NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e003

Editorial

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Volume 1 : Issue 2
Article Ref. #: 1000NPOJ1e003

Article History
Received: June 24th, 2015
Accepted: June 26th, 2015
Published: June 26th, 2015

Citation
Cho J, Izumi K, Huang CK. Androgen and androgen receptor in kidney cancer. *Nephrol Open J*. 2015; 1(2): e7-e8. doi: 10.17140/NPOJ-1-e003

Androgen and Androgen Receptor in Kidney Cancer

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Kidney cancer is one of the top ten most common cancers in men and women. There are four types of kidney cancer, including Renal Cell Carcinoma (RCC), Transitional cell carcinoma, renal sarcoma, and Wilm's tumor. The most common type of kidney cancers is renal cell carcinoma (RCC), with around nine out of ten kidney cancers being RCC (American Cancer Associate). Epidemiology studies have identified several risk factors associated with kidney cancer.[1] Among them, male gender is associated with twice incidence rate of RCC as female.[2] Androgen and Androgen Receptor (AR) are major factors contributing to male-gender-associated-diseases, such as prostate cancer,[3] suggesting that androgen and AR might be involved in RCC development and progression.

In contrast to the results of current epidemiological study, hormonal therapy had been evaluated in clinical trials for RCC patients in early decades.[4-8] Despite the discovery of the therapeutic effects of both progesterone and androgen in RCC patients, their therapeutic outcomes had not been appreciated.[9] Since androgen and AR are involved in male-gender-associated diseases, recent studies have switched the focus to target androgen and AR signaling in RCC. It was first disclosed that high AR expression is correlated with poor prognosis for RCC patients; signifying shorter overall survival, relapse-free survival, and cancer-specific survival.[10] However, another study suggests that AR is actually expressed in more than 90% of normal kidney human samples and that there are no differential AR expressions in normal male and female kidneys.[11] In addition, AR expression levels are inversely correlated with pT Stage and Fuhrman's Grade in RCC patients. This surprising result leads to further investigation of the transactivation activity of AR, as AR mainly exerts its function through transcriptional regulation of target genes.[12] Androgen treatment does not promote the transactivation activity of AR in commonly used RCC cell lines, such as CAKI-2 and OSRC-2, although AR expression could be detected in these cells. These interesting results bring up novel questions. How does male gender predispose RCC development if AR expression is reduced in RCC samples? Can AR be the therapeutic target even if RCC has AR expression without transactivation activity?

It has been demonstrated that targeting AR can be a potential therapy for RCC in pre-clinical model.[13] With *in vitro* malignant transformation assay, AR has been shown to promote normal human kidney epithelial cell transformation with more colony numbers and larger colony in the presence of carcinogen, ferric nitrilotriacetate. In addition, AR promotes cell growth of transformed kidney epithelial cells but not that of normal kidney epithelial cells. Furthermore, AR involves in cancer migration, invasion, and proliferation in RCC cell lines as determined by using overexpression and/or knockdown of AR in RCC cells with cancer progression assays. Using cancer-specific cDNA array, hypoxia-induced factor 2α (HIF2α) and Vascular Endothelial Growth Factor (VEGF) were identified to be the AR downstream targets responsible for AR-mediated RCC progression. By challenging RCC cells with HIF2α and VEGF inhibitors, AR-mediated RCC progressions could be abolished, suggesting that AR might modulate RCC

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e003

progression through HIF2α and VEGF signaling pathways.

To determine whether targeting AR can be a potential therapy for RCC, an AR degradation enhancer, ASC-J9®, was used to determine the effects of targeting AR on RCC progression in *in vitro* cell culture and in *in vivo* preclinical models, subcutaneous and orthotopic xenograft mouse tumor models. ASC-J9® treatment substantially reduces RCC proliferation, colony formation, migration, and invasion in *in vitro* cell assays. Targeting AR with ASC-J9® in RCC preclinical models also shows significant suppression of RCC tumor progression. In addition, ASC-J9 inhibits the expression of AR, HIF2α, and VEGF, suggesting that targeting AR may be a novel therapeutic approach for RCC patients.

Although androgen and AR signaling may be a potential therapy for RCC patients, it remains unclear as to why RCC have significantly less AR expression than normal kidney and why AR is negatively associated with RCC tumor stage. Future studies will be needed to explain these controversial observations.

DISCLOSURE

There is no conflict of interest for authors to disclose.

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