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Mycobacterial manipulation of the host innate immune response

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Mycobacterium tuberculosis (Mtb) is an intracellular pathogen and causative agent of tuberculosis, which remains a major threat to global public health. *M. bovis* bacille Calmette-Guerin (BCG) is the only currently licensed vaccine for tuberculosis. Although adequate to protect against disseminated tuberculosis in children, BCG has not been consistently effective at preventing adult pulmonary tuberculosis. Thus, the effects of BCG on combating the global burden of tuberculosis have been limited. Mtb and BCG share some abilities to subvert host immune responses and suppress immunity. This includes the ability to block phagosome maturation in unstimulated macrophages by accumulating markers of early endosomes and preventing recruitment of late endosome markers. This promotes survival and proliferation within professional phagocytes, but also limits antigen processing for presentation to lymphocytes and immune surveillance by the adaptive response. Human macrophages produce interleukin (IL)-27 that has immunosuppressive activity toward a number of cell types following infection by Mtb and BCG. Blocking IL-27 produced during infection promotes the association of BCG with acidified lysosomes. This is consistent with processing of cathepsin D to the mature proteolytic form and its association with BCG-containing phagolysosomes. The blockade of IL-27 increases IFN-γ production that is required for the increase in lysosomal acidification, association with BCG, and processing of cathepsin D. We have further determined that the increase in phagolysosmal trafficking of BCG is Stat-1-dependent while the ability of IL-27 to oppose this pathway requires Stat-3. BCG also shares with Mtb the ability to impair dendritic cell (DC) migration by limiting expression of heterodimeric integrins that contain CD18 (β2). This delays initiation of an adaptive immune response and is likely to affect the efficacy of BCG vaccination. The mechanism that leads to a reduction and redistribution of CD18 at the cell surface requires the host cell receptor DC-SIGN and is augmented by IL-27. This leads to a reduction of total cellular levels of CD18 protein independent of a significant change in gene expression, impacting adherence to primary lung lymphatic endothelial cells and subsequent migration. Cumulatively, we have identified novel interactions between mycobacteria and host innate immune cells that provide additional insight into bacterial strategies to circumvent host immunity. Measures aimed at modulating expression of IL-27 may have important implications in vaccination by promoting increased antigen processing and more efficient migration of DCs to peripheral lymph nodes.

Biography

Cory M Robinson completed his PhD 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.

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