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Review

Insights into Inter-kingdom Interactions in Human Disease

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ABSTRACT

The bacterial, fungal, virus community within body sites have received considerable study in some diseases, but less attention has been paid to inter-kingdom interactions in the same habitat. Previous studies have begun to map out associations between bacteria, fungi and viruses of the human gut microbiome, they can interact with other species and shape the community and functions of fungi and virus, there are indications of both antagonistic and beneficial interactions within poly-colonized microbiome in human, but again, little is known about the form this takes.

Keywords: Bacteria; Fungi; Virus; Interactions; Disease

INTRODUCTION

Bacteria are not the only residents of human microbial ecosystem; instead, it consists of large populations of bacteria, bacteriophage, viruses, fungi and *archaea*, etc. Microbial cohabitation is deemed to be a complex story of repulse and affection due to their interactions either for competing for resources in similar microhabitats or cooperating for acquisition of nutrients, leading to both antagonistic and beneficial effects on immune systems. It's well-known that a mixed infection instead of a single infection following modulation of virulence and pathogenicity through biofilm virulence mechanisms including adhesion, invasion, quorum sensing, and development of antimicrobial resistance, is more common in some oral, pulmonary and intestinal diseases [1]. Fungal-bacterial interactions have gained increasing attention, whereas the crosstalk between fungi and viruses, bacteria and viruses still remains to be fully explored. These interactions in a physio-pathological context have been poorly studied to date. This review considers what is currently known about inter-kingdom interactions and proposes possible mechanisms underlying, hoping to identify key knowledge gaps and pressing questions for future research.

LITERATURE REVIEW

It has been demonstrated that the mechanisms of synergistic and antagonistic roles of bacterial-fungal interactions are associated with modulations of biofilm virulence, adhesion, invasion, quorum sensing, and development of antimicrobial resistance. Candida, the most common commensal fungus of the human body, have been found to coexist frequently and constantly interact with a wide range of bacteria, such as co-inhabitation with Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus and Streptococcus mutans in respiratory tract, gastrointestinal system, denture surfaces and oral mucosa of denture users [2,3].

BACTERIA-FUNGI INTERACTIONS

The complex interactions promoted or inhibited their growth, and indirectly shaped mammalian immunity either by secreting immunomodulatory compounds or by modulating signaling processes of innate and adaptive immune responses [4-6]. An exemplary publication has added further fundamental understanding of the role of oral microbiome in activating and educating host immunity. Xu et al. Streptococcus oralis and Candida albicans co-infection, but not mono-infection of either species led to more severe inflammation in oral lesions along with the highest TLR2 expression in oral tissue and reduced gene expressions associated with epithelial cell structure, however, TLR2-/- mice a significantly degrade tongue lesion severity with coinfection of the two species, shedding a light upon involvement of TLR2 signaling pathway in the interplay between inter-kingdom interactions and human immune system [7].

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Our most recent research globally investigated airway microbiome equilibrium in asthma patients; we noted a disease-specific pattern for the inter-kingdom networks. We reported the number and the intensity of the correlations between fungi and bacteria were significantly decreased compared with healthy controls. This suggested loose interactions. In detail, both positive and negative correlations from Firmicutes to Basidiomycota and *Proteobacteria*, from *Proteobacteria* to Ascomycota were observed in controls, but these networks were strikingly decreased in asthma patients. We also noted decreased correlations within fungi or bacteria species in asthma patients [8]. Therefore, it showed an imbalanced fungi-bacteria interactions in patients with asthma. However, we did not perform further research to elucidate more precisely the inter-kingdom correlations in context of asthma, such as determining the microbial adherence and pathogenesis to host pulmonary cells by mono-infection or co-infection, which deserved increasing attention. Similarly, recent studies reported positive and negative correlations between bacteria and fungi in Ulcerative Colitis (UC) patients were higher and stronger than those in healthy controls and Crohn's Disease (CD) patients, unravelling disease-specific inter-kingdom network alterations in IBD [9]. Sovran et al. further elucidated more precisely the functional connections between kingdoms in the gut microbiome, they detailed how specific bacteria species influence the fitness of opportunistic fungal pathogen Candida albicans and protective fungus Saccharomyces boulardii in the gut and thereby regulate the outcome of intestinal inflammation. They demonstrated narrowed bacterial and fungal correlations in mice without Enterobacteriaceae compared with antibiotic-treated and control mice, restoration of the Enterobacteriaceae in the gut recovered the beneficial effects of Saccharomyces boulardii and pathogenic effects of Candida albicans on colitis severity [10]. Their findings supported the involvement of Enterobacteriaceae in bacterial interactions with fungi and ecological effect of Enterobacteriaceae in favoring intestinal colonization by fungi Candida albicans and Saccharomyces boulardii to trigger or attenuate inflammation in the context of colitis.

