miR-133a as a tumor suppressive microRNA targeting multiple oncogenes in head and neck squamous cell carcinoma (HNSCC)

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Abstract

miRNAs interact messenger RNAs mutually

MicroRNAs (miRNAs) are an abundant class of small non-protein-coding RNAs that function as negative gene regulators. They regulate diverse biological processes, and bioinformatic data indicates that each miRNA can control hundreds of gene targets, underscoring the potential influence of miRNAs on almost every genetic pathway. Unique feature of miRNAs is that they regulate multiple protein-coding genes. (a) In addition, protein-coding gene is regulated by multiple miRNAs. (b) In fact, there is a complex network of mutual interactions between miRNAs and messenger RNAs. (c)

Background and Aims

We previously identified several down-regulated microRNAs (miRNAs) in head and neck squamous cell carcinoma (HNSCC), esophageal squamous cell carcinoma (ESCC) and bladder cancer. miR-133a was commonly down-regulated and inhibited cell proliferation and invasion, which suggested that miR-133a might be a candidate of tumor suppressive microRNA. Our recent reports revealed that miR-133a had conserved sequences in the 3'UTR of FSCN1 and it repressed FSCN1 expression (Chiyomaru et al, Br J Cancer. 2010, Kano et al, Int J Cancer 2010). miRNAs could regulate multiple genes by mRNA cleavage or translational repression. Hence, the aim of this study is further identification of miR-133a target genes which have oncogenic functions.

Key Findings

1. Quantitative real-time RT-PCR revealed that miR-133a was down-regulated in twenty-five pairs of normal epithelia and HNSCC tissues.
2. Gain-of-function analysis revealed that miR-133a transfected inhibited cell proliferation and cell invasion in cancer cells.
3. For target genes silenced by miR-133a in cancer cells, we performed genome-wide screening (aligo microarray analysis and public database search). Among the genome-wide analysis, several candidate genes were identified, such as, CAVI (caveolin 1) and GSTP1 (glutathione S-transferase PI).
4. miR-133a has conserved sequence in the 3'UTR of CAVI and GSTP1, and directly inhibited CAVI and GSTP1 expression.
5. CAVI, which is the main component of the caveolae plasma membranes found in most cell, mediates cell migration and invasion in HNSCC.
6. GSTP1, which plays an important role in detoxification by catalyzing the conjugation of many hydrophobic and electrophilic compounds with reduced glutathione, promotes cell proliferation and inhibits cell apoptosis in HNSCC.

Conclusions

Tumor suppressive miRNAs and target oncogenes may provide new insight into understanding of the potential mechanisms in cancer. Our findings have therapeutic implications and may be exploited for future treatment of HNSCC.

These studies were recently published in International Journal of Oncology (2011 Jan;38(1):209-17) and International Journal of Molecular Medicine (2011 Mar;27(3):345-52). Related article as for tumor suppressive miR-1 was also published in Oncotarget (2011 Jan-Feb;2(1-2):29-44)