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Host Autophagy Combating *S. aureus*: α-Toxin Will Be Tolerated

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Autophagy regulates the degradation of both cellular components and invading intracellular pathogens. In this issue of *Cell Host & Microbe*, Maurer et al. (2015) reveal that cellular autophagy decreases host sensitivity to *Staphylococcus aureus* α-toxin via reduced expression of the toxin receptor ADAM10, thus rendering the host tolerant to disease.

Autophagy is a conserved host cellular process that targets intracellular contents for degradation at a basal level under nutrient-rich conditions and is highly upregulated during times of cellular starvation. In addition to its housekeeping function, autophagy is a well-appreciated innate immune mechanism for the targeted destruction of intracellular bacteria. The formation of a double-membrane autophagosomal compartment encapsulates the invading organism to restrict bacterial growth and permit delivery to the lysosome for degradation. Bacteria have evolved an array of mechanisms to alter the autophagic process, including inhibition of signaling, blockade of autophagosomal assembly, and production of virulence factors that conceal the bacteria from recognition and prevent lysosomal fusion (Huang and Brumell, 2014). *Staphylococcus aureus* is a formidable human pathogen owing to its ability to cause invasive pneumonia and sepsis, resulting in significant morbidity and mortality. *S. aureus* α-toxin is a highly conserved exotoxin that plays a vital role in the progression of both intrapulmonary and intravascular infection, contributing to pathogen-associated mortality (Bubeck Wardenburg et al., 2007; Powers et al., 2012). Limited in vitro studies have demonstrated that α-toxin upregulates autophagy, allowing for bacterial replication in the autophagosome and escape into the cytosol (Mestre et al., 2010; Schnaith et al., 2007); however, the precise contribution of host autophagy to progression of staphylococcal infection in vivo had remained elusive.

In the current issue of *Cell Host & Microbe*, Maurer et al. utilize autophagy-deficient ATG16L1 hypomorphic mice to address the role of autophagy during invasive *S. aureus* disease. The authors uncover that autophagy mutants display increased mortality during both intravenous and intrapulmonary *S. aureus* infection, a stark contrast to the group's previous observation of protection following *Citrobacter rodentium* infection (Marchiando et al., 2013). Surprisingly, the increased death and organ damage detected in *S. aureus*-infected mice does not correlate with increased bacterial burden, suggesting that the mechanism of increased susceptibility is independent of the most widely proposed innate immune function of autophagy-mediated bacterial clearance. Given the well-characterized contribution of α-toxin to the pathogenesis of pneumonia and sepsis, the authors tested disease progression in autophagy hypomorphs utilizing strains of *S. aureus* lacking the toxin. These experiments not only reveal that the hypersensitivity of autophagy-deficient mice is lost during infection with the isogenic mutant, but autophagy-deficient mice are in fact more tolerant to toxin-deficient

strains of *S. aureus*. Initiation of autophagy therefore appears to serve a vital purpose in innate immunity by allowing the host to withstand cellular exposure to α-toxin.

The enhanced susceptibility to sepsis and the vascular injury observed during pulmonary infection led the authors to hypothesize that defective endothelial autophagy may be relevant to invasive disease. Consistent with this hypothesis, endothelial-specific ATG16L1 mice exhibited increased susceptibility to staphylococcal pneumonia and sepsis. Endothelial cells isolated from these mice exhibit increased cell death in response to intoxication, highlighting an integral role of toxin-mediated endothelial injury in multiple invasive diseases. α-toxin has been shown to intoxicate myeloid lineage cells, facilitating the pathogenesis of pneumonia (Becker et al., 2014). ATG16L1-specific deletion on myeloid lineage cells did not enhance infection, however, suggesting that autophagy-mediated toxin sensitivity exhibits cellular specificity in vivo. α-toxin targets susceptible host cells through an interaction with its cellular receptor A Disintegrin and Metalloprotease 10 (ADAM10) (Wilke and Bubeck Wardenburg, 2010). Both ATG16L1-deficient endothelial cells and endothelial cells treated with an autophagy inhibitor exhibit a marked increase in surface ADAM10 expression, providing an explanation for increased toxin sensitivity. Previous studies corroborate the findings that increased autophagy correlates with decreased ADAM10 expression, as the autophagy inducer rapamycin decreases the production of the neuroprotective ADAM10-derived cleavage product, APP-α (Zhang et al., 2010). The identification of ADAM10 as the α-toxin receptor has facilitated an understanding of pathogenic events downstream of the of toxin-receptor interaction in vivo. α-toxin targets both endothelial cells and epithelial cells, upregulating the enzymatic activity of ADAM10 and culminating in disruption of the tissue barrier in vitro and in vivo (Inoshima et al., 2011; Powers et al., 2012). Intoxication of these cell lineages thereby contributes to mortality associated with sepsis and pneumonia (Inoshima et al., 2011; Powers et al., 2012). The authors' finding that increased ADAM10 expression in autophagy-deficient mice exacerbates *S. aureus* infection confirms the vital interaction of the toxin-ADAM10 complex in bacterial pathogenesis. Moreover, this observation raises the interesting possibility that autophagy may more broadly govern susceptibility to bacterial virulence factors whose action depends on specific host effector proteins or cognate receptor-based interactions.

The novel studies by Maurer et al. enhance our understanding of the contribution of autophagy to host immunity. While autophagy serves a vital role in combating intracellular pathogens through bacterial destruction, these findings provide a mechanistic link between toxin-induced cellular injury and host tolerance. As *S. aureus* triggers fulminant disease while being a predominately extracellular organism, tolerance as an immunodefense capable of "minimizing damage caused by the infection without affecting pathogen burden" is well exemplified by this specific host-pathogen interaction. Ongoing analysis of autophagy in specific cell populations following *S. aureus* infection is therefore anticipated to shed further mechanistic insights on the active contribution of this process to host tolerance. While invasive diseases such as sepsis and pneumonia are a keen focus of therapeutic interventions, owing to their associated morbidity and mortality, on a population level, these infections are only a sliver of the interaction of *S. aureus* with its human host. By and large, these often-lethal infections are not "tolerated" by individual patients, save for the advent of medical interventions including antimicrobial and supportive therapies. This raises two intriguing areas for further inquiry within the field: first, does autophagy shape the ability of *S. aureus* to live as a human commensal, given the highly conserved nature of α-toxin? Second, as there is considerable variability of clinical outcome in patients treated for invasive *S. aureus* disease, is it possible to envision that objective measures of host autophagic function or pathogen tolerance may inform outcomes and clinical management through predictive modeling? As such, a host-specific autophagy "rheostat" may govern the early response to invasive disease and establish an outcome trajectory for the host. The observation by Maurer and colleagues that epirubicin-enhanced autophagy protects mice from disease suggests that deliberate, timely reprogramming of the rheostat set-point in life-threatening *S. aureus* infection may be a novel and viable therapeutic strategy.

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