Targeting cancer metabolism by ketogenic diet

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Cancer metabolism is frequently characterized by low mitochondrial OXPHOS activity due to partially dysfunctional mitochondria and elevated aerobic glycolysis, which is known as Warburg effect. Dietary interventions, such as a low-carbohydrate, high-fat ketogenic diet (KD), are highly attractive approaches to target these metabolic vulnerabilities of tumor cells.
We have used several preclinical cancer models, including the childhood cancer neuroblastoma, melanoma, renal cell carcinoma and breast cancer, to evaluate the effect of the KD on tumor proliferation, mainly in combination with other anti-cancer therapies. Apart from the renal cancer model, which is associated with a paraneoplastic syndrome of the liver, we observed an anti-tumor and a pro- survival effect in the remaining cancer models (1, 2). In addition, KD enhanced the effect of established anti-tumor therapies (3). Interestingly, ketone bodies have been shown to directly inhibit proliferation of only certain types of tumor cells *in vitro*. Therefore, also other mechanisms seem to be responsible for the anti-proliferative effect of the KD. We and others have observed that certain tumor types being responsive to KD lack OXCT1, a key enzyme responsible for ketone body metabolism. Furthermore, integrated multi-omics analysis including transcriptomics, metabolomics and epigenetic analysis indicate tumor type specific effects.
Our data support the anti-tumor effect of KD in immunocompromised and immunocompetent preclinical cancer models and demonstrate that KD can sensitize tumors to other targeted anti-cancer therapies.

(1) Vidali et al. (2017) Oncotarget;8(34):57201-57215
(2) Weber DD (2022) Cancer Metab.18;10(1):12
(3) Catalano L (2023) Metabolites;13(8):910