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DNA repair after irradiation in glioma cells and normal human astrocytes.

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We examined DNA damage responses and repair in four human glioma cell lines (A7, U87, T98G, and U373) and normal human astrocytes (NHAs) after clinically relevant radiation doses to establish whether we could identify differences among them that might suggest new approaches to selective radiosensitization. We used phosphorylation of histone H2AX visualized by immunocytochemistry to assess DNA double-strand break (DSB) formation and resolution. Fluorescence immunocytochemistry was used to visualize and quantify repair foci. Western blotting was used to quantify repair protein levels in the different cell lines before and after irradiation and during different cell cycle phases. Mitotic labeling was used to measure cell cycle parameters after irradiation. We found that the glioma cell lines repaired DSBs more slowly and less effectively than did NHAs in the clinically relevant dose range, as assessed by induction and resolution of H2AX phosphorylation, and this was most marked in the three TP53-mutated cell lines (T98G, A7, and U373). The glioma cells also expressed relatively high repair-protein levels compared with NHAs that were not altered by irradiation. High levels of the repair protein Rad51 in these cells persisted throughout the cell cycle, and a marked increase in Rad51 foci formation, which was not restricted to cells in G2/S phase, occurred at early time points after irradiation. TP53-mutated glioma cell lines demonstrated a very prominent dose-responsive G2 checkpoint and were sensitized to radiation by caffeine, which inhibits G2/S phase checkpoint activation. In conclusion, DNA repair events differed in these four glioma cell lines compared with NHAs. In particular, the three TP53-mutated glioma cell lines exhibited markedly increased Rad51 protein levels and marked, dose-dependent Rad51 foci formation after low radiation doses. This suggests that agents that disrupt Rad51-dependent repair or prevent G2 checkpoint activation may selectively sensitize these cells.

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