

## MicroRNAs in Medullary Thyroid Carcinoma: A New Pandora's Box?

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### MicroRNAs

MicroRNAs (miRNAs) are endogenous short single-stranded noncoding RNAs and they are post-transcriptional negative regulators of gene expression. They selectively bond the complementary 3' UTR mRNAs and, consequently, target them for either cleavage or for translational repression [1]. To date, over 1000 human miRNAs have been identified.

Although their functions have not been fully characterized, miRNAs are known to have important roles in regulating cell differentiation, proliferation and survival. Dysregulation in miRNA expression has recently been implicated in the pathogenesis of various types of human cancers, including esophageal, breast, gastric, colorectal, pancreatic, lung and thyroid tumors [2-4]. A possible role for miRNAs in cancerogenesis may be to function as tumor promoters or tumor suppressors, specifically targeting the genes involved in cancer cell biology [5,6].

Understanding miRNA expression patterns and their effects on gene expression may provide a better understanding of tumor development and progression and pave the way to risk-stratified patient management programs and potential therapies.

Medullary thyroid carcinoma (MTC) is an indolent slow-growing tumor but patients with metastatic disease have a 5-year overall survival rate around 40-50%. At the time, the only definite prognostic factors for MTC are Calcitonin levels and TNM staging at the diagnosis. Many studies were conducted to find the way to distinguish MTCs with better prognosis to MTCs with metastatic evolution. In hereditary MTCs, prophylactic thyroidectomy is the radical therapy but in sporadic MTCs the known RET and RAS point mutations are not sufficient to identify the tumors with the worst prognosis.

Recent studies have demonstrated that differentiated thyroid cancers are characterized by a dysregulation of different sets of miRNAs [2-4], and distinctive miRNA expression profiles cluster also correlating with different degrees of clinical aggressiveness.

However, only few studies have evaluated the role of microRNA expression in MTCs. Initially, Nikiforova et al. found a subset of 10 specific upregulated miRNAs in two FNAB specimens obtained from MTC [7]. More recently, Abraham et al. found a three miRNAs signature (miR-183, miR-375, and miR-9\*) capable of differentiating between familial and sporadic cases. Overexpression of miR-183 and miR-375 also proved to be a molecular predictor of extensive disease at diagnosis and pointed to a worse prognosis during the follow-up [8].

Santarpia et al. identified a miRNA signature associated with metastatic MTC and distinct biological process as epithelial-mesenchymal transition (EMT) and TNFbeta-pathway [9]. Mian et al. reported that a subset of miRNAs (miR-127, miR-154, miR-224,

miR-323, miR-370, miR-183, miR-375, miR-9\*) and in particular miR-21 is upregulated in MTC [10]. Hudson et al. reported an overexpression of miR-10a and miR-375 in MTCs' tissues and a correlated downregulation of the growth inhibitor Yes-associated protein 1 (YAP1) that was identified as a potential important downstream target of miR-375 [11].

In addition to the mere expression levels of different microRNAs in MTC tissues, new data show how their deregulation significantly correlates with prognosis. Two recent studies correlated the overexpression of miR-224 and miR-375 in MTC tissues with the clinic-pathological features and the outcome. Cavedon et al. demonstrated that miR-224 is upregulated in RAS-mutated MTCs and in patients with a better prognosis and could represent an independent prognostic marker in MTC patients [12].

Instead, Galuppini et al. found that miR-375 is significantly associated with tumor progression during the follow-up, suggesting that higher miR-375 levels in MTC tissues could predict a worst prognosis and the progression of the disease and could help the clinicians to program a stricter follow-up [13]. Furthermore, the very high levels of over-expression of miR375 in tumor tissue compared to non-neoplastic tissue would suggest its possible monitoring in the blood, thus supporting the only marker currently available for the follow-up of the disease, the serum Calcitonin.

Also in the MTC field, the curiosity of the Research has led to the opening of the Pandora's Box of microRNAs, now well-recognized as "evils", since they are involved in the acquisition and enhancement of malignant properties by cancer cells.

However, as in the Greek myth, the whole contents of the jar had escaped except for one thing that lay at the bottom, the "Hope". Indeed, miRNAs and their interacting mRNAs are regarded as potential targets for example using a RNA-based therapy by inhibiting miRNA expression using specific 2'-O-methyl-modified antisense RNA (antagomirs) [14]. Therefore, it is important to continue to investigate these promising molecules even in MTC, in the hope of finding new treatments, in particular for metastatic and indolent tumors.

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