Neutrophil function in hypervirulent Klebsiella pneumoniae infection

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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* (hv*Kp*) 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 hv*Kp*.[4] In *The Lancet Microbe*, Joseph Wanford and colleagues[5] explored the interaction of hv*Kp* and other *K pneumoniae* strains (non-hv*Kp*) 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-hv*Kp* strains that are efficiently cleared in the tissues, hv*Kp* strains replicate in the hepatic macrophages and resist neutrophil-mediated clearance, leading to abscess formation.

To study neutrophil responses against hv*Kp* infection, we infected two groups of wild-type mice with 1×10^4 colony-forming units of a carbapenem-resistant hv*Kp* strain or a low-virulence strain. Mice in a control group were mock-infected. This dose of carbapenem-resistant hv*Kp* 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 hv*Kp*, 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 hv*Kp* 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 hv*Kp* 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 hv*Kp* than in mice infected with the low-virulence strain (appendix). The precise mechanism by which carbapenem-resistant hv*Kp* evades neutrophil killing remains unknown.

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