes of the GIT.[136] Globally, virus-activated AGE is responsible for high mortality rates characterized by severe symptoms, including profuse diarrhea and fever.[137,138] Although enteric viruses are generally investigated as pathogens, emerging research highlights the beneficial effects of some enteric viruses in the gut akin to the host-microbiome relationship. Infection

Table 1. Viruses known to replicate/associated with infections in the human gut

Family	Virus	Genome structure	Epidemiology	Reference
Sedoreoviridae	Rotavirus[a]	dsRNA	Endemic in children <5 years	Desselberger, 2017[135]
Astroviridae	Astrovirus[a]	ssRNA	Endemic in children and adults	Donato and Vijaykrishna, 2017[258]
Picornaviridae	Aichivirus[a] Enterovirus Salivirus Parechovirus Poliovirus	ssRNA	Endemic in humans	De Crom et al., 2016; Rivadulla and Romalde, 2020; Yu et al., 2015; Zoll et al., 2009[259–262]
Caliciviridae	Norovirus[a] Sapovirus[a]	ssRNA	Endemic in humans	Payne et al., 2017, Desselberger, 2019[263,264]
Adenoviridae	Adenovirus[a] species F (40, 41)	dsDNA	Children	Qiu et al., 2018[265]
Parvoviridae	Parvovirus	ssDNA	Endemic in children and Immunocompromized adults	Qiu et al., 2017[266]
Cycloviridae	Cyclovirus	ssDNA	Endemic in humans	Li et al., 2010[267]
Anelloviridae	Anellovirus	ssDNA	Endemic in humans	Kaczorowska and Van der Hoek, 2020[268]
Coronaviridae	SARS-CoV-2	ssRNA	Endemic in humans	Lamers et al., 2020[269]

[a]These viruses are associated with gastroenteritis in humans.

of germ-free and antibiotic-treated mice with murine norovirus (MNov) protected mice from intestinal antibiotic-induced injury and from the bacterial pathogen *Citrobacter rodentium*.[139] MNov increased colonization resistance against vancomycin-resistant *Enterococcus faecium* (VRE), a hospital-acquired opportunistic pathogen, by activating dendritic cells and interleukin-2 (IL-22).[140] Potential resistance to colonization mediated by intestinal viruses against a bacterial gut pathogen, *Clostridioides difficile*, was also observed in fecal microbiome transplantation patients (the viral component was retained through filtration).[141] Beyond the gut, MNov enhances the survival of mice with *Pseudomonas aeruginosa* acute lung infection and reduces the production of proinflammatory cytokines *in vivo*.[142] Treatment of mice with inactivated RV or TLR3/7 agonists reduced the severity of dextran sulfate sodium (DSS)-induced colitis.[143] Viral-induced type I IFNs (IFN α/β) promote epithelium turnover and intestinal wound healing through activated macrophages and IFN-stimulated genes (ISGs).[144] Interestingly, chronic infections by murine astrovirus protect immunocompromized mice from intestinal infections of RV and norovirus.[145] This resistance to infection was mediated by prolonged systemic activation of type III IFNs (IFN- λ) in the gut by viral complementation of adaptive immunodeficiency. Also, increased levels of ISGs, Ifit1, and Ifi44 were reported to correlate with the activation of IFN- λ.

CANDIDA ALBICANS BIOFILMS AND VIRAL INTERACTIONS

It is well established that, in most natural environments, microorganisms exist as biofilms attached to different surfaces, including biotic surfaces such as the human GIT.[146,147] Biofilm formation provides sessile microorganisms within the structure with multiple advantages, which include nutrient acquisition (metabolite exchange), survival (protection from environmental stresses and antimicrobial drugs), and cell communication.[2,148] Microbial biofilms are estimated to cause approximately 65% of nosocomial infections and 80% of chronic infections, especially in immunocompromized individuals,[149–151] and pose a greater health risk in healthcare/clinical settings due to high resistance to antimicrobial agents and their inability to be eradicated.[147]

Polymicrobial biofilms are defined as a consortium of diverse groups of organisms (i.e., bacteria, fungi, viruses, and protozoa) attached to a surface and often encased within a self-produced/host-derived extracellular matrix consisting of glycolipids, polysaccharides, and extracellular DNA.[2,152] Interdomain interactions and multi-species communication within microbial biofilms influence the architecture, survival,

synthesis and utilization of nutritional compounds, transfer of genetic material, or release of virulence factors by microorganisms.[2,17,153] Microbial communication within biofilms is generally facilitated by quorum sensing through the production of autoinducing molecules that modulate cell function, biofilm structure, or microbial pathogenesis.[154] However, most reports on polymicrobial interactions and cell signaling within biofilms focus on bacterial species. Recently, an increasing number of reports began to focus on fungal pathogens' biofilm formation and microbial interactions,[155,156] but very few focus on the role of pathogenic viruses in biofilms.[157] The few studies on pathogenic viruses and biofilm interactions mainly target the role of viruses on biofilms in water systems.[158] For instance, the non-enveloped poliovirus-1 was injected into an artificial water distribution system to study virus survival and persistence within biofilms.[159] It was found that the virus persisted within biofilms and was observed to be protected from the disinfectant and chlorine, in comparison to free-floating viruses. Similarly, noroviruses and enteroviruses (other non-enveloped viruses) were recovered from biofilms in drinking water and wastewater samples, with the viruses persisting longer in biofilms than in wastewater.[160] Persistent enteric virions associated with biofilms in wastewater were shown to still be infectious for up to 30 days.[161]

Candida albicans forms biofilms on multiple surfaces such as catheters, medical implants, and host mucosal surfaces, contributing to high resistance to antifungal drugs (e.g., fluconazole and amphotericin B) and a high mortality rate.[147] Alterations in environmental factors such as a shift in pH, oxygen levels, diet or use of antibiotics, and immunosuppressive drugs can promote biofilm formation and over-proliferation of *C. albicans* (Figure 2B).[83,162–164]

Only a few reports on *C. albicans* biofilm interactions with human pathogenic viruses are available. A study by Mazaheritehrani and colleagues[165] assessed the *in vitro* interaction of *C. albicans* biofilms and two human viruses, herpes simplex virus 1 (HSV-1) and coxsackievirus type-B5 (CVB5). The biofilms retained their viability and stability in the presence of the viruses, and high viral titers were recovered from biofilms, even after multiple washes, suggesting that viruses were deeply embedded within the biofilms. The viral particles encompassed within biofilms remained infective, had lower susceptibility to chemical inactivation (i.e., sodium hypochlorite), and were masked from host antibodies, suggesting that biofilms provide protection from antimicrobial agents or host immunity and act as potential reservoirs for viral dissemination.[165] This masking of viruses by *C. albicans* biofilms is possibly enhanced by *C. albicans'* ability to downregulate cytokine release, which can abrogate HSV-1 replication.[166,167] In this regard, another report showed that *C. albicans* biofilms protected HSV-1 from antiviral drugs, acyclovir, and foscarnet.[168] The authors showed that viral titers from biofilm-free cells decreased by a higher margin (>2 log reduction) relative to biofilm-infected cells (0.2 log reduction). In addition, this intra-biofilm residence of HSV-1 further shielded the virus from the antiviral activity of UV A1 (UVA1) laser irradiation, possibly due to the extracellular polymeric substance quenching the UVA1 light and reducing its virucidal activity.[168]

The interactions of *C. albicans* biofilms and viruses may also have a reciprocal effect on the growth and establishment of *C. albicans* biofilms.[169,170] For example, HSV-1 infected macrophages (derived from THP-1, human acute monocytic cell line) show enhanced phagocytosis of *C. albicans* but are impaired in intracellular deactivation of the ingested fungus and ultimate antifungal activity.[171] The study showed that HSV-1 downregulates toll-like receptors (TLRs), TLR-2 and TLR-4, which are essential in host recognition of *C. albicans* infections, suggesting that HSV-1 presence favors fungal survival and immune evasion and may contribute to disease progression.[171] In another study, HSV-1 and HSV-2 were shown to enhance adherence of *C. albicans* to HeLa cells in a virus dose-dependent manner, indicating a possible interaction of both pathogens even at infection sites.[172]

The possibility of viral-fungal interactions in the GIT can also be extrapolated from *Pseudomonas aeruginosa*-derived filamentous bacteriophages, Pf4 and Pf1. These phages have been shown to interact with *C. albicans* biofilms *in vitro* and cause a dose-dependent inhibitory effect on metabolic activity and biofilm formation.[173] Although this study showed phage binding to *C. albicans* and aggregation to the extracellular matrix, the ability of these phages to sequester iron was suggested as a mechanism of inhibition on *C. albicans'* biofilm formation, as iron supplementation reversed the inhibitory effect on biofilms. The Pf phages have also been demonstrated to bind and sequester iron to inhibit *Aspergillus fumigatus* (*A. fumigatus*) biofilms *in vitro*.[174] Both *A. fumigatus* and *C. albicans* interact with *P. aeruginosa* in various clinical settings, especially in immunocompromized individuals, and these results suggest phage-mediated tri-partite interactions, particularly in nutrient-limited niches.[173]

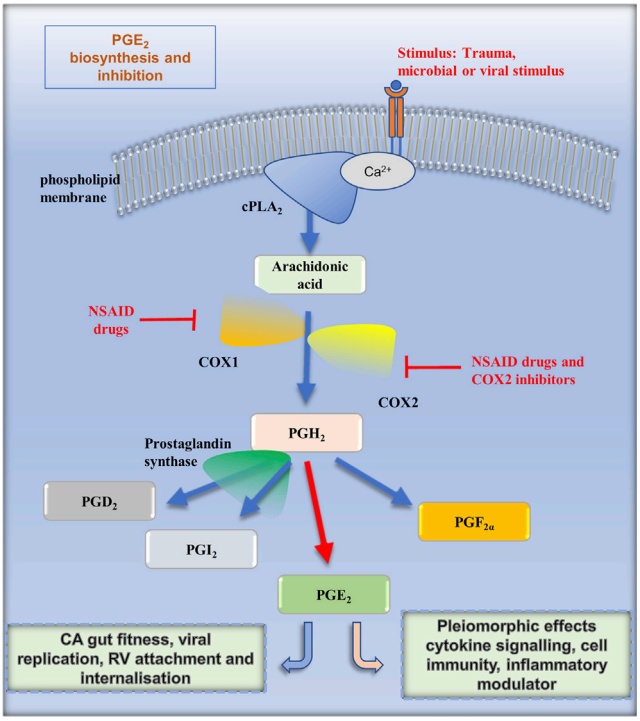

Figure 3. Prostaglandin E_2 biosynthesis and stimulation

Overall synthesis of prostaglandins including prostaglandin E_2 (PGE_2) plus the drug targets of NSAIDs on cyclooxygenase enzymes. COX1 enzyme is constitutively expressed while COX2 is differentially expressed upon stimulation.

Abbreviations: $cPLA_2$ – cytosolic phospholipase A_2, NSAID – Non-Steroidal Anti-Inflammatory Drugs, COX1/2 – Cyclooxygenase1/2, PGD_2 - Prostaglandin D_2, $PGF_{2\alpha}$ - Prostaglandin $F_{2\alpha}$, PGH_2 – Prostaglandin H_2, PGI_2 – Prostaglandin I_2, CA – *Candida albicans*, RV - rotavirus

THE POTENTIAL INFLUENCE OF HOST-DERIVED METABOLITES AND IMMUNITY ON *CANDIDA ALBICANS*—VIRUS INTERACTIONS IN THE GUT

Role of PGE_2

Prostaglandins are lipid mediators that have pleiotropic effects on biological systems. These bioactive lipids are produced from host-derived AA by the activity of cytosolic phospholipase A_2 and the subsequent downstream enzymes, including cyclooxygenases (COXs) and prostaglandin synthases (Figure 3).[175] Prostaglandins are mainly produced in response to stimuli, such as trauma or microbial infections, and exert multiple effects on mammalian cells, especially during inflammatory reactions.[176] PGE_2 is a key modulator of active inflammation and cell immunity, cell-cell communication, cytokine production, apoptosis, and cell migration and maturation, as well as antigen presentation.[177] Owing to its propensity to modulate pro- and anti-inflammatory reactions in response to infections, most microorganisms (including *C. albicans* and various viruses) have developed the ability to exploit host-derived PGE_2 or to stimulate AA release from the host, in order to initiate colonization and infection or to evade host immune responses.[103,178,179]

Candida albicans also produces PGE_2 from host-derived AA through the activation of phospholipase A_2 which hydrolyzes glycerophospholipids at the sn-2 position.[180,181] PGE_2 production by *C. albicans* is upregulated during biofilm formation and is essential for competitive fitness during gut colonization (Figure 2A-iv).[103] In addition, PGE_2 produced by *C. albicans* biofilms stimulates the growth and biofilm formation of pathogenic bacteria such as *Staphylococcus aureus* in dual-species biofilms.[182] It is also well established that PGE_2 interaction with enteric viruses can enhance viral replication, and this activation may ultimately exacerbate the outcome of the disease.[179] This raises the question of how PGE_2 would affect the outcome of the possible *C. albicans*-virus interactions during polymicrobial gut colonization, biofilm formation, or multi-species infections. Here we highlight some enteric viruses that utilize PGE_2 or initiate expression of the COX/PGE_2 pathway for viral replication, which may ultimately influence the unexplored *C. albicans*-viral interactions, especially during gut colonization or in polymicrobial gut infections.

Sedoreoviridae

RV, a leading cause of gastroenteritis in children under the age of five,[27] especially in developing countries, has been shown to increase intestinal PGE_2 levels in malnourished neonatal piglets after infection.[183] These results were consistent with the study by Yamashiro and colleagues[184] that demonstrated high PGE_2 levels in the plasma and stool samples of children with RV-associated diarrhea relative to the control group of children without any sign of diarrhea. Moreover, the authors indicated that oral administration of aspirin, a nonsteroidal anti-inflammatory drug (NSAID) that targets the COX enzymes (COX-1 and COX-2), resulted in a rapid cessation of diarrhea. Similarly, the NSAID indomethacin, a nonspecific drug targeting both COX enzymes, was shown to significantly reduce RV infection in Caco-2 (Caucasian colon adenocarcinoma) cells.[185] Recently, elevated PGE_2 concentrations were detected in RV-infected MA104 cells following supplementation with γ-linolenic acid, a precursor for AA.[186] Notably, increased levels of PGE_2 correlated with RV replication in a time-and dose-dependent manner, suggesting RV dependence on PGE_2 for proliferation. Interestingly, PGE_2 release from RV-infected cells appears to enhance virus attachment and internalization, possibly through clathrin-mediated endocytosis.[186] Collectively, these results show that PGE_2 plays an important role in RV replication and may influence the severity of RV infections.

