ABSTRACT

Stem Cells. 2022 Dec 30:sxac088. doi: 10.1093/stmcls/sxac088. Online ahead of print.

The heterogeneous cellular states of glioblastoma stem cells revealed by single cell analysis.

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Glioblastoma stem cells (GSCs) contributed to the progression, treatment resistance and relapse of glioblastoma (GBM). However, current researches on GSCs were performed usually outside the human tumor microenvironment, ignoring the importance of the cellular states of primary GSCs. In this study, we leveraged single-cell transcriptome sequencing data of six independent GBM cohorts from public databases, and combined lineage and stemness features to identify primary GSCs. We dissected the cell states of GSCs and correlated them with the clinical outcomes of patients. As a result, we constructed a cellular hierarchy where GSCs resided at the center. In addition, we identified and characterized two different and recurrent GSCs subpopulations: proliferative GSCs (pGSCs) and quiescent GSCs (qGSCs). The pGSCs showed high cell cycle activity, indicating rapid cell division, while qGSCs showed a quiescent state. Then we traced the processes of tumor development by pseudo-time analysis and tumor phylogeny, and found that GSCs accumulated throughout the whole tumor development period. During the process, pGSCs mainly contributed to the early stage and qGSCs were enriched in the later stage. Finally, we constructed an 8-gene prognostic signature reflecting pGSCs activity and found that patients whose tumors were enriched for the pGSC signature had poor clinical outcomes. Our study highlights the primary GSCs heterogeneity and its correlation to tumor development and clinical outcomes, providing the potential targets for GBM treatment.

DOI: 10.1093/stmcls/sxac088
PMID: 36583266