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Review Article

Evaluation Molecular in Medullary Thyroid Carcinoma: A Review

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ABSTRACT

Medullary thyroid cancer (MTC) is considered rare, representing from 3% to 10% of cases of malignant tumors. This can occur in sporadic (75% of cases) or family (25% of cases). MTC may present as a multiple endocrine neoplasia type II (MEN II - Multiple Endocrine Neoplasia, Type II), characterized as a hereditary tumoral syndrome presenting as precursor lesion hyperplasia cells of C. It is considered a very aggressive tumor , and its aggressiveness correlated with mutation of the RET gene that is directly linked to regulation of cell growth as well as other molecular markers such as miRNAs, small non-coding RNAs, which are associated with regulation of gene expression. Thus, this study aims to analyze and evaluate aspects of diagnosis, prognosis and treatment attached to them. The study was conducted through an extensive review of the literature investigating the most recent studies that address this issue. Several numerous molecular markers are associated with tumor development, aggressiveness and resistance to treatment, including the latest markers miRNAs, which, are up-expressed or down-expression in tumor cells and is associated with miRNAs directly to cell growth factors. The outlooks from these new markers are that they can be used for the development of new diagnostic tests and for the development of targeted therapies to tumors presenting high efficiency providing a new treatment option.

Keywords: Medullary Thyroid Cancer, miRNAs, diagnosis, treatment.

INTRODUCTION

The thyroid is an endocrine gland, formed by two lobes, located in the neck, in the anterior region, below the cricoid cartilage. It is responsible for the production of thyroid hormones T3 (triiodothyronine) and T4 (tretaodotironina), which are involved in various processes of homeostasis as brain function, cardiovascular, intestinal, cellular metabolism, heat production among others, and the production of these hormones is controlled by TSH hormone produced by the hypophysis. The follicular cells the thyrocyte, is responsible for capturing the iodine from the bloodstream for synthesis of T3 and T4 hormones, already the parafollicular cells secrete the hormone calcitonin, responsible for controlling the metabolism of calcium by maintaining your blood level. [1]

Thyroid cancer (TC) is the most common neoplasm of the head and neck and the most common endocrine cancer, its incidence is increasing in recent years, representing 1% of malignant tumors in the age group of 30-74 years. Considered rare in most of the world, between 2% and 5% of cancers in women and less than 2% in men. The latest global estimates pointed

to occurrence of about 300 thousand new cases per year, and 68,000 in men and 230,000 in women. The TC has prevalence three times higher in females than in males, a difference that declines after 48 years. In Brazil, according to the National Cancer Institute (NCI), the estimate for 2014-2015, new cases of CT is 1,150 among men in which they occur (1.15 / 100 thousand) and 8,050 among women (7, 91 / 100 thousand). [2-4]

Thyroid tumors are classified according to their histological origin, from two strains of predominant cells, the endoderm fear the follicular tumors Thyroid- the Follicular (Follicular Carcinoma of Tireóide- FCT) and papillary (papillary thyroid carcinoma - PTC), originating from the neural crest cells are tumors of the C cells or Para-follicular - Medullary thyroid carcinoma (MTC). Tumors where the lineage of cells is not distinguished are called anaplastic and that keeps some characteristics of differentiated being almost anaplastic carcinomas are a few different. [5,6]

Among the Spinal Cord TC is rare, representing 3% to 10% of malignant tumors and has the highest mortality rate among differentiated tumors. The medullary thyroid cancer (MTC) is the precursor lesion hyperplasia of C cells, with multifocal and multicentric distribution, associated with elevated serum calcitonin. This cancer has 2 types of propagation, the first is the regional lymph nodes, and the second is hematogenic transmission generating local metastases and the distance. It can be diagnosed by an echography in thyroid nodule research or to present palpable neck mass / and or visible. The investigation begins with thyroid echography followed by fine needle aspiration biopsy or resection of the nodule biopsy that if in doubt do themselves to immunophenotyping with tumor markers part biopsied. [7]

