



Thyroid Cancer research at endocrinology and metabolism research institute (EMRI): a report of scientific activities between 2005 and 2020

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Abstract

Purpose Endocrinology and Metabolism Research Institute (EMRI), Tehran University of Medical Sciences, has achieved many advances in the understanding of epidemiology, pathology, and molecular biology of thyroid cancer (TC). This paper will focus on published literature in the field of TC research at EMRI since its inception.

Methods A comprehensive literature search of “Scopus”, “Web of Science (ISI)”, “PubMed”, and “SID” databases was done to identify TC-based studies in EMRI since 2005, using the predefined keywords.

Results All the records were reviewed. Eventually, 46 articles that met the inclusion and exclusion criteria were considered. Timeline, characteristics, and summarized findings of the included most studies have been briefly described.

Conclusion The main focus of the TC research at EMRI is to investigate genetic and epigenetic changes as well as the cellular and molecular aspects seen more frequently in TC patients, and find out how exactly these alterations lead to more aggressive TC behavior and resistance to the conventional treatment approaches in those patients.

Keywords Papillary thyroid carcinoma · Follicular thyroid carcinoma · Medullary thyroid carcinoma · Anaplastic thyroid carcinoma · Endocrinology and metabolism research institute

Introduction

Thyroid cancer (TC) is the most frequent endocrine malignancy and has the highest growing incidence rate among different kinds of solid tumors in the United States [1]. Most of TCs can be treated with conventional surgical treatment followed by Radioiodine (RAI) and long-term thyroid-stimulating hormone (TSH)-suppressive therapy. However, nearly 5 % of

TCs are RAI-resistant cases, which are locally advanced or metastatic with survival rate of less than 5 years [2, 3]. Currently, several advances exist in the diagnosis and treatment of TCs. These include molecular diagnostics, targeted therapies and more effective strategies for personalized medicine of TC patients. New molecular diagnostic methods and targeted therapies lead to specific or personalized treatment of TC patients [4]. Understanding the risk factors and biological

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mechanisms that cause resistance to conventional therapeutic approaches can be useful for recognizing patients who are unresponsiveness to treatment, decreasing the recurrence rate of disease, and also providing more appropriate therapeutic approach for these clinical challenges.

This paper will focus on the research activities, including epidemiology, pathology and molecular biology studies, specifically in the field of TC at Endocrinology and Metabolism Research Institute (EMRI), Tehran University of Medical Sciences, since its inception. Undoubtedly, beside the research purposes, a number of other scientific activities have been carried out in field of capacity building in the line of our research objectives, including PhD and MSc training and hosting various educational courses in the field of thyroid ultrasound as well as radiofrequency thermal ablation of thyroid nodules.

Methods

The main databases in English language including “Scopus”, “Web of Science (ISI)”, and “PubMed” as well as “SID” database for the papers published in Persian language were searched to identify TC-based studies in EMRI since 2005. Moreover, to find more evidence, other sources including “Google Scholar” were searched. Search keywords were: “Papillary Thyroid Carcinoma”, “Follicular Thyroid Carcinoma”, “Medullary Thyroid Carcinoma”, “Anaplastic Thyroid Carcinoma”, “Endocrinology and Metabolism Research Center”, “Endocrinology and Metabolism Research Institute”, and related words and phrases, Medical Subject Headings (MeSH) terms, EBSCO thesaurus terms and Emtree terms and their logical combinations.

The inclusion criteria were articles which related to TC research from 2005 to 2020. The exclusion criteria were defined as articles that were not related to TC, case report, letter to editor, and meeting abstract papers.

Results

All the identified papers were reviewed and after removing the duplicates and unrelated articles in the field of TC research, 46 articles that met the eligibility criteria were finally selected, most of which were briefly described in Table 1. Timeline, characteristics, and summarized findings of the included most studies are shown in this table.

Discussion

In recent years, the main focus of the TC research at EMRI is to investigate molecular changes seen more frequently in TC

patients, and find out how exactly these alterations lead to more aggressive TC behavior and resistance to the conventional treatment approaches in those patients [42–50]. However, at the beginning of our research we studied in the fields of pathology [7] and epidemiology [5, 6, 51, 52].

