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Tumor-Associated Macrophages Promote Invasion while Retaining Fc-Dependent Anti-Tumor Function

Grugan KD, et al. J Immunol. 2012 Dec 1;189(11):5457-66.

C. Nikolowsky

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Medical University Vienna

Monocytes

- Innate immune system
- Produced in bone marrow
- Differentiate to
  - Dendritic cells
  - Macrophages
    - M1 subset
    - M2 (a, b and c) subset
    - TAMs

Murray, P. J., and T. A. Wynn. 2011. Protective and pathogenic functions of macrophage subsets. Nat. Rev. Immunol. 11: 723–737.

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M1 Macrophages

- activated by TLR2/4 ligands, IFN-γ
- pro-inflammatory
- promote Th1 response (AG presentation)
- high Fcγ-Receptor expression
- tumor and tissue destructive

Biswas, S. K., and A. Mantovani. 2010. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat. Immunol. 11: 889–896.

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M2 Macrophages

- activated by
  - IL-4/IL-13: M2a
  - immune complexes: M2b
  - IL-10: M2c
- anti-inflammatory
- promote Th2 response
- immunoregulation, tissue remodeling

Sica, A. et al. 2006. Tumour-associated macrophages are a distinct M2 polarised population promoting tumor progression: potential targets of anti-cancer therapy. Eur. J. Cancer 42: 717–727.

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TAMs

- tumor-associated Macrophages
- M2-like
- anti-inflammatory
- secretion of growth promoting factors
- alleviate metastasis
- high incidence of TAMs → poor clinical prognosis

Sica, A. et al. 2006. Tumour-associated macrophages are a distinct M2 polarised population promoting tumor progression: potential targets of anti-cancer therapy. Eur. J. Cancer 42: 717–727.

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Monoclonal Antibodies (mAb)

- diverse anti-cancer mechanisms:
  - blocking target functionality
  - induction of apoptosis
  - Fc-dependent
    - activation of the complement system
    - recruitment of innate immune effector cells
      → CDC, ADCC, ADCP

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Methods & Results

- Do TAMs from human breast tumors express Fcγ-receptors?
  - tumor tissue from 9 Patients
  - received within 24h of surgical removal
  - detection of FcγRs using flow cytometry

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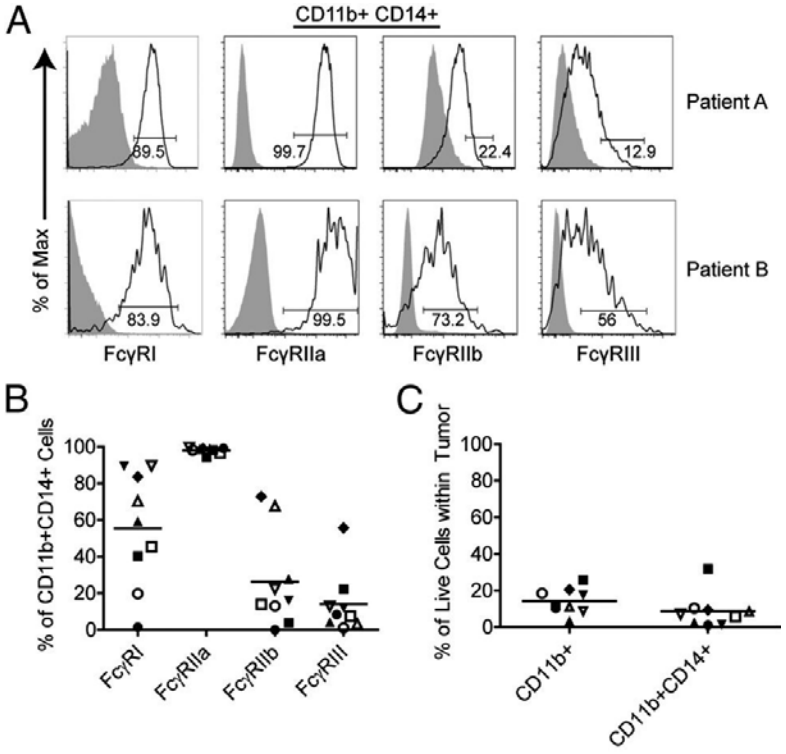

human breast tumor TAMs: FcγR expression

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Methods & Results

- Do in vitro differentiated macrophages express Fcγ-receptors?
  - human PBMCs
    - conditioned medium from MDA-MB-231 breast cancer cells → TCMs
    - incubation with M-CSF + polarization with
      - IFN-γ → M1 macrophages
      - IL-13 → M2a macrophages