Caliciviridae

Human caliciviruses (norovirus and sapovirus) are etiological agents of epidemic gastroenteritis in both adults and young children, causing sporadic cases worldwide and contributing to ~200,000 fatalities in children.[187] Although caliciviruses have such a clinical and socioeconomic impact, only a limited number of studies have demonstrated their role in eliciting the host immune response, especially the COX-PGE_2 pathway, for proviral activities. It was demonstrated that murine norovirus CW-1 and feline calicivirus F9 strains initiated activation of the COX-2/PGE_2 signaling pathway in a time-dependent manner for proviral signaling and replication.[188] In addition, blocking of COX-2 by pharmacological inhibitors (e.g., indomethacin) or small interfering RNAs (siRNAs) significantly reduced PGE_2 production as well as murine norovirus and feline calicivirus replication. Similarly, the effect of inhibitors on COX-2 and virus replication was restored by the addition of exogenous PGE_2. Interestingly, a recent study demonstrated that the induction of COX-2 mRNA expression by feline calicivirus within host cells (i.e., Crandell-Reese feline kidney [CRFK] cells) is mediated by the MAPK (MEK1-ERK1/2) signaling pathway upon activation by the nonstructural protein (VPg).[189]

Sapovirus causes acute viral gastroenteritis in children <5 years old and can cause outbreaks in enclosed facilities like orphanages.[190–192] Infection of porcine kidney cells (LLCPK) with sapovirus (Cowden strain) caused notably increased COX-2 mRNA and protein levels in a time-dependent manner.[193] Inhibition of COX enzymes by NSAIDs and siRNAs caused markedly reduced PGE_2 levels and significant interference in sapovirus replication.[193] Importantly, supplementation of exogenous PGE_2 reversed the inhibitory effects of COX inhibitors and restored sapovirus replication in a dose-dependent manner, confirming the direct proviral effect of PGE_2 on sapovirus replication and possible infection.

Picornaviridae

Picornaviruses are characterized by a single-stranded RNA genome, encased by an icosahedral capsid, and may cause mild to severe diseases including gastroenteritis or viral myocarditis.[194] Although Picornaviruses cause extraintestinal infections, translocation is generally through the intestinal route and may interact with the densely organized intestinal epithelial cells. Some genera within the *Picornaviridae* family utilize the COXs/PGE_2 pathway to mediate viral replication and cause persistent infections. The COXs/PGE_2 signaling pathway in enteric virus infections *in vivo* was also shown to be associated with the replication of coxsackievirus B3 (CVB3) via the activation of the Th17/Interleukin (IL)-17 inflammatory response.[195] Xie and colleagues[195] further demonstrated that blockage of IL-17A with anti-mouse IL-17 antibody in BALB/c mice resulted in increased levels of COX-2 and PGE_2 plus a decrease in viral titers and pathological scores, suggesting the active influence of COX-2/PGE_2 expression in CVB3 infections. In addition, several studies have reported on the expression of COX-2/PGE_2 biosynthesis proteins in cells infected with the enterovirus 71 strain.[196–198] Tung and colleagues have shown that enterovirus 71 can autoregulate its replication by upregulation of COX-2/PGE_2 via the activity of MAPK (mitogen-activated kinase), NF-κB (nuclear factor kappa B), AP-1 (activator protein-1), and cAMP (cyclic adenosine monophosphate) pathways in human neuroblastoma SK-N-SH cells.[196,197] Furthermore, treatment of cells with PGE_2 enhances enterovirus 71 structural protein (VP1), which is essential for viral replication, immunogenicity, or evasion of host immunity.[197,199] Inhibition of the MAPK pathway and PGE_2 expression through the plant-based compound formononetin

suppresses enterovirus 71 replication.[198] As such, the production of secondary molecules such as PGE_2 by *C. albicans* or upregulation of the COX/PGE_2 pathway by enteric viruses can potentially influence *C. albicans*-viral interactions and host immune response.

Role of IFN signaling

The host's capacity to combat microbial invasion depends on the efficacy of the early innate immune response, which may trigger cytokine signaling and priming of adaptive immunity during microbial infections.[200–202] The IFNs are a group of cytokines capable of initiating a cascade of immunological responses against pathogens normally after interaction with pathogen recognition receptors (PRRs).[203] Ultimately grouped into three distinct families (type I, II, or III), IFNs regulate the host's response to a wide variety of pathogenic bacteria, viruses, and fungi by stimulating hundreds of ISGs.[204,205] Type I IFNs (predominantly α and β) are the most diverse and are expressed by a wide variety of cell types.[206] In contrast, type II IFNs are characterized by a single gene product, IFN-γ, secreted by activated natural killer cells or T cells and can act on multiple cells expressing IFN-γ receptor (IFNγR).[205,206] Type III IFNs (IFN- λ) are structurally similar to type I IFNs but have a confined activity as their receptor (IL28Rα/IFNLR1) is mostly expressed at epithelial cell surfaces.[207–209]

Candida albicans and IFN signaling

An alteration in factors mediating *C. albicans* yeast form or colonization can result in a morphological transition to the pathogenic hyphal state (Figure 2B), and coordination between epithelial cells and IFN signaling can regulate the initial stages of fungal invasion. Tissue invasion by *C. albicans* involves two distinct mechanisms: active penetration and induced endocytosis. Meanwhile, *C. albicans* pathogen-associated molecules (PAMPs), β-glucans, and mannoproteins on the cell wall are recognized by PRRs such as c-type lectins and TLRs (e.g., TLR2 and TLR4) expressed on the epithelial cell membrane to initiate antifungal immune response and clearance (Figure 3A).[210] Upon recognition of PAMPs on *C. albicans* cell wall, TLR4, TLR2-TLR6, and intracellular TLR9 interconnect with adaptors MyD88 (myeloid differentiation primary response 88) to facilitate signaling to the interleukin (IL)-1 receptor-associated kinases (IRAKS) and TNF receptor-associated factor 6 (TRAF6) leading to the activation of nuclear factor (NF)-κB.[210,211] The expression of NF-κB ultimately culminates in the production of proinflammatory cytokines (e.g., IL-1, IL-6, or tumor necrosis factor [TNF]), chemokines (e.g., CXCL2 or CCL3), and co-stimulatory molecules (e.g., CD28) essential for regulating *C. albicans* infections.[212,213] Also, TLR4 engages TRIF (TIR-domain-containing adapter-inducing interferon-β) to activate the expression of type I IFNs via IFN regulatory factor 3 (IRF3), a mechanism that overlaps with antiviral immune response. In addition, the intracellular TLR9 (TLR9 detects fungal DNA) can trigger host-protective IFN-I response via IRF-7.[214] Of note, induced endocytosis may lead to systemic candidiasis, and to regulate fungal dissemination, immune cells such as resident macrophages or dendritic cells can express PRRs that recognize *C. albicans'* surface molecules.[112] Bone marrow-derived dendritic cells produce high levels of IFN-β upon infection with *Candida* spp., and invasive candidiasis upregulates type I-associated genes (e.g., IFN-I receptor subunit IFNAR1) in peripheral leukocytes.[215,216] IFN-α/β-associated signaling is essential for eliciting antifungal reactive oxygen species in phagocytic cells (maturation of phagolysosomes) and for recruiting neutrophils to the *C. albicans* infection site.[217] Recently, the coordination between type I and III IFN signaling has been demonstrated to be critical in antifungal response against *Aspergillus fumigatus* (*A. fumigatus*).[218] The authors reported that CCR2+ macrophage-induced type I IFNs mediate the release of type III IFNs which subsequently activate a neutrophil-associated antifungal response against *A. fumigatus*. However, the possible influence of IFN response against fungal infections needs to be fully explored as studies on *C. albicans* and IFN signaling are still emerging.

Enteric viruses and IFN signaling

Infection of mucosal epithelial cells by enteric viruses results in immediate activation of the host cell's intrinsic innate immune response upon recognition of viral PAMPs by membrane-bound PRRs present on cell surfaces (Figure 3B).[219] Multiple host cell surface receptors, including sialylated glucans, glucosaminoglycans, and human blood group antigens can act as receptor molecules recognizing viral PAMPs, eventually mediating viral attachment.[220,221] Other major viral receptors are cellular adhesion molecules, including integrins, phosphatidylserine (PtdSer) family of receptors, and immunoglobulin superfamily of receptors.[222,223] Associations between viruses and receptors activate viral particle conformational changes that activate genome translocation or cell signaling mechanisms to mediate viral entry.[224–226] The critical viral PAMP detected during infections is the viral nucleic acid, although some viral replication

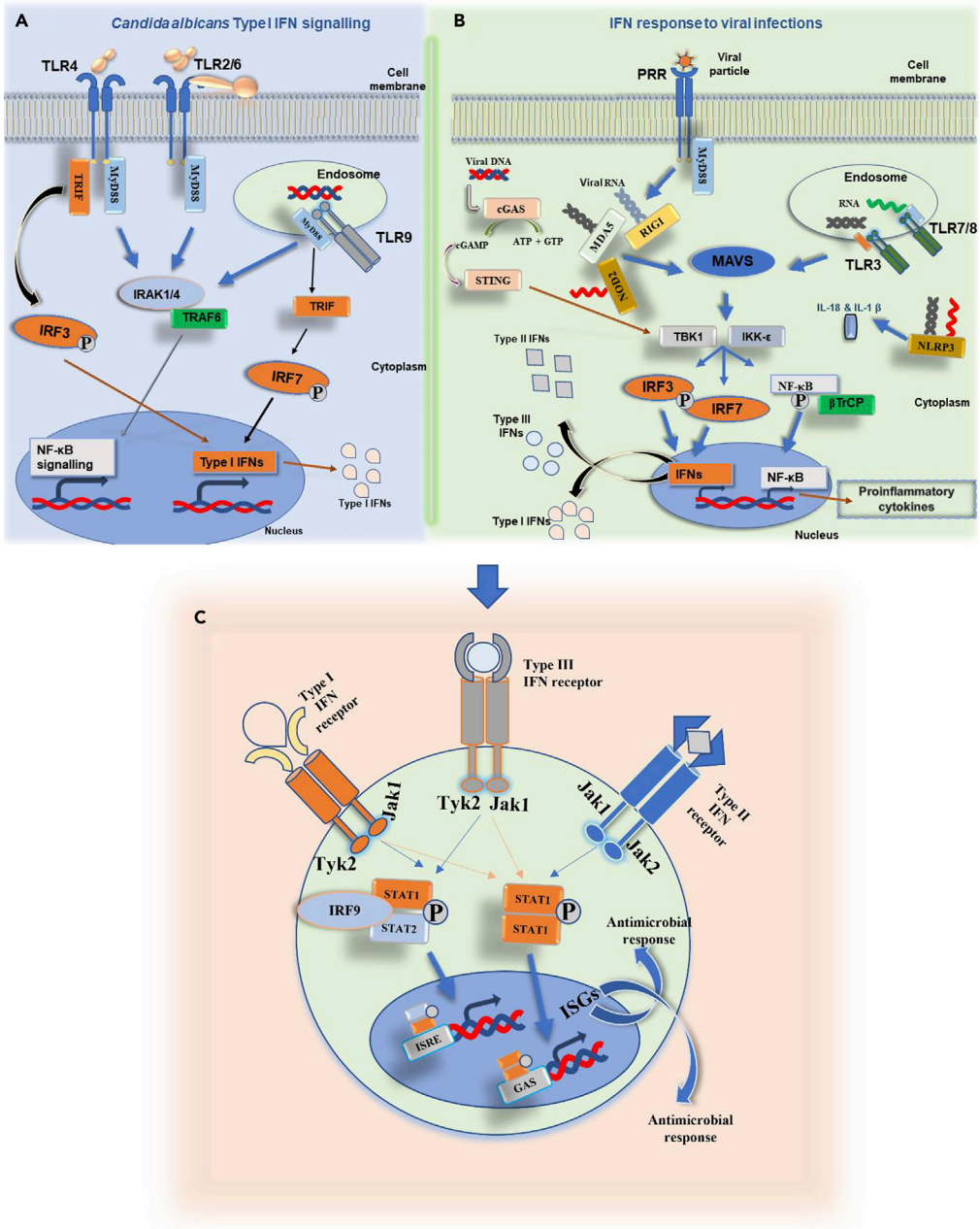

Figure 4. Activation of interferon signaling by *Candida albicans* and viral infections

(A) The PAMPs on *C. albicans'* (e.g., mannoproteins or β-glucans) cell surface are recognized by membrane-bound PRRs (e.g., TLRs) on epithelial cells leading to IFN and proinflammatory cytokine signaling. The surface TLRs (TLR2, 4 and 6) and endosomal TLRs (TLR9) recruit the adaptor MyD88 to mediate NF-κB signaling via the IRAKS/TRAF6 complex as intermediates. The expression of NF-κB promotes proinflammatory cytokine production. The endosomal TLR3 and surface TLR4 engage TRIF to initiate activation of IRF3 and IRF7, respectively, for IFN production. The IFNs act on a similar cell or bystander cell for the expression of ISGs.

(B) The viral molecules (nucleic acids or PAMPs) are recognized by the host's cell PRRs on the cell membrane to initiate the production of IFNs. Binding of double-stranded DNA (dsDNA) to cytosolic nucleotidyltransferase cyclic GMP-AMP (cGAMP) synthase (cGAS) activates the synthesis of cGAMP, which directly attaches to STING (endoplasmic reticulum-located stimulator of IFN genes) to stimulate TANK-binding kinase 1 (TBK1) and subsequent phosphorylation of IRF3. The RIG-I-like receptors (RIG-I, MDA5) and NOD2 detect viral ss/ds RNAs, undergo a conformational change and engage the downstream adaptor mitochondrial antiviral signaling protein (MAVS), leading to the activation of IRF3/7 and NF-κB

Figure 4. *Continued*

through TBK1 and IκB kinase ε (IKK ε). Similar mechanisms are followed by endosomal TLRs (TLR 3, 7, 8). Activation of IRF3/7 and NF-κB initiates IFN production and proinflammatory signaling, respectively. β-TrCP (β-transducin repeat-containing protein) is essential for the activation of NF-κB and translocation into the nucleus. Expression of NLRP3 after viral nucleic acid detection leads to the production of pro-IL18 and pro-IL1β, which recruit neutrophils and induce adaptive immune responses.[257]

(C) The secreted IFNs bind to their respective IFN receptors on the same or bystander adjacent cells to initiate a signaling cascade involving Janus tyrosine kinase (JAK) and tyrosine kinase (TYK), resulting in phosphorylation of STAT1 and/or STAT2. Phosphorylated STAT1 and STAT2 (for type I and II IFNs) complex with IRF9 and attach to ISREs (IFN-stimulated response elements) for expression of IFN-stimulated genes (ISGs). The type II IFN cascade involves phosphorylation of STAT1 dimers binding to GAS (gamma-activated site) to activate the production of ISGs. Meanwhile, ISGs facilitate antiviral or antimicrobial effects from infected cells or activate the innate and adaptive immune response (Compiled from[205,210,231,235]).

intermediates can also be detected.[227] The cytosolic RIG-I (retinoic acid-inducible gene I), MDA5 (melanoma differentiation-associated protein-5), NOD2 (nucleotide-binding oligomerization domain 2), and endosomal TLRs (TLR3, 7 and 8) detect viral RNA, and in combination with mitochondrial MAVS (mitochondrial antiviral signaling protein), form a protein complex that induces a signaling cascade leading to the phosphorylation of NF-κB and IRF3 or IRF7 by TANK-binding kinase (TBK1) and IκB epsilon (IKK ε).[228] Upon activation, NF-κB and IRF3/7 translocate into the nucleus to mediate the production of proinflammatory cytokines and IFNs, respectively. The secreted IFNs bind to their respective IFN receptors on the same and adjacent cells to initiate a signaling cascade involving Janus tyrosine kinase (JAK) and tyrosine kinase (TYK), resulting in phosphorylation of STAT1 and/or STAT2 (Figure 4).[208,229] Phosphorylated STAT1 and STAT2 (for type I and II IFNs) complex with IRF9 and attach to ISREs (IFN-stimulated response elements) for expression of IFN-stimulated genes (ISGs).[230,231] The type II IFN cascade involves phosphorylation of STAT1 dimers binding to GAS (gamma-activated site) to activate the production of ISGs.[205,230]