The incidence rate of TC is increasing in Iranian population [53]. Well-differentiated TC is the most frequent endocrine malignancy and ranks as 7th cancer diagnosed in females [54]. Although the majority of well-differentiated TC patients become disease-free following conventional treatments, 20% of TC patients have local or regional recurrent disease, and 5 % develop distant metastases [55, 56]. Due to lack of the effective treatment for the patients with poorly-differentiated or undifferentiated TCs, these patients have a poor prognosis with survival rate of less than 5 years.

The mechanisms by which genetic and epigenetic changes induce tumorigenesis, progression, and unresponsiveness to treatment in some TC cases are not fully understood. The information we have learned from the mechanisms involved in the initiation and progression of TCs could lead directly to more efficient treatment of TC patients, especially those with aggressive types of TC including radioiodine-refractory differentiated thyroid cancers (RAIR-DTC) and anaplastic thyroid carcinoma (ATC). Our findings revealed that HLA-C alleles and HLA-DRB1*04 are predisposing factors in papillary thyroid carcinoma (PTC) patients in Iranian population [9, 13]. We also investigated the correlation of *survivin* gene polymorphism with the risk of PTC in Iranian population [19]. In another study, we showed that the hypermethylation of *P16*, *TSHR*, and *RASSF1A* gene promoter may have an important role in PTC pathogenesis [16].

In addition, the TC research group at EMRI is focused on translational research in TC. For instance, TC research team is looking for the diagnostic molecular markers including gene expression classification and gene mutation panels to improve accuracy in distinguishing between benign and malignant disease such as follicular thyroid adenoma (FTA) and follicular thyroid carcinoma (FTC) [20].

As part of the advancement of precision medicine in cancer therapy, we hypothesized that attempts to efficiently treat advanced and aggressive TCs, such as RAIR-DTC and ATC, based on the genetic variation of each patient, could enhance therapeutic approaches [29].

Some of the studies, carried out during this period, were mentioned above. Evaluation of TC research at EMRI showed that there is a well-established research plan for investigation of clinical challenges in the fields of diagnosis, treatment, and prognosis of different types of TC.

To this end, the TC research group has done projects in various basic studies including cellular and molecular fields. In addition, this group plans to focus more on Na^+/I^- symporter (NIS), as the main factor in iodine (I^-) uptake and response to RAI therapy, as well as the signaling pathways

Table 1 Timeline, characteristics, and summary of the findings of the included studies

