A HIGH-FAT LOW-CARBOHYDRATES DIET DELAYS THE PROGRESSION OF CASTRATION-RESISTANT PROSTATE CANCER BY TARGETING TUMOR METABOLIC INFLEXIBILITY

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Castration-resistant prostate cancer (CRPC) is an aggressive disease with poor prognosis, marked by profound metabolic reprogramming. While glucose metabolism dominates in CRPC, lipid metabolism is increasingly recognized as a critical factor in prostate cancer progression and therapy resistance. This raises the possibility that lipid-based interventions could exploit this metabolic rigidity as a promising adjuvant strategy. However, the underlying mechanisms remain poorly understood.

To explore this, we combined an in vivo approach using a prostate-specific PTEN knockout mouse model with in vitro metabolic investigations. Mice were fed either a standard diet (SD) o a High Fat-Low Carbohydrate Diet (HFLCD). In vitro, human PNT2 (non-tumoral) and C4-2B (CRPC) cells were cultured for 48 hours under androgen-deprived conditions in media mimicking the mouse diets: with glucose (G+FA-, mimicking SD), or without glucose but supplemented with 10% oleic acid and 5% palmitic acid (G-FA+, mimicking HFLCD).

In H&E-stained prostate sections, HFLCD-fed mice showed a significant reduction in tumor burden, with a -44% decrease in the number of adenocarcinomas and a -14.8% reduction in cell density within prostatic intraepithelial neoplasia (PIN). Furthermore, phosphorylation of AKT and mTOR in PIN regions, dropped by 70.8% and 60.9%, respectively, suggesting that lipid-based energy sources impair tumor progression by inhibiting the AKT/mTOR axis. This was supported by in vitro results with a decreased proliferation in C4-2B cells after 48 hours under G-FA+, while PNT2 cells maintained proliferation. Both cells showed an increase in lipid droplets but only C4-2B showed a decreased □-oxydation, highlighting a cancer-specific metabolic inflexibility.

Interestingly, HFLCD-fed mice did not show elevated plasma β-hydroxybutyrate, indicating that the observed anti-tumor effects are likely due to the inability of CRPC cells to utilize lipid-based energy sources, rather than systemic ketone action.

These findings suggest that a glucose-restricted, lipid-enriched diet slows prostate tumor growth and may be exploited in CRPC management.
Topic/s:Métabolisme et Nutrition