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Potential of epigenetic events in human thyroid cancer

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ABSTRACT

Thyroid cancer remains the highest prevailing endocrine malignancy, and its incidence rate has progressively increased in the previous years. Above 95% of thyroid tumor are follicular cells types of carcinoma in which are considered invasive type of tumor. The pathogenesis and molecular mechanism of thyroid tumors are yet remains elucidated, in spite of activating RET, RAS and BRAF carcinogenesis have been well introduced. Nemours molecular alterations have been defined and have revealed promise for their diagnostic, prognostic and therapeutic capacity but still need further confirmation. Among different types of mechanisms, the current article reviews the importance of epigenetic modifications in thyroid cancer. Increasing data from previous reports demonstrate that acquired epigenetic abnormalities together with genetic changes plays an important role in alteration of gene expression patterns. Aberrant DNA methylation has been well known in the CpG regions and profile of microRNAs (mi-RNAs) expression also involved in cancer development. In addition, the gene expression through epigenetic control contribution to thyroid cancer is analyzed and it is semi considered in the clinic. However the epigenetic of the thyroid cancer is yet remains in its early stages, and it carries encouraging potential thyroid cancer detections in its early stages, assessment of prognosis and targeted cancer treatment.

Contents

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Introduction

Previously, cancer is viewed as a main genetic disorder [1], however, recently it is accepted that the malignancy are not only just influenced by the roles of genetics factors but also by consequence of abnormal epigenetic events [2]. Genetic alterations and aneuploidy are linked with changes in DNA strains, and they are a seal of the malignant pathogenesis [3]. Epigenetic changes are extensively exist in cancer as a result of heritable alterations and changes in gene expression [4] and chromatin structure [5,6] which transmitted to various cell generations without alterations in DNA sequence, [7] resulting to functional costs corresponding to those induced by genetic changes [8]. Significantly, intriguing evidence emerged shows that epigenetic modifications can lead and provoke genetic alterations [9]. In this scenario, epigenetic modifications are mainly events while genetic alterations (such as mutations) may basically be a consequences of changed epigenetic states [10]. And this can explain why some genetics screens confirmed to be bounded with regard to malignancy causality and pathogenicity. Aberrant epigenetic events stimulates cellular pathways [11] and multiple genes [12] in an organized fashion, thus can predispose to beginning and accumulating of genetic alteration in the line of cancer induction and progression [13]. These considerations are crucial for a clear understanding of tumors pathogenesis, cellular and molecular processes [14] underlying the acquisition of drug resistance [15], in addition to development of novel for cancer therapy [16], control and prevention strategies [17].

DNA methylation and carcinogenesis

DNA methylation defines as the addition or subtraction of a methyl group into a cytosine residue in DNA sequence [18]. The methylation of DNA is controlled by DNA methyltransferase enzymes [19]. In genome broad association studies, global reduces in DNA methylation (hypo-methylation) are the main functionally related when they happened in transcriptional area of genes [20], resulting to alternative versions or levels of mRNA [21]. It is viewed that hypomethylation play critical role in carcinogenesis via favoring mitotic recombination, leading to translocations, deletions, and chromosomal rearrangements [22]. Methyl groups addition (hype-rmethylation), is much more gene particularly. The DNA sequence that fulfilled in a cytosine preceding a guanine (CpG dinucleotide) is named CpG islands [23]. In particular, CpG islands occur in the promoter of nearly 50% of all genes [24]. Hyper methylation of promoter (CpG islands), that approximately contains all genes results in its transcriptional silencing and loss of protein expression [25]. Therefore, tumor suppressor genes hyperethylation is now acknowledged as a means of silencing alternative to cancer development [26] (Fig. 1). Genes Hypermethylation is also associated with the DNA repair [27], cell cycle [28], carcinogens metabolism [29], apoptosis, and cell-cell interaction [30] which have been involved in carcinogenesis. Hypermethylation can also block the transcription process of micro RNA leading to carcinogenesis [31]. Although, it necessary to be taken in account that hypermethylation also happened in normal physiological process, for instance, development [32] and during inactivation of the other X chromosome (the second X chromosome in females) [33]. The question is raised up why aberrant DNA methylation appeared is not completely understood. It is acknowledge that variant genes are methylated are in age-related style [34], and others are methylated in a tumor-specific manner [35]. Definitely, some carcinogenetic pathway of specific purpose to the reproductive system is the CpG island methylator phenotype (CIMP). CIMP+ cancers have different pathologic, genetic and clinical features [36]. Even if environmental influences such as diet (e.g., folic acid), carcinogens, or other unknown causative agents contribute to DNA methylation remains to be elucidated and it's an area of interest research.

