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A Stable Cutaneous Mycobiome Exists from Birth

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The skin is our outermost layer of defense against a constant barrage of environmental microbes and antigens. While the majority of microbes encountered are normally harmless, a distinct minority are potential pathogens. Throughout the life span, newly colonizing microbial species will encounter a rich interkingdom community of microbes already living at the skin that provides the host with competitive exclusion of potential pathogens. In return, the host may provide selective pressure on certain microorganisms through the release of sebum, sweat, and small antimicrobial compounds secreted by subcutaneous glands(1,2). Historically, our knowledge of these communities was based on culture-dependent techniques, but recent advances in culture independent methodologies, in particular next generation sequencing, are now elucidating diverse communities of bacteria, fungi and viruses. As with other sites in the body, the majority of cutaneous microbes are bacteria. In contrast, some sites also have a relatively high membership of resident fungi, collectively termed the mycobiome. On the skin in particular, disordered fungal colonization has been linked to various disorders such as dermatophytosis, atopic dermatitis and seborrheic dermatitis. However, in contrast to what is known about the bacterial microbiome, our understanding of the mycobiome remains extremely limited. Cutaneous fungi play important roles in host health, including colonization-resistance against pathogens

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Ethics Declaration

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Patient Consent Statement

Not Required.

and, perhaps more importantly, facilitating immune development and maintenance of the host(1,2).

Culture-based assays have routinely identified *Malassezia* as the dominant taxa of cutaneous fungal communities. Together the members of this genus comprise half of the 14 routinely isolated fungal species(3), with *Candida* often the next most abundant genera found on skin(1). Molecular fungal ecology studies have propelled us to a better understanding of the composition of the mature cutaneous mycobiome and shown that the composition of fungal communities can vary extensively based on biogeography. So, while the dominance of the mycobiome by *Malassezia* was confirmed at most body sites utilizing microbial sequencing for 18S or ITS rDNA, this is less accurate for sites such as the scalp or foot(3).

Changes in microbial community composition occur across the life span. In general, the relative abundance of *Malassezia* has been previously reported as low in children, but increases with age until adulthood(4). At puberty, the dominant species within the genus *Malassezia* shifts from *M. globosa* to more host lipid-dependent members of *Malassezia*(4), as sebum production changes during adolescence. Instead, in early life, a previous study has shown that the cutaneous mycobiome is dominated by the genus *Candida*(5). Simultaneous sampling of the infant skin, oral and anal mycobiomes as well as the vaginal and rectal mycobiomes of their mothers has suggested that the mycobiome during the first month of life is relatively stable, without significant shifts in diversity or community composition. Also, the mycobiome of these infants did not appear to be strongly determined directly by maternal anogenital mycobiome composition(5).

The neonatal skin undergoes a dramatic transition as it emerges from the aqueous environment of the womb into the outside world. In vaginally delivered infants, this may also be accompanied with an inoculum from the mother’s urogenital tract. Regardless of the route of delivery, the skin is exposed to environmental microbes after birth with the skin of the mother likely representing a particularly important source. The skin itself also undergoes significant changes, further compounded in preterm infants, during the first several months of life. This represents a unique developmental window with the potential for significant changes in the cutaneous microbiome from both intrinsic and environmental inputs(6).

In infants, the intestinal microbiome has been linked to multiple important conditions that develop later in life such as obesity, asthma, atopic dermatitis and inflammatory bowel disease(2), as well as critical diseases of prematurity such as necrotizing enterocolitis(2) and bronchopulmonary dysplasia(7). The rapid evolution of the neonatal microbiome suggests an important developmental window with the potential for pathologic disruption.

The mycobiome at birth(8) and in young infants(5) has received only limited focus. In a recent edition of Pediatric Research, Paul and colleagues(10) utilized an exploratory prospective cohort from which they have previously characterized the bacterial cutaneous microbiome(9) to perform a first-of-its-kind analysis of the development of the cutaneous mycobiome in preterm and term newborns.

Paul *et al.*(10) collected longitudinal samples from the forehead, axial and gluteal skin for a cohort of 15 preterm and 15 term newborns at birth and over the first five weeks of life.

