Targeting epithelial and hematologic cancer by Fcγ-CR engineered T cells or long-term NK cells.

In recent years, immunotherapy has been successfully used for the treatment of hematologic and solid malignancies. The immunotherapy success is due to the development of at least four therapeutic strategies: i) tumor-associated antigen (TAA)-specific monoclonal antibodies (mAbs); ii) T cell checkpoint blockade; iii) TAA-specific chimeric antigen receptors (CARs) T cell-based immunotherapy; iv) Natural killer (NK) cell-based cancer therapies. The research team of the IFT-Tumor Immunology and Immunotherapy laboratory focuses on the development of new immune cell-based strategies against epithelial and hematologic malignancies. These strategies include the generation of Fc gamma chimeric receptor (Fcγ-CRs) T cells for solid and hematologic cancers and the use of allogeneic NK cells against acute myeloid leukemia. To date, we have generated three distinct Fcy-CRs: the FcγRIIa (CD16), FcγRIIA (CD32) and FcγRI (CD64). They result from the fusion of the extracellular portion of the over mentioned FcγRs and a chimera composed of the CD28 co-stimulatory molecule and T cell receptor ζ chain. Our experiments have shown encouraging results either in vitro or in vivo. CD16-CR T cells and CD64-CR T cells in combination with commercially available anti-EGFR mAbs eliminated breast and colorectal cancer cells even in the presence of KRAS mutation by antibody-dependent cell cytotoxicity (ADCC). Interestingly, CD32-CR T cells killed EGFR+KRAS wild-type cell lines in the presence of the anti-EGFR, IgG2 mAb, panitumumab which is known to be incapable of mediating ADCC, in the presence of NK cells. Overall, our technology could have a potential additional clinical application than CAR-T cells since could overcome some CAR-T cell limitations. The best characteristics of our CR-T cells are i) the intrinsic multiple tumor-targeting capacities, based on TAA-specific mAb availability with which can be associated; ii) the potential of controlling their off-target toxicity by withdrawing the mAb administration; iii) the capacity of overcoming immuno-escape mechanisms like the surface TAA-loss by redirecting the Fcy-CR T through a second anti-tumor mAb with a distinct specificity if available. To date, the Fcy-CR T cell immunotherapy is in a pre-clinical stage but has got a great potential for a novel therapeutic approach. In 2017, our innovative Fcy-CR-based strategy was granted with an Italian patent, and in 2019, a provisional US patent application was secured. Growing evidence indicates that NK cell-based immunotherapy is useful in the treatment of myeloid leukemia. To optimize the efficacy of NK cell-based immunotherapy of AML, we investigated the interactions of NK cells with AML cells. We found that AML cells damage NK cells limiting the ability of NK cells to control AML cell growth. Our data indicated that the induction of NK cell damage, by the AML leukemia cells, is abrogated by the long-term culture of NK (LTNK) cells at 37°C. LTNK cells showed an improved ability to kill AML cells in vitro and significantly blocked the subcutaneous growth of ML-2 AML cells in CB17 SCID mice. As a future plan, we would like to validate a laboratory procedure for the production of clinical grade LTNK cells in collaboration with the ISS cell factory, FaBio CELL.

References:
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