Year	Title	Main method(s)	Summary of findings	Ref.
2005	Primary thyroid malignancies in Tehran, Iran	Descriptive epidemiology study	Slightly increase in the incidence of TC in Tehran. The survival rate of patients was high. Survival time of men and women with TC in Tehran were similar.	[5]
2006	Endocrine cancer in Iran: based on cancer registry system	Descriptive epidemiology study	Improving the intake of iodine in previously deficient populations was associated with an increase in the incidence of PTC. The frequency of histological forms of thyroid carcinoma was similar to what can be found in iodine-rich areas.	[6]
2006	Immunohistochemical analysis of survivin expression in thyroid follicular adenoma and carcinoma	IHC	Survivin is a potential candidate in the distinction between FTA and FTC.	[7]
2007	Vitamin D receptor gene polymorphisms in patients with thyroid cancer	RFLP	There are no correlation between the polymorphisms located at 3' end of vitamin D receptor gene and risk of TC.	[8]
2009	Associations between HLA-C alleles and papillary thyroid carcinoma	HLA typing	HLA-C alleles are predisposing factors in PTC in Iranian population.	[9]
2009	Expression of EGFRvIII in thyroid carcinoma: immunohistochemical study by camel antibodies	Antibody production Western-blot IHC	Diagnostic value of smaller heavy chain camel antibodies against EGFRvIII in thyroid neoplasms.	[10]
2009	Immunohistochemical analysis of nm23 protein expression in thyroid papillary carcinoma and follicular neoplasm	IHC	There is no relationship between the expression of nm23 protein and patients sex and age. nm23 is not a beneficial biomarker for assessing the invasion of DTC or the distinction between FTC and FTA.	[11]
2009	Prevalence of BRAF ^{V600E} mutation in Iranian patients with papillary thyroid carcinoma: A single-center study	RFLP	The BRAF ^{V600E} mutation is detected in 72% of classical variant of PTC and 100% of tall cell variant of PTC. There is no significance association between BRAF ^{V600E} mutation prevalence and sex, age, lymph node metastasis, and extrathyroid extension.	[12]
2010	HLA-DR association in papillary thyroid carcinoma	HLA typing	HLA-DRB1*04 is predisposing factor in PTC in Iranian population.	[13]
2011	Molecular analysis of the RET proto-oncogene key exons in patients with medullary thyroid carcinoma: A comprehensive study of the Iranian population	Sequencing	17.6% of sporadic cases of medullary thyroid carcinoma (MTC) carried a germ-line mutation in <i>RET</i> gene. Most mutations detected in the families occurred in cysteine codons. Germ-line mutation carriers have an earlier age onset of MTC versus the sporadic ones.	[14]
2011	Evaluating clinical practice guidelines developed for the management of thyroid nodules and thyroid cancers and assessing the reliability and validity of the AGREE instrument	Mixed methods (Systematic search, Secondary data analysis...)	'Scope and purpose' and 'clarity and presentation' clinical guidelines have the highest domain scores based on the AGREE instrument.	[15]
2011	Qualitative and quantitative promoter hypermethylation patterns of the P16, TSHR, RASSF1A and RARβ2 genes in papillary thyroid carcinoma	Combined bisulfite restriction analysis	'Rigor of development' and 'clarity and presentation' acquired the highest correlations with overall evaluation scores. Promoter hypermethylation of P16, TSHR and RASSF1A genes play important role in PTC pathogenesis.	[16]

Table 1 (continued)

Year	Title	Main method(s)	Summary of findings	Ref.
2011	Incidence of second primary malignancies during a long-term surveillance of patients with differentiated thyroid carcinoma in relation to radioiodine treatment	Retrospective cohort study	The overall rate of second primary malignancies was not increased following a minimum interval of 3 years from the first I ¹³¹ therapy. The probability of this occurrence may be profoundly increased in cases who had received a cumulative dose of I ¹³¹ more than 40 GBq (1.08 CI).	[17]
2012	Multifaceted suppression of aggressive behavior of thyroid carcinoma by all-trans retinoic acid induced re-differentiation	Cell culture Proliferation assay C ratio and morphological analysis Colony formation assay qRT-PCR Radioimmunoassay	All-trans retinoic acid treatment could inhibit the aggressive manners of TC and/or potentiate the effect of arsenic trioxide chemotherapy medicine.	[18]
2012	Survivin gene polymorphism association with papillary thyroid carcinoma	Genotyping	Survivin gene polymorphism correlated with the risk of PTC in Iranian population.	[19]
2012	Expression of matrix metalloproteinase-2, but not caspase-3, facilitates distinction between benign and malignant thyroid follicular neoplasms	IHC	The potential value of measuring MMP2 expression in discrimination between FTA and FTC.	[20]
2013	Evaluation of MMP2 and Caspase-3 expression in 107 cases of papillary thyroid carcinoma and its association with prognostic factors	IHC	Evaluating the expression of MMP2 in PTC patients may be a useful marker in predicting of tumor aggressiveness.	[21]
2013	MicroRNAs networks in thyroid cancers: focus on miRNAs related to the fascin	Narrative reviews	There is no significant correlation between Caspase-3 expression and vascular invasion in patients with PTC.	[22]
2013	Essential genes in thyroid cancers: focus on fascin	Narrative reviews	Increased miRNAs expression in 32% of TCs. Decreased miRNAs expression in 38% of TCs.	[23]
2014	Characterization of wild-type and mutated RET proto-oncogene associated with familial medullary thyroid cancer	Sequencing Modeling Molecular docking Simulation	The importance of P53, RAS, RET, BRAF, PPARG and Fascin genes in TC. Mutation-based stability shift findings in RET showed that C.G2901A (P.C634Y) and C.G2901T (P.C634F) mutations were destabilizing, hence the stabilizing factor was C.G2251A (P.G691S) mutations.	[24]
2014	The beneficial effects of valproic acid in thyroid cancer are mediated through promoting redifferentiation and reducing stemness level: an in vitro study	Cell culture assay Cytotoxic assay C ratio and morphological analysis Colony formation assay qRT-PCR	The importance of the simultaneous analysis of the mutations in improved chemotherapy resistance and designing new anticancer drugs. Redifferentiation of ATC cell line and reduction of stemness properties of PTC cell line using Valproic acid.	[25]
2016	Antisense-miR-21 enhances differentiation/ apoptosis and reduces cancer stemness state on anaplastic thyroid cancer	Hoechst 33342 staining Cell culture Virus packaging and transduction Apoptosis assay Cell cycle assay qRT-PCR	miR-21 has a role in stemness properties, growth, differentiation, and apoptosis.	[26]

