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MACROPHAGES

Early antifungal defence in kidneys

Systemic *Candida albicans* infection causes high morbidity and mortality, with the kidneys being the main target organs. Neutrophils have an important role in host defence against systemic candidiasis, and neutropenic patients are particularly susceptible to this infection. But much less is known about the role of mononuclear phagocytes in host defence. Now, Lionakis *et al.* show that CX_3C-chemokine receptor 1 $(CX_3CR1)^+$ kidney-resident macrophages have a crucial role in the early host immune response to systemic fungal infection.

Initial investigations into the role of mononuclear phagocytes in systemic candidiasis in mice identified CX_3CR1, which is used as a marker for tissue-resident macrophages, as being important in host defence — a median lethal dose (LD50; defined in wild-type mice) inoculum of *C. albicans* was uniformly fatal in CX_3CR1-deficient mice. In addition, these mice had higher kidney fungal burden than wild-type mice throughout the course of infection, and the CX_3CR1-deficient mice developed severe kidney failure.

Using confocal microscopy, the authors observed that *C. albicans* rapidly invaded the kidneys of both wild-type and CX_3CR1-deficient mice following intravenous injection. In wild-type kidneys, ~90% of *C. albicans* yeast and pseudohyphal elements were internalized by or encircled by mononuclear phagocytes, respectively, 2 hours after infection. By contrast, only 60% of *C. albicans* elements were in contact with mononuclear phagocytes in CX_3CR1-deficient mice after 2 hours. Furthermore, the fungal load in the kidneys of CX_3CR1-deficient mice was greatly increased compared with infected wild-type mice as early as 12 hours after infection. Together with the confirmation that most CX_3CR1^+ mononuclear phagocytes in the uninfected kidneys of wild-type mice are macrophages, these data suggest that the early interactions of tissue-resident CX_3CR1^+ macrophages with *C. albicans* are crucial for controlling the progress of the infection.

Next, the authors investigated whether CX_3CR1 deficiency influences macrophage accumulation in the kidneys. They observed an ~50% decrease in the number of macrophages in the kidneys of CX_3CR1-deficient mice. This decrease was not due to a defect in monocyte trafficking from the blood to the kidney, in macrophage proliferation or in macrophage differentiation, but instead was attributable to impaired macrophage survival at steady state and throughout infection. This defect in macrophage survival was associated with an increase in caspase-dependent apoptosis.

Finally, in humans, the mutant *CX3CR1-M280* allele (which results in reduced ligand binding to CX_3CR1) was shown to be associated with an increased risk of systemic candidiasis in two patient cohorts.

This study shows that CX_3CR1-mediated survival of kidney-resident macrophages is crucial for the early effective control of systemic *C. albicans* infection.

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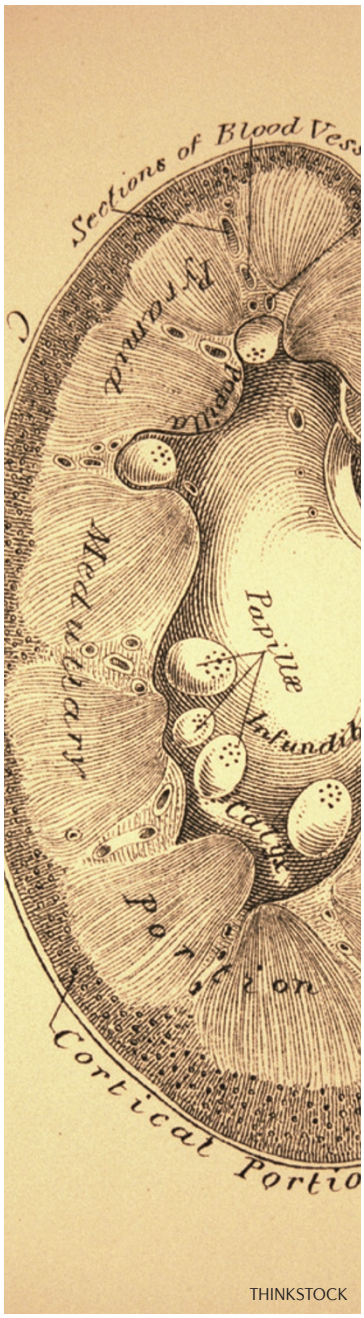
ORIGINAL RESEARCH PAPER Lionakis, M. S. *et al.* CX_3CR1-dependent renal macrophage survival promotes *Candida* control and host survival. *J. Clin. Invest.* **123**, 5035–5051 (2013)



THINKSTOCK

> “CX_3CR1-deficient mice … had higher kidney fungal burden”