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The CD95 Signaling System:
A Novel Mediator of Glioma Cell Invasion in the Brain

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Glioblastoma multiforme (WHO grade IV) constitutes the most common primary brain tumor in the adult central nervous system. This neoplasm is characterized by a highly invasive phenotype, making complete surgical resection impossible. Furthermore, most glioblastomas exhibit a striking proliferation rate and extraordinary resistance towards radio- or chemotherapy, resulting in an extremely poor prognosis with a five year survival rate of less than 5%. So far, extensive research efforts have not allowed to fully unravel the mechanisms of glioma cell migration. New therapeutic concepts are based on the induction of apoptosis in glioma cells, often focusing on the CD95 system (APO-1/FAS), which is well known for its apoptosis-inducing properties.
In our laboratory, we identified CD95 as an important mediator of invasion in glioblastoma multiforme. Stimulation of the CD95 receptor on apoptosis resistant glioblastoma cells fails to induce the formation of a death-inducing signaling complex (DISC), but results in recruitment and activation of the tyrosine kinase YES and the regulatory p85 subunit of the phosphatidylinositol-3-kinase (PI3K) to the CD95 receptor. Through inhibition of the glycogen synthase kinase 3β (GSK-3β) and subsequent translocation of β-catenin into the nucleus, synthesis of matrix metalloproteinases and invasion of glioblastoma cells into the surrounding parenchyma are significantly increased. The invasion-inducing effect of CD95 could not only be shown in established cell lines, but also in short-term glioma cultures derived from human tumor samples.
In the present study, the impact of CD95 on the invasion of glioblastoma cells was assessed *in vivo*. In order to allow for a physiologic tumor-host interaction, a syngeneic glioma model was chosen. After injection of 5.000 SMA-560 cells, a murine glioblastoma cell line, into the striatum of syngeneic Vm/Dk mice, solid tumors developed within fourteen days. These tumors displayed features characteristic of glioblastoma multiforme including diffuse invasion into the surrounding parenchyma, necrosis, bleeding or neovascularization. *Ex vivo* analysis of these tumor cells revealed a significant increase in surface levels of both CD95 receptor and ligand. Blockade of the CD95 system by means of a neutralizing antibody to the CD95 ligand strikingly reduced invasion of the contralateral hemisphere by tumor cells *in vivo* by more than 50%. In comparison to control animals, the invasive behavior was markedly attenuated.
These results demonstrate an important role of the CD95 system for the highly invasive nature of glioblastoma *in vivo*. Furthermore, they provide the basis for the development of new anti-invasive therapeutic strategies via modulation of this signal transduction pathway.