Engineered marrow macrophages to probe solid tumor microenvironments after targeted infiltration & regression

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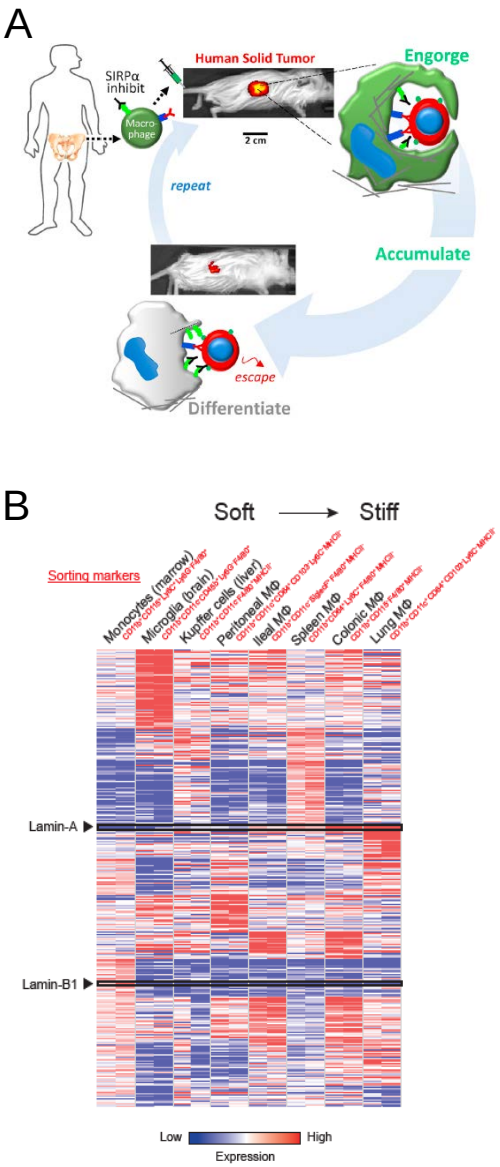
Description

We have developed a method to engineer marrow macrophages after isolation in order to infiltrate tumors and phagocytose cancer cells (Fig. A). Marrow cells from human or mouse donors are fluorescently labeled with CFDA and incubated with a monoclonal antibody that inhibits the macrophage checkpoint receptor, SIRPα, and also with any antibody that can bind any surface antigen on tumors. Following *i.v.* administration to tumor-bearing mice, the engineered cells traffic to, infiltrate, and accumulate in tumors. For maximal phagocytosis and tumor regression, the targeting antibody specific for cancer cell epitopes is injected several hours before the engineered cells and then re-administered every other day for up to two weeks. For the first few days, the CFDA+ macrophages are readily isolated from disaggregated tumors using flow cytometry and molecularly profiled.

Macrophages are highly plastic cell types that exhibit different phenotypes in different tissues (Fig. B). One hypothesis that we have pursued with numerous types of cells is that tissue solidity or stiffness influences differentiation, and more specifically that engineered marrow macrophages will be re-programmed by the stiffness of a tumor microenvironment. To address this, CFDA-labelled donor macrophages are sorted and analyzed by transcriptomics and surface markers. Donor macrophages are readily compared to tumor-associated macrophages (TAMs) and to macrophage populations resident in normal mouse tissues (marrow, spleen, etc.). Public data for the latter already suggests that the nucleoskeletal factor lamin-A (relative to lamin-B) increases with tissue stiffness, but many other factors can obviously be assessed.



(A) Engineered macrophages for a cell-based therapy against solid tumors. **(B)** Systems biology approaches such as RNAseq reveal the microenvironment-dependent plasticity of monocytes and macrophages. Adapted from (Lavin et al. *Cell* 2014).

Publications

- Cory Alvey, K. Spinler, J. Irianto, C. Pfeifer, B. Hayes, Y. Xia, S. Cho, D. Dingal, J. Hsu, L. Smith, M. Tewari, and D.E. Discher. (2017) SIRPA-inhibited, marrow-derived macrophages engorge, accumulate, and differentiate in antibody-targeted regression of solid tumors. ***Current Biology***, 27:2065-2077.

- Cory Alvey and Dennis Discher. (2017) Engineering macrophages to eat cancer: from 'Marker of Self' CD47 and phagocytosis to differentiation. ***Journal of Leukocyte Biology***, 102:1-10.
- Charlotte Pfeifer, C. Alvey and D.E. Discher. (2017) Genomic variation across cancers scales with tissue stiffness – An invasion-mutation mechanism and implications for immune cell infiltration. ***Current Opinion in Systems Biology***, 2: 103-114.