CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Adipocytes Armed against *Staphylococcus aureus*

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Staphylococcus aureus is a harmless commensal microorganism in the skin and mucosa. However, *S. aureus* is also a deadly pathogen responsible for the vast majority of skin infections. Moreover, it causes pneumonia, sepsis, organ abscesses, endocarditis, and osteomyelitis. In Alexander Fleming's laboratory, in 1928, the golden-colored colonies of this gram-positive bacterium grew throughout a petri dish, except on an edge contaminated by the mold *Penicillium notatum*. This led to Fleming's discovery of penicillin, the golden age of antibiotic agents, and then the dreaded consequence of antibiotic resistance.

Antibiotic-resistant strains such as methicillin-resistant *S. aureus* (MRSA) have been endemic in hospitals worldwide since the 1960s. However, the epidemic of community-acquired MRSA infection in the past two decades has resulted in the emergence of virulent and multidrug-resistant strains that cause severe skin infections in healthy persons outside hospitals.[1] Community-acquired MRSA infection contributes increasingly to the annual 14 million outpatient and emergency department visits and nearly 500,000 hospital admissions due to *S. aureus* skin infections in the United States. In an era of declining antibiotic development, rising drug resistance, and lack of an effective vaccine, understanding the immune responses that protect against *S. aureus* skin infections may be helpful in developing future immunotherapies and vaccination strategies.

The skin provides a physical and immunologic barrier, composed of the epidermis (with an outer layer of cornified keratinocytes), followed by the dermis and subcutaneous fat, as well as hair follicles, sebaceous glands, and sweat glands (Fig. 1). *S. aureus* causes different skin infections depending on the anatomical structures it infects. Impetigo is a superficial *S. aureus* infection of the epidermis, which is commonly seen in children with atopic dermatitis. *S. aureus* can cause invasive skin infections such as cellulitis and wound infections, in which the infection involves dermal and subcutaneous tissues. *S. aureus* can also infect hair follicles, causing folliculitis, furuncles, and carbuncles, which can result in subcutaneous abscesses (i.e., boils) often seen with community-acquired MRSA infection.

The skin has several lines of defense. The skin surface and epidermal keratinocytes possess antimicrobial peptides with activity against *S. aureus* (including cathelicidin, β-defensins, and RNase 7).[3] If the epidermis is breached, keratinocytes and resident immune cells in the dermis (macrophages, lymphocytes, mast cells, dendritic cells, and natural killer cells) along with stromal cells, such as fibroblasts, promote the recruitment of neutrophils and the subsequent formation of an abscess, which helps to control the infection. This pyogenic immune response is a hallmark of *S. aureus* infection and is seen clinically as purulent lesions surrounded by erythema, warmth, and induration. However, deep *S. aureus* skin infections that involve the subcutaneous fat, such as abscesses and cellulitis (which can be life-threatening), are not cleared efficiently by the immune system alone, and incision and drainage and antibiotics are necessary.[4,5]

Recently, Zhang et al.[2] found that a subcutaneous community-acquired MRSA infection in mice resulted in expansion of the subcutaneous fat (adipose) tissue, which was due to increases in both the size and the number of fat cells (adipocytes). In particular, they found that robust adipogenesis (caused by the proliferation and then differentiation of preadipocyte stem cells) was mediated by two adipogenesis-inducing transcription factors, zinc finger protein 423 and peroxisome proliferator–activated receptor γ (PPARγ) — proteins that modulate the expression of a variety of genes. In the context of impaired

