Submitted: 23 December, 2020 Accepted: 13 January, 2021 Published: 08 April, 2021 DOI:10.31083/jomh.2021.014

JOMH Journal of Men's Health

Editorial

The molecule that makes prostate cancer easy to find shows why it will be so difficult to cure

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Abstract

PSA is an enzyme that helps liquefy semen after a man ejaculates. Liquifying the semen frees sperm cells so they can swim to an egg and fertilize it. PSA's function is so essential for mammalian reproduction that prostate cancer has evolved a multitude of ways to avoid the body's own defences against cancerous prostate cells. As a testimony to how important PSA is to reproduction, highly mutated prostate cells still produce PSA. This makes the PSA test a good clinical tool for tracking the progression of the disease. At the same time, it also is an ominous sign of how hard it will be to find a simple cure for prostate cancer.

Keywords

Prostate-specific antigen; Prostate cancer; Oncology

One of the greatest advances in cancer care in the last half-century has been the development of screening tests that allow us to find certain cancers before they show symptoms. If caught early, many cancers can be treated and cured without requiring toxic chemotherapy. Screening tests get the credit for a rise in the number of people diagnosed with three of the most common cancers: breast, colorectal and prostate. They also get the credit for the increasing number of people surviving these diseases.

Prostate cancer screening involves measuring the levels of a molecule in the blood called prostate-specific antigen (PSA). PSA is secreted by prostate cells in the prostate gland and leaks into the bloodstream. When a man's PSA level is rising fast, that suggests that prostate cells are multiplying fast-the hallmark of cancer. The test is reliable because prostate cells diligently produce PSA, even when they are cancerous and metastatic. As long as the cancer remains only in the gland, it can be cured through local therapies such as surgery or radiation. Once it has migrated out of the gland, it is considered metastatic and we have no definitive cure.

Ask any physician about what the PSA molecule does and the answer you will probably get is that it allows for prostate cancer screening. But PSA surely doesn't exist for the convenience of diagnosing prostate cancer. In fact, PSA is not an ideal marker for prostate cancer because normal healthy prostate tissue secretes it. PSA serum levels can be elevated from other causes than cancer; i.e., from prostatitis, infection, and trauma. Prostate cells (healthy or otherwise) produce PSA, and a lot of it. That suggests that PSA *must have* a function in healthy males.

Indeed, PSA plays a key role in male reproduction that compliments the essential role of the testicles themselves. In order for males to get their genes into the next generation, they ejaculate semen, which contains sperm cells, at least one of which must reach a female's egg and merge with it to form a viable embryo. But sperm makes up less than five percent of semen. Much more of the semen is made up of two proteins with opposing functions that come from separate glands. One of these proteins is PSA, produced by the prostate gland. We will return to it shortly. The other protein is semenogelin, a protein secreted by the seminal vesicles that binds sperm in a viscous mass.

When a man ejaculates during penile-vaginal sex, the semen is propelled from his pelvis, through the whole length

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of the vagina, leaving the sperm cells en masse right next to the cervix. One can imagine the Herculean (and joyless) task sperm would face, if each cell had to swim that distance on its own.

But now we have a new problem. The sperm cells are trapped in semenogelin and only about halfway to their goal. To meet their mate, they must be freed from the wad and wind their way individually through the cervix and up the uterine tubes.

This gets us to the role of PSA.

PSA is a *protease*; i.e., a protein that can slice, dice, and liquify certain other proteins, including semenogelin. PSA's function is to liberate sperm cells after their initial ballistic voyage to the cervix. If it wasn't for PSA, sperm on their own wouldn't have a chance of getting close to an egg. They would instead end their lives in a viscous ejaculate jail.

PSA's function is so great that most prostate cells keep secreting it, even when they are cancerous and have spread to organs far from the male reproductive system. Everywhere these cells settle in the body, they try (in vain) to form functional prostate glands. The diligence of prostate cells to keep secreting PSA is a testimony to how essential they are for successful reproduction—and why PSA is such a reliable molecule for prostate cancer screening.

From a Darwinian perspective, survival is not about an individual's longevity, but about reproduction. A man can have his body riddled with prostate cancer, but if he can ejaculate viable sperm, his genes can still be passed on. He may be dying from cancer, but the mutations characterizing his disease will now be passed on to his descendants. The grim reality is that PSA enables genes which carry an increased risk of prostate cancer to be passed on from one generation to the next.

