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Individual glioblastoma cells harbor both proliferative and invasive capabilities during tumor progression

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Abstract

Background: Glioblastomas are characterized by aggressive and infiltrative growth, and by striking heterogeneity. The aim of this study was to investigate whether tumor cell proliferation and invasion are interrelated, or rather distinct features of different cell populations.

Methods: Tumor cell invasion and proliferation was longitudinally determined in real time using 3D in vivo two-photon laser scanning microscopy over weeks. Glioblastoma cells expressed fluorescent markers that permitted the identification of their mitotic history or their cycling versus non-cycling cell state.

Results: Live reporter systems were established that allowed to dynamically determine the invasive behavior, and previous or actual proliferation of distinct glioblastoma cells, in different tumor regions and disease stages over time. Particularly invasive tumor cells that migrated far away from the main tumor mass, when followed over weeks, had a history of marked proliferation and maintained their proliferative capacity during brain colonization. Infiltrating cells showed fewer connections to the multicellular tumor cell network, a typical feature of gliomas. Once tumor cells colonized a new brain region, their phenotype progressively transitioned into tumor microtube-rich, interconnected, slower-cycling glioblastoma cells. Analysis of resected human glioblastomas confirmed a higher proliferative potential of tumor cells from the invasion zone.

Conclusion: The detection of glioblastoma cells that harbor both particularly high proliferative and invasive capabilities during brain tumor progression provides valuable insights into the interrelatedness of proliferation and migration - two central traits of malignancy in glioma. This contributes to our understanding how the brain is efficiently colonized in this disease.

Keywords: Glioblastoma; cancer neuroscience; migration; proliferation; tumor microtubes (TMs).