Histone modifications and cancer

Histones are protein molecules of the chromatin, the structure around which DNA is wound. Histones may possibly undergo a number of categories of post-translational alteration, including methylation, acetylation [37], phosphorylation [38], and ubiquitination [39] (Fig. 2). These modifications can influence interactions amid DNA and histones [40], resulting in the alterations of gene transcription [41], DNA repair [42], DNA replication [43], in addition to alignment of chromosomes [44]. Universally, acetylation of histone associated with transcriptional activation [45]. Consequently, deacetylation is involved in the silencing of cancer or tumor suppressive genes in carcinogenesis [46]. Indeed, inhibitors of histone deacetylase are in initial clinical experiments for many cancers treatments, with promising results [47].

CpG island methylator phenotype criteria (CIMP)

In 1999, two various types of colorectal malignancies were described, and identified to display high and low levels of cancer specific methylation, correspondingly [48,49]. The "CpG island methylator phenotype" (CIMP) was found to be exhibited in the latter type of cancer [50]. CIMP is negatively linked with genetic aberrations in colorectal cancer [51,52], which imply that it can offer an alternative pathway for carcinogenesis [53]. Other cancers that demonstrate frequent and accompanied deactivation of certain genes via hypermethylation likewise have been designated as CIMP. These malignancies include liver [54], gastric [55], leukemia [56], lung [57,58], and ovarian [59] and thyroid cancers [60]. Differential expression of the DNA methyltransferase (DNMT) genes in many thyroid cancers has been revealed [61]. However, whether the modifications in DNMT expression could contribute to develop CIMP phenotype of thyroid cancer is unknown. In addition, basic mechanisms that contributing to increases of methylation anomalies in thyroid cancer is needed to be elucidated. Numerous studies demonstrated that patients with CIMP positive tumors have bad prognosis possibly due to increases of their epigenetic plasticity [62–64]. Therefore, determine of the molecular ground of CIMP is very important, to assay the current set of methylation biological markers for detection of CIMP [64,65]. However, CIMP positive tumors are accessible to be diagnosed at initial level because aberrant DNA methylation can be distinguished with high sensitivity [66]. Whether, this phenotype can be capable to predict outcome of treatment in thyroid cancer patients is needed to be answered. Generally, the compactness of methylated CpG area within a locus adds to the number of methylated site was found to increase in late stages of cancer. While the duration of increase-free survival after chemotherapy was found to be considerably shorter for patients with higher levels of methylation compared to those with minimal methylation levels, detection of CIMP cancers may aims in treatment planning and outcome.

Epigenetic alterations in thyroid cancer

A variety of genes implicated in the regulation of cell proliferation and infiltration in addition to specific genes in thyroid differentiation are epigenetically alternated in thyroid tumor are well acknowledged [67]. For examples of those genes are thyroid transcription factor-1 [68], TIMP3 [69], RASSF1A [70] and PTEN [71]. Cumulative epigenetic modification play a critical role in the progressions from indolent well-differentiated thyroid carcinomas (WDTC) to metastasizing carcinomas, via a spectrum of undifferentiated thyroid cancer to poorly differentiated.

