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Commentary

Targeting Bacterial Abscess Formation

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Cutaneous abscesses are some of the most common manifestations of bacterial infections. Abscesses can present as transient painful lumps that resolve without medical intervention, or in severe cases as large deep abscesses associated with bloodstream dissemination. Although many Gram-positive and Gram-negative bacteria cause abscesses, *S. aureus*, in particular community-associated MRSA, is the most common causative agent. Once formed, the pus in the walled-off lesion can significantly interfere with the activity of antibiotics to the extent to make antibiotic treatment moderately ineffective when an abscess exceeds a certain size, with scarring posing as an additional problem. In this issue of *EBioMedicine* (Mansour et al., 2016–in this issue), Hancock and colleagues describe a cationic peptide that primarily targets the formation of abscesses. The peptide was developed from a screen of *anti*-biofilm peptides (de la Fuente-Nunez et al., 2015) and in vitro prevented or eradicated biofilms formed by both Gram-positive and Gram-negative bacteria. In non-vertebrate models of *P. aeruginosa* infection, it enhanced survival of the host (de la Fuente-Nunez et al., 2015).

The target of the cationic peptide is the conserved bacterial stringent stress response mediator (p)ppGpp (De La Fuente-Nunez et al., 2014, 2015). Cellular concentrations of pppGpp and ppGpp increase when bacteria are exposed to stresses, specifically nutrient limitation. (p)ppGpp, as a pleiotropic transcriptional regulator, orchestrates reprogramming of cellular processes by slowing the growth rate and pushes energy to be used for maintenance and stress-defense, including biofilm formation (Wolz et al., 2010). This is known as the stringent response and is an important bacterial survival mechanism. The enzymes responsible for synthesizing and degrading (p)ppGpp are highly conserved among bacteria. In Gram-negative bacteria, (p)ppGpp is synthesized by RelA and degraded by SpoT (Metzger et al., 1989). In Gram-positive bacteria, the RelA/SpoT Homologue (RSH) bifunctional proteins are the main enzymes responsible for synthesizing (p)ppGpp from ATP and GTP/GDP and hydrolyzing (p)ppGpp into GTP/GDP and pyrophosphate (Wendrich and Marahiel, 1997).

In the current study (Mansour et al., 2016–in this issue), Hancock and colleagues further tested inhibition of the bacterial stringent response in murine models of *S. aureus* and *P. aeruginosa* cutaneous abscesses. They demonstrated that *S. aureus* defective in RSH synthase (stringent response mutant) or the universal stress protein Usp2 induces significantly smaller abscesses and cutaneous lesions compared to wild type *S. aureus*, without an effect on bacterial burden. Local or systemic application of a previously characterized stringent-response inhibitor peptide DJK-5 (de la Fuente-Nunez et al., 2015), at the time or shortly after *S. aureus* or *P. aeruginosa* infection, also blocked abscess formation with modest or no effect on bacterial burden. DJK-5 blockade of abscess correlated in vitro to inhibition of one *S. aureus* virulence determinant, phenol-soluble modulin (PSMα), which has been shown previously to be important for cutaneous lesion formation (Berube et al., 2014). Although DJK-5 has antimicrobial activity that is thought to be related to its cationic property, use of sub-MIC peptide dosing and mutant bacteria defective in stringent response in vivo helped to dissociate killing of the bacteria as the mechanism driving the inhibition of abscess formation.

A fundamental question that arises from the study is the relation between the stringent response and abscess formation. The mechanisms responsible for abscess formation have been an important topic of research in the *S. aureus* field. While certain stress defense mechanisms, such as metal limitation, oxidative, and nitric stress seem to have a role in the ability of *S. aureus* to form abscesses, the stringent response in this context has yet to be elucidated. It is likely that a primary connection is due to the stringent response's direct effect on regulator CodY. CodY has been shown to impact disease severity in several animal models by altering expression of master regulators, like *agr* (RNAIII and RNAII) and *saeR*, hemolysins (*hla*), leukocidins (*lukSF*), capsule synthesis (*icaADBC*), as well as many other genes shown to be important for abscess formation (Majerczyk et al., 2008). PSMα expression, which is shown to be inhibited by DJK-5, is up-regulated via RSH independently of CodY (Geiger et al., 2012). The specific factors regulating abscess formation under the stringent response remain to be determined in *S. aureus* and other microbes.

From a clinical angle, blockade of abscess formation would be a potentially useful adjunct to killing of the pathogens. Most frequently, infected individuals present already with a large abscess that requires surgical drainage. For those presenting with smaller or early stage abscesses that are not yet amenable to surgical drainage, antibiotics are routinely used but may not be sufficient to stop progression of abscess formation, particularly if the offending pathogen is relatively antibiotic resistant. Inhibition of the stringent response to block abscess formation could prove to be useful, and would compare to the

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adjunctive use of protein synthesis inhibitors for toxin inhibition in treatment of toxin-mediated infections (Steer et al., 2012). The inhibitors would be particularly useful if they also prevent chronic or recurrent abscesses including hard-to-treat *S. aureus*-related conditions such as hidradenitis suppurativa. Future studies will need to establish that the inhibitors are still effective when used in combination with effective or marginally effective antibiotics.

Disclosure

The authors declare no conflict of interest.

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