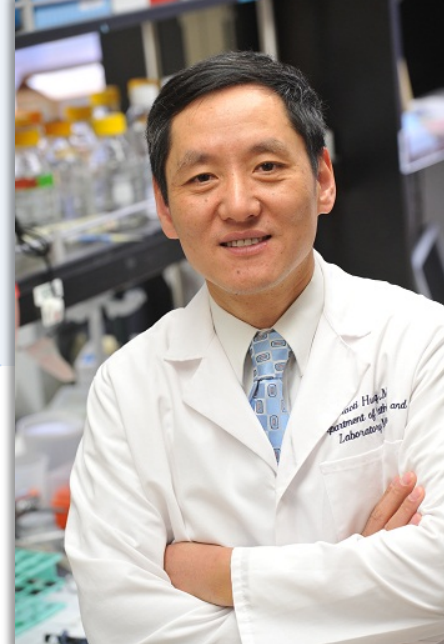


Researchers Discover a Molecular Mechanism for a Lethal Form of Prostate Cancer



Dr. Jiaoti Huang

Prostate cancer is the most common malignancy in American men and the second leading cause of cancer-related deaths. Annually, there are approximately 230,000 new cases and 28,000 men will die of prostate cancer. Most prostate cancers are indolent and will not impact the life expectancy or quality of life of the patients. However, approximately 15-20% of patients have aggressive cancers that are life-threatening.

If the tumor is caught in an early stage, it can be effectively treated with surgery or radiation. However, once the tumor is advanced or recurs after the initial treatment, the only useful form of treatment is hormonal therapy. The principle of hormonal therapy is to inhibit the production of the male hormone androgen, the fuel for prostate cancer. Another approach is to inhibit the function of androgen receptor to block the engine of the cancer cells. In many patients, the two therapies are combined to achieve a better therapeutic efficacy. Nearly all patients respond well to hormonal therapy initially, showing significant symptomatic relief. Unfortunately such treatment is not curative and the therapeutic effects are temporary. The tumor eventually recurs in all patients, after an average of approximately 18 months.

The recurrent tumor is termed castration resistant prostate cancer (CRPC) and a major focus of current research is to combat this disease. Novel agents have been developed to further inhibit androgen receptor signaling pathway in CRPC with significant clinical benefits. However, Some patients develop a variant form of prostate cancer called small cell neuroendocrine carcinoma (SCNC) that do not respond to therapies that target the androgen receptor signaling pathway. The cell of origin and the molecular mechanism of SCNC had been a mystery for a long time. Dr. Jiaoti Huang's lab has been

studying neuroendocrine cells in benign prostate and prostate cancer. In an earlier publication in American Journal of Pathology, Dr. Huang's group discovered that the neuroendocrine cells in benign prostate and prostatic adeno-carcinoma express an inflammatory cytokine Interleukin-8 and its receptor CXCR2 ([Huang, Yao, Zhang, Bourne, Quinn, de Sant'Agnese, Reeder, June 2005](#)). Their group has continued studies in this area and more recently, they discovered that normally, Interleukin-8 activates its own receptor CXCR2 and keeps neuroendocrine cells in a non-proliferative state. A key molecule mediating this function is a tumor suppressor gene P53, which is also the most commonly mutated gene in human cancers. During hormonal therapy for prostate cancer, a P53 mutation occurs in the neuroendocrine cells, removing a major growth-inhibitory signaling pathway, rendering neuroendocrine cells highly proliferative and aggressive, resulting in the development of SCNC. The study has been published in the journal Endocrine-Related Cancer ([Chen, Sun, Wu, Magyar, Li, Cheng, Yao, Shen, Osunkoya, Liang, Huang, 2012](#))

These findings have important clinical implications. They demonstrate that SCNC is a totally different disease than the conventional prostate cancer. The vast majority of the conventional prostate cancers are indolent and do not need treatment, but prostatic SCNC is uniformly aggressive and always lethal. While the conventional prostate cancers respond to hormonal therapy due to cancer cells' dependence on androgen, SCNC does not respond to such therapies because they arise from a different cell population through an entirely different molecular mechanism.