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Editorial - Endocrine Tumor

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Cancer involves genetic and epigenetic abnormalities. While there have been many studies on genetic alterations resulting in the activation of oncogenes and/or the inactivation of tumor suppressor genes leading to the development of cancer, the critical role of epigenetic mechanisms of gene expression is increasingly recognized as an important component in carcinogenesis. This role has been supported by the observation that epigenetic modifications can act as a direct driver of tumor formation (Yu et al., 2014). Epigenetic mechanisms include those functioning at chromatin levels such as DNA methylation and histone methylation/acetylation, methylation of non-histone chromatin remodeling proteins (Baxter et al., 2014), and mechanisms targeted at RNA expression levels such as long non-coding RNAs (lncRNAs) and micro RNAs (miRNAs). These cellular epigenetic changes could potentially be translated to provide biomarkers for diagnosis, prognosis as well as treatment of cancers (Kanwal and Gupta, 2012).

The role of epigenetic regulation is also important in endocrine tumors. This special issue focuses on the epigenetic regulation of “endocrine tumors”, which includes tumors of classical endocrine hormone secreting organs such as the thyroid, parathyroid, pituitary, adrenal gland, and those originated from neuroendocrine cells. The issue starts with five review articles focused on the thyroid, the organ most commonly affected by endocrine tumors. The first review by Asa and Ezzat focuses on the follicular cell-derived well-differentiated thyroid cancers; papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). While the majority of these cancers have an indolent behavior, a significant proportion can show aggressive behavior despite presenting with similar genetic mutations. These differences may be attributed to epigenetic mechanisms. This review particularly focuses on DNA methylation, histone modification and miRNA changes and their roles in clinicopathologic behavior of thyroid cancers.

The second review by Sui et al describes the involvement of lncRNAs that are up- or down-regulated in various thyroid cancers, mainly PTC, but also including some data from anaplastic thyroid carcinoma (ATC). Pathways in which lncRNAs are involved leading to thyroid cancers are presented, clearly demonstrating their critical roles in thyroid carcinogenesis. The third review by Sasanakietkul et al focuses on epigenetic alterations in poorly differentiated thyroid cancer (PDTC) and ATC. These cancers are amongst the most aggressive tumors in human malignancy and this review discusses altered signaling, genetic and epigenetic modifications including DNA methylation, histone modification and noncoding RNAs found in these cancers.

The focus of the fourth review by Celano, et al is on histone modifications. This review provides an overview of histone modifications in cancers with a focus on the use of histone activity modifiers as re-differentiating or anti-proliferating agents in targeted treatment of thyroid cancer. The final review on the thyroid by Joo, et al focuses on medullary thyroid carcinoma (MTC), a rare but aggressive type of non-follicular cell derived thyroid cancer. The review describes the *RET* proto-oncogene, the main driver of MTC, and its role in MTC. Alterations in DNA and histone methylations in MTC and *RET* transcription and miRNAs involved in MTC are discussed. Histone deacetylase (HDAC) inhibitors and miRNAs may hold potential as a therapeutic target in MTC.

The following two reviews are on parathyroid cancers. Parathyroid tumors are the second most common endocrine neoplasms and are most commonly benign, with parathyroid malignancy being rare. The first review by Silva-Figueroa and Perrier focuses on three epigenetic mechanisms; DNA methylation, regulation of gene expression by noncoding RNAs, particularly of miRNAs, and posttranslational histone methylation found in parathyroid tumors. Most miRNAs are down-regulated in parathyroid carcinomas whereas those in benign tumors tend to be upregulated, which may have diagnostic value. The second review by Guarnieri et al discusses DNA methylation separately of global genes and genes specifically involved in parathyroid pathophysiology and function, as well as the regulation of proteins involved in chromatin remodeling in parathyroid tumors.

The special issue is followed by the review on pituitary tumors by Ezzat et al and adrenocortical carcinoma by Jonker, et al. In pituitary tumors, epigenetic mutations are more frequent than genetic mutations, illustrating the importance of epigenetics in pituitary carcinogenesis. The review summarizes the emerging role of epigenetics in understanding pituitary tumors pathology, including DNA methylation, histone modification, and miRNAs. Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy with a poor prognosis. The review discusses the role of DNA methylation and histone modification in the pathology of ACC. Epigenetic dysregulation in ACC that may provide diagnostic value such as DNA methylation levels and the CpG island methylation phenotype (CIMP) is highlighted.

The last four reviews focus on neuroendocrine (NE) derived tumors. The first by Gundara et al discusses pancreatic NE tumors (PNET). This review provides a thorough summary for the current understanding of epigenetic regulations in PNET, from the point of DNA methylation, histone modification, and miRNAs. The second review by Björklund and Backman is on pheochromocytomas and paragangliomas (PPGLs), rare tumors arising from the medullae of the adrenal gland or paraganglia. The review provides general background of PPGLs and describes the mutations of genes involved in their development, including the Krebs cycle enzymes, succinate dehydrogenase (SDH) subunits. Mutations in SDH genes, their roles in epigenetic regulations in PPGLs and studies on miRNAs are discussed. The third review from the NE derived tumors by Li, et al is on multiple endocrine neoplasia type 1 (MEN1) syndrome, the condition manifested by pituitary, parathyroid and pancreatic islet adenomas. This review covers the background of gene *MEN1* and MENIN, the protein encoded by *MEN1*, *MEN1* mutation, mouse models for *Men1* loss, MENIN function, and its epigenetic regulation. The last of the four by Settas et al focuses on the Carney triad (CT), a

rare disease with at least three different tumor presentations, namely gastrointestinal stromal tumor (GIST), PGL and pulmonary chondroma, and the Carney-Stratakis syndrome (CSS), sharing the two of the tumor components of CT, namely GIST and PGL. Both CT and CSS are caused by deficiency of SDH enzymes. The review provides general background of CT and CSS and discussion on SDH gene mutations and the promoter DNA methylations.

While similar epigenetic modifications such as histone methylation/acetylation and/or the involvement of similar noncoding RNAs may be found in many cancers derived from different cell types and/or organs, a distinct pattern of combination of these modifications could be used to create an oncogenic signature of that cancer, which could provide useful diagnostic and prognostic markers and may even lead to the development of epigenetic drugs to improve treatment. While more research is required to reach to the point where a combinatory signature of genetic and epigenetic biomarkers can be routinely used for patient care, the recent advance in knowledge of the role of epigenetic modifications in endocrine tumors has already yielded a much deeper understanding of their tumor biology, demonstrating the potential for future improved outcomes in the clinic.

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