

Weng W.H.¹, Yu K.J.¹, Jhan J.W.¹, Pang S.T.²

¹National Taipei University of Technology, Department of Chemical Engineering and Biotechnology, and Graduate Institute of Biochemical and Biomedical Engineering, Taipei, Taiwan, ²Chang Gung Memorial Hospital, Department of Urology, Taoyuan, Taiwan

Introduction & Objectives: Sarcomatoid renal cell carcinoma (sRCC) is the most aggressive subtype of dedifferentiated renal cell carcinoma (RCC). Clinically, it is more likely to spread to other parts of the body, and represented drug resistance type of malignancy with average median survival of less than 1 year. Recently, microRNA (miRNA) profiling has been emerged as one of the important cancer specific biomarkers to predictive tumor growth or tumor progression in various cancer types, such as pancreatic cancer, colorectal cancer, osteosarcoma as well as clear cell RCC (ccRCC). We have demonstrated that elevate the expression of miR-378 in tumor cells might significantly inhibit ERK1/2 protein expression and further effect the downstream cell cycle progression resulted in cell death. Similar to the current study, lower expression level of miR-378 was observed in both subtypes of ccRCC as well as sarcomatoid RCC (sRCC) when compare to the normal cells. Besides, as known that suppression of POLR2A could selectively inhibit the tumorigenesis of cancer cells; same as upregulation of RUNX2 that may promote tumor viability, invasion, and activated the PTEN/PI3K/AKT pathway. Therefore, we hypothesized that modulate the expression level of miR-378 in RCC cells may effect the expression of genes POLR2A and RUNX2, then further inhibit tumor cell proliferation and activate the intrinsic pathway of apoptosis.

Materials & Methods: In total five cell lines (included three ccRCCs, one sRCC and one control cells) were involved in this study. Firstly, the ingenuity pathway analysis (IPA) system was applied to analyze the RCC related signaling pathways, such as pVHL/HIF-1 α , PI3K/AKT/mTOR, and HGF/c-Met pathways, after cross-matching to our previous RCC microarray data, the candidate genes POLR2A and RUNX2 were then selected. We then further interpreted the correlation of miR-378 and both genes in RCCs by using quantitative RT-PCR, western blotting and flow cytometry analysis to compare before and after transfected miR-378 in the study.

Results: Increased the expression level of miR-378 in tumor cells could significantly induced apoptosis in sRCC (RCC52) and ccRCC (Caki-1) cells with P value ≤ 0.05 . Most notably, sRCC represented significant down-regulation of mRNA and protein expression of POLR2A and RUNX2 (p value < 0.001) when compare to ccRCC cells or control cells.

Conclusions: Our data indicated that miR-378 might act as an important role of tumor suppressor, which may significantly inhibit tumor cell proliferation, and the potential effects of the POLR2A and RUNX2 genes on the prognosis of sRCC should be considered. However, molecular mechanisms underlying patterns of tumorigenesis differ from ccRCC and sRCC, that might result from the different type of mutations should always be considered.