Killer fat
Adipocytes in the skin release an antimicrobial factor to fight staphylococcus infection

By John F. Alcorn1 and Jay K. Kolls

The skin, the largest organ in the human body, plays a critical role as a barrier to pathogen entry into tissues. Its disruption can lead to invasive bacterial disease. When this does happen, many resident cells in the skin’s dermal layers, including immune cells, limit bacterial colonization. The role of fat cells (adipocytes) in the skin’s host defense function is only recently emerging. On page 67 in this issue, Zhang et al. (1) add to this view by showing that dermal adipocytes participate directly in innate immunity against Staphylococcus aureus (see the figure).

The skin is composed of an outermost stratified epidermis and an underlying dermis that is inlaid with vascular tissue, fibroblasts, phagocytes, lymphocytes, and adipose tissue. Epidermal keratinocytes produce antimicrobial peptides that kill invading pathogens and, in concert with dermal phagocytes, promote pathogen clearance (2).

S. aureus is a commonly found commensal bacterium on human skin. Infection with methicillin-resistant S. aureus (MRSA) is responsible for more deaths in the United States than any other infectious pathogen (3). Susceptibility to S. aureus infection in the skin (and lung) (2, 4) has been associated with decreased production of cytokines in these organs that regulate the production of antimicrobial peptides by epithelial and immune cells (5, 6). S. aureus also triggers the production of interleukin-6 by adipocytes, a cytokine that stimulates the production of the bacteriostatic, iron-binding protein hepcidin (7). This suggests a role for these cells in host defense against this pathogen (8, 9).

A breach in the epidermis can cause the underlying dermis to become infected with S. aureus, resulting in dangerous inflammation (cellulitis and fasciitis). To model this, Zhang et al. used subcutaneous injection of MRSA in mice to introduce infection directly into the underlying dermis. MRSA infection results in the recruitment of myeloid, lymphoid, and mast cells, all of which have been implicated in the bacterial clearance and successful host defense. However, the dermis is also characterized by connective tissue containing fibroblasts and adipocytes. The authors noted that MRSA infection caused a marked increase in dermal adipose tissue in part due to hyper trophy and proliferation of the adipocytes. Adipogenesis was partly due to expression of the transcription factor zinc finger protein 423 (ZFP423), whose expression controlled another transcription factor called peroxisome proliferator-activated receptor gamma (PPAR-γ). Using mice with a mutation in ZFP423, or treating normal mice with a PPAR-γ inhibitor, Zhang et al. reveal the requirement for these transcription factors in the expansion of dermal adipose in response to MRSA infection. Blocking adipogenesis in mouse skin also impaired host defenses against MRSA infection.

Cathelicidin is an antimicrobial peptide with anti-staphylococcal activity. By showing that a murine adipocyte cell line and primary human adipocytes produce this peptide in response to S. aureus conditioned media or inactivated bacteria, Zhang et al. suggest that fat cells can directly sense the pathogen. As well, conditioned media from wild-type murine adipocytes, but not adipocytes from cathelicidin-deficient mice, controlled S. aureus growth in mice. Animals with deficient adipogenesis (mice lacking ZFP423 or mice treated with the PPAR-γ inhibitor) had impaired cathelicidin production upon S. aureus infection and were as susceptible to infection as cathelicidin-deficient mice. Moreover, PPAR-γ inhibition in cathelicidin-deficient mice did not exacerbate infection, suggesting that the major anti-staphylococcal protein controlled by adipogenesis is cathelicidin.

In addition to its well-known role in growth and metabolism, adipocytes play key roles in controlling soft tissue infection. From an evolutionary perspective, this makes sense, as this function would provide the host with an additional layer of defense against an abraded or trau-

