USE OF A RAT GLIOMA CELL MODEL SYSTEM TO ISOLATE NEW MOLECULAR TARGETS FOR HUMAN GLIOBLASTOMA.

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Despite the numerous efforts and important recent advances, early diagnosis and treatment of glioblastoma still pose difficult barriers. Although glucocorticoids (GCs) are used in chemotherapy, surgical ressection still remains as the sole resource for this commonly fatal tumor of the Central Nervous System. In search for new diagnostic molecular markers and novel therapeutic targets, we adopted the C6 rat glioma cell model system and its variants: ST1 and P7, which are, respectively, hyper-responsive and resistant to GC treatment. Oligo DNA microarrays (Affymetrix platform) and subtractive hybridization were used to isolate differentially expressed genes between these the ST1 and P7 cell lines in the absence and in the presence of GC. Upon identification of 1,300 candidate differentially expressed genes in this cell system, with ratios varying from 2 to >3,000, some (49) genes were selected for confirmation using qPCR and 27 of these were identified as putative differentially expressed. The expression levels of some of these genes were determined, by qPCR, in 64 human clinical samples of both normal brain and GBM tissue.A number of these genes were found to be coordinately overexpressed both in human GBM cell lines and in human astrocytoma samples, when compared to non-tumoral brain samples, with a highly significant Pearson correlation. This indicates that they may belong to an oncogenic pathway relevant to human astrocytomas, and, therefore, could be further explored as potentially novel therapeutic/diagnostic targets. In order to probe the functional activity of some of these gene products, the corresponding full length cDNA and/or alternatively spliced isoforms of these genes were obtained, and RNAi-based functional assays were also employed. The results indicate that molecular markers from experimental rat glioma cell lines may be associated with human glioma and contribute for the discovery of novel therapeutic targets for the human disease.

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