It is an aggressive tumor, the aggressiveness is correlated with the mutation of RET gene and microRNAs (miRNA) - small non-coding RNAs, not proteins translated, and are connected to regulation of cellular processes. So it is always appropriate to carry out an assessment to molecular mutations of the RET gene, as well as the study of miRNAs associated with the development of the MTC. [6,8]

The MTC can occur in the sporadic form (75% of cases) or family (25% of cases), or present as a Multiple Endocrine Neoplasia Type II (MEN II - Multiple Endocrine Neoplasia, Type II), characterized as a hereditary tumor syndrome. And an autosomal dominant disorder involving gene Rearranged During Transfection (RET). [9,10]

The genetic changes in tumors ranging from changes such as deletions, mutations, translocations and numerical changes in chromosomes, such as changes in gene expression, where miRNAs are considered one of the most current molecular biomarkers related to development and tumor aggressiveness. [11] In this way, this study aims to evaluate molecular aspects related to the pathogenesis, diagnosis and prognosis of MTC.

Oncogenes associated with Medullary Thyroid Cancer (MTC)

In relation to genetic factors, the role of genetics in thyroid carcinogenesis considers the presence of family history on MTC and molecular aspects including genetic mutations nuclear and mitochondrial; furthermore, there is the CMT gene rearrangements and chromosome loss of heterozygosity and also the role of miRNAs in their development. [12]

The MTC can occur in most family members. In patients affected with MTC and family history the tumor is more aggressive than in MTC patients with no family history. The molecular aspects are associated with oncogenes, which when present and active are responsible for stimulating mitosis, cell proliferation

without control, giving the order for reproducing clones without stopping for high replication. Oncogenes activators Rat Sarcoma Viral Oncogene (RAS), V-raf Murine Sarcoma Viral Oncogene homolog B1 (BRAF), Rearranged During Transfection (RET), Neurotrophic Tyrosine Kinase, receptor type 1 (NTRK1), work with different functions: growth factors which bind to the receptor without signaling control cell reproduction; membrane receptors that carry the signal without stopping; signal transducers which perform stimulation altered mitosis; and Nuclear Transcription Factors responsible for stimulating the replication of DNA. [13]

Another factor which induces the appearance of cancers is the silencing that occurs when there is a lack of normal function of tumor suppressor genes, and there are two more important in the MTC: Silencing of tumor suppressor P.TEIN and P53 tumor suppressor. MiRNAs can suppress or silence a tumor suppressor and can also disrupt and cause malignant transformation events. [14]

The normal cells have membrane receptors that stimulate intracellular system involved in cell signaling, the tyrosine kinase system, the MAPK system (Mitogen-Activated Protein Kinases) and Protein System G, called signal transducers act in the nucleus signaling doubling DNA in this way these factors when activated stimulate transcription factors, to initiate cell division. If a growth factor or an oncogene to stimulate a transmembrane receptor unchecked, there will be the initiation of an uncontrolled production. Mutations in these receptors incentives unrestrained triggers of the cell production, in addition, nuclear transcription factors can also mutate promoting proliferative stimulus as well as changes in miRNAs. [15]

The BRAF gene encodes a family of protein tyrosine kinases (serine-threonine kinase) activator of the mitosis, which are expressed wildly stimulates tumorigenesis. The BRAF polymorphisms associated with the MAPK act synergistically inhibit apoptosis, stimulating cell immortality of cancer. The MTC presenting BRAF are more aggressive with metastases in the lymph nodes and other organs. [12]

The RAS gene encodes a protein of Protein G system, releasing GTP (guanosine triphosphate) in activating the MAPK cell signaling system. The RAS mutation is present in 10 to 20% of MTCs and in 40% of follicular adenomas (benign version of the FCT). In vitro studies of RAS mutation shown to promote chromosomal instability (mutations such as deletion, chromosome transcription), the presence of the mutation indicates more aggressive behavior of the tumor and poor prognosis in the future, which shows that the RAS predisposed abnormality and silencing tumor suppressor p53. [16,17]

