Anti-HIV-1 Restriction in Hematopoietic Stem Cells

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Some cells have factors that halt virus infection after the virus has already entered the cell, make such cells resistant against certain viruses. Hematopoietic stem cells, which are cells in the bone marrow that can generate all types of blood cells, are resistant against infection by the HIV virus, but the factors responsible for this resistance have not been identified. Using HIV vectors, which are model viruses that replicate the early stages of the HIV life cycle but cannot generate new viruses, we have shown that only a small portion of hematopoietic stem cells can be infected, indicating that these cells can halt the early steps of HIV replication, thereby resisting infection. However, treating cells briefly with the drug rapamycin drastically increases the amount of cells that are infected by HIV vectors. Rapamycin is a clinically tested drug that has been used in suppressing organ transplant rejection and more recently in treating cancer; however, its use in managing susceptibility of hematopoietic stem cells to HIV infection is a novel finding. We hereby propose to study how rapamycin relieves the resistance against HIV in these cells. Understanding the molecular basis of HIV resistance is important for two reasons. Firstly, we may be able to modulate the cellular factors in question to make the target cells of HIV less susceptible to infection, allowing us to better combat HIV infection. Secondly, HIV vectors – non-replicating virus surrogates – can be used to insert therapeutic genes into hematopoietic stem cells, thus treating and potentially curing a number of blood-borne diseases including HIV infection and X-linked immunodeficiency (the bubble-boy syndrome). By providing a way to better target HIV vectors into hematopoietic stem cells, we can more efficiently utilize gene therapy to combat these diseases.