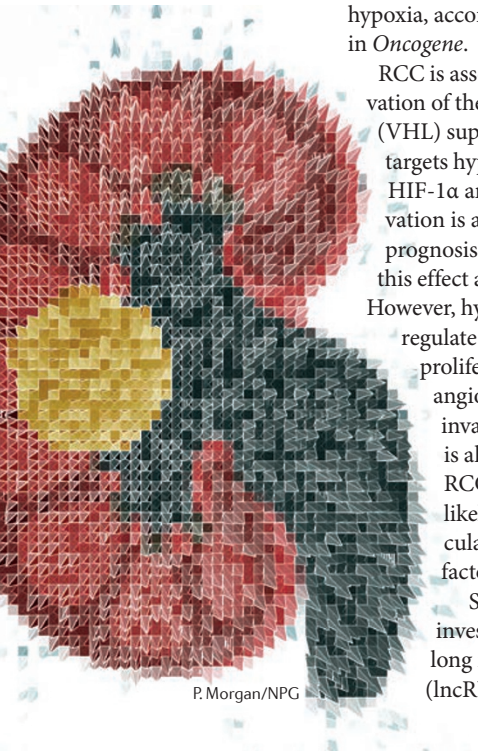
Nature Reviews Urology | Published online 5 Apr 2016; doi:10.1038/nrurol.2016.61

KIDNEY CANCER

AR promotes RCC via lncRNA interaction



P. Morgan/NPG

The androgen receptor (AR) regulates progression of renal cell carcinoma (RCC) via a mechanism dependent on *VHL* status and hypoxia, according to data published in *Oncogene*.

RCC is associated with inactivation of the von Hippel–Lindau (VHL) suppressor protein, which targets hypoxia-inducible factors HIF-1α and HIF-2α. *VHL* inactivation is associated with a good prognosis, but the mechanisms of this effect are not well understood. However, hypoxia is known to regulate processes including proliferation, apoptosis, angiogenesis, and tumour invasion. Like VHL, AR is also known to promote RCC progression, most likely via HIF-2α and vascular endothelial growth factor regulation.

Several studies have investigated the role of long noncoding RNAs (lncRNAs) in hypoxia. Thus, a team led by Dr Chawnshang Chang analysed the differential expression of lncRNAs in RCC tissue compared with benign tissue using RCC cell lines that were both positive and negative for *VHL* expression, under both normoxia and hypoxic conditions. "Kidney cancer, particularly ccRCC , has been known to implicate hypoxia signalling during its genesis and progression as well as having a clear gender bias," explains Chang. "We have found that AR can have a positive role in promoting ccRCC progression, but the exact details of AR's role are not clear."

First, the team introduced *VHL*-wild type (*VHL*-wt) DNA into *VHL*-mutant (*VHL*-mut) RCC cell lines and exposed them to normoxic or hypoxic conditions. They observed that hypoxia differentially modulated RCC cell proliferation, suppressing proliferation in *VHL*-mut cells, whilst enhancing it in *VHL*-wt cells. Next, they compared lncRNA expression in *VHL*-wt and *VHL*-mut cells under normoxia and hypoxia, identifying three lncRNAs that were differentially expressed under hypoxia in the mut and wt cell lines. RNA precipitation analysis showed that one of these, which the researchers named lncRNA-SARCC, could physically interact with the AR. Interestingly, hypoxia tended to cause downregulation of lncRNA-SARCC in cell lines considered to be *VHL*-wt, but induced it in *VHL*-mut cell lines. Overall, it seems that hypoxia might differentially mediate lncRNA-SARCC expression and AR interaction in a *VHL*-dependent manner. Furthermore, binding of lncRNA-SARCC to the AR could destabilize the AR protein and suppress signalling via HIF2α/C-MYC pathways.

Enhancing the expression of lncRNA-SARCC could offer a novel therapeutic option for patients with RCC. "This differential regulation might contribute to the better cancer-free survival and cancer-specific survival for those patients with stage I–III ccRCC with *VHL*-mutant than those with *VHL*-wildtype," says Chang.

Annette Fenner

ORIGINAL ARTICLE Zhai, W. *et al.* Differential regulation of LncRNA-SARCC suppresses VHL-mutant RCC cell proliferation yet promotes VHL-normal RCC cell proliferation via modulating androgen receptor/HIF-2α/C-MYC axis under hypoxia. *Oncogene* http://dx.doi.org/10.1038/onc.2016.19 (2016)