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Commentary

# How *S. aureus* blinds the inflammasome to escape immune control

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*Staphylococcus aureus* (*S. aureus*) is a dangerous pathogen in and outside hospitals. However, much more commonly, the pathobiont behaves as an innocuous member of the human microbiome of the nose, skin or gastrointestinal tract, and in most people the immune system can control the opportunist for life. The equilibrium is based on multiple interactions between pathogen and host, which are well adapted to each other, and it can only be maintained at high cost to the immune system. Although *S. aureus* carriers gradually build up clinical protection, there appears to be no sterile immunity, and recurrent infections are common [1–3]. In this issue of EBioMedicine, Jian-Dong Huang and coworkers add another facet to our knowledge of the fascinating interplay between *S. aureus* and its human host, showing how the microorganism manipulates the inflammasome [4].

Inflammasomes are cytosolic sensors, critical for triggering and polarizing the host immune response. Of all inflammasomes, NOD-like receptor (NLR)-containing protein 3 (NLRP3) is the best characterized. It can recognize *S. aureus* virulence factors, such as Panton-Valentine leukocidin (PVL), leukocidin (Luk) AB as well as proteoglycan, and also ATP, a damage-associated molecular pattern (DAMP) released from dying host cells during infection. Activation of the inflammasome leads to the release of interleukin (IL)-1$\beta$, thereby orchestrating a Th17 response in the adaptive immune system. Th17 cells and IL-17 cytokines are essential for the elimination of *S. aureus* in humans and mice [5]. IL-17 deficient mice and patients with hyper IgE syndrome (HIES), who lack Th17 cells, cannot effectively fight *S. aureus*. HIES patients suffer from recurrent severe infections [6,7].

Jian-Dong Huang and coworkers show that *S. aureus* has means to disrupt NLRP3 activation and IL-1$\beta$ release [4]. The bacteria possess a cell surface enzyme, adenosine synthase A (AdsA), which degrades ATP, ADP, and AMP to adenosine [8]. Adenosine acts on host cellular adenosine receptors (A2aR) and inhibits the inflammasome [9]. With AdsA, *S. aureus* mimics a host mechanism of immune regulation, as anti-inflammatory immune cells generate adenosine from ATP in a two-step process involving two surface-expressed ectoenzymes, CD39 and CD73 [9] (Fig. 1).

The group of Huang used an AdsA deletion mutant of *S. aureus* and showed that it induces more inflammation than the wild-type (WT) strain. Inhibition of the A2aR on immune cells had the same effect as AdsA deletion, whereas adenosine decreased the IL-1$\beta$ production in cell cultures and infected animals. The authors then show that adenosine acts by inhibiting the NLRP3 inflammasome, thereby reducing IL-1$\beta$ production (Fig. 1). This attenuates the adaptive Th17 response and weakens immune protection against *S. aureus* as demonstrated by the authors in a mouse model of recurrent infections. Their system could also be interpreted as a model of repeated live immunization. In this model, repeated infection with a low inoculum of the AdsA deletion mutant conferred superior protection against a lethal challenge infection with *S. aureus* than the same pre-treatment with AdsA competent bacteria.

This opens interesting perspectives: Inclusion of AdsA in a multivalent *S. aureus* vaccine could neutralize the immune escape mechanism and help establish an effective immune memory upon re-exposure to the pathogen. In cases of existing chronic or recurrent *S. aureus* infections, pharmacological inhibition of the enzyme or adenosine might be an option to be explored.

## Contributors

Both authors contributed to the final version of the commentary.

