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Drosophila melanogaster as a model system for human brain cancers.

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Abstract

Glioblastomas (GBM), the most common primary brain tumors, infiltrate the brain, grow rapidly, and are refractory to current therapies. Signature genetic lesions in glioblastomas include mutation of the epidermal growth factor receptor tyrosine kinase (EGFR) receptor tyrosine kinase and activating mutations in components of the PI-3 kinase (PI3K) pathway. Despite years of study, how these pathways specifically regulate glial pathogenesis is unclear. To address the genetic and cellular origins of this disease, a novel *Drosophila* GBM model has been developed in which glial progenitor cells give rise to proliferative and invasive neoplastic cells that create transplantable tumors in response to constitutive co-activation of the EGFR-Ras and PI3K pathways. Standing with a rich literature demonstrating the direct relevance of *Drosophila* to studies on human cancer, neurological disease, and neurodevelopment, this model represents a robust cell-type specific *Drosophila* neurological disease model in which malignant cells are created by mutations in genetic pathways thought to be driving forces in a homologous human disease. Using lineage analysis and cell-type specific markers, neoplastic glial cells were found to originate from committed glial progenitor cells, rather than from multipotent neuroblasts. Genetic analyses demonstrated that EGFR-Ras and PI3K induce fly glial neoplasia through activation of a combinatorial genetic network composed, in part, of other genetic pathways also commonly mutated in human glioblastomas. In the future, large-scale forward genetic screens with this model may reveal new insights into the origins and treatments of human glioblastoma. © 2011 Wiley-Liss, Inc.

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