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One population, multiple lifestyles: commensalism and pathogenesis in the human mycobiome

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Summary

Candida auris and *Candida albicans* can result in invasive fungal diseases. And yet, these species can stably and asymptomatically colonize human skin and gastrointestinal tracts. To consider these disparate microbial lifestyles, we first review factors shown to influence the underlying microbiome. Structured by the damage response framework, we then consider the molecular mechanisms deployed by *C. albicans* to switch between commensal and pathogenic lifestyles. Next, we explore this framework with *C. auris* to highlight how host physiology, immunity, and/or antibiotic receipt are associated with progression from colonization to infection. While treatment with antibiotics increases the risk an individual will succumb to invasive candidiasis, the underlying mechanisms remain unclear. Here, we describe several hypotheses that may explain this phenomenon. We conclude by highlighting future directions integrating genomics with immunology to advance our understanding of invasive candidiasis and human fungal disease.

eTOC.

In this review, Proctor and colleagues spotlight two fungal pathogens – *Candida auris* and *Candida albicans* -- named by the World Health Organization as urgent health threats. They explore the role of the microbiome, host physiology, host immunity, and antibiotics in modulating switches between commensalism, pathogenesis, and infection, in *Candida* species.

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Declaration of Interests

The authors declare no competing interests.

Keywords

Candida ; mycobiome; antibiotics; damage response framework; commensal; pathogen; medical mycology; microbiome; antibiotic stewardship

Introduction

We often think of the components of the human microbiota as commensals and deploy these concepts with some degree of equivalence, but these are not synonymous terms. A useful framework for considering the organisms that live on our body is the damage response framework, developed by Pirofski and Casadevall, which defines a lexicon based on a synthesis of the history of the field of microbial pathogenesis[1]. In this framework, microbiota consists simply of microbes that colonize the body at a given time point while commensalism or pathogenesis denote behavioral lifestyles, most easily identified by the outcome of a given interaction, between a host and a colonist. Following adherence, the outcome which denotes commensalism is colonization with the apparent absence of disease. The outcome that defines pathogenesis is colonization with "damage that affects host homeostasis"[2], which may manifest as inflammation, tissue destruction, or disease. The damage response framework importantly resolves the paradox that even organisms like *Malassezia* species, which are widely regarded as commensals of the skin of virtually all healthy adults[3], have been implicated in inflammatory responses such as atopic dermatitis[4], inflammatory bowel disease (IBD)[5], and invasive disease and mortality[6–8]. Conversely, *C. auris*, one of the world's most feared fungi, asymptomatically colonizes up to 90% of humans while adopting the lifestyle of a commensal, challenging our best efforts at detection during surveillance[9]. Whether an organism adopts the commensal or pathogenic lifestyle depends on the immune and health status of the host, the local tissue environment (e.g., pH, salivary flow rates, oxygen concentration, etc.), the microbe's genetic potential, its epigenetic profile, as well as microbial consortium at the site of adherence. It is even possible that individual microbes within a population will adopt different lifestyles simply because one or more of these variables differs between adherence sites.

Irrespective of behavior or lifestyle (commensal, pathogen), a microbe must adhere either to host tissue directly or to other microbial colonists to engage with the host. Initial adherence is followed by an outcome, either clearance of an individual microbe or its successful growth and colonization of a tissue, shaped by intrinsic and extrinsic microbial factors. For example, outcomes for *Candida* engagement with a host depend upon the intrinsic adoption of either yeast or hyphal forms, each necessary for pathogenesis[10]. The yeast morphology arises after budding of daughter cells following cytokinesis and nuclear division. The hyphal morphology is filamentous and includes one or more tubular cells separated by porous septa. In *C. albicans*, *Ume6* is a master regulator of the shape-shifting yeast to hyphal switch[11]. *Ume6* is variably expressed based on the intensity of different host cues, such as pH, and tunes production of an adhesin and secreted aspartic protease 6 (Sap6). Levels of these proteins determine whether individual cells are hyper-competitive for colonization or get rapidly cleared by activating a pro-inflammatory response, permitting yeast and hyphal forms of *C. albicans* to co-exist in a single host's gut. **Within a microbial population,**

different microbes will experience different outcomes, following adherence, depending on the interaction of each organism with the host (Table 1).

Genetically encoded *C. albicans* regulatory switches also govern metabolic programs, potentially optimizing organismal fitness within the population for differential nutrient utilization regimes at spatially segregated locations along the gastrointestinal (GI) tract[12]. Population substructure encompassing individual cells with distinct morphologies, cell surface properties, levels of metabolic activity, and gene expression profiles have been observed in other host-associated fungi, such as *Cryptococcus neoformans*[22]. These studies suggest that microbes are genetically hardwired to fine-tune organismal behavior towards commensalism on the one hand or pathogenesis on the other, using transcriptional switches, depending on environmental cues. Rather than designating microbes that are "sometimes commensal", "sometimes pathogen" as opportunists, the damage response framework considers that at any given moment microbes within a population may adopt different lifestyles, leading to divergent outcomes – in line with the emergent belief that single cell behavior is an important determinant of the population as a whole.

In this review, we consider two *Candida* species, designated by the World Health Organization (WHO) as critical priorities[23], because they famously adopt both commensal and pathogenic lifestyles in humans. Given that both species must compete with and embed themselves into the microbiota, we begin by discussing factors that modulate the human microbiota, often triggering a switch in colonists to transition from commensal to pathogenic lifestyle. Next, we review the literature on molecular determinants of *Candida* colonization, dissecting known molecular cues that underly the switch from commensal to pathogenic lifestyle in *Candida* species, as well as mechanisms by which *Candida* colonization may shape the host's systemic health. We then use the emerging fungal pathogen *C. auris* as a case study to contextualize the damage response framework, while introducing how colonization and invasive disease drive both acute outbreaks and endemic spread. Finally, we review the evidence behind multiple alternative hypotheses that explain the increased risk of *C. auris* infection and associated mortality following antibiotic treatment.

Factors that shape the human microbiota and can provoke microbial lifestyle switches

The human microbiota is comprised of the bacteria, fungi, archaea, viruses, and protists that colonize our bodies. Some microbial species establish stable colonization and are detected on an individual on the timescale of months to years while other species transiently colonize[24]. Regardless of the duration of association, microbial colonists potentially shape host health long past their physical contact with the host[25]. The ability of an organism to colonize successfully may depend on a host's experience with prior colonists. This is well illustrated by the observation that *C. albicans* engenders Th17 producing cells that are cross-reactive against a wide variety of fungi, ranging from *Malassezia* to *Aspergillus*[26]. More broadly, microbial services include training the host immune system locally and at distal anatomical sites[27] and serving as keystone species to organize microbial communities. On time scales ranging from days to a lifespan, the human microbiome experiences an onslaught of disturbances[28], both exogenous and those associated with host physiology. These disturbances can reconfigure the community and facilitate adoption of a pathogenic lifestyle

by colonists. Here, we briefly spotlight several sources of disturbance – antimicrobials, host physiology, and microbial invasion – that influence outcomes associated with microbial adherence.