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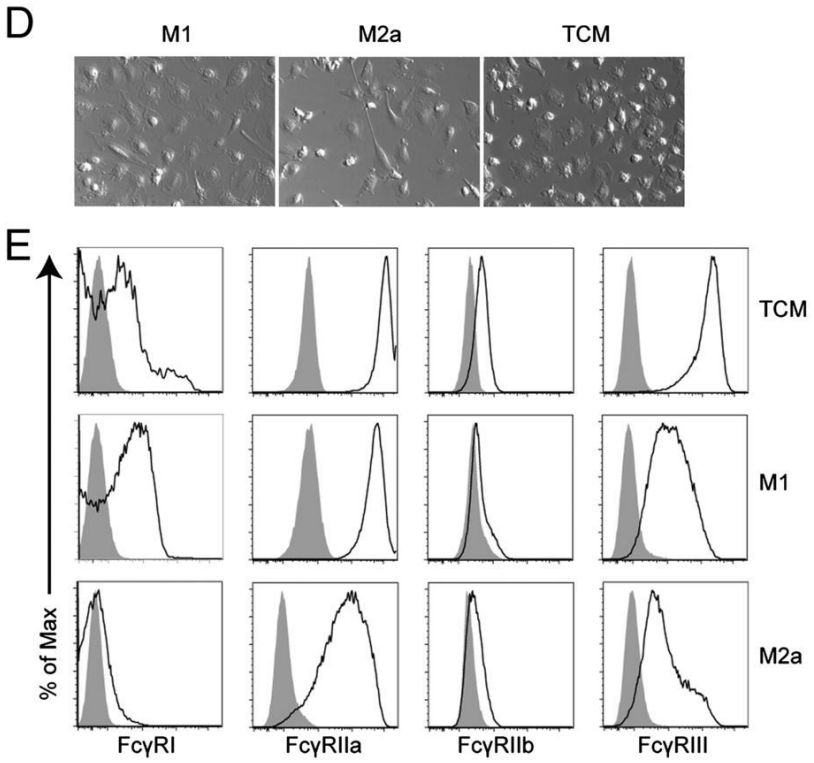

