The hypoxic microenvironment at different sites of melanoma metastasis

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BACKGROUND

- Whilst immune checkpoint inhibitors (ICI) have greatly improved survival rates in patients with advanced melanoma, a majority will still present with innate resistance or develop resistance during treatment[1].
- Hypoxia is a known feature of the tumour microenvironment and certain hypoxic profiles have been associated with a poorer prognosis and reduced response to ICI[2,3].
- The site of metastasis has also emerged as a predictive feature of response to ICI. Liver metastases in particular are associated with a reduction in response to ICI in melanoma patients[4,5].
- To date, the differences in the hypoxic environment between different sites of melanoma metastasis are understudied, and this may highlight hypoxia related mechanisms of resistance on an organ-specific basis.

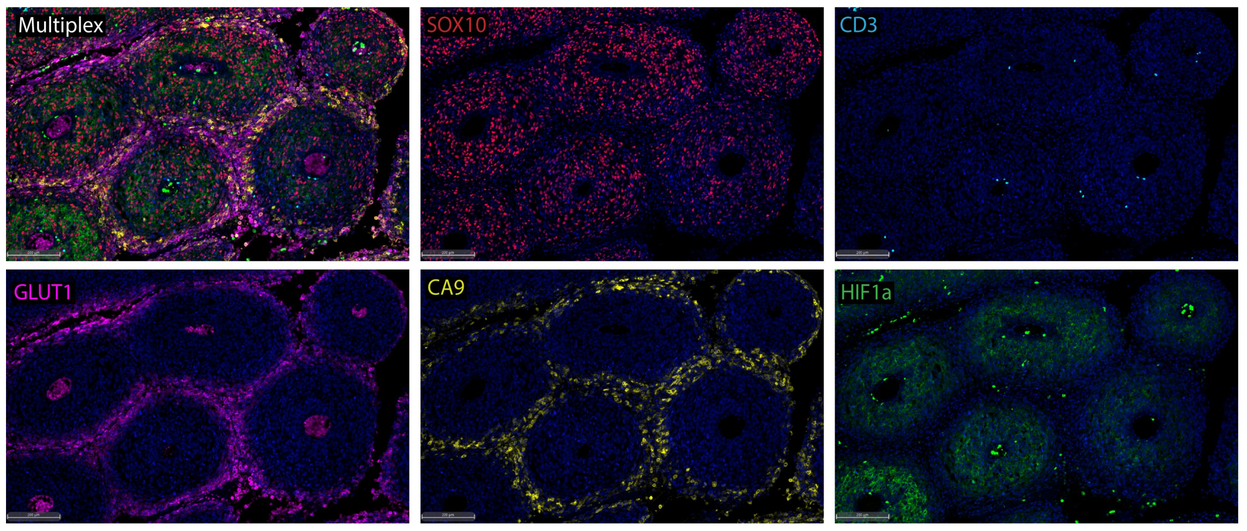
OBJECTIVES

- To characterise and compare the hypoxic environment between different sites of metastasis
- To provide insight into the biology of melanoma metastases at different sites of disease and identify potential mechanisms of resistance to immune checkpoint inhibitors

METHODS

- RNA sequencing and differential expression analysis (between patients with liver metastases [n=58] versus patients without liver metastases [n=28]) was performed on FFPE melanoma samples from non-liver biopsies from patients with untreated metastatic melanoma.
- 43 FFPE melanoma biopsies (liver metastases [n=16], brain metastases [n=14] and lung metastases [n=13]) from untreated metastatic melanoma patients were identified and used for opal multiplex IHC (mIHC):
  - *mIHC Panel*: T cell marker (CD3), melanoma marker (SOX10) and the hypoxia markers (CA9, HIF1α and GLUT1)
  - *Analysis*: Total cell densities, co-expression, and spatial distribution.