Humans are exposed to various chemicals – ranging from antibiotics to antifungals to disinfectants – that can modulate the microbiota, often in unexpected ways. For example, oral administration of several antibiotics used to treat dermatologic disorders can select for antibiotic resistance genes in skin commensals such as *Staphylococcus epidermidis*, which may then serve as a reservoir for the horizontal transfer of resistance genes to other species, such as *S. aureus*[29]. In addition, antibiotics used to treat bacterial infections can lead to an expansion of *Candida* in the oral cavity[30], vagina[31], or the gut[32], the latter of which may facilitate invasive fungal infection via bloodstream translocation from the gut[33]. While antifungals treat fungal infections, they also deplete the gut mycobiota which surprisingly elicits inflammation in the lungs as well as the gut[34]. Specifically, in a mouse model of allergic airway disease, the anti-fungal drugs fluconazole, amphotericin-B, or 5-fluorocytosine were associated with immunopathology characterized by heightened eosinophilic pulmonary infiltration, elevated serum IgE and IgG1, and increased production of Th2 cytokines (IL-4, IL-5, IL-10), presumably in response to depletion of the gut mycobiota[34]. Finally, the antiseptic chlorhexidine is commonly used to “decolonize skin” to prevent surgical site infections and/or to reduce the risk of bloodstream infections in hospitalized patients[35], but decolonization is indiscriminate, inducing a shift in the skin microbiota[36]. Aside from antimicrobial agents meant to eliminate certain microbes from the host or otherwise reduce microbial load, commonly used prescription medications can modulate the composition of the bacterial component of the microbiota[37] with many expected to have impacts on the fungal community[38], though this merits further exploration.

Ecosystems ranging from rocky inter-tidal ecologic environments to the human microbiota are shaped by disturbance regimes, defined here as periodic processes that govern the dynamics and health of the ecosystem[39]. For humans, disturbance regimes arise with a full range of changes to host behavior, physiology or health status. For example, the microbiota of the human oral cavity is shaped by diurnal fluctuations in salivary flow rates[40,41], which are tuned by the parasympathetic nervous system. Additionally, flow rates periodically rise or fall due to autonomic responses related to chewing, tasting acidity, or even thinking salacious or anxious thoughts. These periodic and frequent fluctuations in salivary flow rates mark a disturbance regime that maintains the oral microbiota. Medications with anti-cholinergic effect or radiation therapy to the head, nose or throat ablate these fluctuations in salivary flow, resulting in hyposalivation[42,43]. The chronic loss of punctuated increases and decreases in salivation (i.e., the loss of the disturbance regime) leads to a marked shift in the spatial organization of the microbiota[44], predisposing the host to anterior dental caries[45] and oral candidiasis[46]. In other words, the loss of this disturbance regime provokes the switch from a commensal to pathogenic lifestyle in *Candida* and other species. As a second example, at puberty, hormonal fluctuations, secondary gland maturation, and subsequent lipid availability on the skin modify the composition of the human microbiome by facilitating colonization of skin by auxotrophic and lipophilic *Malassezia* species[47]. Puberty thus marks the onset of a disturbance regime that is characterized by the glandular production of antimicrobials and sebum, as well as immunological responses. Once adults

pass the seventh decade of life, however, androgen levels fall, and the sebaceous glands eventually succumb to dysfunction and hyperplasia, potentially accounting for the increased diversity of the skin microbiota of elderly individuals, and subsequent increased risk of skin infection[48]. Thus, host physiological processes maintain the health of the microbiota, whereas losses of periodic physiological disturbances provoke shifts in ecosystem health.

Invasion or predominance of the microbiota by microbes that tend not to colonize (or only colonize at low abundance) also represents a disturbance. This is for several reasons[49]. First, invasive species potentially modify existing disturbance regimes. The antibiotic-mediated loss of the commensal microbiota and ascension of *Candida* species in the gut, for example, is associated with the loss of tonic immunity[50], a disturbance regime underlying host homeostasis. Second, invasive species can modify the biotic or abiotic properties of an ecosystem, such as the local destruction of teeth, nails, or soft tissue, which can create an environment favorable for the invasion or expansion of other species[51].Third, through competition, cooperation or metabolic cross-feeding[52], invasive species can moderate interactions among the community[32] and facilitate the successful invasion of other species. The Rakoff-Nahoum group observed that the gut microbiota of preterm infants is initially predominated by *Staphylococcus* species, and that *Staphylococci* are often succeeded by either *Klebsiella* or *Enterococcus*[53]. *In silico* modeling and animal experiments revealed the basis for these disparate patterns of succession. When *Klebsiella* ascends to dominance over *Staphylococcus*, it inhibits *Staphylococcus* while promoting the ascension of *C. parapsilosis*. Importantly, *Candida* was inhibited by *Staphylococcus* so its displacement by *Klebsiella* is needed prior to its expansion. Likewise, *Enterococcus* appears to ascend and inhibit *Klebsiella*, explaining empirical patterns in humans. In the extreme, succession patterns such as these can culminate in an over-abundance in the microbiota of multiple species typically found circulating in hospital environments[54], leading to community composition of older adults residing in nursing homes that differs markedly from that of similarly aged community dwellers[55].

***C. albicans* as a model to understand the diversity of lifestyles—**In the United States, *Candida* species are reported to cause up to 22% of bloodstream infections with patients in intensive care units accounting for 50% of cases[56]. The burden of invasive fungal disease is increasing due to an aging global population, as well as the increasingly sophisticated iatrogenic treatments used to manage complex patient populations, such as those undergoing transplantation or cancer treatment. While *Candida* is a leading cause of bloodstream infection, it silently colonizes the GI tract of the majority of adults. *Candida* also colonizes the skin of healthy adults, although typically at low abundance and prevalence compared to the more dominant *Malassezia* species[57]. Some have proposed that the prevalence of *Candida*-colonized adults may be higher in the western world, linked to high sugar and fat diets[58–60] and high antibiotic utilization. An increased load of *Candida* within the gut can increase the risk of systemic *Candida* infection[33], and in recent years has been associated with a multitude of diseases ranging from allergic lung inflammation and GI tract cancers to alcohol-associated liver disease[61–63]. Therefore, there is a clear need to improve understanding of the molecular cues that drive the switch from the commensal to the pathogenic lifestyle in *Candida* species.