Table 1 (continued)

Year	Title	Main method(s)	Summary of findings	Ref.
2016	Cancer stem-like cell behavior in anaplastic thyroid cancer: A challenging dilemma	IRMA Cell culture MACS qRT-PCR	This study reconfirmed the concept of CSC as origin of ATC.	[27]
2017	Meta-analysis of promoter methylation in eight tumor-suppressor genes and its association with the risk of thyroid cancer	Meta-analysis	Among <i>RASSF1</i> , <i>TSHR</i> , <i>PTEN</i> , <i>SLC5A8</i> , <i>DAPK</i> , <i>PI6</i> , <i>RARβ2</i> , and <i>CDH1</i> tumor suppressor genes, promoter methylation of <i>SLC5A8</i> and <i>CDH1</i> is associated with the risk of TC development.	[28]
2017	Precision medicine approach to anaplastic thyroid cancer: advances in targeted drug therapy based on specific signaling pathways	Narrative reviews	To appoint the best strategy for ATC therapy, personalized medicine can use different data such as a patient's genetics and clinical background.	[29]
2018	Decreased apolipoprotein A4 and increased complement component 3 as potential markers for papillary thyroid carcinoma: A proteomic study	Proteomics study	Proteomic study showed that the apolipoprotein A4 decreased and complement component 3 increased in serum of patients with PTC.	[30]
2018	Serum-based metabolic alterations in patients with papillary thyroid carcinoma unveiled by non-targeted 1H-NMR metabolomics approach	1H-NMR	Serum metabolites are different between malignant and benign thyroid nodules.	[31]
2019	Promoter methylation of four tumor suppressor genes in human papillary thyroid carcinoma	MS-HRM assay	Among <i>SLC5A8</i> , <i>RASSF1</i> , <i>MGMT</i> , and <i>DNMT1</i> tumor suppressor genes, promoter methylation of <i>SLC5A8</i> , <i>RASSF1</i> , and <i>MGMT</i> is different between PTC and goiter tissue samples.	[32]
2019	Circulating ctDNA methylation quantification of two DNA methyltransferases in papillary thyroid carcinoma	Bisulfite treatment MS-HRM assay	A number of ctDNA promoter regions of <i>MGMT</i> and <i>DNMT1</i> genes are hypermethylated in plasma and tissue samples of PTC patients. The methylation status of ctDNA promoter regions of <i>MGMT</i> and <i>DNMT1</i> genes and tissue DNA are related to each other.	[33]
2019	Transcript-level regulation of MALAT1-mediated cell cycle and apoptosis genes using dual MEK/Aurora kinase inhibitor “BJ-847325” on anaplastic thyroid carcinoma	3D cell culture qRT-PCR	Targeting the regulatory network of lncRNA MALAT1 may be a more effective therapeutic approach for ATC.	[34]
2019	The role of ATP-binding cassette transporters in the chemoresistance of anaplastic thyroid cancer: a systematic review	Systematic review	ABC transporters are the major determinants of chemotherapy resistance in ATC.	[35]
2019	Determination of ATP-competitive inhibitor drug toxicity in anaplastic thyroid cancer based on cell characteristics and three-dimensional cell culture	3D cell culture Cytotoxic assay CFSE staining	The 3D cell culture systems are useful for obtaining the most appropriate anticancer drug with the most effective dose in ATC cell lines.	[36]
2020	Investigation of promoter methylation of FSCN1 gene and FSCN1 protein expression in differentiated thyroid carcinomas	Bisulfite treatment IHC	<i>FSCN1</i> promoter is hypomethylated in patients with PTC while the methylation status is not altered in FTC. Hypomethylation of <i>FSCN1</i> promoter in PTC does not promote to overexpression of <i>FSCN1</i> .	[37]
2020	Hypermethylated <i>RASSF1</i> and <i>SLC5A8</i> promoters alongside <i>BRAF</i> ^{V600E} mutation as biomarkers for papillary thyroid carcinoma	qRT-PCR Bisulfite treatment MS-HRM assay	Plasma ctDNAs originate from tumor tissue because the pattern of methylation and mutation of <i>BRAF</i> ^{V600E} in plasma and tissue DNA is the same. The <i>BRAF</i> ^{V600E} ctDNA mutation is the best predictive biomarker for PTC. Hypermethylation in the proximal promoter regions to the <i>RASSF1</i> and <i>SLC5A8</i> genes has sensitivity and specificity for discriminating between PTC and benign thyroid nodules.	[38]
2020		Mini review		[39]

