CRM1 regulates androgen receptor stability and impacts DNA repair pathways in prostate cancer, independent of the androgen receptor

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Background: CRM1 is the most studied prototype among the known nuclear exportins. Dysregulation of CRM1 occurs in many cancers; hence, understanding the role of CRM1 in cancer can help develop synergistic therapeutics. The study investigates how CRM1 affects prostate cancer growth and survival. It examines the role of CRM1 in regulating androgen receptor (AR) and DNA repair in prostate cancer.

Methods: Prostate cancer cell lines LNCaP, LAPC4, PC3, DU145, and HEK293T were cultured under standard conditions. CRISPR-Cas9 was used to generate HSP90-A knockout cells in LNCaP and LAPC4 and was verified through western blotting. Quantitative real-time PCR (qPCR) and western blotting were employed to assess gene expression and protein levels. Immunofluorescence was used for cell imaging and colony formation, and comet assays were conducted to evaluate cell viability and DNA damage. Phosphotag gel analysis and co-immunoprecipitation followed by qPCR were performed to study CRM1 and AR interactions, while homologous recombination efficiency was measured using an HR sensor plasmid and flow cytometry. Drug combination assays were performed for Selinexor with ATR inhibitor VE821, ATM inhibitor AZ32, PARP inhibitor Olaparib, and DNA-PK inhibitor M3814.

Results: Our findings reveal that CRM1 influences AR mRNA and protein stability, leading to a loss of AR protein upon CRM1 inhibition. Furthermore, it highlights the involvement of HSP90 alpha, a known AR chaperone, in the CRM1-dependent regulation of AR protein stability. The combination of CRM1 inhibition with an HSP90 inhibitor demonstrates potent effects on decreasing prostate cancer cell growth and survival. The study further explores the influence of CRM1 on DNA repair proteins and proposes a strategy of combining CRM1 inhibitors with DNA repair pathway inhibitors to decrease prostate cancer growth. Overall, the findings suggest that CRM1 plays a crucial role in prostate cancer growth, and a combination of inhibitors targeting CRM1 and DNA repair pathways could be a promising therapeutic strategy.

Conclusions: CRM1 can affect prostate cancer growth by regulating the stability of the androgen receptor and impacts DNA repair in prostate cancer cells independent of the androgen receptor.

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