Determinants of *Candida* colonization resistance

Unlike humans, mice are typically resistant to persistent *Candida* GI colonization by standard laboratory strains, which provides an opportunity to study the mechanisms by which *C. albicans* colonizes the host. Colonization resistance may be overcome by depleting the microbiota, host deficiency of key mucosal defense molecules, or by strain-specific *C. albicans* resistance to host defenses, as outlined below. Depleting the gut microbiota with broad-spectrum antibiotics prior to oral delivery of *C. albicans* breaks colonization resistance. The bacteria *Bacteroides* and *Firmicutes* are essential for promoting *Candida* colonization resistance in the gut, and their depletion activates a signaling axis involving hypoxia inducible factor (HIF)-1– and cathelicidin-related antimicrobial peptide (CRAMP)[64]. Specifically, HIF-1α activation in intestinal epithelial cells mediates downstream production of the antimicrobial peptide CRAMP (LL-37 in humans) that helps to expel *Candida* from the GI tract. Indeed, mice deficient in CRAMP are less resistant to *Candida* gut colonization and can be stably colonized with the *C. albicans* lab strain SC5314[65] without antibiotic treatment. Strains of *C. albicans* that can colonize the murine GI tract in the absence of antibiotics (e.g., strain 529L) are more resistant to CRAMP-mediated killing[65], further underscoring the HIF-1α/CRAMP axis as a critical determinant of colonization resistance. Treatments that boost HIF-1α activation help to reduce *Candida* colonization in mice, which is important for preventing mortality from invasive infection[64]. Invasive *C. albicans* infections that originate from the GI tract cause a hepato-splenic pattern of infection in patients with prior expansion of commensal *Candida* populations and disrupted mucosal barrier and/or innate immune defenses[33,66,67].

Within the gut, *C. albicans* typically exists as yeast but recent studies have also uncovered its presence in the filamentous (hyphal) form[11]. The mechanisms governing the ratio of yeast to hyphae in the gut are unclear, and the degree to which immune selection or fungal factors moderate outcomes is unknown. Of note, strains with differing capacities to overcome GI colonization resistance in mice have significantly different responses to hyphal-inducing growth conditions *in vitro* yet form a similar cell morphology within the gut lumen *in vivo*[65]. Colonizing yeast cells, called GI-induced transition (GUT) cells, are distinct from yeast cells grown in the lab or found within tissues during systemic *Candida* infection[12]. For example, GUT cells down-regulate genes involved in iron acquisition, adhesion, and other gene modules typically associated with infection. The master regulator of GUT morphology is the transcription factor Wor1, and over-expression of Wor1 in *C. albicans* results in increased fitness to colonize the murine GI tract. Furthermore, the Noble lab recently showed that the master regulator Ume6 inhibits gut colonization by modulating the expression of hypha-associated proteases and adhesion molecules, rather than by directly affecting fungal morphogenesis[11]. However, why some fungal virulence factors, such as adhesins, should alter GI colonization capacity, is still unknown. Another genetic determinant of colonization “fitness” within the mouse GI tract was recently uncovered by the Bennett lab[68]. They showed that loss of the filamentation regulator Efg1 during gut passage in mice, as well as *Candida* strains cultured from the gut of colonized humans, was associated with increased fitness for gut commensalism and increased virulence during systemic infection. Collectively, the expanding knowledge of molecular factors that regulate

fitness within the GI tract shows promise for developing targeted strategies to modulate fungal colonization and subsequent invasive fungal infections in humans.

Candida and its crosstalk with the mammalian host

The microbiota and the mucosal immune system both exert significant influence over *Candida* morphological transitions. For example, IL-17 is significantly induced by *C. albicans* hyphae[69], and Th17 and γδ T cells are critical for clearing this morphology during murine mucosal *Candida* infections[70,71]. In the gut, there is a high concentration of Th17 cells within the intestinal lamina propria, which may inhibit or quickly clear hyphae from the gut. Indeed, *Candida* expands within the GI tract and invades intestinal tissue when Th17 cells are depleted by broad-spectrum antibiotics[72]. *Candida* also secretes mediators to inhibit IL-17 immune responses during invasive infection. Specifically, secretion by *C. albicans* of the lipase Lip2, made predominantly by hyphae, suppressed IL-23 production from tissue-resident dendritic cells that in turn dampened IL-17 production by γδ T cells[73]. Infection of mice with a *lip2*-null *C. albicans* mutant resulted in exaggerated IL-17 production and enhanced clearance and protection from infection. Therefore, *Candida* can modulate the lipid microenvironment using secreted mediators, which may have significant consequences for host-fungal interactions. Whether *C. albicans* can directly modulate the metabolic milieu of the gut is unclear, although initial studies have indicated that *Candida* GI colonization of infants can affect the production of immune-stimulatory metabolites (discussed below).

Gut colonizing *Candida* yeasts appear to induce Th17 cells systemically. Humans colonized with *Candida* have increased frequency of circulating antifungal Th17 cells which are cross-reactive to unrelated fungi including *Malassezia* and *Aspergillus*[26]. Intestinal inflammation boosts the number of circulating antifungal Th17 cells, which may act in a pathologic manner at distant anatomical sites. For example, Th17 cells cross-reactive to *Aspergillus* spores were found to augment allergic-type inflammation within the lung, thus exacerbating asthma pathology and sensitization to inhaled fungal spores. In mice, colonization with *Candida* also induces systemic Th17 cells that exacerbated lung inflammation in allergic disease but had no impact on control of viral pneumonia[74]. However, Th17 cells induced by *C. albicans* gut colonization were protective against invasive infection caused by *C. albicans* or *S. aureus*. Protection against systemic fungal (*Aspergillus*) and bacterial (*Staphylococcus, Pseudomonas*) infections also occurred independently of adaptive immunity when mice were colonized with gut-adapted *Candida* strains, implicating trained immunity in this phenomenon[75]. Taken together, these studies show that *Candida* gut colonization modulates both local and systemic host immunity. While this tradeoff may afford protection against invasive infections, it could promote pathology in multiple organs along the gut-lung axis. Indeed, young babies with increased carriage of *Candida* had a higher risk of developing childhood asthma[76]. Mechanistically, early colonization with *Candida* changed the metabolite profile within the gut, skewing T cell polarization *ex vivo*. Adult T cells exposed to the metabolite cocktail derived from the guts of *Candida* colonized babies prevented the differentiation of regulatory T cells (Tregs) and favored the production of the Th2 cytokine IL-4. Similar functional skewing *in vivo* may explain the increased susceptibility to allergic pathology in the lung that is driven by IL-4 and lack of suppression by Tregs. Moreover, recent work from the Corry lab identified the peptide toxin candidalysin

as the *C. albicans*-derived factor that drives direct type-2 allergenic responses within the lung following inhalation by *C. albicans*[77]. Continued investigations into *Candida* colonization and subsequent systemic pathology may thus reveal insight into molecular mediators of host homeostasis, and physiologic disturbance regimes that shape microbial communities.