Table 1 (continued)

Year	Title	Main method(s)	Summary of findings	Ref.
	Gut microbiome and radioiodine-refractory papillary thyroid carcinoma pathophysiology			
2020	Molecular mechanisms of long non-coding RNAs in anaplastic thyroid cancer: A systematic review	Systematic review	GM might be related to RAI-PTC through different molecular mechanisms associated with the NIS regulation as the main factor in Γ uptake. LncRNAs such as GAS5, CASC2, and MIR22HG may serve as prognosis markers. LncRNAs Khlh14-AS, PCA3, and HOTAIRM1 may act as molecular therapeutic targets.	[40]
2020	Bioinformatic study on effect of Xanthohumol as bioactive compound of hop in the inhibition of the MAPK/ERK pathway in thyroid cancer	Evaluation of physicochemical, pharmacokinetic, and pharmacodynamic characteristics Molecular docking	Xanthohumol acts as an inhibitor of MAPK/ERK pathway in TC cells. Xanthohumol, as a natural small molecule, does not have the potential to develop resistance in TC cells.	[41]

Abbreviations: $^1\text{H-NMR}$, hydrogen-1 nuclear magnetic resonance; 3D, three-dimensional; ABC, ATP binding cassette; AGREE, Appraisal of Guidelines Research and Evaluation; ATC, anaplastic thyroid carcinoma; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CASC2, cancer susceptibility candidate 2; CDH1, cadherin 1; cfDNA, circulating cell-free DNA; CFSE, 5,6-carboxyfluorescein N-hydroxysuccinimidyl ester; CSC, cancer stem cell; cfDNA, circulating tumor DNA; Ci, cure; DAPK, death associated protein kinase; DNNMT1, DNA methyltransferase 1; DTC, differentiated thyroid cancer; EGFRvIII, epithelial growth factor receptor variant III; FSCN1, fascin actin-bundling protein 1; FTA, follicular thyroid adenoma; FTC, follicular thyroid carcinoma; GAS5, growth arrest special 5; GBq, gigabecquerel; GM, gut microbiome; HLA-C, major histocompatibility complex class I C; HLA-DR, major histocompatibility complex class II DR; HLA-DRB1, major histocompatibility complex class II DR beta 1; HOTAIRM1, HOX antisense intergenic RNA myeloid 1; iHC, immunohistochemical; Γ , iodine; LncRNA, long non-coding RNA; IRMA, immunoradiometric assay; Khlh14, kelch like family member 14; MACS, magnetic-activated cell sorting; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MEK, mitogen-activated protein kinase kinase 1; MEN 2A, multiple endocrine neoplasia type 2A; MGMT, O-6-methylguanine-DNA methyltransferase; MIR22HG, MIR22 host gene; miRNA, micro RNA; MMP2, matrix metalloproteinase 2; MRI, magnetic resonance imaging; MS-HRM, methylation-sensitive high resolution melting; MTC, medullary thyroid carcinoma; NIS, sodium/iodide symporter; P16, cyclin dependent kinase inhibitor 2A; P53, tumor protein P53; PPAR γ , peroxisome proliferator activated receptor gamma; PCA3, prostate cancer antigen 3; PTC, papillary thyroid carcinoma; PTEN, phosphatase and tensin homolog; RAI, radioiodine-refractory; RAR β 2, retinoic acid receptor beta; RASSF1A, Ras association domain family member 1; RFLP, restriction fragment length polymorphism; qRT-PCR, quantitative real-time polymerase chain reaction; RAS association domain family member 1; RET, ret. proto-oncogene; SLC5A8, solute carrier family 5 member 8; TC, thyroid cancer; TSHR, thyroid stimulating hormone receptor

