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PDGF autocrine stimulation dedifferentiates cultured astrocytes and induces oligodendrogliomas and oligoastrocytomas from neural progenitors and astrocytes in vivo.

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We present evidence that some low-grade oligodendrogliomas may be comprised of proliferating glial progenitor cells that are blocked in their ability to differentiate, whereas malignant gliomas have additionally acquired other mutations such as disruption of cell cycle arrest pathways by loss of Ink4a-Arf. We have modeled these effects in cell culture and in mice by generating autocrine stimulation of glia through the platelet-derived growth factor receptor (PDGFR). In cell culture, PDGF signaling induces proliferation of glial precursors and blocks their differentiation into oligodendrocytes and astrocytes. In addition, coexpression of PDGF and PDGF receptors has been demonstrated in human gliomas, implying that autocrine stimulation may be involved in glioma formation. In this study, using somatic cell type-specific gene transfer we investigated the functions of PDGF autocrine signaling in gliomagenesis by transferring the overexpression of PDGF-B into either nestin-expressing neural progenitors or glial fibrillary acidic protein (GFAP)-expressing astrocytes both in cell culture and in vivo. In cultured astrocytes, overexpression of PDGF-B caused significant increase in proliferation rate of both astrocytes and neural progenitors. Furthermore, PDGF gene transfer converted cultured astrocytes into cells with morphologic and gene expression characteristics of glial precursors. In vivo, gene transfer of PDGF to neural progenitors induced the formation of oligodendrogliomas in about 60% of mice by 12 wk of age; PDGF transfer to astrocytes induced the formation of either oligodendrogliomas or mixed oligoastrocytomas in about 40% of mice in the same time period. Loss of Ink4a-Arf, a mutation frequently found in high-grade human gliomas, resulted in shortened latency and enhanced malignancy of gliomas. The highest percentage of PDGF-induced malignant gliomas arose from of Ink4a-Arf null progenitor cells. These data suggest that chronic autocrine PDGF signaling can promote a proliferating population of glial precursors and is potentially sufficient to induce gliomagenesis. Loss of Ink4a-Arf is not required for PDGF-induced glioma formation but promotes tumor progression toward a more malignant phenotype.

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