In addition to driving systemic pathology, *Candida* can exacerbate localized GI inflammatory disease. During intestinal inflammation, *Candida* may produce candidalysin, which forms pores that penetrate the membrane of epithelial cells to induce damage and enable hyphal invasion across mucosal barriers[78]. The GI tract of patients with IBD are enriched in *Candida* species[13], which when cultured are more likely to produce candidalysin than are strains isolated from healthy controls. Candidalysin activated the inflammasome and IL-1β production from macrophages, both of which strongly correlated with the severity of ulcerative colitis. Candidalysin-mediated immune cell damage and activation drove pathologic Th17 immunity in the gut, contributing towards the inflammatory sequalae seen in IBD. Similarly, patients with either gastric or colonic cancers were found to have an increased abundance of *Candida* species in their microbiome[61]. Moreover, *Candida* was detected directly within solid tumors, suggesting that the fungus may be capable of invading tumor tissues. Of interest, the presence of fungi within GI tract tumors was predictive of mortality in humans. Collectively, these studies demonstrate that *Candida* colonization has far-reaching consequences for health and disease, which calls for further mechanistic understanding.

***C. auris* as a model to understand the damage response framework—**Genomic sequencing of *C. auris* revealed that four clades from distinct continents separated by tens of thousands of single nucleotide polymorphisms (SNPs) emerged nearly simultaneously[79]. Efforts to ascertain the origin of *C. auris* identified the first isolate in banked *Candida* isolate collections from 1996[80]. However, how *C. auris* quickly emerged as 4 distinct clades remains an enigma. Over the last decade, outbreaks have been reported across the globe. In New York City, a highly inter-connected web of healthcare facilities, including skilled nursing homes, long-term care facilities, long-term acute care hospitals and acute care hospitals, have reported a regional outbreak detected as both clinical and surveillance cases[81]. Of concern, recent reports suggest the COVID-19 pandemic was associated with an apparent increase in *C. auris* transmission in acute care hospitals[82]. Due to its high propensity for spread and high frequency of resistance to antifungals and disinfectants, the U.S. Centers for Disease Control and Prevention (CDC) described *C. auris* as an urgent health threat in 2019[83], and the WHO listed it as one of the world's most threatening fungi in 2022[23]. Cases of colonization can escape detection as a result of its ability to colonize human skin long-term, without provoking a clinically apparent inflammatory response. Consequently, *C. auris* readily establishes outbreaks in congregant settings including cycles of endemic infection. Here, we explore what is known about its ability to colonize skin, the consequences of persistent colonization, and explanations for how antibiotics increase the likelihood of colonization and infection with *C. auris* Consideration of the impact of antibiotics on invasive *C. auris* infection fits within the damage response framework and highlights a role for antibiotic stewardship in the management of fungal disease.

Persistent colonization of skin

Skin and nares are the primary sites of colonization for *C. auris* while bloodstream infection is the major clinical risk. Patients who are colonized with *C. auris* can remain persistently, asymptomatically colonized for months or even as long as a year[84]. Colonization of individuals in healthcare facilities experiencing endemic spread tends to be multi-focal with more than one body site testing positive, but without any single site identifying all colonized patients[54]. Bioburden of *C. auris* is strikingly high with colony forming unit (CFU) counts exceeding a million in nares, axilla/groin, fingertips, and toe web samples[54,85]. The bioburden of *C. auris* on humans exceeds that observed for low abundance members of the skin mycobiome, *C. parapsilosis, C. orthopsilosis*, and *C. tropicalis*[57]. *Ex vivo* studies suggest that *C. auris* can form dense, multi-layer biofilms on porcine skin cultivated in sweat with population densities exceeding that of other *Candida* species[86]. *C. auris* colonization does not induce clinically apparent skin inflammation in humans, an observation recapitulated in animal studies which report a lack of skin erythema or histological evidence of hyperkeratosis or spongiosis[87]. The lack of skin inflammation cannot be attributed to superficial colonization of skin, where immune cells may not infiltrate, as *C. auris* has been found to reside within deeper skin tissue, including in glands and hair follicles[88]. Moreover, colonization with *C. auris* leads to enrichment of CD4+ IL-17A+ and CD4+ IL-17F+ (Th17) cells as well as CD8+ IL-17A (Tc17) cells, γδ T cells, and type-3 innate lymphoid cells within the skin compartment. Ablation of IL-17 signaling results in an increase in *C. auris* colonization with contributions noted for both innate and adaptive IL-17–producing lymphoid cell populations, suggesting intimate tuning of *C. auris* colonization bioburden by the host immune system. While recognized as a human pathogen, *C. auris* behaves essentially as a skin commensal.

Current work has focused on elucidating the molecular determinants of virulence in *C. auris* using experimental infection paradigms, rather than paradigms meant to identify commensal-pathogen switches (Table 1). Such studies have revealed genes such as Hog1[21] and at least one long non-coding RNA, DINOR[20], that drive the regulation of stress response and virulence programs in *C. auris*. Moreover, passage of *C. auris* through a mammalian host induces atypical morphology, giving rise to subpopulations of aggregative and filamentous isolates, a phenomenon observed in some clinical studies. Importantly, aggregative strains appear to be less virulent than non-aggregative strains and exhibit divergent transcriptional profiles[89,90]. ACE2 and TOR3 were identified as transcriptional switches underlying the aggregating phenotype in *C. auris* while ELM1 was identified as a regulator of filamentation[90]. It is intriguing to speculate that these transcriptional switches govern the transition between the commensal to pathogenic lifestyle in *C. auris*, though future work is needed to elucidate the molecular determinants of *C. auris* colonization.

Clinical significance of persistent colonization

Skin colonization with *C. auris* is the largest risk factor for a subsequent bloodstream infection, highlighting the importance of controlling fungal colonization. Moreover, early clinical studies have reported patients who resolve one bout of systemic *C. auris* infection often experience recurrent infection[84], reinforcing the need to decolonize patients. Contamination of the hospital environment (Figure 1A) by live *C. auris* is a reservoir for

recolonization and/or infection with a required minimum contact period of 4 hours[91]. In the environment, a higher count of live cells was recovered from non-porous compared to porous hospital surfaces[85]. In the UK, *C. auris* isolates were detected on reusable equipment, including axillary skin-surface temperature probes, more often than in the general environment[92]. Investigators have postulated that bedding and clothing may serve as sources of *C. auris* exposure, contributing to persistent multi-focal colonization[91]. In addition to these environmental sources, autoinoculation from sites experiencing occult or even sub-surface colonization may play a contributing role in perpetuating colonization[54,88]. Together, these studies demonstrate that an integrated approach will be required to prevent and control *C. auris* colonization.

In addition to the risk posed to patients, persistent colonization is clinically important as it permits the genomic diversification and possible adaptive evolution of *C. auris* which poses a longer-term risk (Figure 1B). An investigation of the genomic diversity of *C. auris* isolates revealed its micro-diversification across body sites on a single individual[93]. Samples from 5 body sites of a single individual yielded clones separated by 4-9 SNPs. A larger study revealed that more than 20% of patients were colonized by multiple *C. auris* isolates that differed from each other by more than 5 SNPs[92]. Population metagenomes of *C. auris* isolates from temperature probes matched the mixed colonization of some patients, suggesting that micro-diversity on the patient is reflected on environmental surfaces. These findings have been replicated with surveillance and clinical cultures[94,95]. In addition to human samples, *C. auris* strains can also colonize organic surfaces such as apples[96]. Intriguingly, *C. auris* isolates on individual apples were separated by as few as 1-8 or as many as 107 SNPs. This suggests that the apples were colonized more than once with distinct *C. auris* strains and that microevolution occurred after colonization, consistent with observations in humans.

