Neuro Oncol. 2024 May 2:noae085. doi: 10.1093/neuonc/noae085. Online ahead of print.

Immunotherapy drives mesenchymal tumour cell state shift and TME immune response in glioblastoma patients

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PMID: 38695342 DOI: 10.1093/neuonc/noae085

Abstract

Background: Glioblastoma is a highly aggressive type of brain tumour for which there is no curative treatment available. Immunotherapies have shown limited responses in unselected patients, and there is an urgent need to identify mechanisms of treatment resistance to design novel therapy strategies.

Methods: Here we investigated the phenotypic and transcriptional dynamics at single-cell resolution during nivolumab immune checkpoint treatment of glioblastoma patients.

Results: We present the integrative paired single-cell RNA-seq analysis of 76 tumour samples from patients in a clinical trial of the PD-1 inhibitor nivolumab and untreated patients. We identify a distinct aggressive phenotypic signature in both tumour cells and the tumour microenvironment in response to nivolumab. Moreover, nivolumab-treatment was associated with an increased transition to mesenchymal stem-like tumour cells, and an increase in TAMs and exhausted and proliferative T cells. We verify and extend our findings in large external glioblastoma dataset (n = 298), develop a latent immune signature and find 18% of primary glioblastoma samples to be latent immune, associated with mesenchymal tumour cell state and TME immune response. Finally, we show that latent immune glioblastoma patients are associated with shorter overall survival following immune checkpoint treatment (p = 0.0041).

Conclusions: We find a resistance mechanism signature in a quarter of glioblastoma patients associated with a tumour-cell transition to a more aggressive mesenchymal-like state, increase in TAMs and proliferative and exhausted T cells in response to immunotherapy. These patients may instead benefit from neuro-oncology therapies targeting mesenchymal tumour cells.

Keywords: Glioblastoma; TME; immunotherapy; mesenchymal; scRNA-seq.

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