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KIDNEY CANCER

Androgen receptor—a new target in renal cell carcinoma?

New research suggests that targeting the androgen receptor (AR) might provide a new therapeutic option for treatment of renal cell carcinoma (RCC).

A study published in *Cancer Research* reports that AR signalling via hypoxia-inducible factor 2α (HIF-2α) and vascular endothelial growth factor (VEGF) promotes RCC progression in preclinical models *in vitro* and *in vivo*. Researchers also found that treatment with the newly developed agent ASC-J9®—an AR degradation enhancer—suppressed HIF-2α and VEGF signalling in experimental models, resulting in reduced RCC progression.

In vitro experiments using normal human kidney epithelial cells transfected to express AR and treated with the carcinogen ferric nitrilotriacetate showed that the presence of AR enhanced colony formation, colony diameter and proliferation. Further *in vitro* studies revealed that treatment of three human AR-expressing RCC cell lines with dihydrotestosterone increased proliferation, migration and invasion. These findings suggest that the presence of AR might have a role in promoting the initiation and growth of RCC in normal and cancerous cells.

Investigations into the signalling mechanism by which AR might affect cell growth revealed an increase in the transcription of HIF-2α and VEGF, which are known to be upregulated in RCC, where they stimulate angiogenesis and, therefore, promote cancer progression. Inhibition of HIF-2α and VEGF reduced the invasive capacity of AR-expressing RCC cells, further implying signal transduction through AR via the HIF-2α and VEGF pathway.

Xenografts of AR-expressing renal epithelial and RCC cells in male mice, planted subcutaneously and orthotopically, revealed that AR promoted the growth of larger tumours and increased tumour formation; one mouse also developed metastatic tumours. HIF-2α and VEGF expression was increased in tumours from xenografted AR-expressing RCC cells, supporting the *in vitro* findings.

> “...AR might have a role in promoting the initiation and growth of RCC...”

Treatment of AR-expressing cells with ASC-J9® suppressed proliferation *in vitro*, reduced the growth of xenografts *in vivo* and reduced expression of AR, HIF-2α and VEGF in xenografts.

These findings not only highlight a potential role for the AR in RCC, but also provide a possible explanation for the observed difference in incidence of RCC between men and women.

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Original article He, D. *et al.* New therapy via targeting androgen receptor→HIF-2α→VEGF signals with ASC-J9® to suppress renal cell carcinoma progression. *Cancer Res.* doi:10.1158/0008-5472.CAN-13-2681