Proceedings of German Society for Stem Cell Research (PGSSCR)
(5th Annual Meeting)
Tumor stem cells – P62

Acquired resistance to cytostatics triggers cancer stem-cell-like phenotype in different tumor entities

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Published on 23 Oct 2010

Background: Relapse of cancer occurs months or even years after apparently successful treatment. The principal cause of failure in second line chemotherapy is the acquired resistance to cytostatics. Probably, the reason for the appearance of chemotherapy refractory cancers is the survival of cancer stem cells (CSCs) since they are known to show MDR phenotypes and radio resistance. Our previous studies demonstrate that cancer cell lines of different tumor entities show characteristics of CSCs after induction of chemotherapy resistance to etoposide or doxorubicin. Here, we aim at characterizing the CSC properties in chemotherapy refractory cell lines.

Methods: Resistance and cross-resistance to etoposide and doxorubicin were monitored by MTT proliferation assay. The gene expression of CSC markers was performed using both conventional RT-PCR and qPCR. The protein expression of these markers was corroborated applying ICC and IHC. The resistance to ionizing radiation was analyzed by exposition of cells to gamma radiation.

Results: Our studies revealed that etoposide resistant entities displayed significant differences in the expression of stem cell markers compared to their parental cell lines. For neuroblastoma, prostate and glioblastoma cancer cell lines characteristic stem cell markers (CD34, CD44, CD117, CXCR4 and p75NTR) were found to be significantly and sustainably upregulated in etoposide-resistant sublines which also show cross-resistance to doxorubicin and high radioresistance. Furthermore, we corroborated that many of these pleiotropic effects were maintained when cells were xenographed into nude mice.

Conclusions: In view of the fact that etoposide and doxorubicin are commonly used clinical agents for treatment of many different types of cancer, the induction of CSCs by these cytostatics should be investigated in order to disclose selection of chemorefractory CSC during treatment, a phenomenon which might account for an eventual progression to intractable tumors. Moreover, such undesirable adverse events must be investigated for others MDR-phenotype inducing cytostatics. These novel findings could generate more knowledge about the pleiotropic effects of therapeutics on the cell biology particularly of clinically aggressive tumors. Consequently, improved cure rates...
may be achieved via identification and therapeutic targeting of remanent chemotherapy resistant metastatic CSCs.