MicroRNAs in Thyroid Cancers Prognosis

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Current prognostication systems have inherent limitations associated with the prediction of recurrence risk from thyroid cancer (TC). Recent studies identified associations between specific levels of microRNAs and aggressive TC clinicopathological features.

Keywords: thyroid cancer ; papillary thyroid cancer ; medullary thyroid cancer ; microRNA ; miRNAs ; mir-146b ; mir-221/222 cluster ; biomarker ; prognosis ; survival ; recurrence

1. Introduction

The epigenetic profile of TC, namely alterations in microRNAs (miRNAs) expression, has been determined to modulate gene expression[1]. MiRNAs are a class of non-coding RNAs approximately 19–24 nucleotides in length that can function as oncogenes or tumor suppressors by inhibiting the translation of tumor suppressor genes or blocking the translation of oncogenes, respectively[1]. Such activities have been demonstrated under normal human physiological conditions and implicated as contributors to the pathological process of carcinogenesis[2].

Genome-wide analyses have generated specific miRNA profiles of different histotypes of TCs and identified the upregulated and downregulated miRNAs related to various carcinogenesis stages and prognoses. Most miRNAs studies concern PTC, which is the most common type of DTC with excellent 5-year survival. However, in up to 5–10% of cases, PTC patients experience a more aggressive clinical course, which is characterized by early metastases, increased mortality, resistance to radioactive iodine, and disease recurrence[3][4]. A characteristic miRNA signature associated with PTC involves the overexpression of miR-146b, miR-221, miR222, miR-21, and miR-181b[5][6][7], and downregulation of let-7f[8].

In particular, miRNA 146b is predominantly overexpressed in PTC[5][9]. It is associated with a more aggressive phenotype, BRAF mutations, extrathyroid invasion, advanced stages of the disease, and a poorer prognosis[10][11]. Similar results have been found in other studies for the miR-221 and miR-222 families, which are overexpressed in tumors with worse prognostic characteristics such as increased tumor size, capsular, vascular or lymphatic invasion, or the presence of metastases[12][13].

The plasma levels of miR-222 and miR-146b were higher in PTC patients when compared with the plasma of healthy volunteers, and their levels dropped to similar levels of healthy subjects after total thyroidectomy[3]. These findings raised the potential of using miRNAs as a noninvasive, alternative recurrence surveillance tool. However, the majority of studies have measured miRNAs expression in thyroid tumor tissue and remains unclear whether circulating miRNAs levels can accurately reflect miRNAs expression in specific tissues[14].

Studies on FTC patients found a limited set of deregulated miRNAs, specifically the overexpression of miR-197 and miR-346[15].

ATC as the most aggressive subtype of TC is the least responsive to therapy and has a poor clinical outcome due to fast-growing tumors and metastatic spread[1][16]. Analysis of miRNAs expression in ATC demonstrated a decreased expression of miR-30, miR-26, miR-125, miR-92, and let-7, together with an increase in miR-21, miR-146, miR-221, miR-22, miR-17, and miR-19 levels[5][9][17][18].

MTC accounts for 3% of TC incidence. Its prognosis is not as favorable as DTC, with a reported 10-year survival rate of 65% overall[19]. The overexpression of miRs-183 and 375 in MTC are predictors of lateral lymph node metastases, residual disease, distant metastases, and mortality[20].

A previous systematic review of the literature was conducted to examine the associations between expression levels of specific miRNAs and aggressive clinicopathologic features in PTC[21]. However, to authors' knowledge, there is no published systematic review examining the miRNAs expression role as prognostic biomarkers in the long-term

surveillance of TCs. The objective of this systematic review and meta-analysis is to summarize the current knowledge regarding dysregulated miRNAs and to evaluate their prognostic impact in patients with TC.

2. The Prognostic Value of MicroRNAs in Thyroid Cancers

Several clinical studies have suggested that elevated miR-146b expression may play a role in advanced malignant tumor characteristics, including extra-thyroidal invasion and advanced stages of PTC[22][23][24]. Furthermore, several recent research studies, including our own, have provided evidence that miR-146b overexpression even plays a critical role in PTC patients' prognosis. MiR-146b levels were higher in Hürthle and tall cell papillary carcinoma, suggesting an association of these miRNAs with histologies of worse prognosis[25]. Thus, miR-146b has the chance to become a new marker in PTC outcome, associated with a malignant phenotype, as its deregulation occurs almost exclusively in TC[26].

MiR-221 and miR-222 are other highly overexpressed miRNAs in different follicular cell-derived TCs, similar to findings regarding miR-146b[26]. In vitro studies have identified that the miR-221/222 cluster regulates cell cycle and apoptosis downstream of the mitogen-activated protein kinase (MAPK) pathway; thus, its deregulation has been associated with treatment resistance, recurrence, worse prognosis, and aggressive disease behavior[8]. According to tumor histology, miR-222 levels were found to be twofold to threefold higher in tall cell papillary carcinoma than in the rest of histologies, suggesting an association with a worse prognosis[25]. Given the results of our meta-analysis, the miR-221/222 cluster has the chance to become a novel biomarker of recurrence in PTC patients.

