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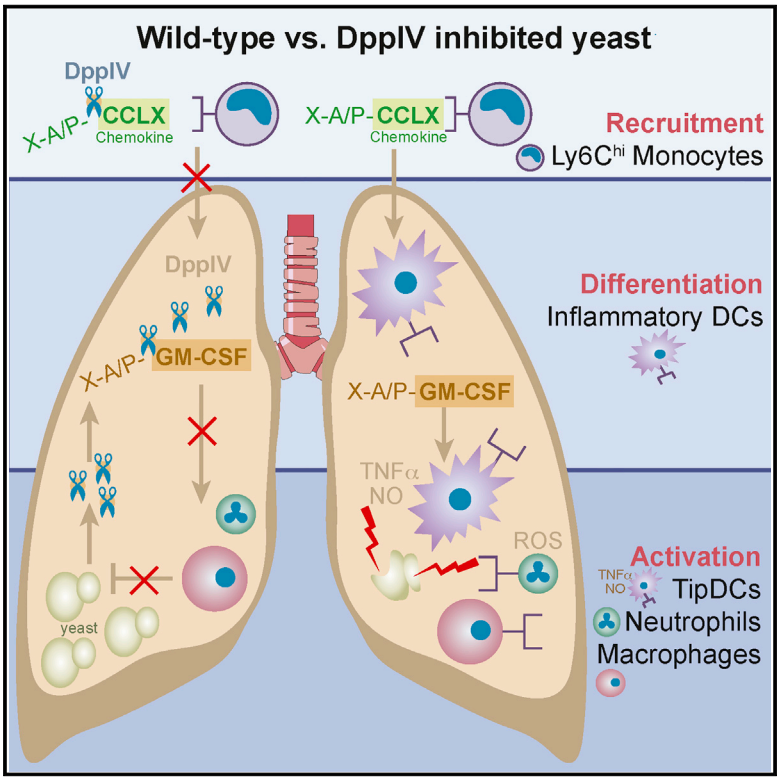
# Fungal Mimicry of a Mammalian Aminopeptidase Disables Innate Immunity and Promotes Pathogenicity

## Graphical Abstract




## Highlights

- A fungal protease, DppIVA, cleaves and inactivates host cytokines and chemokines
- Fungal DppIVA blunts recruitment, differentiation, and activation of Ly6c$^{hi}$ monocytes
- Fungal protease cleavage of GM-CSF tempers activation of a variety of leukocytes
- An FDA-approved inhibitor of DppIV ameliorates progressive fungal lung infection

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## In Brief

Mammalian proteases regulate the immune response by altering the activity of cytokines and chemokines. Here, Sterkel, Lorenzini, and colleagues identify a fungal protease that promotes virulence and suppresses innate immunity to infection by mimicking the immune-modulatory activity of its mammalian counterpart.

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# Fungal Mimicry of a Mammalian Aminopeptidase Disables Innate Immunity and Promotes Pathogenicity

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## SUMMARY

**Systemic fungal infections trigger marked immune-regulatory disturbances, but the mechanisms are poorly understood. We report that the pathogenic yeast of *Blastomyces dermatitidis* elaborates dipeptidyl-peptidase IVA (DppIVA), a close mimic of the mammalian ectopeptidase CD26, which modulates critical aspects of hematopoiesis. We show that, like the mammalian enzyme, fungal DppIVA cleaved C-C chemokines and GM-CSF. Yeast producing DppIVA crippled the recruitment and differentiation of monocytes and prevented phagocyte activation and ROS production. Silencing fungal *DppIVA* gene expression curtailed virulence and restored recruitment of CCR2$^{+}$ monocytes, generation of TipDC, and phagocyte killing of yeast. Pharmacological blockade of DppIVA restored leukocyte effector functions and stemmed infection, while addition of recombinant DppIVA to gene-silenced yeast enabled them to evade leukocyte defense. Thus, fungal DppIVA mediates immune-regulatory disturbances that underlie invasive fungal disease. These findings reveal a form of molecular piracy by a broadly conserved aminopeptidase during disease pathogenesis.**

## INTRODUCTION

Pathogenic fungi have been dubbed the hidden killers due to the mounting rates of fungal infections. Immune-compromised patients such as those with AIDS, organ transplants, and cancer and chemotherapy are among those at risk of serious fungal infections. The endemic dimorphic fungi are primary pathogens that collectively account for nearly one million systemic infections annually in North America (Pfaller and Diekema, 2010). These agents infect previously healthy individuals but can also reactivate from a latent state when immunity is impaired. Among these systemic mycoses, the proportion of immune-competent persons with symptomatic illness varies according to pathogen. At one end of the spectrum, about 50% become overtly ill after infection with *Blastomyces dermatitidis* (Klein et al., 1986), whereas about 10% manifest clinically significant illness with *Histoplasma capsulatum* (Ward et al., 1979). The high ratio of illness to infection and the potential severity of disease underscore the pathogenic and immune-evasive potential of dimorphic fungi and make them challenging pathogens from a clinical vantage point.

Several factors have been linked to virulence in dimorphic fungi (Rappleye and Goldman, 2008). Some include calcium binding protein (CBP) and superoxide dismutase (SOD) in *H. capsulatum*, glucan synthase in *Coccidioides* sp., α-1,3-glucan and Drk1 (dimorphism-regulating kinase) in several members, and *Blastomyces* adhesin-1 (BAD-1) in *B. dermatitidis*. Immune dysregulation is a hallmark of infections with dimorphic fungi, but there is limited insight about how fungal factors subvert immunity. SOD protects *Histoplasma* from oxidative stress (Youseff et al., 2012), and surface α-1,3-glucan shields this fungus from recognition by dectin-1 (Rappleye et al., 2007). BAD-1 has multiple functions: it mediates binding of *Blastomyces* to macrophages and lung tissue, modulates expression of host TNF-α and TGF-β, binds calcium and other divalent cations, and impairs T cell activation and function by engaging heparin sulfate modifications of surface CD47 (Brandhorst et al., 2013).

Failure of vaccination at the lung mucosa reveals features of immune dysregulation induced by dimorphic fungi. An attenuated, BAD-1 deletion strain of *B. dermatitidis*, which protects against lethal experimental blastomycosis when given subcutaneously, fails to protect when given via the respiratory route (Wüthrich et al., 2012). Vaccine delivery at the respiratory mucosa induces a host immune regulatory circuit, which hampers the recruitment of Ly6C$^{hi}$ monocytes into the lungs and undermines the priming of antigen-specific CD4$^{+}$ T cells within this compartment.

Ly6C$^{hi}$ monocytes recruited to sites of inflammation play a key role in the control of infections due to bacteria (e.g., *Listeria monocytogenes*), parasites (e.g., *Toxoplasma gondii*), and fungi (e.g., *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *H. capsulatum*) (Serbina et al., 2003, 2008). Upon arrival in tissue, Ly6C$^{hi}$ inflammatory monocytes have the ability to differentiate into macrophage and inflammatory dendritic cells (DCs),