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Tumor-associated macrophages

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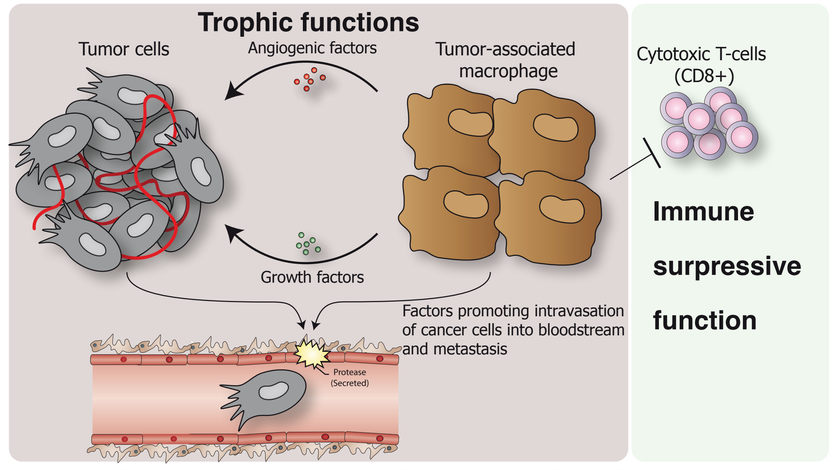
Background

Macrophages are among the most abundant non-cancerous cell in the tumor microenvironment and involvement of tumor-associated macrophages in immune suppression and the pathways leading to invasive disease and metastasis are well documented (Noy and Pollard 2014). Recent advances in the understanding of macrophage biology has revealed that the disease-associated macrophages are very heterogeneous, both in terms of expression profile, origin and role in disease progression. In fact, clinical evidence suggests that most cancers are infiltrated by both pro- and anti-tumoral macrophage subsets. Nevertheless, the specific function of distinct macrophages subsets in disease pathology is still not clear. Our group is focussed on developing new tools using mouse tumor-models as well as genetic and antibody-mediated targeting to further explore the function of distinct macrophage subsets in cancer