The NTRK1 gene is located on chromosome 1 and encodes a transmembrane receptor for growth factor, especially for Nerve Growth Factor (NGF) and oncogene activation as occurs when there is a chromosomal rearrangement involving chromosome 1q22. [18]

The RET (rearranged during transfection) located on chromosome band 10q11.2, encodes a tyrosine kinase receptor expressed in cells derived from the neural crest. The RET ligand is a superfamily peptide of TGF (transforming growth factor) called GDNF (glial neurotrophicderivad factor) acts via receptor-GDNF, many growth factors stimulate especially receptor neutróficos factors such as, for example, neutrin, neutrinampersephin, artemin and GDNF. The binding of these factors to promote transmembrane receptor tyrosine kinase stimulation system responsible for inducing cell proliferation. The occurrence of mutations in the RET gene leads to tyrosine kinase activation system triggering a proliferative process that affects the thyroid cells. [15]

The RET oncogene linked to receptor tyrosine kinases is associated MTC, both SCMT, the Family Medullary Carcinoma Isolated and found the OR-2. Among the contributions the molecular pathogenesis is the ability to diagnose individuals with RET gene mutations as predictive diagnostics, which would allow the cure of disease by prophylactic surgery before their clinical presentation. It is recommended DNA test for the presence of RET gene mutated in all MTC patients, which are present in 80% of cases of SCMT and the formation of metastases in lymph nodes. [19-21]

In relation to the tumor suppressor genes and the RAS fusion between RAS protein and the protein RET / PTC, is a cell signaling substance reaction and fosfotidilinositol3quinase (AKAT) induces suppression P TEIN. Reactions involving AKAT are critical in regulating cell for growth, proliferation and cell survival. [22] The TP53 gene encodes the p53 protein considered the "DNA Guardian", essential in cellular regulation acting in DNA repair after the duplication, if the protein is unable to perform repair it induces cell apoptosis. The inactivation or silencing of tumor suppressor p53 protein becomes unable to perform the repair DNA. [23]

miRNA

The miRNAs are molecules that do not encode proteins are single chain mRNA, short, transcribed from endogenous genes, initially with long precursors (pre-miRNAs). Instead of being translated into proteins, they are processed from primary transcripts known as pre-microRNA until they are converted to functional miRNA. The mature miRNAs are only partially complementary to one or more mRNAs, these regulatory molecules are located in parts of the genome that do not encode proteins. [24]

Currently miRNAs have been identified as one of the most important molecules that act in the regulation of gene expression, increasing or decreasing the expression of a gene in various organisms. As some miRNAs impede or eliminate the function of a gene, one may describe this as a gene silencing function; some have constitutive expression, while others are subject to control temporal-specific expression and tissue specific. In some tissues evaluated, miRNAs regulate more than 30% of the expression of the mRNAs and are evolvidos long in a variety of cellular processes, are responsible for various functions such as development, differentiation, proliferation, metabolism and the stress response and apoptosis. [25-27]

The changes in miRNA expression contribute to the pathogenesis of most or human malignancies. Changes can be caused by several mechanisms, including deletions, amplifications or mutations involving miRNA locus for epigenetic silencing or by dysregulation of specific transcription factors targeting microRNAs. Once the malignant cells demonstrate dependence on the unregulated expression of miRNA genes, it is known that miRNAs provide important opportunities for the development of future therapies focused on the action of modulation of miRNAs. [26,28]

In the evaluation of tumor tissue miRNAs are over-expressed, are considered currently oncogenes through inhibition of tumor suppressor genes they have just stimulating tumor growth, these molecules denoting a bookmark function of tumor development. [29]

