

High-fat diet-dependent activation of the DNA damage response as an underlying mechanism of prostate cancer aggressiveness

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Background: The large worldwide disparity in prostate cancer (PCa) incidence points to a key role of environmental factors, such as diet, in PCa etiology. Epidemiological studies have reported that increased consumption of saturated fat can severely affect PCa progression and mortality, but the molecular underpinnings of this association are poorly understood.

Methods: We used a genetically engineered mouse model of PCa driven by *c-MYC* overexpression (Hi-MYC) and the associated MyC-CaP murine PCa cell line to investigate the effect of high-fat diet (HFD) *in vivo* and *in vitro*. Transcriptomics analyses (RNA-seq), immunofluorescence staining and western blot analyses were performed on tumor tissues. Plasma collected from mice fed defined diets was used for *in vitro* treatments. We also leveraged dietary intake and transcriptomics data from the Health Professional Follow-up Study (HPFS) and Physicians' Health Study (PHS).

Results: Dietary manipulation of MYC-driven murine PCa models showed that tumors grown in mice maintained on a HFD rich in animal-derived saturated fats were more aggressive, displayed an enhanced DNA repair transcriptional signature and elevated levels of γ H2A.X (a marker of DNA damage) compared to tumours from control diet (CTD)-fed mice. We hypothesized that metabolic alterations associated with HFD affect the execution of the DNA damage response (DDR) in PCa cells, inducing increased genomic instability that ultimately fuels PCa aggressiveness. Accordingly, an activation of the ATM/Chk2/p53 pathway was observed in tumours from the HFD-fed mice. Importantly, *in vitro* treatment of MyC-CaP cells with plasma collected from mice submitted to a short-term HFD intervention recapitulated the activation of the ATM/Chk2/p53 pathway and induced a down-regulation of the ATR/Chk1 pathway, two different arms of DDR signaling. Finally, we show that saturated fat intake, but not monounsaturated or polyunsaturated fat intake is also associated with an enhanced DNA repair transcriptional signature in the tumor of PCa patients.

Conclusions: Our findings suggest that a HFD rich in saturated fats fuels genomic instability and tumour aggressiveness at least partly by deregulating the DDR, setting the stage for therapeutic approaches involving changes to the diet.

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