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**Responding to the breach.** Disruption of the epidermis can introduce pathogens into the dermis. This provokes the proliferation of adipocytes (involving transcription factors ZFP423 and PPAR-γ). Adipocytes secrete cathelicidin, whose anti-staphylococcal activity can control skin infections.
matic wound to the epidermis. However, there is likely a healthy amount of dermal fat and an unhealthy amount. Zhang *et al.* address this in part by studying a high-fat diet. Interestingly, induction of adipogenesis in mice through a high-fat diet also increased the production of cathelicidin by the proliferating adipocytes. However, mice harboring disabling mutations in the receptor for leptin—a hormone produced by fat cells that suppresses food intake—gain weight and develop type 2 diabetes, but are more susceptible to *S. aureus* infection (10). Likewise, in humans, obesity has been associated with an increased risk of skin and soft tissue infection (11). One possible explanation for this discrepancy is that insulin resistance or other aspects of metabolic syndrome perturb the infection-adipogenesis-cathelicidin pathway identified by Zhang *et al.* Thus, signaling by adipose-derived hormones that control energy expenditure (adipokines) could influence the expression of cathelicidin. This antimicrobial peptide also is posttranslationally cleaved to its active form, a process that may also be influenced by obesity and metabolic syndrome.

The mechanism underlying the recognition of *S. aureus* by adipocytes remains unclear, although it likely involves toll-like receptor 2 (TLR2). Adipocytes express many members of the toll-like receptor family, including TLR2 (9, 12), which recognizes lipopeptides produced by bacteria. This may be an operative pathway that controls cathelicidin production. Moreover, a TLR2-ZFP423-PPAR-γ-cathelicidin pathway might be augmented pharmacologically by PPAR-γ agonists, thereby increasing host resistance to infection in susceptible individuals such as those with diabetes and metabolic syndrome. ❯

**EVOLUTIONARY GENOMICS**

**Conundrum of jumbled mosquito genomes**

Multiple *Anopheles* mosquito genome sequences reveal extreme levels of mixing

*By Andrew G. Clark* and *Philipp W. Messer*

Malaria is caused by injection of *Plasmodium* parasites into the human bloodstream via the bites of infected mosquitoes. This simple description overlooks a fantastic biological complexity: Some 60 anopheline mosquito species can serve as vectors for five distinct species of *Plasmodium* that produce varying levels of illness in many animal species. Comparative genomic studies may shed light on the mechanisms whereby *Anopheles gambiense* specifically target humans, why the mosquitoes can tolerate *P. falciparum* infection, and how the parasite has adapted to this lifestyle. In this issue, Neafsey *et al.* ([1], page 43) and Fontaine *et al.* ([2], page 42) analyze the genome sequences of 16 species of anopheline mosquitoes and reveal a complex pattern of evolution that defies the classic concept of a phylogenetic tree.

Sequencing of multiple related species has revealed many attributes of the evolutionary pressures faced by those species (3–6). For example, multiple genome alignments can show which genes are most conserved and which evolve the fastest. In general, *Anopheles* genomes appear to evolve faster than do *Drosophila* genomes, perhaps because the former depend on hosts that may provide opportunities for coevolutionary arms races. This is especially evident in the families of closely related genes that formed from the duplication of a single original gene. Fontaine *et al.* show that the 16 *Anopheles* species gain and lose such gene family members at five times the rate of the 12 sequenced *Drosophila* species.

*Anopheles* genomics also sheds light on the genes involved in the specialization of *An. gambiae* on human hosts. Olfactory and gustatory receptors help the mosquitoes to identify and be attracted to hosts. Although these gene families are generally highly conserved across *Anopheles* genomes, *An. gambiae* shows a remarkable gain of 12 olfactory receptors, suggesting a possible role for these genes in guiding human host preference [as seen in *Aedes* mosquitoes (7)]. Many of the olfactory and gustatory receptors also display accelerated protein evolution, consistent with response to positive natural selection. Future studies should test the adaptive benefit of specific odorant chemicals and the specific associations between odorant chemicals and odorant receptors.

The genome sequences generated by Neafsey *et al.* provide the opportunity to investigate whether the observed evolutionary patterns in sequence divergences between the 16 mosquito species are consistent with a single phylogenetic tree. That the *Anopheles* phylogeny might be complex has been suspected since the first *An. gambiae* genome was sequenced (8) from a lab strain that included two distinct subtypes [today recognized as two separate species, *An. gambiae* and *An. coluzzii* (9)]. The observations that these two species readily hybridize and also have largely overlapping ranges suggest that there might be gene flow between them. Despite this, the *Anopheles* phylogeny has generally been described by a species tree, constructed from the informa-
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