389 ENGINEERED MICROENVIRONMENT CONVERTERS (EM-C): MACROPHAGES EXPRESSING SYNTHETIC CYTOKINE RECEPTORS REVERSE IMMUNOSUPPRESSIVE SIGNALS IN SOLID TUMORS

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Background Immune homeostasis is regulated by a balance of pro- and anti-inflammatory cytokine signals. Dysregulated cytokine expression can cause deleterious immunosuppression or inflammation, which drives disease pathology. In solid tumors, cytokines such as IL10 and TGFβ induce an immunosuppressive tumor microenvironment (TME) that blunts endogenous and therapeutic anti-tumor immunity. Therapeutic strategies to block immunosuppressive cytokines have primarily focused on monoclonal antibodies targeting cytokines/cytokine receptors. While this approach can reduce immunosuppressive signaling, it fails to provide an inflammatory signal that could initiate anti-tumor immunity. Here, we engineered macrophages with synthetic cytokine switch receptors (SR) to develop a cell therapy platform for modulation of pro-/anti-inflammatory signals. Macrophages are homeostatic regulators capable of both initiating inflammation and infiltrating solid tumors, and we leveraged this natural proficiency using SRs that convert tumor-related immunosuppressive (M2) signals into pro-inflammatory (M1) responses for tumor microenvironment (TME) modulation. We termed this engineered myeloid cell platform 'Engineered Microenvironment Converters' (EM-C) and evaluated its modular ability to target several tumor-associated cytokines.

Methods EM-Cs targeting IL10 or TGFβ were generated by expressing SR in primary human macrophages and monocytes. M2-to-M1 SR were designed to convert IL10 or TGF-β into pro-inflammatory signals based on interferon or toll-like receptor (TLR) signaling pathways. The response of EM-Cs to target cytokines was monitored using phenotypic characterization of surface molecules, measurement of cytokine release, mRNA profiling, and biochemical analysis of downstream signaling. Co-culture assays with bystander immunosuppressive cells were used to assess the ability of EM-Cs to alter their microenvironment. Additionally, combinatorial EM-C were designed to target both IL10 and TGFβ for multiplexed TME conversion.

Results Pro-inflammatory EM-Cs efficiently sequestered IL10 and TGFβ, two prevalent immunosuppressive cytokines in the TME, and converted them into pro-inflammatory signals by upregulating M1 markers, cytokines, and pathways in a dose-dependent manner. EM-Cs furthermore repolarized bystander M2 macrophages towards a pro-inflammatory phenotype following co-culture.

Conclusions We present a novel immunotherapy platform that harnesses macrophages as 'living converters' to locally regulate inflammation in solid tumors. We establish EM-C that convert IL10 or TGFβ into pro-inflammatory signals, showcasing a modular ability to control the inflammatory status of microenvironments without systemic cytokine antagonism. EM-Cs enable the development of target antigen agnostic myeloid cell immunotherapies for solid tumors.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0389