Staphylococcus aureus: A Blemish on Skin Immunity

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Staphylococcus aureus is the leading cause of human skin infections. In this issue of *Cell Host & Microbe*, new research probes how a change in surface hydrophobicity mediated by a single *S. aureus* protein renders the pathogen resistant to key molecular effectors of skin innate immunity, including cationic antimicrobial peptides and fatty acid constituents of sebum. Novel treatment strategies for *S. aureus* infection may lie in supplementing the very same innate defense molecules to therapeutic levels.

In a complex environment, higher organisms, including humans, exist in perpetual contact with diverse microbial species. Our outermost layer, the skin, mediates a large proportion of these encounters. The common outcome is transient and innocuous; impervious to water, the keratinized skin epithelium physically restricts access of microbes to deeper tissues. The barrier function of the skin is further enhanced by soluble antimicrobial defense molecules synthesized at low levels under resting conditions (e.g., in sweat) and greatly induced following any break in epithelial integrity. These include the antimicrobial peptides cathelicidin, β-defensin, lysozyme, and dermcidin, together active against a broad array of bacterial and fungal species and certain enveloped viruses. Rarely, the interaction between microbe and our skin produces an untoward outcome—infection. When this occurs, the culprit more often than not is *Staphylococcus aureus*. The formidable capacity of this singular pathogen to resist the multifaceted innate immune defenses of human skin fascinates microbiologists as much as it vexes physicians. A new facet of this dynamic is explored by Clarke et al. in this issue of *Cell Host & Microbe* (Clarke et al., 2007).

The iron-responsive surface determinant A (IsdA) protein is anchored via its C terminus to the peptidoglycan of the *S. aureus* cell wall by the action of sortase enzymes (Mazmanian et al., 2002). Coordinately induced with other bacterial factors in response to iron restriction, IsdA contains a so-called NEAT (*near* iron *t*ransporter) domain forming a clathrin adaptor-like β sandwich fold and hydrophobic pocket that binds heme in a 1:1 ratio (Grigg et al., 2007). While a likely role in *S. aureus* iron acquisition is only partially understood, additional intriguing features of the IsdA protein have been revealed through a series of careful targeted mutagenesis and heterologous expression studies. Simon Clarke, Simon Foster, and colleagues have shown that the IsdA NEAT domain also mediates physiologically relevant binding of *S. aureus* to the extracellular matrix components fibronectin and fibrinogen (Clarke et al., 2004), contributing to the ability of the pathogen to colonize the nasal mucosa in the cotton rat model (Clarke et al., 2006). Now, the research group has identified a fascinating contribution of IsdA expression to the biophysical properties of the *S. aureus* cell surface (Clarke et al., 2007). By reducing the overall hydrophobicity of the bacterium, IsdA blocks the action of several antibacterial molecules present in normal skin, including cathelicidin and β-defensin peptides, human sebum, and its constituent hydrophobic fatty acids. Consequently, IsdA promotes *S. aureus* survival on human skin. Analysis of deletion constructs revealed that the IsdA domain mediating decreased hydrophobicity and resistance to innate immune defense molecules is distinct from the NEAT domain and situated toward the protein's C terminus (Figure 1).

Clarke et al. have also documented IsdA promotion of *S. aureus* resistance to certain bacteriocins (lantibiotics), antimicrobial peptides of bacterial origin (Clarke et al., 2007). The primary constituents of the normal human skin microflora are coagulase negative staphylococci such as *S. epidermidis*, and these organisms produce bacteriocins with in vitro activities against *S. aureus*. An overlooked element of normal skin innate immunity may be the recruitment of commensal bacteria capable of participating in defense against potential pathogens. A logical area for future study would be to examine whether IsdA in fact allows *S. aureus* to resist *S. epidermidis* bacteriocins and compete for a niche alongside the dominant microflora.