ISGs facilitate antiviral or antimicrobial effects from infected cells or activate the innate and adaptive immune response. The main etiological agents (norovirus, sapovirus, rotavirus, adenovirus, and astrovirus) of viral gastroenteritis have been implicated in inducing the host's IFN signaling. Human norovirus (HNov, GII.4 strain) activates IFN signaling predominated by type III IFNs response in intestinal epithelial cells as STAT1 and STAT2 binding sites were highly enriched in the promoter regions of genes highly upregulated after infection with HNov.[232,233] RV infections induce the expression of the three major signaling pathways (type I, II, and III IFN), although the response may be strain-dependent.[234–236] In mice lacking type I and type III IFN receptors, RV replicates to higher titers, and infected intestinal epithelial cells express ISGs associated with type III IFN signaling.[237] Similar results were observed with mammalian reovirus and human astrovirus in inducing the expression of type III IFN in 3D colonoids and organoids.[145,231,238] Studies involving human adenovirus and IFN response are limited, but one such study showed that pre-treatment of human intestinal enteroids with IFN-β or IFNλ3 attenuates adenovirus replication.[239]

Candida albicans-viral interactions and possible implications on IFN signaling

Enteric viral infections occur within the milieu of gut microbiota which plays a significant role in determining viral infectivity and the host's immune response.[140,240] Interdomain interactions between enteric viruses, resident gut microorganisms, and host IFN signaling have shown distinct dependence of viruses on commensal organisms for persistent infection or in evading viral clearance.[241] Although little to no studies have been reported on the host immune response to interactions or co-infections between *C. albicans* and enteric viruses, manipulation of host immunity by enteric viruses or *C. albicans* can provide the strongest indications of the possible role of cytokine signaling in these interactions. Some enteric viruses such as RV manipulate type I IFN signaling, which may favor persistent *C. albicans* infections or even translocation from the intestinal space into the bloodstream.[242] For example, RV NSP1 (nonstructural protein 1) antagonizes type I IFN signaling and is a potent inhibitor of IFN-mediated STAT1 activation.[236,243,244] Specifically, RV NSP1 activates proteasome-mediated degradation of IFN regulatory factors (IRFs), of which some are involved in IFN-β signaling (e.g., IRF3) (Figure 5).[245–247] Similarly, murine reovirus viral matrix protein (μNS) inhibits interferon-mediated IFN response by impairing nuclear translocation of IRF3 and sequestering it into viral factories.[231] In addition, RV NSP1 mediates the degradation of the β-transducin repeat-containing protein (β-TrCP), a component essential for multiple biological processes, including cell apoptosis and host innate immunity (essential in the activation of NF-κB).[248] The NF-κB plays a significant role in the antifungal proinflammatory response, especially in recruiting phagocytic cells during invasive candidiasis.[211]

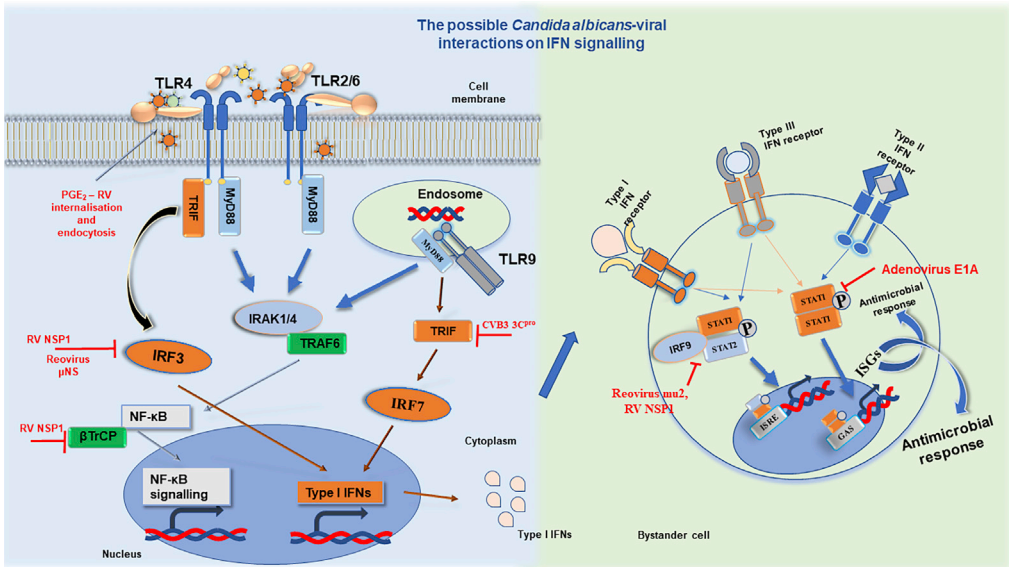

Figure 5. Possible implications of *Candida albicans*-enteric virus interactions on IFN signaling

Enteric viruses have developed several mechanisms to attenuate antiviral IFN responses within the host which may be beneficial for *C. albicans* infections. Rotavirus NSP1 and reovirus μNS proteins target the phosphorylation of IRF3.[231,235,236] Rotavirus NSP1 mediates the degradation of β-TrCP essential in the phosphorylation of NK-κB.[248]. Coxsackievirus B3 3Cpro protease cleaves TRIF and may prevent activation of IRF7.[249] Reovirus mu2 and adenovirus E1A proteins inhibit the STAT1/STAT2/IRF9 complex, preventing nuclear translocation and production of ISGs.[251,252] In contrast, *C. albicans* initiates the release of arachidonic acid from membranous phospholipids for PGE_2 production, and PGE_2 is known to facilitate replication and internalization of viruses such as rotavirus.[103,179] Abbreviations – RV- rotavirus, NSP1 – non-structural protein, CVB3 – coxsackievirus B3, PGE_2 – prostaglandin E_2

This interference of host immunity by RV and reovirus may impair fungal clearance in polymicrobial infections similar to herpes simplex virus 1 (HSV-1), as HSV-1 downregulates gene expression of TLR2 and antigen detection of TLR4 of infected monocytic cells (THP-1) and impairs *C. albicans* degradation by immune cells.[169,171] Coxsackievirus B3 attenuates the host's antiviral signaling by cleavage of adaptor molecules MAVS and TRIF through the $3C^{pro}$ cysteine protease to evade host immunity.[249] Interestingly, RV VP3 protein is associated with MAVS degradation to inhibit type III IFN signaling.[250] In addition, adenovirus antagonizes IFN signaling (type I and type II) by sequestering phosphorylated STAT1 protein to viral replication centers, thereby inhibiting the expression of ISGs.[251] This mechanism of STAT1 inhibition is attributed to the adenovirus E1A proteins, which have been shown to downregulate JAK1 expression.[252] Similarly, STAT1 inhibition by RV was reported both *in vitro* (RV-infected cells) and *in vivo* (suckling mice).[235,244] Taken together, viral interference of IFN signaling may increase the host's susceptibility to fungal pathogens such as *C. albicans*, especially in overlapping IFN responses.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Emerging studies thus far support the fundamental role played by the gut microbiome in health and disease. This extensive amount of data has demonstrated the influence of gut microbiota on human metabolism, immune homeostasis, and the contribution to colonization resistance by preventing the invasion of pathogenic organisms. However, our understanding of the gut microbiome signature is still lacking, mostly due to multifactorial effects (e.g., lifestyle, therapy, or nutrition) that influence the stability or shifting of microbial spp. (especially the gut mycobiome or virome) over time. Microbiome fluctuations over time in infants especially in developing countries affect vaccine efficacy;[253,254] therefore, discovering the interplay in gut microbiome "identity", polymicrobial interactions, and host-microbial interactions will inform antimicrobial therapy and vaccine development. Also, the beneficial effects of the gut microbiome combined with understanding the mechanisms involved in host-microbe interactions call for comprehensive studies to combat diseases such as IBD or infantile diarrhea.

Host antifungal response, genetic determinants, metabolic plasticity, and interactions with the gut microbiota play a critical role in regulating *C. albicans'* commensalism and preventing a switch from commensal

to a pathogenic state. Multiple seminal studies have provided a better overview of *C. albicans* colonization, epithelial invasion, translocation, host immune response, and infection in both mouse models and humans. This improved understanding will help develop mechanisms that prevent systemic candidiasis originating from the intestinal epithelium. Conversely, knowledge about the polymicrobial interactions between *C. albicans* and the gut microbiome, particularly the gut virome and enteric viruses, is still limited. The cohabitation of fungal spp. and viruses at different mucosal sites has been documented, and fungal pathogens such as *Aspergillus* spp. have been shown to complicate viral infections including influenza, pneumonia, and SARS-CoV-2 infections.[255] *Candida albicans* biofilm formation in clinical settings poses a major health risk due to antimicrobial resistance and the association with deep-seated infections or invasive candidiasis. Notably, studies on *C. albicans* biofilms and viral interactions demonstrate virions or viral particles deeply dispersed within biofilms and protected from chemical inactivation.[165] Biofilms can encompass pathogenic enteric viruses such as RV and caliciviruses. Therefore, it is critical to comprehend how viruses persist in biofilms, their dispersal mechanisms, cross-infectivity, and co-pathogenesis with biofilm-forming fungal pathogens like *C. albicans*, which may act as reservoirs for infectious viruses.

The host response to microbial or viral infections results in activation of the immune response and production of lipid immune modulators such as PGE_2. *Candida albicans* colonization induces host cells to release AA as a PGE_2 precursor to promote competitive fitness within the gut.[103] In addition, several enteric viruses discussed in this review activate the host's $COX2/PGE_2$ expression pathway to mediate viral replication. However, it remains unclear if viral-induced $COX2/PGE_2$ solely facilitates optimal viral replication or if this expression is also essential for exacerbating viral pathogenesis. The seminal work on PGE_2 promoting RV attachment and internalization in mammalian cells[186] provides a basis for further exploration of viral PGE_2 utilization during infections beyond viral replication. Meanwhile, the outstanding questions regarding how PGE_2 will affect *C. albicans*-enteric virus co-pathogenesis, trans-kingdom interactions, host immune modulation during multi-species infections, and the overall viral replication remain to be explored, particularly in the context of gastroenteritis. The use of human intestinal enteroids (HIEs) will provide a better opportunity for studying these interactions in the future as HIEs epitomize the nuances involved in *in vivo* gastrointestinal epithelium.[256] The $COX2/PGE_2$ pathway can be a therapeutic target for regulating viral infections and understanding viral dependence on PGE_2 during co-infections.

Lastly, research on the key role of interferon (IFN) signaling in inhibiting viral pathogenesis and proliferation at mucosal sites has increased knowledge of host-viral interactions, especially in murine models. The major enteric viruses discussed here are reported to induce type I, type II, and type III IFNs, although certain aspects remain understudied due to limitations in culturing techniques, especially for viruses such as human noroviruses (Nolan and Baldridge,[256] review the use of human organoids in overcoming these limitations). Compared to type I and III, type II IFNs are well studied for controlling bacterial and fungal infections but are less characterized in the context of viral infections. Some enteric viruses stimulate type I and type III IFNs while others stimulate exclusively type III activation, and the reason behind this is still unclear Here, we discussed the IFN-associated immune response against *C. albicans* and enteric viruses, including the molecular aspects involved in the production of IFN-stimulated genes. The understanding of the IFN-stimulated genes' effect on fungal-viral interactions is still limited, and this warrants further investigation for insight into the host's response to polymicrobial infections. Furthermore, the overlapping synergistic effect of type I and type III IFNs remains to be studied during co-pathogenesis with fungal pathogens like *C. albicans* which induces type I signaling.

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AUTHOR CONTRIBUTIONS

Conceptualization, B.M.M., C.H.P., and H.G.O.; Writing – Original Draft, B.M.M.; Writing – Review & Editing, B.M.M., C.H.P., and H.G.O.; Visualization, B.M.M.; Supervision, C.H.P. and H.G.O. All authors approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Dave, M., Higgins, P.D., Middha, S., and Rioux, K.P. (2012). The human gut microbiome: current knowledge, challenges, and future directions. Transl. Res. *160*, 246–257. https://doi.org/10.1016/j.trsl.2012.05.003.

2. Ponde, N.O., Lortal, L., Ramage, G., Naglik, J.R., and Richardson, J.P. (2021). Candida albicans biofilms and polymicrobial interactions. Crit. Rev. Microbiol. *47*, 91–111. https://doi.org/10.1080/1040841X.2020.1843400.

3. Tierney, B.T., Yang, Z., Luber, J.M., Beaudin, M., Wibowo, M.C., Baek, C., Mehlenbacher, E., Patel, C.J., and Kostic, A.D. (2019). The landscape of genetic content in the gut and oral human microbiome. Cell Host Microbe *26*, 283–295.e8. https://doi.org/10.1016/j.chom.2019.07.008.

4. Savage, D.C. (1977). Microbial ecology of the gastrointestinal tract. Annu. Rev. Microbiol. *31*, 107–133. https://doi.org/10.1146/annurev.mi.31.100177.000543.

5. Lozupone, C.A., Stombaugh, J.I., Gordon, J.I., Jansson, J.K., and Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. Nature *489*, 220–230. https://doi.org/10.1038/nature11550.

6. Lloyd-Price, J., Abu-Ali, G., and Huttenhower, C. (2016). The healthy human microbiome. Genome Med. *8*, 51. https://doi.org/10.1186/s13073-016-0307-y.

7. Proctor, L. (2019). Priorities for the next 10 years of human microbiome research. Nature *569*, 623–625.

8. Proctor, L.M., Creasy, H.H., Fettweis, J.M., Lloyd-Price, J., Mahurkar, A., Zhou, W., Buck, G.A., Snyder, M.P., Strauss, J.F., Weinstock, G.M., et al. (2019). The integrative human microbiome project. Nature *569*, 641–648. https://doi.org/10.1038/s41586-019-1238-8.

9. Lepage, P., Leclerc, M.C., Joossens, M., Mondot, S., Blottière, H.M., Raes, J., Ehrlich, D., and Doré, J. (2013). A metagenomic insight into our gut's microbiome. Gut *62*, 146–158. https://doi.org/10.1136/gutjnl-2011-301805.

10. Lee, K.A., Luong, M.K., Shaw, H., Nathan, P., Bataille, V., and Spector, T.D. (2021). The gut microbiome: what the oncologist ought to know. Br. J. Cancer *125*, 1197–1209. https://doi.org/10.1038/s41416-021-01467-x.

11. Rajilić-Stojanović, M., Smidt, H., and De Vos, W.M. (2007). Diversity of the human gastrointestinal tract microbiota revisited. Environ. Microbiol. *9*, 2125–2136. https://doi.org/10.1111/j.1462-2920.2007.01369.x.

12. Rajilić-Stojanović, M., and De Vos, W.M. (2014). The first 1000 cultured species of the human gastrointestinal microbiota. FEMS Microbiol. Rev. *38*, 996–1047. https://doi.org/10.1111/1574-6976.12075.

13. Hyland, N.P., and Cryan, J.F. (2016). Microbe-host interactions: influence of the gut microbiota on the enteric nervous system. Dev. Biol. *417*, 182–187. https://doi.org/10.1016/j.ydbio.2016.06.027.

14. Karl, J.P., Meydani, M., Barnett, J.B., Vanegas, S.M., Barger, K., Fu, X., Goldin, B., Kane, A., Rasmussen, H., Vangay, P., et al. (2017). Fecal concentrations of bacterially derived Vitamin K forms are associated with gut microbiota composition but not plasma or fecal cytokine concentrations in healthy adults. Am. J. Clin. Nutr. *106*, 1052–1061. https://doi.org/10.3945/ajcn.117.155424.