Figure 1. Representative staining of the multiplex IHC panel



RESULTS

Figure 2. RNA sequencing differential expression analysis in patients with (n=58) versus without (n=28) liver metastases

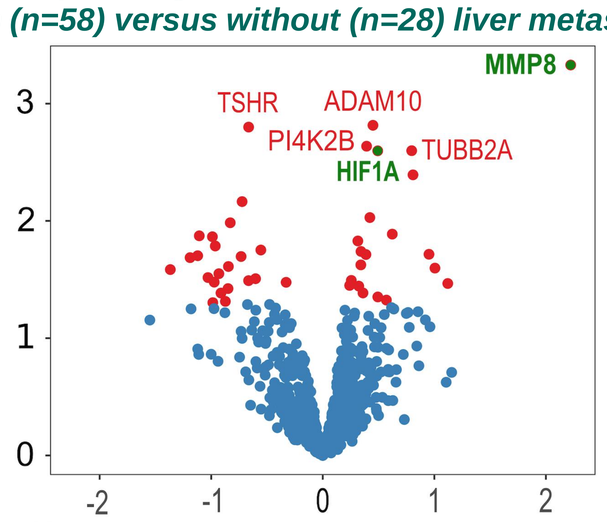


Figure 3. Expression of hypoxic markers (mIHC) in different metastatic sites

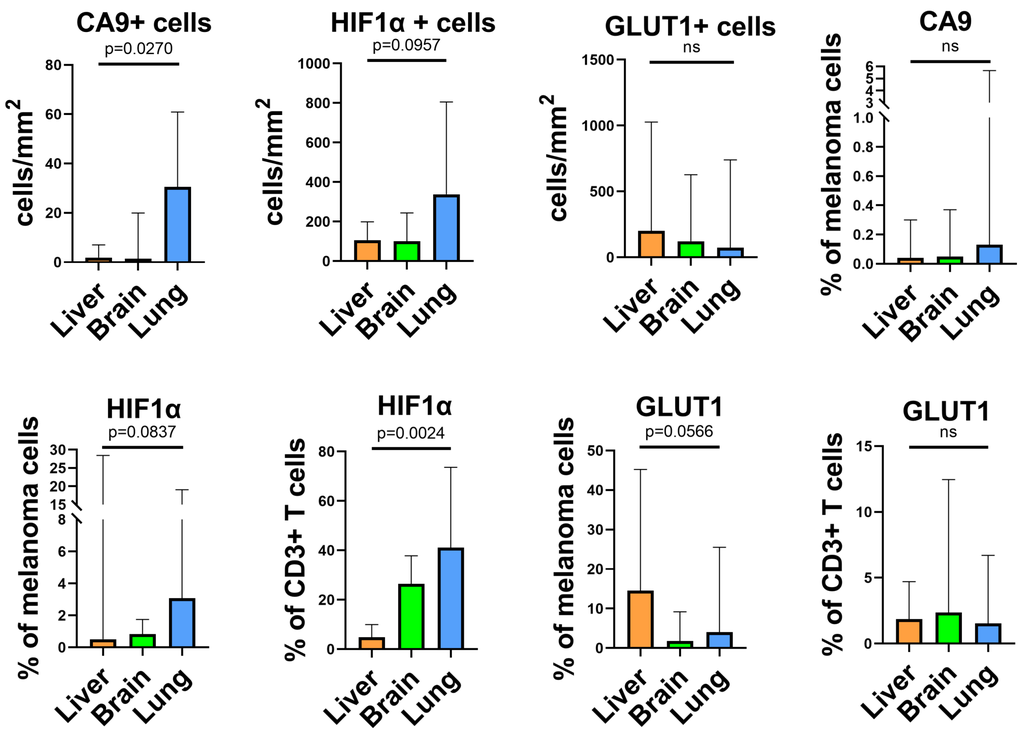


Figure 4. Representative images of a vascularized and non vascularized tumour

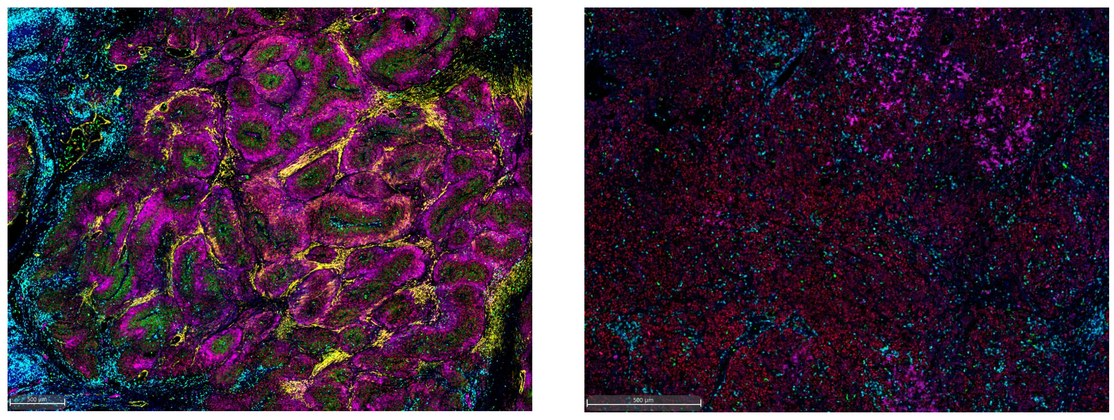
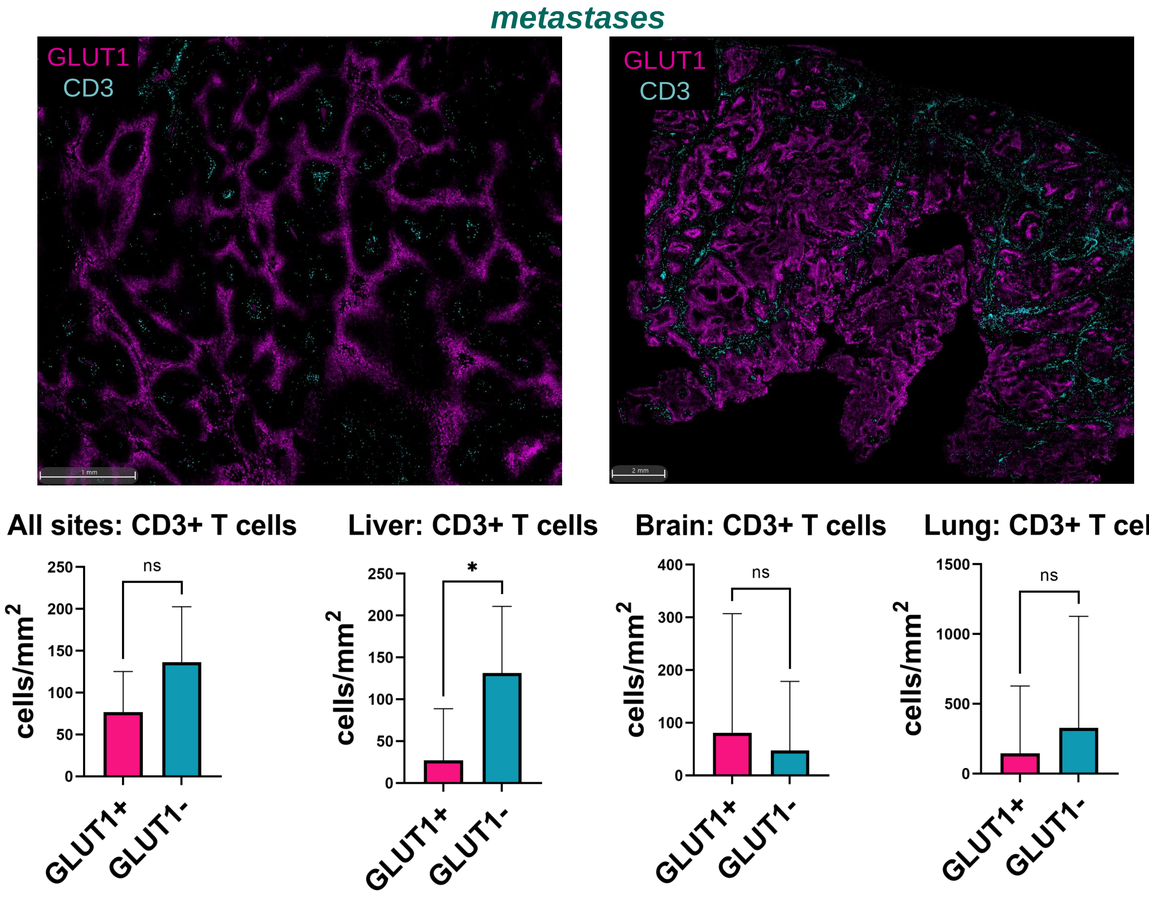


Figure 5. GLUT1 positive tumour regions have fewer CD3+ T cells in liver metastases



CONCLUSIONS

- **Biopsies from non-liver metastases in patients with concurrent liver metastases have higher transcriptional expression of hypoxia markers compared to patients without liver metastases.**
- **There are differences in the hypoxic profiles between different sites of metastasis.**
- **GLUT1 expressing tumour regions in melanoma liver metastases have a reduced T cell density compared to GLUT1 negative regions.**

REFERENCES

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