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The therapeutic ketogenic diet as an adjuvant therapy for cancer

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Patients with malignant gliomas have a dismal prognosis, regardless of currently available treatments including surgery, radiation and chemotherapy. Improvement in the survival of these patients requires the design of new therapeutic modalities. While there have been advances in the development of novel targeted treatments, the tumor heterogeneity that is a hallmark of this disease often lessons their efficacy since not all cells contain specific targets. One phenotypic trait shared by virtually all cancer cells is metabolic dysregulation. Thus, this presents a unique therapeutic opportunity for these patients. We have shown that altering cellular metabolism through the use of a therapeutic ketogenic diet (KD), high fat, low carbohydrate and adequate protein is very effective in prolonging the survival of mice implanted with brain tumors. The KD increases circulating ketones and lowers blood glucose, effectively starving the tumor of nutrients. While, its antitumor effects were first thought to be due to primarily reducing blood glucose, newer studies are now showing that ketones themselves also play a role in the antitumor effects of this diet. The KD has a multitude of effects: It potentiates the effects of radiation and chemotherapy and increases the anti-tumor immune response in vivo. In addition, it causes a decrease in peri-tumoral edema, hypoxia and angiogenesis in the tumors of mice maintained on a KD. In light of these positive results and the long-established safety record for the use of this diet, investigation of metabolic alteration as an adjuvant therapy for brain tumors and other cancers is beginning.

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RORC1 regulates tumor-promoting "emergency" granulo-monocytopoiesis

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Cancer-driven granulo-monocytopoiesis stimulates expansion of tumor promoting myeloid populations, mostly myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). We identified subsets of MDSCs and TAMs based on the expression of retinoic-acid-related orphan receptor (RORC1/RORγ) in human and mouse tumor bearers. RORC1 orchestrates myelopoiesis by suppressing negative (Socs3 and Bcl3) and promoting positive (C/EBPγ regulators of granulopoiesis, as well as the key transcriptional mediators of myeloid progenitor commitment and differentiation to the monocytic/macrophage lineage (IRF8 and PU.1). RORC1 supported tumor-promoting innate immunity by protecting MDSCs from apoptosis, mediating TAM differentiation and M2 polarization, and limiting tumor infiltration by mature neutrophils. Accordingly, ablation of RORC1 in the hematopoietic compartment prevented cancer-driven myelopoiesis, resulting in inhibition of tumor growth and metastasis. Thus, inhibition of RORC1-dependent myelopoiesis may represent a therapeutic approach to prevent the induction of the tumor-promoting host macro- and micro-environments.

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