They then used MiSeq of the pan-fungal ITS-2 region to characterize the cutaneous fungal communities of these sites. The mycobiome was composed of a limited number of taxa in both preterm and term infants with *Malassezia, Candida, Cladosporium, Fusarium* and *Cryptococcus* the most common genera in order of relative abundance. This is in distinct contrast with Ward *et al.*(5), who noted over the first month of life that infantile oral, anal and skin fungal communities were composed of only about 2% *Malassezia* and were instead dominated by *Candida*. In the current study, the relative abundance of *Malassezia* was primarily driven by *M. restricta*, which was the most abundant species. Interestingly, this is also the most prevalent fungal species on adult skin(1). This discrepancy is difficult to resolve without further data, but it could result because the majority of infants in this study were in the neonatal intensive care unit (NICU) environment where they are more isolated from close contact with their mothers non-cutaneous mycobiomes and were more directly exposed to the hands of multiple caregivers than the term born infants studied by Ward *et al.* (5). While both studies utilized amplification of the ITS2 region, without the findings of this study being replicated in a larger multi-center study, it is difficult to more than speculate about the abundance of *Malassezia* in these infants. However, it should also be noted that systematic differences in the DNA isolation, amplification and biostatistical pipelines could also impact the relative abundances observed.

Paul *et al.* also noted increased abundance of *Candida* in vaginal delivered infants, which is in line with previous work(5). However, they also noted previously undetected differences in beta diversity between vaginal and operative deliveries, which could be related to small sample size, hospitalization or differences in biostatistical analysis. This study also noted differences in the skin mycobiome related to different diet exposures; which deserves further investigation in a diet controlled study.

One particularly valuable aspect of this study by Paul *et al.* was that the authors collected longitudinal samples from this cohort. This allowed them to note that while the bacterial cutaneous microbiome rapidly assembles during the newborn period(9), the fungal communities remain relatively static. This finding is consistent with Ward *et al.*(5), who showed limited development of mycobiome over time in young infants. Intriguingly, there were no significant differences between fungal community development between preterm and term-born infants. This finding contrasts with a recent study that used a combination of MiSeq, culture-based assays and machine learning models to demonstrate that fungal biomass gradually develops with length of gestation(8). A relatively uniform cutaneous mycobiome could suggest that the origin of the cutaneous microbiome is primarily from the general environment.

The uniformity of the cutaneous microbiome raises the possibility that the host strongly shapes fungal community composition. To test this hypothesis, Paul *et al.*(10) used blood samples from these infants to test if host single nucleotide polymorphisms (SNPs), previously associated with increased risk of fungal infections, were associated with different compositions of the neonatal mycobiome. They found SNPs in the pattern recognition receptors TLR4 and NOD-1 as well as the danger-sensing NLRP3 inflammasome were associated with differences in fungal colonization (Fig. 1). This was a particularly elegant demonstration that showed the ability of the host to select its colonizing microorganisms,

even at our outermost surface, which broadened the impact of this study and deserves further exploration in larger cohorts. Further work to clone these alleles into relevant isogenic cell lines may help elucidate their role in anti-fungal immunity.

As the composition of the cutaneous mycobiome comes into focus through studies like Paul *et al.* (10), the next step requires determining functional outcomes of colonization with respect to diseases of the skin and systemic infection. The current study has identified several potential determinants of the cutaneous mycobiome that provide intriguing avenues for further investigation in larger more diverse cohorts. Neonatal sepsis is often associated with organisms that colonize the skin of neonates and the mycobiome is also likely important to immune development during early life(1). This study underscores the exciting potential of the mycobiome to influence human development in newborns.

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Impact Statement

What does this article add to the existing literature?

This article discusses the recent work by Paul *et al.* in *Pediatric Research* that explored the development of the cutaneous mycobiome and discusses their novel findings in light of the limited previous research in this underexplored area.

