Identifying Host-directed Therapies for TB

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Tuberculosis still kills 1.8 million people annually. 35% of all HIV deaths were due to TB (2015, WHO)

Robert Koch, 1882

Metchnikoff, 1888

HIV Co-infection
**Mycobacterium tuberculosis** pathogenesis

**Stage I**
- Alveolar macrophage
- Ingested tubercle bacillus
- Alveolar lumen
- Alveolar wall
- Capillary

**Stage II**
- Infiltrating macrophage
- Tubercle

**Stage III**
- Unactivated Macrophage
- Partially Activated Macrophage
- Caseous Center
- Intact and Fragmented Bacilli

Dannenberg, 1993
Mycobacterium marinum infection of zebrafish recapitulates many aspects of TB pathogenesis
Granulomas are highly-organized structures
Conserved granuloma features in humans

Multi-drug resistant *Mycobacterium tuberculosis*, lymph node biopsy

Jason Stout, Duke Infectious Diseases

Cronan et al. *Immunity* 2016
Tuberculous granulomas in humans associate with vasculature


Is this analogous to tumor angiogenesis? What are the consequences of neovascularization? Can we examine this process in zebrafish?
Stereotypical zebrafish vasculature

8 dpf Tg(kdr:egfp)

Dorsal aorta
Cardinal vein
Dorsal longitudinal anastomotic vessel
Intersegmental vessels
Mycobacterial granulomas induce angiogenesis within days

*Endothelial cells flk1:egfp*

*Mycobacterium marinum-tomato*
Live imaging of granuloma-associated angiogenesis

What are the host signals driving angiogenesis and what is their cellular source?
Vegfa is highly expressed by granuloma macrophages in fish

Oehlers et al. *Nature* 2015
Human TB granulomas: macrophage induction of VEGFA

Datta et al. PNAS 2015
Small molecule inhibition of VEGFR signaling limits granuloma-associated angiogenesis.
Small molecule VEGFR inhibitors decrease burden, improve outcome in established infections

Oehlers et al. *Nature* 2015
Summary

• Mycobacteria promote pathogenic angiogenesis during granuloma formation through specific lipid modifications

• Inhibition of VEGFR signaling limits mycobacterial disease
  – Reduces burden
  – Reduces dissemination
  – Enhances antitubercular drug efficacy

• Understanding of host-pathogen biology suggests potential for host-directed therapies
Counteracting Ang-2 reduces vascular leakiness and bacterial burden

Oehlers et al. J Infect Dis 2017
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