Abstract (english)

Natural Killers – NK cells play an important role in immune surveilance and regulation either by direct cytotoxicity towards infected, transformed or otherwise damaged cells, or by production of cytokines and chemokines. The resulting response of NK cells is given by the sum of stimulating and inhibiting signals, tranduced by a wide array of receptors. Killer Ig–like receptors KIR2DL4 and LILRB1, which recognize self HLA–G molecules in pregnancy, as well as NKR–P1 receptors, which differ in the number of isotypes, are species–dependent and reduced during phylogenesis. NKG2D, reacting to stress–inducible proteins, and adenosine receptors (AR), which supress the inflamatory reaction, remain evolutionary conserved.

The aim of this work was to study the involvement of NK cells and their receptors in several immune disorders and in various species, to provide new insights into their function and posisible immune modulation.

We have shown here, that the choice of species in the study of NK cell effector functions may be crucial in some cases. The reaction to glycans, using synthetic GlcNAc–terminated glycomimetics GN8P, exerted opposing effects on NK cell function in humans and C57Bl/6 mice. In humans, the glycomimetic decreased cytotoxic activity of high NKR–P1A expressing NK cells, while in mice it mounted an NK cell–mediated antibody formation and tumor–specific IgG2a production with subsequent increase in antibody dependent cellular cytotoxicity (ADCC). This effect was observed only in C57BL/6 mice expressing *Nkr–p1c(T)* gene (coding NK1.1 receptor). Endogenous hormone human chorionic gonadotropin (hCG), exerted as most other hormones a degree of pleiotropy in its effect. We observed a preference of cytotoxic over helper T cells and increased KIR2DL4 expression on NK cells, which renders them more prone toward cytokine production. Moreover, this effect proved to be antagonistic to the original intent of the hCG use – that is to improve the outcome of assisted reproduction courses, since such profile was observed during failed embryotransfers. A_{2A} adenosine receptor agonist CPCA on the other hand, was used to prove the evolutionary conserved mechanisms in its function, by thwarting NK cell cytotoxicity in healthy and immunocompromised subjects equally (human, pig, goat, rat, mouse). *In vivo* tumor–localized hyperthermia (LHT) proved to have beneficial effect on NK cell–mediated lytic activity, despite the NK cell distribution remained unchanged. This procedure is however limited to localized, primary tumors. For further optimization of LHT, multifunctional ferritin–based nanoparticles with tumor targeting structures were developed. This nanoplatform may increase the efficacy of LHT therapy onto circulating cancer cells or metastatic foci.

Our results proved the key involvement of NK cells in the development and regulation of immune response in autoimmune and reproductive disorders, tumor transformation or heat–induced stress. This work brings new options for NK cell–mediated immune modulation, but further research is needed to achieve their full potential. We here provide the basis for this research and its possible clinical applications in the future. It would be perspective in future studies to observe the hormonal levels or autoimmune changes in murine strains with varying NKR–P1 and Ly49 phenotypes.