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Title:	A study on homing and memory transition of murine effector CD8 + T cells during viral infections
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Abstract:	The cytotoxic T lymphocytes (CD8 + T cells) are critically involved in controlling intracellular pathogens. Once activated such cells home to the infected tissues, recognize and kill the infected targets and in so doing control the infection. Only 5-10% of the effector cells further differentiate to become persisting memory cells to provide a rapid protection during secondary homologous infection. Understanding the differentiation process of antigen-specific CD8 + T cells is pursued with high interest as this could help devise strategies to boost immunological memory, a cherished goal of vaccinologists. The study was planned to investigate these issues. In the first part, the role of an orphan adhesion G protein coupled receptor, GPR114, was investigated in the differentiation process and migration of murine CD8 + T cells during viral infection. As no antibodies were available to detect surface expressed GPR114, a single domain antibody (sdAb) was selected from an in-house constructed phage display library. Role of GPR114 in differentiating T cells was investigated using this antibody. GPR114 showed basal expression on naïve CD8 + T cells but was gradually upregulated following in vitro and in vivo activation. A biphasic expression was observed in the responding antigen-specific CD8 + T cells during infection with influenza A virus (IAV) and a gamma herpes virus (MHV68). Accordingly, effector cells in the contraction phase downregulated GPR114 but the persisting memory cells showed a higher expression. During recall response GPR114 localized to immune synapse and influenced the activation process. Infusion of anti-GPR114 sdAb in virus infected mice reduced effector CD8 + T cells responses at the infected tissue site. Differential expression of GPR114 in CD8 + as could be achieved by genetic ablation or FACS sorting established the role of GPR114 in cellular homing during virus infection. GPR114 deficiency in activated CD8 + T cells also compromised the recall response. The study therefore, unearths the role of GPR114 in migration of CD8 + T cells to tissue sites during an acute infection and elevating central memory pool. 9In the second part, a strategy that involved a transient inhibition of translation to promote differentiation of effector CD8 + T cells into persisting memory cells was investigated. Effector CD8 + T cells transiently exposed to low doses of puromycin survived preferentially and differentiated into memory cells following adoptive transfer in naïve animals. Such cells could be efficiently recalled during a subsequent homologous infection. Low doses of puromycin when administered in vivo in influenza A virus (IAV) infected animals enhanced survival and generated a larger pool of memory CD8 + T cells which were efficiently recalled by a heterotypic strain of IAV. The magnitudes of generated memory cells following puromycin and rapamycin, a known inhibitor of mTOR, were comparable. Puromycin exposed cells upregulated molecules such as ID3 and CD127 that are associated with the transition of effectors cells into memory. Therefore, a transient inhibition of translational machinery in the responding CD8 + T cells preferentially promoted memory differentiation.
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