In-vitro macrophages: FcγR expression

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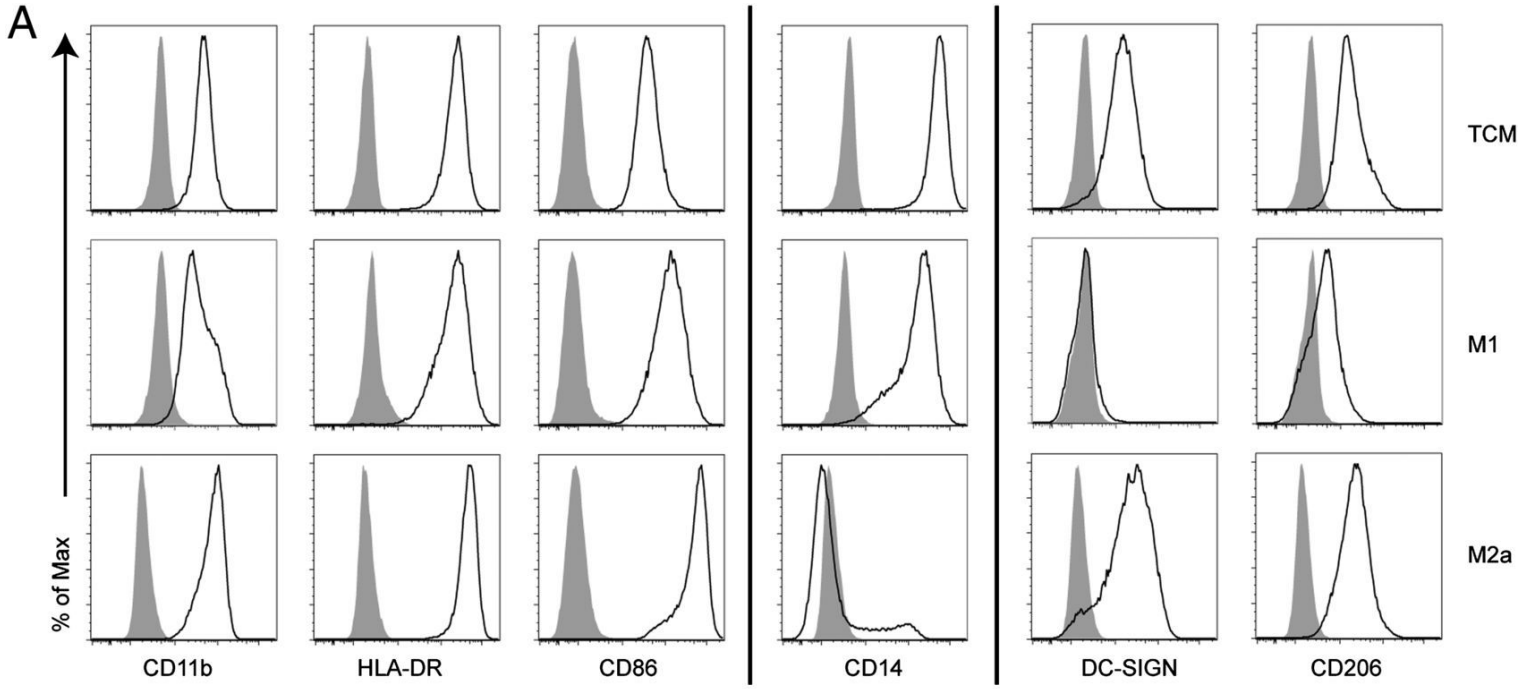

TCMs express both M1- and M2a-associated markers

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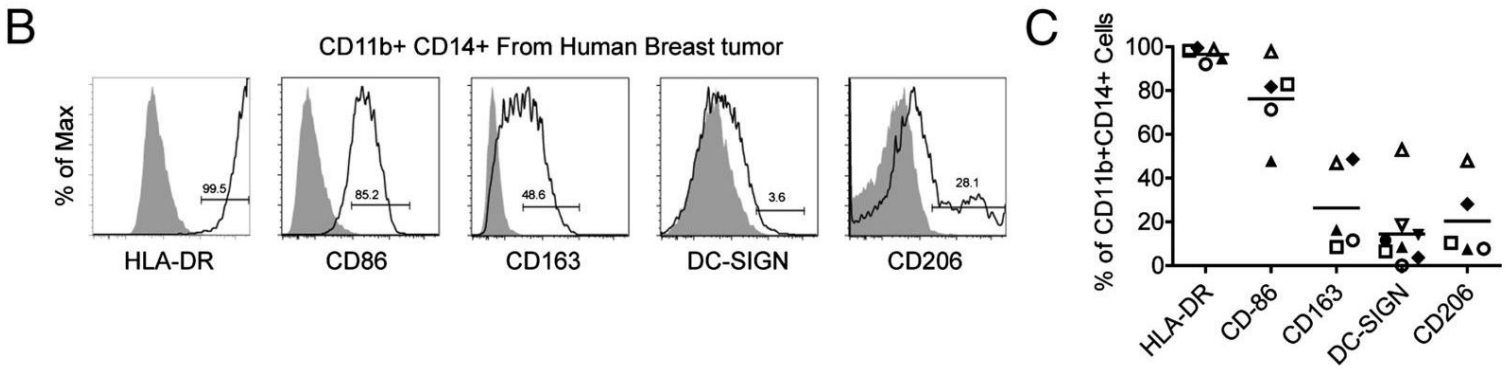