Given that *C. auris* chronically colonizes individuals at high densities, and standard clinical surveillance tends to sample limited body sites, the full extent to which *C. auris* micro-diversification occurs is not yet known. Nor have studies yet illuminated the functional consequences of *C. auris* micro-diversification. However, we can gain insight into the significance of this population structure by considering other microbes that colonize patients long term. Micro-diversification of *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) generates functional diversity soon after initial colonization[97] with adaptation to chronic infection occurring via parallel evolution within 3 years[98]. Specifically, isolates evolved along independent trajectories towards reduced mobility, exhibiting lineage specific evolution in terms of the elaboration of quorum-sensing molecules and secretion of proteases. Intriguingly, parallel evolution of antibiotic resistance occurred at spatially segregated sites with population variants diversifying according to sub-lineage specific mutation rates. Similar results are seen for other bacteria in which the co-existence of distinct sub-lineages in the CF lung extends over the course of years[99].

Providing parallel evidence, *in vitro* evolution of *C. auris* recapitulates clinical reports in humans; that is, population diversity with the evolution of several distinct sub-lineages occurring *in vitro* in just a handful of passages[100]. Recurrent mutations were found in multiple clinical isolates in 15 genes involved in nutrient acquisition, as well as in

transcriptional and cell cycle regulation genes. A hypermutator clinical isolate of *C. auris* was identified with a missense mutation in the *C. auris* homolog of the mismatch DNA repair component MLH1. Mutations in DNA mismatch repair genes have arisen during micro-evolution underlying hyper-mutator strains of *A. fumigatus, Saccharomyces cerevisiae, C. albicans, C. glabrata, Cryptococcus deuterogattii,* and *C. neoformans*[101]. In the *C. albicans* diploid genome, the rate of micro-evolution is driven in part by recombination-induced mutagenesis[102]. Moreover, the rate of mutation in *C. albicans* is roughly 100 times higher during passage through the murine oral cavity than during *in vitro* passage, suggesting that a multitude of host factors select for enrichment of SNPs[103]. In the haploid genome of *C. glabrata*, frameshift and nonsynonymous mutations have been associated with enrichment in cell surface genes, as well as genes associated with antifungal resistance, including ERG4 and FKS2[104]. Thus, micro-diversification potentially permits sub-lineages to evolve along distinct lines – generating an insurance policy that permits survival in the face of a fluctuating host environment. Just as a viral quasi-species is adaptive, so too might be the micro-diversity of fungal species.

Multiple alternative hypotheses to explain antibiotics as a risk factor for *C. auris* infection—Antibiotic receipt is an independent risk factor for *C. auris* infection in global studies from South Korea, Venezuela, India, Pakistan, and the United States[80,105,106]. A large-scale study examining the role of antimicrobial drug exposure found that cephalosporins, carbapenems, clindamycin, trimethoprim-sulfamethoxazole, and colistin use is associated with a significantly increased odds of colonization by fluconazole-resistant *Candida* species[107]. Our work previously reported receipt of antibiotics as a risk factor for colonization of humans with *C. auris*[54]. What factors may contribute to this outcome? We propose several alternative, non-mutually exclusive hypotheses that may explain this phenomenon including disruption of colonization resistance and tonic immune stimulation (Figure 2A1–4), sepsis induced immunosuppression (Figure 2B), and modulation of organismal fitness by the antibiotic (Figure 2C). Herein, we survey the literature supporting each hypothesis, and highlight critical gaps in our knowledge.

Depletion of colonization resistance and/or loss of tonic immune stimulation: Antibiotic-mediated depletion of the commensal microbiota may permit *C. auris* to colonize a site from which it would otherwise be excluded (Figure 2A.1). Studies of humans have been observational and cannot be used to infer causality. Nonetheless, some consistent themes have emerged. In an observational study of surveillance samples from 3 nursing homes in California, Illinois, and New York, we reported that *C. auris* colonization is associated with an apparent enrichment of Proteobacteria commonly involved in nosocomial infection such as *Acinetobacter baumannii, K. pneumoniae*, and *E. faecalis*[108]. Surveillance samples, in that study, were not linked to clinical data, so it was impossible to determine the extent to which factors such as antibiotic usage or health status were associated with the apparent bloom of Proteobacteria or *C. auris* colonization. A larger point prevalence survey of a ventilator skilled nursing facility in Illinois revealed that the relative abundance of species that tend to be highly abundant on the skin of healthy adults – including *Staphylococcus hominis, Corynebacterium striatum, Corynebacterium accolens,* and *Staphylococcus caprae* – is negatively correlated with *C. auris* abundance[54]. Concomitantly, the relative abundance

of multidrug-resistant organisms (MDROs) – including *P. aeruginosa, A. baumannii, Proteus mirabilis, K. pneumoniae, and Providencia stuartii* – is positively correlated with *C. auris* relative abundance. Where MDROs predominated, bacterial diversity was reduced. Intriguingly, a reduction of *C. auris* abundance over time, as measured by ITS1 sequencing, was accompanied by an increase in bacterial diversity, as well as a transition to a more 'normal' bacterial community, as measured by 16S sequencing. Yet, due to the observational nature of this report, it was not possible to determine whether *C. auris* colonization led to the depletion of commensal species and apparent enrichment of Proteobacteria, or whether the antibiotic (or some other factor) did. Thus, we still do not understand which potential mechanism (Figure 2A) explains the association between *C. auris* colonization and antibiotic administration in humans, highlighting a critical gap in our understanding.

A murine model of invasive candidiasis could provide insight into the modes of action of antibiotics against *C. auris*[109]. Using germ free, antibiotic treated, and control mice, the De Jesus group examined the role of the microbiome in moderating systemic infection following intravenous (IV) injection or gavage of a *C. auris* Clade I isolate. They reported a significant increase in uterine *C. auris* after IV administration of *C. auris* in immunocompetent mice following treatment with antibiotics compared to mice with an intact microbiome, with no other differences across other examined organ systems (i.e., heart, lungs, cecum, liver, spleen, kidney, stomach, and brain). Following gavage, immunocompetent mice experienced a significant increase in liver tissue bioburden following treatment with antibiotics, but no other organ systems carried higher burdens of *C. auris* in germ free or antibiotic exposure conditions, compared to controls. Differences between germ free immunocompetent mice and controls were not significant. Taken together, these data suggest that the antibiotic rather than the microbiota may have mediated the increased risk of uterine or liver infection following IV injection or gavage of *C. auris*. Neutropenic germ-free mice, in contrast, showed significantly higher risk of infection in the heart and lungs following IV injection of *C. auris*, while antibiotics appeared to increase infection of the cecum and stomach in neutropenic mice, suggesting that the microbiota may play a role in protecting against infection in the immunocompromised host. While *C. auris* appeared to be the dominant fungus, in that study, results from the 16S survey were not reported, so it was not possible to understand the specific bacteria involved in conferring colonization resistance, or their response to immunosuppression or to the antibiotic exposure. Additional work that aims to disambiguate the timing of *C. auris* colonization relative to the enrichment of Proteobacteria, the delivery of antibiotics, the specific antibiotic classes that mediate these effects, and immunological status will help elucidate these complex relationships.

