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Commentary

Metabolic Reprogramming and Epigenetic Regulation in Prostate Cancer

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DESCRIPTION

The intricate relationship between metabolic reprogramming and epigenetic modifications in prostate cancer reveals new therapeutic targets and biomarkers for disease management. Prostate cancer exhibits unique metabolic characteristics that distinguish it from other solid tumors. Unlike most cancers that rely heavily on glycolysis, prostate cancer cells maintain significant oxidative phosphorylation capacity while also upregulating lipid biosynthesis pathways. This metabolic flexibility is intimately connected to epigenetic regulation, creating a complex regulatory network that influences tumor progression and treatment response.

The Androgen Receptor (AR) signaling pathway, central to prostate cancer biology, directly regulates both metabolic and epigenetic processes. AR activation promotes the expression of lipogenic enzymes such as Fatty Acid Synthase (FASN) and Acetyl-CoA Carboxylase (ACC), driving lipid synthesis essential for membrane biogenesis and cellular proliferation. Simultaneously, AR regulates the expression of epigenetic modifiers, including *EZH2* and *LSD1*, which modify chromatin structure to facilitate AR-mediated gene expression.

DNA methylation patterns in prostate cancer are closely linked to metabolic enzyme expression. The promoter of Glutathione S-Transferase Pi 1 (GSTP1) is hypermethylated in over 90% of prostate cancers, leading to reduced detoxification capacity and altered redox homeostasis. This methylation event occurs early in prostate carcinogenesis and serves as a valuable biomarker for disease detection and monitoring.

The metabolite alpha-Ketoglutarate (α-KG) serves as a crucial link between metabolism and epigenetics in prostate cancer. α-KG is a cofactor for TET enzymes, which catalyze DNA demethylation, and Jumonji domain-containing histone demethylases. Alterations in α-KG levels, resulting from mutations in Isocitrate Dehydrogenase (IDH) or changes in TCA cycle flux, directly impact the epigenetic landscape of prostate cancer cells.

Histone modifications play essential roles in metabolic reprogramming. The histone demethylase *LSD1* is overexpressed in Castration-Resistant Prostate Cancer (CRPC) and regulates genes involved in lipid metabolism. *LSD1* inhibition disrupts lipid synthesis and reduces tumor growth, making it an attractive therapeutic target. Clinical trials evaluating *LSD1* inhibitors in prostate cancer patients are currently underway.

The metabolic enzyme ATP Citrate Lyase (ACLY) connects glucose metabolism to lipid synthesis and epigenetic regulation. ACLY generates acetyl-CoA, which serves as a substrate for both fatty acid synthesis and histone acetylation. Inhibition of ACLY reduces both lipid production and histone acetylation levels, leading to altered gene expression patterns and reduced tumor growth. The tumor microenvironment significantly influences metabolic-epigenetic interactions in prostate cancer. Hypoxic conditions, common in advanced prostate tumors, activate Hypoxia-Inducible Factor-1α (HIF-1α), which promotes glycolytic metabolism and regulates the expression of epigenetic modifiers. The interplay between hypoxia, metabolism, and epigenetics creates a feed-forward loop that promotes tumor progression.

Epigenetic regulation of metabolic enzymes is also evident in treatment resistance. The development of resistance to Androgen Deprivation Therapy (ADT) is associated with epigenetic silencing of tumor suppressor genes and activation of alternative metabolic pathways. Understanding these mechanisms is crucial for developing strategies to overcome treatment resistance. The clinical implications of metabolic-epigenetic interactions in prostate cancer are significant. Metabolic biomarkers, such as citrate levels and lipid profiles, can complement traditional PSA measurements for disease monitoring. The integration of metabolomics and epigenomics data provides a more comprehensive understanding of tumor biology and treatment response.

CONCLUSION

Therapeutic targeting of metabolic-epigenetic interactions represents a promising approach for prostate cancer treatment. Combination therapies that simultaneously target metabolic pathways and epigenetic modifiers may be more effective than single-agent treatments. For example, combining FASN inhibitors with HDAC inhibitors has shown synergistic effects in preclinical models. Future research should focus on developing personalized treatment approaches based on individual

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metabolic and epigenetic profiles. The identification of metabolic-epigenetic biomarkers that predict treatment response will be essential for optimizing therapeutic outcomes. As our understanding of these complex interactions continues to evolve, new opportunities for intervention will emerge.