human breast tumor TAMs: marker expression

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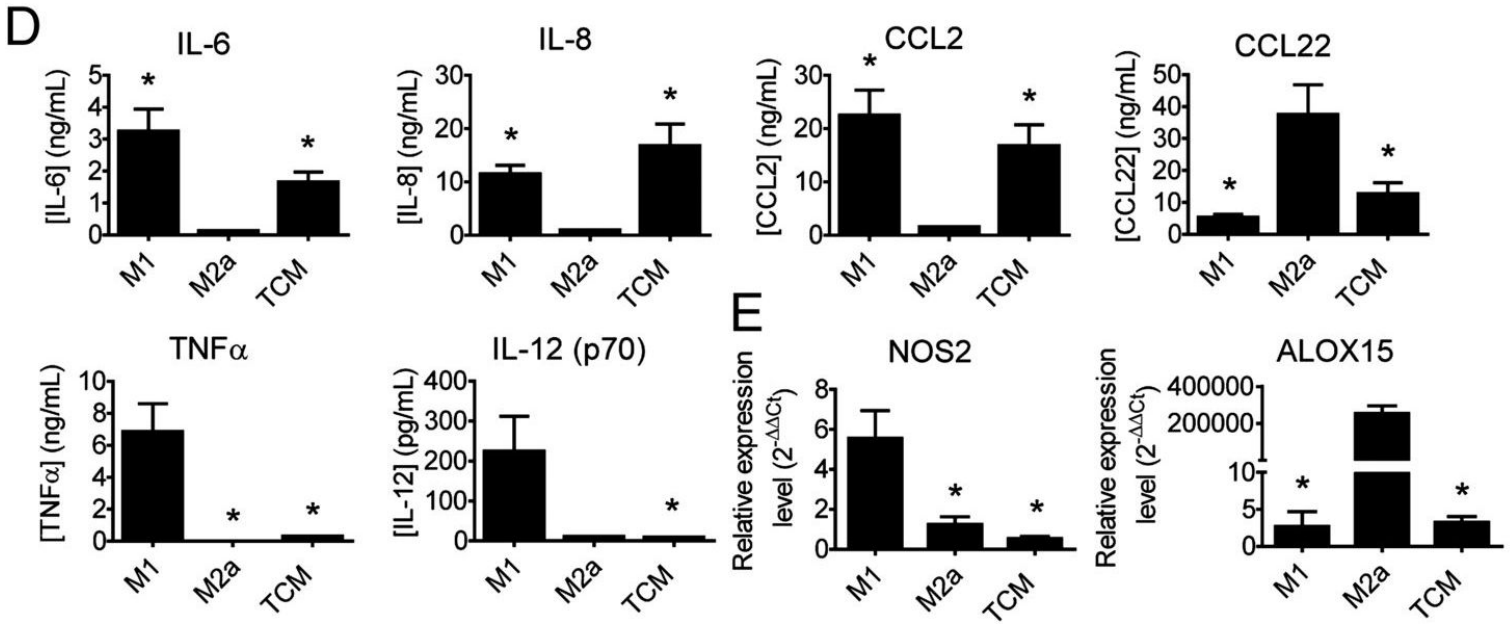