15. Li, N., Ma, W.T., Pang, M., Fan, Q.L., and Hua, J.L. (2019). The commensal microbiota and viral infection: a comprehensive review. Front. Immunol. *10*, 1551. https://doi.org/10.3389/fimmu.2019.01551.

16. Yoshii, K., Hosomi, K., Sawane, K., and Kunisawa, J. (2019). Metabolism of dietary and microbial Vitamin B family in the regulation of host immunity. Front. Nutr. *6*, 48. https://doi.org/10.3389/fnut.2019.00048.

17. Orazi, G., and O'Toole, G.A. (2019). "It takes a village": mechanisms underlying antimicrobial recalcitrance of polymicrobial biofilms. J. Bacteriol. *202*, 005300-19. https://doi.org/10.1128/JB.00530-19.

18. Peters, B.M., Jabra-Rizk, M.A., O'May, G.A., Costerton, J.W., and Shirtliff, M.E. (2012). Polymicrobial interactions: impact on pathogenesis and human disease. Clin. Microbiol. Rev. *25*, 193–213. https://doi.org/10.1128/CMR.00013-11.

19. Pereira, R., dos Santos Fontenelle, R.O., de Brito, E.H.S., and de Morais, S.M. (2021). Biofilm of Candida albicans: formation, regulation and resistance. J. Appl. Microbiol. *131*, 11–22. https://doi.org/10.1111/jam.14949.

20. Berger, A.K., and Mainou, B.A. (2018). Interactions between enteric bacteria and eukaryotic viruses impact the outcome of infection. Viruses *10*, 19. https://doi.org/10.3390/v10010019.

21. Pullen, L.C., Park, S.H., Miller, S.D., Dal Canto, M.C., and Kim, B.S. (1995). Treatment with bacterial LPS renders genetically resistant C57BL/6 mice susceptible to Theiler's virus-induced demyelinating disease. J. Immunol. *155*, 4497–4503. https://doi.org/10.4049/jimmunol.155.9.4497.

22. Dhalech, A.H., Fuller, T.D., and Robinson, C.M. (2021). Specific bacterial cell wall components influence the stability of coxsackievirus B3. J. Virol. *95*, e0142421. https://doi.org/10.1128/JVI.01424-21.

23. Kuss, S.K., Best, G.T., Etheredge, C.A., Pruijssers, A.J., Frierson, J.M., Hooper, L.V., Dermody, T.S., and Pfeiffer, J.K. (2011). Intestinal microbiota promote enteric virus replication and systemic pathogenesis. Science *334*, 249–252. https://doi.org/10.1126/science.1211057.

24. Robinson, C.M., Jesudhasan, P.R., and Pfeiffer, J.K. (2014). Bacterial lipopolysaccharide binding enhances virion stability and promotes environmental fitness of an enteric virus. Cell Host Microbe *15*, 36–46. https://doi.org/10.1016/j.chom.2013.12.004.

25. Robinson, C.M. (2019). Enteric viruses exploit the microbiota to promote infection. Curr. Opin. Virol. *37*, 58–62. https://doi.org/10.1016/j.coviro.2019.06.002.

26. Uchiyama, R., Chassaing, B., Zhang, B., and Gewirtz, A.T. (2014). Antibiotic treatment suppresses rotavirus infection and enhances specific humoral immunity. J. Infect. Dis. *210*, 171–182. https://doi.org/10.1093/infdis/jiu037.

27. Baker, J.M., Hasso-Agopsowicz, M., Pitzer, V.E., Platts-Mills, J.A., Peralta-Santos, A., Troja, C., Archer, H., Guo, B., Sheahan, W., Lingappa, J., et al. (2021). Association of enteropathogen detection with diarrhoea by age and high versus low child mortality settings: a systematic review and meta-analysis. Lancet Global Health *9*, e1402–e1410. https://doi.org/10.1016/S2214-109X(21)00316-8.

28. Harper, A., Vijayakumar, V., Ouwehand, A.C., ter Haar, J., Obis, D., Espadaler, J., Binda, S., Desiraju, S., and Day, R. (2020). Viral infections, the microbiome, and probiotics. Front. Cell. Infect. Microbiol. *10*, 596166. https://doi.org/10.3389/fcimb.2020.596166.

29. Mayer, F.L., Wilson, D., and Hube, B. (2013). Candida albicans pathogenicity mechanisms. Virulence *4*, 119–128. https://doi.org/10.4161/viru.22913.

30. Upfold, N.S., Luke, G.A., and Knox, C. (2021). Occurrence of human enteric viruses in water sources and shellfish: a focus on africa. Food Environ. Virol. *13*, 1–31. https://doi.org/10.1007/s12560-020-09456-8.

31. Anwar, H., Iftikhar, A., Muzaffar, H., Almatroudi, A., Allemailem, K.S., Navaid, S., Saleem, S., and Khurshid, M. (2021). Biodiversity of gut microbiota: impact of various host and environmental factors. BioMed Res. Int. *2021*, 5575245. https://doi.org/10.1155/2021/5575245.

32. Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D.R., Fernandes, G.R., Tap, J., Bruls, T., Batto, J.M., et al. (2011). Enterotypes of the human gut microbiome. Nature *473*, 174–180. https://doi.org/10.1038/nature09944.

33. Davenport, E.R., Sanders, J.G., Song, S.J., Amato, K.R., Clark, A.G., and Knight, R. (2017). The human microbiome in evolution. BMC Biol. *15*, 127. https://doi.org/10.1186/s12915-017-0454-7.

34. Turnbaugh, P.J., Ley, R.E., Hamady, M., Fraser-Liggett, C.M., Knight, R., and Gordon, J.I. (2007). The human microbiome project. Nature *449*, 804–810. https://doi.org/10.1038/nature06244.

35. Flores, G.E., Caporaso, J.G., Henley, J.B., Rideout, J.R., Domogala, D., Chase, J., Leff, J.W., Vázquez-Baeza, Y., Gonzalez, A., Knight, R., et al. (2014). Temporal variability is a personalized feature of the human microbiome. Genome Biol. *15*, 531. https://doi.org/10.1186/s13059-014-0531-y.

36. Odamaki, T., Kato, K., Sugahara, H., Hashikura, N., Takahashi, S., Xiao, J.Z., Abe, F., and Osawa, R. (2016). Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC Microbiol. *16*, 90. https://doi.org/10.1186/s12866-016-0708-5.

37. Chey, W.D., Kurlander, J., and Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA *313*, 949–958. https://doi.org/10.1001/jama.2015.0954.

38. Halfvarson, J., Brislawn, C.J., Lamendella, R., Vázquez-Baeza, Y., Walters, W.A., Bramer, L.M., D'Amato, M., Bonfiglio, F., McDonald, D., Gonzalez, A., et al. (2017). Dynamics of the human gut microbiome in inflammatory bowel disease. Nat. Microbiol. *2*, 17004. https://doi.org/10.1038/nmicrobiol.2017.4.

39. Dridi, B., Raoult, D., and Drancourt, M. (2011). Archaea as emerging organisms in complex human microbiomes. Anaerobe *17*, 56–63. https://doi.org/10.1016/j.anaerobe.2011.03.001.

40. Hoffmann, C., Dollive, S., Grunberg, S., Chen, J., Li, H., Wu, G.D., Lewis, J.D., and Bushman, F.D. (2013). Archaea and fungi of the human gut microbiome: correlations with diet and bacterial residents. PLoS One *8*, e66019. https://doi.org/10.1371/journal.pone.0066019.

41. Kim, J.Y., Whon, T.W., Lim, M.Y., Kim, Y.B., Kim, N., Kwon, M.S., Kim, J., Lee, S.H., Choi, H.J., Nam, I.H., et al. (2020). The human gut archaeome: identification of diverse haloarchaea in Korean subjects. Microbiome *8*, 114. https://doi.org/10.1186/s40168-020-00894-x.

42. Bang, C., Weidenbach, K., Gutsmann, T., Heine, H., and Schmitz, R.A. (2014). The intestinal archaea Methanosphaera stadtmanae and Methanobrevibacter smithii activate human dendritic cells. PLoS One *9*, e99411. https://doi.org/10.1371/journal.pone.0099411.

43. Ferrari, A., Brusa, T., Rutili, A., Canzi, E., and Biavati, B. (1994). Isolation and characterization of methanobrevibacter oralis sp. nov. Curr. Microbiol. *29*, 7–12. https://doi.org/10.1007/BF01570184.

44. Kulik, E.M., Sandmeier, H., Hinni, K., and Meyer, J. (2001). Identification of archaeal rDNA from subgingival dental plaque by PCR amplification and sequence analysis. FEMS Microbiol. Lett. *196*, 129–133. https://doi.org/10.1111/j.1574-6968.2001.tb10553.x.

45. Blais Lecours, P., Marsolais, D., Cormier, Y., Berberi, M., Haché, C., Bourdages, R., and Duchaine, C. (2014). Increased prevalence of methanosphaera stadtmanae in inflammatory bowel diseases. PLoS One *9*, e87734. https://doi.org/10.1371/journal.pone.0087734.

46. Pimentel, M., Lin, H.C., Enayati, P., van den Burg, B., Lee, H.R., Chen, J.H., Park, S., Kong, Y., and Conklin, J. (2006). Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. Am. J. Physiol. Gastrointest. Liver Physiol. *290*, G1089–G1095. https://doi.org/10.1152/ajpgi.00574.2004.

47. Pimentel, M., Gunsalus, R.P., Rao, S.S., and Zhang, H. (2012). Methanogens in human health and disease. Am. J. Gastroenterol. Suppl. *1*, 28–33. https://doi.org/10.1038/ajgsup.2012.6.

48. Lukeš, J., Stensvold, C.R., Jirků-Pomajbíková, K., and Wegener Parfrey, L. (2015). Are human intestinal eukaryotes beneficial or commensals? PLoS Pathog. *11*, e1005039. https://doi.org/10.1371/journal.ppat.1005039.

49. Chabé, M., Lokmer, A., and Ségurel, L. (2017). Gut protozoa: friends or foes of the human gut microbiota? Trends Parasitol. *33*, 925–934. https://doi.org/10.1016/j.pt.2017.08.005.

50. Nieves-Ramírez, M.E., Partida-Rodríguez, O., Laforest-Lapointe, I., Reynolds, L.A., Brown, E.M., Valdez-Salazar, A., Morán-Silva, P., Rojas-Velázquez, L., Morien, E., Parfrey, L.W., et al. (2018). Asymptomatic intestinal colonization with protist blastocystis is strongly associated with distinct microbiome ecological patterns. mSystems *3*, e00007-18. https://doi.org/10.1128/mSystems.00007-18.

51. Parfrey, L.W., Walters, W.A., Lauber, C.L., Clemente, J.C., Berg-Lyons, D., Teiling, C., Kodira, C., Mohiuddin, M., Brunelle, J., Driscoll, M., et al. (2014). Communities of microbial eukaryotes in the mammalian gut within the context of environmental eukaryotic diversity. Front. Microbiol. *5*, 298. https://doi.org/10.3389/fmicb.2014.00298.

52. Scanlan, P.D., Stensvold, C.R., Rajilić-Stojanović, M., Heilig, H.G.H.J., de Vos, W.M., O'Toole, P.W., and Cotter, P.D. (2014). The microbial eukaryote Blastocystis is a prevalent and diverse member of the healthy human gut microbiota. FEMS Microbiol. Ecol. *90*, 326–330. https://doi.org/10.1111/1574-6941.12396.

53. Barratt, J.L.N., Harkness, J., Marriott, D., Ellis, J.T., and Stark, D. (2011). A review of Dientamoeba fragilis carriage in humans: several reasons why this organism should be considered in the diagnosis of gastrointestinal illness. Gut Microb. *2*, 3–12. https://doi.org/10.4161/gmic.2.1.14755.

54. Sarzhanov, F., Dogruman-Al, F., Santin, M., Maloney, J.G., Gureser, A.S., Karasartova, D., and Taylan-Ozkan, A. (2021). Investigation of neglected protists blastocystis sp. and Dientamoeba fragilis in immunocompetent and immunodeficient diarrheal patients using both conventional and molecular methods. PLoS Neglected Trop. Dis. *15*, e0009779. https://doi.org/10.1371/JOURNAL.PNTD.0009779.

55. Smits, H.H., and Yazdanbakhsh, M. (2007). Chronic helminth infections modulate allergen-specific immune responses: protection against development of allergic disorders? Ann. Med. *39*, 428–439. https://doi.org/10.1080/07853890701436765.

56. Gazzinelli-Guimarães, P.H., Bonne-Année, S., Fujiwara, R.T., Santiago, H.C., and Nutman, T.B. (2016). Allergic sensitization underlies hyperreactive antigen-specific CD4+ T cell responses in coincident filarial infection. J. Immunol. *197*, 2772–2779. https://doi.org/10.4049/jimmunol.1600829.

57. Maizels, R.M., and McSorley, H.J. (2016). Regulation of the host immune system by helminth parasites. J. Allergy Clin. Immunol. *138*, 666–675. https://doi.org/10.1016/j.jaci.2016.07.007.

58. Gazzinelli-Guimarães, P.H., de Freitas, L.F.D., Gazzinelli-Guimarães, A.C., Coelho, F., Barbosa, F.S., Nogueira, D., Amorim, C., Dhom-Lemos, L.d.C., Oliveira, L.M., da Silveira, A.B., et al. (2017). Concomitant helminth infection downmodulates the Vaccinia virus-specific immune response and potentiates virus-associated pathology. Int. J. Parasitol. *47*, 1–10. https://doi.org/10.1016/j.ijpara.2016.08.007.

59. Fiers, W.D., Gao, I.H., and Iliev, I.D. (2019). Gut mycobiota under scrutiny: fungal symbionts or environmental transients? Curr. Opin. Microbiol. *50*, 79–86. https://doi.org/10.1016/j.mib.2019.09.010.

60. 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., et al. (2017). The gut mycobiome of the Human Microbiome Project healthy cohort. Microbiome *5*, 153. https://doi.org/10.1186/s40168-017-0373-4.

61. Hallen-Adams, H.E., Kachman, S.D., Kim, J., Legge, R.M., and Martínez, I. (2015). Fungi inhabiting the healthy human gastrointestinal tract: a diverse and dynamic community. Fungal Ecology *15*, 9–17. https://doi.org/10.1016/j.funeco.2015.01.006.

62. Hallen-Adams, H.E., and Suhr, M.J. (2017). Fungi in the healthy human gastrointestinal tract. Virulence *8*, 352–358. https://doi.org/10.1080/21505594.2016.1247140.

63. Raimondi, S., Amaretti, A., Gozzoli, C., Simone, M., Righini, L., Candeliere, F., Brun, P., Ardizzoni, A., Colombari, B., Paulone, S., et al. (2019). Longitudinal survey of fungi in the human gut: ITS profiling, phenotyping, and colonization. Front. Microbiol. *10*, 1575. https://doi.org/10.3389/fmicb.2019.01575.

64. Benno, Y., Sawada, K., and Mitsuoka, T. (1984). The intestinal microflora of infants: composition of fecal flora in breast-fed and bottle-fed infants. Microbiol. Immunol. *28*, 975–986.

65. Kondori, N., Nowrouzian, F., Ajdari, M., Hesselmar, B., Saalman, R., Wold, A.E., and Adlerberth, I. (2020). Candida species as commensal gut colonizers: a study of 133 longitudinally followed Swedish infants.

Med. Mycol. *58*, 485–492. https://doi.org/10.1093/MMY/MYZ091.

