Gene makes some HIV-infected patients more at risk for fungal disease

August 27 2013

HIV-infected people who carry a gene for a specific protein face a 20-fold greater risk of contracting cryptococcal disease, according to a study published in *mBio*, the online open-access journal of the American Society for Microbiology.

Cryptococcus neoformans is the most common cause of fungal meningitis among HIV-infected individuals. While the disease is a risk for everyone with HIV who has a very low level of CD4+ T cells, researchers have discovered that those with the gene for the protein FCGR3A 158V have an immune cell receptor that binds tightly to antibody-bound *C. neoformans*. Perversely, this tight binding by a vigilant immune system may mean the patient's own immune system strength becomes a weakness when facing the fungus.

"We found that this high affinity Fc receptor polymorphism was very highly overrepresented in the patients that got cryptococcal disease," says corresponding author Liise-anne Pirofski of the Albert Einstein College of Medicine & Montefiore Medical Center in The Bronx, New York. Patients with two copies of the high affinity Fc receptor gene had an almost 20-fold increased risk of contracting the disease.

"It's surprising that a receptor involved with a higher capacity to bind immune complexes would be associated with susceptibility in patients with HIV," says Pirofski, since phagocytosis of immune complexes is thought of as a mechanism for fighting invading microorganisms.

Differences among Fc gamma receptors (FCGR) have already been linked to cryptococcosis susceptibility among people who are not infected with HIV, but this new information sheds light on how these receptors could influence susceptibility in HIV patients, who are at elevated risk of developing cryptococcosis and are known to have high levels of antibodies to *C. neoformans*. FCGRs are proteins expressed on the outsides of different kinds of immune cells, including B lymphocytes, natural killer cells, macrophages, neutrophils, and mast cells. They bind to antibodies that have grabbed onto invading pathogens, then stimulate the immune cells to destroy the invaders.

The researchers performed PCR-based genotyping on banked samples from 164 men enrolled in the Multicenter AIDS Cohort Study (MACS), including 55 who were HIV-infected and developed cryptococcal disease, a control group of 54 who were HIV-infected and 55 who were HIV-uninfected. After correcting for a number of factors like demographics and T cell counts, they found a strong association between the gene for the high-affinity FCGR3A 158V allele and the risk of cryptococcal disease in HIV-infected men.

To figure out what that meant, they followed up with binding studies and showed that cells that express FCGR3A 158V bind more strongly to antibody-*C. neoformans* complexes. Greater affinity for the antibody-*C. neoformans* complex could increase the attachment of the fungus to monocytes or macrophages, which could in turn increase the numbers of fungi living and replicating inside immune cells. And there's also the possibility that these infected immune cells could act like a Trojan horse, delivering *C. neoformans* cells across the blood-brain barrier and allowing them to infect the brain. Pirofski says these possibilities are now under investigation.

C. neoformans is found all over the environment and studies show that nearly everyone is exposed to the fungus during their lifetime. However,

the organism rarely causes disease in healthy people, but strikes most often in people with weakened immune systems. It is the main cause of fungal meningitis in people living with HIV, and causes devastating disease in those with profound CD4+ T cell deficiency.

But not everyone with serious T cell deficiency develops cryptococcosis, and there is currently no way of knowing which patients will develop disease. Pirofski says a test that could distinguish who is most at risk has the potential to save countless lives, particularly in sub-Saharan Africa, which is home to 69% of all people living with HIV.

"This could be the beginning of a predictive test, at least in high-risk people" says Pirofski. "I think that we're ready to study this receptor further as a risk factor for disease in larger cohorts."

Provided by American Society for Microbiology