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Rapamycin induces differentiation of glioma stem/progenitor cells by activating autophagy.

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Abstract

Glioma stem/progenitor cells (GSPCs) are considered to be responsible for the initiation, propagation, and recurrence of gliomas. The factors determining their differentiation remain poorly defined. Accumulating evidences indicate that alterations in autophagy may influence cell fate during mammalian development and differentiation. Here, we investigated the role of autophagy in GSPC differentiation. SU-2 cells were treated with rapamycin, 3-methyladenine (3-MA) plus rapamycin, E64d plus rapamycin, or untreated as control. SU-2 cell xenografts in nude mice were treated with rapamycin or 3-MA plus rapamycin, or untreated as control. Western blotting and immunocytochemistry showed up-regulation of microtubule-associated protein light chain-3 (LC3)-II in rapamycin-treated cells. The neurosphere formation rate and the number of cells in each neurosphere were significantly lower in the rapamycin treatment group than in other groups. Real-time PCR and immunocytochemistry showed down-regulation of stem/progenitor cell markers and up-regulation of differentiation markers in rapamycin-treated cells. Transmission electron microscopy revealed autophagy activation in rapamycin-treated tumor cells in mice. Immunohistochemistry revealed decreased Nestin-positive cells and increased GFAP-positive cells in rapamycin-treated tumor sections. These results indicate that rapamycin induces differentiation of GSPCs by activating autophagy.

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