In-vitro macrophages: Luminex analysis of secreted cytokines

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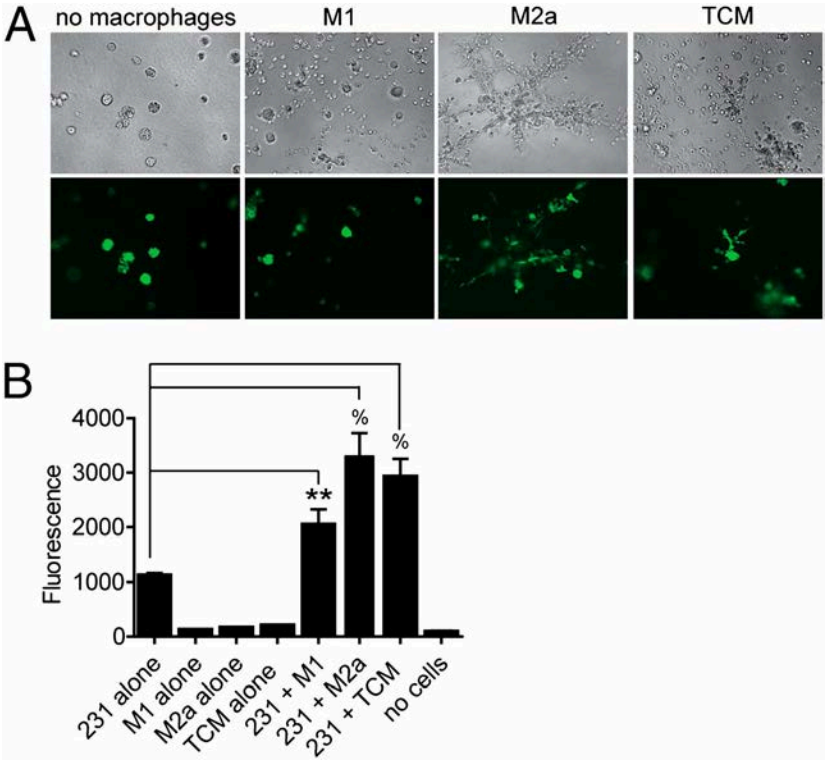

In-vitro macrophages: 3D culture (Cultrex), assessment of tumor invasion after 24h coculture

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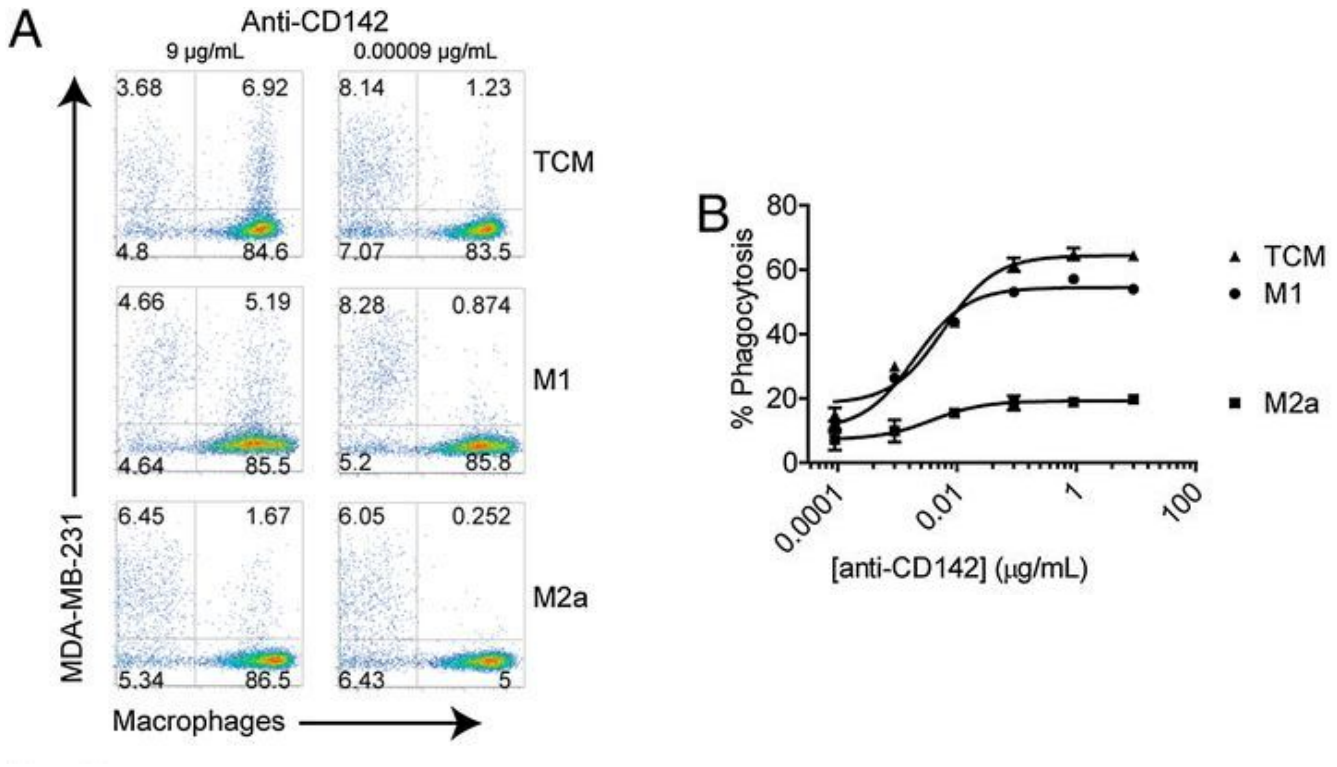

