Discern the Impact of Cryptochrome 1 (CRY1) on Metabolic Rewiring in PCa

Arwa Fallatah[1,2], Stefan DiFazio[1,2], Lakshmi Ravindranath[1,2], and Ayesha A. Shafi[1,2]

Affiliations: [1]Center for Prostate Disease Research, Murtha Cancer Center Research Program, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, Maryland, 20817, USA
[2]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, Maryland, 20817 USA

Background: Disruptions in circadian rhythm are linked to prostate cancer (PCa). Previous studies indicate that a core circadian clock factor cryptochrome 1, CRY1, is pro-tumorigenic and associated with poor outcome in PCa. Furthermore, metabolic reprogramming is oncogenic – promoting cancer cell growth through nutrient imbalance. While evidence links circadian rhythm disruptions to metabolic health risks, the underlying biological mechanism(s) remain not fully elucidated. Preliminary data indicate that CRY1 regulates metabolic homeostasis in preclinical and clinical models of PCa. This study shows that CRY1 is a crucial modulator of PCa growth and survival through metabolic rewiring and understanding its role in metabolic deregulation will improve management strategies for PCa patients.

Methods: To address this, we utilized hormone therapy-sensitive (HTS) and castration-resistant prostate cancer (CRPC) models with pharmacological and genetic perturbations of CRY1 to elucidate the role of CRY1 in disease progression, interplay with metabolic rewiring, and identify novel mechanism(s) of action. Bulk RNA-seq, steady state metabolomics, and metabolic focused CRISPR screen were done to investigate the role of CRY1 in prostate cancer disease progression, which ultimately helps better understanding the molecular mechanisms of PCa progression and developing an enhanced targeted therapy.

Results: Transcriptomic analyses revealed that CRY1 is integral to regulation of oncometabolic pathways, including glycolysis, oxidation phosphorylation, and bile acid metabolism in both HTS and CRPC PCa models. Interestingly, global metabolomic analysis of our models identified the role of CRY1 in maintaining redox balance by driving the increased synthesis of glutathione in CRPC but decreased in HTS, suggesting that progression to CRPC may be due to CRY1 driving redox imbalance. Therefore, using CRY1 inhibitors has the potential to be an effective therapy for these patients to resensitize to conventional hormonal therapy since reactive oxygen species are known to be elevated in CRPC. Additional analyses involved integration of transcriptomic and metabolomic data revealing oxidative stress pathways are significantly altered upon CRY1 knockdown across the PCa disease continuum. Furthermore, CRY1 perturbation via knockdown using inducible system as well as chemical inhibition using pharmacological inhibitors decreased cell growth *in vitro* and *in vivo* underscoring the importance of CRY1 in tumor growth. Lastly, a metabolic focused CRISPR KnockOut screen is ongoing in the CRY1 depleted PCa models to identify potential targets for functional validation. This has the potential to reveal novel candidates to be therapeutically targeted as monotherapy or in combination with CRY1 inhibitors.

Conclusions: In sum, our findings demonstrate that CRY1 promotes tumor growth, and its suppression disrupts metabolic hemostasis in PCa. Thus, targeting PCa with CRY1 inhibitors in combination with metabolic inhibitors has the translational potential to improve PCa patient outcome.

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