Cancer Biology

Prostate Cancer

Castration-Resistant Prostate Cancer & Androgen Receptor Splice Variants

In prostate cancer patients, most mortality is caused by castration-resistant cancer, which no longer responds to androgen deprivation therapy. One mechanism of castration resistance in prostate cancer is the generation of androgen receptor (AR) splice variants. These variants lack the androgen binding domain and are thus active independent of androgen.

These variant AR proteins are more active than their full-length counterpart in patients after androgen deprivation therapy. This is due to the fact that they 1) exist primarily in the nucleus with no nuclear export signal, 2) they are always active independent of androgen, and 3) they help the wild-type receptor to locate to the nucleus and become active in the absence of androgen.

The lab of **Yan Dong** studies these splice variants in the context of castration-resistant cancer. Unique among labs in this area, they study the role of dimerization in the action of these variants and their interactions with the full-length AR, with an eye toward inhibiting dimerization of these molecules. The ultimate goal is to find a way to make dimerization inhibition a clinically-viable treatment option for castration-resistant prostate cancer patients.

Cell Lines & Xenografts: Splice Variant Function

Patient-Derived Xenografts are pieces of human tumors transplanted into mice. In this context, human tumors can be studied for their reactions to treatments and analyzed in a living system. The lab employs the use of both patient-derived xenografts and genetically-modified prostate cancer cell lines injected into mice. Here, androgen levels can be manipulated and the cell response monitored to model human disease. The lab leverages this data…

Cell Line & Xenographs ... (Continued)

with publicly-available Second-Generation Sequencing data from prostate cancer patients to predict how the splice variants behave in human patients. Contrary to the prevailing opinion that the increase in AR variant expression in castration-resistant cancer tissues over castration-sensitive tissues is due to a shift in splice products, it has been discovered that a global increase in expression of all AR, both full-length and spliced variants, also contributes to the increase. It is hoped that this better understanding of basic AR variant biology will open up new avenues for prostate cancer treatment in castration-resistant disease.

AR Variant Biology and Dimerization

A major focus of the lab is examining the mechanisms behind AR variant function and dimerization. The steps leading to the activation of the full-length AR prior to downstream pathway activation are well characterized. However, the behavior of the splice variants is poorly understood.

Specific research interests include 1) how the variants dimerize, 2) if variant monomers can locate to the nucleus and bind chromatin, and 3) how the full-length and splice variant AR interact and the importance of this interaction in castration-resistant disease. The lab is currently focused on finding inhibitors to AR variant dimerization, in which two methods are employed -- an *in silico* screen being conducted in conjunction with an industry partner and a small molecule screen being conducted in partnership with another academic institution.

Ultimately, it is hoped that an inhibitor could be used clinically to treat castration-resistant prostate cancer patients.

Contact & Further Info:

James R Zanewicz, RTTP
Chief Business Officer
zanewicz@tulane.edu
504.919.3800 (m)

Claiborne M Christian, PhD
Business Development Assoc.
christian@tulane.edu
504.909.3905 (m)

engage.tulane.edu
t: engagetulane

Tulane
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