Even with all the knowledge in cell biology and cell signaling involving the MTC, numerous cases have unfavorable outcomes. Current therapies have not achieved desirable results in this way there is a huge need to develop new therapies. In this scenario miRNA appears as an important post-transcriptional regulator of many cellular biological processes and are emerging as an important diagnostic tool, and can be a prognostic indicator of patient studies conducted on different types of thyroid tumors has miRNAs differentially expressed indicating that miRNAs can

become the newer therapeutic targets for the pathology in cancer therapy. [30-32]

Microarrays

The Microarray technology is developed from a DNA chip in which is allowed to investigate the gene expression of hundreds or thousands of gene of a single sample simultaneously by a hybridization reaction. In this technique probes and targets are used, the probes are the known gene fragments and correspond to the gene of interest, these fragments immobilized on a solid matrix. Since the targets are obtained from the biological sample to be screened, these samples pass through a process of molecular techniques resulting in the end in cDNA are targets. [33]

In the microarray technique of the DNA sequences or complementary RNA to the genes are known and hybridized with labeled RNA from a tumor so that the signal intensity is proportional to the intensity of tumor gene expression, as demonstrated by hybridization. This technique has become a very important global analysis tool, having applicability in the fields of biology, developmental, study of metabolic pathways, the disease classification also being used in drug discovery and in the field of toxicology. [33]

In oncology research, the use of microarray has been used to identify genes associated with the development of a cancer in particular. Different studies based on gene expression profile in tumor samples have revealed the transcriptional heterogeneity of cancer and enabling the classification of new clinical and biological subclasses that has a great importance in disease of new drugs and in the field of toxicology. [34]

The array technique provides diagnostic tools and prognosis, in which the identification of the genes are not critical but the quantitative information that is associated with gene expression. Being able to determine the molecular changes that determine the progression of the disease, the occurrence of specific molecular diagnostic markers as well as prognostic markers and for the predisposition to the pathology, which will potentiate the development of new therapeutic targets. [35,36]

The use of microarray technique to diagnose MTC and / or MEN II is of fundamental importance because it guides the clinical procedure as well as the therapeutic approach being used. Through molecular diagnostics the patient and especially their families carry mutations in oncogenes can be instructed to perform total thyroidectomy for the prevention of disease development. [37]

The MTC was divided into 3 risk levels leading to a prognosis for the disease depending on the level at which the family carried the mutation is found and on the actions to be taken next, which can lead to healing of the patient:

-Level 1: the risk is moderate to develop the aggressive form of the disease, bearing children should undergo total thyroidectomy before 5 or 10 years or when there is an increase in calcitonin levels.

-Level 2: the risk is high for developing aggressively; children must perform thyroidectomy removing the central lymph nodes, before age 5.

-Level 3: is the maximum risk to develop aggressive and children with the disease must undergo before 6 months of age surgery does not occur for the development of metastases, removing also the central nodes. [38]

For affected family members discover they are carriers which have become mature, surgery should be performed after confirmation of being carrier mutated oncogenes, because the surgery greatly increases the chances of cure of patients when identifying them genes associated with MTC should initiate preventive measures or treatment depending on prognostic factors. [38]

The microarray technique is being used in gene therapy studies already in the experimental stage in animal models, allowing a promising approach for the treatment of CMT. This methodology is developed after the listing of tumor gene expression which directs the best procedure as introducing tumor suppressor genes, transfer of genes that determine the drug activation to toxic forms (known as suicide genes), the transfer of genes that increase immune response against cancer (genetic immunization), and combined therapies. [33]

MATERIALS AND METHODS

This work consists of a review article, was conducted through a literature search. The bibliographies for the molecular diagnosis of MTC using biomolecular techniques of DNA sequencing, miRNA Microarray and evaluating the latest updates and applicability to the diagnosis were evaluated.

The selection of items came from reading the abstracts / articles. The search took place in the NCBI databases, SciELO, PubMed, among the articles published in the last ten years (2005 - to the present). We used the following keywords: Medullary, Thyroid Cancer, miRNAs, diagnosis, treatment. After some research, we selected the most relevant articles for the development work, the refinement of the articles as shown in Figure 1.

