

Contribution of Host Signaling and Virome to the Mycobiome

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Abstract

Formation of the host mycobiome is dependent on interactions between the members of multiple kingdoms. To control the initial step in the biofilm formation process, i.e., adherence, it is important to understand how host chemical communication signals, e.g. hormones, and the virome interact with the mycobiome.

Keywords Herpes simplex; Adherence; Microbiome; Insulin; Steroids

Introduction

Colonization of the host occurs in an environment replete with a variety of complex factors. Thus fungal colonization, whether by commensal or pathogen, is informed by multiple factors from available nutrients, presence of inter-kingdom signaling chemicals, and recognized presence of viruses as members of the microbiota. A fundamental mechanism through which the host can control its mycobiome is hormonal signaling. It is well established that fungi communicate with each other via quorum signaling chemical compounds [1]. It is also increasingly recognized that bacteria and fungi communicate with each other via quorum signaling as well as a variety of other mechanisms including the physical interactions that can occur within biofilms [2-5].

However, there is still a paucity of knowledge regarding host-fungal inter-kingdom communication. The pioneering studies of Le Roith et al. [6] in the early 1980's as well as studies by Thim and Silva [7] show that insulin and insulin-like compounds may function as a multi-kingdom communication signaling system. In addition to *E. coli* and *Tetrahymena*, upon growth in minimal medium, several fungal genera, e.g. *Neurospora crassa*, *Saccharomyces cerevisiae* and *Aspergillus fumigatus* could be induced to release a proinsulin and insulin-mimics with antigenic and bio-activity similar to that of mammalian insulins [6-12]. Some of the most compelling evidence for insulin and fungi involved in the host microbiome are findings that in a mouse animal model of diabetes (db/db mouse), the hormonal and metabolic changes associated with type-2 diabetes in the host together with *Saccharomyces boulardii* can modulate both gut microbial flora and affect host metabolism [13-15]. Taken together these findings provide evidence that host insulin may be able to function as a host chemical signal for certain opportunistic fungal pathogens, or alternatively, secretion of insulin-like factors by members of the fungal microbiota may influence host metabolism. This hypothesis is further supported by studies that showed that *S. cerevisiae* and *N. crassa* possess human insulin-specific and insulin-like receptors [8,9,16,17]. Whether consistently present commensals that are normal members of the microbiota release insulin-like proteins in the host remains to be determined.

Significantly more evidence concerning host compound signaling effects on fungal metabolism and presumably biofilm formation exists for the steroidal hormones [17]. Progesterone analogs inhibit radial growth of several fungi via prevention of both cellular synthesis and enzyme action [18]. *Curvularia lunata* is inhibited by 21,21-dimethoxy progesterone and 21,21-diethoxy progesterone, while dimethoxy progesterone, inhibits *Trichophyton mentagrophytes*, *Colletotrichum coffeanum*, *Fusarium moniliforme*, *Fusarium sativum*, and *Rhizoctonia solani* [18]. However, progesterone's effects are not confined to inhibition of fungal metabolism since in a concentration specific manner it can either inhibit or stimulate *Coccidioides immitis*, *Candida albicans*, *Microsporum canis*, *Saccharomyces cerevisiae*, *Aspergillus clavatus*, *A. fumigatus* and *A. niger* growth [19-25].

Similarly, α -estradiol, 17 β - estradiol, and norethisterone also inhibit or stimulate growth in a concentration specific manner for *M. canis*, *Trichophyton purpureum*, *T. mentagrophytes*, *A. clavatus*, *A. fumigatus*, and *A. niger* [26-28]. Another study shows that estrogen is the dominant hormone that supports and maintains experimental vaginal *Candida* infection, indicating that estrogen plays a role in *C. albicans vaginitis* [29,30]. Estrogen (17 β -estradiol) also has a stimulatory effect on multiple morphologic phases having stimulatory effects on *Coccidioides immitis* growth and increased the rate of spherule maturation and endospore release as well as functioning as an inducer of *Candida* germination by increasing the percentage of germination and germ tube length in a concentration specific manner [21,31-34].

This transition to germ tubes may help *Candida* colonization [31-34]. Taken together, these data show that estradiol is capable of increasing the virulence of *C. albicans*, at least in part through modulation of its biofilm formation capabilities. Similar to the estrogen effects, testosterone is shown to be fungistatic for the dermatophytes *T. purpureum*, *T. gypseum* and *M. canis* [20,27]. In fact, topical applications of methyl testosterone ointment were curative for *T. purpureum* infection in castrated rabbits [27]. In contrast, testosterone stimulates the growth of the pulmonary pathogen *Coccidioides immitis* [21].

Polymicrobial-Fungal Interactions

Metagenomics have allowed researchers to make great inroads into identification of the respective members of the microbiome. These

studies describe several novel viruses of the Adenoviridae, Picornaviridae, Reoviridae families shown to be the cause of acute onset diarrhoea and enteropathy in the paediatric population located in underdeveloped areas of Australia [35]. However, despite this fast growing list of microbiome members, there is still little known concerning their interactions. This is particularly true for viral-fungal interactions. Recent findings indicate a cooperative interaction between the host and its resident viruses in controlling both the specific members of the microbiota as well as their precise geographic areas of colonization within the host [36]. Upon attachment and entry into host cells there is a turnover in available receptors along, with an

alteration in cell membrane architecture due to viral entry perturbation (Figure 1). In addition, virus entry typically results in triggering of cell signalling which not only results in alterations in host cell metabolism which could affect invasive fungal elements (hyphae) if present, but the secretion of a variety of cytokines and chemokines which may also have profound effects on the surrounding microbiota [37]. However, it is only recently that the virus-fungal-bacterial inter-kingdom interactions as they relate to biofilm initiation have been studied. This study focused on how herpes simplex virus 1 and 2 (HSV-1, HSV-2) affected adherence of *C. albicans* with and without *Staphylococcus aureus* [36].

