Rheb Promotes Cancer Cell Survival Through p27Kip1-Dependent Activation of Autophagy

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Resumen

We previously found that the small GTPase Rheb regulates the cell-cycle inhibitor p27KIP1 (p27) in colon cancer cells by a mTORC1-independent mechanism. However, the biological function of the Rheb/p27 axis in cancer cells remains unknown. Here, we show that siRNA-mediated depletion of Rheb decreases survival of human colon cancer cells under serum deprivation. As autophagy can support cell survival, we analyzed the effect of Rheb on this process by detecting the modification of the autophagy marker protein LC3 by western blot and imunofluorescence. We found that Rheb promotes autophagy in several human cancer cell lines under serum deprivation. Accordingly, blocking autophagy inhibited the pro-survival effect of Rheb in colon cancer cells. We then analyzed whether p27 was involved in the biological effect of Rheb. Depletion of p27 inhibited colon cancer cell survival, and Rheb induction of autophagy. These results suggest that p27 has an essential role in the effect of Rheb in response to serum deprivation. In addition, we demonstrated that the role of p27 in autophagy stands on the N-terminal portion of the protein, where the CDK-inhibitory domain is located. Our results indicate that a Rheb/p27 axis accounts for the activation of autophagy that supports cancer cell survival. Our work therefore highlights a biological function of Rheb and prompts the need for future studies to address whether the mTORC1-independent Rheb/p27 axis could contribute to tumorigenesis and/or resistance to mTOR inhibitors. (C) 2015 Wiley Periodicals, Inc.

Palabras clave

Palabras clave de autor: Rheb GTPase; N-terminal of p27; mTORC1-independent
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