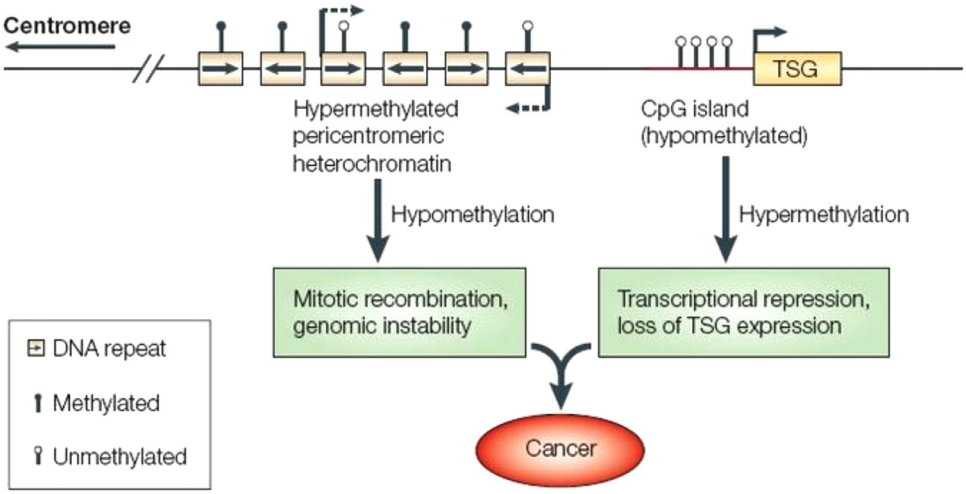

Fig. 1. Schematic picture for the role of DNA methylation in cancer development.

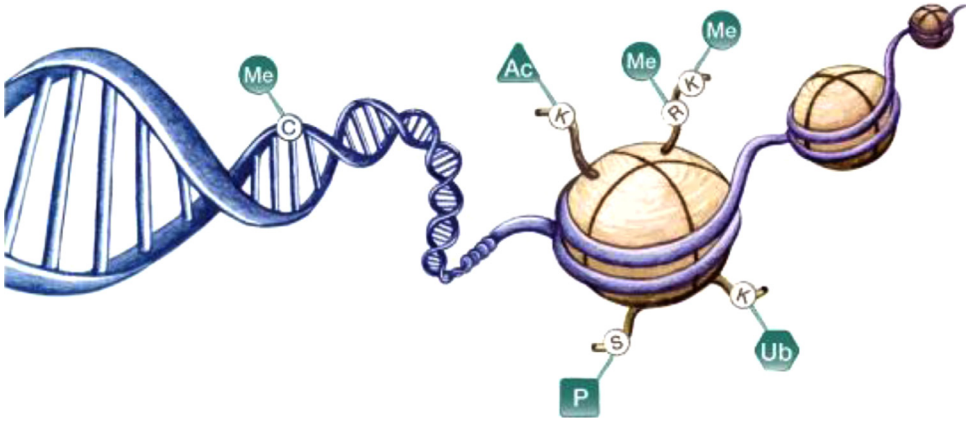

Fig. 2. Schematic picture for histone modifications: methylation, acetylation, phosphorylation and ubiquitination.

