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Impact of Mycobacterium tuberculosis and HIV-1 on innate immune mechanisms

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ABSTRACT

Human immunodeficiency virus type 1 (HIV-1), a causative agent of acquired immunodeficiency syndrome (AIDS), and Mycobacterium tuberculosis (Mtb), a causative agent of tuberculosis (TB), are among the leading causes of death from infectious disease worldwide. Interplay between HIV-1 and Mtb leads to the detrimental dysregulation of immune system mechanisms, which provides the conditions facilitating progression of the disease in co-infected individuals.

In order to investigate the impact of Mtb and HIV-1 on innate immune responses we set up in vitro infection models comprising human monocyte-derived macrophages (Mφs) and dendritic cells (DCs). Firstly, we examined the influence of mycobacterial cell wall-derived glycolipids on the function of DCs. We found that two cell wall components, ManLAM and PIM, modulate DC function in an opposite manner, where ManLAM stimulates the production of pro-inflammatory cytokines, while PIM inhibits cytokine production triggered by activated DCs. Next, we analyzed several clinical Mtb isolates causing a large TB outbreak in Sweden. We found that the clinical isolates are characterized by the ability to trigger increased production of TNF from in vitro infected Mφs, above that triggered by the Mtb reference strain. Knowing that different mycobacterial glycolipids may differently impact DC and having several Mtb clinical isolates characterized, we investigated the effects of ongoing Mtb infection on the function of bystander DCs. Here we demonstrated that mycobacteria-infected Mφs create a pro-inflammatory milieu in which DCs undergo partial maturation, produce pro-inflammatory cytokines and additionally increase their ability to mediate HIV-1 trans-infection of T cells. Finally, we investigated mechanisms behind the altered cytokine response to Mtb during concurrent HIV-1 infection. We observed that the levels of cytokines released from Mtb-infected Mφs are lower after HIV-1 pre-exposure than those observed from singly Mtb-infected Mφs. Next, we measured levels of miR-146a, a microRNA known to inhibit signaling cascades leading to production of pro-inflammatory cytokines. We found that miR-146a was up-regulated upon Mtb infection and also after HIV-1 exposure, suggesting that HIV-triggered miR-146a expression may be responsible for cross-tolerance of Mφs to following Mtb infection. Furthermore, we showed that exposure to the HIV-1 envelope glycoprotein gp120 is sufficient to up-regulate miR-146a, which in turn is paralleled by down-modulated responsiveness of Mφs to a secondary stimulus, i.e. the Mtb glycolipid ManLAM.

In conclusion, this thesis highlights that several innate immune mechanisms are modulated by either HIV-1 or Mtb, which may hamper adequate immune responses against the two pathogens. These studies also suggest that the effects may be triggered in a bystander manner, where impacted cells are not infected and may be even localized distantly from the site of infection.

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