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Close Encounters of the Viral Kind: Cross-Kingdom Synergies at the Host–Pathogen Interface

Hannah M. Rowe, Jason W. Rosch

Department of Infectious Diseases St. Jude Children's Research Hospital Memphis, TN 38105, USA

Abstract

The synergies between viral and bacterial infections are well established. Most studies have been focused on the indirect mechanisms underlying this phenomenon, including immune modulation and alterations to the mucosal structures that promote pathogen outgrowth. A growing body of evidence implicates direct binding of virus to bacterial surfaces being an additional mechanism of synergy at the host–pathogen interface. These cross-kingdom interactions enhance bacterial and viral adhesion and can alter tissue tropism. These bacterial–viral complexes play unique roles in pathogenesis and can alter virulence potential. The bacterial–viral complexes may also play important roles in pathogen transmission. Additionally, the complexes are recognized by the host immune system in a distinct manner, thus presenting novel routes for vaccine development. These synergies are active for multiple species in both the respiratory and gastrointestinal tract, indicating that direct interactions between bacteria and virus to modulate host interactions are used by a diverse array of species.

Keywords

viruses; streptococcus; co-infection

1. Introduction

Pathogenic bacteria and viruses have evolved mechanisms to take advantage of both modulation of the host environment and each other for mutually beneficial interactions as they often occupy the same niche simultaneously. These interactions can be between bacterial pathogens and the resident bacterial flora, an area of active research.^[1–4] Additional research is focused on the interactions between viruses and bacterial pathogens and commensal species at the mucosal surface.^[5,6] These interactions are especially important as mucosa surfaces are typically the sites of initial infection of both bacterial and viral pathogens and the site for transmission to new hosts. Bacterial–viral co-infections can have dramatically enhanced lethality, as demonstrated by influenza A virus and *Streptococcus pneumoniae*.^[7] Much research has been focused on the effects of immune

Jason.Rosch@stjude.org.

Conflict of Interest

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modulation by the initial bacterial or viral infection that enhances susceptibility to the second pathogen, providing critical insight into how immunomodulation by one or both pathogens can enhance the virulence of both pathogens.^[8,9] The host environment during viral infection is a distinct environmental niche that fundamentally alters the transcriptional landscape of bacterial pathogens during co-infection, underscoring the impact of viral infection on the bacterial response to niches within the host.^[10,11] More recent evidence has revealed that bacterial–viral synergies can operate on a much closer basis than realized, with the bacteria and the virus directly interacting. These direct interactions can be beneficial to both organisms, beneficial to only one partner, or detrimental to one partner. In this review, we will discuss recent insights into direct interactions between eukaryotic viruses and bacteria that alter pathogenesis and immune stimulation and potential roles in pathogen transmission.

2. Role of Bacterial–Viral Complexes in Pathogenesis

Direct bacterial–viral interactions enhancing viral pathogenesis were initially noted in interactions between gastrointestinal viruses and the enteric bacterial microbiome. Many families of enteric viruses directly bind to both gram-positive and gram-negative bacteria, including picornaviruses,^[12,13] caliciviruses,^[14,15] and reoviruses.^[16] This viral binding to bacteria has important consequences, as further research demonstrated that such viruses can exploit the bacteria and their surface adhesins to mediate viral binding to host cells. Bacterial products are essential co-factors for infection with picornaviruses^[13,17] and caliciviruses.^[14,18,19] Poliovirus uses bacterial lipopolysaccharide to enhance binding to its cellular receptor and infection of host cells.^[13] These studies underscore the importance of the resident bacterial flora for promoting viral infection in the gastrointestinal tract.

Given the observation that many enteric viruses mediate strong associations with the bacterial flora, it is not surprising that perturbing the resident bacterial flora can also have profound consequences for enteric viruses. Extensive antibiotic treatment of mice confers resistance to infection by both poliovirus^[13] and rotavirus.^[20] Norovirus cannot establish persistent infection in mice continuously treated with antibiotics,^[21] nor replicate in cell culture without supplementation with either enteric bacteria or bacteria-derived glycans such as histo-blood group antigen (HBGA),^[18] or in the context of a more complex stem-cell derived organoid cell culture system.^[22] These studies underscore the importance of microbial flora for promoting infection by enteric viruses.

