MOLECULAR CHARACTERIZATION OF GRANULOMATOUS LESIONS IN PRIMATES INFECTED WITH MYCOBACTERIUM TUBERCULOSIS.

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Tuberculosis (TB) is a major infectious disease killer of humans. The advent of drug-resistant strains of M. tuberculosis (Mtb), synergy between AIDS and TB, and the failure of the anti-TB vaccination, have all conspired to aggravate the global TB pandemic. The long-term control of TB requires the development of efficacious vaccines. In turn, this requires a complete understanding of the bacterial mediators of virulence and host mediators of protection.

Mouse, guinea-pig and rabbit models of TB have all contributed to our understanding of TB. However, it is accepted that nonhuman primates best represent critical aspects of human TB. Macaques experimentally infected with Mtb generate various clinical outcomes depending on the inoculum, and present the complete spectrum of pathological lesions that are observed in human lungs during natural infection. Unlike mice, primate granulomas exhibit highly ordered architecture, mostly with central caseous necrosis surrounded by a peripheral rim of fibrosis. Such lesions are thought to be critical for containing Mtb replication, and conversely, permitting the latent survival program of the pathogen.

Using our aerosol-infection based nonhuman primate model of TB, we characterized the lung granuloma’s of primates with active TB, at an early, and a late stage of infection. We show that the host mounts a massively inflammatory Th1-type immune response to aerosol Mtb infection. This is characterized by the recruitment of highly activated CD4+ lymphocytes and macrophages to the lungs, and expression of interferon, TNF, cytokine and chemokine signaling pathways, four weeks post-infection (p-i). However, by week 13 p-i, the inflammatory response is largely silenced, even though the primates continue to exhibit clinical signs of active TB. Instead, these lesions are characterized by a Th2-type response with high levels of expression of TGFβ and SOCS molecules. The possible role of microRNA’s in modulating this response will be discussed.

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