The Pro-Angiogenic Growth Factor, FGF-2, as a Host-Response Against Invasive Fungal Infections

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Objectives:

Angioinvasion and tissue injury are hallmarks of infections mediated by *Mucor circinelloides* (mucormycosis) and *Candida albicans* (systemic candidiasis). Several studies have shown that pro-angiogenic Fibroblast Growth Factor-2 (FGF-2) is essential for tissue repair. Recently, studies have shown that FGF-2 treatment increased survival rates of murine models of aspergillosis. However, the role of FGF-2 and its regulated angiogenesis is understudied in systemic candidiasis and mucormycosis infections. *C. albicans* is a dimorphic fungus that exhibits yeast and hyphae morphologies. Our lab was able to generate an *M. circinelloides* mutant that exhibits yeast morphology in most conditions. We have previously shown that immune cells such as macrophages and lymphoblastoid cell lines overexpress FGF-2 when challenged with either *C. albicans* or *M. circinelloides* hyphae, but not yeast. The main objective of the current study is to determine if the FGF-2 response from a non-immune cell line, Human Umbilical Vein Endothelial Cells (HUVECs) is specific to hyphae form of fungal pathogens. Our second goal is to identify the fungal factors that affect host FGF-2 expression.

Methods:

HUVEC cells were challenged with either *C. albicans* or *M. circinelloides* yeast or hyphae strains for 24 hours. PBS was used as a mock control. The supernatants were collected to perform FGF-2 ELISA. To determine if live hyphae are essential for FGF-2 expression, we compared FGF-2 expression in HUVECs by challenging them with either live, heat-killed or PFA treated *C. albicans* or *M. circinelloides* hyphae. To determine if secreted or released factors from fungi are linked with host FGF-2 overexpression, we have grown the fungal pathogens overnight in tissue culture medium, and then we used the spent medium to infect HUVECs.

Results:

Our results show that HUVECs challenged with *C. albicans* or *M. circinelloides* hyphae show a significant increase in FGF-2 expression when compared to their yeast counterparts. Unlike *M. circinelloides*, only viable *C. albicans* hyphae is linked with increase in FGF-2 response. We also found that *C. albicans* strains deficient in candidalysin cannot increase host FGF-2 expression. Our data also show that secreted factors from *M. circinelloides* hyphae, but not yeast causes an increase in host FGF-2 expression. We also found that cell damage is significantly reduced in monocultures pre-treated with FGF-2 nAb followed by challenge with *M. circinelloides*

Conclusion:

Host FGF-2 response is specific to hyphae form of fungal pathogens. Our results suggest that secretion of candidalysin by *C. albicans* hyphae into host cells is essential to provoke an FGF-2 response. Hyphae specific factors from *M. circinelloides* can increase host FGF-2 response. Our future studies will focus on determining the role of FGF-2 in murine models of candidiasis and mucormycosis.

Increase in host FGF-2 response is specific to hyphae form of *C. albicans*

Only viable *C. albicans* hyphae is linked with increase in FGF-2 response

Candidalysin is linked with increase in FGF-2 expression

Increase in host FGF-2 response is specific to hyphae form of *Mucor*

Secreted/released proteins from *Mucor* is linked with FGF-2 expression

Blocking of FGF-2 resulted in lower cell damage by *Mucor*