Aberrant gene methylation in thyroid cancer

Aberrant DNA methylation of proto-oncogenes and tumor suppressor genes are reported in thyroid cancer, and it found to occur in other human cancers. Certain specific tumor suppressor genes in the thyroid are DAPK, PTEN, RAPβ2, RAP1GAP, RASSF1A, SLC5A8, and TIMP3. PTEN was known as a tumor suppressive gene, it is mutated in several types of cancers. PTEN encodes phosphatidylinositol-3, 4, 5-triphosphate 3-phosphatase protein. This gene is negatively regulates signaling pathway of the AKT/PKB and is plays an essential role in the cell cycle regulation, opposing cell rapid cell division and growth [72]. Aberrant DNA methylation of PTEN is frequently reported in FTC and PTC [71]. The RASSF1A gene encodes a protein analogue to the RAS effectors protein [28]. The deregulations of RASSF1A mRNA expression are associated with cancer, and aberrant DNA methylation has been acknowledged as a central mechanism underlie in the inactivation of this gene [70,73]. In contradiction of FTC, only a small ratio of PTC harbored the aberrant methylation of RASSF1A, which may play a critical role in thyroid carcinogenesis, independent of the BRAF/MAPK kinase (MEK) MAPK pathway [73]. TIMP3 is a tissue suppressor of metalloproteinase enzyme, which inhibits the cell develop, infiltration, angiogenesis, and metastasis of numerous tumors [74]. TIMP3 gene has been found to be hyper methylated in thyroid cancer [26,69]. It is also associated with lymph node metastasis and extra thyroidal invasion [26]. The RAP1GAP gene encodes a class of GTPase-activating protein which deactivates the RAS-related protein. RAP1GAP is participating in the regulation of oncogenic and mitogenic pathways in thyroid cells [75,76]. RAP1 plays a vital role in the activation of the BRAF-MEK-ERK pathway and regulation of the ERK-dependent pathway [77–79]. The immunohisto chemistry method findings revealed the down regulation of RAP1GAP gene in PTC [80] associated with its proliferation and invasion in thyroid tumor cell lines [81]. In addition, DNA hypo methylation plays fundamental role in carcinogenesis; yet, its role is not fully understood. Only one study reported the international patterns of abnormal DNA methylation in thyroid malignancy subtypes via DNA methylation arrays [82]. 262 and 352 genes were discovered to be hyper methylated in PTC whereas, 13 and 21 genes were hypo methylated in FTC. Additionally, 280 and 393 hypomethylated genes and 86 and 131 hyper methylated genes were determined, which were identified in anaplastic and MTC, correspondingly. Among these genes, four oncogenes including DPPA2, INSL4, NOTCH4 and TCL1B were commonly regulated by hypo methylation [82].

Histone modification in thyroid cancer

Unluckily, little studies about the histone modifications present in thyroid cancer and the association between those modifications and thyroid tumors behavior is presently available. However, recently, only one study reported global levels of histones acetylation alteration in thyroid cancer tissues [83]. They detected that in undifferentiated cancers have lower levels of acetylated H3 at K18