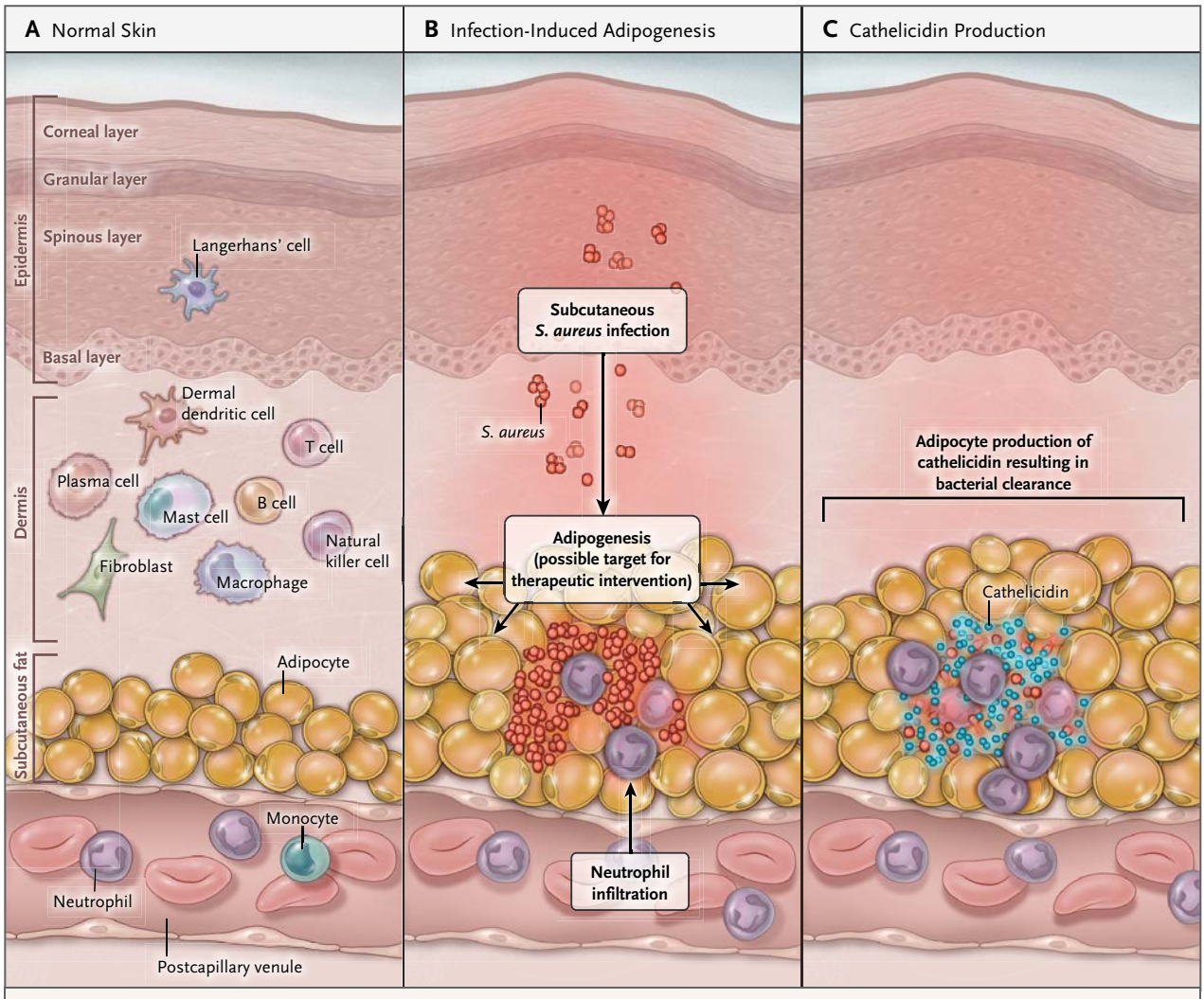

Figure 1. Adipocytes and Skin Infection with *Staphylococcus aureus*.

The skin is an important physical and immunologic barrier that protects the body from environmental insults, including pathogenic bacteria such as *S. aureus*. The skin is composed of the epidermis, dermis, and subcutaneous fat layers, and the immune cells that normally reside in the skin are shown (Panel A). Using a mouse model of infection, Zhang et al.[2] found that fat cells (adipocytes) markedly increase in size and number during subcutaneous infection with *S. aureus* (Panel B). They then found that adipocytes produce cathelicidin, an antimicrobial peptide that has activity against *S. aureus* (Panel C). Adipocytes play a previously unrecognized role in host defense, and drugs that induce adipogenesis (e.g., peroxisome proliferator–activated receptor γ [PPARγ] agonists) might represent a new therapeutic strategy to help combat *S. aureus* skin infection.

adipogenesis, which the authors brought about by inhibiting these transcription factors, the skin infection was more severe than that observed in the context of unimpaired adipogenesis, and the bacteria spread to the bloodstream, which suggests that adipocytes promote host defense. Unexpectedly, though, the adipocyte impairment did not affect neutrophil recruitment. Rather, cultured preadipocytes or mouse and human subcutaneous adipose tissue produced high levels of cathelicidin, and mice deficient in cathelicidin (*Camp*-deficient mice) had increased bacterial burden (as seen in the context of impaired adipogenesis). Finally, blocking adipogenesis in *Camp*-deficient mice did not further exacerbate the infection, showing that cathelicidin is the key molecule by which adipocytes mediated host defense.

The finding that cathelicidin produced by adipocytes is critical to host defense in mice

raises the possibility that an experimental approach to combat invasive *S. aureus* skin infections in humans — involving abscesses, cellulitis, and wound infections — could involve a pharmacologic boost to the relevant transcription factors in subcutaneous fat. The thiazolidinediones (e.g., rosiglitazone and pioglitazone) are agonists of PPARγ that have been approved by the Food and Drug Administration for use in the treatment of type 2 diabetes, to increase tissue sensitivity to insulin. Because Zhang et al. found that PPARγ inhibitors exacerbated infection by *S. aureus*, perhaps the induction of PPARγ activity with these agonists (or potentially other agents that induce adipogenesis) might do the opposite and provide a therapeutic benefit.

This study by Zhang et al. raises new questions. How do adipocytes recognize *S. aureus*, and which mechanisms, specifically, induce their production of cathelicidin? Does this occur directly by means of pattern-recognition receptors (e.g., toll-like receptors) or indirectly by means of inflammatory signals from other cells? The cathelicidin peptide produced by adipocytes is larger than the active cathelicidin peptide produced by other cells. Do adipocytes process the precursor protein for cathelicidin differently from other cells, and does the larger isoform have distinct functions? Finally, vitamin D has been shown to induce cathelicidin and promote host defense.[3] Is vitamin D important for inducing cathelicidin in adipocytes? Future research will provide answers to these questions, but it is clear that adipocytes have arrived — armed and ready — to join the fight against *S. aureus* and community-acquired MRSA skin infections.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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