Interception of host angiogenic signaling limits mycobacterial growth

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Pathogenic mycobacteria induce the formation of complex cellular aggregates called granulomas that are the hallmark of tuberculosis. Here we examine the development and consequences of vascularization of the tuberculous granuloma in the zebrafish-Mycobacterium marinum infection model characterized by organised granulomas with necrotic cores that bear striking resemblance to those of human tuberculosis. Using intravital microscopy in the transparent larval zebrafish, we show that granuloma formation is intimately associated with angiogenesis. The initiation of angiogenesis in turn coincides with the generation of local hypoxia and transcriptional induction of the canonical pro-angiogenic molecule VEGFA. Pharmacological inhibition of the VEGF pathway suppresses granuloma-associated angiogenesis, reduces infection burden and limits dissemination. Moreover, anti-angiogenic therapies synergize with the first-line anti-tubercular antibiotic rifampicin as well as with the antibiotic metronidazole, which targets hypoxic bacterial populations. Our data suggest that mycobacteria induce granuloma-associated angiogenesis, which promotes mycobacterial growth and increases spread of infection to new tissue sites. We propose the use of anti-angiogenic agents, now being used in cancer regimens, as a host-targeting TB therapy, particularly in extensively drug-resistant disease where current antibiotic regimens are largely ineffective.