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Caloric Restriction Mimetics Enhance Anticancer Immunosurveillance

Highlights

- Short-term fasting improves anticancer chemotherapy
- Treatment with caloric restriction mimetics (CRMs) inhibits tumor growth in vivo
- CRMs trigger an autophagy-dependent anticancer immune response
- CRMs deplete regulatory T Cells from tumor bed

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In Brief

Pietrocola et al. show that short-term fasting or autophagy-inducing caloric restriction mimetics, such as hydroxycitrate and spermidine, improves the antitumor efficacy of chemotherapy in vivo. The effect is specific for autophagy-competent tumors and depends on regulatory T cell depletion from the tumor bed.

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SUMMARY

Caloric restriction mimetics (CRMs) mimic the biochemical effects of nutrient deprivation by reducing lysine acetylation of cellular proteins, thus triggering autophagy. Treatment with the CRM hydroxycitrate, an inhibitor of ATP citrate lyase, induced the depletion of regulatory T cells (which dampen anticancer immunity) from autophagy-competent, but not autophagy-deficient, mutant KRAS-induced lung cancers in mice, thereby improving anticancer immunosurveillance and reducing tumor mass. Short-term fasting or treatment with several chemically unrelated autophagy-inducing CRMs, including hydroxycitrate and spermidine, improved the inhibition of tumor growth by chemotherapy in vivo. This effect was only observed for autophagy-competent tumors, depended on the presence of T lymphocytes, and was accompanied by the depletion of regulatory T cells from the tumor bed.

Significance

Fasting can improve the efficacy of anticancer chemotherapy. We show here that this effect involves induction of autophagy in malignant cells, as well as an anticancer immune response. Fasting can be replaced by the administration of caloric restriction mimetics (CRMs), which—without causing weight loss—improve the efficacy of chemotherapy as well. The tumor growth-inhibitory effects of hydroxycitrate were epistatic to the inhibition of regulatory T cells. Altogether, our results reveal a common mechanism for the cancer protective properties of CRMs and point to the possibility of stimulating anticancer immune responses by inducing autophagy with well-tolerable CRMs in vivo.