Serine protease activity contributes to control of Mycobacterium tuberculosis in hypoxic lung granulomas in mice.

Abstract:
The hallmark of human Mycobacterium tuberculosis infection is the presence of lung granulomas. Lung granulomas can have different phenotypes, with caseous necrosis and hypoxia present within these structures during active tuberculosis. Production of NO by the inducible host enzyme NOS2 is a key antimycobacterial defense mechanism that requires oxygen as a substrate; it is therefore likely to perform inefficiently in hypoxic regions of granulomas in which M. tuberculosis persists. Here we have used Nos2-/- mice to investigate host-protective mechanisms within hypoxic granulomas and identified a role for host serine proteases in hypoxic granulomas in determining outcome of disease. Nos2-/- mice reproduced human-like granulomas in the lung when infected with M. tuberculosis in the ear dermis. The granulomas were hypoxic and contained large amounts of the serine protease cathepsin G and clade B serine protease inhibitors (serpins). Extrinsic inhibition of serine protease activity in vivo resulted in distorted granuloma structure, extensive hypoxia, and increased bacterial growth in this model. These data suggest that serine protease activity acts as a protective mechanism within hypoxic regions of lung granulomas and present a potential new strategy for the treatment of tuberculosis.