mAb mediated phagocytosis of tumor cells

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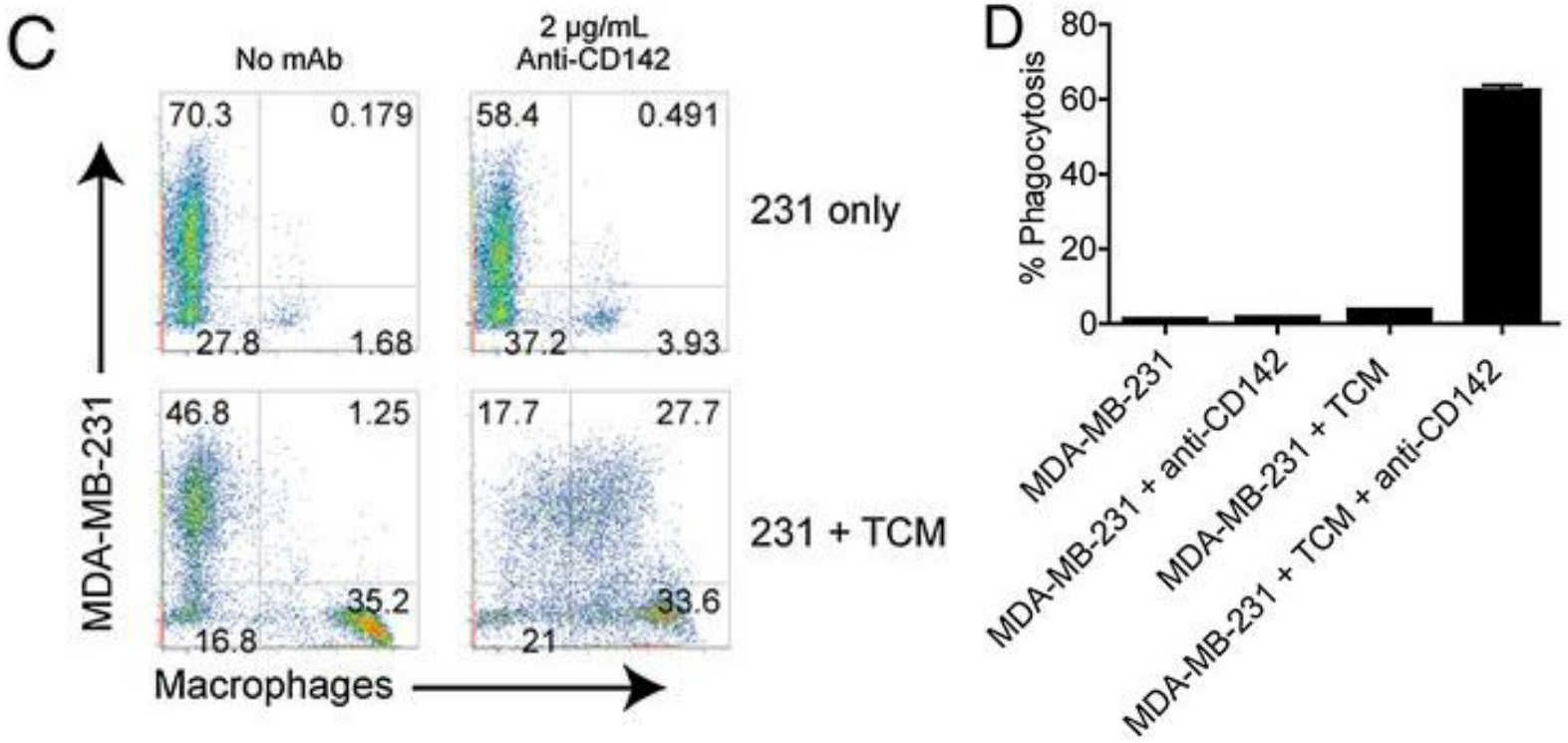

mAb mediated phagocystosis of tumor cells (3D culture)

