Neutralization of Interferon-Beta Promotes HIV-Specific CAR T-cell Engraftment and Proliferation

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HIV infection is characterized by a sustained activation of type I interferon (IFN-I) pathways, even in people with HIV (PWH) on effective antiretroviral therapy (ART). Though IFN-I signaling is mediated by several IFN species that signal through the same IFN receptor (IFNAR), interferon-beta (IFNβ) has been shown to have immunosuppressive and antiproliferative effects. Moreover, IFNβ is selectively expressed in tissue-resident monocytes in rectal biopsies sampled from ART-suppressed PWH. We hypothesize that IFNβ functions as an immunosuppressive cytokine in HIV infection with the potential to attenuate endogenous HIV-specific T cell responses as well adoptively transferred HIV-specific CAR T cells. Here, we studied the effects of chronic IFNβ exposure on CAR T cell proliferation in vitro and in vivo and devise a genetic engineering strategy to protect CAR T cells from the deleterious effects of IFNβ exposure.

IFNβ exposure increased markers of apoptosis and cell death in CAR T cells as soon as 30 minutes following exposure, both in the presence and absence of antigen sensing. Furthermore, analysis of bulk RNAseq data from CD4+ T cells exposed to IFNβ reflect elevated Fas ligand and receptor expression with significant KEGG reactome enrichment for the extrinsic apoptosis pathway. To confirm the clinical relevance of IFNβ exposure on HIV-specific CAR T cells, we adoptively transferred HIV-specific CAR T cells into HIV-infected, ART-suppressed humanized mice and treated with an IFNβ-neutralizing antibody. We observed a significant advantage in engraftment and persistence of CAR T cells in mice treated with IFNβ-neutralizing antibody over anti-IFNα2 or IgG controls. These data support a negative regulatory role for IFNβ in ART-suppressed HIV infection on T-cell lineages.

Our current efforts are focused on evaluating whether ablation of key components of the IFNAR architecture can ablate or dampen IFNβ-mediated attenuation of CAR T cell proliferation both *in vitro* and *in vivo*. Together, this work highlights a hurdle to adoptive CAR T cell therapy for chronic viral infections such as HIV and proposes genetic engineering approaches aimed at protecting CAR T cells from the anti-proliferative effects of IFNβ while retaining host immunocompetency through preserving IFNβ-mediated restriction of virus replication.