Higher Activities of Hepatic versus Splenic CD8+ T Cells in Responses to Adoptive T Cell Therapy and Vaccination of B6 Mice with MHC Class-1 Binding Antigen

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Abstract:

The liver has unique microenvironment which is known to induce tolerance of cytolytic CD8+ T cells to hepatic and extra hepatic antigens, resulting in persistence of infection of the liver by the hepatitis B and C viruses. However, under some conditions, functional immune responses can be elicited in the liver in particular to show preferential retention of activated CD8+ T cells. It is not clear whether this retention depends on the type of the exogenous immunostimulatory or the endogenous innate immune cells. The T cell receptor (TCR) transgenic OT-1 (CD8+) mouse model was used in which OT-1 cells were harvested from the spleen of the donor and transferred into recipient mice followed by immunization with OVA peptide followed by injection of GM-CSF, CCL21 chemokine, or cytokines (IL-2, IL-12, or IL-15), or the toll-like receptor 3 agonist poly(I:C). Co-administration of any of these immunostimulatory agents relatively augmented the retention of CD8+ T cells with different levels of effects. Compared to spleen, the Ag-specific CD8+ T cells in the liver showed higher activities including expansion, proliferation, apoptosis and memory responses as well as cytolytic function. While depletion of natural killer cells significantly decreased the hepatic retention of the antigen-specific T cells, depletion of Kupffer cells showed opposite effect. Taken together, the antigen reactive T cells in the liver have higher activities than their counterparts in the peripheral tissues such as spleen. These data have important clinical implications for designing immunotherapeutic protocols toward the liver diseases.

Keywords:

CD8+ cyclophosphamide; Kupffer cells; Natural killer cells; Ovalbumin-specific OT-I; OVA; Poly(I:C); T cells; Toll-like receptor; Vaccination

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