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IDENTIFICATION OF TRANSCRIPTION FACTORS ASSOCIATED TO DIFFERENTIALLY EXPRESSED GENES IN IRRADIATED GLIOBLASTOMA CELL LINES

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Glioblastoma multiforme (GBM) is among the most lethal of all human tumors, and radiotherapy remains one of the main treatment, besides surgery and chemotherapy. New strategies and Improvements in the therapies are required to overcome the cellular resistance of GBM. The identification of transcription factors (TFs) associated with significantly modulated genes in irradiated GBM could give clues for searching interesting molecular targets. In the present work, we studied four GBM cell lines (T98G, U251MG, U343MG-a and U87MG) under irradiation condition (gamma-rays), and characterized cellular and molecular signaling pathways involved in radiation responses. Gene expression profiles analyzed by the cDNA microarray method indicated a list of differentially expressed genes in irradiated cells (8 Gy), which was used as a data basis to search TFs that were associated to the significant differentially expressed genes, using an in silico approach (FatiGO+). Several TFs were correlated with the lists of modulated genes, whose functions were related to apoptosis, cell cycle, cell adhesion, and DNA repair. The results indicated the following TFs: AP-1 (T98G and U87MG), SREBP1 and CEBPG (U87MG), and HEB (T98G, U87MG and U251). We also found that HEB was up-regulated in U87MG, T98G and U251 cells, as confirmed by the Real Time qPCR analysis. Western Blot also confirmed HEB up-regulation in irradiated and sham-irradiated cells. HEB is a member of the basic-helix-loophelix (B-HLH) domain proteins, being involved in the nervous system development. The knockdown of HEB by siRNA achieved 70% of inhibition (72h after transfection), as confirmed by Western Blot, but the down-regulation of HEB did not cause any significant effect on clonogenic survival, cell proliferation, and cell viability in U87MG irradiated cells (0.5 Gy/min, 2, 4, and 8 Gy) analyzed between 48 and 72h after siRNA HEB transfection. The results of the present work can pinpoint some potential TFs that may possibly be associated to the resistance of GBM cells to radiotherapy, but other TFs should be investigated as molecular targets for therapies to increase cell death in glioma cells. (Supported by FAPESP Proc. Nº 2009/10925-6; CNPq; CAPES).

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