Prostate cancer cells are so relentlessly determined to produce PSA that they circumvent two of the body's normal defences against cancers. One of these relates to the hormonal regulation of the male reproductive system. The other relates to the immune system.

The initial growth of prostate cells depends on a hormonal surge at puberty, when testosterone first activates the whole male reproductive system. As well as sperm, the testicles start to produce testosterone, the hormone which prepares the prostate gland to contribute PSA to the ejaculate. Knowing that fact, a Canadian researcher, Charles Huggins, thought he might be able to stop prostate cancer by removing the testicles, literally cutting off the cancer's supply of testosterone. Huggins castrated advanced prostate cancer patients and their condition improved enough that it earned him a Nobel Prize.

A diminished sex drive comes with aging and is a product of the natural decline in testosterone that all men face as they get older. That drop in testosterone can be viewed as a defence against prostate cancer later in life. However, removing testosterone merely shuts down prostate cells and doesn't kill them outright. The Darwinian drive to produce offspring is so great that highly mutated prostate cells are able to grow *even without testosterone.* And even then they can continue producing PSA. Indeed, advanced prostate cancer is aptly called "castrate-resistant prostate cancer" because it can grow without testosterone. Simply put: the longer men live, the more likely they are to get prostate cancer, even if the testicles themselves are completely shut down.

Testosterone deprivation demonstrably works to control prostate cancer in the short-term for men who have an early-stage and castrate-sensitive disease. But that treatment ends a man's reproductive capability. To be blunt, to stop the prostate cells from doing their job, we must shut off the testicles completely and remove the driving force behind male virility. This is the difficult trade-off—we can enhance individual longevity, but only at the cost of fertility.

The body's other defence against most cancers is the immune system. Prostate cancers have evolved ways around this too.

When things work well, the immune system detects tumorous cells and kills them before they can multiply. Malignant cells, however, evolve strategies to dodge the immune system, and circumvent this defense. Immunotherapies are among the most promising areas of cancer medicines, since some can boost the immune system's ability to find and destroy cancer cells. Some immunotherapies can even counter the cancer's ways of dodging the immune system. Immunotherapies have increased the survival of patients with cancers such as melanoma, breast and lung cancer. However, they have so far been largely disappointing when applied to prostate cancer.

Prostate cancer is unusual in that it has an enormous number of cancerous mutations that can keep the cells alive and capable of producing PSA. This affirms the tireless evolutionary drive for those cells to produce PSA and help continue the genetic line. However, this means that an immunotherapeutic approach that attacks just one of two of those mutations is not likely to stop or kill the cancer outright.

Throughout our evolution, the immune system has evidently tried to attack cancerous prostate cells. The multitude of mutations carried by prostate cancer cells show that the immune system has failed in that regard. This suggests that it will be a major challenge to find an immunotherapy that is effective against prostate cancer, since it is already so adept at sneaking past the body's natural defenses. [It would be nice, though, if we were proven wrong here].

The biological role of PSA and the Darwinian drive for fatherhood, even in the face of death from cancer, suggest that an immunotherapy-sure cure for prostate cancer is unlikely. The limited progress in this area of cancer research demonstrates the harsh realities that evolution forces upon us in old age.

In sum, the same molecule that makes prostate cancer so easy to detect also reveals why it will be so difficult to cure. PSA is the gold standard for cancer screening. But it is a dastardly, durable molecule whose role in liberating sperm makes it essential for reproduction and contributes to the cross-generational spread of cancer genes.

Evolution clearly doesn't care whether prostate cancer wipes out a man's bones and other organs-and humiliates his immune system. If he can still ejaculate sperm and PSA can

free those sperm to venture onward, not only is he at risk of dying of prostate cancer, but so are his male descendants who receive his genes.

Abbreviations

PSA, prostate-specific antigen.

Author contributions

R.J.W. conceptualized the paper R.J.W. and I.N.F. wrote and edited the paper.

Acknowledgment

We thank our colleagues and the reviewers for JOMH who provided contstructive criticism on drafts of this essay.

Conflict of interest

The authors declare no conflict of interest.