A most interesting aspect of the new observations of Clarke et al. is a reemphasis of the importance of sebum lipids as a dynamic aspect of skin innate immunity. Like antimicrobial peptides, fatty acids are induced in skin upon injury or microbial stimuli through Toll-like receptor-dependent pathways (Schauber et al., 2007; Georgel et al., 2005), and knockout mice deficient in biosynthesis of either component fail to restrict bacterial proliferation (Nizet et al., 2001; Georgel et al., 2005). Reduced levels of sebum fatty acids as well as antimicrobial peptides

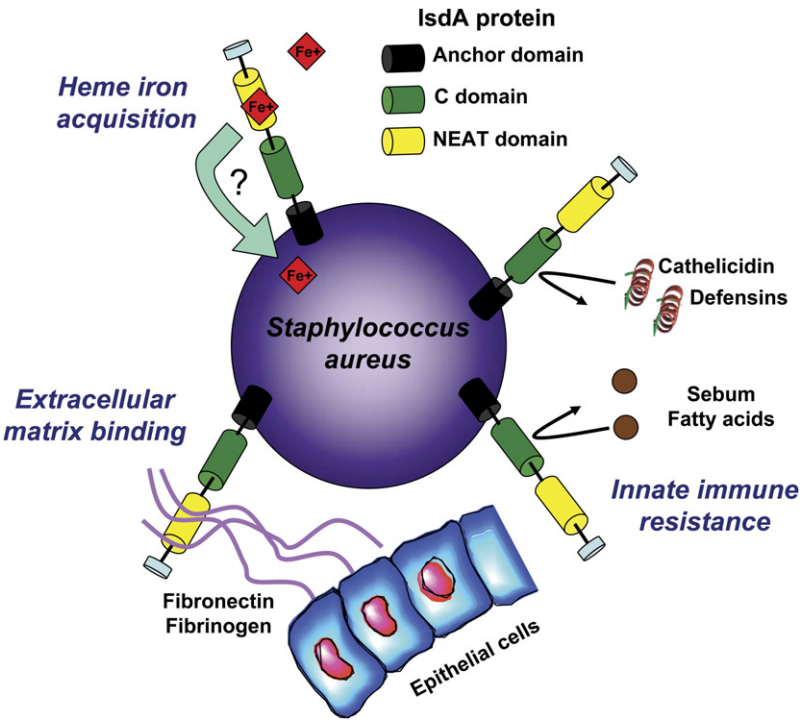

Figure 1. Multiple Potential Contributions of the Surface-Expressed IsdA Protein to *Staphylococcus aureus* Pathogenesis

are seen in atopic dermatitis (eczema), an inflammatory skin condition predisposed to recurrent bacterial infection (Takigawa et al., 2005; Ong et al., 2002). While several mechanisms of *S. aureus* resistance to antimicrobial peptides have been described (i.e., cell wall charge modifications, proteolytic inactivation, extracellular trapping), the hydrophobicity-modifying properties of IsdA represent the first identified molecular resistance mechanism of the pathogen to host fatty acid defenses. Clarke et al. have also identified several novel effects exerted by subinhibitory levels of sebum fatty acids on *S. aureus*, including decreased transcription of genes encoding virulence factors and an antibiotic resistance determinant; these processes are similarly blocked by IsdA.

Can one get too much of a good thing? Recognizing the implicit importance of sebum lipids in innate immunity, the authors tested pharmacologic administration of the constituent fatty acid C-6-H in topical and systemic *S. aureus* murine infection models, documenting significant reductions in bacterial loads, and apparently overcoming any protection IsdA afforded the bacterium. Whether this therapeutic benefit reflects direct bactericidal or bacteriostatic activity, transcriptional or posttranslational interference with virulence factor production or action, or an unanticipated propitious effect on host immune function remains to be proven. Nevertheless, it raises an interesting concept. Natural products form the basis of the vast majority of effective antibiotic treatments in medical practice, in particular those derived from the secondary metabolites of microbes such as the *Penicillium* mold or soil actinomycetes. If we can appreciate a pimple not as a cosmetic woe, but rather as a focused confluence of innate immune molecules, a new generation of natural product antibiotics could be staring us right in the mirror.

This study reminds us that in an important sense, immunity is only skin deep. The indifference of *S. aureus* to many of the key effectors of skin innate defense undoubtedly accounts for its status as the foremost etiologic agent of infection in both normal and wounded human skin, which may account for over 11 million doctor visits each year in the U.S. alone (McCaig et al., 2006). Continued identification of the specific virulence factors of this leading cutaneous pathogen (and of those vulnerabilities in skin innate defense that it exploits) promises new therapeutic approaches in an era of increasing resistance to classical antibiotics.

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