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SPECIAL MOLECULAR REVIEW

# Micro-RNAs signatures in papillary thyroid carcinoma

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## *Summary*

*Among biomarkers that should be useful for a molecular discrimination of patients regarding treatment strategies and prognosis in solid malignancies, novel micro-RNAs (miRs) are under investigation. Quite recently, miRs are considered very promising and significant genetic markers for categorizing patients by their molecular characteristics, as well as extending their complicated genetic signatures. miRs are short, non-coding RNAs consisting of 20-25 nucleotides located at intra- or inter-gene regions. Functional miRs mediate a positive regulation of posttranscriptional gene silencing. Their deregulation in cancer cells due to genetic (e.g., mutations, translocations), epigenetic (e.g., DNA hyper-methylation of tumor suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) and transcriptional alterations lead to a loss of miRs-mediated repression of target mRNA. Interestingly, a biphasic role of miRs in cancers of different histogenetic origin has been confirmed. In some of them, their upregulation is correlated with an increased oncogenic activity, whereas in others, the same miR type acts as a suppressor agent. Thyroid carcinoma comprises different histological subtypes, such as papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), anaplastic thyroid cancer (ATC), and medullary thyroid carcinoma. In the current molecular review, we explored the role of a specific fraction of miRs in PTC subtype by categorizing them according to their up- or down-regulation status.*

***Key words:*** *gene, thyroid, carcinoma, microRNAs*

## Introduction

Concerning solid tumors, a variety of gene functions and numerical imbalances in crucial molecular pathways such as cell cycle regulation, signaling transduction, apoptosis or angiogenesis have been identified and explained [1,2]. Malignant transformation of a cell is mediated by an aberrant gene expression, including predominantly upregulation of oncogenes combined with downregulation of suppressor genes that lead to cell cycle deregulation [3]. In fact, cancer genome consists of all genetic alterations that modify the normal DNA/m RNA sequences triggering a cataract of molecular reactions inside and outside the nucleus micro-environment [4]. Point mutations, polymorphisms, abnormal gene copy number (amplification, deletion), or structural chromosomal rearrangements (translocations), and epigenetic modifications, which are detectable by different molecular techniques, provide critical information to oncologists for handling those patients in a rational therapeutic way regarding their isolated molecular landscape [5]. Quite recently, mi-

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cro-RNAs (miRs) are considered novel significant markers for categorizing patients based on their molecular characteristics extending their genetic signatures.

## miRs: structure and function

Balanced regulation of gene expression secures genomic homeostasis in normal cells. Among the molecular mechanisms that are involved in this crucial process, microRNas (miRNAs) demonstrate an increasing interest for understanding their role in cancer, as well as guiding physicians in treating patients via targeted therapeutic agents [6]. miRs are short and non-coding RNA molecules consisting of 20-25 nucleotides located at intra- or inter-gene regions [7]. RNA polymerase II is responsible for their transcription. Initially, pri-miRNAs are reformed to pre- miRs followed by a maturation process. In the nucleus, the RNase III enzyme Drosha complex provides the release of pre- miRs into the cytoplasm where the final single-stranded mature miR is produced [8]. Functional miRs mediate a positive regulation of posttranscriptional gene silencing. miRNA deregulation in cancerous cells due to genetic (e.g., mutations, translocations), epigenetic (e.g., DNA hyper-methylation of tumor suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) and transcriptional alterations lead to a loss of miR-mediated repression of target mRNA [9-11]. Interestingly, a biphasic role of miRs in cancers of different histogenetic origin has been detected. In some of them, their upregulation seems to be correlated with increased oncogenic activity, whereas in others, the same miRNA type acts as a suppressor agent (miRNA 29 in hepatocellular carcinoma and lung cancer, miRNA 26a in lung and breast cancer, respectively) [12,13]. Understanding the biogenesis, maturation, and functional aspects of miRNAs, we realize that their transcriptional-expression profile should be useful molecular tool for typing and classifying subgroups of patients with the same histopathological cancer type, as well as targeting specific genes and modifying the corresponding response rates to specific inhibitor molecules [14].

