AB070. Roles and mechanisms of soybean isoflavones in androgen-independent transformation of prostate cancer

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Abstract: The aims of this study were to investigate the impact of soybean isoflavones (SIFs) on the cellular oxidative stress levels in hormone-sensitive type (LNCap) and hormone-insensitive type (DU145) of prostate cancer, and to elucidate the main components and their roles in the transformation of androgen dependency (AD)/androgen independency (AI). The LNCap and DU145 cells were treated with different concentrations of SIFs monomer (including daidzin, genistin, daidzein, and genistein), and the activities of superoxide dismutase (SOD) and malondialdehyde (MDA) were then measured. The content of reactive oxygen species (ROS) in these two cells was also determined after treated with certain effective monomer. The contents of MDA in the two kinds of cells treated with genistein and daidzein were increased, but the contents of SOD were decreased in a concentration-dependent manner. There was no significant difference between daidzin and genistin. The content of MDA in the DU145 cells was higher than that in the LNCap cells under the same conditions, but the content of SOD was decreased, indicating that the oxidative stress level in DU-145 was higher than LNCap, and the ROS level in DU145 treated with effective component was significantly higher than that in LNCap. Genistein and daidzein in SIFs can affect the apoptosis and proliferation of prostate cancer cells through increasing their oxidative stress levels, thus inhibit the transformation of prostate cancer toward androgen-independent type.

Keywords: Soybean isoflavones (SIFs); androgen-independent; prostate cancer

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AB071. The role of long non-coding RNAs in sunitinib resistance of renal cancer

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Background: The incidence of renal cell carcinoma (RCC) has been rising throughout the world. Approximately 20% of RCC patients presented with advanced stage disease at the time of diagnosis, and in patients with localized RCC, nearly 30% will develop recurrence and metastasis after tumor resection. Recently, improved comprehension of RCC pathogenesis led to the development of receptor tyrosine kinase (RTK) inhibitors, such as sunitinib, as the mainstay of therapeutic options for advanced RCC patients. Sunitinib is an oral multi-targeted RTK inhibitor, which has potent anti-angiogenic effects and direct anti-tumor activities due to the inhibition of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptors (PDGFR), stem-cell growth factor receptor (KIT) and FMS-like tyrosine kinase 3 (FLT3). However, 10–20% of advanced RCC patients are inherently refractory to sunitinib therapy, and most of the remaining patients end up with drug resistance and tumor progression after 6–15 months of therapy, resulting in failure of sunitinib to efficiently prolong the survival of RCC patients. Several studies have proposed the activation of compensatory signaling pathways for the acquisition of

sunitinib resistance, but the picture remains unclear. On the other hand, few prognostic factors have been validated as predictive biomarkers of sunitinib response. Thus, it is urgent to elucidate the underlying mechanisms of sunitinib resistance and discover reliable biomarkers that can predict sunitinib response in RCC patients.

Methods: Exosomes can be secreted from multiple types of cells and participate in intercellular communication by transmitting intracellular cargoes, such as proteins and nucleic acids. Increasingly, some studies have suggested that exosomes from stromal cells could potentially affect therapeutic response though transfer of proteins and miRNAs. However, whether exosomes derived from resistant cancer cells can confer drug resistance to sensitive cells needs to be illustrated. Moreover, components embedded in circulating exosomes may serve as easily accessible biomarkers for the evaluation of drug response in patients. Long non-coding RNA (lncRNA) is a heterogeneous class of transcripts with a minimum length of 200 bases and without protein-coding potential. lncRNAs are involved in multilevel regulation of gene expression, including transcriptional regulation by recruiting chromatin-modifying complexes and post-transcriptional regulation by interacting with miRNAs, mRNAs or proteins. Emerging evidence supports the notion that lncRNAs modulate numerous hallmarks of cancer, including proliferation, apoptosis, metastasis and metabolism. However, the roles of lncRNAs in sunitinib resistance are poorly understood. In this study, we identify an upregulated lncRNA (lncARSR) in sunitinib-resistant RCC cells. We then investigate the contributions of lncARSR to sunitinib resistance and its therapeutic implications for sunitinib-resistant RCC patients.

Results: Herein we identified an lncRNA, named lncARSR (lncRNA Activated in RCC with Sunitinib Resistance), that correlated with clinically poor sunitinib response. lncARSR promoted sunitinib resistance via competitively binding miR-34/miR-449 to facilitate AXL and c-MET expression in RCC cells. Furthermore, bioactive lncARSR could be incorporated into exosomes and transmitted to sensitive cells, thus disseminating sunitinib resistance. Treatment of sunitinib-resistant RCC with locked nucleic acids (LNA) targeting lncARSR or an AXL/c-MET inhibitor restored sunitinib response.

Conclusions: lncARSR may serve as a predictor and a potential therapeutic target for sunitinib resistance.

Keywords: Sunitinib; renal cancer; receptor tyrosine kinase (RTK); long non-coding RNA (lncRNA)

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AB072. A feed forward loop between lncARSR and YAP activity promotes expansion of renal tumor-initiating cells

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Background: Renal cell carcinoma (RCC) is the most common kidney cancer in adults prognosis. Increasing appreciation of cell heterogeneity and a challenging disease with poor within clear cell renal cell carcinoma (ccRCC) has focused attention on a distinct subpopulation of cells called tumour initiating cells (T-ICs) or cancer stem cells (CSCs) in ccRCC. T-ICs exhibit extended self-renewal potential and tumour initiating ability. Tumours that harbour an abundant T-IC population or have high expression of stemness-related genes may signal a poor clinical outcome in RCC patients. Therefore, identification of the underlying mechanisms governing renal T-ICs propagation may lead to the discovery of promising therapeutic strategies for RCC patients.

Methods: Long non-coding RNA (lncRNA) is a subgroup of transcripts with more than 200 nt and limited coding potential. lncRNAs modulate biological process via diverse mechanisms, including mobilizing transcriptional co-regulators or chromatin-modifying complex at transcription level, and interacting with RNAs and protein complex or modifying signal proteins at post-transcription level. Several lncRNAs have been reported to regulate the self-renewal of T-ICs especially liver T-ICs. Nevertheless, the role of

