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## Hematopoietic stem cell-based therapy for HIV disease: 'Berlin' versus 'Essen' patients

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The goal of our work is to develop insight and understanding of the effect of deleting the chemokine receptor CCR5 in T cells, and its interplay with immune regulation of human immunodeficiency virus type – 1 (HIV-1), to enable a novel technology platform to cure HIV disease. A critical point is the use hematopoietic stem cell (HSC) transplantation of the cells resistant to HIV such as CCR5Δ32 cells, which harbor deletion in the CCR5 promoter. Such mutation confer resistance to CCR5-tropic HIV-1 in homozygous individuals and could cure HIV-1 disease based on the outcome of bone marrow engraftment in HIV+ leukemic patients using a CCR5Δ32 homozygous donor ('Berlin Patient'). However, a shift of HIV tropism to CXCR-4 tropic strains of HIV-1 might be limiting after HSC transplantation with CCR5Δ32/Δ32 mutation since it could lead to recurrence of viremia ('Essen patient'). In addition, patients receiving allogeneic bone marrow transplantation often suffer from graft versus-host disease (GvHD), and for that reason HIV infection is not considered an indication, unless a hematologic malignancy warrants transplantation. To advance this field, it is, however, vital to search for novel determinants to HIV susceptibility using genome-wide analyses and exploit mechanisms, which play a crucial role in repression of CD4+ T conventional cells (Tcons) by naturally occurring CD4+CD25+ T regulatory cells (nTregs). In order to ameliorate GvHD further understanding of the mechanisms of immunological self tolerance will also provide insights into how strong immune responses such as graft rejection could be restrained and engraftment of HIV resistant cells in HIV+ leukemic patients could be augmented.

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## Manipulating the immune response to inhibit virus infection

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The innate immune response to virus infection plays a critical role in limiting virus multiplication and pathogenesis. Central to the innate antiviral response is the rapid induction of type I interferon (IFN) expression; IFN gene expression is tightly regulated by the recognition of extra- and intra-cellular signals, generated during primary infection. The viral genome or viral replicative intermediates containing 5'triphosphate (5'ppp) RNA binds to RIG-I and ultimately leads to the production of pro-inflammatory cytokines and anti-viral factors, as well as type I interferons (IFNs) that amplifies the antiviral immune response. Given that viral RNA-RIG-I interaction is the initial trigger of the innate and adaptive immune response, an attractive strategy for the development of an efficient and broad spectrum antiviral therapy to inhibit virus infection, involves the use of RIG-I agonist that mimic viral RNA to activate the host defense. Our previous study demonstrated that treatment of various cell lines and primary cells with 5'ppp RNA *in vitro* led to protection against infection and replication of a broad range of RNA and DNA viruses. In vivo, intravenous administration of 5'ppp RNA protected mice from a challenge with H1N1 and H5N1 Influenza virus. Our recent study shown that 5'ppp RNA has the ability to counteract Ebola virus infectivity *in vitro*. We identified STING among a plethora of differentially expressed genes induced by the RIG-I agonist 5'ppp RNA. STING has been identified as an RIG-I signaling cofactor and a critical adaptor protein required for cytosolic DNA and cyclic dinucleotides (CDNs) triggered immune responses. We further detail the mechanism of STING regulation. Furthermore, our results also unveiled an essential contribution of STING in the establishment of the 5'ppp RNA induced antiviral responses during HSV1 infection.Taken together, these observations demonstrate that the STING is induced via RIG-I signaling and up-regulated STING is essential for 5'ppp RNA mediated HSV restriction.

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