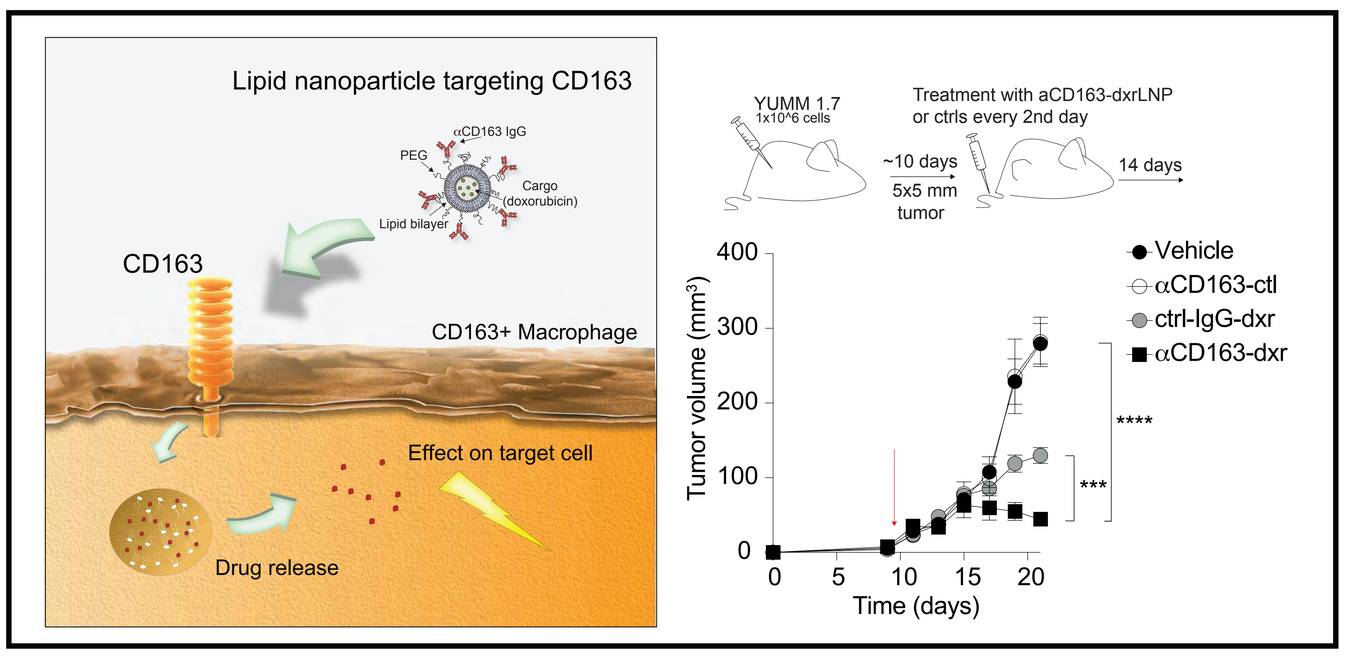


Macrophages are among the most abundant non-cancerous cell in the tumor microenvironment and play a key role in tumor progression. A large body of clinical and experimental evidence has shown that tumor-associated macrophages (TAMs) in addition to immune surpression (e.g. ihibition of cytotoxic T-cells), also promote pathways leading to increased cell invasion and metastasis, including angiogenesis (by release of angiogenic factors), stimulation of proliferation (by release of growth factors), matrix remodeling and epithelial to mesenchymal transition (EMT)

Projects and techniques

When joining our group a wide range of different project will be available and your specific project will depend on your background and interest. In general our group focusses on targeting and understanding the function of distinct macrophage subsets in cancer using a large varity of techniques including antibody generation, cloning, recombinant protein expression, protein engineering, in vitro assays, flow cytometry, cell sorting, confocal microscopy, advanced in-vivo tumor models and RNAseq.

Examples of specific projects: 1. Identification of novel targets on macrophage subsets in cancer. This project involes bioinformatic analysis of own and publicly available datasets from single cell RNAseq. 2. Development of new lipid nanoparticle (LNP) formulations for macrophage targeting. The project will involve encapsulating of small-molecule drugs and optimization of lipid composition and size as well as in vitro and potentially in-vivo validation. 3. Generation of single-chain antibodies against macrophage specific receptors for subset-specific targeting of lipid nanoparticles.



Example of subset specific targeting of tumor-associated macrophages. We have previously developed a cytotoxic lipid nanoparticle that specifically targets cells that expresses the macrophage specific scavenger receptor CD163. (Left) Schematic of aCD163 mAb conjugated lipid nanoparticles (LNP). The LNP contains doxorubicin (dxr) that is a DNA alkylating agent, which induces cell death. (right) Therapeutic depletion of CD163+ TAMs in melanoma bearing mice. Mice (n=6 per group) were injected with $1x10^6$ YUMM1.7 cell s.c. on right flank. When tumours were approx. 5 mm x 5 mm, mice received treatment with doxorubicin containing LNP (dxrLNP) specifcally targeting $CD163^+$ macrophage (aCD163-dxrLNP) or dxrLNPs that target all macrophages (ctrlIgG-dxrLNP) (2 mg/kg dxr) every 2nd day for 2 weeks. PBS (vehicle) or empty aCD163-LNP was used a control. In contrast to pan-targeted LNPs, aCD163-dxrLNP only deplete $CD163^+$ macrophages, which results in an anti-tumor response

Further reading

Noy, Roy, and Jeffrey W Pollard. 2014. "Tumor-Associated Macrophages: From Mechanisms to Therapy." Immunity 41 (1): 49–61.
Etzerodt, A., Maniecki, M. B., Graversen, J. H., Møller, H. J., Torchilin, V. P., & Moestrup, S. K. (2012). Efficient intracellular drug-targeting of macrophages using stealth liposomes directed to the hemoglobin scavenger receptor CD163. Journal of Controlled Release, 160(1), 72–80.