Not only can bacteria and bacterial products be cofactors for viral adherence to host cells but the enzymes on the bacterial cell envelope can also modify the virions, enhancing their virulence. Nascent influenza virions require enzymatic activation of hemagglutinin to become infectious. A staphylococcal protease can serve this function and, thus, promote infection by the virus during co-infection.^[23,24] Bacterial surface and secreted proteases are common features of many bacterial species in the upper respiratory tract, so it is likely that this activation capacity is not restricted to *Staphylococci* and could be a factor in enhanced influenza viral pathogenesis in other bacterial–viral co-infections.

Metagenomic studies of the lungs^[25] have shown that chronic airway diseases such as COPD,^[26] asthma,^[27] or cystic fibrosis^[28] lead to alterations in both the lower and upper airway microbiome with anaerobic bacteria typical of the oral cavity able to survive in the lung and further exacerbate pulmonary inflammation. Acute infections in intubated patients also alter the respiratory microbiome.^[29] Perturbation of these populations may allow for specific pathogens to emerge and take advantage of co-infecting viral populations to promote invasive disease. Conversely, outgrowth of bacterial species that do not take advantage of viral co-infection may confer additional protection against the development of invasive disease. Additionally, oral streptococci exploit neuraminidase produced by competing species to expose hidden receptors for adherence to mucosal sites^[30] and may exploit viral neuraminidases for similar purposes.

Other modifications of viruses by bacteria may also occur. Given the overlap in substrates, bacterial glycosylases and deglycosylases could modify viral glycoproteins to modulate viral virulence. The converse situation, whereby enzymes on the virion surface could alter bacterial cell surfaces to enhance bacterial pathogenesis, is also important to note. Influenza virus neuraminidase can degrade the *Neisseria meningitidis* serogroup A polysialic acid capsule to promote bacterial adherence to epithelial cells.^[31] Sialic acid modification of bacterial surface structures is common to many bacterial pathogens as a method of immune evasion.^[31,32] As such, these modifications by influenza neuraminidase could be both helpful and harmful for bacterial pathogens. For example, removal of sialic acid residues could enhance bacterial access to the host cell surface but could also unmask immunogenic bacterial epitopes and promote immune clearance of bacterial pathogens. Further, pneumococcal deglycosylases can expose immunogenic human proteins to break immune tolerance and promote development of pediatric haemolytic uremic syndrome.^[33] Combined action of bacterial and viral deglycosylases acting at the same site in the bacterial–viral complex could serve a similar function.

Studies of benefits of bacterial pathogens' interactions with mammalian viruses have traditionally been focused on indirect interactions whereby the viral pathogen alters the immune response or modifies the mucosal surface to enhance bacterial pathogenesis, leading to fundamental advances in our understanding of the consequences of co-infections on disease severity. However, recent work shows that direct interactions occur between influenza virus and respiratory pathogens that commonly colonize the human upper respiratory tract, including *S. pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.^[34] Such direct interactions between these bacterial species and influenza A virus had important consequences for how the bacteria interacted with host cells, enhancing bacterial adherence to cultured respiratory cells and promoting enhanced colonization and invasion in murine models of *S. pneumoniae* infection. The enhanced tissue tropism caused by bacteria directly binding to influenza virus has also been observed in the swine pathogen *Streptococcus suis*, with these direct interactions enhancing *S. suis*'s adherence in tissue culture and pathogenesis in pigs.^[35] These results suggest that coating the bacterial surface with influenza virus particles can promote enhanced adherence capacity and can promote fitness benefits to the bacterium that are operative at the initial stages of infection.

