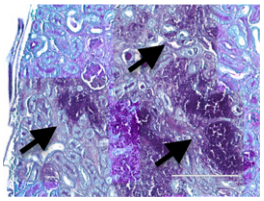
In This Issue

The Journal of Immunology

CARD9 Curbs *C. tropicalis*

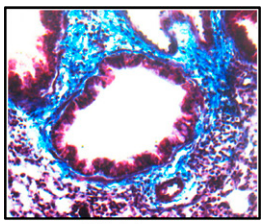


Candida albicans often serves as the model organism for antifungal immunity, even though about half of candidemia cases are caused by other *Candida* species. Immune control of *C. albicans* involves sensing by C-type lectin receptors that signal through caspase-associated recruitment domain adaptor 9 (CARD9) to induce many cytokines, including TNFα and the IL-17 family. In this issue, Whibley et al. (p. 3781) investigated whether *C. tropicalis* infection is similarly dependent on this immune signaling axis. IL-17RA$^{-/-}$ mice were not more susceptible to disseminated *C. tropicalis* infection than wild-type (WT) mice, both of which experienced ∼40% mortality after several weeks, but all CARD9$^{-/-}$ mice succumbed to infection within 10 d. When fungal burdens were examined 5 d p.i., CARD9$^{-/-}$ mice had higher fungal burden in the brain, liver, and kidneys, but equivalent fungal levels in the spleen, as compared with WT mice. Rag2$^{-/-}$Il2rg$^{-/-}$ mice did not experience increased susceptibility to *C. tropicalis* infection, but mice depleted of monocytes and neutrophils experienced 100% mortality by d8, highlighting the importance of myeloid cells in combating infection. Stimulation of myeloid cells with heat-killed *C. tropicalis* revealed that CARD9$^{-/-}$ monocytes and neutrophils, unlike WT cells, were incapable of producing TNFα. This TNFα deficiency was detectable in the blood and kidneys early in infection of CARD9$^{-/-}$ mice. Continuous treatment of WT mice with the soluble TNFR blocking agent etanercept resulted in enhanced susceptibility to *C. tropicalis*, confirming that TNFα plays a role in combating this pathogen. Although TNFα can induce chemokine production, neutrophil recruitment was not impaired in CARD9$^{-/-}$ mice; in fact, neutrophil and monocyte numbers were higher at 5 d p.i. in the kidneys, possibly leading to immunopathogenesis. Incubation with TNFα enhanced neutrophil, but not monocyte, fungal killing by both WT and CARD9$^{-/-}$ cells. Taken together, these results indicate that unlike *C. albicans*, protection against *C. tropicalis* is dependent on CARD9 and TNFα, but not IL-17 or the adaptive immune system.

Mini-Abs May Manage MRSA

The human pathogen *Staphylococcus aureus* can cause potentially fatal inflammation and employs a variety of mechanisms to evade host immunity, including secreting extracellular fibrinogen-binding protein (Efb), which inhibits complement activation by binding to C3 and its fragments C3b and C3d. The emergence of antibiotic-resistant strains of *S. aureus* such as methicillin-resistant *S. aureus* (MRSA) has stimulated an urgent need for new ways to treat infection, and Georgoutsou-Spyridonos et al. (p. 3946) have characterized Abs that may help meet this need. In human serum, anti-Efb IgG Abs were identified that could block the interaction between C3 and the C-terminal portion of Efb (Efb-C), allowing neutrophil-mediated killing of *S. aureus,* presumably via complement activation. The authors then screened a phage library consisting of human F(ab)$_2$ to detect human Abs (mini-Abs) that bound Efb-C. The highly selective mini-Abs identified in this screen inhibited binding of Efb-C to C3, C3b, and C3d and could reverse Efb-mediated promotion of *S. aureus* survival in a human whole blood model of bacteremia. In this model, the blocking mini–Ab-A1 could restore complement activation and neutrophil-mediated *S. aureus* killing while reducing plasma levels of IL-6. In an *S. aureus*-induced sublethal renal abscess mouse model, a single dose of mini–Ab-A1 given prior to *S. aureus* infection conferred prolonged protection against bacterial colonization and kidney inflammation. These observations support the further development of these mini-Abs as potential therapeutic agents to protect against dangerous infectious agents like MRSA.

FSTL1 Fosters Asthma



FSTL1

Follistatin like 1 (Fstl1) is a TGFβ-responsive inflammatory mediator that has been studied in the context of arthritis, fibrosis, and organogenesis. In this issue, Miller et al. (p. 3546) examined the role Fstl1 plays in asthma pathogenesis. Bronchial biopsies from severe asthmatics had a significantly greater number of Fstl1$^+$ cells than biopsies from normal subjects. To study Fstl1 and asthma in vivo, mice were chronically challenged with ovalbumin (OVA), which led to increased Fstl1 mRNA expression in the lung and higher levels of Fstl1 protein in the bronchoalveolar lavage (BAL) as compared with mice that had not been challenged with OVA. Immunofluorescence microscopy of lung sections revealed that these Fstl1-expressing cells were F4/80$^+$ macrophages, over half of which also expressed the M2 macrophage marker arginase. In vitro stimulation with TGFβ1 or Fstl1 induced Fstl1 mRNA in fibroblasts, macrophages, and epithelial cells, indicating that Fstl can act in a paracrine or autocrine fashion. Following chronic OVA challenge, Lys-Cre^{tg}/Fstl$^{\Delta/\Delta}$ mice, whose myeloid cells are unable to produce Fstl1, had relatively reduced asthma symptoms, although there was no difference in airway responsiveness relative to OVA-challenged WT mice. Intranasal delivery of Fstl1 for 15 d caused increased mucus production and periobronchial fibrosis, decreased airway responsiveness, increased eosinophilia in the lungs and BAL, and increased serum IgE. mRNA expression of TNFα, IL-5, and the IL-6 family member oncostatin M (OSM) were also increased in