Enhancing Angiogenesis in Invasive Aspergillosis: A Novel Therapeutic Approach

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(See the major article by Ben-Ami et al on pages 1066–74.)

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Invasive aspergillosis is one of the most devastating opportunistic infections in immunocompromised hosts, such as those with hematologic malignancies and those undergoing hematologic cell transplantation (HCT). Despite the recent availability of potent antifungal agents, mortality rates remain unacceptably high for invasive aspergillosis in these 2 patient groups, at 42% and 58%–72%, respectively [1–3]. One of the reasons for this lack of improvement in outcomes with current therapeutic regimens may lie in the pathogenesis of invasive aspergillosis.

The major risk factors for invasive aspergillosis are neutropenia (ie, chemotherapy-induced neutropenia in patients with hematologic malignancies and HCT recipients in the early, preengraftment phase) and corticosteroid treatment (ie, for graft-versus-host disease during the postengraftment phase of HCT). The immunosuppression induced by these agents and the resulting pathogenesis of invasive aspergillosis may differ between these 2 immunosuppressive states.

Aspergillus conidia are inhaled through the sinopulmonary tract and land in the pulmonary alveoli. In the immunocompetent host, the first lines of defense are the alveolar macrophage and the neutrophil. If the patient is immunosuppressed, either with cytotoxic agents (inducing neutropenia) or corticosteroids (impairing macrophage function), conidia survive and go on to germinate into hyphae. These hyphae then proceed to invade the alveolar endothelial cells and extend into the pulmonary arterioles, the final act of angioinvasion. Penetration of endothelial cells results in endothelial cell damage, proinflammatory cytokine release, activation of the coagulation cascade, and intravascular coagulation [4]. These events, in turn, lead to tissue hypoperfusion and tissue necrosis. Intravascular coagulation, tissue hypoperfusion, and necrosis lead to an ideal state for the survival and progression of Aspergillus hyphae, a sequenced infection in a privileged site without access to fungicidal macrophages or neutrophils or antifungal agents. There are differences, however, between the responses in neutropenic and corticosteroid-treated hosts. While the pulmonary lesions in neutropenic patients consist predominantly of angioinvasion and intravascular hemorrhage, the lesions in corticosteroid-treated patients consist mainly of neutrophilic and monocytic infiltrates and inflammatory necrosis [5]. Thus, although the result, tissue necrosis, is the same in both types of immunosuppression, the mechanisms, coagulative vs inflammatory necrosis, differ.

Angiogenesis, the formation of new blood vessels from existing blood vessels, is a physiologic response to tissue inflammation and ischemia [6]. Thus, it is not surprising that Aspergillus infection induces angiogenesis. It was demonstrated that Aspergillus fumigatus hyphae stimulate the production of the proangiogenic cytokines tumor necrosis factor α (TNF-α) and interleukin 8 (IL-8) by endothelial cells [7] and that these are potent inducers of proangiogenic signaling pathways involving vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) [8]. A. fumigatus, however, produces many metabolites, including fumagillin and gliotoxin, that demonstrate antiangiogenic activity [9–12]. Thus, to determine the balance between proangiogenic and antiangiogenic factors in invasive aspergillosis, Ben-Ami et al [13] studied angiogenesis in a neutropenic model of cutaneous invasive aspergillosis. They noted that angiogenesis was suppressed by Aspergillus-infected mice, when compared to uninfected mice. The antiangiogenic effect was completely abolished.
by the deletion of laeA, which is the global regulator of secondary metabolism, and of gliP, which controls gliotoxin production. Gliotoxin, itself, inhibited angiogenesis. Downregulation of host genes encoding for important mediators of angiogenesis, such as bFGF, VEGF, and their receptors, occurred within 24 hours of infection in cyclophosphamide/cortisone-treated (neutropenic) mice but not corticosteroid-suppressed (nonneutropenic) mice [13]. It was hypothesized that, in the neutropenic host, the compensatory angiogenic response is attenuated by Aspergillus, leading to further hypoxia; necrosis, resulting in decreased migration of effector cells and antifungal agents; and unsuccessful outcomes. It was suggested that repletion of the repressed production of proangiogenic growth factors (eg, bFGF and VEGF) might overcome the antiangiogenic effect of Aspergillus infection, at least in neutropenic patients.