While results for *C. auris* are inconclusive, recent work using *C. albicans* has begun to illuminate our understanding of the interaction between antibiotics, colonization resistance, and immunity. Huang and colleagues compared the gut microbiome of rats infected with *C. albicans* after antibiotic treatment, rats inoculated with fungi only, and rats without any treatment[110]. Strikingly, infection with fungi after antibiotic treatment is associated with a significant decrease in bacterial diversity as compared to infection with fungi alone. This suggests that treatment with the antibiotic, rather than infection with the fungus, results in reduced bacterial diversity, an important distinction considering *C. albicans*

produces the quorum sensing compound farnesol which could act directly against a wide range of bacteria[111]. Consistent with this finding, a small-scale survey of the human gut microbiome following a 6-day course of antibiotics (of varying classes) revealed a significant decrease in bacterial diversity accompanied by a significant increase in fungal diversity[32]. In particular, *Candida spp*. increased 15-fold from baseline to treatment for most antibiotics. Of special interest, over 1/3 of fungi present before treatment showed significant changes in relative abundance 90 days after treatment, suggesting a long-lasting imprint of antibiotics on the mycobiome. Persistent perturbation of the mycobiome is particularly consequential considering our recent work reporting that antibiotic treatment triggers not just a net decrease in bacterial diversity and an expansion of Enterobacteriaceae/*Candida* in the gut, but also immune dysregulation characterized by low local levels of Th17, IL-22, and GM-CSF producing lymphoid cells[72] (Figure 2A.4). The concerted changes in the composition of the microbiota and loss of IL-17A and GM-CSF, but not IL-22, enhanced Candida-associated mortality in mice, facilitated by the joint translocation of *C. albicans* with bacterial species (e.g., *Escherichia coli, Lactobacillus murinus*, and *Enterococcus gallinarum*) from the gut into the bloodstream. Additionally, Artis and colleagues proposed that the commensal microbiota primes the innate immune system for a robust interferon response to viral challenge. They demonstrated increased mortality and tissue pathology in the murine lung as a result of an aberrant transcriptional profile underlying dampened interferon signaling, preventing clearance of influenza following antibiotic treatment[112]. Gut colonization by *C. albicans* was sufficient to reverse this effect, promoting tonic stimulation, and conferring protection against mortality due to viral infection[113]. It is tempting to speculate that *C. auris*, which typically colonizes the skin rather than the GI tract, may also take advantage of loss of colonization resistance as well as dysregulated immunity following antibiotics. Finally, as reviewed elsewhere, it is possible that reciprocal interactions between fungi and bacteria play a pivotal role in determining the fate of fungal species following antibiotic mediated ablation of bacterial diversity[114].

Collateral damage from prior systemic infection: Anecdotal data suggest that infection with a bacterial MDRO or a prior bout of candidemia is a risk factor for future colonization with *C. auris*[80,105,115,116]. Given that bacteremia or candidemia often precedes infection with *C. auris* it may be possible that antibiotics serve as a red herring and that immune dysregulation related to sepsis may be the underlying risk factor. While initially controversial, it is now accepted that prior sepsis induces states of immunosuppression[117–119] after resolution of the cytokine storm, which may increase the permissiveness of the host for *C. auris* colonization or infection (Figure 2B). However, clinical studies reporting the incidence of infection with *C. auris* after antibiotic treatment have not reported immunological data. Additional work is thus needed to understand the extent to which immunosuppression related to sepsis underlies the association between *C. auris* and antibiotic use. Given that bloodstream infections involving *Candida* spp. and various MDROs is associated with increased mortality[120], future clinical studies reporting antibiotics as a risk factor should report immunological status of the host, so that this risk factor can be disentangled.

Antibiotics may directly modulate fungal fitness: In 1929, Alexander Fleming famously reported that fungi produce antibiotics that can kill bacteria by observing the effects of fungal contamination on bacterial plates. Before they were used as pharmaceuticals to kill bacteria infecting humans, antibiotics were simply compounds used by microbes to optimize their fitness in their native environments where they had to compete against both fungal and bacterial species for space and nutrients. Indeed, a rich history of literature from the 1940s-1950s suggests that antibiotics that kill bacteria have direct effects on fungi, which may be inhibitory or stimulatory[38]. For example, trimethoprim is commonly used to treat urinary tract infections and is active against both gram-positive and gram-negative bacteria[121]. Trimethoprim also has inhibitory activity against certain fungi including *Paracoccidioides brasiliensis* and *Pneumocystis jirovecii*[122]. Sulfa drugs similarly target folate synthesis and are broad spectrum antagonists of bacteria. When tested against 70 *Aspergillus* strains, encompassing 6 species, most sulfonamides exhibited fungistatic activity, except for pentamidine, which was fungicidal for *A. nidulans*[123]. Pentamidine is also active and fungicidal against *Fusarium* species, particularly *F. oxysporum*[124,125].

Intriguingly, penicillin was shown to stimulate, rather than inhibit, the growth of *C. albicans in vitro*, leading Foley & Winter to conclude that the antibiotic directly or indirectly (via the metabolites released by the lysis of antibiotic-sensitive *Candida* cells) stimulated the growth of survivors[126]. Other data conflict, reporting that penicillin does not stimulate growth of *C. albicans*[127]. These discrepant results are likely due to differences in growth media and the *Candida* species deployed in each study. More recently, work examining the impact of vancomycin, rifampin, and amoxicillin on the growth of *C. auris* also reported antibiotics as stimulating the growth of *Candida*[128]. Specifically, vancomycin resulted in a 28% increase in CFUs in *C. auris* biofilms cultivated *in vitro*, an effect not observed with either amoxicillin or rifampicin. Second, treatment of the *C. auris* biofilm with vancomycin increased the tolerance of the biofilm towards the antifungal caspofungin. Finally, using an insect model, larvae infected with *C. auris* in the presence of vancomycin resulted in a significant increase in mortality compared to *C. auris* alone. Taken together, these data suggest that antibiotics may modulate the fitness of *C. auris* directly via unknown mechanisms (Figure 2C). In a murine model, we did not see an increase in *C. auris* skin colonization following pre-treatment with tetracycline or a combination of ampicillin, metronidazole, neomycin, and vancomycin[88]. Therefore, additional work examining the effects of different classes of antibiotics on the fitness of *C. auris* is needed. It is also worth noting that certain antibiotics may suppress the host immune system[129], providing another mechanism by which antibiotics may modulate fungal fitness, predisposing the host to invasive infection. Finally, as reviewed elsewhere, it is possible that specific reciprocal interactions between fungi and bacteria will play a pivotal role in determining the fate of fungal species following antibiotic mediated ablation of bacterial diversity[114].

