Cancer Biology
Prostate Cancer

The Zhang Lab: Androgen Receptor Splice Variants

The Androgen Receptor (AR) is important to all prostate cancer development. Shorter AR variants generated through alternative splicing have also been recently discovered. These variants of the AR lack the androgen binding domain and are constantly active, and can confer resistance to hormone deprivation therapy.

The lab of **Haitao Zhang** studies how these variants function in the prostate cancer cell to confer this resistance to both hormone therapy and chemotherapy.

The Splice Variants

The altered forms of the AR are a minor population of the AR protein in the prostate cancer cell. While originally only observed in late-stage cancers, it has been found that they can be expressed at low levels during early-stage disease. While they are less abundant, they are actually a more active form of the AR due to: 1) not needing androgen to be active, 2) having a longer half-life, and 3) not being exported out of the nucleus.

Additionally, these variants have recently been observed in breast cancer and their expression correlates with disease severity. These splice variants are both a potential novel prognostic indicator in prostate cancer and – more excitingly – a targetable, treatable option. In addition to presenting themselves as a potential therapeutic target, the mechanisms that are responsible for transporting these variants to the nucleus could also be druggable.

The Zhang Lab is interested in the specific mechanisms of nuclear transport and entry of these proteins. Specifically, they study the potential role of microtubules in the transport of the AR to the nucleus. It has been initially observed that full-length AR can be sequestered through association with microtubules. In contrast, the variants are not as strongly associated with the microtubules.

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Prognostic Assay Development

Currently, the detection of splice variants in patients is both fairly laborious and technically challenging. Current assays utilize circulating tumor cells as a substrate, necessitating difficult and specialized purification protocols.

In collaboration with a prostate cancer oncologist, The Zhang Lab is developing a droplet digital PCR (ddPCR)-based assay that utilizes patient peripheral whole blood. This assay uses the whole blood for variant detection (opposed to the circulating tumor cells) due to the exquisite sensitivity of ddPCR, making it much more user-friendly without sacrificing accuracy.

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