In this issue of the Journal, Ben-Ami et al [14] take their interesting findings a logical step further in testing whether, in a neutropenic model of infection, the proangiogenic growth factors bFGF and VEGF, alone or in combination with amphotericin B, reverse angiogenesis inhibition at the site of Aspergillus infection and improve survival rates. They used an in vivo Matrigel assay to measure angiogenesis in cutaneous aspergillosis in cyclophosphamide-treated mice. In their neutropenic model of invasive aspergillosis in mice, animals were immunosuppressed with 2 doses of cyclophosphamide on days 4 and 1 before challenge and with 1 dose of cortisone acetate on day 1 before challenge. They report that amphotericin B monotherapy was not effective at reducing the mortality rate or tissue fungal burden. However, treatment with recombinant human VEGF (rh-VEGF), recombinant human bFGF (rh-bFGF), or both prolonged the survival duration. rh-bFGF had a greater effect on survival than rh-VEGF and, in addition, significantly reduced the tissue fungal burden. rh-bFGF and rh-VEGF potentiated the in vivo activity of amphotericin B, leading to significantly improved survival rates and to lower pulmonary fungal burdens in mice receiving the rh-bFGF/AmB combination. The vasculocentric “sunburst” formations were absent in treated mice, suggesting that therapy prevented vascular spread of infection. Finally, it was noted that, although these mice were systemically neutropenic, the bFGF/amphotericin B–treated mice had lungs showing neutrophilic infiltrates in infected tissues that the authors suggested might be responsible for improved outcomes.

Ben-Ami et al [14] have noted recent discoveries regarding the pathogenesis and pathophysiology of invasive aspergillosis and angiogenesis. They suggest the following scenario: Aspergillus, in its own survival interests, prefers to promote angioinvasion resulting in thrombosis and necrosis, which is the perfect milieu for survival and proliferation, and angiogenesis would be the natural human compensatory response to this Aspergillus–induced inflammation, infarction, and necrosis. This would also promote chemotaxis of effector cells and drug delivery to the site of infection. Counteracting Aspergillus’ suppression of angiogenesis and enhancing angiogenesis via administration of growth factors is a unique and exciting approach. However, there may be a few bumps in the road toward the realization of this clinical goal.

The idea of enhancing a general, broad physiologic response such as angiogenesis is fraught with potential consequences. Proangiogenic growth factors might be useful in diseases such as stroke, myocardial infarction, and diabetic foot ulcers, and inhibitors of angiogenesis might useful in diseases such as solid tumors and hematologic malignancies. But the promise shown in animal studies of these factors has not always translated to clinical success. For example, the use of recombinant bFGF in animals with acute ischemic stroke was shown to reduce volume and promote functional recovery and new synapse formation, but subsequent clinical studies failed to show superiority of bFGF over placebo when given 6 hours from stroke onset, owing to hypotension and increased mortality rates [15].

As alluded to by Ben Ami et al, the major concern is that the intended target population with invasive aspergillosis consists primarily of individuals with hematologic malignancies and those undergoing HCT for hematologic malignancies. Markers for angiogenesis correlate with poor prognosis in acute leukemias, myelodysplastic syndrome, multiple myeloma, and lymphomas [16], and promotion of angiogenesis in this population is fraught with danger. Conversely, antiangiogenic therapy research is well underway. Also, bFGF and VEGF probably play roles in other human physiologic responses and pathways that we are not aware of yet.

Another possible problem is the timing of the administration of these growth factors. Presumably, they would be given only after a diagnosis of invasive aspergillosis is made or highly suspected. In the mouse model used in the current study, the growth factors were administered 3 hours after challenge with conidia. This timing is probably before the development of any pulmonary lesions and would not likely occur in a patient with developing invasive aspergillosis in “real time.” The angiogenesis or neovascularization probably occurred before there was much necrosis in the mouse model. Clinically, once there is significant necrosis present, the only way to obtain a cure is to surgically resect the necrotic lesion.

Finally, administration of these growth factors is only anticipated to work in neutropenic patients with invasive aspergillosis. But, possibly a more important population to target is allogeneic hematologic cell transplant recipients being treated with high doses of corticosteroids for prolonged periods for graft-versus-host disease.

Despite these potential problems, Ben-Ami et al [14] should be congratulated for their elegant work on the enhancement of angiogenesis in invasive aspergillosis;
for their understanding of the way that the human host responds to invasive infection and their attempt to enhance this response; and for leading us to novel approaches to a most devastating infection in our most defenseless of patients.

Note

**Potential conflict of interest.** Author certifies no potential conflict of interest.

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References