related to cancer stem cell properties, as important molecular mechanisms in the development and progression of poorly-differentiated/undifferentiated TC.

We hope to use these studies as well as the results of future findings to identify patients based on molecular testing and to treat patients with advanced and aggressive TC with novel targeted therapies directed at the specific genetic mutations.

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Prof. Mohammad Hasan Bastan Hagh was the founder of the Thyroid Research Group of Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences and left long-lasting scientific attainments.

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Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

Abbreviations 1H-NMR, hydrogen-1 nuclear magnetic resonance; 3D, three-dimensional; ABC, ATP binding cassette; AGREE, Appraisal of Guidelines Research and Evaluation; ATC, anaplastic thyroid carcinoma; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CASC2, cancer susceptibility candidate 2; CDH1, cadherin 1; cfDNA, circulating cell-free DNA; CFSE, 5,6-carboxyfluorescein N-hydroxysuccinimide ester; CSC, cancer stem cell; ctDNA, circulating tumor DNA; Ci, cuire; DAPK, death associated protein kinase; DNMT1, DNA methyltransferase 1; DTC, differentiated thyroid cancer; EGFRvIII, epithelial growth factor receptor variant III; EMRI, endocrinology and metabolism research institute; FSCN1, fascin actin-bundling protein 1; FTA, follicular thyroid adenoma; FTC, follicular thyroid carcinoma; GAS5, growth arrest special 5; GBq, gigabecquerel; GM, gut microbiome; HLA-C, major histocompatibility complex class I C; HLA-DR, major histocompatibility complex class II DR; HLA-DRB1, major histocompatibility complex class II DR beta1; HOTAIRM1, HOX antisense intergenic RNA myeloid 1; IHC, immunohistochemical; I⁻, iodine; LncRNA, long non-coding RNA; IRMA, immunoradiometric assay; Klf14, kelch like family member 14; MACS, magnetic-activated cell sorting; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MEK, mitogen-activated protein kinase kinase 1; MEN 2A, multiple endocrine neoplasia type 2A; MGMT, O-6-methylguanine-DNA methyltransferase; MIR22HG, MIR22 host gene; miRNA, micro RNA; MMP-2, matrix metalloproteinase 2; MRI, magnetic resonance imaging; MS-HRM, methylation-sensitive high resolution melting; MTC, medullary thyroid carcinoma; NIS, sodium/iodide symporter; P16, cyclin dependent kinase inhibitor 2A; P53, tumor protein P53; PPAR γ , peroxisome proliferator activated receptor gamma; PCA3, prostate cancer antigen 3; PTC, papillary thyroid carcinoma; PTEN, phosphatase and tensin homolog; RAI, radioiodine; RAIr, radioiodine-refractory; RAIr-DTC, radioiodine-refractory differentiated thyroid cancer; RAR β 2, retinoic acid receptor beta; RASSF1A, Ras association domain family member 1; RFLP, restriction fragment length polymorphism; qRT-PCR, quantitative real-time

polymerase chain reaction; RAS association domain family member 1; RET, ret. proto-oncogene; SLC5A8, solute carrier family 5 member 8; TC, thyroid cancer; TSH, thyroid-stimulating hormone; TSHR, thyroid-stimulating hormone receptor.

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