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DIFFERENTIAL EXPRESSION PROFILE OF CIRCULATING MICRORNAS IN PATIENTS WITH IN-STENT STENOSIS

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Background MicroRNAs (miRNA) are noncoding small RNA molecules that are involved in the control of a wide range of biological functions and processes, such as growth, development, differentiation, proliferation, metabolism, and apoptosis by mRNA degradation or translational inhibition. Most recently, miRNAs are showed to regulate many cardiovascular disorders. However, the role of miRNAs in the development of in-stent restenosis (ISR) is still unknown.

Objectives We used miRNA microarrays to compare the plasma miRNAs expression in patients with ISR with those without ISR. Using bioinformatics to predict the target genes of differentially expressed miRNAs and further analyse their possible function in ISR.

Methods Patients underwent stent implantation between June in 2008 and October in 2010 were enrolled in this study. All enrolments received optimal medical treatment during the follow up. Angiograph follow up was performed during six months to 12 months after stenting. Blood samples were collected at follow up time. ISR is defined angiographically as a ≥ 50% loss in luminal diameter at follow up. MiRNAs isolated from 18 patients (ISR, n=9; Control, n=9) were used for microarray analysis to establish miRNA expression profile of ISR and controls. Real-time fluorescent quantitative polymerase chain reaction (qRT-PCR) was used for validation. We use seven available bioinformatics softwares to predict the target genes of differential miRNAs. The target genes predicted at least by 5 databases were used for subsequent analysis. These genes were then used to GO annotation, classification enrichment analysis. Furthermore, we perform the biology pathway enrichment analysis using current available biology pathway database.

Results By analysing 1891 miRNAs using miRNA microarray, 139 miRNAs were showed differentially expressed between the patients with and without ISR, of which 61 were up-regulated and 78 were down-regulated. Six miRNAs (miR-let-7i, miR-let-7d, miR-9, miR-29a, miR-16, and miR-7) were selected to validate the results of microarray using qRT-PCR. The results showed that the expression of miR- let-7i, miR-let-7d, miR-9, miR-29a, and miR-7 was significantly higher and miR-16 was lower in ISR compared with controls, which was consistent with the result of microarray. Thirty five miRNAs and 398 corresponding target genes sets were finally determined for later analysis. The results of GO classification enrichment analysis showed that these genes were enriched in some basic biological process, such as transcriptional control, cell proliferation, and apoptosis, and molecular function like protein kinase activity. KEGG analysis revealed that these genes mainly enriched in MAPK pathway, cell cycle, local adhesion, external cellular matrix receptor interaction, and tight junctions.

Conclusions Microarray chip is the effective approach for the high-throughput analysis of miRNAs expression profile in patients with ISR. There were 139 miRNAs differentially expressed in ISR by Microarray chip. Six miRNAs (miR-let-7i, miR- let-7d, miR-9, miR-29a, miR-16, and miR-7) were selected for relative quantification by qRT-PCR. All results was conformable to the result of array which confirmed the reliability of microarray chip results. The predicted target genes of differential miRNA were mainly enriched in basic biological process of cell proliferation, apoptosis, inflammation and cell adhesion. KEGG analysis also revealed that these genes were mainly enriched in the pathways associated with cell proliferation, apoptosis, inflammation and cell adhesion.