Commentary

Exosome-transmitted lncARSR: a novel therapeutic target in renal cancer

Chunlin Ou[1,2], **Guiyuan Li**[1,2]

[1]Key Laboratory of Carcinogenesis of the Chinese Ministry of Health, Xiangya Hospital, Central South University, Changsha 410078, China; [2]Key Laboratory of Carcinogenesis and Cancer Invasion of the Chinese Ministry of Education, Cancer Research Institute, Central South University, Changsha 410078, China

Correspondence to: Guiyuan Li. Cancer Research Institute, Central South University, 110 Xiangya Road, Changsha 410078, China. Email: lgy@csu.edu.cn.

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Renal cell cancer (RCC) is the most common kidney cancer and has a poor prognosis (1). Although some achievements have been made to date, radical therapy for RCC remains challenging (2). It is now generally accepted that recurrence and metastasis are the main cause of reducing survival of RCC patients attributed to causing tumor resistance for conventional therapies. Recently, sunitinib is an important therapeutic option for advanced RCC patients. However, it is reported that 10–20% of advanced RCC patients are resistant to sunitinib therapy because of the patient's inherent drug resistance (3). Emerging evidence have shown that the acquisition of sunitinib resistance was associated with the activation of compensatory signaling pathways (4), but the underlying mechanisms remain unclear. Further investigations of the mechanisms of resistance in RCC are necessary to clarify the pathogenesis and development of novel combination therapies (5).

Exosomes generally refer to a mixed population of small extracellular vesicles (sEVs) that display a diverse range of sizes (40 to 100 nm in diameter) (6). They can transfer information (e.g., proteins, RNAs, and DNAs) to target cells by a manner of specific cell-to-cell communication. This process was completed through three main mechanisms: endocytosis by phagocytosis, direct fusion with the plasma membrane and receptor–ligand interactions (7). The weight of evidence supports that exosomes can transfer noncoding RNAs (ncRNAs) (e.g., miRNAs, lncRNAs, and circRNA) to achieve the cell-to-cell communication (8). These exosome-associated ncRNAs play pivotal roles in a variety of human diseases, including cancer (9,10). However, it is not clear whether resistant cancer cells can confer drug resistance to sensitive cells via exosomes, and whether EV-associated lncRNAs have therapeutic potential in cancer.

In a recently published study by Qu *et al*. (11) demonstrated an insight to search for novel targets for sunitinib resistance. In this study, the authors identified lncARSR (lncRNA Activated in RCC with Sunitinib Resistance, ENST00000424980) plays important role in mediating sunitinib resistance in RCC cells. It acts as a competing endogenous RNA for binding to miR-34/miR-449, thereby facilitating the expression of their targets AXL and c-MET to reactivate the receptor tyrosine kinase (RTK), while sunitinib is a novel multitargeted PTK inhibitor. Recently, studies have reported that drug resistance can be disseminated to sensitive cells by exosomes that transmit these regulatory RNAs (12,13). Interestingly, Qu *et al*. clearly illustrated that when lncARSR was bio-activated, could be encapsulated by exosomes and released into the extracellular environment, thereby conferring sunitinib resistance to neighbouring sensitive cells. These findings indicated that exosome-transmitted lncARSR may be as a novel therapeutic target for sunitinib resistance in RCC, thereby improving the clinical benefits in the future.

In summary, Qu *et al*. clearly established that sunitinib resistance can be disseminated to sensitive cells by exosomes that transmit these regulatory RNAs, and exosome-transmitted lncARSR could act as a diagnostic biomarker as well as a therapeutic target for sunitinib resistance. Exosomes were previously regarded functionally as "junk" to remove from cells; however, it is now clear that they play important roles in tumorigenesis and drug resistance in specific cell-to-cell communication via the transfer of a

series of small molecules, including lncRNAs. Because of exosome-associated lncRNAs stability and abundance in serum, they show a strong potential to act as new molecular biomarkers and therapeutic targets for cancer. The application of next-generation sequencing and RNA-seq technology has enabled the identification of an increasing number of exosome-transmitted lncRNAs. However, exosome-associated lncRNA functions *in vivo* remain an outstanding question, and additional research need to utilize suitable *in vivo* model systems. In addition, it is necessary to explore functional exosome-associated lncRNAs to establish whether they are specifically associated with one or more diseases and to determine the molecular mechanisms underlying these associations. In brief, further research is urgently needed to enable clinical applications. Although our current knowledge of exosome-associated lncRNAs only represents the tip of the iceberg, novel methods and technologies will eventually clarify these processes, thereby providing a novel strategy for the prevention, early diagnosis, and treatment of cancer.

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References

1. Motzer RJ, Escudier B, Choueiri TK. Treatment of Advanced Renal-Cell Carcinoma. N Engl J Med 2016;374:889-90.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
3. Molina AM, Lin X, Korytowsky B, et al. Sunitinib objective response in metastatic renal cell carcinoma: analysis of 1059 patients treated on clinical trials. Eur J Cancer 2014;50:351-8.
4. Rini BI. Vascular endothelial growth factor-targeted therapy in metastatic renal cell carcinoma. Cancer 2009;115:2306-12.
5. Rankin EB, Giaccia AJ. The Receptor Tyrosine Kinase AXL in Cancer Progression. Cancers (Basel) 2016;8:E103.
6. Tkach M, Thery C. Communication by Extracellular Vesicles: Where We Are and Where We Need to Go. Cell 2016;164:1226-32.
7. Zhang X, Yuan X, Shi H, et al. Exosomes in cancer: small particle, big player. J Hematol Oncol 2015;8:83.
8. Ma P, Pan Y, Li W, et al. Extracellular vesicles-mediated noncoding RNAs transfer in cancer. J Hematol Oncol 2017;10:57.
9. Stamatopoulos B, Van Damme M, Crompot E, et al. Opposite Prognostic Significance of Cellular and Serum Circulating MicroRNA-150 in Patients with Chronic Lymphocytic Leukemia. Mol Med 2015;21:123-33.
10. Takahashi K, Yan IK, Haga H, et al. Modulation of hypoxia-signaling pathways by extracellular linc-RoR. J Cell Sci 2014;127:1585-94.
11. Qu L, Ding J, Chen C, et al. Exosome-Transmitted lncARSR Promotes Sunitinib Resistance in Renal Cancer by Acting as a Competing Endogenous RNA. Cancer Cell 2016;29:653-68.
12. Wu H, Zhou J, Mei S, et al. Circulating exosomal microRNA-96 promotes cell proliferation, migration and drug resistance by targeting LMO7. J Cell Mol Med 2017;21:1228-36.
13. Mikamori M, Yamada D, Eguchi H, et al. MicroRNA-155 Controls Exosome Synthesis and Promotes Gemcitabine Resistance in Pancreatic Ductal Adenocarcinoma. Sci Rep 2017;7:42339.

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