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CD8⁺ T cell-mediated suppression of viral replication
following de novo human immunodeficiency virus type 1 (HIV-1)
infection in lymphocytes of asymptomatic HIV-1 carriers

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CD8⁺ T lymphocytes of asymptomatic HIV-1 carriers (ACs) suppress replication of human immunodeficiency virus type 1 (HIV-1). Peripheral blood mononuclear cells (PBMC) of patients with acquired immunodeficiency syndrome do not show such phenomenon, implying that CD8⁺ T cell-mediated suppression of HIV-1 replication plays an important role in maintaining the asymptomatic stage. HIV-1-specific CD8⁺ cytotoxic T lymphocyte (CTL) activity is readily detectable in fresh clinical materials of HIV-1-infected. These CTL presumably eliminate HIV-1-infected cells in the PBMC. However, it is still controversial whether the CD8⁺ T cell-mediated suppression of HIV-1 replication is solely mediated by CTL in the PBMC of HIV-1 carriers. The CD8⁺ T cells suppress HIV production without decreasing the number of infected cells. Secretion of antiviral soluble factors by the CD8⁺ T cells has also been suggested. The precise mechanisms of the suppression remained to be clarified.

PBMC of asymptomatic HIV-1 carriers do not support HIV-1 replication in vitro even after super-infection of a laboratory strain of HIV-1. Depletion of CD8⁺ cells from the PBMC at the beginning of culture abrogates this suppression, indicating that CD8⁺ T-cells inhibit not only spontaneous but also replication of newly infecting HIV-1.

Following in vitro HIV-1 infection, the PBMC of ACs transiently supported a low level of viral replication, then the virus production rapidly decreased. PCR analysis revealed that HIV-1

proviral DNA integrated in the PBMC of ACs following infection gradually decreased. Such tapering consequences of in vitro HIV-1 infection in the PBMC of ACs were abrogated by depletion of CD8⁺ T cells from the culture. Furthermore, the viruses subsequently produced by the PBMC of an AC were less able to replicate than the virus produced by CD8⁺ cell-depleted PBMC of the same donor. In addition, an experimental system using pseudotype HIV which allowed a single cycle of infection revealed that CD8⁺ T cells also suppressed viral gene expression in the target cells.

Decrease of integrated proviral DNA indicates that some population of the infected cells underwent cell death. This was highly likely mediated by CD8⁺ CTL. The amount of virus production could be reduced when the cells were killed by the CTL. However, the reduction of the replication ability of the virus implies that the second mechanism affects the quality of the virus produced by the target cells. Reduction of viral infectivity could be resulted from qualitative or quantitative alteration of cellular components incorporated into the virion which influences viral infectivity. Finally, CD8⁺ T-cells of ACs may suppress the intracellular activation pathway required for HIV-1 gene expression. Although the precise mechanism of the suppression remain to be clarified, these differ from the suppression of virus entry by chemokines.

In conclusion, the CD8⁺ T cell-mediated suppression of HIV-1 replication in ACs involve both cytoidal and non-cytoidal mechanisms:

the former is presumed to kill the cells producing viruses, and the latter inhibits viral spread by reducing viral expression and infectivity.

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Recent Topics of Rabies Epidemiology and Researches

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After brief introduction of the recent emergence of bat and human rabies in England and Australia and of the recent topics of rabies researches such as the success of the construction of infectious cDNA of rabies virus, our study on the mechanisms of protection against rabies virus conferred by vaccine was introduced and discussed. The results of our studies so far obtained were summarized as follows.

(1) While the mechanism of protection by pre-exposure vaccination could be explained only by the presence of virus-neutralizing (NT) antibodies, prophylaxis of rabies by post-exposure vaccination (PET) could not be achieved only by the NT antibodies produced by vaccine and required additional mechanisms such as T cell contribution.

(2) Transfer of CTL clone, recognizing the glycoprotein (G) of rabies virus with H-2K

determinant of the MHC, 2 to 3 days after virus infection, protected approximately 50% of the mice which were lethally infected with the ERA strain of rabies virus and treated with cyclophosphamide. Greater protection was obtained in mice receiving both anti-rabies NT antibodies and CTL cells.

(3) Inactivated rabies vaccine induced CTL response in mice against the G protein but not for other internal structural proteins of rabies virion.

(4) In the PET, the interferon produced by vaccinations accelerated and enhanced the IgM and IgG antibody responses to rabies virus.

(5) Mice vaccinated either with a recombinant vaccinia expressing the G (rVacG), N (rVacN) or with phosphoprotein (rVacNS) showed strong resistance to peripheral lethal infection with street rabies virus.

(6) Mice vaccinated with rVacN developed