66. Liang, G., and Bushman, F.D. (2021). The human virome: assembly, composition and host interactions. Nat. Rev. Microbiol. *19*, 514–527. https://doi.org/10.1038/s41579-021-00536-5.

67. Adiliaghdam, F., and Jeffrey, K.L. (2020). Illuminating the human virome in health and disease. Genome Med. *12*, 66. https://doi.org/10.1186/s13073-020-00766-x.

68. Taboada, B., Morán, P., Serrano-Vázquez, A., Iša, P., Rojas-Velázquez, L., Pérez-Juárez, H., López, S., Torres, J., Ximenez, C., and Arias, C.F. (2021). The gut virome of healthy children during the first year of life is diverse and dynamic. PLoS One *16*, e0240958. https://doi.org/10.1371/journal.pone.0240958.

69. Edwards, R.A., Vega, A.A., Norman, H.M., Ohaeri, M., Levi, K., Dinsdale, E.A., Cinek, O., Aziz, R.K., McNair, K., Barr, J.J., et al. (2019). Global phylogeography and ancient evolution of the widespread human gut virus crAssphage. Nat. Microbiol. *4*, 1727–1736. https://doi.org/10.1038/s41564-019-0494-6.

70. Rascovan, N., Duraisamy, R., and Desnues, C. (2016). Metagenomics and the human virome in asymptomatic individuals. Annu. Rev. Microbiol. *70*, 125–141. https://doi.org/10.1146/annurev-micro-102215-095431.

71. Lim, E.S., Zhou, Y., Zhao, G., Bauer, I.K., Droit, L., Ndao, I.M., Warner, B.B., Tarr, P.I., Wang, D., and Holtz, L.R. (2015). Early life dynamics of the human gut virome and bacterial microbiome in infants. Nat. Med. *21*, 1228–1234. https://doi.org/10.1038/nm.3950.

72. Aguado-García, Y., Taboada, B., Morán, P., Rivera-Gutiérrez, X., Serrano-Vázquez, A., Iša, P., Rojas-Velázquez, L., Pérez-Juárez, H., López, S., Torres, J., et al. (2020). Tobamoviruses can be frequently present in the oropharynx and gut of infants during their first year of life. Sci. Rep. *10*, 13595. https://doi.org/10.1038/s41598-020-70684-w.

73. Chowdhary, A., Sharma, C., and Meis, J.F. (2017). Candida auris: a rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. PLoS Pathog. *13*, e1006290. https://doi.org/10.1371/journal.ppat.1006290.

74. Lockhart, S.R., Etienne, K.A., Vallabhaneni, S., Farooqi, J., Chowdhary, A., Govender, N.P., Colombo, A.L., Calvo, B., Cuomo, C.A., Desjardins, C.A., et al. (2017). Simultaneous emergence of multidrug-resistant candida auris on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin. Infect. Dis. *64*, 134–140. https://doi.org/10.1093/cid/ciw691.

75. Moran, G.P., Coleman, D.C., and Sullivan, D.J. (2012). Candida albicans versus Candida dubliniensis: why Is C. albicans more pathogenic? Internet J. Microbiol. *2012*, 205921. https://doi.org/10.1155/2012/205921.

76. Pappas, P.G. (2006). Invasive candidiasis. Infect. Dis. Clin. *20*, 485–506. https://doi.org/10.1016/j.idc.2006.07.004.

77. Akpan, A., and Morgan, R. (2002). Oral candidiasis. Postgrad. Med. *78*, 455–459. https://doi.org/10.1136/pmj.78.922.455.

78. Pfaller, M.A., and Diekema, D.J. (2007). Epidemiology of invasive candidiasis: a persistent public health problem. Clin. Microbiol. Rev. *20*, 133–163. https://doi.org/10.1128/CMR.00029-06.

79. Williams, D.W., Jordan, R.P.C., Wei, X.-Q., Alves, C.T., Wise, M.P., Wilson, M.J., and Lewis, M.A.O. (2013). Interactions of Candida albicans with host epithelial surfaces. J. Oral Microbiol. *5*, 22434. https://doi.org/10.3402/jom.v5i0.22434.

80. Ellis-Pegler, R.B., Crabtree, C., and Lambert, H.P. (1975). The faecal flora of children in the United Kingdom. J. Hyg. *75*, 135–142. https://doi.org/10.1017/s002217240004715x.

81. Moyes, D.L., Richardson, J.P., and Naglik, J.R. (2015). Candida albicans-epithelial interactions and pathogenicity mechanisms: scratching the surface. Virulence *6*, 338–346. https://doi.org/10.1080/21505594.2015.1012981.

82. Odds, F.C., and Kerridge, D. (1985). Morphogenesis in candida albicans. Crit. Rev. Microbiol. *12*, 45–93. https://doi.org/10.3109/10408418509104425.

83. Mishra, A.A., and Koh, A.Y. (2021). The microbial and host factors that govern Candida gastrointestinal colonization and dissemination. Curr. Opin. Microbiol. *63*, 29–35. https://doi.org/10.1016/j.mib.2021.05.012.

84. Chen, C., Pande, K., French, S.D., Tuch, B.B., and Noble, S.M. (2011). An iron homeostasis regulatory circuit with reciprocal roles in Candida albicans commensalism and pathogenesis. Cell Host Microbe *10*, 118–135. https://doi.org/10.1016/j.chom.2011.07.005.

85. Huang, G., Wang, H., Chou, S., Nie, X., Chen, J., and Liu, H. (2006). Bistable expression of WOR1, a master regulator of white-opaque switching in Candida albicans. Proc. Natl. Acad. Sci. USA *103*, 12813–12818. https://doi.org/10.1073/pnas.0605270103.

86. Pande, K., Chen, C., and Noble, S.M. (2013). Passage through the mammalian gut triggers a phenotypic switch that promotes Candida albicans commensalism. Nat. Genet. *45*, 1088–1091. https://doi.org/10.1038/ng.2710.

87. Witchley, J.N., Penumetcha, P., Abon, N.V., Woolford, C.A., Mitchell, A.P., and Noble, S.M. (2019). Candida albicans morphogenesis programs control the balance between gut commensalism and invasive infection. Cell Host Microbe *25*, 432–443.e6. https://doi.org/10.1016/j.chom.2019.02.008.

88. Lu, Y., Su, C., Wang, A., and Liu, H. (2011). Hyphal development in Candida albicans requires two temporally linked changes in promoter chromatin for initiation and maintenance. PLoS Biol. *9*, e1001105. https://doi.org/10.1371/journal.pbio.1001105.

89. Lu, Y., Su, C., and Liu, H. (2014). Candida albicans hyphal initiation and elongation. Trends Microbiol. *22*, 707–714. https://doi.org/10.1016/j.tim.2014.09.001.

90. Shao, T.Y., Kakade, P., Witchley, J.N., Frazer, C., Murray, K.L., Ene, I.V., Haslam, D.B., Hagan, T., Noble, S.M., Bennett, R.J., and Way, S.S. (2022). Candida albicans oscillating UME6 expression during intestinal colonization primes systemic Th17 protective immunity. Cell Rep. *39*, 110837. https://doi.org/10.1016/j.celrep.2022.110837.

91. Cao, F., Lane, S., Raniga, P.P., Lu, Y., Zhou, Z., Ramon, K., Chen, J., and Liu, H. (2006). The Flo8 transcription factor is essential for hyphal development and virulence in Candida albicans. Mol. Biol. Cell *17*, 295–307. https://doi.org/10.1091/mbc.e05-06-05022011.

92. Prieto, D., Román, E., Correia, I., and Pla, J. (2014). The HOG pathway is critical for the colonization of the mouse gastrointestinal tract by Candida albicans. PLoS One *9*, e87128. https://doi.org/10.1371/journal.pone.0087128.

93. Hirakawa, M.P., Martinez, D.A., Sakthikumar, S., Anderson, M.Z., Berlin, A., Gujja, S., Zeng, Q., Zisson, E., Wang, J.M., Greenberg, J.M., et al. (2015). Genetic and phenotypic intra-species variation in Candida albicans. Genome Res. *25*, 413–425. https://doi.org/10.1101/gr.174623.114.

94. Tso, G.H.W., Reales-Calderon, J.A., Tan, A.S.M., Sem, X., Le, G.T.T., Tan, T.G., Lai, G.C., Srinivasan, K.G., Yurieva, M., Liao, W., et al. (2018). Experimental evolution of a fungal pathogen into a gut symbiont. Science *362*, 589–595. https://doi.org/10.1126/science.aat0537.

95. Pierce, J.V., and Kumamoto, C.A. (2012). Variation in Candida albicans EFG1 expression enables host-dependent changes in colonizing fungal populations. mBio *3*, 001177-12. https://doi.org/10.1128/mBio.00117-12.

96. Vautier, S., Drummond, R.A., Chen, K., Murray, G.I., Kadosh, D., Brown, A.J.P., Gow, N.A.R., MacCallum, D.M., Kolls, J.K., and Brown, G.D. (2015). Candida albicans colonization and dissemination from the murine gastrointestinal tract: the influence of morphology and Th17 immunity. Cell Microbiol. *17*, 445–450. https://doi.org/10.1111/cmi.12388.

97. Böhm, L., Torsin, S., Tint, S.H., Eckstein, M.T., Ludwig, T., and Pérez, J.C. (2017). The yeast form of the fungus Candida albicans promotes persistence in the gut of gnotobiotic mice. PLoS Pathog. *13*, e1006699. https://doi.org/10.1371/journal.ppat.1006699.

98. Childers, D.S., Raziunaite, I., Mol Avelar, G., Mackie, J., Budge, S., Stead, D., Gow, N.A.R., Lenardon, M.D., Ballou, E.R., MacCallum, D.M., and Brown, A.J.P. (2016). The rewiring of ubiquitination targets in a pathogenic yeast promotes metabolic flexibility, host colonization and virulence. PLoS Pathog. *12*, e1005566. https://doi.org/10.1371/journal.ppat.1005566.

99. Sandai, D., Yin, Z., Selway, L., Stead, D., Walker, J., Leach, M.D., Bohovych, I., Ene, I.V., Kastora, S., Budge, S., et al. (2012). The evolutionary rewiring of ubiquitination targets has reprogrammed the regulation of carbon assimilation in the pathogenic yeast Candida albicans. mBio *3*, 004955-12. https://doi.org/10.1128/mBio.00495-12.

100. Ramírez-Zavala, B., Mottola, A., Haubenreißer, J., Schneider, S., Allert, S., Brunke, S., Ohlsen, K., Hube, B., and Morschhäuser, J. (2017). The Snf1-activating kinase Sak1 is a key regulator of metabolic adaptation and in vivo fitness of Candida albicans. Mol. Microbiol. *104*, 989–1007. https://doi.org/10.1111/mmi.13674.

101. Du, H., Guan, G., Li, X., Gulati, M., Tao, L., Cao, C., Johnson, A.D., Nobile, C.J., and Huang, G. (2015). N-Acetylglucosamine-induced cell death in Candida albicans and its implications for adaptive mechanisms of nutrient sensing in yeasts. mBio *6*, 013766-15. https://doi.org/10.1128/mBio.01376-15.

102. Mamouei, Z., Zeng, G., Wang, Y.M., and Wang, Y. (2017). Candida albicans possess a highly versatile and dynamic high-affinity iron transport system important for its commensal-pathogenic lifestyle. Mol. Microbiol. *106*, 986–998. https://doi.org/10.1111/mmi.13864.

103. Tan, T.G., Lim, Y.S., Tan, A., Leong, R., and Pavelka, N. (2019). Fungal symbionts produce prostaglandin E2 to promote their intestinal colonization. Front. Cell. Infect. Microbiol. *9*, 359. https://doi.org/10.3389/fcimb.2019.00359.

104. Fan, D., Coughlin, L.A., Neubauer, M.M., Kim, J., Kim, M.S., Zhan, X., Simms-Waldrip, T.R., Xie, Y., Hooper, L.V., and Koh, A.Y. (2015). Activation of HIF-1α and LL-37 by commensal bacteria inhibits Candida albicans colonization. Nat. Med. *21*, 808–814. https://doi.org/10.1038/nm.3871.

105. Matsuo, K., Haku, A., Bi, B., Takahashi, H., Kamada, N., Yaguchi, T., Saijo, S., Yoneyama, M., and Goto, Y. (2019). Fecal microbiota transplantation prevents Candida albicans from colonizing the gastrointestinal tract. Microbiol. Immunol. *63*, 155–163. https://doi.org/10.1111/1348-0421.12680.

106. Zaborin, A., Smith, D., Garfield, K., Quensen, J., Shakhsheer, B., Kade, M., Tirrell, M., Tiedje, J., Gilbert, J.A., Zaborina, O., and Alverdy, J.C. (2014). Membership and behavior of ultra-low-diversity pathogen communities present in the gut of humans during prolonged critical illness. mBio *5*, 013611-1–4. https://doi.org/10.1128/mBio.01361-14.

107. Zhai, B., Ola, M., Rolling, T., Tosini, N.L., Joshowitz, S., Littmann, E.R., Amoretti, L.A., Fontana, E., Wright, R.J., Miranda, E., et al. (2020). High-resolution mycobiota analysis reveals dynamic intestinal translocation preceding invasive candidiasis. Nat. Med. *26*, 59–64. https://doi.org/10.1038/s41591-019-0709-7.

108. Guinan, J., Villa, P., and Thangamani, S. (2018). Secondary bile acids inhibit Candida albicans growth and morphogenesis. Pathog. Dis. *76*. https://doi.org/10.1093/femspd/fty038.

109. Guinan, J., Wang, S., Hazbun, T.R., Yadav, H., and Thangamani, S. (2019). Antibiotic-induced decreases in the levels of microbial-derived short-chain fatty acids correlate with increased gastrointestinal colonization of Candida albicans. Sci. Rep. *9*, 8872. https://doi.org/10.1038/s41598-019-45467-7.

110. Mason, K.L., Erb Downward, J.R., Mason, K.D., Falkowski, N.R., Eaton, K.A., Kao, J.Y., Young, V.B., and Huffnagle, G.B. (2012). Candida albicans and bacterial microbiota interactions in the cecum during recolonization following broad-spectrum antibiotic therapy. Infect. Immun. *80*, 3371–3380. https://doi.org/10.1128/IAI.00449-12.

111. Shao, T.Y., Ang, W.X.G., Jiang, T.T., Huang, F.S., Andersen, H., Kinder, J.M., Pham, G., Burg, A.R., Ruff, B., Gonzalez, T., et al. (2019). Commensal Candida albicans positively calibrates systemic Th17 immunological responses. Cell Host Microbe *25*, 404–417.e6. https://doi.org/10.1016/j.chom.2019.02.004.

112. Leonardi, I., Li, X., Semon, A., Li, D., Doron, I., Putzel, G., Bar, A., Prieto, D., Rescigno, M., McGovern, D.P.B., et al. (2018). CX3CR1 mononuclear phagocytes control immunity to intestinal fungi. Science *359*, 232–236. https://doi.org/10.1126/science.aao1503.

113. Li, X.V., Leonardi, I., and Iliev, I.D. (2019). Gut mycobiota in immunity and inflammatory disease. Immunity *50*, 1365–1379. https://doi.org/10.1016/j.immuni.2019.05.023.

114. Doron, I., Leonardi, I., Li, X.V., Fiers, W.D., Semon, A., Bialt-DeCelie, M., Migaud, M., Gao, I.H., Lin, W.Y., Kusakabe, T., et al. (2021). Human gut mycobiota tune immunity via CARD9-dependent induction of anti-fungal IgG antibodies. Cell *184*, 1017–1031.e14. https://doi.org/10.1016/j.cell.2021.01.016.