Direct interaction between the bacterial flora of the upper respiratory tract and respiratory viruses is not limited to influenza virus. Such interactions also occur between respiratory syncytial virus (RSV) and both *S. pneumoniae* and *H. influenzae*.^[36–38] Similar to what was observed with influenza virus, these direct interactions enhance bacterial adherence to mammalian cells.^[36,37] The fitness benefits of direct interactions between virus and bacteria have also been observed in vivo, as incubation of *S. pneumoniae* with RSV or purified viral glycoprotein enhanced pneumococcal virulence in murine models of infection.^[37] There is also evidence of enhanced bacterial binding to infected cells via viral membrane proteins^[37,39] and as these proteins are present in the virion as well may also extend to interactions of the virions with the bacteria. These studies underscore the notions that the capacity of bacterial pathogens to directly bind to various respiratory viruses may be more widespread than previously appreciated and that these direct interactions have important functional consequences for enhancing pathogenesis during co-infection.

3. Immune Recognition of Bacterial–Viral Complexes

The bacterial–viral complex offers a unique and distinct target for recognition by the host immune system that is distinct from either pathogen alone. A bacterial–viral complex can be internalized into a single epithelial or phagocytic cell, as shown after mixing pneumococcus and influenza virus.^[40] This interaction can have multiple consequences. For example, direct binding to the bacteria followed by internalization could allow multiple viruses to infect the same host cell, promoting viral recombination and generation of progeny virus that have enhanced fitness or vaccine escape variants.^[12] This can be through reassortment of viral gene segments, mammalian recombinases or through bacterial recombinases recognizing viral DNA sequences as is seen with human adenoviruses and bacterial RecA.^[41] The internalization of the bacterial–viral complex can also promote the activation of multiple toll-like receptors, recognizing both bacterial and viral products. These co-infected cells can present antigens from both the bacterial and the viral pathogen, enhancing the inflammatory response to the initial infection and resulting in distinct adaptive and memory responses. Following this logic, recent work has shown that vaccination with bacterial–viral complexes of *S. pneumoniae* and influenza A virus promote protection superior to that of non-complexed bacteria and virus, leading to potential strategies for vaccine development against both pathogens simultaneously.^[40] The extension of this strategy to additional bacterial or viral species may provide unique avenues for future vaccine development that both broaden and enhance the protective capacity of such vaccines.

Bacteria and bacterial products can also alter the innate anti-viral response of the host. Signals from commensal bacteria can alter the threshold for immune activation in either direction, either magnifying or diminishing them, which can impact the interferon response to viral infection.^[42] Bacterial ribonucleases can be internalized into host cells to specifically degrade influenza virus RNAs,^[43] reducing both viral burden and pro-inflammatory signaling from activation of cytosolic toll-like receptors recognizing viral RNA. The S-layer of *Lactobacillus acidophilus* prevents alphaviruses and flaviviruses from interacting with dendritic cells,^[44] key cells for initiation of adaptive immune responses. Expression of pneumolysin by *S. pneumoniae* induces expression of arginase by alveolar macrophages, reducing subsequent inflammation from secondary influenza A viral

challenge.^[45] These findings underscore both the positive and negative effects that bacterial species can have on viral replication and the mechanisms deployed by the host to control viral infection. Likewise, interactions between viruses and bacteria should be considered in vaccine development. Live attenuated vaccines need to be understood in the context of the mucosal microbiome they will be introduced into, as the microbiome could enhance or abrogate the responses generated to the live vaccine.^[46] Live attenuated influenza vaccine has been shown to increase bacterial colonization density in murine and human studies.^[47–49] Combination vaccines also need to be considered in the context of enhanced and reduced protection conferred from the potential interactions of the pathogens with each other.

