Chemokine receptor expression identifies pre-Th1, pre-Th2 and non-polarized cells among human $CD4^+$ central memory T cells

Jens Geginat, PhD

Institute for Research in Biomedicine (IRB), Via Vela 6, CH-6500 Bellinzona, Switzerland.

E-mail: jens.geginat@irb.unisi.ch

Cental memory T cells (T_{CM}) express lymph node homing receptors CCR7 and CD62L are largely devoid of effector functions but acquire characteristics of effector memory cells (T_{EM}, i.e. $CCR7^-$ Th1 or Th2) following stimulation with TCR agonists or homeostatic cytokines. Here we show that three chemokine receptors identify functional subsets within the human $CD4^+$ T_{CM} pool. T_{CM} expressing CXCR3 secreted low amounts of IFN-γ, whereas $CCR4^+$ T_{CM} produced some IL-4, but not IL-5. In response to IL-7 and IL-15 $CXCR3^+$ T_{CM} and $CCR4^+$ T_{CM} invariably generated fully differentiated $CCR7^-$ Th1 and Th2 cells, respectively, suggesting that they represent pre-Th1 and pre-Th2. Conversely, $CXCR5^+$ T_{CM} lacking CXCR3 and CCR4 remained non-polarized and retained CCR7 and CD62L expression upon cytokine-driven expansion. Unlike naïve cells all memory subsets had a low TREC content, spontaneously incorporated BrdU *ex vivo* and contained cells specific for tetanus toxoid. Conversely, recall responses to CMV and vaccinia virus were largely restricted to $CXCR3^+$ T_{CM} and T_{EM}. We conclude that antigen-specific memory T cells are distributed between T_{EM} and different subsets of T_{CM}. Our results also explain how the quality of primary T cell responses could be maintained by T_{CM} in the absence of antigen.