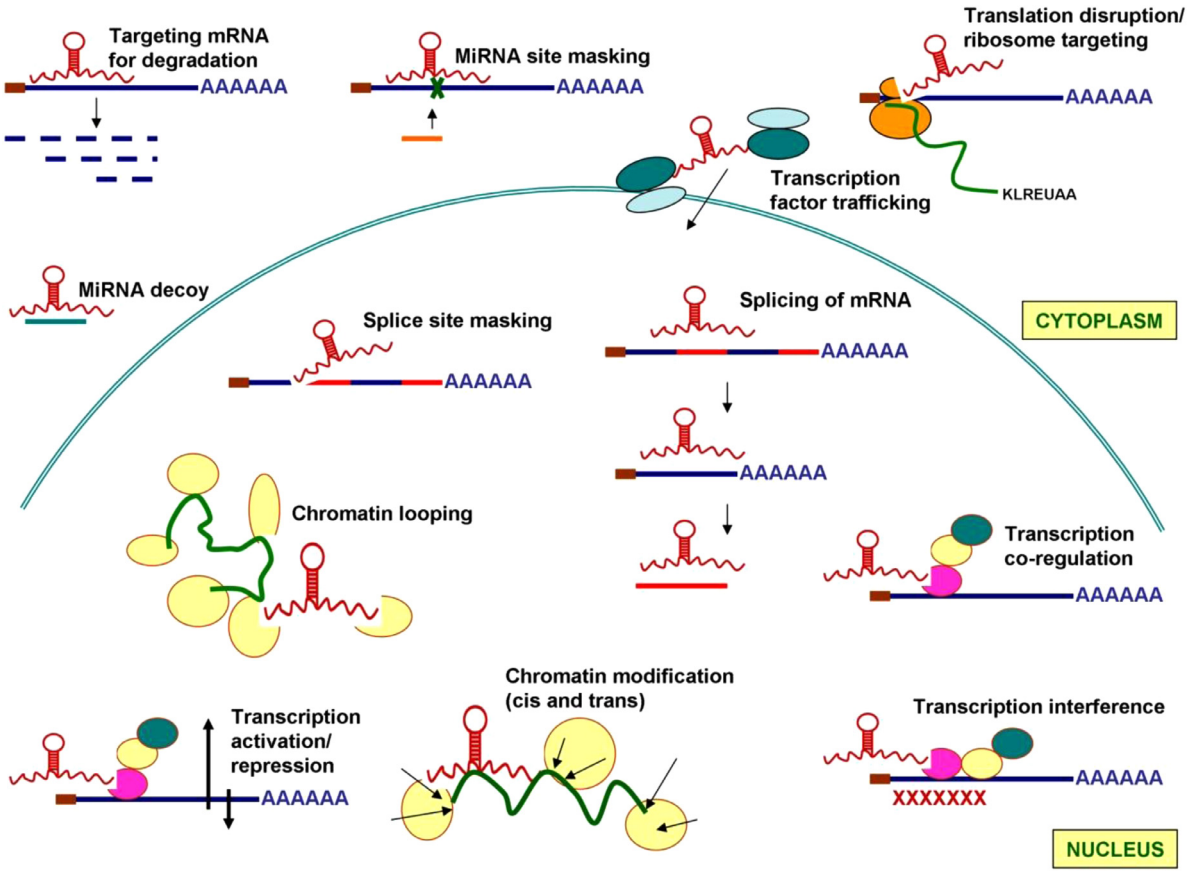

Fig. 3. The role of lncRNAs in regulation of expression.

residue in compared with differentiated types of cancers, identifying that thyroid tumor transition are switched off by acetylation. Hyper methylation of the thyroid transcription factor-1, that is critical for thyroid carcinogenesis, concomitantly with reduces acetyl-H3-K9 and increased dimethyl-H3-K9, has been seen in a subset of thyroid cancer cells that had lost the expression of TTF-1 [68]. Furthermore, it has lately been confirmed that the enhancer of zeste homolog 2 (EZH2), a histone lysine methyl transferase are belong to the poly-comb group protein family, is particularly up-regulated in ATC, and it directly differentiation [84].

The biological roles of long non coding RNAs (lncRNAs)

lncRNAs are nucleotides in length [85], do not contain genetic information (Codes) to be translated into proteins during the central dogma process [86]. They are shorter than mRNAs as lncRNAs containing fewer exons [87]. These RNA molecules differ in size and length range from 200 bp to 100 kb [88]. Lately, the ENCODE project discovered that ~80% of the human genome is transcribed into 14,880 lncRNAs from 9277 loci [89]. The theory of lncRNAs introduced more than two decades ago [90, 91]. Yet, the attention of researchers on lncRNAs has been ignored in general since the expression of lncRNAs were much lesser than those of mRNAs [89, 92], consequently they displayed evolutionarily poor sequence conservation among different organisms [93]. Newly, the research on lncRNA has been motivated to the forefront of human cancer research [94] in particular after confirmed a vital role of lncRNAs in gene modulation [95]. lncRNAs are essentially involved in the epigenetic regulation of expression of a variety of genes at different molecular levels including chromatin [96,97], splicing [98], transcriptional and post-transcriptional (Fig. 3) [99,100]. lncRNAs epigenetically control expressions of several salient genes that involved in crucial cellular biological processes such as cell differentiation [101], cellular autophagy [102], cell cycle regulation [103], cell proliferation [104], apoptosis [105], invasion [106], migration [107], and differentiation of stem cell [108].

