



Prostate Cancer

The You Lab: Prostate Cancer & Inflammatory Signaling

Proinflammatory processes are important for cancer origin and progression. The Lab of **Zongbing You** studies the IL17 signaling pathway in the context of prostate cancer, using both tissue culture and murine models to understand IL17 Receptor C (IL17RC) and castration-resistant, metastatic prostate cancer. This approach and context is unique in several ways, including 1) the focus on the IL17RC gene, 2) the use of castration-resistant, treatment-refractory, metastatic prostate cancer as a baseline model system, and 3) the clinical utility of targeting the IL17 signaling pathway.

IL7 Signaling in Prostate Cancer

In humans, IL17RC is minimally expressed in normal prostate tissue, somewhat expressed in early-stage prostate cancer tissue, and highly expressed in castration-resistant/metastatic prostate tissue. This points to its possible role in the progression of the disease from indolent to potentially life-threatening. Overactive IL17 signaling is present in several autoimmune diseases, and multiple clinically-applicable antibody-based treatments exist for the diseases targeting this pathway.

The lab has shown that cancer development in the PTEN knockout mouse model of prostate cancer is dependent on the presence of the IL17RC gene. Mechanistically, the lab has shown that IL17 signaling contributes to disease specifically through influencing the protease MMP7, whose expression enables the process known as epithelial-to-mesenchymal transition (EMT). EMT marks the turning point for cancer from a localized, contained disease (epithelial-like cells) to a systemic, metastatic disease (mesenchymal cells). Thus, by targeting and interrupting the IL17 signaling pathway, prostate cancer can be arrested in a localized, more treatable form. This is true for both androgen dependent and independent disease, which could provide a treatment option for patients with advanced or refractory disease. To that end, the lab has established treatment models in mice in support of pursuing a clinical trial in the near future.

Inhibiting IL17 Signaling In Prostate Cancer

Using a mouse model, the lab has shown that inhibition of IL17 signaling can halt the progression of prostatic disease. In humans, anti-IL17 antibodies are already clinically exploited to treat autoimmune disease with very little side effects – so Dr. You is planning a small-scale clinical trial using patients who have failed first-line therapy. The treatment would consist of already-approved anti-IL17 antibodies and an androgen receptor-targeting drug. Other anti-inflammatory response drugs have been tested in oncology clinical trials before with mixed results, but IL17 is a master cytokine and able to regulate the expression of additional, downstream pro-inflammatory molecules. By cutting off this master cytokine (opposed to a more downstream molecule), the treatment response should be much more robust.

Obesity & Prostate Cancer: IL17 Signaling

Obese patients are known to be at increased risk for a variety of cancers, including prostate. IL17 and the excess insulin in these patients have a synergistic effect on proinflammatory signaling, possibly driving them toward carcinogenesis. The pathways responsible for this phenomenon remain poorly understood – but it is known that due to increased insulin, the kinase GSK3 beta is inhibited. This leads to an increased and sustained IL17 signal in obese patients through this receptor, perhaps driving prostate cancer formation. The lab is using an obese mouse model to study the possible involvement of IL17 signaling in the development of prostate cancer.

Stem Cell-Based Treatments for Cartilage Damage

The lab also studies ways in which fat-derived stem cells can be used to repair damaged connective tissue. Currently, serious connective tissue injury can only be repaired through cadaver grafts. It was discovered that fat-derived stem cells can be reprogrammed to cartilage-producing cells if they overexpress the doublecortin gene. This has obvious clinical implications, and is currently being tested in animal as part of a DOD-sponsored grant. While distinct from the prostate cancer focus of most of the lab, it is in line with the lab's operating principles of tying basic biology and discovery to clinically-applicable outcomes and treatment options for patients.

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