115. Mateus, M.D. (2017). Bridging the gap between knowing and modeling viruses in marine systems—an upcoming frontier. Front. Mar. Sci. *3*, 284. https://doi.org/10.3389/fmars.2016.00284.

116. Maqsood, R., Rodgers, R., Rodriguez, C., Handley, S.A., Ndao, I.M., Tarr, P.I., Warner, B.B., Lim, E.S., and Holtz, L.R. (2019). Discordant transmission of bacteria and viruses from mothers to babies at birth. Microbiome *7*, 156. https://doi.org/10.1186/s40168-019-0766-7.

117. Clooney, A.G., Sutton, T.D.S., Shkoporov, A.N., Holohan, R.K., Daly, K.M., O'Regan, O., Ryan, F.J., Draper, L.A., Plevy, S.E., Ross, R.P., and Hill, C. (2019). Whole-virome analysis sheds light on viral dark matter in inflammatory bowel disease. Cell Host Microbe *26*, 764–778.e5.

118. Emlet, C., Ruffin, M., and Lamendella, R. (2020). Enteric virome and carcinogenesis in the gut. Dig. Dis. Sci. *65*, 852–864. https://doi.org/10.1007/s10620-020-06126-4.

119. Liang, G., Conrad, M.A., Kelsen, J.R., Kessler, L.R., Breton, J., Albenberg, L.G., Marakos, S., Galgano, A., Devas, N., Erlichman, J., et al. (2020). Dynamics of the stool virome in very early-onset inflammatory bowel disease. J. Crohns Colitis *14*, 1600–1610. https://doi.org/10.1093/ecco-jcc/jjaa094.

120. 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., et al. (2015). Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell *160*, 447–460. https://doi.org/10.1016/j.cell.2015.01.002.

121. Zhao, G., Vatanen, T., Droit, L., Park, A., Kostic, A.D., Poon, T.W., Vlamakis, H., Siljander, H., Härkönen, T., Hämäläinen, A.M., et al. (2017). Intestinal virome changes precede autoimmunity in type I diabetes-susceptible children. Proc. Natl. Acad. Sci. USA *114*, E6166–E6175. https://doi.org/10.1073/pnas.1706359114.

122. Liang, G., Zhao, C., Zhang, H., Mattei, L., Sherrill-Mix, S., Bittinger, K., Kessler, L.R., Wu, G.D., Baldassano, R.N., DeRusso, P., et al. (2020b). The stepwise assembly of the virome is modulated by breastfeeding. Nature *581*, 470–474. https://doi.org/10.1038/s41586-020-2192-1.

123. Mogotsi, M.T., Mwangi, P.N., Bester, P.A., Mphahlele, M.J., Seheri, M.L., O'Neill, H.G., and Nyaga, M.M. (2020). Metagenomic analysis of the enteric rna virome of infants from the oukasie clinic, north west province, South Africa, reveals diverse eukaryotic viruses. Viruses *12*, 1260. https://doi.org/10.3390/v12111260.

124. Manrique, P., Dills, M., and Young, M.J. (2017). The human gut phage community and its implications for health and disease. Viruses *9*, 141. https://doi.org/10.3390/v9060141.

125. Dutilh, B.E., Cassman, N., McNair, K., Sanchez, S.E., Silva, G.G.Z., Boling, L., Barr, J.J., Speth, D.R., Seguritan, V., Aziz, R.K., et al. (2014). A highly abundant bacteriophage discovered in the unknown sequences of human faecal metagenomes. Nat. Commun. *5*, 4498. https://doi.org/10.1038/ncomms5498.

126. Guerin, E., Shkoporov, A., Stockdale, S.R., Clooney, A.G., Ryan, F.J., Sutton, T.D.S., Draper, L.A., Gonzalez-Tortuero, E., Ross, R.P., and Hill, C. (2018). Biology and taxonomy of crAss-like bacteriophages, the most abundant virus in the human gut. Cell Host Microbe *24*, 653–664.e6. https://doi.org/10.1016/j.chom.2018.10.002.

127. Shkoporov, A.N., Khokhlova, E.V., Fitzgerald, C.B., Stockdale, S.R., Draper,

L.A., Ross, R.P., and Hill, C. (2018). ΦCrAss001 represents the most abundant bacteriophage family in the human gut and infects Bacteroides intestinalis. Nat. Commun. *9*, 4781. https://doi.org/10.1038/s41467-018-07225-7.

128. Fong, T.T., and Lipp, E.K. (2005). Enteric viruses of humans and animals in aquatic environments: health risks, detection, and potential water quality assessment tools. Microbiol. Mol. Biol. Rev. *69*, 357–371. https://doi.org/10.1128/mmbr.69.2.357-371.2005.

129. Natarajan, A., Zlitni, S., Brooks, E.F., Vance, S.E., Dahlen, A., Hedlin, H., Park, R.M., Han, A., Schmidtke, D.T., Verma, R., et al. (2022). Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection. Med *3*, 371–387.e9. https://doi.org/10.1016/j.medj.2022.04.001.

130. Zollner, A., Koch, R., Jukic, A., Pfister, A., Meyer, M., Rössler, A., Kimpel, J., Adolph, T.E., and Tilg, H. (2022). Postacute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases. Gastroenterology *163*, 495–506.e8. https://doi.org/10.1053/j.gastro.2022.04.037.

131. Qi, F., Qian, S., Zhang, S., and Zhang, Z. (2020). Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem. Biophys. Res. Commun. *526*, 135–140. https://doi.org/10.1016/j.bbrc.2020.03.044.

132. Xu, J., Chu, M., Zhong, F., Tan, X., Tang, G., Mai, J., Lai, N., Guan, C., Liang, Y., and Liao, G. (2020). Digestive symptoms of COVID-19 and expression of ACE2 in digestive tract organs. Cell Death Dis. *6*, 76. https://doi.org/10.1038/s41420-020-00307-w.

133. Bernard-Raichon, L., Venzon, M., Klein, J., Axelrad, J.E., Zhang, C., Sullivan, A.P., Hussey, G.A., Casanovas-Massana, A., Noval, M.G., Valero-Jimenez, A.M., et al. (2022). Gut microbiome dysbiosis in antibiotic-treated COVID-19 patients is associated with microbial translocation and bacteremia. Nat. Commun. *13*, 5926. https://doi.org/10.1038/s41467-022-33395-6.

134. Clark, B., and McKendrick, M. (2004). A review of viral gastroenteritis. Curr. Opin. Infect. Dis. *17*, 461–469. https://doi.org/10.1097/00001432-200410000-00011.

135. Desselberger, U. (2017). Viral gastroenteritis. Medicine *45*, 690–694. https://doi.org/10.1016/j.mpmed.2017.08.005.

136. Makimaa, H., Ingle, H., and Baldridge, M.T. (2020). Enteric viral co-infections: pathogenesis and perspective. Viruses *12*, 904. https://doi.org/10.3390/v12080904.

137. Liu, L., Oza, S., Hogan, D., Chu, Y., Perin, J., Zhu, J., Lawn, J.E., Cousens, S., Mathers, C., and Black, R.E. (2016). Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet *388*, 3027–3035. https://doi.org/10.1016/S0140-6736(16)31593-8.

138. Perin, J., Mulick, A., Yeung, D., Villavicencio, F., Lopez, G., Strong, K.L., Prieto-Merino, D., Cousens, S., Black, R.E., and Liu, L. (2022). Global, regional, and national causes of under-5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. Child Adolesc. Health *6*, 106–115. https://doi.org/10.1016/S2352-4642(21)00311-4.

139. Kernbauer, E., Ding, Y., and Cadwell, K. (2014). An enteric virus can replace the beneficial function of commensal bacteria. Nature *516*, 94–98. https://doi.org/10.1038/nature13960.

140. Abt, M.C., Buffie, C.G., Sušac, B., Becattini, S., Carter, R.A., Leiner, I., Keith, J.W., Artis, D., Osborne, L.C., and Pamer, E.G. (2016). TLR-7 activation enhances IL-22-mediated colonization resistance against vancomycin-resistant enterococcus. Sci. Transl. Med. *8*, 327ra25. https://doi.org/10.1126/scitranslmed.aad6663.

141. Ott, S.J., Waetzig, G.H., Rehman, A., Moltzau-Anderson, J., Bharti, R., Grasis, J.A., Cassidy, L., Tholey, A., Fickenscher, H., Seegert, D., et al. (2017). Efficacy of sterile fecal filtrate transfer for treating patients with Clostridium difficile infection. Gastroenterology *152*, 799–811.e7. https://doi.org/10.1053/j.gastro.2016.11.010.

142. Thépaut, M., Grandjean, T., Hober, D., Lobert, P.E., Bortolotti, P., Faure, K., Dessein, R., Kipnis, E., and Guery, B. (2015). Protective role of murine norovirus against Pseudomonas aeruginosa acute pneumonia. Vet. Res. *46*, 91. https://doi.org/10.1186/s13567-015-0239-3.

143. 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., et al. (2016). Enteric viruses ameliorate gut inflammation via toll-like receptor 3 and toll-like receptor 7-mediated interferon-β production. Immunity *44*, 889–900. https://doi.org/10.1016/j.immuni.2016.03.009.

144. Sun, L., Miyoshi, H., Origanti, S., Nice, T.J., Barger, A.C., Manieri, N.A., Fogel, L.A., French, A.R., Piwnica-Worms, D., Piwnica-Worms, H., et al. (2015). Type I interferons link viral infection to enhanced epithelial turnover and repair. Cell Host Microbe *17*, 85–97. https://doi.org/10.1016/j.chom.2014.11.004.

145. Ingle, H., Lee, S., Ai, T., Orvedahl, A., Rodgers, R., Zhao, G., Sullender, M., Peterson, S.T., Locke, M., Liu, T.C., et al. (2019). Viral complementation of immunodeficiency confers protection against enteric pathogens via interferon-λ. Nat. Microbiol. *4*, 1120–1128. https://doi.org/10.1038/s41564-019-0416-7.

146. Besemer, K. (2015). Biodiversity, community structure and function of biofilms in stream ecosystems. Res. Microbiol. *166*, 774–781. https://doi.org/10.1016/j.resmic.2015.05.006.

147. Nobile, C.J., and Johnson, A.D. (2015). Candida albicans biofilms and human disease. Annu. Rev. Microbiol. *69*, 71–92. https://doi.org/10.1146/annurev-micro-091014-104330.

148. Elias, S., and Banin, E. (2012). Multi-species biofilms: living with friendly neighbors. FEMS Microbiol. Rev. *36*, 990–1004. https://doi.org/10.1111/j.1574-6976.2012.00325.x.

149. Hall-Stoodley, L., Stoodley, P., Kathju, S., Høiby, N., Moser, C., Costerton, J.W., Moter, A., and Bjarnsholt, T. (2012). Towards diagnostic guidelines for biofilm-associated infections. FEMS Immunol. Med. Microbiol. *65*, 127–145. https://doi.org/10.1111/j.1574-695X.2012.00968.x.

150. Preda, V.G., and Săndulescu, O. (2019). Communication is the key: biofilms, quorum sensing, formation and prevention. Discoveries *7*, e100. https://doi.org/10.15190/d.2019.13.

151. Rumbaugh, K.P. (2020). How well are we translating biofilm research from bench-side to bedside? Biofilms *2*, 100028. https://doi.org/10.1016/j.bioflm.2020.100028.

152. Van Acker, H., Van Dijck, P., and Coenye, T. (2014). Molecular mechanisms of antimicrobial tolerance and resistance in bacterial and fungal biofilms. Trends Microbiol. *22*, 326–333. https://doi.org/10.1016/j.tim.2014.02.001.

153. Van Dyck, K., Pinto, R.M., Pully, D., and Van Dijck, P. (2021). Microbial interkingdom biofilms and the quest for novel therapeutic strategies. Microorganisms *9*, 412. https://doi.org/10.3390/microorganisms9020412.

154. De Sordi, L., and Mühlschlegel, F.A. (2009). Quorum sensing and fungal-bacterial interactions in *Candida albicans*: a communicative network regulating microbial coexistence and virulence. FEMS Yeast Res. *9*, 990–999. https://doi.org/10.1111/j.1567-1364.2009.00573.x.

155. Nett, J.E., and Pohl, C.H. (2021). Editorial: fungal biofilms in infection and disease. Front. Cell. Infect. Microbiol. *11*, 753650. https://doi.org/10.3389/fcimb.2021.753650.

156. Pohl, C.H. (2022). Recent advances and opportunities in the study of Candida albicans polymicrobial biofilms. Front. Cell. Infect. Microbiol. *18*, 836379. https://doi.org/10.3389/fcimb.2022.836379.

157. Nishimoto, A., Wohlgemuth, N., Rosch, J., Schultz-Cherry, S., Cortez, V., and Rowe, H.M. (2021). Transkingdom interactions important for the pathogenesis of human viruses. J. Infect. Dis. *223*, S201–S208. https://doi.org/10.1093/infdis/jiaa735.

158. Von Borowski, R.G., and Trentin, D.S. (2021). Biofilms and coronavirus reservoirs: a perspective review. Appl. Environ. Microbiol. *87*, e0085921. https://doi.org/10.1128/AEM.00859-21.

159. Quignon, F., Sardin, M., Kiene, L., and Schwartzbrod, L. (1997). Poliovirus-1 inactivation and interaction with biofilm: a pilot-scale study. Appl. Environ. Microbiol.

63, 978–982. https://doi.org/10.1128/aem.63.3.978-982.1997.

160. Skraber, S., Ogorzaly, L., Helmi, K., Maul, A., Hoffmann, L., Cauchie, H.M., and Gantzer, C. (2009). Occurrence and persistence of enteroviruses, noroviruses and F-specific RNA phages in natural wastewater biofilms. Water Res. *43*, 4780–4789. https://doi.org/10.1016/j.watres.2009.05.020.

161. Storey, M.V., and Ashbolt, N.J. (2003). Enteric virions and microbial biofilms-a secondary source of public health concern? Water Sci. Technol. *48*, 97–104.

162. Cavalheiro, M., and Teixeira, M.C. (2018). Candida biofilms: threats, challenges, and promising strategies. Front. Med. *5*, 28. https://doi.org/10.3389/fmed.2018.00028.

163. Lohse, M.B., Gulati, M., Johnson, A.D., and Nobile, C.J. (2018). Development and regulation of single- and multi-species Candida albicans biofilms. Nat. Rev. Microbiol. *16*, 19–31. https://doi.org/10.1038/nrmicro.2017.107.

164. Kumamoto, C.A., Gresnigt, M.S., and Hube, B. (2020). The gut, the bad and the harmless: Candida albicans as a commensal and opportunistic pathogen in the intestine. Curr. Opin. Microbiol. *56*, 7–15. https://doi.org/10.1016/j.mib.2020.05.006.

165. Mazaheritehrani, E., Sala, A., Orsi, C.F., Neglia, R.G., Morace, G., Blasi, E., and Cermelli, C. (2014). Human pathogenic viruses are retained in and released by Candida albicans biofilm in vitro. Virus Res. *179*, 153–160. https://doi.org/10.1016/j.virusres.2013.10.018.

166. Chandra, J., McCormick, T.S., Imamura, Y., Mukherjee, P.K., and Ghannoum, M.A. (2007). Interaction of Candida albicans with adherent human peripheral blood mononuclear cells increases C. albicans biofilm formation and results in differential expression of pro- and anti-inflammatory cytokines. Infect. Immun. *75*, 2612–2620. https://doi.org/10.1128/IAI.01841-06.