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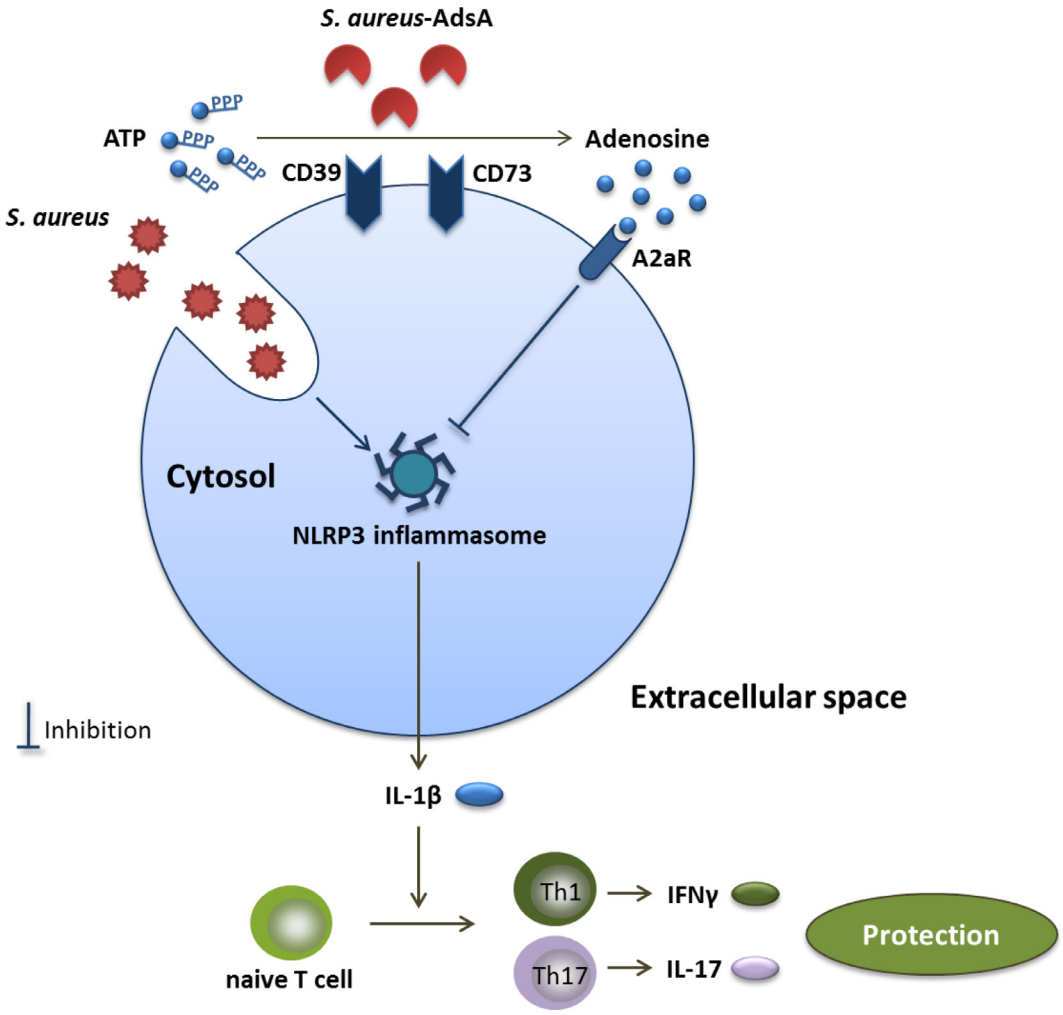


**Fig. 1. *S. aureus*' means of escape from the inflammasome.** Adenosine synthase A of *S. aureus* as well as ectoenzymes of host cells convert ATP to adenosine. Adenosine activates the adenosine receptor, inhibiting the NLRP3 inflammasome and IL-1$\beta$ release. This dampens the protective adaptive immune response.

A2aR: Adenosine receptor; AdsA: Adenosine synthase A; ATP: Adenosine triphosphate; CD39: Ecto-ATP diphosphohydrolase; CD73: Ecto-5′-nucleotidase; NLRP3: NOD-like receptor (NLR)-containing protein 3.

## Declaration of Competing Interest

Murthy N. Darisipudi declares no conflict of interest.

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