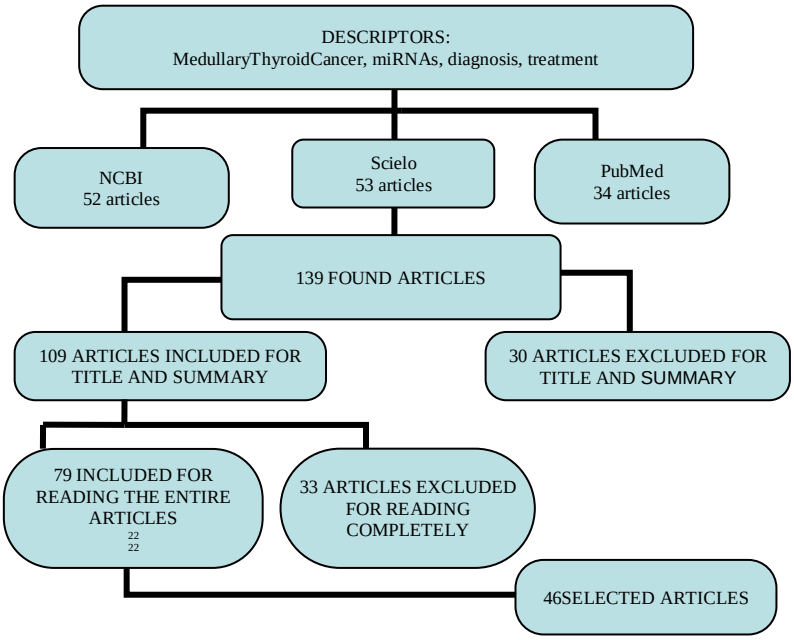

Figure 1- Flowchart analysis of the articles.

RESULTS AND DISCUSSION

Recent studies have demonstrated that differentiated thyroid cancers are characterized by dysregulation of different groups of different miRNAs and miRNA expression profiles and are significantly related to somatic mutation levels and different degrees of aggressiveness of the disease. The presence of abnormally expressed miRNAs CMT has not been different, since the analysis of the expression of these miRNAs by either PCR or microarray -RT exhibit abnormal expression of several miRNAs aberrant. [4]

The first study was conducted by Nikiforova and collaborators (2008), which analyzed the expression of miRNAs in MTC and demonstrated significant miRNA expression profiles, to determine and compare the miRNA expression patterns and specific oncogenic mutations, described the diagnostic value and prognostic in detecting these miRNAs in the preoperative evaluation of thyroid

nodules. [39] They have found a subset of 10 miRNAs (miR-9, miR-10, miR-124 a, miR-127, miR129, miR-137, miR-154, miR-224, miR-323 and miR-370) with significant dysregulation and high levels of over expression associated with MTCs, demonstrating the diagnostic accuracy, thus establishing the basis for the use of distinct miRNAs profiles for the MTC as an effective diagnostic tool in the preoperative evaluation of thyroid nodules. [40]

The results obtained through detection in the microarray were compared between the SMTC and hMTC and demonstrated the over expression of miR-183 and miR-375, while miR-9 was expressed in sub-SMTC compared with those in hMTC. They also found that miR-183 and miR-375 are predictors of metastases in lateral lymph nodes; residual disease, distant metastases and mortality are linked to aggression and could be used to change the current guidelines for the management and conduct of surgery, indicating not just a thyroidectomy with central dissection but also the side of the lymph nodes. And the suppression of miRNA miR-183 induces cell death by autophagy, indicating that it may serve as a potential therapeutic target. [40]