## miRs in papillary thyroid carcinoma

Thyroid carcinoma demonstrates a spectrum of different histological subtypes, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), anaplastic thyroid cancer (ATC), and medullary thyroid carcinoma. Besides specific genes, such as BRAF or RET oncogenes that are involved in its development and progression, modern molecular studies have confirmed that a variety of miRs are implicated in their regulation [15]. Concerning PTC, several studies have identified miRs alteration patterns that are potentially implicated in their development and prognosis (Figure 1). In one study, miR 214 was found to be downregulated, which is also associated with an aggressive tumor phenotype (e.g., lymph node metastasis, larger tumor size, and advanced TNM stage). Furthermore, the study group showed that upregulation of this specific miR significantly decreased cell proliferation and induced apoptosis, inhibiting cell cycle progression in cell lines *in vitro* analyses [16]. Similarly, miR-1266 demonstrates the same anti-tumor activity in PTC. Another study group analyzing its expression concluded that its upregulation is correlated with cell proliferation inhibition, tumor invasion, and migration (reduced metastatic potential). Interestingly, miR-1266 anti-tumor activity was mediated by targeting Fibroblast Growth Factor Receptor-2 (FGFR2) molecules. This event leads to suppression in cell proliferation in PTCs [17]. Additionally, elevated expression in miR-146a and miR-146b has been observed in a PTC series analysis based on a semi-quantitative RT-PCR assay. The study group concluded that their over-activation was associated with increased cell proliferation and tumor migration (advanced stage) [18]. In addition, another study focusing on miR-146b confirmed its crucial role in an aggressive PTC phenotype by its oncogenic activity in the corresponding epithelial cells [19]. In conjunction to previous referred micro-molecular markers, a member of let-7 miR family -the let-7b- seems to be a very promising molecule for PTC

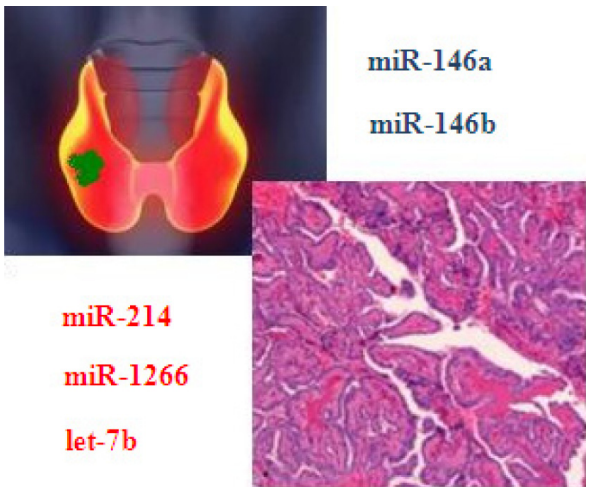


**Figure 1.** MicroRNAs (miRs) deregulation in papillary thyroid carcinoma (PTC). Downregulation is demonstrated by red colour, whereas blue colour represents upregulation in PTCs (inside images: potential localization of a case of PTC in the right thyroid lobe-green spot, histological diagnosis of PTC).

development and prognosis. Analyzing the marker by implementing a quantitative reverse transcription polymerase chain reaction and western blot assays, a study group reported a significant reduction of let-7b expression, which was correlated with an increased metastatic potential (cell migration and invasion) in the corresponding cell lines [20]. Interestingly, high-mobility group A2 (HMGA2) protein was a target for let-7b. The researchers concluded that this specific miR should be considered a novel, reliable marker, and a potential therapeutic target acting as a suppressor gene in PTCs.

In conclusion, miRs in thyroid carcinoma may be useful biomarkers for understanding the micromolecular substrate that explains the biological behavior of tumor (metastatic potential). By focusing on PTCs, due to the down- or up- regulations of the miR 214, miR-1266, miR-146a, miR-146b, and let-7b, provide critical biological information in detecting patients with specific genetic signatures.

## Conflict of interests

The authors declare no conflict of interests.

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