Roles of DNA repair genes in astrocytoma progression and resistance to therapies

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Astrocytomas are the most common and lethal type of primary brain tumors in adults. Among them, glioblastoma (GBM) is the most frequent and aggressive type due to prominent invasiveness, high proliferation indexes and the elevated resistance of tumor cells against radio and chemotherapy. We identified several DNA repair genes overexpressed in astrocytomas and also strongly correlated with patient survival, suggesting that an exacerbation of DNA repair activity is necessary for astrocytoma progression. Among these genes is the Holliday Junction-Recognition Protein (HJURP), primarily characterized as the chaperone of the centromeric variant of histone H3, the Centromeric Protein A (CENPA). HJURP is responsible for CENPA loading at the centromeres, being required for proper chromosome segregation. This function is well established and quite characterized, regarding mechanisms, protein domains involved and the regulation during cell cycle, but its involvement with DNA repair is only preliminary. Here, we further investigated the involvement of HJURP with DNA repair in GBM cells. Our results revealed the recruitment of HJURP/CENPA to sites of double-strand breaks (DSBs) immediately after damage induction by irradiation. We also demonstrated that recruitment is dependent on PARP1 and is required for proper ATM activation and H2AX phosphorylation, an important response in DNA damage signaling. Furthermore, HJURP knockdown impaired the anchoring of CtIP and RAD51 at DNA lesions and lessened repair activity by the homologous recombination pathway. These defects promoted an overall reduction in DSB repair competence, once larger amounts of broken DNA persisted for extended periods in silenced cells. Finally, we observed that HJURP overexpression conferred proliferative competence and resistance to ionizing radiation for GBM cells. These results demonstrated that DNA repair facilitation is a key phenomenon in the development of astrocytomas that confers proliferative capacity and radioresistance for cancer cells, allowing progression to high-grade lesions.