Angiogenesis at the mold-host interface: a potential key to understanding and treating invasive aspergillosis

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sent on both sides. A large infarct was found in the right upper lobe and a smaller infarct in the middle lobe; the pulmonary arteries to these areas showed thrombosis. In eosinophils could be seen. Branching mycelium was present throughout the necrotic zone, invading the inflammatory zone and large and small vessels at the edge. The left

“It seemed to have a marked predilection for the blood vessels”
The microenvironment in invasive aspergillosis: angioinvasion, inflammation, and tissue hypoxia.
The site of invasive aspergillosis is an hypoxic environment

<table>
<thead>
<tr>
<th>Immunosuppression</th>
<th>Day 3</th>
<th>Day 3.5</th>
<th>Day 4</th>
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<tbody>
<tr>
<td>Triamcinolone</td>
<td>![Image]</td>
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<td>Chemotherapy</td>
<td>![Image]</td>
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</tr>
</tbody>
</table>

Hypoxyprobe = orange

Grahl et al. PLoS Pathog 2011
Aspergillus: adaptation to hypoxia requires a sterol regulatory element binding protein

- Sterol regulatory element-binding protein (SrbA) is required for growth in hypoxic conditions
- ΔSrbA essentially avirulent in neutropenic mice
- SrbAp also affects azole resistance and hyphal morphology
- Adaptation to hypoxia is a virulence requirement

Willger et al., PLoS pathog 2008
The host: angiogenesis is an adaptive response to hypoxia and inflammation

Carmeliet et al. Nature 2011

HIF
VEGF
FGF
NOTCH
ANG-2
Semaphorins
Integrins
Oxygen sensing in host cells: HIF/NFkB pathway essential for neutrophil survival and angiogenesis

HIF 1α transcription factor

DNA

TNF α

NF κB

GT

Oxygen

PHD

-ΟΗ

Ub

FLT1

bFGF

VEGF

Angiogenesis

Neutrophil survival

Walmsley et al., JEM 2005
The angiogenesis tipping point: equilibrium between pro- and anti-angiogenic signals?

Fungal secondary metabolites

Hypoxia (HIF)

Proinflammatory cytokines
TNFα, IL-1

Angiogenesis

VEGF
bFGF
Aspergillus fumigatus culture filtrates inhibit angiogenesis in vitro

Ben-Ami et al. Blood 2009
Suppression of angiogenesis is dependent on secondary metabolism

**P < 0.001

Ben-Ami et al. Blood 2009
Cutaneous murine aspergillosis as a model to monitor angiogenesis at the site of infection.
Angiogenesis is suppressed in animal model of cutaneous aspergillosis

**Ben-Ami et al. Blood 2009**
Gliotoxin is responsible for part of culture filtrate-induced angiogenesis inhibition

Ben-Ami et al. Blood 2009
Gliotoxin suppresses angiogenesis at concentrations measured in pulmonary tissue

Lewis et al. *Infect Immun* 2005
Ben-Ami et al. *Blood* 2009

*P<0.01
**P<0.001
Expression of angiogenesis-relevant genes during the initial 24 h of IPA depends on method of immunosuppression

Ben-Ami et al. Blood 2009
The pro/anti angiogenic equilibrium: a potential therapeutic target?

Chemotherapy → Angiogenesis → Proinflammatory cytokines

Hypoxia → Angiogenesis → Gliotoxin

Steroids

VEGF, bFGF

Fungal secondary metabolites: Gliotoxin
Invasive pulmonary aspergillosis

- Pathogen (A. fumigatus)
- Immune Response
- NF-κB
- GT
- Antifungal Drug
- Vasculopathy