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Skin-deep strategies of intraspecific competition

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Staphylococcus epidermidis isolates from the facial skin of human hosts show abundant and diverse mechanisms of antagonism. Intraspecies antagonism is reduced between isolates co-existing in the same host, revealing ecological principles shaping skin microbial ecology.

Humans host many microbial communities on and inside their bodies that play important roles in health and disease[1]. As our understanding of microbiomes and disease has increased, there has been a corresponding increase in the need to effectively manipulate human microbiome communities to benefit human health. One important function of our microbiomes is colonization resistance: the ability of an existing microbial community to prevent invasion by pathogenic species. However, the same principles and mechanisms that underpin colonization resistance against pathogens may also prevent engraftment with probiotic species. Understanding the interactions between existing and invading species of a microbial community is key in the quest to rationally manipulate microbiome communities for our medical benefit. What has received far less attention is how an existing microbial community interacts with invading strains of species that are already present in the community. In this issue of *Nature Microbiology*, Mancuso and colleagues[2] use the common skin surface commensal species, *Staphylococcus epidermidis*, isolated from the human facial skin surface, to reveal the importance of bacterial antagonism in intraspecific interactions. This work provides critical insights into the principles of intraspecific competition in microbial communities, and how these interactions play a key — and thus far underappreciated — role in human microbiomes.

The facial skin surface microbiome provides a useful model system to investigate intraspecific interactions, as it often harbours one or more strains of a single species, *S. epidermidis*, alongside occasional other staphylococci such as *Staphylococcus aureus*. As toxins are known to mediate competition between staphylococci isolated from other host environments[3], the authors developed a new imaging-based quantitative analysis method for classic spot-on-lawn in vitro agar plate assays to identify signals of antagonism between 122 staphylococcal isolates from the facial skin surface of 18 people from 6 different families. Assessing 21,025 pairwise combinations, the authors found that a large proportion of *S. epidermidis* lineages could inhibit other lineages, identifying four 'superantagonist' lineages that were able to inhibit more than half of the tested strains and were distributed widely across different families. There were at least 34 different patterns of antagonism, with the authors uncovering antimicrobial peptides, iron chelation and bioactive molecules from uncharacterized biosynthetic gene clusters as possible mechanisms.

Intriguingly, despite extensive antagonism, the authors found no significant difference between inter- and intraspecific interactions. This is somewhat surprising, as the selective advantage for antagonism is expected to be greatest between competitors with a high degree of niche overlap[4], such as members of the same species. Thus, similar levels of intra- and interspecific antagonism indicate that not just *S. epidermidis* strains, but also other staphylococcal species, may have highly overlapping niches that lead to a positive selective advantage for *S. epidermidis* that engage in warfare against other staphylococci.

The authors then shifted their focus to intraspecific antagonism on individual hosts. Further in vitro competition assays, plus multiple statistical analyses, revealed that intraspecific warfare between strains isolated from the same host was extremely low, finding that isolates from the same individual were less likely to antagonize each other than random ones. Again, given considerable potential niche overlap between strains from the same host, this result might also be initially surprising. However, the facial skin surface is thought to have little spatial structure[5], and low spatial structure increases strain mixing and interactions, which is important for selection on toxin-producing strains[6–8]. Indeed, a lack of warfare in communities characterized by coexistence is expected[9], regardless of whether the interactions are intra- or interspecific. The authors also found that individuals carrying antagonistic lineages had distinct skin microbial profiles compared with their family members who carried sensitive strains. This implied that antagonism prevents colonization by competing sensitive strains, suggesting that antimicrobial production may confer a competitive advantage. Interestingly, the lack of global dominance by a single antagonist highlighted that other factors such as ecological trade-offs or evolution of resistance could be at play.

Looking for such trade-offs, the authors found that 97% of interactions demonstrated no evidence of intra-lineage variation in toxin sensitivity, implying that individual strains very rarely evolve to become sensitive to a toxin that they were previously resistant to or produced. There were, however, two outlier cases where toxin-sensitive strains appeared to evolve from toxin-resistant ancestors on an individual host. Curiously, both strains had slower in vitro growth rates than their toxin-resistant ancestors, despite there being no toxins in the growth media. This contradicts the expected 'rock–paper–scissors' dynamics between toxin-producing, toxin-resistant and toxin-sensitive strains[6], whereby toxin-producing strains outcompete toxin-sensitive strains in a manner mediated by lethal toxins, toxin-resistant strains outcompete toxin-producers owing to a growth-rate advantage and toxin-sensitive strains outcompete toxin-resistant strains, again based on a growth-rate advantage. This suggested that the evolved toxin-sensitive phenotype may confer some other selective advantage rather than increased growth rate. Further investigation revealed that both strains had mutations in *vraF* and *vraG* genes that are known to increase sensitivity to cationic peptides via the modification of the cell wall[10]. Interestingly, another lineage on a different host also had a similar pattern of sensitivity and mutations in the same pathway.

Therefore, one possible explanation for this counterintuitive simultaneous slow growth and antimicrobial sensitivity could be that these cell wall modifications might increase resistance to bacteriophage infection. Although the authors verified that one of the strains with evolved sensitivity to toxins did, indeed, have increased resistance to phage infection, more work will be required to establish this connection.

This work provides a major advance in our understanding of intraspecific interactions and microbial competition in the context of microbial community ecology. Certain outcomes of this study rely on the assumption that species identification is a useful proxy for niche overlap and resource competition. Future work investigating levels of resource competition between different staphylococcal strains and species would help contextualize our understanding of how investment in warfare is directed at different types of ecological competitors. Indeed, the results presented by Mancuso and colleagues indicate that patterns of antagonism are difficult to predict through basic phylogenetic clustering and instead are likely to require a deeper investigation into strain- and species-level metabolic capability and potential niche opportunities. This work opens the door for future experimental studies that implement intraspecific interactions into microbiome composition and the corresponding impacts on human health.

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Competing interests

The authors declare no competing interests.