Autophagy contributes to resistance of tumor cells to ionizing radiation.

Abstract:
Autophagy signaling is a novel important target to improve anticancer therapy. To study the role of autophagy on resistance of tumor cells to ionizing radiation (IR), breast cancer cell lines differing in their intrinsic radiosensitivity were used. Breast cancer cell lines MDA-MB-231 and HBL-100 were examined with respect to clonogenic cell survival and induction of autophagy after radiation exposure and pharmacological interference of the autophagic process. As marker for autophagy the appearance of LC3-I and LC3-II proteins was analyzed by SDS-PAGE and Western blotting. Formation of autophagic vacuoles was monitored by immunofluorescence staining of LC3. LC3-II formation differs markedly in radioresistant MDA-MB-231 versus radiosensitive HBL-100 cells. Western blot analyses of LC3-II/LC3-I ratio indicated marked induction of autophagy by IR in radioresistant MDA-MB-231 cells, but not in radiosensitive HBL-100 cells. Indirect immunofluorescence analysis of LC3-II positive vacuoles confirmed this differential effect. Pre-treatment with 3-methyladenine (3-MA) antagonized IR-induced autophagy. Likewise, pretreatment of radioresistant MDA-231 cells with autophagy inhibitors 3-MA or chloroquine (CQ) significantly reduced clonogenic survival of irradiated cells. Our data clearly indicate that radioresistant breast tumor cells show a strong post-irradiation induction of
autophagy, which thus serves as a protective and pro-survival mechanism in radioresistance.

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