Projekttitel: **Natural Killer (NK) cell "memory" during human cytomegalovirus (HCMV) infection**

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Hintergrund: The adaptive immune system responds to pathogen infection by employing distinct effector modules, namely type 1 (IFN-γ and TNF), type 2 (IL-4, IL-5 and IL-13) and type 17 (IL-17, IL-22), which are tailored to eliminate the different infectious agents. It is now evident that an emerging family of innate lymphocytes lacking the TCR and collectively known as innate lymphoid cells (ILCs), exhibit a similar heterogeneity of effector programs. The ILC family comprises of three main groups of cells: group 1 ILCs, including cytotoxic Natural Killer (NK) cells and the IFN-γ producing ILC1; ILC2 producing IL-13/IL-5; ILC3 secreting IL-22/IL-17 (*reviewed in Annunziato et al, JACI 2014*).

NK cells play a crucial role in the defense against intracellular pathogens, especially herpesvirus. Other and we have previously demonstrated that, although belonging to the innate immune system, NK cells undergo a complex process of terminal differentiation in the periphery, similar to T cells (*Luetke-Eversloh et al. 2014a; Killig et al. 2014; Juelke et al. 2010; Juelke et al. 2009; Romagnani et al. 2007; reviewed in Luetke-Eversloh et al. 2013*). During mouse (M) and human (H) cytomegalovirus (CMV) infection, defined NK cell subsets (Ly49H+ in mice and NKG2C+ in humans) undergo antigen-driven expansion and persist over time, displaying high effector functions during secondary infection (1-3). Despite these observations, the molecular mechanisms underlying these properties have not been completely elucidated. In particular, it still needs to be clarified whether these properties might be driven by a unique signature of gene imprinting shared by T cells. We have recently shown that NKG2C+ NK cells expanded in HCMV+ individuals undergo a dramatic epigenetic remodeling of their genome, similar to CD8+ memory and Th1 cells and display an open configuration at the *IFNG* CNS1, which acts as enhancer of IFNG transcriptional activity not only in Th1 cells after TCR stimulation but also in NKG2C+ NK cell expansions in response to NKG2C engagement (*Luetke-Eversloh et al. 2014b*). Thus, our data clearly suggest that epigenetic reprogramming might contribute to drive memory-like features in NK cells, but we still need to identify the genes responsible for such features and to understand when such properties are acquired. Based on these data, we would like to define the unique and/or T cell-like transcriptional and epigenetic signature of memory-like NK cells generated during the primary or recall response of HCMV infection. To this aim, peripheral blood samples (and correspondent serum) from a cohort of 40 transplanted patients who underwent or not acute HCMV primary infection or reactivation (10 patients) have been already collected at different time points after transplantation. In the project, in addition to further collect samples for newly transplanted patients, NKG2C+ NK cells will be sorted and analysis for phenotype and

functions by Multicolour Flow cytometry and PCR/Fluidigm as well as DNA methylation (cooperation with Varionostic and Saarland University) will be performed.
Understanding the mechanisms underlying adaptive properties in NK cells will help us to improve vaccination strategies and will possibly facilitate the adoptive transfer of NKG2C+ NK cells for prevention/therapy of HCMV infection in immunodeficient hosts.

External References

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List of topic-related publications

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*****Equal contribution