Infection with HIV usually results in chronic activation of the immune system, with profound quantitative and qualitative changes in the T cell compartment. To better understand the mechanistic basis for T cell dysfunction and to discern whether such mechanisms are reversed after effective antiviral treatment, we analyzed changes in signaling pathways of human CD4(+) and CD8(+) T cells from 57 HIV-infected subjects in varying stages of disease progression and treatment, including long-term nonprogressors, progressors, and chronically infected subjects provided effective antiretroviral therapy (responders). A previously described PhosFlow method was adapted and optimized so that protein phosphorylation could be visualized in phenotypically defined subpopulations of CD4(+) and CD8(+) T cells (naive, memory, and effector) by flow cytometry. T cell signaling induced by TCR cross-linking, IL-2, or PMA/ionomycin was found to be blunted within all T cell subpopulations in those with progressive HIV disease compared with long-term nonprogressors and responders. Although alterations in cellular signaling correlated with levels of basal phosphorylation, viral load, and/or expression of programmed death-1, it was the level of basal phosphorylation that appeared to be the factor most dominantly associated with impaired signaling. Notably, provision of effective antiretroviral therapy was associated with a normalization of both basal
phosphorylation levels and T cell signaling. These data, in aggregate, suggest that generalized
dysfunction of the T cell compartment during progressive HIV disease may be in part dependent upon
an increased basal level of phosphorylation, which itself may be due to the heightened state of
immune activation found in advanced disease.

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