Armed with the new evidence, we suggested globally microbial community-level interactions and their paramount role in affecting disease development, nonetheless more precise understanding of the complex picture of the interactions between bacteria and fungi is still in urgent need to provide clues in the search of mechanisms underlying these interactions.

INTERACTIONS BETWEEN VIRUS AND BACTERIA, FUNGI ALONE OR IN COMBINATION

Virus-bacteria and virus-fungi co-infections have been recognized in some diseases, such as chronic obstructive pulmonary disease and asthma exacerbations, providing a plausible rational for the increased disease severity. For instance, in asthma patients, detection of pathogenic Streptococcus pneumoniae or Moraxella cattarhalis during human rhinovirus infection is associated with increased respiratory symptoms and exacerbations [11]. Bacterial pneumonia following virus infection also postulated the synergistic co-pathogenesis of bacteria-virus crosstalk. A clear example of this crosstalk was recently shown in an elegant study by Kash et al. who showed lethal disease and increased mortality in mice co-infected with pandemic H1N1 virus (Mex09) and Streptococcus pneumoniae through expediting the breach of lung epithelial cell, as evidenced by prominent attachment of Streptococcus pneumoniae to epithelial cells, decreased protein expression of cell proliferation and tissue repair [12]. Clinically, polymicrobial infections are not uncommon, their interactions and their effects on patient outcomes remain poorly studied. Human pathogenic viruses Herpes Simplex Virus type 1 (HSV1) and type 2 (HSV2) inhabited in oral or genital tract, both viruses can cause oral lesions, where in Streptococcus aureus and Candida albicans co-colonization and HSV-1 and Candida albicans co-colonization existed. HSV1 and HSV2 could be antagonist towards Streptococcus aureus adherence to cell surfaces and exert synergistic effect on Candida albicans [13]. The mutualistic relationships between HSV and Candida albicans were demonstrated by that HSV1 can be protected by Candida biofilm, reciprocally; HSV1/2 could promote C. albicans yeast forms, germ tube forms and adherence, and protect it from phagocytic killing [13-15]. However, co-inhabitation of the three pathogens affected Streptococcus aureus adherence in varying degrees. For instance, presence of Streptococcus aureus significantly inhibited adherence of germ tube forms to HSV2-infected cells, it can also significantly decreased yeast forms adherence to HSV1-infected cells [13]. Meanwhile, HSV1/2 were suggested to be important in regulating the co-localization adherence pattern of Streptococcus aureus and Candida albicans in host cells, subsequently modulating cytokines release and immune systems [13]. These results supported the combination of polymicrobial organisms resulted in microbial virulence and adherence that were either enhanced or partially weakened depending on both the viral species and the fungal or bacterial phenotype present. However, the research of relevant signaling pathways in polymicrobial disease is still in its infancy and remaining to be elucidated.

In addition, bacteria-phage interaction enabled therapeutic phages as a potential method for pathogen control in diseases. Some studies have shown bacteriophage could break down the thick polysaccharide alginate matrix elaborated by Pseudomonas aeruginosa during lower airway infection of the cystic fibrosis [16], reduce bacterial load of Staphylococcus epidermidis [17] and improve survival of mouse infected with Pseudomonas aeruginosa in burn wounds [18]. These data showed potential applications of phage therapy for controlling disease. More information about fungi-phage interaction tempting to move its steps to identify new avenues for disease treatment merits continued research.

CONCLUSION AND FUTURE DIRECTIONS

It is now appreciated that most of the polymicrobial infections brought about more intricate and stubborn outcome and manifestations in human disease than mono-infection, the underlying mechanisms may be attributed to the complex cross-kingdom interactions, which enabled a synergistic or antagonistic relationship between the parties involved in the networks. Moreover, the byproducts with host immune-regulatory roles in this process further brought the interplay into the spotlight of scientific interest. In addition, recent

microbiome research has enormously developed and characterized the unbalanced trans-kingdom networks between bacteria and fungi in some diseases. Even though, the physical and chemical forms in bacteria-fungi interactions have been demonstrated, the far more multitude of interactions between virus, bacteria and fungi are intriguing and still in its infancy, deserving further research for better understanding of the infective pathology. Metagenomic, transcriptomic, metabolomic analyses may pave the way for a reappraisal of co-infections and depicting interactive mechanism and host immune responses in polymicrobial ecosystems, and furthermore, identifying new preventive measures for future antimicrobial strategies.

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