Molecular Targets Regulated By Tumor Suppressive Microrna-1 and Microrna-133a in Bladder Cancer

Introduction and Objective: Our expression signatures of human cancer including bladder cancer (BC) revealed that the expression levels of *microRNA-1* (*miR-1*) and *microRNA-133a* (*miR-133a*) were significantly reduced in cancer cells. In human genome, *miR-1* and *miR-133a* located same chromosomal regions (*miR-1-2* and *miR-133a-1* on 18q11.2, and *miR-1-1* and *miR-133a-2* on 20q13.33) called cluster. In this study, we investigated the functional significance of *miR-1* and *miR-133a* and identify the novel molecular targets commonly regulated by both *miR-1* and *miR-133a* in BC.
Materials and Methods: Cell proliferation, invasion and apoptosis assay was performed by restoration of mature *miR-1* and/or *miR-133a* in BC cell lines. Genome-wide gene expression analysis was performed to identify the molecular networks of *miR-1* and *miR-133a* by microarray technique. A luciferase reporter assay was used to identify the actual binding site between *miR-1* and *miR-133a* and its candidate target genes. Cell proliferation, invasion and apoptosis assays were performed to investigate the targets genes in BC cell lines. To investigate of expression of target genes, immunohistochemistry was performed by using BC tissue microarray.
Results: Restoration of *miR-1* and/or *miR-133a* significantly inhibited cell proliferation and invasion in cancer cells ($P < 0.05$). Apoptosis assay showed that significant apoptotic cells were induced by *miR-1* and/or *miR-133a* transfection ($P < 0.05$). Genome-wide molecular targets search and luciferase reporter assay showed that *Transgelin2 (TAGLN2), prothymosin-alpha* (*PTMA*) and *purine nucleoside phosphorylase* (*PNP*) were directly regulated by *miR-1* and *miR-133a* commonly ($P <0.0001$). Silencing of the target genes studies demonstrated significant inhibition of cell proliferation and invasion, and increase of apoptosis in BC cells ($P < 0.05$). Immunohistochemistry showed that TAGLN2 and PTMA expression level was significantly higher in BC than normal bladder epitheliums (respectively, $P=0.0202$ and $P =0.0048$).
Conclusions: miR-1 and miR-133a function as tumor suppressor in BC. *TAGLN2, PTMA* and *PNP* were directly regulated by tumor suppressive *miR-1* and *miR-133a* commonly. These genes may function as oncogenes contributed to cell proliferation and invasion in BC. Tumor suppressive *miR-1* and *miR-133a* mediates novel molecular targets provide new insights into the potential mechanisms of BC oncogenesis.