Triggering the resolution of inflammation with agonistic anti-ChemR23 antibody dampens inflammation-driven carcinogenesis and metastasis

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AACR 2021
Poster #1766

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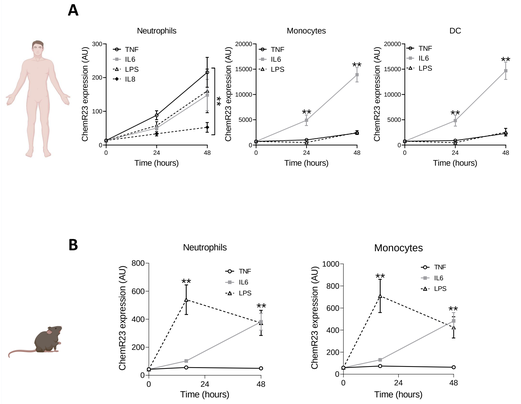
Abstract

Chronic inflammation is associated with abnormal non-phlogistic clearance (efferocytosis) of apoptotic cells by macrophages and a defect of the resolution of inflammation pathways. The **resolution of inflammation** is an **active immunological process** mediated by specialized pro-resolving mediator (SPM) which target specific resolutive G-protein coupled receptors expressed by different immune cells and participate at the return to tissue homeostasis after an injury. Defects in the clearance of (chemotherapy-induced) apoptotic tumor cell debris strengthens inflammation and has been associated with exacerbated tumor growth in several preclinical models. Proresolutive therapeutic approaches, such as using exogenous resolvin E1 (RvE1), the natural lipidic proresolutive ligand of GPCR ChemR23, have been shown to dampen tumor-associated inflammation and to reduce tumor growth. We found that **ChemR23** is inducible on myeloid cells by inflammatory stimuli and mainly **expressed** by **tumor associated macrophages** in melanoma and lung cancers. We identified an agonist anti-ChemR23 mAb that **accelerates the resolution** of inflammation in acute inflammatory model in mice. Finally, we report that **agonist anti-ChemR23** mAb **limits chronic inflammation** in the tumor microenvironment and **inhibits metastasis development**.

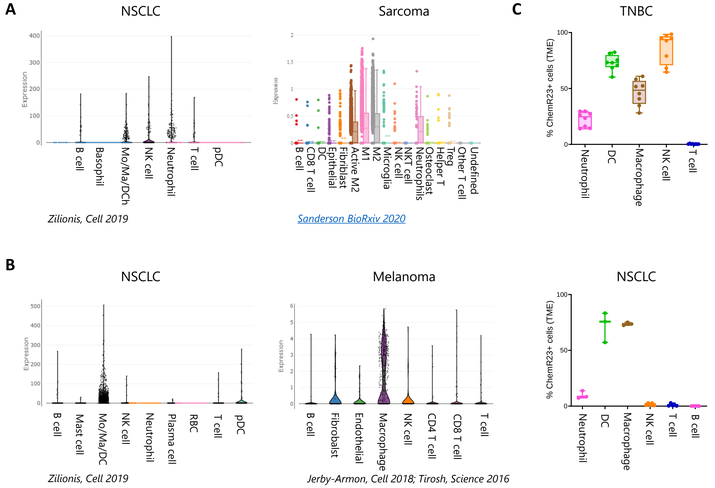
1 ChemR23 expression is inducible upon inflammatory settings

Human PBMCs and neutrophils (A) or bone marrow myeloid cells were subjected to inflammatory cytokines (IL-6, IL-8, TNFα) or TLR ligands (LPS) for 18-24h or 48h and stained for flow cytometry analysis with an anti-ChemR23 mAb.



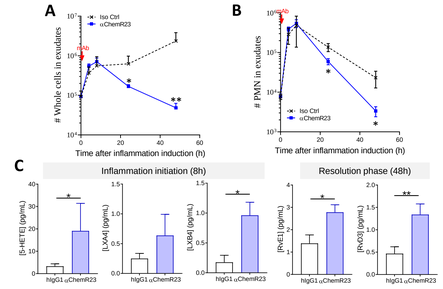
2 ChemR23 is expressed by tumor associated myeloid cells

ChemR23 expression was analyzed on publicly available datasets of scRNAseq from murine tumors (NSCLC:GSE127465 & sarcoma:GSE149751) (**A**) and human tumors (NSCLC:GSE127465 & melanoma:GSE72056 & GSE115978) (**B**) or by flow cytometry on mouse Percoll-isolated immune cells from TNBC and NSCLC solid tumor models (**C**).



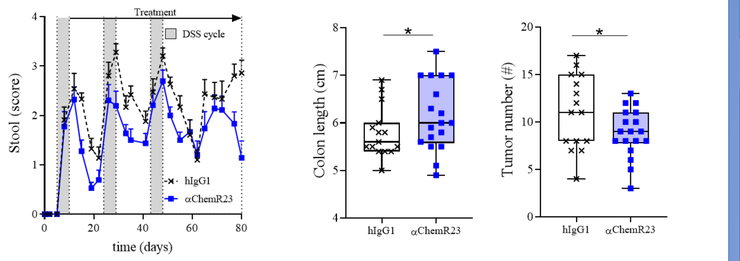
3 Agonist anti-ChemR23 mAb **triggers resolution pathways** in mouse acute inflammation model

Dorsal air pouches were formed on male Balb/c mice (6-8 weeks old) by injecting subcutaneously 3mL of sterile air at d0 and d3. Anti-ChemR23 mAb or hIgG1 control mAb at 1mg/kg were i.p. administered (d5 & d6). On day 6, inflammation was induced by intra-pouch injection of recombinant murine TNF (50ng). Pouch lavages (PBS-EDTA 2mM) were collected at 4, 8, 24, or 48 hours, cells were stained for phenotyping by flow cytometry and SPM dosage was performed by LC-MS/MS.