The role of long noncoding RNAs (lncRNAs) in thyroid cancer pathogenesis

lncRNAs are known to play a fundamental role in various key cellular physiology [108]. The deregulations of lncRNAs have been reported in numerous complex human disorders including cancers [109]. Newly, a genome-wide study (GWAS) of lncRNA expression profile in papillary thyroid carcinoma (PTCs) [110], identified diverse upregulated and downregulated of lncRNAs in PTC samples [111,112]. The same research group studies both mRNA and lncRNA and expression patterns in 62 PTC tissues compared with normal thyroid tissues using microarray and confirmed 10 differentially expressed lncRNAs via quantitative RT-PCR. The functions of gene were studies by gene ontology and KEGG pathway analysis. In addition, two independent algorithms methods were used to predict potential target genes of those lncRNAs [113]. In this microarray-based study, [114] with his coworkers found expression of thousands significant different of lncRNAs and mRNAs when compared to non thyroid cancer tissue [114]. Moreover, 1805 deregulated of lncRNAs found to have *cis* or *trans* target genes. In the *cis* target genes, about 463 were differentially expressed and they have been implicated to be regulated by lncRNAs in PTC carcinogenesis. Among the top 20 upregulated lncRNAs, 86-fold to 204-fold changes have been observed. Additionally, they found a minimum of 47-fold to a maximum of 148-fold changes among

Table 1
The roles of mi-RNAs in the development of various types of cancers.

MicRNA	Role in the development of certain types of cancer	Functions
miR-21,-17 Cluster,-221,-222	suppression and stimulation of growth	Growth stimulation
miR-16-1,-17,-20A,-1	Genome instability	Induction of genome instability
miR-146a,-101,-200		Suppression of metastasis
miR-10b,-21,-373,-520c,-155,–335,-206,-126,Let-7	Metastasis	Stimulation of metastasis
miR-17-92Cluster,-155,-20a,-93,-106b,-372,-373,-520c	Escape from immune system	Escape from immune response
miR-15,-16,-20a,-20b		Suppression of angiogenesis
MiR-17-92Cluster,-378,-996,-27b,-130,-126,Let-7f	Induction of angiogenesis	Stimulation of angiogenesis
miR-290,-24,-34a	Unlimited cell proliferation potential	Aging control and immortality
miR-290,-24,-34a		Suppression of apoptosis
miR-34Cluster,-29,-15,-10	Escape from Apoptosis	Stimulation of apoptosis
miR-519,-146a,Let-7		Suppression of cell growth

Table 2
the roles of mi-RNAs in differentiated thyroid cancer.

Type of cancer	Upregulated	Downregulated
Papillary Carcinoma	miR-26a-1,-345,-138,-319,-218,-300,-292,-30c	miR-146,-221,-222,-21,-181a, -155,-213,-181b,-31,-172,-34a,-223,-224,-187,-146b,-220
Medullary Carcinoma		miR-323,-370,-129,-137,-10a,-124a,-224,-127,-9,-154
Anaplastic Carcinoma	miR-30d,-125b,-26a,-30a,-5p	miR-302c,-205,-137,-187,-214,-155,-224,-222,-22
Follicular Carcinoma		miR-197,-346,-187,-221,-222,-224,-203,-183,-339,-31

the top 20 downregulated lncRNAs. Among those lncRNAs, 10 lncRNAs were identified as statistically significant different and were differentially expressed as upregulated or downregulated with the similar tendency [114]. Human lncRNA based microarray study showed abnormal expression of 675 lncRNAs in 3 pairs of PTC when compared to paired normal thyroid tissues [115]. Besides this, analysis of 12 samples compared with normal tissue via RNA sequencing and quantitative RT-PCR detected about 188 differentially expressed lncRNAs. Among them, NONHSAT122730 and NONHSAT076747 were found to be associated with lymph node metastasis (LNM) [116], whereas, the NONHSAG051968 expression was negatively correlated with size of tumor [116]. However, the majority of lncRNAs detected in these GWAS study are basically uncharacterized. However, there several lncRNAs including H19, MALAT1, HOTAIR, and BANCR that have been confirmed as a key contributors in development of thyroid cancer, and thus can be used as novel biomarkers for early detection, diagnosis and even treatment [117].

