Letter

Surviving innate immunity

In a complex environment, higher organisms face the constant threat of microbial infection. To defend against this onslaught of potential pathogens, all known members of the plant and animal kingdoms use an innate immune system. A key component of innate immunity is the production of small, cationic antimicrobial peptides (CAMPs). In mammals, recent discoveries from gene therapy and gene-knockout studies have confirmed that CAMPs play a crucial role in defense against invasive bacterial disease [1,2]. As is increasingly the case with pharmaceutical antibiotics, bacteria exposed to human CAMPs appear to have evolved under selective pressure to develop mechanisms of resistance. Although these selective pressures existed before the dawn of modern medicine, and indeed have existed throughout evolution, CAMPs still exhibit a broad spectrum of activity against diverse Gram-positive and Gram-negative bacterial species. The ability to resist killing by CAMPs, as discussed by Andreas Peschel in a recent issue of *Trends in Microbiology* [3], is likely to be a discriminating feature of several bacterial pathogens.

In humans, CAMPs are elaborated by skin keratinocytes and mucosal epithelial cells at low levels under baseline conditions, but can be induced specifically in response to injury or infectious stimuli [4,5]. CAMPs are also concentrated in the granules of circulating bone-marrow-derived cells and are recruited to the sites of epithelial inflammation. Bacteria such as *Staphylococcus aureus* and *Salmonella* spp. that generally exhibit intrinsic CAMP resistance should possess a survival advantage on damaged epithelium, in deeper body tissues and in the phagocytic vacuoles of leukocytes. This is supported by the observations that *S. aureus* is the most common cause of human wound infections and deep-tissue abscesses and *Salmonella* spp. are leading agents of chronic systemic infections, including enteric fever. Bacterial species generally more sensitive to CAMPs, such as *Escherichia coli*, can occupy a niche on mucosal surfaces with local or toxin-mediated disease effects, invading deep tissues only in groups with broader defects in innate or acquired immunity (e.g. neonates, the elderly or chemotherapy patients).

As discussed by Dr Peschel, the genetic approach of generating and screening bacterial mutants for alterations in CAMP sensitivity has been fruitful in elucidating a feature common to several resistant species – and supports an unattractive (*sic*) hypothesis: bacteria that can successfully modify the normal anionic constituents of their cell walls with cationic substitutions repulse rather than attract positively charged natural antibiotics. These charge alterations have been achieved in diverse fashions such as modifications of lipoteichoic acid polymers with D-alanine (*S. aureus*), phosphotidylglycerol with L-lysine (*S. aureus*), or lipopolysaccharide lipid A with aminoarabinose (*Salmonella enterica* and *Legionella pneumophila*). Alternative resistance mechanisms include proteolytic digestion of the antimicrobial peptide (*S. enterica*) or proton-motive-force-dependent efflux pumps (*Neisseria gonorrhoeae*). Confirming the importance of CAMP in host defense, isogenic bacterial mutants with decreased CAMP resistance are less virulent than their wild-type parent strains in animal models of invasive bacterial infection [6–8].

A puzzling consideration is how some bacterial species that are sensitive to killing by human CAMPs *in vitro* sometimes produce invasive infections in healthy individuals. The intestinal pathogen *Shigella* spp. and the skin and respiratory tract pathogen group A *Streptococcus* (GAS) are examples. For *Shigella*, the solution could lie in the ability of the organism to suppress the production of CAMPs by intestinal epithelial cells [9]. Resistant GAS mutants can be identified in the laboratory upon serial exposure to increasing concentrations of CAMPs, and these mutants are hypervirulent upon challenge of animals [2]. It is interesting to speculate that a mutation conferring CAMP resistance might not prove advantageous to the organism in epithelial colonization or host–host transmission where even greater evolutionary selective pressures exist. For many human bacterial pathogens, the number of individuals colonized asymptomatically greatly exceeds the low incidence of invasive infection. Is it possible that in rare events a quantum 'switch' to higher CAMP resistance allows invasion? Alternatively, do some patients have congenital or acquired defects in their specific ability to mount an appropriate CAMP response to minor injury? When considering the pathogenesis of infections through epithelial barriers, the ability of the microorganism to avoid or resist CAMP-mediated defenses must be considered.

The defining quality of some important human pathogens thus could be an 'innate immunity to innate immunity'. Such a strategy will require mechanisms to circumvent multiple immune defense events, both soluble and cellular, that have evolved at the epithelial interface with our environment. Increased appreciation of the molecular and genetic basis of CAMP resistance offers fundamental new insights into pathogen–host interactions and could reveal several promising new targets for antibiotic therapy.

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