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CD95 identifies glioblastoma stem cells

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CD95 (also known as FAS and APO-1) is well known as a classical death receptor able to induce apoptosis - programmed cell death. Recently however, knowledge about the function of CD95 is evolving in another direction. Non-apoptotic CD95 signaling has been shown to mediate the activation of neural stem cells and the recruitment of immune cells in response to injury. In a variety of malignancies, CD95 promotes invasion, tumor growth and cancer stem cell activity. Based upon this knowledge, this study seeks to elucidate, whether CD95 does identify and is relevant for the biological properties of glioblastoma stem cells.

Surgical glioblastoma samples were obtained from neurosurgical clinics in Berlin and Mannheim. Within these samples, a population of $CD95^{high}$ cells co-expressing well known glioblastoma stem cell markers is identified. These potential, $CD95^{high}$ glioblastoma stem cells display marked self-renewal *in vitro* - a property that can be abrogated by blockade of CD95 signaling.
In vivo, $CD95^{high}$ glioblastoma stem cells are able to craft tumors with high efficiency over serial passages while showing superior tumor growth properties. Tracking of individual, lentivirally marked $CD95^{high}$ glioblastoma stem cell clones highlights their ability to establish a hierarchical lineage within a tumor.
Fitting the notion that cancer stem cells are highly resistant to therapy, expression of CD95 - as well as its ligand - increases in recurrent patient tumors after treatment.
In the comprehensive dataset provided by The Cancer Genome Atlas, CD95 is overexpressed in glioblastoma compared to normal brain tissue. Even more, low CD95 expression is a prognostic marker indicating a favorable prognosis regarding overall and recurrence-free survival in glioblastoma patients.
An epithelial-to-mesenchymal transition process has been shown to maintain the cancer stem cell state and strikingly, a mesenchymal gene expression profile is detected in $CD95^{high}$ GSCs.

Taken together, the findings presented here identify CD95 as a novel, bona fide surface marker for glioblastoma stem cells. Blocking CD95 signaling by a CD95-Fc fusion protein (APG101) has already successfully been tested as a novel therapeutic approach in GBM patients based on the idea that CD95 promotes invasion of glioblastoma cells. The results of this study indicate, that the remarkable effect of APG101 might partially be to a direct therapeutic effect on the glioblastoma stem cell pool.