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KIDNEY CANCER

Exosome transmission of sunitinib resistance

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Sunitinib resistance in renal cell carcinoma (RCC) can be mediated by a long noncoding RNA (lncRNA) and this resistance can be transmitted between cells via exosomes. High expression of this lncRNA also correlates with poor response to sunitinib therapy in patients with RCC, according to new research published in *Cancer Cell*.

Qu and colleagues compared lncRNA profiles of sunitinib-resistant and parental RCC cells, and validated lncRNAs were then compared with lncRNA profiles obtained from sunitinib-resistant patient-derived xenografts. Loss-of-function analysis on matched lncRNAs revealed that RNA interference of lncRNA RP11-375O18.2-001 suppressed resistance to sunitinib. Qu and co-workers named this lncRNA ‘lncRNA activated in RCC with sunitinib resistance’ (IncARSR).

Levels of IncARSR were high in sunitinib-resistant RCC cells and were higher in patients who had tumour relapse after receiving sunitinib than in those patients who had a good response to therapy.

IncARSR levels in blood plasma from patients with RCC were elevated and correlated with levels observed in tumour tissue. Furthermore, IncARSR plasma concentrations decreased after

tumour resection and increased on tumour relapse. Pretreatment circulating IncARSR levels were higher in patients who experienced disease progression when receiving sunitinib than those whose disease did not progress. High IncARSR plasma levels also correlated with reduced progression-free survival and poor response to sunitinib treatment. These observations suggest that IncARSR could be a predictive marker of response to sunitinib therapy.

Stable knockdown of IncARSR in sunitinib-resistant cells resulted in reduced growth on treatment with sunitinib *in vitro* and significantly restored sunitinib sensitivity in resistant xenografts *in vivo*. AXL and c-MET were downregulated on IncARSR knockdown and high expression of these proteins was observed in sunitinib-resistant xenografts. Restoration AXL and c-MET expression in IncARSR-knockdown cells recapitulated sunitinib resistance. Treatment with BMS777607, a small-molecule inhibitor of AXL and c-MET, resensitized resistant cells to sunitinib.

Extracellular IncARSR was found to be packaged in exosomes, a process that is mediated by hnRNP A2B1 (an RNA binding protein known to regulate microRNA trafficking).

Interaction between IncARSR and hnRNP A2B1 was increased in sunitinib-resistant cells and knockdown of hnRNP A2B1 reduced IncARSR levels in exosomes.

Cell incubation with exosomes derived from sunitinib-resistant cells increased intracellular IncARSR levels and sunitinib resistance in recipient cells, which was sustained for at least 7 days. *In vivo*, administration of exosomes derived from sunitinib-resistant cells into xenografts reduced xenograft tumour response to sunitinib and increased tumour IncARSR expression. These results indicate that resistance to sunitinib can be transferred intercellularly via exosomes.

In vivo, targeting IncARSR with an optimized locked nucleic acid in an orthotopic xenograft model of RCC restored sunitinib sensitivity in these tumours. No tumour growth was observed after treatment discontinuation for up to 2 months and survival was prolonged. Moreover, sunitinib sensitivity was restored in a patient-derived xenograft model of acquired sunitinib resistance. Combination treatment with BMS777607 and sunitinib resulted in suppression of tumour growth in sunitinib-resistant xenografts, and pretreatment with this combination prevented the emergence of sunitinib resistance.

Drs Lin-Hui Wang and Hong-Yang Wang, corresponding authors, told *Nature Reviews Urology* “Our results demonstrate that inhibition of IncARSR restores sunitinib response and these results reinforce the concept that adopting combined therapies against specific resistance mechanisms could overcome sunitinib resistance.”

Louise Stone

ORIGINAL ARTICLE Qu, L. et al. Exosome-transmitted lncARSR promotes sunitinib resistance in renal cancer by acting as a competing endogenous RNA. *Cancer Cell* <http://dx.doi.org/10.1016/j.cccell.2016.03.004> (2016)

Correction

In the original version of this article published online Dr Ying-Hao Wang was mistakenly referred to as a corresponding author, in place of Dr Lin-Hui Wang. This error has now been corrected.