Dissection and manipulation of antigen-specific T cell responses

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Scope of this thesis

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T cells recognize pathogen-derived antigens bound to Major Histocompatibility Complex (MHC) molecules and are crucial for fighting pathogens such as viruses and bacteria. In addition, T cells are able to recognize and attack certain types of tumors, in particular virally induced tumors. Cytotoxic (CD8+) T cells recognize antigens presented by MHC class I molecules that are present on virtually all nucleated cells, and are specialized in destroying the aberrant cells via the induction of apoptosis. Helper (CD4+) T cells recognize antigens presented by MHC class II molecules, which are only expressed on so called professional antigen presenting cells (APCs), such as dendritic cells (DCs) and B cells. CD4+ T cells are specialized in providing supporting signals to other cell types within the immune system, including CD8+ T cells. After development in the thymus, CD4+ and CD8+ T cells continuously migrate through lymphoid organs and scan the pool of peptides presented by APCs. Whether a naïve T cell becomes activated not only depends on the number of peptide-MHC complexes present on the APC and the affinity of the T cell receptor (TCR) that recognizes this complex, but also on additional signals provided by the APC in the form of cytokines and costimulatory molecules. Upon activation, T cells proliferate and differentiate into a large pool of effector T cells that are ready to combat viruses and tumors throughout the body.

Because of the role of antigen-specific T cells in tumor- and pathogen-specific immune control, the enhancement of antigen-specific T cell frequency or activity is an ideal method to protect or treat individuals against/with infections or certain types of cancer. The most widely used approach to enhance antigen-specific T cell responses is vaccination, i.e. the exposure of individuals to pathogen- or tumor-derived antigens in an immunostimulatory context. In settings where disease-specific T cells are absent or reduced in number/activity, vaccination alone is likely to be of limited value. In these circumstances, the adoptive transfer of antigen-specific T cells that have been generated in vitro is likely to be a good alternative or addition. An efficient way to produce antigen-specific CD8+ T cells is to modify CD8+ T cells in vitro, by the introduction of MHC class I restricted TCR genes using retroviral gene transfer.

In this thesis we aimed 1) to obtain more insight into antigen-specific T cell responses and 2) to study how antigen-specific T cell responses can be improved. For the first aim we generated new tools that by enabling the visualization of antigen-specific CD4+ and CD8+ T cells allow the study of the dynamics of antigen-specific T cell responses in time throughout an ongoing immune response (chapter 2). In addition, we developed a novel technique that enables the study of family relationships between different T cell populations. This technique for instance allows us to determine whether two different types of effector T cell populations arise from the same or different pool(s) of naïve T cells (chapter 5). For the second aim, we analyzed whether antigen-specific T cell responses can be manipulated by providing increased costimulation in the form of constitutive triggering of CD27 (chapter 3) or by generating CD4+ T cells that are modified by the introduction of MHC class I restricted TCRs (chapter 4).