Growth regulation and cellular crosstalk in human glioma

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Abstract

Objective:

Malignant brain tumors are amongst the most lethal solid tumors. The standard treatment consists of surgical resection followed by adjuvant radio- and chemotherapy. It has been proposed that glioma cells with stem cell features, designated SCLC hereafter, contribute to initiation and progression of primary and recurrent glioma. Regulation of SCLC and non-SCLC growth and the crosstalk amongst them remains largely elusive.

Material and methods:

Up to now, we screened 80 human brain tumors for the presence and features of SCLC. We expanded brain tumor cells in vitro and analyzed the expression of receptor tyrosine kinases and peptide growth factors in SCLC and non-SCLC by means of immunological staining as well as Western blot analysis and real time PCR. In addition, we investigated mitogen dependence (growth curves, proliferation and cell survival assays) and differentiation (immunocytochemistry) in the absence of exogenously provided growth factors.

Results and conclusions:

We identified stem cell-like cells (SCLC) in all brain tumor biopsies analyzed so far. These cells exhibited a substantial heterogeneity with respect to morphology, proliferation rate, growth modus and the expression of neural markers and stemness factors. Therefore, we refer to these cells as SCLC subtypes. Both, SCLC and non-SCLC from the same tumor co-expressed several receptor tyrosine kinases (RTK), including EGFR/HER1 and the SCF (stem cell factor) receptor cKIT. Co-expression of RTKs and their corresponding ligands was observed in several cultures, indicating that SCLC and non-SCLC might stimulate themselves by autocrine mechanisms. Besides the full-length receptors, a truncated EGFR/HER1 and cKIT was observed in several cultures, indicating that these brain tumor cells may be activated in the absence of HER1 ligands and SCF, respectively. Secretion of the growth factors EGF and SCF was observed using cytokine ELISA techniques. In keeping with this, the dependence on growth factors supplied with the medium was low and varied amongst the various SCLC and non-SCLC cultures. In addition, the RTK expression level of SCLC and non-SCLC from the same tumor differed. Together our data suggest that the human brain tumors cells exert intracrine and autocrine growth control and cross-talk via paracrine mechanisms.