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Human CAR-NK cells: A new non-viral method allowing high efficient transfection and target cell killing- Ingegnere T IRCSS Bambino Gesù Pediatric Hospital, Italy

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Cell-mediated immune responses play a central role in the control of infections and tumor growth. In particular, cytolytic T lymphocytes (CTL) and natural killer (NK) cells are fundamental effectors against virus-infected, tumor and leukemia cells. Both T and NK cells are particularly efficient also in allogeneic settings such as the allogeneic haemopoietic stem cell transplantation (HSCT) to cure hematologic malignancies. Another particularly promising approach of cellular therapy is the use of genetically-engineered autologous T cells with chimeric antigen receptors (CAR) conferring specificity for antigens expressed by tumor cells. Also NK cells can be genetically engineered with CAR. Different from CAR-T, NK cells, equipped with an array of receptors involved in tumor cell recognition and killing, retain their ability to target neoplastic cells through such receptors, possibly making tumor escape mechanisms less effective. In addition, they may be complementary to CAR-T cells. However, NK cell transfection resulted quite challenging. Thus, viral transduction display to have variable levels of transgene expression and may compromise NK cell viability. Moreover, viral transduction requires dedicated facilities, high costs and lengthy preparation. Recently, electroporation of mRNA has been proposed as alternative of viral methods. Although the mRNA electroporation has a very low effect on the vitality and good efficacy, a relevant drawback are represented by the short-time expression of the transgene. Here we show a new procedure for NK cells transfection with plasmid DNA. With an efficiency of up to 50% and viability up to 65% it is the most efficient, non-viral, methodology existing so far to deliver exogenous DNA into NK cells. By applying this method, we transfected exogenous CCR7 chemokine receptor conferring to the NK cells the ability to efficiently migrate in response to the chemokines. Moreover, the introduction of an anti-CD19 CAR confer to transfected NK cells a specific and powerful cytotoxicity against CD19+ leukemic cells. These results illustrate some of potential important applications of this novel transfection approach. Notably, the electroporation of DNA may allow to a non-integrating gene transfer with episomal vectors.

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