How the brain is protected against fungal pathogens by CARD9-mobilized neutrophils

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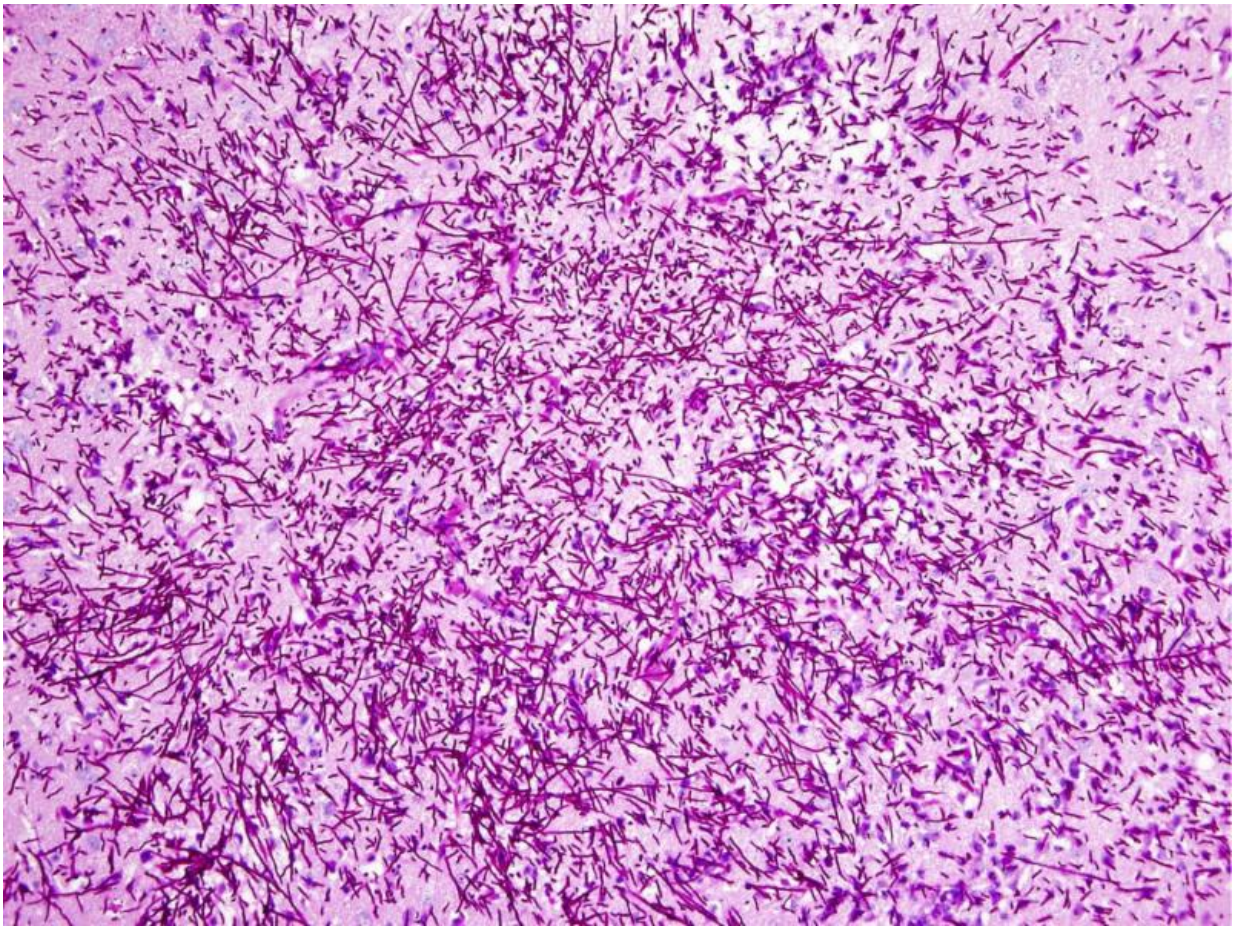

The micrograph depicts a representative section from PAS-stained mouse brain in which *Candida* (magenta) is seen invading throughout the tissue and no apparent acute inflammatory response is noted (magnification, 200x). Credit: Lionakis et al, CC-BY

CARD9 is a molecule that plays a role in defending mammals, including humans, against fungal infections. A study published on December 17th in *PLOS Pathogens* reveals how CARD9 specifically protects the mammalian central nervous system (CNS), findings that might help the development of immune therapies against dangerous fungal infections.

Despite potent available drugs, fungal infections, including those caused by the common pathogen Candida, can cause serious disease and deaths in human patients. Researchers hope to improve the treatment of fungal infections by boosting a patient's immune response in addition to the standard drug treatment. In order to develop such immune therapies, it is necessary to understand the human anti-fungal immune defense.

Humans born with a defect in the gene coding for the CARD9 protein get fungal infections that target the CNS. In their quest to understand how CARD9 protects the CNS against fungal disease, Michail Lionakis, from the US National Institute for Allergy and Infectious Diseases in Bethesda, USA, and colleagues studied a human patient without functional CARD9 and mice engineered to lack Card9 (the mouse equivalent).

The patient, an 11 year-old girl, was diagnosed with a Candida infection of the brain, meninges and surrounding tissues. When the researchers sequenced her CARD9 gene, they found a mutation that impaired the function of the CARD9 protein. They then undertook a detailed analysis of the girl's immune cells to see how their functions were affected by the mutation, and found that cells called neutrophils (known to be crucial for an anti-fungal immune response) were virtually absent from the infected CNS of the patient.

The girl had normal numbers of and apparently functional neutrophils, but rather than moving into her CNS following infection (as happens in patients with intact CARD9), the neutrophils failed to accumulate in the

CNS. Upon closer inspection, this turned out to be due to the fact that—without intact CARD9—factors that normally attract neutrophils to the infected CNS (so-called chemoattractants) were not produced.

The researchers then switched their analysis to mice, and found that in mice with intact Card9, fungal infection of the CNS results in production of chemoattractants and neutrophil recruitment that correlate with the extent of fungal burden in the brain. In contrast, when they examined mice infected with Candida but without functional Card9, the researchers found that these mice were unable to promote neutrophil accumulation to control Candida infection in the CNS.

To determine the specificity of Card9 function, the researchers also examined neutrophil recruitment in the kidney of Card9 mutant mice—which was impaired to a much smaller extent—and the effect of CNS infection with a non-fungal pathogen in Card9 mutants, which resulted in normal recruitment of neutrophils in the brain. These experiments show that the function of Card9 in promoting neutrophil recruitment is specific to fungal infections in the CNS.

"We show", the researchers summarize, "that the antifungal adaptor molecule CARD9 is critical for neutrophil recruitment from the blood into the CNS during fungal infection in mice and humans". Their results, they suggest, "form the foundation for devising immune-based therapies for bypassing CARD9 in the production of neutrophil-targeted chemokines such as via the potential direct intrathecal delivery of these molecules in infected CARD9-deficient patients."

More information: Drummond RA, Collar AL, Swamydas M, Rodriguez CA, Lim JK, Mendez LM, et al. (2015) CARD9-Dependent Neutrophil Recruitment Protects against Fungal Invasion of the Central Nervous System. *PLoS Pathog* 11(12): e1005293. DOI: 10.1371/journal.ppat.1005293