CHRONIC KIDNEY DISEASE

Uraemia disarms neutrophils against *Candida*

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Uraemia is common in patients with kidney failure, and the accumulation of uraemic toxins in the blood has been linked to immune dysfunction. Such defects might underlie the higher susceptibility to infection and infection-related mortality observed in patients with kidney disease compared with healthy individuals. Now, Parthas Biswas and colleagues report that uraemia might induce a metabolic defect in neutrophils that impairs antifungal immunity. "Disseminated *Candida albicans* infection accounts for 79% of systemic fungal infections in patients with kidney disease but its diagnosis is challenging, and treatment is often complicated by antifungal drug resistance and nephrotoxicity," explains Biswas. "Systemic fungal infections are therefore extremely difficult to control in these patients."

The researchers modelled kidney damage-induced uraemia by injecting mice with a nephrotoxic derivative of aristolochic acid (AAI); mice injected with AAII, which is also mutagenic but does not cause kidney damage, or with phosphate-buffered saline were used as controls. Only the mice injected with AAI (AAI-mice) developed uraemia after 3 days (blood urea nitrogen levels peaked after 6–10 days). When challenged with an intravenous *C. albicans* injection 4 days after the induction of kidney disease, AAI-mice were more susceptible to infection and had higher mortality than controls. By contrast, in the unilateral ureteral obstruction mouse model, in which kidney damage did not lead to uraemia, fungal load did not differ between mice with kidney dysfunction and their controls.


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Neutrophils have a key role in antifungal immunity, and the researchers therefore investigated whether uraemia affected the ability of these innate immune cells to kill *C. albicans*. In vitro, exposure to serum from AAI-mice (AAI-serum), but not to similar concentrations of AAI alone, reduced neutrophil cytoplasmic reactive oxygen species (ROS) production and impaired *C. albicans* killing. Accordingly, in infected AAI-mice, the frequency of kidney-infiltrating neutrophils that had internalized and killed *C. albicans* was reduced compared with controls. ROS production in neutrophils requires oxygen and NADPH, which is produced via two glucose-dependent processes — glycolysis and the pentose phosphate pathway. Compared with AAI alone, exposure to AAI-serum reduced *C. albicans*-induced neutrophil glucose uptake and glycolysis; levels of the GLUT1 glucose transporter were also reduced. In vivo, glucose uptake in neutrophils from AAI-mice was also reduced, and healthy mice infected with *C. albicans* that were treated with a GLUT1 inhibitor had a higher fungal burden and lower neutrophil ROS levels than untreated mice.

The researchers noted that exposure to AAI-serum in vitro inhibited AKT activation, reduced phosphorylation-induced inhibition of GSK3β and inhibited mTORC1 activity in neutrophils. These observations suggested that, by disrupting AKT activation, AAI-serum promoted GS3Kβ activation, which could reduce GLUT1 expression by inhibiting mTOR. The researchers then tested the effects of GSK3β inhibitors, including clinically approved lithium chloride (LiCl), on neutrophils. Blocking GSK3β in vitro restored GLUT1 expression, glucose uptake and *C. albicans* killing in neutrophils cultured with AAI-serum. Similarly, infected AAI-mice treated with LiCl had higher neutrophil glucose uptake, increased ROS production, lower fungal burden and improved survival compared with untreated controls. "The use of GSK3β inhibitors to restore fungicidal activity of neutrophils in a pre-clinical model of kidney disease is a novel approach," notes Biswas. "Our work provides a rationale for future clinical studies to test the use of GSK3β inhibitors to treat or prevent systemic candidiasis in patients with kidney disease."

Human neutrophils from healthy volunteers that were cultured with *C. albicans* in the presence of pre-dialysis serum from patients with kidney failure produced less ROS and were less fungicidal than neutrophils cultured in the presence of post-dialysis serum from the same patients. In vitro treatment with LiCl minimized the neutrophil defects induced by the pre-dialysis serum.

"We plan to identify which uraemic toxins cause neutrophil dysfunction in patients with kidney disease, especially in patients treated with dialysis," explains Biswas. "We also want to define how uraemia or uraemic toxins suppress adaptive immunity to inform vaccine development strategies for these patients."

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ORIGINAL ARTICLE Jawale, C. V. et al. Restoring glucose uptake rescues neutrophil dysfunction and protects against systemic fungal infection in mouse models of kidney disease. *Sci. Transl. Med.* **12**, eaay5691 (2020)