The micro-RNAs roles in thyroid cancer

MicroRNAs (mi-RNAs) are collection of small endogenous encoding RNAs controlling gene expression in various biological processes, including differentiation, proliferation and apoptosis [118]. The modifications in mi-RNA expression are thought to be an important regulator of cancer progress and development of thyroid cancer [119]. MicroRNAs are short molecules of 19–23 nucleotide that able to block translation of target mRNA or degradation of mRNA through complementary binding to the 3- un-translated region (UTR) of mRNAs. Increasing evidence has proposed the contribution of mi-RNAs in human carcinogenesis [120,121]. The deregulation of mi-RNA expression is proposed to be an essential regulator of malignancies and progression [122]. As a result of its repression effect, deregulation of certain mi-RNA may possibly lead to the down-regulation of tumor suppressor gene and/or up-regulation of oncogenes [123]. Thus, these molecular alterations favor cell differentiation, proliferation and apoptosis. Profiling of MicroRNA in human cancers has revealed signatures linked with cancer diagnosis, prognosis, staging, and response to therapy [124,125]. The roles of mi-RNAs in the development of various types of cancers (Table 1), differentiated thyroid cancer (Table 2) and various types of thyroid malignancies (Table 3) have been reported [119,126]. These findings strongly suggested critical roles for specific mi-RNAs in the progression and development of thyroid cancer.

Epigenetic targets for treatment of thyroid cancer

The anomalies in the epigenetic regulation of chromatin function and can cause aberrant gene expression and cancer initiation and development [9]. As a result, epigenetic therapies plan to reinstate normal chromatin modification patterns via the inhibition of a variety of mechanism of the epigenetic machinery [127]. DNA methyl-transferase and Histone deacetylase inhibitors consider the first acknowledged epigenetic therapies; nevertheless, these agents have pleiotropic property and it remains less clear how they direct to therapeutic responses. More newly, drugs that inhibit histone methyl-transferases were developed, maybe representing more specific agents. The above mentioned findings together reveal that complex epigenetic patterns, including DNA methylation, histone alterations and mi-RNA abnormalities contribute to thyroid cancer progression and drug resistance. The assessing epigenetic modification profile may provide valuable predictive information for thyroid cancer. Accordingly, reversing epigenetic modifications may nearby itself as a promising treatment modality. While genetic deletions, mutations or allelic losses are irreversible, epigenetic abnormalities are potentially correctable and can be reversed [128,129]. In this scenario, a number of drugs that inhibit DNMT or HDAC action are nowadays in clinical practice or under trial. In preclinical studies, different DNMT inhibitors, for instance azacitidine were found to evoke DNA hypo-methylation and reverse chemoresistance of platinum-resistant thyroid cancer cells [130,131] laying the fundamental concept for the clinical assessment of DNMT inhibitors for chemotherapy re-sensitization in thyroid cancer patients [132].

Epigenetic therapy

Epigenetic drug is one of recent epigenetic mechanisms which activate genes aberrant silenced in malignancy. Epigenetic drugs are projected to target the two main mechanisms of epigenetic modifications, acetylation and methylation of the DNA, controlling via the differentiation and proliferation of abnormal or transformed cells. To date, various epigenetic treatments are in experimental trials for thyroid malignancy treatment. For instance, Decitabine targets DNMT whereas; Depsipeptide, Vorinostat

Table 3
the roles of mi-RNAs various types of thyroid cancers.

Type of cancer	Upregulated	Downregulated
PTC vs non-PTC	miR-146b, miR-221, and miR-222	
PTC and FTC	PTC: miR-187, miR-221, miR-222, miR-181b, miR-146b, miR-155	
FTC vs. PTC/NT	FTC vs. NT: 37 mi-RNAs FTC vs. FTA: 12 mi-RNAs miR-146b, miR-221, and miR-222	FTC vs. NT: 113 mi-RNAs FTC vs. FTA: 44 mi-RNAs
FTC	miR-192, miR-197, miR-328, and miR-346	
PTC	miR-146b, miR-221, and miR-222	
PTC	miR-181b, miR-221, and miR-222	
PTC	miR-21, miR-31, miR-34a, miR-172, miR-181a, miR-181b, miR-213, miR-221, miR-222, miR-223, and miR-224	miR-19b-1,2, miR-30a-5p, miR-30c, miR-130b, miR-145sh, miR-218, miR-292-as, miR-300, and miR-345

(SAHA), Valproic acid (VPA) and Panobinostat (LBH589) target a class of HDAC types.