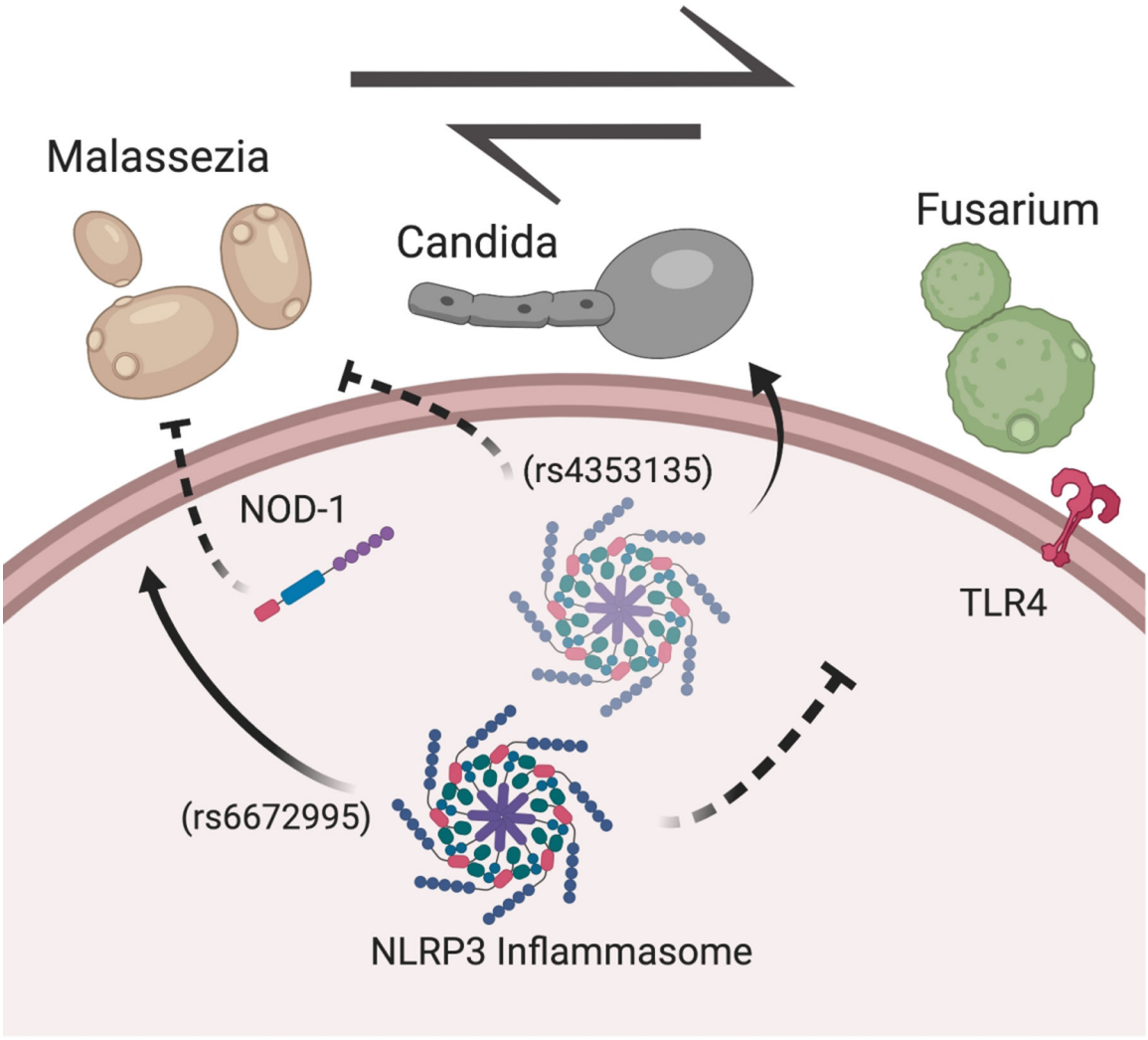

Fig. 1. Host single nucleotide polymorphisms are associated with compositional changes in the cutaneous mycobiome in human newborns.

Paul *et al.* identified 10 single nucleotide polymorphisms (SNPs) in innate immune genes that correlated with altered neonatal mycobiome composition. For example, NLRP3 (*rs6672995*) was associated with a decrease in the abundance of *Fusarium*, but an increase in *Malassezia*, while NLRP3 (*rs4353135*) was associated with increased abundance of *Candida* but decreased abundance of *Malassezia*. Figure generated with the aid of BioRender.