Contribution of the GR-LEDGF/p75 Axis to Prostate Cancer Chemoresistance

Evelyn S. Sanchez-Hernandez, Greisha L. Ortiz-Hernandez, Pedro T. Ochoa, Carlos A. Casiano

Center for Health Disparities and Molecular Medicine, Loma Linda University School of Medicine, Loma Linda, California, USA

Prostate cancer (PCa) is the second leading cause of cancer deaths in U.S. men, disproportionally affecting men of African ancestry (AA) such as African American, Afro-Caribbean, and West-African. AA men have more aggressive PCa caused by the interplay between socioeconomic and genetic/biological factors. Advanced PCa is treated with anti-androgen therapy and chemotherapy using the drug docetaxel (DTX). Glucocorticoids are administered to PCa patients to offset the side effects of chemotherapy and have been implicated in PCa resistance to anti-androgen therapy via the “androgen receptor (AR) bypass” mechanism and in resistance to chemotherapy. This may be critical to AA men with PCa since they have chronically elevated endogenous glucocorticoid levels compared to Caucasian American (CA) men. These high glucocorticoid levels are associated with cumulative life stressors linked to low socioeconomic status such as living in areas with poverty, racism, crowded living, high crime, and low access to quality healthcare. Potentially, these chronically high levels may predispose AA men with PCa to increased therapy resistance. Glucocorticoids bind to the glucocorticoid receptor (GR) to exert their actions, but the GR mediated mechanisms of PCa chemoresistance are unknown, as well as their possible contribution to PCa mortality disparities. Our group has previously reported that glucocorticoids upregulate the chemotherapy resistance-associated protein LEDGF/p75 in PCa cells and identified consensus GR binding sites in the promoter region of the gene encoding this protein. We **hypothesize** that GR transcriptionally regulates and interacts with LEDGF/p75 to enhance chemoresistance in PCa cells. In the present study, we provide evidence that activation of GR with glucocorticoids leads to increased expression of the LEDGF/p75 protein in PCa cells, and that this increase can be pharmacologically inhibited using the selective GR modulator CORT. We also observed that genetic knockdown of GR in PCa cells, including chemoresistant cells, leads to LEDGF/p75 downregulation, suggesting that LEDGF/p75 expression is dependent on GR activation. In addition, we found that GR and LEDGF/p75 interact in PCa cells, as assessed by co-immunoprecipitation and confocal microscopy co-localization studies. These results link for the first-time these two chemoresistance-associated proteins in PCa, and will be further expanded to establish the role of the GR-LEDGF/p75 axis as a major contributor to PCa aggressiveness and chemoresistance, particularly in the context of racial disparities in PCa mortality.

Contact: Carlos Casiano, PhD, ccasiano@llu.edu