4. Impact of Co-Infections on Pathogen Transmission

One of the most interesting potential consequences of direct bacterial–viral interactions is the promotion of transmissibility of both bacterial and viral pathogens. As the “success” of a pathogen typically lies not in its ability to cause devastating illness in its host, but instead in its ability to successfully infect a new host, many bacterial and viral pathogens are under selection to improve transmissibility. Pathogens may exploit members of the microbiome or other pathogens to further their own transmission allowing them to be the most “successful.” In hospital-associated outbreaks of *S. aureus*, respiratory viruses have been shown to be major drivers of bacterial shedding from a colonized patient^[50] and health care worker.^[51,52] This could be explained by increased bacterial colonization density, which has been recapitulated in animal models of infection^[49,53] and observed in humans^[47,54,55] to occur as a result of co-infection with respiratory viruses. Sneezing and coughing during upper respiratory viral infections can physically promote shedding of the respiratory bacterial population. In mammalian transmission experiments in ferrets, co-infection with influenza A virus dramatically enhanced the distance at which animals were able to transmit co-infection *S. pneumoniae*.^[53] In infant mouse models of influenza virus transmission, colonization of contact animals with *S. pneumoniae* reduced acquisition of virus from contact animals, suggesting that synergistic and antagonistic roles may be operative during transmission.^[56] Whether transmission is contact-dependent or airborne may be a key factor in these processes: murine models of transmission are typically contact-dependent, whereas models in ferrets typically support both contact-dependent and airborne transmission. Given that human influenza transmission occurs via both contact dependent and airborne routes, both models offer critical insight into the factors underlying transmission.

Direct bacterial–viral interactions may also support transmission between mammalian hosts. While virus is being actively shed by the host, members of the bacterial community adherent to the virus particles could bind to and be released with the virus. During the process of colonization of new individuals, the coating of bacterial species with viral particles, and their respective adhesins, could promote initial adherence in new hosts.^[34] For viral transmission, the bacterial partner, likewise, could contribute release factors in the old host and adhesion factors in the new host. Additionally, bacteria or their components could promote the environmental stability of the virus. Whole bacteria and the bacterial envelope components peptidoglycan, lipopolysaccharide, and lipoteichoic acid can stabilize picornaviruses under heat and bleach stress^[57] and enhance reovirus thermostability.^[16] HBGA-expressing

bacteria can protect noroviruses from heat stress.^[19] However, bacterial stabilization of viruses is not a universal phenomenon, as lipopolysaccharide destabilizes influenza viruses.^[58] Promoting viral stability in the environment via direct interactions may be an important component of the virus' strategy to successfully transmit between hosts, particularly via airborne routes.

Direct bacterial–viral interactions have been implicated in vertical transmission of viruses in both mammals and insects. For example, interaction with bacterial lipopolysaccharide in the maternal milk is necessary for the transmission of murine mammary tumor virus from dam to pup.^[59] Rice dwarf virus binds to the outer membrane of the insect commensal bacteria *Sulcia* and is transmitted by the transovarial route in the leafhopper insect pest.^[60] Additionally, co-infection of tick cells with arthropod-borne bacterial and viral pathogens enhanced replication of Semliki Forest virus,^[61] representing an additional route of enhanced transmission in the vector.

Inter-pathogen interactions in the agricultural sector^[62] also represent an area with increasing interest in transmission control. Such interactions have important consequences for both plant and food animal diseases, but also for food borne human pathogens. The ability for a pathogenic virus to form a complex with the normal flora of the plant^[63] or human and animal commensals introduced in irrigation water^[64,65] could allow the stabilization of that virus through food processing and shipping. Modulation of the bacterial communities on plants both in the field and during processing could represent a novel way to control foodborne illness transmission. Citrus huanglongbing, or “greening” is a devastating bacterial infection of plants vectored by an insect. Control has been attempted through spraying of trees with human relevant antibiotics, which has concerns for antimicrobial resistance.^[66] Better control has been seen with combination of antibiotic and salicylic acid, a plant defense molecule,^[67] though no cure is yet reported. These observations underscore the critical importance of taking a global view of the host environment of both viral and bacterial flora when investigating factors promoting disease progression and transmission.

