Induction of autophagy promotes differentiation of glioma-initiating cells and their radiosensitivity.

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Abstract

Glioblastoma (GBM) is a highly aggressive brain tumor characterized by increased proliferation and resistance to chemotherapy and radiotherapy. Recently, the identification of tumor initiating cells with stem-like properties in diverse human cancers including glioblastoma represents an important conceptual advance in cancer biology with therapeutic implications. However, the factors determining the differential development and radiosensitization of glioma-initiating cells (GICs) remain poorly defined. Here, we report that rapamycin induced differentiation of GICs and increased their sensitivity to radiation by activating autophagy. Transient in vitro exposure to rapamycin and radiation abolished the capacity of transplanted GICs to establish intracerebral glioblastomas. Most importantly, in vivo combination of rapamycin and radiation effectively blocked the tumor growth and associated mortality that occurs in mice after intracerebral grafting of human GICs. We demonstrate that rapamycin activated their autophagy and triggers the differentiation cascade in GICs isolated from human glioblastomas. This was followed by a reduction in proliferation, cell viability, clonogenic ability and increased expression of neural differentiation markers after radiation. Our results suggest that autophagy plays an essential role in the regulation of GICs self-renewal, differentiation, tumorigenic potential and radiosensitization, suggesting autophagy could be a promising therapeutic target in a subset of glioblastomas. We propose that autophagy defect in GICs contributes to GICs radioresistance by desensitizing GICs to normal differentiation cues. Activating autophagy may abrogate the resistance of GICs to radiation and could lead to the development of novel therapeutic approaches for the treatment of glioblastomas.

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