CD68+ macrophages were found to be closely associated with tumor cells, PD-L1+ macrophages were found to have the closest interaction with tumor cells. The potential of these cell phenotypes to generate a strongly immunosuppressive microenvironment need to be explored in additional cases.

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548 CD8+ TISSUE-RESIDENT MEMORY T CELLS ARE TUMOUR REACTIVE AND INCREASE AFTER IMMUNOTHERAPY IN A CASE OF METASTATIC MUCOSAL MELANOMA

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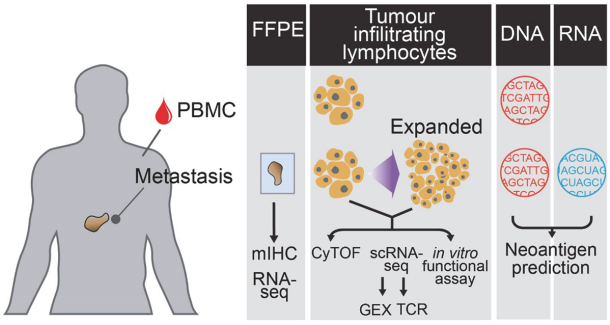
Background Mucosal melanoma is a rare subtype of melanoma originating from mucosal tissues,[1] metastases are very aggressive and respond poorly to therapy, including immune checkpoint inhibitors (ICI) such as anti-CTLA4 and anti-PD1 antibodies.[2–5] CD8+ T cells constitute the most abundant immune infiltrate in metastatic melanoma, of which the Tissue Resident Memory subset (TRM) is of particular interest.[6] CD8+ TRM cells express the highest levels of immune checkpoint receptors, proliferate in response to ICI and correlate with longer disease-free and overall survival.[6–8] The immune landscape in mucosal melanoma remains poorly characterized. We aimed to: 1) phenotype CD8+ T cells and TRM infiltrating metastatic mucosal melanoma, 2) characterize the clonality of TRM in relation to other CD8+ T cell subsets and 3) define the capacity of CD8+ T cells and TRM to respond to melanoma cells and to in vivo and in vitro anti-PD1 treatment.

Methods We investigated the CD8+ T and TRM cells infiltrating two temporally- and spatially-distant subcutaneous metastases, these originated from a primary vaginal mucosal melanoma. One metastasis was excised prior to anti-PD1 treatment and one was anti-PD1 refractory, having progressed on treatment. We used mass cytometry and single-cell RNA and TCR sequencing to characterise the phenotype and clonality of the T cells, multiplex immunohistochemistry to define their spatial relationship with tumour cells and other T cells, and functional assays to determine TRM response to tumour cells (figure 1).

Results CD8+ TRM frequency increased with time and anti-PD1 treatment, forming clusters at the tumour margin. T cells in the anti-PD1 refractory lesion were more activated than T cells in the first tumour and were bound by anti-PD1 antibody in vivo. T cells could not be stimulated by anti-PD1 directly ex vivo. Both metastatic lesions shared common T cell clusters including TRM. Furthermore, TRM in each tumour shared T cell clones, suggesting the presence of common antigens between metastatic sites. Indeed, the two metastases had a similar mutational profile. In vitro expanded tumour infiltrating lymphocytes from both lesions recognized tumour cells from both lesions and the same neoantigen generated from a single point mutation in the gene CDKN1C. Finally, tumour cells stimulated TRM cells more robustly than other T cells subsets.



Abstract 548 Figure 1 Graphical depiction of the methods used to characterise T cells in mucosal metastatic melanoma

Conclusions In this patient with vaginal mucosal melanoma, subsequent melanoma metastases of clonal origin attracted CD8+ T cells of similar specificity, among which TRM cells responded more vigorously to tumour cells than other T cells subsets.

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Ethics Approval Patients diagnosed with stage 3 or 4 metastatic melanoma and undergoing clinically indicated surgery were enrolled in prospective studies approved by the Peter MacCallum Cancer Centre human ethics research committee (13/141). All experimental protocols have been approved and clinical data has been collected prospectively.

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549 CHARACTERIZING DOUBLE POSITIVE T CELLS IN THE TUMOR MICROENVIRONMENT: A TALE OF PROMISCUOUS CELL FATES

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