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 Se-
quencing data from prostate cancer patients to pre-
dict how the splice variants behave in human pa-
tients. Contrary to the prevailing opinion that the 
increase in AR variant expression in castration-re-
sistant cancer tissues over castration-sensitive tis-
ues 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 con-
tributes 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 charac-
terized. 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.