Functional Restoration of Exhausted Anti-HIV CTL

Masakazu Kamata
University of California, Los Angeles
Basic Biomedical Sciences
2014

Adaptive immune responses are initially effective at controlling infection, but do not eliminate HIV and are ultimately unable to prevent chronic infection even in the presence of effective suppression by antiretroviral drugs. One reason for lack of control is the conversion of originally functional effector T cells into dysfunctional (exhausted) T cells. T cell exhaustion is a dysfunctional state with defined phenotypes and is a primary cause for inability to clear chronic viral infections.

Exhausted T cells have gone through extensive cellular programming leading to a, thus far, irreversible loss of the T cell functions. Clinically, this is important following interruption of combination antiretroviral therapy in HIV infection, wherein even vaccine-stimulated cells rapidly revert to their exhausted state upon re-encounter with antigen and are unable to control infection. To reverse loss of T cell function, reprogramming technology can be used to convert T cells from exhausted to functional state, thus restoring antiviral T cell response.

We expect to provide proof of concept for whether reprogramming of T cells will fully erase imprints of their previous differentiation state and regenerate effective T cell memory. The next step will be to test reprogramming of exhausted T cells directly from patients. These studies will provide the pre-clinical foundation to translate these approaches into humans.