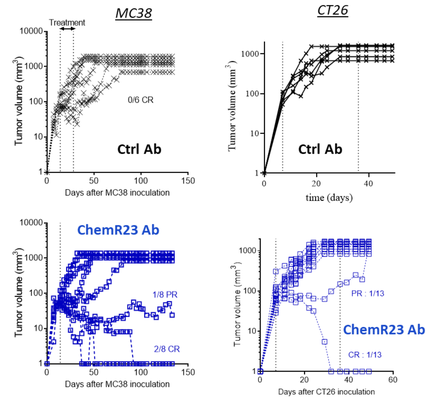
4 Anti-ChemR23 mAb treatment **dampens inflammation** and **limits** inflammatory driven **tumor development**

For the AOM-DSS model, 7-week-old female C57BL/6J mice were intraperitoneally injected with azoxymethane (AOM, 7.5mg/kg, Sigma-Aldrich). 5 days post-injection of AOM, three 5-day cycles of 1% DSS in drinking water separated by 14days of drinking regular water were performed. 80 days after AOM injection, the mice were sacrificed, colon length was measured and the aberrant crypt foci were counted.



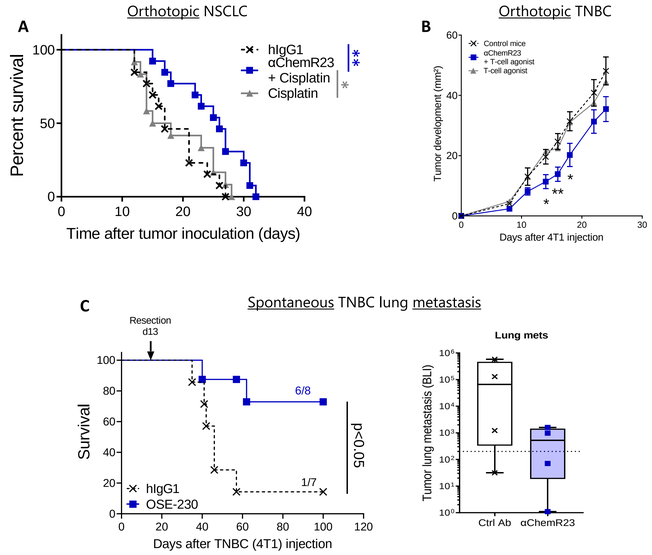
5 Agonist anti-ChemR23 **monotherapy** induces some **complete antitumor response** in CRC

Colorectal carcinoma MC38 cells or CT26 (0.5 x 106 cells/mouse) were injected subcutaneously in 8-week-old C57BL/6J male mice or 8-week-old Balb/c female mice, respectively. Tumor development was measured 3 times a week and calculated as follows: (length*width) 1.5*0.52. Anti-ChemR23 or hIgG1 control mAbs were administered at 1mg/kg when the tumor volume was between 50 and 100mm³ for MC38 and from d7 after tumor inoculation for CT26 for 3 weeks.



6 Anti-ChemR23 **combination** is efficient in **poorly immunogenic cancer** and limits **metastasis** development

The murine non-small cells lung cancer (NSCLC) LLC (0.1x10⁶/mouse) were orthotopically injected into the lung of 7-week-old C57Bl/6J female mice. The anti-ChemR23 mAb, the isotype control (1mg/kg) and/or the chemotherapy (cisplatin 5mg/kg) were i.p. administered from d8 for 3 weeks (N=13 in each group) (**A**). The murine triple negative breast cancer (TNBC) 4T1 cells (0.25x10⁶/mouse) were injected into the fat of the mammary gland of 8-week-old Balb/c female mice. The anti-ChemR23 mAb, the isotype control (1mg/kg, from d8 for 3 weeks), and/or T-cell agonist (anti-4-1BB agonist mAb 3mg/kg, d4 & d8 inj) were i.p. administered (N=5/group) (**B**). The murine Triple Negative Breast Cancer 4T1 cells (0.25x10⁶/mouse) were injected into the fat of the mammary gland of 8-week-old Balb/c female mice. Tumor resection was performed at d13 by surgically removing the primary tumor and metastasis spreading was analyzed on the overall survival and by biochemoluminescence on lungs at d30 (**C**).



Conclusion

- ChemR23 is induced by inflammation and expressed by tumor associated macrophages
- Agonist anti-ChemR23 mAb accelerates the resolution of inflammation and activates resolution circle in acute inflammatory models
- Agonist anti-ChemR23 mAb treatment promotes anti-tumor responses and, limits inflammatory driven tumor development and metastasis spread

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