INVESTIGATING MACROPHAGE MODULATION IN A MURINE MODEL OF SOFT TISSUE SARCOMA

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Background Soft tissue sarcomas (STSs) are a heterogeneous group of malignancies that arise from mesodermal tissue. Generally, STSs are treated with morbid surgical resection and radiation therapy. The STS tumour microenvironment (TME) contains an abundance of macrophages and few lymphocytes. In many malignancies, macrophages can be associated with tumour progression and suppression of lymphocytes. The role of macrophages in STSs needs further investigation. Therefore, the purpose of this study was to modulate macrophages in an immune competent model of STS, and assess the changes in tumour growth and the immune landscape.

Methods Two models were used to modulate macrophages in an immune competent murine STS model; the Macrophage Fas-Induced Apoptosis (MaFIA) model, and the C-C chemokine receptor-2 Knockout (CCR2 KO) model. MaFIA mice express a transgene and can be given a pharmacological agent to induce cell death in CSF1R+ cells. The CCR2 KO model shows a deficiency in recruiting monocytes to inflamed tissue. Both models have reduced tumour macrophages in other murine models. MaFIA and CCR2 KO mice were engrafted with STS cells in the right hindlimb. Tumour volume, macrophages (CD45+, CD11b+, F4/80+, and CD80+ or CD206+), as well as lymphocytes (CD45+, CD3e+, and CD4+ or CD8+) were assessed using flow cytometry.

Results MaFIA mice showed a ~84% decrease (p<0.01) in tumour volume, whereas the CCR2 KO mice and control mice showed no differences in tumour volume. MaFIA mice showed a significant reduction of CSF1R+ macrophages (53%; p<0.01) and CSF1R+, CD206+ macrophages (54%; p<0.05), but no changes to total macrophages. Interestingly, the CCR2 KO mice showed a significant decrease in tumour macrophages (47%; p<0.01), as well as CD206+ macrophages (41%; p<0.01). The MaFIA model showed no differences in lymphocytes, but the CCR2 KO model showed a significant increase in CD8 T cells (360% increase; p<0.01). Interestingly, CSF1R+ ablative treatment was associated with an increased expression of PD1 in the MaFIA model (211%; p<0.01).

Conclusions Both CSF1R and CCR2 modulation diminished macrophage subtypes, but CSF1R modulation did not diminish the total macrophage population. However, only the CCR2 KO model improved lymphocyte (CD8 T cell) infiltration, which did not improve disease outcome. Additionally, CSF1R modulation was associated with an increased PD1 expression. Thus, modulating the CCR2 axis influenced the TME but did not change tumour burden. The CSF1R axis diminished STS tumour burden and macrophage subtypes, and could potentially also sensitize STS tumours to anti-PD1 therapy.

REFERENCES

Ethics Approval Studies involving animals were be conducted according to the Canadian Council on Animal Care guidelines. Ethics approval was obtained from the University of Calgary Health Sciences Animal Care Committee (AC19-0072, 6/25/2021). All mice are housed at the University of Calgary Foothills Campus in a level 2 containment facility.