5. Conclusions

Direct bacterial–viral interactions are an additional route of synergy in co-infections. Bacterial and viral partners can exploit each other's adhesins to adhere to host cells. This could increase the strength of binding when both bacterial and viral adhesins are binding the same cell. However, if the bacterial and viral partner utilize the same receptor, then competitive interactions may occur. Additionally, exploiting the other partners' adhesins could allow invasion and replication in non-typical host cells and tissues, increasing available host niches and enhancing disease progression. These bacterial–viral complexes could also promote transmission of both bacterial and viral pathogens, enhancing release, environmental survival, and initial adherence in the new host. The bacterial–viral complex also offers new and different antigens to the host immune system. The immune cross-talk caused by encountering both viral and bacterial antigens could enhance pathogenesis if the cross-talk leads to inhibition of protective immune responses or inhibit pathogenesis if the crosstalk leads to enhanced immune stimulation and clearance. The gastrointestinal and respiratory mucosa are unlikely to be the only sites of potential bacterial–viral complex

formation and synergy. Skin, oral, and urogenital microbial communities of commensals and pathogenic bacteria and viruses could also be sites where bacterial–viral complexes form and have synergistic interactions promoting colonization, disease, and transmission.

The varying composition of the microbiome and virome in different individuals and in the same individual over time would provide different players in the bacterial–viral complexes. A pathogen arriving in one community might not be able to build a complex to effectively disseminate beyond the mucosal site, whereas arriving into a different community could build a complex to allow invasion into deeper tissues and systemic disease in the host. This could be through the availability of adhesins and surface localized enzymes to allow physical barrier breaches and binding to and internalization into new host cells, or through the availability of immunomodulatory molecules in the complex to alter the response to the invading pathogen in a way beneficial to the pathogen. This could partially explain seasonal transmission dynamics, as environmental cues could alter the microbiome making a host more susceptible to invasive diseases during certain seasons. This could also provide a mechanism for spillover transmission. A pathogen in the context of its native hosts' microbiome is not transmissible to new species. However, once it gains a foothold in a new species the microbiome of that host directly interacts and provides new tools to that pathogen, allowing it to spread widely in its new host species.

Clinical interest for the role of the microbiome is high for a number of areas including modulation of immune responses, responses to therapy, and infection susceptibility. The findings summarized here suggest that attention should be paid to the factors that enhance pathogenesis and the factors that enhance stability. Understanding bacterial and viral factors that promote adherence of the pathogens to each other, but do not promote association with host tissues, or promote stabilization of the virus could be a novel means for blocking infection. Bacteria or bacterial products that bind to, but do not stabilize viruses in the environment could be used to competitively block transmission, by allowing the virus to be naturally destabilized in the environment and fail to transmit. Additionally, cultivating a microbiome at a mucosal site that does not associate with pathogens, or does not enhance adherence to host cells at disseminated sites of infection, could prevent progression of disease from a colonization to an infection or a mucosal infection to a systemic infection. Understanding the composition of these favorable and non-favorable microbiomes, for both transmission and for invasive potential could allow prediction of high risk hosts. This could be operative in the clinic to prevent infection in immunocompromised individuals. It also could be operative in the “one health” prospective by understanding wild and domesticated animal microbiomes that enhance spillover potential of novel infectious diseases. Additionally, understanding and modulating agricultural plant and animal microbiome could enhance agricultural output by preventing disease in the plant or animal, and prevent transmission of foodborne infectious diseases in humans.

Bacterial–viral interactions, in addition to their well-characterized indirect interactions, can also be through direct binding of virions to the bacterial surface. These interactions have important consequences to pathogenesis, immune responses and transmission potential of both bacterial and viral pathogens. Understanding the mechanisms of these interactions to enhance or disrupt would have clinical consequences in prevention of human disease and the

design of vaccines. Additionally, understanding bacterial–viral interactions in agriculture could promote plant and animal health and crop yields in addition to preventing transmission of human food borne pathogens. The impact of such cross-kingdom interactions on a myriad of cellular processes underscore the inherent complexity and importance of these systems at the host–pathogen interface.

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