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Neoplasia. 2011 Sep;13(9):784-91.

Invasion precedes tumor mass formation in a malignant brain tumor model of genetically modified neural stem cells.

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Abstract

Invasiveness, cellular atypia, and proliferation are hallmarks of malignant gliomas. To effectively target each of these characteristics, it is important to understand their sequence during tumorigenesis. However, because most gliomas are diagnosed at an advanced stage, the chronology of gliomagenesis milestones is not well understood. The aim of the present study was to determine the onset of these characteristics during tumor development. Brain tumor-initiating cells (BTICs) were established by overexpressing H-Ras(V12) in normal neural stem/progenitor cells isolated from the subventricular zone of adult mice harboring a homozygous deletion of the Ink4a/Arf locus. High-grade malignant brain tumors were then created by orthotopic implantation of 10(5) BTICs into the forebrain of 6-week-old wild-type mice. Micewere killed every week for 5 weeks, and tumors were assessed for cellular atypia, proliferation, hemorrhage, necrosis, and invasion. All mice developed highly invasive, hypervascular glioblastoma-like tumors. A 100% penetrance rate and a 4-week median survival were achieved. Tumor cell migration along fiber tracts started within days after implantation and was followed by perivascular infiltration of tumor cells with marked recruitment of reactive host cells. Next, cellular atypia became prominent. Finally, mass proliferation and necrosis were observed in the last stage of the disease. Video monitoring of BTICs in live brain slices confirmed the early onset of migration, as well as the main cell migration patterns. Our results showed that perivascular and intraparenchymal tumor cell migration precede tumor mass formation in the adult brain, suggesting the need for an early and sustained anti-invasion therapy.

PMID: 21969812 [PubMed - in process] PMCID: PMC3182271 **Free PMC Article**

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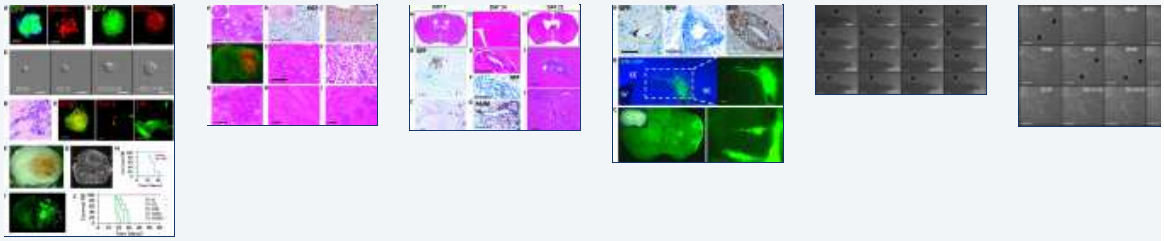

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