Perspectives and future directions

Given the urgent concern posed by *C. auris* infections, we are not accustomed to considering that *C. auris* behaves, at times, like a commensal. We have historically used dichotomous thinking to describe the organisms that live on our bodies -- either they are commensals, or they are pathogens. The damage response framework provides a useful lexicon[1] whereby

members of the microbiota adopt different behaviors, either the commensal or pathogenic lifestyle, and they can transition from one to the other depending on environmental cues, including shifts in disturbance regime, invasion of the microbiota by other organisms, or disturbance associated with chemicals, like antibiotics. Moreover, different members of a given population may exist in the commensal or pathogenic lifestyle at the same time, as evidenced by the simultaneous presence of yeast and hyphal forms of *C. albicans* in the gut. Fully incorporating recognition of behavioral phenotypes into our understanding of the microbiota permits us to define and target a set of switches that regulate the behavioral lifestyle of any given microbe.

A consensus has emerged that *C. auris* undergoes micro-diversification on its host on the timescale of months. As additional studies of *C. auris* outbreaks are undertaken, it is critically important investigators build on this consensus. Integrating spatial and longitudinal genomic data with clinical data will permit us to identify the ecological and evolutionary forces shaping the adaptation of *C. auris* to the human host and its hospital environment. In turn, we hope that this information may inspire therapeutic modalities to prevent colonization and infection with *C. auris* or to lock it out of the pathogenic state.

Furthermore, *C. albicans* remains a leading cause of nosocomial bloodstream infection with high mortality despite treatment. Leveraging this well-defined model system, future work must continue to innovate, developing experimental paradigms that elucidate fungal-derived and host immune factors that govern the balance between commensalism and pathogenesis. Such work should continue to build on our nascent understanding of how colonization at one site modulates immune responses at distal anatomical sites. At the same time, future work should begin to elucidate the role other members of the human microbiota play in promoting protective or pathogenic immune responses to *C. albicans* commensalism and pathogenesis.

More broadly, it is currently difficult to determine the extent to which each hypothesis proposed in Figure 2 increments the risk of invasive candidiasis following antibiotic treatment. This gap in our knowledge limits our power to intervene. Consequently, future studies should illuminate the mechanisms by which antibiotics act on fungi. Moreover, studies quantifying risk factors for invasive fungal infection should include host immunological profiles in their models to increase our understanding of the extent to which sepsis-induced immunosuppression, or loss of tonic immunity, increases the risk of invasive fungal disease post-antibiotic treatment. Moving forward, the challenge will be to develop translational strategies that integrate information from basic science, genomic, and clinical studies in order to flip the fungal switch in favor of patient outcomes.

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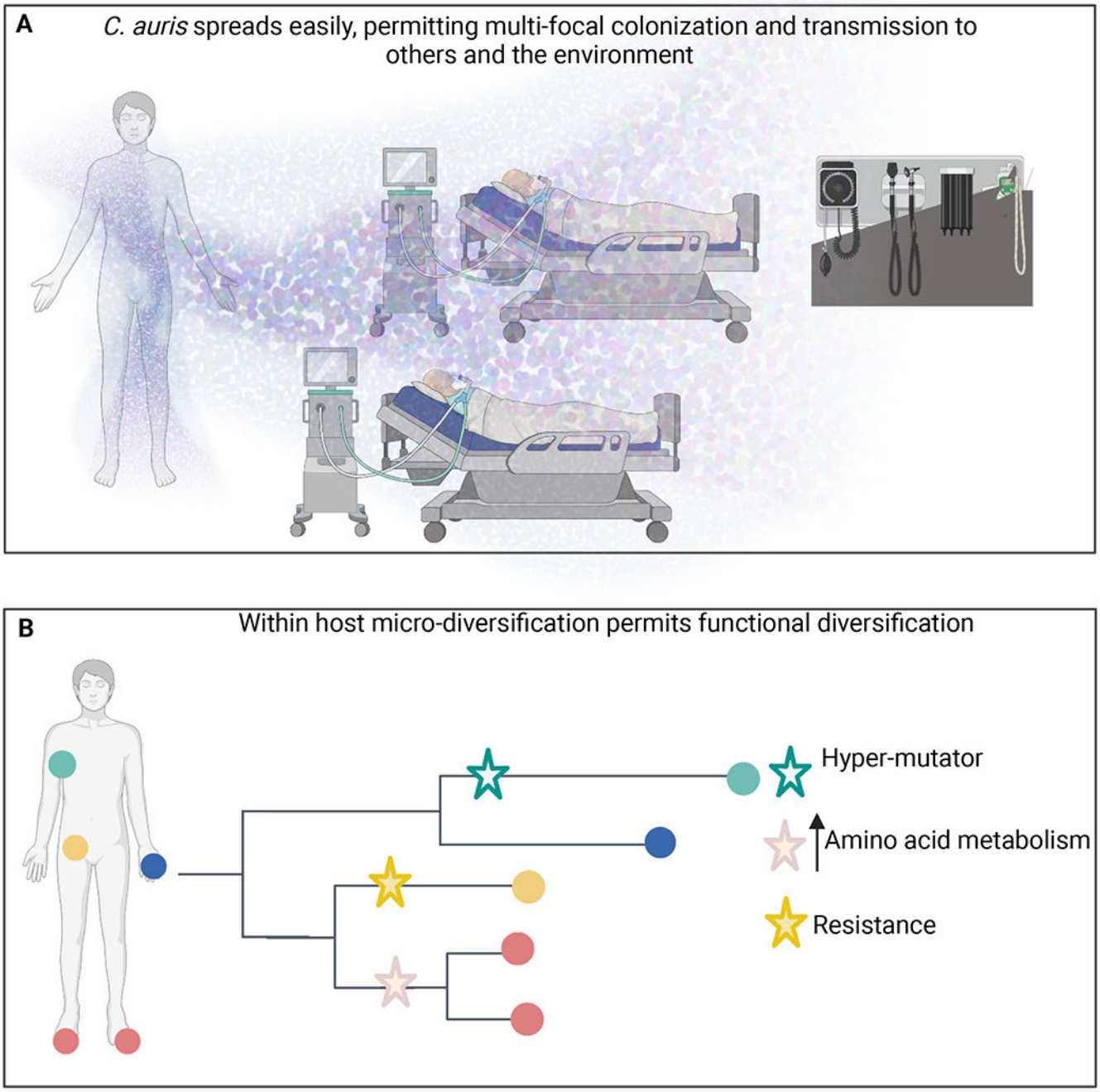

Figure 1: Implications of persistent skin colonization by *Candida auris*.

