Precision nutrition potentiates radiotherapy in prostate cancer

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Background: While curative treatment is achievable for localized prostate cancer (PCa), radiotherapy is not universally effective, with recurrence rates ranging from 20-50%. This underscores the need for strategies to improve radiotherapy efficacy and reduce disease progression. Chronic high-saturated fat intake (SFI) accelerates PCa progression but also induces metabolic vulnerabilities, such as obesity-driven increases in tumor glycolysis, that may be therapeutically exploited. Transiently harnessing and targeting these vulnerabilities through precision nutrition could represent a breakthrough approach.

Methods: We investigated the impact of chronic and short-term SFI on radiotherapy response using the Hi-MYC genetically engineered mouse model, MyC-CaP and TRAMP-C2 murine PCa cell lines (including castrate-resistant sublines), and the LuCaP castration-resistant PCa (CRPC) PDX models. Experiments were conducted in immunocompetent (FVB, C57BL/6N) and immunodeficient (CB17 SCID, NOD SCID) mouse strains. Dietary intake, tumor transcriptomic data, and clinical outcomes in patient cohorts from the Health Professionals Follow-up Study (HPFS) and Physicians' Health Study (PHS) were also analysed.

Results: Transcriptomic analysis from the PHS/HPFS cohorts revealed that SFI was associated with an enriched DNA damage signature in localized PCa. In Hi-MYC prostates, chronic SFI induced a DNA damage response at the transcriptional level and elevated γH2A.X levels compared to control diet (CTD)-fed mice. Critically, short-term SFI (sSFI) was sufficient to induce DNA damage in MyC-CaP tumors allografted into FVB mice.

To assess radiosensitization, MyC-CaP tumors grown in immunocompetent mice were subjected to a 10-day sSFI regiment with radiotherapy, resulting in significantly improved responses versus CTD-fed mice. This effect was confirmed using TRAMP-C2 syngeneic model, demonstrating that sSFI-enhanced radiotherapy efficacy is independent of MYC expression and mouse strain.

In contrast, sSFI did not enhance radiotherapy efficacy in 15 LuCaP CRPC PDX models grown in immunodeficient CB17 SCID hosts. To determine immune dependency, we repeated the experiments with MyC-CaP and TRAMP-C2 cells in CB17 and NOD SCID mice. Notably, sSFI-mediated radiosensitization was abolished in immunodeficient hosts. Immune profiling in FVB mice revealed that sSFI rapidly primed the immune system to respond to radiotherapy and reshaped the tumor immune microenvironment post-treatment.

We further examined post-diagnostic fat intake and survival in 3,959 patients with stage T1–T3 PCa from the HPFS. Among those treated with radiotherapy (n = 1,765), replacing 10% of energy intake from

carbohydrates with saturated fat was associated with a 34% reduction in PCa-specific mortality (HR 0.66, 95% CI 0.42–1.04), trending toward statistical significance (p = 0.07). No association was observed in patients undergoing radical prostatectomy (n = 2,194).
Conclusion: Our findings demonstrate that sSFI enhances radiotherapy efficacy in preclinical PCa models with an intact immune system and shows translational relevance in clinical cohorts. Altogether, precision nutrition (*i.e.*, tailoring diet to treatment modality) may optimize therapeutic outcomes in PCa.

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