Aspergillus fumigatus inhibits angiogenesis through the production of gliotoxin and other secondary metabolites

Ronen Ben-Ami, Russell E. Lewis, Konstantinos Leventakos, and Dimitrios P. Kontoyiannis

Asbtract

In susceptible hosts, angioinvasion by *Aspergillus fumigatus* triggers thrombosis, hypoxia, and proinflammatory cytokine release, all of which are stimuli for angiogenesis. We sought to determine whether *A fumigatus* directly modulates angiogenesis. *A fumigatus* culture filtrates profoundly inhibited the differentiation, migration, and capillary tube formation of human umbilical vein endothelial cells in vitro. To measure angiogenesis at the site of infection, we devised an in vivo Matrigel assay in cyclophosphamidetreated BALB/c mice with cutaneous invasive aspergillosis. Angiogenesis was significantly suppressed in Matrigel plugs implanted in *A fumigatus*–infected mice compared with plugs from uninfected control mice. The antiangiogenic effect of *A fumigatus* was completely abolished by deletion of the global regulator of secondary metabolism, *laeA*, and to a lesser extent by deletion of *gliP*, which controls gliotoxin production. Moreover, pure gliotoxin potently inhibited angiogenesis in vitro in a dose-dependent manner. Finally, overexpression of multiple angiogenesis mediator–encoding genes was observed in the lungs of cortisone-treated mice during early invasive aspergillosis, whereas gene expression returned rapidly to baseline levels in cyclophosphamide/cortisone-treated mice. Taken together, these results indicate that suppression of angiogenesis by *Afumigatus* both in vitro and in a neutropenic mouse model is mediated through secondary metabolite production.

Blood, 17 December 2009, Volume 114, Number 26