Immunomodulatory Effects of Human Immunodeficiency Virus (HIV-1) on Dendritic Cell and T cell Responses

Studies of HIV-1 effects on Dendritic cell functionality reflected in primed T cells

Akademisk avhandling
som för avläggande av Medicine Doktorsexamen vid Hälsouniversitet, Linköpings universitet, öfentligen kommer att försvaras i Eken, ingång 65, Campus US, Universitetssjukhuset i Linköping.
Fredag den 2 september 2011 Kl 9:00

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ABSTRACT

The human immunodeficiency virus (HIV)-1 is the causative agent of acquired immune deficiency syndrome (AIDS) worldwide. Till date there are no vaccines or cure for this infection as the virus has adapted myriad ways to remain persistent in the host where it causes severe damage to the immune system. Both humoral and cellular immune responses are mounted against HIV-1 during the initial phase of infection but fail to control viral replication as these responses are severely depleted during disease progression. Of great importance in HIV-1 research today is the in depth understanding of the types of immune responses elicited, the mechanisms behind their decline and how these responses can be maintained overtime.

The focus of this thesis was to examine the possibility of priming HIV-1 specific T cell responses in vitro from whole viral particles and in detail, scrutinize the type of T cell responses and epitope specificities generated. Next was to investigate in vitro the factors responsible for impaired immune responses in HIV-1 infected individuals. We were also interested in understanding the underlying mechanisms through which HIV-1 initiate suppression of T cell functionality.

Results showed that using HIV-1 pulsed monocyte derived dendritic cells (DCs), we were able to prime HIV-1 specific CD4⁺ and CD8⁺ T cells from naïve T cells in vitro. The epitopes primed in vitro were located within the HIV-1 envelope, gag, and pol proteins and were confirmed ex vivo to exist in acute and chronically infected individuals. We established that many of the novel CD4⁺ T cell epitopes primed in vitro also existed in vivo in HIV-1 infected individuals during acute infection. These responses declined/disappeared early on, which is in line with HIV-1 preferential infection of HIV-1 specific CD4⁺ T cells.

Besides declining HIV-1 specific T cell responses, many HIV-1 infected individuals also have impaired T cell functionality. We established that one reason behind the decline and impairment in immune responses was the increased expression of inhibitory molecules PD-1, CTLA-4, and TRAIL on HIV-1 primed T cells. These T cells had the capacity to suppress new responses in a cell-cell contact dependent manner. The ability of the HIV-1 primed T cells to proliferate was severely impaired and this condition was reversed after a combined blockade of PD-1, CTLA-4 and TRAIL. Furthermore, more inhibitory molecules TIM-3, LAG-3, CD160, BLIMP-1, and FOXP3 were also found increased at both gene and protein levels on HIV-1 primed T cells. Additionally, we showed decreased levels of functional cytokines IL-2, IFN-