Mycobacterium tuberculosis and human immunodeficiency virus type 1 interaction: Pathogenesis and disease modulation in dual infection

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Summary

In this thesis, we have looked at the clinical and immunological impact of Mycobacterium tuberculosis (MTB) on HIV-1 infection and disease. We showed that, unlike other HIV related opportunistic infections, successful treatment of MTB disease may in some patients be associated with some degree of decrease in HIV-1 load. However this is partial, and not sustained, and does not halt the progress of HIV disease. In fact, active MTB disease is often associated with unrelenting progression of HIV to AIDS thereafter, with death often following within a couple of years without the intervention of HAART.

We looked at some mechanisms of the impact of MTB disease on HIV-1 infection, including the role of expression of cytokines, chemokines and chemokine receptors in the progression of HIV-1 disease. Here we showed that active TB up-regulates these molecules, and this may play a role in increased HIV-1 replication and load. Much as these immune responses may be beneficial in MTB control, they are deleterious with regards to HIV-1 progression. Beta-chemokines by blocking CCR5 receptors may limit HIV-1 progression; but their expression is limited in HIV-1 with active PTB, which effect may mitigate their potentially beneficial role in HIV-1/PTB.

We then investigated the impact of in vitro amelioration of HIV potentiating cytokines and chemokine receptors on the effect of HIV activity in cells from dual HIV-1 PTB subjects. In vitro, blockage of chemokine receptor was associated with a decrease in HIV-1 entry into cells, but the effect seemed variable, with better effect in macrophages than in lymphocytes among patients with PTB. This means the effect of chemokine receptor blockage may have some benefit in patients with MTB infection and disease, an area that merits further study. Lastly we studied the role of in vivo immune modulation with corticosteroids on the impact of MTB on HIV infection. The effect was transient, and the side effects a limiting factor to using high doses that are required to ameliorate the deleterious immune circuits that potentiate HIV-1 replication in MTB disease. Our studies however contribute to a better understanding of the role of corticosteroid treatment in other HIV-1 related disorders where steroid therapy may be life saving. All these studies were done before the advent of wide spread use of HAART in Africa and in Uganda in particular. Even today, with the advent of HAART, understanding the HIV-1/MTB interaction and pathogenesis is important in the management of HIV-1 patients before and during HAART. Our studies have contributed to the current policy of early HAART among...
patients with HIV infection and active tuberculosis, as well as strengthened the importance of MTB disease prevention in HIV infection with the major effect of halting HIV progression.