167. Feller, L., Khammissa, R.A.G., Chandran, R., Altini, M., and Lemmer, J. (2014). Oral candidosis in relation to oral immunity. J. Oral Pathol. Med. *43*, 563–569. https://doi.org/10.1111/jop.12120.

168. Ascione, C., Sala, A., Mazaheri-Tehrani, E., Paulone, S., Palmieri, B., Blasi, E., and Cermelli, C. (2017). Herpes simplex virus-1 entrapped in Candida albicans biofilm displays decreased sensitivity to antivirals and UVA1 laser treatment. Ann. Clin. Microbiol. Antimicrob. *16*, 72. https://doi.org/10.1186/s12941-017-0246-5.

169. Cermelli, C., Orsi, C.F., Cuoghi, A., Ardizzoni, A., Tagliafico, E., Neglia, R., Peppoloni, S., and Blasi, E. (2009). Gene expression profiling of monocytes displaying herpes simplex virus 1 induced dysregulation of antifungal defences. J. Med. Microbiol. *58*, 1283–1290. https://doi.org/10.1099/jmm.0.011023-0.

170. Plotkin, B.J., Sigar, I.M., Tiwari, V., and Halkyard, S. (2016a). Determination of biofilm initiation on virus-infected cells by bacteria and fungi. JoVE *113*, 54162. https://doi.org/10.3791/54162.

171. Cermelli, C., Orsi, C.F., Ardizzoni, A., Lugli, E., Cenacchi, V., Cossarizza, A., and Blasi, E. (2008). Herpes simplex virus type 1 dysregulates anti-fungal defenses preventing monocyte activation and downregulating toll-like receptor-2. Microbiol. Immunol. *52*, 575–584. https://doi.org/10.1111/j.1348-0421.2008.00074.x.

172. Plotkin, B.J., Sigar, I.M., Tiwari, V., and Halkyard, S. (2016b). Herpes simplex virus (HSV) modulation of Staphylococcus aureus and Candida albicans initiation of HeLa 299 cell-associated biofilm. Curr. Microbiol. *72*, 529–537. https://doi.org/10.1007/s00284-015-0975-7.

173. Nazik, H., Joubert, L.M., Secor, P.R., Sweere, J.M., Bollyky, P.L., Sass, G., Cegelski, L., and Stevens, D.A. (2017). Pseudomonas phage inhibition of Candida albicans. Microbiology *163*, 1568–1577. https://doi.org/10.1099/mic.0.000539.

174. Penner, J.C., Ferreira, J.A.G., Secor, P.R., Sweere, J.M., Birukova, M.K., Joubert, L.M., Haagensen, J.A.J., Garcia, O., Malkovskiy, A.V., Kaber, G., et al. (2016). Pf4 bacteriophage produced by Pseudomonas aeruginosa inhibits Aspergillus fumigatus metabolism via iron sequestration. Microbiology *162*, 1583–1594.

175. Funk, C.D. (2001). Prostaglandins and leukotrienes: advances in eicosanoid biology. Science *294*, 1871–1875. https://doi.org/10.1126/science.294.5548.1871.

176. Medeiros, A., Peres-Buzalaf, C., Fortino Verdan, F., and Serezani, C.H. (2012). Prostaglandin E_2 and the suppression of phagocyte innate immune responses in different organs. Mediat. Inflamm. *2012*, 327568. https://doi.org/10.1155/2012/327568.

177. Kalinski, P. (2012). Regulation of immune responses by prostaglandin E2. J. Immunol. *188*, 21–28. https://doi.org/10.4049/jimmunol.1101029.

178. Castro, M., Ralston, N.V., Morgenthaler, T.I., Rohrbach, M.S., and Limper, A.H. (1994). Candida albicans stimulates arachidonic acid liberation from alveolar macrophages through alpha-mannan and beta-glucan cell wall components. Infect. Immun. *62*, 3138–3145. https://doi.org/10.1128/iai.62.8.3138-3145.1994.

179. Sander, W.J., O'Neill, H.G., and Pohl, C.H. (2017). Prostaglandin E2 as a modulator of viral infections. Front. Physiol. *8*, 89. https://doi.org/10.3389/fphys.2017.00089.

180. Ghannoum, M.A. (2000). Potential role of phospholipases in virulence and fungal pathogenesis. Clin. Microbiol. Rev. *13*, 122–143. https://doi.org/10.1128/CMR.13.1.122.

181. Murakami, M., and Kudo, I. (2004). Recent advances in molecular biology and physiology of the prostaglandin E2-biosynthetic pathway. Prog. Lipid Res. *43*, 3–35. https://doi.org/10.1016/s0163-7827(03)00037-7.

182. Krause, J., Geginat, G., and Tammer, I. (2015). Prostaglandin E2 from Candida albicans stimulates the growth of Staphylococcus aureus in mixed biofilms. PLoS One *10*, e0135404. https://doi.org/10.1371/journal.pone.0135404.

183. Zijlstra, R.T., McCracken, B.A., Odle, J., Donovan, S.M., Gelberg, H.B., Petschow, B.W., Zuckermann, F.A., and Gaskins, H.R. (1999). Malnutrition modifies pig small intestinal inflammatory responses to rotavirus. J. Nutr. *129*, 838–843. https://doi.org/10.1093/jn/129.4.838.

184. Yamashiro, Y., Shimizu, T., Oguchi, S., and Sato, M. (1989). Prostaglandins in the plasma and stool of children with rotavirus gastroenteritis. J. Pediatr. Gastroenterol. Nutr. *9*, 322–327. https://doi.org/10.1097/00005176-198910000-00010.

185. Rossen, J.W.A., Bouma, J., Raatgeep, R.H.C., Büller, H.A., and Einerhand, A.W.C. (2004). Inhibition of cyclooxygenase activity reduces rotavirus infection at a postbinding step. J. Virol. *78*, 9721–9730. https://doi.org/10.1128/JVI.78.18.9721-9730.2004.

186. Sander, W.J., Kemp, G., Hugo, A., Pohl, C.H., and O'Neill, H.G. (2022). Rotavirus-mediated prostaglandin E2 production in MA104 cells promotes virus attachment and internalisation, resulting in an increased viral load. Front. Physiol. *13*, 805565. https://doi.org/10.3389/fphys.2022.805565.

187. Burrell, C.J., Howard, C.R., and Murphy, F.A. (2017). Caliciviruses. In Fenner and White's medical virology (Academic Press), pp. 465–471.

188. Alfajaro, M.M., Cho, E.H., Park, J.G., Kim, J.Y., Soliman, M., Baek, Y.B., Kang, M.I., Park, S.I., and Cho, K.O. (2018). Feline calicivirus- and murine norovirus-induced COX-2/PGE2 signaling pathway has proviral effects. PLoS One *13*, e0200726. https://doi.org/10.1371/journal.pone.0200726.

189. Liu, Y., Shi, W.D., Xie, Q.Q., Wang, J.G., Gu, C.C., Ji, Z.H., Xiao, J., and Liu, W.Q. (2022). Induction of COX-2 by feline calicivirus via activation of the MEK1-ERK1/2 pathway, and attenuation of feline lung inflammation and injury by MEK1 inhibitor AZD6244 (selumetinib). Biochem. Biophys. Res. Commun. *604*, 8–13. https://doi.org/10.1016/j.bbrc.02.060.

190. Oka, T., Wang, Q., Katayama, K., and Saif, L.J. (2015). Comprehensive review of human sapoviruses. Clin. Microbiol. Rev. *28*, 32–53. https://doi.org/10.1128/CMR.00011-14.

191. Makhaola, K., Moyo, S., and Kebaabetswe, L.P. (2020). Distribution and genetic variability of sapoviruses in africa. Viruses *12*, 490. https://doi.org/10.3390/v12050490.

192. Rivera-Gutiérrez, X., Morán, P., Taboada, B., Serrano-Vázquez, A., Iša, P., Rojas-Velázquez, L., Pérez-Juárez, H., López, S., Torres, J., Ximénez, C., and Arias, C.F. (2022). High prevalence and diversity of caliciviruses in a community setting

determined by a metagenomic approach. Microbiol. Spectr. *10*, e0185321. https://doi.org/10.1128/spectrum.01853-21.

193. Alfajaro, M.M., Choi, J.S., Kim, D.S., Seo, J.Y., Kim, J.Y., Park, J.G., Soliman, M., Baek, Y.B., Cho, E.H., Kwon, J., et al. (2017). Activation of COX-2/PGE2 promotes sapovirus replication via the inhibition of nitric oxide production. J. Virol. *91*. e01656016566-16. https://doi.org/10.1128/JVI.01656-16.

194. Cifuente, J.O., and Moratorio, G. (2019). Evolutionary and structural overview of human picornavirus capsid antibody evasion. Front. Cell. Infect. Microbiol. *9*, 283. https://doi.org/10.3389/fcimb.2019.00283.

195. Xie, Y., Chen, R., Zhang, X., Yu, Y., Yang, Y., Zou, Y., Ge, J., Chen, H., and Garzino-Demo, A. (2012). Blockade of interleukin-17A protects against coxsackievirus B3-induced myocarditis by increasing COX-2/PGE2 production in the heart. FEMS Immunol. Med. Microbiol. *64*, 343–351. https://doi.org/10.1111/j.1574-695X.2011.00918.x.

196. Tung, W.H., Hsieh, H.L., and Yang, C.M. (2010). Enterovirus 71 induces COX-2 expression via MAPKs, NF-kappaB, and AP-1 in SK-N-SH cells: role of PGE2 in viral replication. Cell. Signal. *22*, 234–246. https://doi.org/10.1016/j.cellsig.2009.09.018.

197. Tung, W.H., Hsieh, H.L., Lee, I.T., and Yang, C.M. (2011). Enterovirus 71 modulates a COX-2/PGE2/cAMP-dependent viral replication in human neuroblastoma cells: role of the c-Src/EGFR/p42/p44 MAPK/CREB signaling pathway. J. Cell. Biochem. *112*, 559–570. https://doi.org/10.1002/jcb.22946.

198. Wang, H., Zhang, D., Ge, M., Li, Z., Jiang, J., and Li, Y. (2015). Formononetin inhibits enterovirus 71 replication by regulating COX- 2/PGE$_2$ expression. Virol. J. *12*, 35. https://doi.org/10.1186/s12985-015-0264-x.

199. Liu, Z.W., Zhuang, Z.C., Chen, R., Wang, X.R., Zhang, H.L., Li, S.H., Wang, Z.Y., and Wen, H.L. (2019). Enterovirus 71 VP1 protein regulates viral replication in SH-SY5Y cells via the mTOR autophagy signaling pathway. Viruses *12*, 11. https://doi.org/10.3390/v12010011.

200. Schoggins, J.W., and Rice, C.M. (2011). Interferon-stimulated genes and their antiviral effector functions. Curr. Opin. Virol. *1*, 519–525. https://doi.org/10.1016/j.coviro.2011.10.008.

201. Wilks, J., and Golovkina, T. (2015). Interfering with interferons. Science *347*, 233–234. https://doi.org/10.1126/science.aaa5056.

202. Crosse, K.M., Monson, E.A., Beard, M.R., and Helbig, K.J. (2018). Interferon-stimulated genes as enhancers of antiviral innate immune signaling. J. Innate Immun. *10*, 85–93. https://doi.org/10.1159/000484258.

203. Negishi, H., Taniguchi, T., and Yanai, H. (2018). The interferon (IFN) class of cytokines and the IFN regulatory factor (IRF) transcription factor family. Cold Spring Harbor Perspect. Biol. *10*, a028423. https://doi.org/10.1101/cshperspect.a028423.

204. Ingle, H., Peterson, S.T., and Baldridge, M.T. (2018). Distinct effects of type I and III interferons on enteric viruses. Viruses *10*, 46. https://doi.org/10.3390/v10010046.

205. Walker, F.C., Sridhar, P.R., and Baldridge, M.T. (2021). Differential roles of interferons in innate responses to mucosal viral infections. Trends Immunol. *42*, 1009–1023. https://doi.org/10.1016/j.it.2021.09.003.

206. McNab, F., Mayer-Barber, K., Sher, A., Wack, A., and O'Garra, A. (2015). Type I interferons in infectious disease. Nat. Rev. Immunol. *15*, 87–103. https://doi.org/10.1038/nri3787.

207. Broggi, A., Tan, Y., Granucci, F., and Zanoni, I. (2017). IFN-lambda suppresses intestinal inflammation by non-translational regulation of neutrophil function. Nat. Immunol. *18*, 1084–1093.

208. Wells, A.I., and Coyne, C.B. (2018). Type III interferons in antiviral defenses at barrier surfaces. Trends Immunol. *39*, 848–858. https://doi.org/10.1016/j.it.2018.08.008.

209. Zhou, J.H., Wang, Y.N., Chang, Q.Y., Ma, P., Hu, Y., and Cao, X. (2018). Type III interferons in viral infection and antiviral immunity. Cell. Physiol. Biochem. *51*, 173–185. https://doi.org/10.1159/000495172.

210. Salgado, R.C., Fonseca, D.L.M., Marques, A.H.C., da Silva Napoleao, S.M., França, T.T., Akashi, K.T., de Souza Prado, C.A., Baiocchi, G.C., Plaça, D.R., Jansen-Marques, G., et al. (2021). The network interplay of interferon and Toll-like receptor signaling pathways in the anti-Candida immune response. Sci. Rep. *11*, 20281. https://doi.org/10.1038/s41598-021-99838-0.

211. Netea, M.G., Joosten, L.A.B., van der Meer, J.W.M., Kullberg, B.J., and van de Veerdonk, F.L. (2015). Immune defence against Candida fungal infections. Nat. Rev. Immunol. *15*, 630–642. https://doi.org/10.1038/nri3897.

212. Smeekens, S.P., Ng, A., Kumar, V., Johnson, M.D., Plantinga, T.S., van Diemen, C., Arts, P., Verweil, E.T.P., Gresnigt, M.S., Fransen, K., et al. (2013). Functional genomics identifies type I interferon pathway as central for host defense against Candida albicans. Nat. Commun. *4*, 1342. https://doi.org/10.1038/ncomms2343.

213. Majer, O., Bourgeois, C., Zwolanek, F., Lassnig, C., Kerjaschki, D., Mack, M., Müller, M., and Kuchler, K. (2012). Type I interferons promote fatal immunopathology by regulating inflammatory monocytes and neutrophils during Candida infections. PLoS Pathog. *8*, e1002811. https://doi.org/10.1371/journal.ppat.1002811.

214. Biondo, C., Signorino, G., Costa, A., Midiri, A., Gerace, E., Galbo, R., Bellantoni, A., Malara, A., Beninati, C., Teti, G., and Mancuso, G. (2011). Recognition of yeast nucleic acids triggers a host-protective type I interferon response. Eur. J. Immunol. *41*, 1969–1979. https://doi.org/10.1002/eji.201141490.

215. Zaas, A.K., Aziz, H., Lucas, J., Perfect, J.R., and Ginsburg, G.S. (2010). Blood gene expression signatures predict invasive candidiasis. Sci. Transl. Med. *2*, 21ra17. https://doi.org/10.1126/scitranslmed.3000715.

216. Bourgeois, C., Majer, O., Frohner, I.E., Lesiak-Markowicz, I., Hildering, K.S., Glaser, W., Stockinger, S., Decker, T., Akira, S., Müller, M., and Kuchler, K. (2011). Conventional dendritic cells mount a type I IFN response against Candida spp. requiring novel phagosomal TLR7-mediated IFN-β signaling. J. Immunol. *186*, 3104–3112. https://doi.org/10.4049/jimmunol.1002599.