Similar results concerning MTC have been reported in the previous studies, which confirmed the presence of significant miR-183 overexpression in lymph nodes of patients with MTC, knowing that lymph node involvement is one of the most important prognostic factors for poor survival in MTC[26]. At the same time, experiments on thyroid follicular cell line cultures demonstrated that miR-183 overexpression stimulates migration and led to a reduced apoptosis rate[27]. Some research has shown an opposing dual oncogenic potential of miR-183 explained by the target tissue type and mRNA targets expressed in that specific tissue. Therefore, the miR-183 overexpression has been implicated in the pathogenesis of various neoplasms such as hepatocellular carcinoma [28], melanoma[29], and colorectal cancer[30]. However, it also appears to have a suppressive effect on long-term cancer cells[31].

We showed that upregulated miR-375 is associated with residual disease in MTC patients, advocating its involvement in the prognosis of the disease. Several previous studies have already proven that miR-375 is indeed upregulated in MTC, indicating that it might play a central role in the tumorigenesis of MTC, via targeting multiple crucial pathways, mainly the phosphatidylinositol 3-kinase/ serine/threonine protein kinase B (PI3K/Akt) pathway [32]. So far, SEC23A is the only validated target gene of miR-375 in MTC[33].

We have to consider some limitations when interpreting the results of the current study. First, the number of available studies was limited, especially those evaluating serum miRNAs as circulating biomarkers, as they can be assayed before surgery and monitored throughout the lifespan, and they could be more valuable than tissue biomarkers. Second, small numbers of patients were analyzed in each study, raising questions about achieving adequate statistical power. Third, we observed a marked heterogeneity in some of the analyses, which is partly due to differences in patient characteristics, the use of different assay methods, endogenous normalization control, cut-off values for miRNA expression levels, follow-up durations, multiple outcomes, and effect sizes. Fourth, a low to moderate overall methodological quality of the included studies could have led to imprecise assumptions. Fifth, the absence of studies to cover the more aggressive histological subtypes, such as ATC or PDTC, make our findings of the potential prognostic role of the miR-146b, miR-221/222 cluster be assigned to just PTC and minimally invasive FTC.

If comparing the miRNAs versus traditional surveillance biomarkers, Thyroglobulin (Tg), Calcitonin (Ctn), and Carcinoembryonic Antigen (CEA), there are concerns about inter-laboratory assay variability, the cost–benefit, and the accessibility constraints of the new biomarkers. Future feasibility studies and standardized protocol-based studies should approach these issues in the future. Despite these uncertainties, the serum miRNAs could replace or supplement Tg in long-term surveillance of the PTC patients who have had less than total thyroidectomy, in up to a quarter of PTC patients with high anti-Tg antibodies titers [103] or to those who have not had postoperative RAI[3].

Rosignolo et al. found that postoperative changes in circulating levels of miR-146a-5p and miR-221-3p in PTC patients display a good correlation with American Thyroid Association (ATA)-defined response-to-therapy classes, even in cases in which serum Tg assay results are unreliable or difficult to interpret. These findings suggest that serum levels of miR-146a-5p and miR-221-3p might be used as complementary biomarkers for the early noninvasive detection of

persistent/recurrent PTC, particularly in the expanding population of patients undergoing more conservative management of PTC[34] Similarly, specific miRNAs can replace the Ctn in cases of non-secreting poorly differentiated MTC, in which the diagnosis and surveillance are often challenging and delayed[35].

Many DTC dedifferentiate and become radioactive iodine (RAI)-refractory with worse outcomes[36]. MiRNAs deregulation may play a role in TC dedifferentiation and resistance to RAI therapy. A in vitro study found that miR-146b binds to PAX8 and sodium/iodide symporter (NIS), leading to impaired protein translation and a subsequent reduction in iodide uptake[37]. Accordingly, the existence of the miR-146b/PAX8/NIS regulatory chain may be exploited therapeutically in the future to modulate thyroid cell differentiation and iodide uptake for improved targeted treatment. Besides, with the knowledge that the activated MAPK signaling pathway suppresses the uptake of RAI, later studies investigating the use of miRNA-directed therapy that inhibit this pathway in the restoration of RAI sensitivity could be implemented[38].

Further efforts should focus on the collaborative research, with well-designed studies, rigorously reported, adhering to the Reporting Recommendations for Tumour Marker Prognostic Studies guidelines (REMARK) [108]. Moreover, the establishment of the miRNAs status as biomarkers and surrogate endpoints will be decided after the evaluation of their clinical relevance and validity. Between now and then, the comparison of miRNAs with currently available biomarkers, refinement of the assay technology, evaluation of the sensitivity, specificity, and cut-off values, testing their performance in PDTC and ATC will be the next steps to accomplish. Furthermore, there is a need for a complete understanding of the miRNAs implication in the molecular signaling pathways and their downstream targets.

As an increasingly sophisticated biological model of TC is developed, it is clear that the measurement of miRNA expression might facilitate and optimize the management of patients with TC. Moreover, the integration of these molecular markers together with clinicopathological factors into a complex prognostication system may enable better predictions, assuming that every single biomarker plays a small role in the summative outcome of interest. The development of a safe and specific method to implement miRNA-targeted therapy would help improve the treatment of unresponsive TC. Given the limited research available, the clinical application of these findings has yet to be verified. Large-scale standardized protocol-based studies are required to improve the accuracy and reduce the bias.

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