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KIDNEY CANCER

DA transporter a ccRCC biomarker?

The dopamine (DA) transporter protein SLC6A3 is overexpressed in clear cell renal cell carcinoma (ccRCC) and is a hypoxia-inducible factor (HIF) target gene, representing a potential novel diagnostic or possible therapeutic target.

The renal epithelium expresses a wide range of transporter proteins, expression of which has been linked to drug resistance, and polymorphisms of which have been linked to cancer development. Thus, a multi-institutional team from Sweden and Denmark used The Cancer Genome Atlas (TCGA) database to carry out an unbiased investigation of differences in solute carrier (SLC) and ATP-Binding Cassette (ABC) membrane transporter expression between ccRCC and normal kidney tissue.

The team found that the most upregulated transporter gene between ccRCC and normal kidney tissue was the DA reuptake transporter *SLC6A3*, which was expressed at almost 25-fold higher levels in ccRCC tissue than normal kidney. Interestingly, no previous reports have described a function for SLC6A3 in the kidney, although DA receptors are expressed throughout the nephron and are involved in vasodilation, control of diuresis, and sodium homeostasis.

The loss of *VHL* expression in ccRCC results in a state of pseudohypoxia; thus, the team then investigated whether *SLC6A3* might be a HIF target gene by comparing its expression with the well established HIF target *CAIX*. The expression pattern of *SLC6A3* was very different to that of *CAIX*, suggesting it is not a conventional HIF target. However, when primary normal renal cells were exposed to hypoxia, they upregulated expression of *SLC6A3*. The investigators went on to determine the functionality of SLC6A3 in ccRCC by measuring [^{3}H]DA uptake in cultured ccRCC cells, finding that DA uptake mirrored *SLC6A3* mRNA levels. Furthermore, blocking SLC6A3 with an inhibitor, the cocaine analogue GBR12909, reduced DA uptake, an effect also observed with *SLC6A3* knockdown using siRNA.

The authors speculate that, as *SLC6A3* overexpression is accompanied by active DA uptake in ccRCC cells, *SLC6A3* could represent a potential functional biomarker for ccRCC.

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