

Insulin -sensitizing Drugs to Treat Obese Prostate Cancer Patients

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ABSTRACT

Background: Prostate cancer (PC) in obese men is more likely to cause a more aggressive disease that recurs after radical prostatectomy than in non-obese men; also, risks of advanced PC or death from PC are increased when associated with obesity. The biological mechanisms underlying the association between obesity and the progression of PC have yet to be established. Insulin resistance is associated with obesity. Insulin sensitizing (IS) drugs used currently to treat insulin resistance have been shown to have an effect on signaling pathways that are commonly dysregulated in cancer. Adipokines and growth factors that are elevated due to obesity are able to be regulated by IS drugs. **Purpose:** IS drugs, metformin and rosiglitazone, were used to investigate their impact on PC cell lines DU145, PC-3 and LNCaP. **Methods:** The IC₅₀ for each drug was established for each cell line. We used a proliferation assay to determine the impact of the IS drugs on cell survival. Also, to understand how cell death was occurring in the PC cells, a FACS (Fluorescence Activated Cell Sorting) analysis was performed. To further examine the direct targets of the IS drugs, protein analysis using Western blotting was completed for all PC cell lines. Conditional media that represented obesity was created to discover the affect of adipokines and growth factors on the migration of PC cells. **Results:** IS drugs do indeed cause decreases in cell growth for all PC cell lines. The FACS analysis showed that the IS drugs caused cell cycle arrest if used at their IC₅₀ levels for 48 hours. Western analysis showed that rosiglitazone directly targets the key protein commonly mutated in PC, AKT and metformin has a direct impact on the energy sensing target protein AMPK and surprisingly, AKT. PC cells grown in obese media had a much higher rate of migration (i.e. metastasis) and IS drugs had a significantly greater effect in this media. **Conclusions:** The preceding results show that obesity does indeed affect the growth and progression of PC cells in culture. Also, IS drugs could have a clinical impact on reducing the proliferation of PC cells by causing cell cycle arrest and ideally, decreasing their potential to metastasize to distant locations.

KEY WORDS: Obesity, Prostate cancer, Insulin sensitizing drugs