A) Skin shedding distributes a million microbes per hour into the environment, creating a reservoir for transmission. **B)** Persistent colonization of multiple body sites permits micro-diversification, which may prove to be adaptive. Created with BioRender.com.

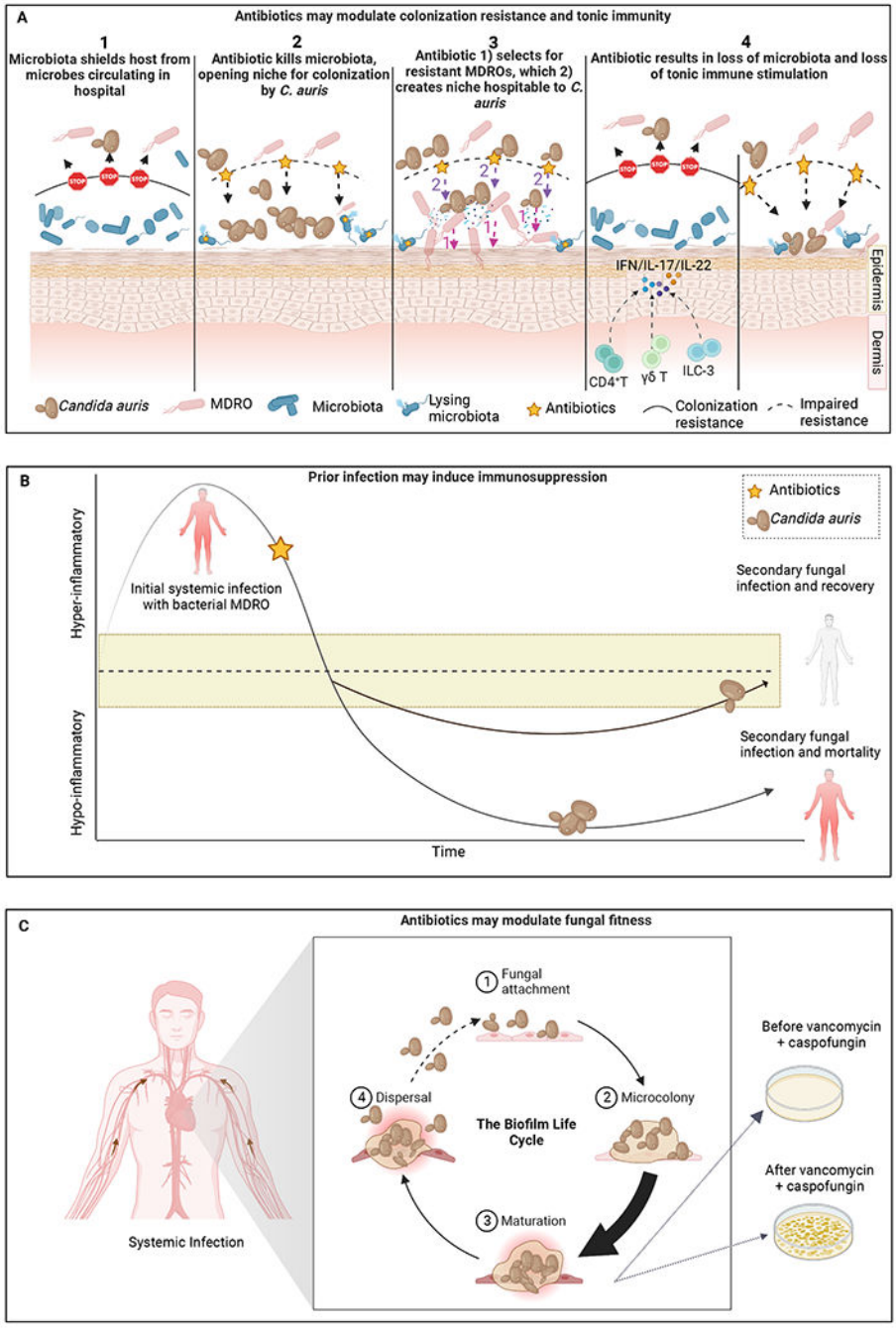

Figure 2: Alternative hypotheses explaining host susceptibility to infection and colonization with *C. auris*.

A) Antibiotics may open a niche for *C. auris* colonization by modulating the commensal microbiota via several potential mechanisms. **B)** Adapted from[117], an initial bout of bacterial sepsis may induce immunosuppression, paving the way for secondary infection and mortality, with antibiotic serving as a red herring. The yellow banding indicates a range of immune-competence. **C)** Vancomycin and other antibiotics may directly modulate the

fitness of *C. auris* by increasing biofilm formation and inducing a state of tolerance, or via other mechanisms. *Created with* BioRender.com.

Table 1:

Examples of genetically encoded microbial circuitry in bacteria (*A. veronii*) and fungi that determine organismal lifestyle in a wide variety of hosts ranging from invertebrates to plants and mammals.

Within the "Experimental model paradigm" column, "Infection model" represents microbe-centric studies that permit investigation of genes required for virulence, often measured by mortality, while "Commensal-pathogen switch" experimental paradigms permit examination of gene function governing transitions between commensal and pathogenic lifestyles.

Microbial population	Host Model	Experimental model paradigm	Body site	Microbial Switch	Outcomes	Citation
C. albicans	Mouse	Commensal-pathogen switch	Gut	Ume6/Sap6	Colonization vs. Pro-inflammatory clearance	11
C. albicans	In vitro / Mouse	Commensal-pathogen switch	Gut	Efg1/Wor1	Phenotypic switch to optimize metabolism and colonization vs. clearance	12
C. albicans	In vitro / Mouse	Commensal-pathogen switch	Gut	Efg1-Ec1-dependent factor Candidapepsin	Phenotypic switch to activate IL-1β dependent pro-inflammatory program	13
C. albicans	In vitro / Mouse	Commensal-pathogen switch	Gut	Sef1/Sfu1	Activates or represses iron uptake genes involved in virulence or colonization	14
Botrytis cinerea	*Arabidopsis thaliana*	Commensal-pathogen switch	Leaves	BcSpd1	Suppression of plant defense and activation of virulence genes or clearance	15
Aeromonas veronii	Zebrafish	Commensal-pathogen switch	Gut	AimA	Colonization vs. clearance by activation of neutrophils	16
Parastagonospora nodorum	Wheat	Infection	Seedlings	PnPf2	Activates transcriptional program that results in expression of 12 effector genes involved in necrosis	17
Blastomyces dermatitidis B. gilchristii	In vitro / Mouse	Infection	Lung	BAD1	Inhibits TGF-α production permitting adherence and pathogenic switch. Null mutants are avirulent	18
Aspergillus fumigatus	Mouse	Infection	Lung	CpCA	Activates stress response program required for virulence	19
C. auris	Mouse	Infection	Bloodstream	IncRNA, *DINOR*	Tunes stress response program, modulating genome integrity, cell filamentation, and virulence	20
C. auris	*Caenorhabditis elegans*	*Infection*	*C. elegans*	Hog1	Activates a stress response program that's required for virulence	21