Improving T cell functionality for adoptive T cell therapy in metastatic colon cancer
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Abstract
Colorectal cancer is the second leading cause of cancer death in the United States. Unfortunately, current FDA approved immunotherapies such as checkpoint blockade, fail to benefit majority of patients with colorectal cancer. Adoptive T cell therapy on the other hand, is challenging due to the molecular heterogeneity and functionally impaired tumor infiltrating T cells (TILs), in most cases of colorectal cancer. Thus, this study aims at developing a novel strategy to expand patient’s tumor specific T cell ex-vivo, for an effective adoptive T cell transfer in patients with colorectal cancer. A novel combination of drugs and tumor membrane vesicles (TMVs) are utilized to activate and expand antigen-specific T cells and their effects are evaluated via their adoptive transfer to patient derived xenograft (PDX) mouse models established using patient derived tumors.

Expanding functional T cells ex-vivo
- Functional and proliferative capacity of T cells diminish with ex-vivo T cell expansion
- Poor quality of adoptively transferred T cells can result in cancer relapse

Functional capacity

Days of expansion

T cells+ anti-CD3/CD28

Increased T cells from healthy donors and DLBCL patients were expanded in vitro in the presence or absence of idelalisib and/or VIPhyb for fourteen days. (A) Expansion profiles of healthy controls under the indicated culture conditions. (B) Representative flow plots showing the expression of CD27 and CD28 on the total T cell population. (C) Quantification of double positive and double negative T cells from 10 lymphoma patients. (Petersen et al. Blood Advances 2018)

Tumor membrane vesicles (TMVs) for patient specificity
- TMVs developed using patient tumors is a source of all tumor associated antigens.
- In vitro studies with human tumor cell lines co-cultured with GPI anchored IL-12 show improved anti-tumor activity of T cells.

TMVs prepared from human mammary carcinoma (MDAMB231, MCF7), renal cell carcinoma (RCC1), melanoma (SKMEL-28), and B-cell lymphoma (JY) cell lines, were incubated with purified glycosylphosphatidylinositol linked human IL-12 (GPI-hIL-12). Proliferation of activated T cells using GPI-hIL-12-positive (closed bar) tumor membrane vesicles induced T cell proliferation (A) and IFNγ synthesis (B) compared to human TMVs treated with buffer (open bar). (Nagarajan et al. Vaccine 2006)

Approach to expand tumor specific T cells with enhanced anti-tumor activity

Due to the minimal number of T cells in the patient samples, the tumors will be grown in PDX mice, to enable testing the different experimental conditions

Increased polyfunctionality of CD4+ T cells with VIPhyb and idelalisib

T cells from blood of colon cancer patients were expanded ex-vivo in the presence or absence of idelalisib and/or VIPhyb for 14 days. On day 14, the PS1 of CD4+ T cells (A) and CD8+ T cells (B) were determined via in-depth analysis on the IsoCode Chip from Isoplexis.

PDX models of human colon cancer and decorated TMVs

Patient Tumor Implant Day 0

TMV

TMV-unstained

Decorated TMV

Proof of concept – Increased anti-tumor T cells using mouse models of pancreatic cancer
- T cells from B6 mice were expanded with TMVs from murine pancreatic tumors and in the presence of VIPhyb and/or idelalisib

Splenocytes from B6 mice were cultured in media with anti-CD3/CD28 beads, low dose IL-2 (30U/ml), with/without decorated or undecorated murine pancreatic cancer TMV and VIPhyb and/or idelalisib for 7 days.

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