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Up-regulation of the androgen receptor co-repressor; prohibitin, leads to cell cycle arrest in an androgen dependent prostate cancer cell line; LNCaPs

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Prostate cancer (PC) is a worldwide health dilemma. Initially, PC cell growth is dependent upon androgen stimulation carried out by the androgen receptor (AR). Therapies which inhibit this androgen stimulation are initially successful until the tumor becomes non-reliant upon androgen supply through aberrant AR signaling, thus relapse occurs. Once the cancer transitions to an androgen-independent state, treatment options are scarce and prognosis becomes increasingly poor. The mechanisms for androgen independence and anti-androgen therapy resistance are inadequately understood, but may involve AR cofactors and co-repressors. Interestingly, a known co-repressor of the AR, namely prohibitin (PHB) has been previously identified to be down-regulated in metastatic PC when compared to healthy controls both in vivo and in vitro. PHB has also been shown to be down-regulated in bicalutamide resistant prostate cancer cells. PHB normally suppresses the cell cycle via unknown mechanisms; however this is disrupted upon AR activation. The aims of this project are to identify how PHB affects the cell cycle in a doxycycline inducible LNCaP cell line. Moreover, to identify key genes involved in both DNA replication and cell cycle regulation that PHB directly influences. Further, to understand how PHB's interaction with these key genes is altered in the presence of androgen stimulation. RNA-Seq was used to assess genes that were modulated in response to PHB over-expression. These genes were then validated by SYBR green real time Q-PCR. A luciferase assay was used to assess PHB's repressive function of genes involved in DNA replication; MCMs. FACs analysis was used to assess PHB's effect on the cell cycle phases. An immunoprecipitation (IP) assay was carried out to identify the direct interaction of PHB and E2F1 (a known cell cycle activator) and how this interaction is altered in the presence of androgen. Increased expression of PHB showed a decreased expression in family members of the MCM, E2Fs, cyclins and an increase in cell cycle inhibitors (n=2). These results were further confirmed with real time SYBR green Q-PCR. FACs analysis demonstrates that PHB over-expression caused an increase in the G1 sub-population of cells and a decrease in the G2 sub-population. Activity of both MCM5 and MCM6 were significantly reduced in the presence of increasing concentrations of PHB, highlighted by a luciferase assay. Finally, an IP demonstrated the direct interaction of PHB with E2F1 in the WT LNCaP cell line that was lessened in the presence of androgen. Data presented here confirm that PHB plays a key role in halting the cell cycle by down-regulation of genes associated with the cell cycle. Such genes include members of the E2F family, that are crucial in progressing the cell cycle and members of the MCM family that enable DNA replication. As AR signaling initiates the repression of PHB expression, PHB over-expression could unveil mechanisms underlying the transition of PC from androgen dependence to androgen independence, that is essential to improve the limited options available at the moment for patient therapy.

Biography

Sarah Koushyar has completed an undergraduate degree in Biomedical Science. She has also completed a Master's and is now undertaking a PhD at Cardiff University. The PhD project is focused on mechanisms involved in androgen independence in Prostate Cancer. She has published two abstracts and two reviews during her PhD studies.

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