

MIRNA GENES REGULATED BY DNA METHYLATION IN PAPILLARY THYROID CARCINOMAS

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BACKGROUND: Thyroid cancer (TC) is the most common endocrine neoplasm, among which the papillary carcinoma (PTC) is the more frequent histological type. The initiation and progression of PTC involves multiple genetic and epigenetic alterations. The regulation by DNA methylation and microRNAs are considered effective mechanisms of epigenetic control of gene expression. In addition, similarly to genes that encode proteins, microRNAs genes are also targets for epigenetic events, such as DNA methylation. In this study, we investigate the differential DNA methylation profile of microRNA genes in PTC.

HYPOTHESIS: Differential methylation in microRNAs genes is correlated with altered miRNA expression, which is associated with PTC development.

METHODS: Forty-one PTC patients treated with total thyroidectomy and radioiodine therapy were included in this study. The methylation profiles of the 41 tumor samples (PTC=41) were compared with the corresponding adjacent normal tissues (NT=41) using the Methylation 450 Human Infinium®BeadChip platform (Illumina), according to the manufacturer's recommendations. The data were analyzed with watermelon and limma packages. The results were confirmed with The Cancer Genome Atlas (TCGA) data (same platform). In addition, microRNA expression data from TCGA were used to perform an integrative analysis. microRNA targets were predicted using MirWalk 2.0 database.

RESULTS: A total of 51 miRNAs coding genes were differentially methylated in tumor samples, most of them hypermethylated in comparison to NT (91 probes) (adjusted p value<0.05 and $|\Delta\beta| \geq 0.1$). All miRNA genes were confirmed as differentially methylated using TCGA data (74 probes). The integrative analysis between gene expression and methylation data revealed three microRNA genes (1 hypomethylated and 2 hypermethylated) with significant negative correlation (Pearson correlation test $P < 0.05$) using TCGA miRNA expression data. These three microRNAs are highly predicted to regulate 1512 targets genes (more than 8 of 12 miRNA target prediction tools in miRWalk 2.0).

CONCLUSION: DNA methylation patterns play a role in the regulation of miRNA expression in PTC. These data could be useful for clinical purposes in the foreseeable future.

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