

## Diet-induced obesity enhances MYC-driven prostate cancer through metabolic and epigenetic rewiring

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**Background:** Men diagnosed with prostate cancer (PCa) on a Western diet or who are obese are more likely to die of their disease. In primary PCa chromosome 8q gain or focal amplification of 8q24.21 are associated with amplification of the *MYC* oncogene and poor disease-specific survival. A hallmark of *MYC* overexpression is a global metabolic reprogramming that supports anabolic processes and cell growth, and in the murine prostate *MYC* overexpression recapitulates the primary human disease; thus, *MYC* is believed to function as a key oncogenic driver. The landscape of epigenetic alterations in PCa that rely on metabolites as substrates or cofactors varies greatly with cancer progression, however, the interplay between metabolic and epigenetic rewiring in this disease remains unexplored.

**Methods:** We used the Hi-MYC PCa mouse model for global metabolic and chromatin profiling, chromatin immunoprecipitation followed by sequencing (ChIP-seq) and transcriptomic analyses (RNA-seq). We also leveraged dietary intake and transcriptomic data from the Health Professional Follow-up Study (HPFS) and Physicians' Health Study (PHS).

**Results:** Using the Hi-MYC PCa mouse model, we found that high fat diet-induced obesity (DIO) enhances the *MYC* transcriptional program through metabolic alterations that favour histone hypomethylation. This in turn leads to a DIO-dependent phenotype characterized by increased cellular proliferation and tumor burden. More specifically, DIO aggravates the global H4K20 hypomethylation that is triggered by *MYC* overexpression. This feature is greatly exacerbated by increased activity of the H4K20me1 histone demethylase PHF8 (known to be a *MYC* transcriptional coactivator and regulator of proliferation) at the promoter region of *MYC* regulated genes. Notably, we show that saturated fat intake in human prostate tumors is also associated with an enhanced *MYC* signature, which in turn increases the risk of lethal PCa, irrespectively of the tumor genetic landscape.

**Conclusions:** Our findings support an interplay between DIO, metabolic, and epigenetic alterations geared towards an enhanced *MYC* signature, and suggest that in primary PCa, extrinsic risk factors such as dietary fat intake contribute to tumor progression by mimicking *MYC* amplification.

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