The role of helper CD4$^+$ T cells for primary and secondary CD8$^+$ T cell responses

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Primary CD8$^+$ T cell responses against infectious pathogens are thought to be largely independent of CD4 T cell help, due to the ability of these infectious agents to directly activate antigen presenting cells via pattern recognition receptors. However, more recent reports indicated that even in the setting of infections, CD4$^+$ T cells play a crucial role in shaping the CD8$^+$ T cell response, in particular with respect to maintenance of memory CD8$^+$ T cells and their recall proliferative potential. As the requirement for T help as well as its time requirements seems to vary significantly with the experimental system, it is of importance to determine the mechanisms by which T helper cells confer help to CD8$^+$ T cell responses in the context of specific experimental systems.

We used an experimental system consisting of CD8$^+$ T cell priming with replication-incompetent virus like particles (VLPs) followed by secondary challenge either with vaccinia virus (VV), lymphocytic choriomeningitis virus (LCMV) or VLPs, and we found that CD4 T cell help is only crucial for secondary infections with in case of VV challenge. Furthermore, also the primary CD8$^+$ T cell response specific for VV was highly diminished in the absence of T help, indicating that that the requirement for T help is rather linked to the type of infection rather than a general feature of secondary CD8$^+$ T cell responses.

We investigated whether a co-infection with VV and various other pathogens would overcome the T help requirement for induction of CD8$^+$ T cell responses. To this end, antigen-specific CD8$^+$ T cell were primed by Vaccinia virus in presence (“helped”) or absence (“helpless”) of T helper cells in combination with a heterologous LCMV, MCMV or *Listeria monocytogenes* infection. Interestingly, co-infection with LCMV completely restored the proliferation of helpless VV-specific CD8$^+$ T cells to the level of helped VV-specific CD8$^+$ T cells, whereas neither MCMV nor *Listeria monocytogenes* infection improved the proliferation capacity of helpless CD8$^+$ T cells. We are currently investigating diverse mechanisms by which CD4$^+$ T cells influence priming and/or re-challenge of VV-specific CD8$^+$ T cells.