217. del Fresno, C., Soulat, D., Roth, S., Blazek, K., Udalova, I., Sancho, D., Ruland, J., and Ardavín, C. (2013). Interferon-β production via Dectin-1-Syk-IRF5 signaling in dendritic cells is crucial for immunity to C. albicans. Immunity *38*, 1176–1186. https://doi.org/10.1016/j.immuni.2013.05.010.

218. Espinosa, V., Dutta, O., McElrath, C., Du, P., Chang, Y.J., Cicciarelli, B., Pitler, A., Whitehead, I., Obar, J.J., Durbin, J.E., et al. (2017). Type III interferon is a critical regulator of innate antifungal immunity. Sci. Immunol. *2*, eam5357. https://doi.org/10.1126/sciimmunol.aan5357.

219. Hoffmann, H.H., Schneider, W.M., and Rice, C.M. (2015). Interferons and viruses: an evolutionary arms race of molecular interactions. Trends Immunol. *36*, 124–138. https://doi.org/10.1016/j.it.2015.01.004.

220. Casasnovas, J.M. (2013). Virus-receptor interactions and receptor-mediated virus entry into host cells. Subcell. Biochem. *68*, 441–466. https://doi.org/10.1007/978-94-007-6552-8_15.

221. Maginnis, M.S. (2018). Virus-receptor interactions: the key to cellular invasion. J. Mol. Biol. *430*, 2590–2611. https://doi.org/10.1016/j.jmb.2018.06.024.

222. Moller-Tank, S., and Maury, W. (2014). Phosphatidylserine receptors: enhancers of enveloped virus entry and infection. Virology *468–470*, 565–580. https://doi.org/10.1016/j.virol.2014.09.009.

223. Bhella, D. (2015). The role of cellular adhesion molecules in virus attachment and entry. Philos. Trans. R. Soc. Lond. B Biol. Sci. *370*, 20140035. https://doi.org/10.1098/rstb.2014.0035.

224. Marsh, M., and Helenius, A. (2006). Virus entry: open sesame. Cell *124*, 729–740. https://doi.org/10.1016/j.cell.2006.02.007.

225. Grove, J., and Marsh, M. (2011). The cell biology of receptor-mediated virus entry. J. Cell Biol. *195*, 1071–1082. https://doi.org/10.1083/jcb.201108131.

226. Stencel-Baerenwald, J.E., Reiss, K., Reiter, D.M., Stehle, T., and Dermody, T.S. (2014).

The sweet spot: defining virus-sialic acid interactions. Nat. Rev. Microbiol. *12*, 739–749. https://doi.org/10.1038/nrmicro3346.

227. Broquet, A.H., Hirata, Y., McAllister, C.S., and 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. https://doi.org/10.4049/jimmunol.1002862.

228. Liu, S., Cai, X., Wu, J., Cong, Q., Chen, X., Li, T., Du, F., Ren, J., Wu, Y.T., Grishin, N.V., and Chen, Z.J. (2015). Phosphorylation of innate immune adaptor proteins MAVS, STING, and TRIF induces IRF3 activation. Science *347*, aaa2630. https://doi.org/10.1126/science.aaa2630.

229. Lee, A.J., and Ashkar, A.A. (2018). The dual nature of type I and type II interferons. Front. Immunol. *9*, 2061. https://doi.org/10.3389/fimmu.2018.02061.

230. Schneider, W.M., Chevillotte, M.D., and Rice, C.M. (2014). Interferon-stimulated genes: a complex web of host defenses. Annu. Rev. Immunol. *32*, 513–545. https://doi.org/10.1146/annurev-immunol-032713-120231.

231. Stanifer, M.L., Mukenhirn, M., Muenchau, S., Pervolaraki, K., Kanaya, T., Albrecht, D., Odendall, C., Hielscher, T., Haucke, V., Kagan, J.C., et al. (2020). Asymmetric distribution of TLR3 leads to a polarized immune response in human intestinal epithelial cells. Nat. Microbiol. *5*, 181–191. https://doi.org/10.1038/s41564-019-0594-3.

232. Hosmillo, M., Chaudhry, Y., Nayak, K., Sorgeloos, F., Koo, B.K., Merenda, A., Lillestol, R., Drumright, L., Zilbauer, M., and Goodfellow, I. (2020). Norovirus replication in human intestinal epithelial cells is restricted by the interferon-induced JAK/STAT signaling pathway and RNA polymerase II-mediated transcriptional responses. mBio *11*, e00215–e00220. https://doi.org/10.1128/mBio.00215-20.

233. Jahun, A.S., and Goodfellow, I.G. (2021). Interferon responses to norovirus infections: current and future perspectives. J. Gen. Virol. *102*, 001660. https://doi.org/10.1099/jgv.0.001660.

234. Hernández, P.P., Mahlakoiv, T., Yang, I., Schwierzeck, V., Nguyen, N., Guendel, F., Gronke, K., Ryffel, B., Hoelscher, C., Dumoutier, L., et al. (2015). Interferon-λ and interleukin 22 act synergistically for the induction of interferon-stimulated genes and control of rotavirus infection. Nat. Immunol. *16*, 698–707. https://doi.org/10.1038/ni.3180.

235. Sen, A., Sharma, A., and Greenberg, H.B. (2018). Rotavirus degrades multiple interferon (IFN) type receptors to inhibit IFN signaling and protects against mortality from endotoxin in suckling mice. J. Virol. *92*, e013944-17. https://doi.org/10.1128/JVI.01394-17.

236. Sen, A., Siyuan, D., and Greenberg, H.B. (2020). The role of innate immunity in regulating rotavirus replication, pathogenesis, and host range restriction and the implications for live rotaviral vaccine development. In Mucosal vaccines, Hiroshi Kiyono, D.W. Pascual, ed., pp. 683–697.

237. Lin, J.D., Feng, N., Sen, A., Balan, M., Tseng, H.C., McElrath, C., Smirnov, S.V., Peng, J., Yasukawa, L.L., Durbin, R.K., et al. (2016). Distinct roles of type I and type III interferons in intestinal immunity to homologous and heterologous rotavirus infections. PLoS Pathog. *12*, e1005600. https://doi.org/10.1371/journal.ppat.1005600.

238. Pervolaraki, K., Stanifer, M.L., Münchau, S., Renn, L.A., Albrecht, D., Kurzhals, S., Senís, E., Grimm, D., Schröder-Braunstein, J., Rabin, R.L., and Boulant, S. (2017). Type I and type III interferons display different dependency on mitogen-activated protein kinases to mount an antiviral state in the human gut. Front. Immunol. *8*, 459. https://doi.org/10.3389/fimmu.2017.00459.

239. Holly, M.K., and Smith, J.G. (2018). Adenovirus infection of human enteroids reveals interferon sensitivity and preferential infection of goblet cells. J. Virol. *92*. e00250002500-18. https://doi.org/10.1128/JVI.00250-18.

240. Ganal, S.C., Sanos, S.L., Kallfass, C., Oberle, K., Johner, C., Kirschning, C., Lienenklaus, S., Weiss, S., Staeheli, P., Aichele, P., and Diefenbach, A. (2012). Priming of natural killer cells by non-mucosal mononuclear phagocytes requires instructive signals from commensal microbiota. Immunity *37*, 171–186. https://doi.org/10.1016/j.immuni.2012.05.020.

241. Lee, S., and Baldridge, M.T. (2017). Interferon-Lambda: a potent regulator of intestinal viral infections. Front. Immunol. *8*, 749. https://doi.org/10.3389/fimmu.2017.00749.

242. Iaconis, G., Jackson, B., Childs, K., Boyce, M., Goodbourn, S., Blake, N., Iturriza-Gomara, M., and Seago, J. (2021). Rotavirus NSP1 inhibits type I and type III interferon induction. Viruses *13*, 589. https://doi.org/10.3390/v13040589.

243. Holloway, G., Dang, V.T., Jans, D.A., and Coulson, B.S. (2014). Rotavirus inhibits IFN-induced STAT nuclear translocation by a mechanism that acts after STAT binding to importin-α. J. Gen. Virol. *95*, 1723–1733. https://doi.org/10.1099/vir.0.064063-0.

244. Sen, A., Rott, L., Phan, N., Mukherjee, G., and Greenberg, H.B. (2014). Rotavirus NSP1 protein inhibits interferon-mediated STAT1 activation. J. Virol. *88*, 41–53. https://doi.org/10.1128/JVI.01501-13.

245. Barro, M., and Patton, J.T. (2007). Rotavirus NSP1 inhibits expression of type I interferon by antagonizing the function of interferon regulatory factors IRF3, IRF5, and IRF7. J. Virol. *81*, 4473–4481. https://doi.org/10.1128/JVI.02498-06.

246. Arnold, M.M., Sen, A., Greenberg, H.B., and Patton, J.T. (2013). The battle between rotavirus and its host for control of the interferon signaling pathway. PLoS Pathog. *9*, e1003064. https://doi.org/10.1371/journal.ppat.1003064.

247. Arnold, M.M. (2016). The rotavirus interferon antagonist NSP1: many targets, many questions. J. Virol. *90*, 5212–5215. https://doi.org/10.1128/JVI.03068-15.

248. Graff, J.W., Ettayebi, K., and Hardy, M.E. (2009). Rotavirus NSP1 inhibits NFkappaB activation by inducing proteasome-dependent degradation of beta-TrCP: a novel mechanism of IFN antagonism. PLoS Pathog. *5*, e1000280. https://doi.org/10.1371/journal.ppat.1000280.

249. Mukherjee, A., Morosky, S.A., Delorme-Axford, E., Dybdahl-Sissoko, N., Oberste, M.S., Wang, T., and Coyne, C.B. (2011). The coxsackievirus B 3C protease cleaves MAVS and TRIF to attenuate host type I interferon and apoptotic signaling. PLoS Pathog. *7*, e1001311. https://doi.org/10.1371/journal.ppat.1001311.

250. Ding, S., Zhu, S., Ren, L., Feng, N., Song, Y., Ge, X., Li, B., Flavell, R.A., and Greenberg, H.B. (2018). Rotavirus VP3 targets MAVS for degradation to inhibit type III interferon expression in intestinal epithelial cells. Elife *7*, e39494. https://doi.org/10.7554/eLife.39494.

251. Sohn, S.Y., and Hearing, P. (2011). Adenovirus sequesters phosphorylated STAT1 at viral replication centers and inhibits STAT dephosphorylation. J. Virol. *85*, 7555–7562. https://doi.org/10.1128/JVI.00513-11.

252. Look, D.C., Roswit, W.T., Frick, A.G., Gris-Alevy, Y., Dickhaus, D.M., Walter, M.J., and Holtzman, M.J. (1998). Direct suppression of Stat1 function during adenoviral infection. Immunity *9*, 871–880. https://doi.org/10.1016/s1074-7613(00)80652-4.

253. Harris, V.C., Armah, G., Fuentes, S., Korpela, K.E., Parashar, U., Victor, J.C., Tate, J., de Weerth., C., Giaquinto, C., Wiersinga, W.J., et al. (2017). Significant correlation between the infant gut microbiome and rotavirus vaccine response in rural Ghana. J. Infect. Dis. *215*, 34–41. https://doi.org/10.1093/infdis/jiw518.

254. Harris, V., Ali, A., Fuentes, S., Korpela, K., Kazi, M., Tate, J., Parashar, U., Wiersinga, W.J., Giaquinto, C., de Weerth, C., and de Vos, W.M. (2018). Rotavirus vaccine response correlates with the infant gut microbiota composition in Pakistan. Gut Microb. *9*, 93–101. https://doi.org/10.1080/19490976.2017.1376162.

255. Salazar, F., Bignell, E., Brown, G.D., Cook, P.C., and Warris, A. (2022). Pathogenesis of respiratory viral and fungal coinfections. Clin. Microbiol. Rev. *35*, e00094-. https://doi.org/10.1128/CMR.00094-21.

256. Nolan, L.S., and Baldridge, M.T. (2022). Advances in understanding interferon-mediated immune responses to enteric viruses in intestinal organoids. Front. Immunol. *13*, 943334. https://doi.org/10.3389/fimmu.2022.943334.

257. Zhao, C., and Zhao, W. (2020). NLRP3 Inflammasome-A Key Player in Antiviral Responses. Front Immunol. *11*, 211. https://doi.org/10.3389/fimmu.2020.00211.

258. Donato, C., and Vijaykrishna, D. (2017). The Broad Host Range and Genetic Diversity of Mammalian and Avian Astroviruses. Viruses *9*, 102. https://doi.org/10.3390/v9050102.

259. De Crom, S.C., Rossen, J.W., van Furth, A.M., and Obihara, C.C. (2016). Enterovirus and parechovirus infection in children: a brief overview. Eur. J. Pediatr. *175*, 1023–1029. https://doi.org/10.1007/s00431-016-2725-7.

260. Rivadulla, E., and Romalde, J.L. (2020). A Comprehensive Review on Human Aichi Virus. Virol. Sin. *35*, 501–516. https://doi.org/10.1007/s12250-020-00222-5.

261. Yu, J.M., Ao, Y.Y., Liu, N., Li, L.L., and Duan, Z.J. (2015). Salivirus in Children and Its Association with Childhood Acute Gastroenteritis: A Paired Case-Control Study. PLoS One *10*, e0130977. https://doi.org/10.1371/journal.pone.0130977.

262. Zoll, J., Erkens Hulshof, S., Lanke, K., Verduyn Lunel, F., Melchers, W.J., Schoondermark-van de Ven, E., et al. (2009). Saffold virus, a human Theiler's-like cardiovirus, is ubiquitous and causes infection early in life. PLoS Pathog. *5*, e1000416. https://doi.org/10.1371/journal.ppat.1000416.

263. Payne, S. (2017). Family Caliciviridae. In Viruses, Payne, S. ed. (Academic Press), pp. 115–119. https://doi.org/10.1016/B978-0-12-803109-4.00012-X.

264. Desselberger, U. (2019). Caliciviridae Other Than Noroviruses. Viruses *11*, 286. https://doi.org/10.3390/v11030286.

265. Qiu, F.Z., Shen, X.X., Li, G.X., Zhao, L., Chen, C., Duan, S.X., et al. (2018). Adenovirus associated with acute diarrhea: a case-control study. BMC Infect. Dis. *18*, 450. https://doi.org/10.1186/s12879-018-3340-1.

266. Qiu, J., Söderlund-Venermo, M., and Young, N.S. (2017). Human Parvoviruses. Clin. Microbiol. Rev. *30*, 43–113. https://doi.org/10.1128/CMR.00040-16.

267. Li, L., Kapoor, A., Slikas, B., Bamidele, O.S., Wang, C., Shaukat, S., et al. (2010). Multiple diverse circoviruses infect farm animals and are commonly found in human and chimpanzee feces. J. Virol. *84*, 1674–1682. https://doi.org/10.1128/JVI.02109-09.

268. Kaczorowska, J., and Van der Hoek, L. (2020). Human anelloviruses: diverse, omnipresent and commensal members of the virome. FEMS Microbiol. Rev. *44*, 305–313. https://doi.org/10.1093/femsre/fuaa007.

269. Lamers, M.M., Beumer, J., van der Vaart, J., Knoops, K., Puschhof, J., Breugem, T.I., et al. (2020). SARS-CoV-2 productively infects human gut enterocytes. Science *369*, 50–54. https://doi.org/10.1126/science.abc1669.