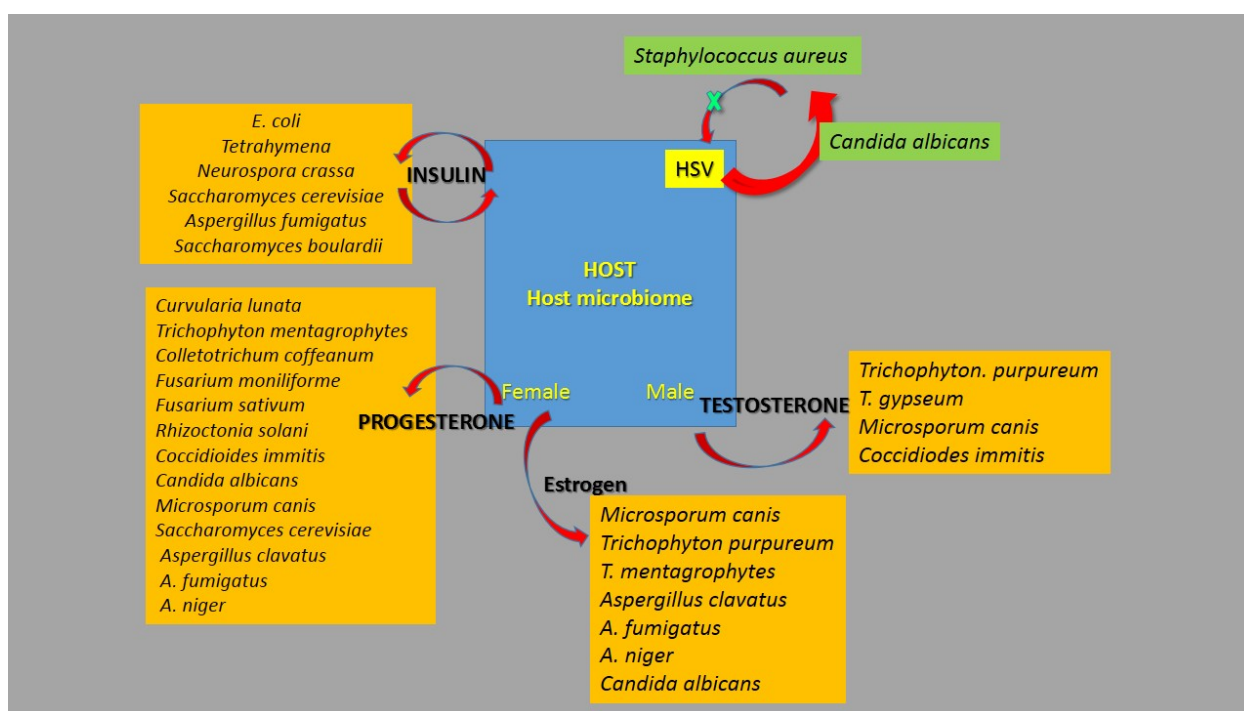


Figure 1: Interactions between various chemical signals the host and host microbiome. Production of various chemical signals by the host and/or commensal and pathogenic members of the microbiome; effect of herpes simplex virus type 1 or type 2 as a permanent members of the microbiome on subsequent adherence of *S. aureus* or *C. albicans*.

These members of the host microbiome have overlapping sites of colonization (oronasopharynx and vagina). *S. aureus* and *C. albicans* colonize or sequentially colonize individuals with cystic fibrosis, burn wounds, cystitis and diabetic foot ulcers, in addition to biofilm-associated prosthetic infections, e.g. dentures, voice prostheses, implants, endotracheal tubes, feeding tubes, and catheters [38-40]. There are also indications that *S. aureus* enhances onset of fungal-mediated allergic sinusitis [41-43]. *In vitro* *S. aureus* and *C. albicans* interact promoting polymicrobial biofilm formation [44].

However, *in vivo* *S. aureus* does not co-localize with HSV-1, HSV-2 or *Candida* in the oronasopharynx wherein *S. aureus*, *C. albicans* and HSV inhabit distinct geographical niches. In normal hosts, the oral mucosa is shared by HSV and *C. albicans*; the anterior nasal nares are occupied by *S. aureus* [45]. Only rarely is *S. aureus* isolated from oral-pharyngeal specimens, despite *S. aureus*' ability to adhere *in vitro* to buccal epithelial cells [46,47]. This colonization site specificity is traversed when an abiotic surface, i.e., dentures, are introduced upon which *S. aureus* forms a robust biofilm together with *C. albicans*

[48,49]. Co-incubation testing reveals that while HSV enhances fungal adherence, it inhibited staphylococcal binding to virally infected cells. Of additional interest, is that there was a viral specificity for the fungal morphology affected; HSV-1 enhanced yeast adherence while HSV-2 enhanced germ tube adherence.

This differential fungal phenotype adherence mediated by HSV-1 (yeast form) vs. HSV-2 (germ-tube form) begins to explain host colonization sites and how a permanent viral member of the virome may play a role directing maintenance of the candidal commensal (YF) vs. pathogenic state (GT) *in vivo*. Whether this was accomplished via an alteration in available cell surface receptors or alterations in cell signalling has yet to be determined. [43,45,50-56].

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