Molecular-Detailed Mechanistic Modeling of Stem-Cell Based Therapies for HIV Using Combinations of Restriction Factors

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Motivation. Continuous HAART treatment ensures that millions of people with HIV lead normal lives. However, cures are needed to eliminate long-term costs and issues of adherence to HAART regimens. In 2008, a HIV-infected individual known as the "Berlin patient" underwent an allogeneic hematopoietic stem cell transplant (HSCT) from a donor with a homozygous mutation in CCR5, the co-receptor for HIV entry into target cells. Since then, the Berlin patient has been "functionally cured", i.e. has shown no signs of active HIV-1 replication in the absence of HAART. Finding a donor with a CCR5Δ32 mutation is generally challenging, however, replacing HIV-susceptible cells with more resistant cells by inserting anti-HIV genes or gene networks into patients' own stem cells or into stem cells from matched donors before transplantation could provide HIV-resistance to the progeny target cells and lead to a functional HIV cure.

Methods. We have developed a molecular-detailed, multiscale, mechanistic model of HIV infection, with the goals of designing stem-cell based therapies for HIV using combination of anti-HIV genes and giving insights into the logistics of successful treatments. The model simulates the dynamics of HIV infection using coupled equations to track key endogenous restriction factors and their interactions with HIV-encoded proteins, the virus itself, and multiple immune cell types: uninfected and infected CD4+ T cells, macrophages (thought to be responsible for the high viral load during the late stage of the disease), latently-infected T cells (the major hurdle to achieving a cure), and cytotoxic T lymphocytes (CTLs) to simulate the effects of the immune response on the target cells and virus. Allogeneic HSCT is represented by addition of a new population of donor stem cells that, in competition with the host stem cells, will generate "graft" CD4+ T cells, macrophages and CTLs.

Results. Our model predicted that overexpression of the endogenous restriction factor APOBEC3G (A3G) at medium or high transfection efficiency could effectively stop HIV replication and increase the T cell count to normal levels. On the other hand, overexpression of SAMHD1 in macrophages even at high transfection efficiency is not a potent inhibitor of HIV replication, as it only stabilizes the viral loud and slightly improves the T cell count. The model further predicted, however, that the combination of A3G and SAMHD1 leads to synergy: faster viral decay and a return to normal T cell counts at lower A3G expression levels. Surprisingly, the model suggested that HIV-triggered pro-apoptosis gene circuits combined with A3G overexpression would have a negative impact on blocking HIV replication if expressed in a low percentage of T cells. This is because some infected T cells die at a faster rate, which in turn weakens the effect of immune response in killing the remaining infected cells.