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The Department of Microbiology, Tumor and Cell Biology

HUMANIZED MICE AS A MODEL TO STUDY HUMAN IMMUNITY

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ABSTRACT

Mice with human immune systems have evolved over the last three decades. Over the years, these humanized mouse models have provided us with valuable information on human immunity. Recent developments in recipient mouse strains and engraftment protocols have resulted in models with high level of de novo formation of human immune cells. Here we describe the development and improvements of humanized BALB/c/Rag2$^{-/-}$/IL2Rγ$^{-/-}$ and NOD/SCID/IL2Rγ$^{-/-}$ mice and employ such mice or studies on various aspects of human immunity.

We show that engraftment with human cells depends on the recipient strain and conditioning regiment. While we confirm that T cells that developed in the mouse are functional and respond to allogeneic cells and mitogens *in vitro*, no rejection was observed *in vivo* after transplantation of human β-islets under the kidney capsule of humanized mice (**Paper I**).

In a second study, we showed that human CD56^{dim} NK cells in humanized mice and in recipients of a bone marrow transplant are subject to further differentiation. We observed that CD57 and killer cell immunoglobulin-like receptors (KIRs) are acquired during differentiation of CD56^{dim} cells. (**Paper II**)

Infection studies in humanized mice have thus far been almost exclusively limited to infections with pathogens specifically targeting human immune cells. We explored the use of humanized mice for mycobacterial infections, which are not restricted to infection of human cells. We found that humanized mice contained higher bacterial titers in comparison to controls. While this finding could be attributed to dysfunctional T cell responses and impaired anti-mycobactericidal responses by human macrophages, we found that humanized mice infected with *Mycobacterium bovis* BCG or *Mycobacterium tuberculosis* developed organized granulomas similar to those found in humans. Furthermore, we demonstrated that human CD4^{+} cells impair mycobacterial control but are essential for the development or maintenance of granulomas (**Paper III**).

Finally, we used humanized mice to shed light on Epstein Barr Virus induced latency. Infections with this human specific virus resulted in a CD4/CD8 T cell ratio skewed towards CD8 and the differentiation of T cells from naïve to effector memory cells. A variable number of infected mice showed tumors and B-cell proliferation *ex vivo*. *In vivo* depletion of CD8^{+} cells increased the frequency of tumors and *ex vivo* proliferation of transformed B cells. Surprisingly, *ex vivo* proliferation of B cells from CD8^{+} cell depleted or non-depleted mice was inhibited in presence of cyclosporine A, suggesting that CD4^{+} T cells exerted a supporting effect on cells displaying a latency type which otherwise would not proliferate *in vitro*. This finding was confirmed by analysis of viral promoters in CD4^{+}, CD8^{+} and non-depleted infected animals (**Paper IV**).

In conclusion, our studies show that current humanized mouse models can be used to improve our knowledge of various aspects of human immunity, such as alloreactivity, the ontogeny of hematopoietic cells, the immunobiology of human-lymphoid specific as well as non-species specific microorganisms and the regulation of granuloma formation in infectious and non-infectious diseases.

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