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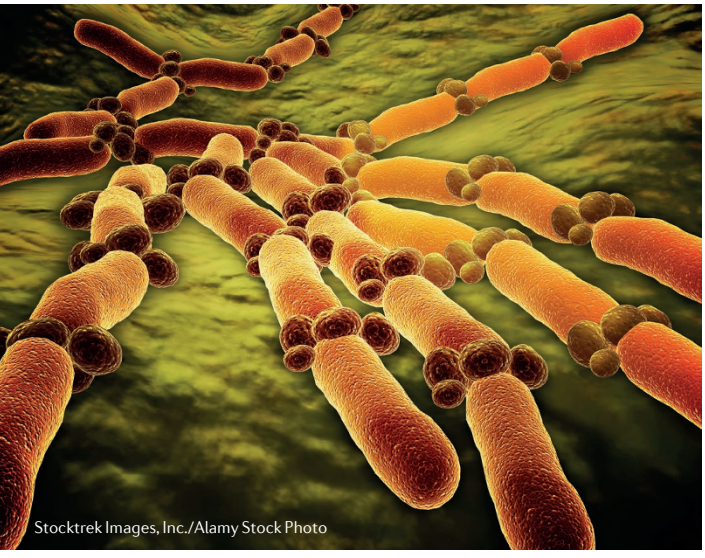
ANTIFUNGALS

JNK inhibitors boost antifungal immunity

Invasive fungal infections, particularly with *Candida albicans*, kill approximately 1.5 million people worldwide a year. Current drugs are relatively toxic and fungal resistance is high, so there is an urgent need for new therapeutics. Now, reporting in *Nature Medicine*, Zhao, Lin and colleagues show that JUN amino-terminal kinase 1 (JNK1) acts as a negative regulator of CD23 (also known as immunoglobulin-ε Fc receptor), which is a novel C-type lectin receptor, and demonstrate that CD23 has a key role in antifungal immunity. Treatment with JNK inhibitors significantly improved survival rates in mice infected with *C. albicans*.

> “Treatment with two different JNK inhibitors … significantly increased survival after *C. albicans* infection”



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JNK1 and JNK2 are known to have important roles in T cell activation and T helper cell differentiation, apoptosis, insulin resistance and cancer, which has led to the development of numerous inhibitors. JNK1 and JNK2 are also known to be activated by pattern recognition receptors on innate immune cells; however, the functional role of JNKs in innate immunity has not been well characterized.

The authors now show that JNK1 and JNK2 are phosphorylated in response to stimulation of bone marrow-derived macrophages (BMDMs) with *C. albicans* and also show that *Jnk1*$^{-/-}$ mice infected with *C. albicans* have significantly higher survival rates than *Jnk2*$^{-/-}$ or wild-type (WT) mice. This protective effect was still evident in WT mice that were reconstituted with bone marrow derived from *Jnk1*$^{-/-}$ or *Jnk1*$^{-/-}$*Rag1*$^{-/-}$ mice — which lack B and T cells — indicating that JNK1-deficient innate immune cells mediate the antifungal activity.

The protective effect of JNK1 deficiency did not seem to be due to differences in proinflammatory cytokine expression. Instead, RNA-sequencing analysis of *C. albicans*-stimulated BMDMs revealed elevated expression levels of *Fcer2a*, the gene encoding CD23, in JNK1-deficient cells. CD23 had previously been shown to induce nitric oxide synthase (NOS) activity in monocytes in response to bacterial infection, leading to the production of nitric oxide and killing of the bacteria. Similarly, the *Jnk1*$^{-/-}$ BMDMs were found to produce more nitric oxide in a CD23-dependent manner than WT when exposed to *C. albicans*, and cellular binding assays showed that CD23 directly binds to the fungal cell wall components α-mannan and β-glucan. Treatment with a CD23-blocking peptide or with inhibitors of inducible NOS abrogated the protective effect of JNK deficiency in *C. albicans* infection.

Experiments in T cells had previously linked JNK deficiency to elevated activation of nuclear factor of activated T cells (NFAT) and had shown that NFAT can directly upregulate the expression of *Fcer2a*. Likewise, *C. albicans*-infected *Jnk1*$^{-/-}$ BMDMs had higher levels of activated nuclear NFAT than WT BMDMs, and NFAT was found to bind directly to the *Fcer2a* promoter. Interestingly, in WT BMDMs, both JNK phosphorylation and NFAT activation were dependent on the binding of *C. albicans* cell wall components to the C-type lectin receptor dectin 1 (also known as CLEC7A), implying that JNK1 signalling negatively regulates NFAT activation via dectin 1, thereby limiting CD23 expression and nitric oxide production.

The therapeutic relevance of these findings was confirmed in mouse models showing that treatment with two different JNK inhibitors — SP600125 and JNK-IN-8 — significantly increased survival after *C. albicans* infection. Likewise, a human monocytic cell line and human peripheral blood-derived monocytes killed *C. albicans* more efficiently when treated with JNK inhibitors, indicating that JNK inhibition may be a novel therapeutic strategy to protect from lethal *C. albicans* sepsis.

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ORIGINAL ARTICLE(S) Zhao, X. *et al.* JNK1 negatively controls antifungal innate immunity by suppressing CD23 expression. *Nat. Med.* http://dx.doi.org/10.1038/nm.4260 (2017)