Proceedings of German Society for Stem Cell Research (PGSSCR)
(5th Annual Meeting)
Tumor stem cells – P43

Therapy responsiveness of stem-like human glioma cells
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Published on 23 Oct 2010

Glioblastoma multiforme (GBM) is one of the most lethal solid tumors. GBMs grow invasively, develop resistance to radiation and chemotherapy, and frequently recur. The gold standard in GBM therapy is concurrent radiochemotherapy, using the alkylating compound temozolomide (TMZ). It has been proposed that stem-like tumor cells mediate therapy resistance and regrowth. Furthermore, resistance against TMZ seemed related to an altered apoptotic and autophagic death machinery. We determined the responsiveness of subtypes of stem-like glioma cells to TMZ and chloroquine, compared it to the behaviour of the established glioma cell line U87, related it to the expression of MGMT and ABC-transporters, and analyzed apoptotic and autophagic processes.

All of the primary cultures with stem-like cells exhibited self-renewal, although growth behaviour and proliferation rate differed largely. CD133 expression varied between different cell lines. Dose curves showed that responsiveness to TMZ was significantly different between the various stem-like cell lines, as BrdU incorporation was inhibited with different efficacy. Strong responsiveness to TMZ was related to the methylation of the MGMT promoter, but not to the expression levels of the ABC-transporters analyzed or p53. Co-application of chloroquine, a drug used in malaria prevention, which presumably affects autophagy, enhanced responsiveness of stem-like cells and U87 to TMZ in vitro. Western blot analysis showed that TMZ induced apoptotic cell death in stem-like cells, although less efficiently in the MGMT-positive cell lines. In addition, MGMT+ cells showed down-regulation of autophagy related proteins, which might contribute to processes that impair TMZ-induced cytotoxicity. The co-application of chloroquine and TMZ resulted in an increase of autophagic cell death in most cases. In addition, in several subtypes of stem-like cells, co-application of TMZ and chloroquin could additionally promote apoptotic cell death. Our results suggest that co-application of chloroquine might in part overcome the resistance to TMZ by promoting cell death.