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Methods & Results

- In vivo mouse studies
  - SCID/beige mice
    - no B cells, no T cells, no functional neutrophils and NK cells
    - functional macrophages
  - Macrophage depletion utilizing clodronate-encapsulated liposomes (CEL)

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Methods & Results

- In vivo mouse studies
  - 6 groups á 10 mice
  - 2 groups each received 100 µl CEL, EmptyLipo or PBS i.p.
  - **Day 1:** MDA-MB-231 tumor cells implanted into mammary fat pad
  - **Day 3:** mAb therapy started with anti-CD142 (control: PBS)
  - mAb injections weekly, tumor volume measured twice weekly
  - **Day 42:** The End

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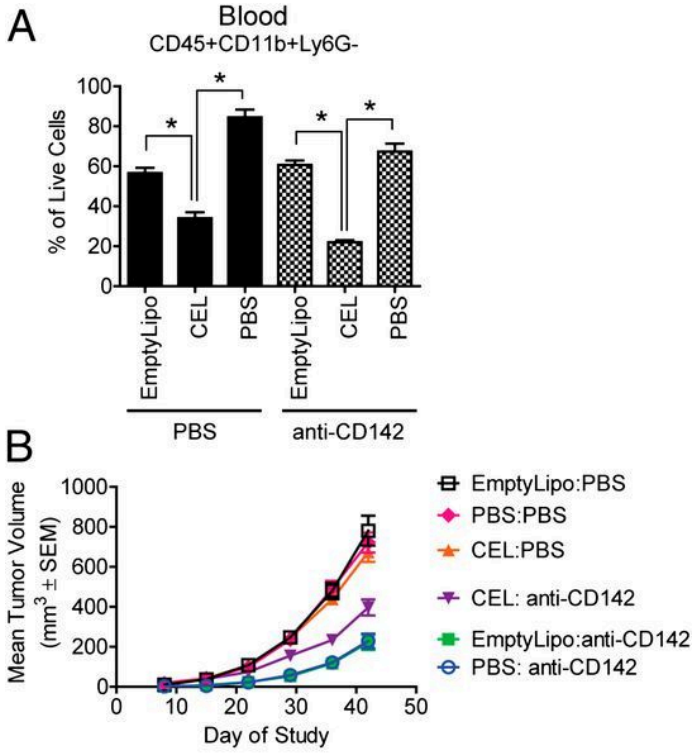

In vivo TAMs enhance tumor suppression under mAb therapy

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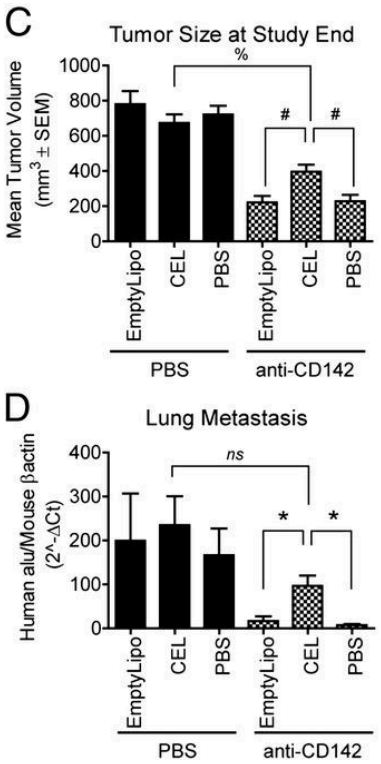