At the investigate the hypothesis that different mines profiles are related to the status of the RET gene and prognosis in patients with hMTC and SMTC, Mian and colleagues (2012) compared the gene expression profiles of normal samples with the hMTC and of SMTC and observed a super expression of miRNAs 9 - miR-9, miR-21, miR-127, miR-154, miR-183, miR-224, miR-323, miR-370 and miR-375 and miR-9 showed the highest level of over expression. [41] In particular miR-21 evaluation, an important oncogenic miRNA called Oncomir, there was disruption in various human tissues involved in tumor carcinogenesis of differentiated and anaplastic thyroid and their deregulation cause neoplastic transformation of the cell to act by inhibiting the activity of tumor suppressors such as PTEN. Also, the study demonstrated that an over expression of miR-9, miR-183 and miR-375 is associated with MTC; that miR-224 has a over expressing the MTCs and the presence of high levels of miR-224 were significantly correlated with absence of lymph node metastasis and lower aggressiveness of the tumor and biochemical disease-free status by dosing calcitonin when diagnosed at stage initial and / or if you have a good prognosis during follow-up, proving their prognostic value in patients with MTC. Already the miR-127 have their over expression when there is presence of RET wild type than mutated RET, thus suggesting that miR-127 connection with the RET gene and its oncogenic role. These results demonstrate that these miRNAs may be used in the future to better clinical management of the patient.

Duanet al. (2014),they point out that miR-129-5p has down regulating the expression MTC RET, being able to induce cell death in ST cells, indicating that the biomarker characteristic of one miRNA as a potential therapeutic target because it has influence on growth cell, cell apoptosis induction. [42] The expressions of miR-129-5p can significantly suppress the growth of MSC cells through inhibition of RET protein levels, suggesting a potential role of suppressor.

In the study of Sammy and colleagues (2013), has described the relation of miRNAs linked to fascinate - protein involved in the process Epithelial Mesenchymal Transition (EMT) and associated with tumor metastasis processes. Changes in gene expression that lead to increase fascinates the EMT are determining the metastatic process and increased aggressiveness of tumor cells. The miR 200a / 200b / 429 / 200c / 141 are the most important regulators of protein synthesis fascinates and miR-200c with the

greatest increase in activity in protein translation. [43]

After testing gene expression in Hudson MTC cells and colleagues (2013) showed that miR-375, miR-10a, miR-409-3p, miR-190b, miR-642, miR-99b and miR-889 are upregulated in tumor cells while others miR-455, miR-20b and miR-30a-3p are down regulated, demonstrating the biological importance of miRNAs as biomarkers in tumorigenesis of medullary thyroid carcinomas. [44]

In similar study of the Hudson (2013), Santarpia and colleagues (2013) evaluated miRNAs in tumor cells with respect to MTC tumor aggressiveness, where the miR-10a, miR-200b- 200c, miR-7 and miR-29 were downregulated while miR-130a, miR-138, miR-139a-3p, miR-373 and miR-498 were upregulated in metastasis. [45] Having the miRNAs an important role in regulating metastatic activity, these were indicated to be evaluated as a new therapeutic target in the development of the tumor cells targeted drug, inhibiting their proliferative action and invasive, allowing a more effective and less toxic treatment than existing .

According to the analysis Santarpia and Jimenez (2014) made of existing studies, the gene expression profiles of tumor cells numerous proteins, receptors, etc., are being identified as specific therapeutic targets, which may enable a targeted pharmacological treatment, with good clinical response and especially without the toxic effects of currently available drugs allowing an increase in the pathology cure rates. [32]

CONCLUSION

The MTC is the rarest among thyroid cancers in this regard studies regarding miRNAs and other molecular markers are still poorly described, the molecular aspects of MTC support the diagnosis, stratification of disease, prognosis and treatment, and some markers already have been identified oncogenes from the most current, miRNAs, these molecular markers has been established with a diagnostic way, and prognostic model for development of new medicines.

By knowing miRNAs involved in the MTC and SCMT, can develop a diagnostic panel in which patients suspected of being carriers of hereditary markers of cancer may make an early clinical evaluation and laboratory even perform thyroidectomy prophylactically. The promising prospects make it possible for future drug therapies are developed that allow the cure or prevention of these cancers so that they will not develop. Although there is still a long way to implement the markers in clinical practice, it is indisputable that are fundamental, since the diagnosis, prognosis and the development of specific drugs tumor lines.

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