Molecular Pathways Regulated by Tumor Suppressive microRNA in Renal Cell Carcinoma Based on microRNA Expression Signature

Introduction and Objective: Renal cell carcinoma (RCC) is the most common neoplasm of the adult kidney, and clear cell RCC represents the most common renal cancer histology. However surgical treatment is provided for localized disease, relapse or metastasis of the patient is caused in a considerable ratio. It is needed to find molecular mechanisms based on recent genome analysis in RCC oncogenesis and metastasis. Growing evidences suggested that microRNAs (miRNAs) contribute to the initiation, development and metastasis of various types of cancer. Some lower expressed miRNAs could function as tumor suppressors by negatively regulating oncogenes. In this study, we identified down-regulated miRNAs based on RCC expression signature and investigated the functional significance of these down-regulated miRNAs. Furthermore, molecular pathways regulated by tumor suppressive miRNAs were identified.
Materials and Methods: The expression levels of 667 human mature miRNAs were examined using real-time quantitative PCR (Taq Man MicroRNA Assay; Human Panel v2.0) of 10 paired RCC and the normal tissues. Cell proliferation assay was performed to investigate functional significance of top 20 down-regulated miRNAs by RCC signature using mature miRNA transfectant RCC cells.
Genome-wide gene expression analysis was performed to identify the molecular targets of miR-1285 by microarray technique.
Results: We identified 104 down-regulated miRNAs based on miRNA expression signature. Among the down-regulated miRNAs, transient transfection of miR-1285, miR-206, miR-1, miR-200c, miR-135a, miR-429, and miR-133b inhibited cell growth in cancer cell lines by XTT assay (each, $P<0.0001$). In this study, we focused on miR-1285 which was most inhibited cell proliferation. Genome-wide molecular targets search showed that seven genes (LHPP, TGM2, NF2, CERCAM, SYNPO, LYPLA2 and AHNAK) were down-regulated more than 4.0-fold in miR-1285 transfectants compared to the controls, and they have putative target sites on their 3'UTR region. We also found that the expression level of TGM2 was elevated in RCC specimens compared with matched normal tissues ($P<0.0037$).
Conclusion: We identified tumor suppressive miRNAs (miR-1285, miR-206, miR-1, miR-200c, miR-135a, miR-429 and miR-133b) according to the expression signature and functional screening in RCC. Genome-wide analysis revealed that tumor suppressive *miR-1285* regulates molecular pathways involved in RCC development. Tumor suppressive miRNA mediates novel molecular pathways provide new insights of molecular mechanisms of RCC oncogenesis.