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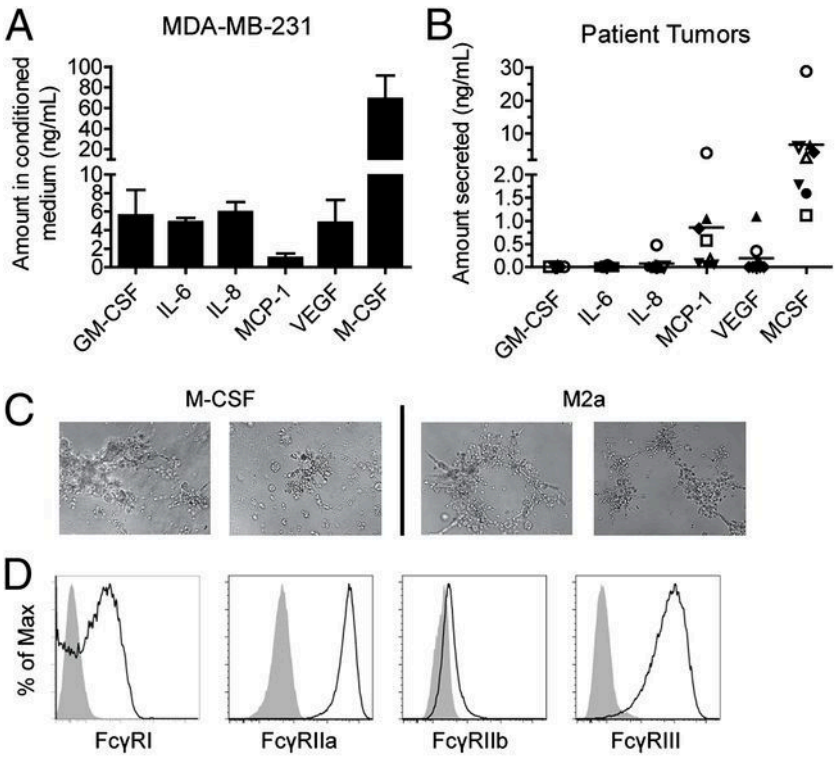

Assessment of differentiating cytokines

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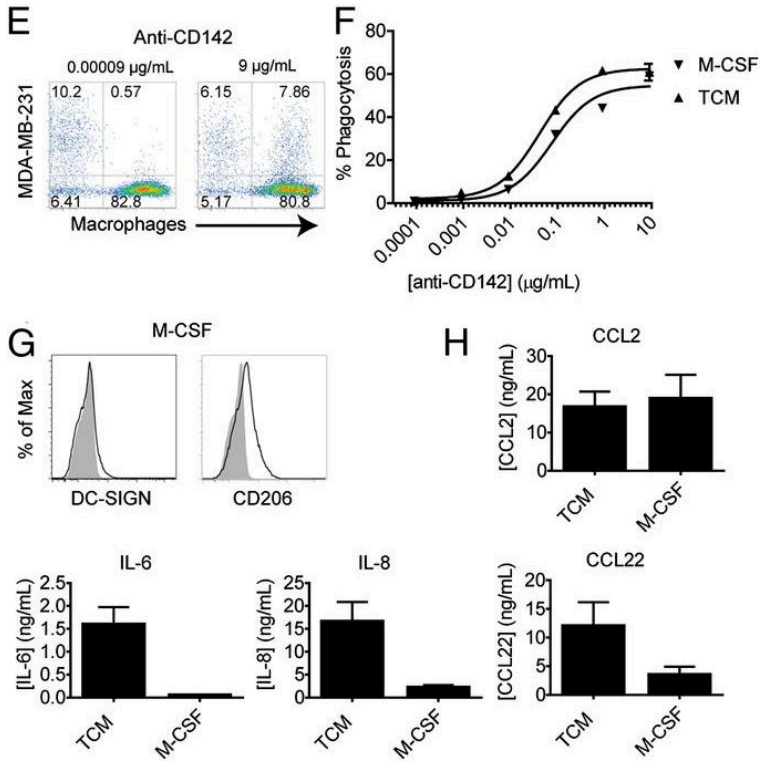

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Discussion

- TCMs
  - promote tumor cell invasion in the absence of tumor-targeting mAbs
  - display potent anti-tumor properties in the presence of tumor-targeting mAbs
- Complex interactions between immune cells, tumor cells and tumor stroma
- Macrophages might play a more important role in mAb therapies than NK cells
- TAMs as therapeutic targets in mAb therapy