A novel potential therapeutic target for advanced prostate cancer.

By Kalli Spencer

A recent study by Paschalis et al from the Institute of Cancer Research at the Royal Marsden Hospital London examined the sampled tissue of 74 participants in an effort to search for a new potential therapeutic target site for metastatic castrate resistant prostate cancer.

Translational medicine (TM) is defined as "an interdisciplinary branch of the biomedical field supported by three main pillars: bench side (in the lab), bedside, and community"[1]. The ultimate aim of TM is to synthesize expertise, resources, disciplines and techniques within these pillars to promote developments in prevention, diagnosis, and therapies. It's a highly interdisciplinary field, the primary focus of which is to combine assets of various natures within the individual pillars in order to make an impact on the global healthcare system.

Prostate cancer may metastasise (spread) locally in the area surrounding the prostate into neighbouring structures like the bladder or ureters or surrounding lymph nodes (glands) in the pelvis. There may also be distant spread to bones such as the spine, as well as organs including the lungs and liver. Rare sites of metastases may include the brain and adrenal glands. We know that prostate cancer growth and spread is dependant to a great extent on the availability and effects of androgens (testosterone). Therefore, the major objective of treatment for this stage of disease is to suppress the testosterone levels in the body, otherwise known as castration. This can be medical or surgical. Surgical castration involves removal of the testicles (bilateral orchidectomy) which is a more permanent treatment option but obviates the need for ongoing medication or injections. Medical castration or androgen deprivation therapy (because the treatment is depriving the prostate of testosterone), is most commonly used in Australia. Tablets may include bicalutamide or flutamide. Monthly or three-monthly injections using degarelix, leuprolide, goserelin, buserelin may be prescribed. In certain instances, an intravenous chemotherapy drug like docetaxel may be added. Abiraterone and enzalutamide are standards of care, improving both progression-free and overall survival.

Over the course of time the prostate cancer itself develops evolutionary mechanisms to insulate itself from the effects of these medications and hence castrate resistance develops. There are a multiplicity of mechanisms that it employs to create this resistance but they involve adaptations in the androgen receptors in the various tissues of the human body at a molecular level, which render conventional medications unable to target these sites. This is known as persistent androgen receptor signalling. When castrate resistance occurs, there are limited therapeutic options available to manage this stage of disease.

In this study, the investigators explored the concept of endocrine resistance (EnR, a term used interchangeably with castrate resistance). EnR can be mediated by androgen receptor (AR) splice variants, with AR splice variant 7 (AR-V7) arguably the most clinically significant variant. They identified proteins that are central to generating AR-V7 and studied splicing regulatory mechanisms in prostate cancer models. Researchers identified JMJD6 as a key regulator of AR-V7, as evidenced by its upregulation with *in vitro* (in the lab) endocrine resistance. JMJD6 protein levels increased with castration resistance and were associated with higher AR-V7 levels and shorter survival. Inhibition of JMJD6 reduced prostate cancer cell growth. It is suggested that JMJD6 activity is key to the generation of AR-V7, with the catalytic machinery residing within a druggable pocket (defined as "sites that harbors physiochemical and geometric properties consistent with binding orally bioavailable small molecules"). This relationship between JMJD6 and AR-V7 suggests that JMJD6 may be a potential therapeutic target for metastatic castrate resistant prostate cancer in the future[2].

References

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2. Paschalis A, Welti J, Neeb AJ. JMJD6 is a druggable oxygenase that regulates AR-V7 expression in prostate cancer. *Cancer Res* 2021: 81 (4): 1087-1100.

About the Author

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Kalli is an internationally renowned Urological Surgeon, specialising in oncology and robotic surgery. He trained and worked in South Africa, before relocating to Australia where he has worked at Macquarie University Hospital and Westmead Hospital. His passion for what he does extends beyond the operating room, through publichealth advocacy, education and community awareness of men's health, cancer and sexuality.

Kalli has been involved with the Prostate Cancer Foundation of Australia for many years, advocating for improved cancer care and facilitating community prostate cancer support groups.