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

*David P. Labbé*1,2, *Giorgia Zadra*1,3, Meng Yang4, Jaime M. Reyes1, Charles Y. Lin5, Stefano Cacciatore6, Ericka M. Ebot7, Amanda L. Creech8, Francesca Giunchi9, Michelangelo Fiorentino9, Habiba M. Elfandy3, Sudeepa Syamala3, Jacob D. Jaffe8, Anthony V. D’Amico10, Philip W. Kantoff1,11, James E. Bradner1, Lorelei A. Mucci7,12, Jorge E. Chavarro4,7,12, Massimo Loda3,8,13, Myles Brown1,2

*These authors contributed equally to this work

Co-corresponding authors

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.

Conflict of Interest: The authors declare no competing financial interests.
**Funding Acknowledgments:** D.P.L is a Young Investigator of the Prostate Cancer Foundation funded by a Scholarships for the Next Generation of Scientist from the Cancer Research Society and recipient of a Canadian Institute of Health Research Fellowship. G.Z. is a recipient of the Idea Development Award from the U.S. Department of Defense (DoD; PC150263). L.A.M. was a Young Investigator of the Prostate Cancer Foundation. Support for HPFS/PHS cohorts was provided by grants from the DoD (W81XWH-11-1-0529) and grants from the National Institute of Health (NIH; CA42182, CA58684, CA90598, CA141298, CA97193, CA34944, CA40360, CA131945, P50CA090381, 1U54CA155626-01, P30DK046200, HL26490 and HL34595). This work was specifically supported by grants from the NIH (R01CA131945, R01CA187918 to M.L. and P50CA090381 to P.W.K., M.L. & M.B.), the National Cancer Institute (1P01CA163227 to M.B) and the Prostate Cancer Foundation to M.L. and M.B.