

INTRODUCTION: Recent resurgence of mycobacterial infections is in part due to the spread of AIDS in developing countries. Both Mycobacteria and HIV are successful pathogens in evading immunity. We previously showed they are potent inducers of interleukin-10 (IL-10) expression via their activation of protein kinase PKR and also mycobacterial inhibition of GSK3 in primary human blood macrophages [J Immunol 2005, Immunol 2007, J Leuk Biol 2009]. IL-10, a potent anti-inflammatory cytokine, in turn activates its primary mediator STAT3 to exert inhibitory effects on immunity including interferon- γ (IFN- γ) signaling leading to deactivation of macrophages and suppression of cell mediated antigen presentation. We further delineated the mechanisms in demonstrating that HIV suppresses the MHC-II molecule expression via induction of regulatory gene SOCS-2 [Blood 2009].

OBJECTIVES: It is known that during the maturation of MHC-II, a cysteine protease (cathepsin S) plays a key role in the antigen processing. We investigated whether HIV and mycobacteria-induced IL-10 activity interferes with IFN- γ -induced immune responses including MHC-II expression and pathogen recognition via its effect on cathepsin S expression in blood macrophages.

METHODS: Primary human blood-derived macrophages were first pretreated with IL-10 (10 ng/ml) for 1 h and then incubated with IFN- γ (20 ng/ml) for the indicated time course. Quantitative RT-PCR, Flow cytometry and Western analysis were performed afterwards.

RESULTS: We showed that IL-10-induced STAT3 plays a critical role in the perturbation of IFN- γ -induced antigen presentation, not merely on the protein expression of HLADR, but also by suppressing cathepsin S levels for the MHCII presenting process. Additionally, we revealed that the inhibitory effect of IL-10 was demonstrated to be independent of the classical IFN- γ -induced JAK2/STAT1 signaling cascade or the NF- κ B pathway. Following STAT3 suppression with siRNA, the expression of IFN- γ -induced surface MHC-II antigens and cathepsin S levels was restored, even in the presence of IL-10.

CONCLUSION: Our results demonstrated that the immunosuppressive effects of IL-10-induced STAT3 on MHC-II antigen presentation may occur via the inhibition of cathepsin S expression. These results provide additional insights into the mechanisms of mycobacterial evasion of immunity.