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Investigating the role of Indoleamine dioxygenase in modulating immune responses to Mycobacterium tuberculosis

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Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is a major health concern worldwide resulting in over a million deaths annually. Furthermore, the TB and HIV co-pandemic continues to be a major healthcare burden. HIV co-infection predisposes the host to TB reactivation, resulting in significant mortality. The expression of indoleamine 2,3, dioxygenase (IDO), a robust immunosuppressant, is significantly induced in macaque TB granulomas. Its expression is localized on on interferon-responsive macrophages and myeloid derived suppressor cells. IDO expression is also highly induced in the human TB granuloma, and products of its activity are detected in TB patients. In-vivo blockade of IDO activity reorganizes the macaque granuloma with significantly more T cells being recruited to the core of the lesions, correlating with better immune control of TB and reduced lung Mtb burdens1. IDO blockade concurrent with anti-TB therapy significantly reduces the progression of macaques to active TB2. Thus, D1MT is a bon-a-fide TB host directed therapy (HDT) candidate. Our recent work shows that D1MT is safe and efficacious in Mtb/SIV co-infected macaques treated with antiretroviral therapy (cART) and significantly improves immune reconstitution. We also discovered that a leading preclinical anti-TB vaccine candidate being developed by our group, □sigH induces strong IFNG-mediated T cell responses which are required for protection, by inhibiting the role of IDO. We show that T cell IFNG responses repress pDC generated Type I IFN responses, and significantly reduce the expression of IDO on IFN-responsive macrophages in the lungs of □sigH vaccinated macaques. Thus, while macrophages in the lungs of macaques with active TB are conditioned to be inflammatory, □sigH vaccination alters this conditioning and inhibits IDO expression. These results strongly implicate IDO as an immunoregulatory molecule that is expressed on recruited, inflammatory cells during TB and participates

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Conflicts of Interest

None