EDITORIAL
Korean J Intern Med 2012;27:391-393
http://dx.doi.org/10.3904/kjim.2012.27.4.391

pISSN 1226-3303 eISSN 2005-6648
http://www.kjim.org

Epigenetic Regulation of *RUNX3* in Thyroid Carcinoma

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Epigenetics studies the heritable chromatin changes in gene expression or cellular phenotypes caused by mechanisms other than changes in the underlying DNA sequence [1]. Epigenetic modifications around a gene alter expression without gene mutation and play a prominent role in the control of all DNA-based processes, such as transcription, DNA repair, and replication [1,2]. Therefore, abnormalities in epigenetic modification can have immense consequences for gene expression, and provide the underlying molecular causes for the development or maintenance of cancers. In the past decade, great effort has gone into identifying the role of epigenetic processes in the initiation of carcinogenesis. Recently, these efforts have provided an epigenetic molecular basis for progression, and have identified new therapeutic targets in the treatment of cancer. In short, current epigenetic studies validate the hypothesis that cancer is a disease of epigenetic abnormality [2].

Most epigenetic changes associated with cancer are linked to abnormal gene expression patterns or other genomic alterations, and include methylation or acetylation of specific sites on DNA or histones [3]. Around 1980, various cancers were shown to have abnormal DNA methylation status, highlighting the relationship between DNA methylation status and tumorigenesis [2]. *De novo* methylation of CpG islands in a specific gene promoter results in chromatin remodeling, and suppresses gene expression through recruitment of transcriptional repressors that bind to DNA sequences modified by methylation. In other cases, DNA methylation in CpG regions of promoters causes structural changes that hamper the recruitment or binding of transcription factors [4]. It has been reported that about 10% of promoter CpG islands become abnormally hypermethylated in various types of cancer [1]. Interestingly, such hypermethylation has frequently been found to occur in genes known to act as tumor suppressors. Hypermethylation of promoter CpG islands may also lead to the expression of various noncoding RNAs, which play a role in malignant transformation as well as in inappropriate silencing of protein-coding genes [2]. Consequently, promoter CpG hypermethylation in tumor suppressor genes can be associated with tumorigenesis through inappropriate silencing of genes.

Thyroid cancer derived from follicular epithelial cells is the most common endocrine cancer. It is well known that genetic alterations, such as *BRAF* mutation, rearranged during transfection/papillary thyroid carcinoma (PTC) rearrangement, *RAS* mutation, and *PAX8-PARγ* rearrangement, play critical roles in the initiation, progression, and aggressiveness of thyroid cancers [5]. In addition, recent studies have shown that aberrant epigenetic modifications,

Received: October 2, 2012
Accepted: October 6, 2012

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particularly hypermethylation of tumor suppressor genes, occur concurrently in PTC [4]. These studies suggest that epigenetic alteration is another important mechanism in the development of thyroid cancer. For example, genes for tissue inhibitor of metalloproteinase 3 (TIMP3), SCL5A8, and death-associated protein kinase (DAPK), which are known to be tumor suppressors, are hypermethylated in PTCs. Silencing of these genes by hypermethylation is frequently associated with poor clinical characteristics [5]. TIMP3 suppresses tumor growth and angiogenesis through the inhibition of metalloproteinase. Methylation of the *TIMP3* gene in PTC is correlated with extrathyroidal invasion, lymph node metastasis, and tumor multifocality [5]. SLC5A8, a sodium/solute symporter family member, is expressed in many types of normal tissue, and plays a role in proapoptosis. Hypermethylation of this gene is correlated with extrathyroidal invasion, multifocality, and advanced stage of PTC [6]. DAPK is a calcium/calmodulin-dependent serine threonine kinase also associated with proapoptosis [5,7]. Hypermethylation of its gene is also correlated with multifocality of PTC [5].

Research demonstrating that epigenetic alteration plays a role in determining the development of thyroid cancers has led to additional studies examining the interactions between genetic mutation and epigenetic alteration in such cancers. A recent study suggested that a CpG island methylator phenotype could be closely associated with *BRAF* mutation in colorectal cancer [8]. Also, some studies suggested that cluster of a methylation of tumor suppressor genes associated with *BRAF* mutation could increase invasion and aggressiveness of PTC [5]. However, it remains to be determined whether the process of epigenetic alteration precedes that of *BRAF* mutation, which is known to be the single most frequent gene alteration associated with the development of PTC.

Runt-related transcription factor (*RUNX*) genes include three different isoforms in mammals and encode the DNA-binding α-chain partners of the heterodimeric core-binding factor (CBF) complex. RUNX provides high-affinity DNA-binding and stability for the CBF complex to regulate gene expression in promoters or enhancer elements of target genes [9,10]. The importance of the *RUNX* genes in cancer was realized following the discovery of specific chromosomal translocations that affect RUNX1 and CBFβ in acute myeloid leukemia (AML). Chromosomal translocations involving the *RUNX1* gene are associated with several types of leukemia, including M2 AML [9]. Recent studies suggest that the loss of *RUNX3* expression by gene deletion or by promoter CpG island hypermethylation is linked with the development of solid tumors, such as gastric, colorectal, and lung cancers. Abnormal methylation patterns in CpG islands of the *RUNX3* promoter were found in 45% to 60% of human gastric cancer cell lines examined, and in 64% of primary gastric carcinomas. More interestingly, 27% of gastric adenomas, which are defined as premalignant lesions for gastric carcinoma, also showed similar hypermethylation patterns in the *RUNX3* promoter. These findings suggest that *RUNX3* methylation may provide molecular mechanisms in multistep gastric carcinogenesis [10].

Although *RUNX3* methylation is observed in various types of cancer, patterns of *RUNX3* gene expression have not been fully studied in PTC. In a study by Ko et al. [11], the promoter CpG islands of *RUNX3* in thyroid cancer cell lines had increased methylation, as compared to normal thyroid tissue. This study is interesting because it showed that the *RUNX3* gene may be an epigenetic target in PTC. However this study did not examine the expression of RUNX3 protein in the context of CpG methylation status. In addition, it remains unclear whether RUNX3 protein and its transcriptional targets are consistently controlled by CpG methylation status in human thyroid cancer tissues. Despite these limitations, the study by Ko et al. [11] provided a new perspective on the role of *RUNX3* in PTC. It has led to questions about whether *RUNX3* expression is specifically altered in PTC, and about whether its expression in such cancers is solely controlled by CpG methylation status. Additionally, it appears reasonable to pursue investigation of the relationship between CpG methylation status and *BRAF* mutation in thyroid cancer.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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