Tuberculosis-driven expression of CD169 (Siglec-1) and localization in tunneling nanotubes leads to exacerbation of HIV-1 infection in human macrophages

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Tuberculosis (TB) is risk factor in HIV-1+ patients. Yet, the mechanisms by which HIV-1 infection is worsened in coinfection with Mycobacterium tuberculosis (Mtb) remain poorly understood. Macrophages represent a convergent cellular target for both pathogens. Recently, we demonstrated that HIV-1 infection and spread is increased in macrophages exposed to supernatants from Mtb-infected cells (cmMTB), a condition that mimics a TB-associated microenvironment. Here, we show that these cells are characterized by an increase in the cell-surface expression of CD169 (Siglec-1), a pro-viral lectin receptor involved in HIV-1 capture and transfer. High CD169 expression is confirmed in circulating monocytes from TB/HIV co-infected patients, and also in macrophages found in lung lesions from non-human primates (NHP) co-infected with Mtb and simian immunodeficiency virus (SIV), which correlates with high lung pathological scores. Since CD169 is an IFN-stimulated gene (ISG), we determine IFN-I as the responsible component for CD169 induction, as the blocking of IFNAR2 during cmMTB treatment resulted in the abolishment of its expression. In addition, we validate the overexpression of phosphorylated STAT1 (main transcription factor in IFN-I signalling) in lung macrophages from co-infected NHP. Intriguingly, we observe CD169 localized on tunneling nanotubes (TNT), which we previously identified as cell-to-cell bridges responsible for HIV-1 spread in macrophages. Inactivation of CD169 by siRNA-mediated gene silencing approach resulted in: i) decrease TNT stability, ii) diminished viral transfer, and iii) abrogation of the exacerbation of HIV-1 infection induced by cmMTB. These results are validated in cells obtained from CD169 null individuals. Altogether, our results uncover an unexpected role for CD169 in the TB/HIV co-infection context, and open venues to better understand TNT dynamics in the infectious context.

Keywords : Tuberculosis, AIDS, HIV, mycobacterium tuberculosis, macrophages, siglec-1, CD169, tunneling nanotubes, STAT1, IFN-I, IFNAR
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