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Sustained High Levels of Circulating Galectin-9 Despite Viral Suppression Among HIV infected Elite Controllers

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Background: HIV "elite" controllers are typically defined by serial HIV RNA levels below the limit of detection in the absence of anti-retroviral therapy (ART). They represent less than 1% of the HIV population. Despite having limited HIV replication, most controllers have evidence of elevated T cell activation and chronic inflammation, and some exhibit evidence of early atherosclerosis and/or exhibit progressive CD4 T-cell depletion. Chronic exposure (over decades) to viruses like CMV is known to reshape the adaptive immune system. We hypothesized that upregulation of receptors and their ligands known to contain CD8+ T cell activation might be pathogenic in controllers. Galectin-9 is a β-galactoside binding lectin, and functions as an eosinophil chemoattractant and immunomodulator in physiological and pathological setting. Galectin-9 can induce CD4 T cell apoptosis and exerts its immunosuppressive function through engagement with the Tim-3 receptor.

Method: We measured circulating plasma Galectin-9 levels in 20 HIV-infected elite controllers, and 20 demographically-matched HIV-uninfected controls using a Galectin-9 specific ELISA and further assessed the activity of Gal-9 on T cell activity *ex vivo* using a recombinant Galectin-9 protein (rGal-9).

Result: HIV controllers had significantly elevated levels of Galectin-9 compared to uninfected controls (median 263 pg/ml; interquartile range (IQR) 209, 674 versus median 61 pg/ml; IQR 18,143; $p< 0.0001$). Controllers also had significantly higher frequencies of Tim-3^+ $CD8^+$ T cells compared to uninfected controls (median, 9.1%; IQR 6.4,14.18 versus 3.0% IQR 1.58,5.8; $p=0.0007$). *Ex vivo*, rGal-9 stimulation (5µg/ml) induced IFN-γ release by $CD8^+$ T cells (unstimulated, median 0.05% IQR 0.03,0.12 versus rGal-9, median 0.64% IQR 0.33,1.14; $p< 0.05$), from peripheral blood mononuclear cells. This was reversed by competitive blockade with α-lactose.

Conclusion: Our data suggests that Gal-9 - Tim-3 cross talk is elevated in controllers, presumably as a consequence of persistent activation of CD8+ T cells. This elevation may be harmful as it could lead to organ specific co-morbidities. Controlling HIV in these individuals with antiretroviral therapy may prevent activation of this pathway, thus avoiding some of the harmful effects of chronic inflammatory states.