Disrupting the immunosuppressive tumor microenvironment using genetically engineered macrophages for triple negative breast cancer therapy

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Introduction

- Triple negative breast cancer (TNBC) = aggressive subtype and difficult to treat
- Cold tumor microenvironment (TME) limits success of immunotherapies in TNBC (1)
- IL-10 and TGFβ are important immunosuppressive cytokines in the TME (2-3)
- Tumor associated macrophages (TAMs) are highly abundant in the TME of TNBC (4)
- Depending on the microenvironment, macrophages have different phenotypes:
  - Proinflammatory M1 macrophages: Induced e.g. by IFNγ, Anti-tumoral activity by inducing inflammation and by direct tumoral activity
  - Immunosuppressive M2 macrophages: Induced e.g. by IL-10, IL-4, TGFβ. Pro-tumoral activity by supporting tumor growth, migration and vascularization and inhibiting anti-tumoral immune response, TAMs usually have a M2-like phenotype
- High number of intratumoral M2-like macrophages correlates with poor TNBC prognosis (5-8)

Results

Figure 1: Macrophages are successfully transduced with IL-10 and TGFβ ChCR

Figure 2: IL-10 and TGFβ stimulation induces pSTAT1 signaling in ChCR expressing macrophages

Figure 3: ChCR expressing macrophages show M1-like phenotype upon IL-10 or TGFβ stimulation

Figure 4: TGFβ ChCR expressing macrophages are tumoricidal upon TGFβ stimulation

Conclusion & outlook

- Macrophages are successfully engineered to express ChCR at high rate
- ChCR leads to pSTAT1 signaling upon binding of IL-10 or TGFβ
- ChCR expressing macrophages induce M1-like phenotype, including IP-10 secretion  implicating a potential to attract immune cells to generate a hot TME
- ChCR expressing macrophages are tumoricidal
- Outlook: Testing in 3D co-cultures and in vivo

Bibliography

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Study sponsored by USZ Foundation, Innovate (103.487.1 IP.15), Eidgenössische Forschungsstiftung, UZH Postdoc Grant. 
ST has no conflicts of interest to declare.

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