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Neutrophil function in hypervirulent *Klebsiella pneumoniae* infection

Klebsiella pneumoniae is a Gram-negative, human commensal and opportunistic pathogen that has acquired additional antibiotic resistance genes or virulence genes, which limits therapeutic options.¹⁻³ Hypervirulent *K pneumoniae* (hvKp) is an evolving pathotype that causes pyogenic tissue abscesses and is considered a substantial threat to global public health. A crucial gap in knowledge exists in how macrophages, sentinel immune cells positioned strategically within tissue environments such as the liver, augment host defense against invading hvKp.⁴ In *The Lancet Microbe*, Joseph Wanford and colleagues⁵ explored the interaction of hvKp and other *K pneumoniae* strains (non-hvKp) with tissue macrophages using a mouse infection model and an ex-vivo pig organ perfusion model. The evidence from Wanford and colleagues' investigation suggested that, in contrast to non-hvKp strains that are efficiently cleared in the tissues, hvKp strains replicate in the hepatic macrophages and resist neutrophil-mediated clearance, leading to abscess formation.

To study neutrophil responses against hvKp infection, we infected two groups of wild-type mice with 1×10^4 colony-forming units of a carbapenem-resistant hvKp strain or a low-virulence strain. Mice in a control group were mock-infected. This dose of carbapenem-resistant hvKp led to 100% animal death at 24 h, whereas mortality was not recorded for mice infected with the low-virulence strain throughout the experiment (appendix). After 12 h of infection, mice had reduced activity and fast breathing. Therefore, we analysed the infected animals 12 h after infection. Mice infected with carbapenem-resistant hvKp, but not mice infected with the low-virulence strain, showed significant

weight loss at 12 h compared with before infection (appendix). Correspondingly, lungs and spleens from mice infected with carbapenem-resistant hvKp had increased infiltration of neutrophils compared with non-infected animals (appendix). Similar to the results reported by Wanford and colleagues, we also found that carbapenem-resistant hvKp was more resistant to neutrophil-mediated killing than the low-virulence strain (appendix) and consequently, we observed more bacterial burden in mice infected with carbapenem-resistant hvKp than in mice infected with the low-virulence strain (appendix). The precise mechanism by which carbapenem-resistant hvKp evades neutrophil killing remains unknown.

In conclusion, further experiments are required to explore how hvKp evades detection by neutrophils and to develop methods to manipulate neutrophil killing against hvKp. Future studies also should focus on the differences between hvKp and non-hvKp strains in eliciting phagocyte-mediated immune responses and identify the mechanisms by which neutrophils and macrophages clear hvKp in vivo. Manipulation of neutrophil killing during hvKp infection holds promise for the development of improved immunotherapies against hvKp infection in the face of emerging multi-antibiotic resistance of this clinically important human pathogen.

We declare no competing interests.

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See Online for appendix