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Characterization of a side population of astrocytoma cells in response to temozolomide.

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Abstract

OBJECT: Cancer progenitor-like cells isolated by Hoechst 33342 dye efflux (termed the "side population" [SP]) have been studied in a variety of cancers, including malignant brain tumors. In this study, the authors investigate the nature of the SP phenotype in 2 glioma cell lines, U87MG and T98G, and their response to temozolomide. The roles of several adenosine triphosphate-binding cassette (ABC) multidrug transporters expressed by SP cells, in particular ABCG2, are also examined.

METHODS: Using fluorescence-activated cell sorting, the cells were separated into SP and non-SP fractions and analyzed for progenitor cell-like properties with immunofluorescence staining, quantitative real-time polymerase chain reaction, and their ability to reform glioma mass in an immune-compromised mouse. The response of the SP cells to temozolomide was investigated at the cellular and molecular levels. Small interfering RNA knockdown was used to examine the specific role of the ABCG2 transporter, and the cells' tumorigenic potential was measured using the soft agar clonogenic assay.

RESULTS: Side population cells are characterized by the presence of progenitor cell-like properties: increased expression of nestin, musashi-1, and ABCG2 were observed. In addition, only SP cells were able to reconstitute cellular heterogeneity; these cells were also more invasive than the non-SP cells, and possessed tumorigenic capacity. Temozolomide treatment increased the number of SP cells, and this corresponded to more progenitor-like cells, concurrent with elevated expression of several ABC transporters.

CONCLUSIONS: Knockdown of ABCG2 transporters did not abrogate the SP cell response to temozolomide. Upregulation of several other ABC drug transporter genes is proposed to account for this chemoresistance.

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