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BSIP SA/Alamy

The cytokine thymic stromal lymphopoietin (TSLP) is produced by various cell types and is known to promote allergic diseases, such as asthma and atopic dermatitis, in a T helper 2 cell-dependent manner. A role for TSLP in host defence against infections has been less clear, but now West *et al.* show that TSLP increases the killing of methicillin-resistant *Staphylococcus aureus* (MRSA) in a neutrophil- and complement-dependent manner.

Infections by MRSA typically begin as skin infections but can lead to life-threatening and invasive infections. As TSLP is highly expressed in the skin, the authors investigated whether TSLP could have a role in the immune defence against skin MRSA infections. They found that TSLP treatment resulted in significantly enhanced MRSA killing in *in vitro* whole-blood killing assays using mouse and human blood. As neutrophils are important for host defence against *S. aureus*, the authors investigated whether neutrophils could mediate the TSLP-induced killing of bacteria. Indeed, mRNA expression of *CRLF2* — which encodes the TSLP receptor cytokine receptor-like factor 2 — increased the response to heat-killed *S. aureus* by human neutrophils. TSLP had no effect on MRSA killing in neutrophil-depleted blood. Hence, TSLP acts on neutrophils to enhance their killing of MRSA.

> “TSLP acts on neutrophils to enhance their killing of MRSA”

Next, the authors investigated whether TSLP treatment could increase killing of MRSA *in vivo*. Injection of MRSA together with TSLP into the ears of wild-type mice significantly reduced the bacterial burden at 2 days post-infection, compared with control mice injected with MRSA and phosphate-buffered saline. The effect was sustained for several days and was associated with decreased inflammation in the skin. Of note, MRSA-infected *Crlf2*$^{-/-}$ mice had similar bacterial burdens to neutrophil-depleted wild-type mice, which indicates that TSLP-mediated killing of MRSA *in vivo* depends on neutrophils. In experiments in which wild-type and *Crlf2*$^{-/-}$ bone marrow-derived neutrophils were transferred to naive mice, the authors could show that TSLP acts directly on neutrophils to decrease the bacterial burden.

Finally, the authors investigated the mechanism for neutrophil-killing of MRSA and found a role for reactive oxygen species (ROS). Neutrophils from MRSA-infected *Crlf2*$^{-/-}$ mice had lower levels of ROS compared with infected wild-type mice, and intradermal administration of a ROS scavenger abolished the effect of TSLP on MRSA killing. Further experiments showed that complement drives the production of ROS by neutrophils. Local injection of antibodies specific for complement component C5 into mice with an intradermal MRSA infection decreased ROS production by neutrophils, and TSLP had no effect on MRSA killing in wild-type mice treated with this antibody. Similarly, an antagonist of C5a receptor 1 inhibited TSLP-enhanced killing of MRSA by human neutrophils.

In summary, TSLP can enhance neutrophil killing of MRSA in a complement- and ROS-dependent manner. These findings provide new insights into the actions of this cytokine, with possible therapeutic implications related to the control of MRSA infections.

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