Suggested Reference


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Towards re-educating macrophages in the melanoma microenvironment with DMXAA

Henare, Kimiora¹, Dunbar, Rod²,³, Print, Cristin²,⁴ and Ching, Lai-Ming¹,²

¹Auckland Cancer Society Research Centre, University of Auckland, Auckland, New Zealand
²Maurice Wilkins Centre for Molecular Biodiscovery, Auckland, New Zealand
³School of Biological Sciences, University of Auckland, Auckland, New Zealand
⁴Department of Molecular Medicine and Pathology, University of Auckland, Auckland, New Zealand

Cancer cells are capable of recruiting macrophages into the tumour and polarising them to adopt phenotypes that facilitate angiogenesis, tissue remodelling, and immunosuppression (M2 protumour phenotype) to perpetuate a microenvironment that is conducive to tumour growth, survival, and metastasis. It has recently been established that M2 macrophages can be repolarised to facilitate immune-mediated tumour rejection and to impede tumour growth (M1 antitumour phenotype). Exploiting macrophage plasticity and developing strategies that can re-educate tumour-associated macrophages from M2 to M1 phenotype is rapidly gaining interest as a novel and powerful approach to cancer intervention.

Several studies in recent years have indicated that the stromal targeting agent, DMXAA can alter the cytokine milieu in murine models of cancer that favours the conversion of M2 to M1 macrophages. These effects are consistently observed with subcutaneous tumour models but there are very few studies investigating the effect of DMXAA on intratumoral macrophages in other sites. This study aimed to characterize the immune infiltrate of murine B16-F10 murine melanomas implanted subcutaneously as well as two other common sites of metastases; pulmonary and intracranial. Immunofluorescence-immunohistochemistry and flow cytometry were used to identify, quantify, and locate leukocyte populations within B16-F10 tumours at each site.

Macrophages and monocytic myeloid cells were the most common leukocytes associated with tumours at all three sites and were predominantly localised at the tumour periphery at the interface with neighbouring normal tissue. In pulmonary and intracranial tumours, many were resident cells such as alveolar macrophages or microglia. Leukocyte abundance was increased by nearly 70% ($p < 0.05$) in the lungs with metastases compared to healthy lungs, due largely to an increase in lymphocytes. Lymphocytes were not specifically localised to metastatic foci and were scattered throughout the lung tissue. Lymphocyte numbers varied significantly between individual subcutaneous B16-F10 melanomas, and were barely quantifiable in brain tissue either with or without an inoculated tumour.

The effect of DMXAA against B16-F10 in different sites is being investigated. DMXAA induced haemorrhagic necrosis in subcutaneous B16-F10 tumours, and caused a modest delay in tumour growth. For reasons yet unclear, preliminary studies of DMXAA against pulmonary B16-F10 nodules showed no significant effects, and activity against intracranial B16-F10 tumours were not attempted following studies from our laboratory that showed DMXAA does not enter the brain efficiently and had no activity against implanted GL261 gliomas. We are investigating immune suppression as a potential explanation for the resistance of B16-F10 tumours to DMXAA.