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Mycobacterial manipulation of the host innate immune response

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Abstract

Tuberculosis remains a major threat to global public health accounting for nearly two million deaths worldwide each year. The primary target cells for *Mycobacterium tuberculosis* (MTB) are phagocytic cells of the lung. Mycobacteria employ a number of strategies to circumvent host responses and we report novel interactions between the bacterium and human macrophages and dendritic cells that also influence the immune response. Human macrophages produce interleukin (IL)-27 following infection by MTB. IL-27 has been shown to have immunosuppressive activity toward a number of cell types including macrophages. Neutralization of IL-27 produced during infection promotes trafficking of mycobacteria to lysosomes and control of the bacterial burden in human macrophages. The mechanism involves increased protein levels and/or colocalization of vacuolar ATPase (VATPase), CD63, and cathepsin D with the bacteria. In a separate body of work, we also demonstrate nitric oxide (NO) production by human macrophages during mycobacterial infection. Interestingly, the intracellular environment in macrophages that produce NO does not inhibit but rather augments growth of MTB. Mycobacterial growth in macrophages that produce NO requires a functional nitrate reductase. Following infection by MTB, dendritic cells in the lung that have become infected or internalized mycobacterial antigens migrate to regional lymph nodes to initiate an adaptive response. This process is delayed in response to MTB as compared with other bacteria. We have demonstrated that human dendritic cells infected with MTB exhibit redistribution and decreased surface expression of heterodimeric □/□ integrins that contain CD18 (□2). This decrease is not recovered in infected cells and is maintained over time. Consistent with the change in surface integrins we report a significant decrease in adherence to primary lung lymphatic endothelial cells and migration through an endothelial monolayer toward lymphatic chemokines. Cumulatively, we have identified novel interactions between mycobacteria and host innate immune cells that provide additional insight into bacterial strategies to persist in the human host. Measures aimed at modulating expression of IL-27 and overcoming the MTB-mediated inhibition of □2 integrin expression and migration may have important implications in vaccination and therapeutic approaches.

Biography

Cory M. Robinson completed his Ph.D in Microbiology from Miami University in 2004. This was followed by postdoctoral studies at the Uniformed Services University of the Health Sciences under the direction of Dr. Alison O'Brien and at the University of Pittsburgh School of Medicine under the direction of Jerry Nau. He is currently an Assistant Professor at the University of South Carolina School of Medicine.