Demethylating agents

Throughout thyroid tumor development, several specific thyroid genes (e.g., TSH and NIS receptor genes) are found to be hypermethylated and, thus silenced. Demethylating therapies may reverse the cancer cell phenotype. It was found that demethylating drugs such as decitabine were able to return and TSH-R NIS expression in human thyroid cancer cell lines [133–135]. Additionally, decitabine treatment inhibited the growth of undifferentiated and dedifferentiated thyroid cancer cells [136]. Currently, the methyltransferase inhibitors azacitidine and decitabine have been approved for clinical treatment only in myelodysplastic syndrome, however, new hypomethylation drugs such isothiocyanates and zebularine are can be used in various levels of development for cancer therapy [137]. In general, a phase II scientific trial is continuing for therapy with decitabine of patients suffers from metastatic thyroid cancers insensitive to radioiodine.

Histone deacetylase inhibitors

Histone acetylation and de-acetylation are main events of gene transcription regulation process; HATs and HDACs; catalyze these reactions and catalyze also non-histone proteins such as transcription factors. HDAC inhibitors are promising agents in carcinogenic treatment therapy as they, targeting multiple tumor genesis pathways, preferentially kill transformed cells, and are comparatively non-toxic to natural cells [138]. A number of structural family of HDAC suppressors have been recognized, including short chain fatty acids for instance valproic acid and phenyl butyrate; cyclic peptides such as apicidin and depsipeptide; cyclic tetra peptides such as trapoxin A; benzamides such as CI-994 and MS27-275; hydroxamic acids such as oxamflatin, suberoylanilide hydroxamic acid (SAHA), trichostatin A, and the more newly developed paninhibitors LBH589, LAQ824 and PXD101 [139–141].

Conclusion and future directions

Despite the amazing rapidly increasing plethora of information, the field of epigenetics in thyroid cancer is still in its beginnings. During the last decades, epigenetic revolution has become doubtful. The genetic codes are the basic determinant for gene function. Reports in epigenetic patterns of tumor have confirmed that genome packaging is the key as the genome by itself in controlling the vital cellular functions. Understanding the epigenetic changes is essential for molecular therapeutic design. Like in other types of cancer, the majority of genetic and epigenetic changes are somatic, and evaluating the epigenetic model in thyroid cancer showed an important role for these changes in the diagnosis, classification and prognosis of cancers. The reversible epigenetic modifications that take place in cancer result in the possibility of epigenetic therapy as an optional treatment. Inhibitors of DNA methylation were among the first epigenetic drugs projected for use as cancer drugs. While mi-RNAs are associated with cell differentiation, proliferation and invasion, these molecules and their bio target genes are considered as potential targets for cancer diagnosis and cure. Moreover, epigenetically silenced or activated cancer genes offer new targets for therapeutic intervention via de-methylating drugs and HDAC inhibitors in single or combination therapies. It seems that epigenetic therapy regimens are now shifting into new territory, giving promising novel therapy approaches and hopes for increase patient survival. However, there is still a lot to understand at the basic scientific level and much to be done to translate thyroid cancer epigenetics into clinical practice. While several of genes that undergo aberrant epigenetic modifications linked with thyroid malignancy, a number of questions need to be resolve before we completely understand the biologic implication and outcome of this process. For instance, what is the mechanism deriving selective methylation of genes in thyroid cancer which is raises the activity and expression of DNMTs. Why do hyper methylation and hypo methylation occur in thyroid cancer cells Is there an active de-methylating process which could explain for the hypomethylation or it is caused by reduced hyper methylation?

Declaration of Competing Interest

All authors of Potential of epigenetic events in human thyroid cancer, acknowledge that, there are no conflict of interests exists.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.08.006.

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