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Review

The Landscape of Single Nucleotide Polymorphisms in Papillary Thyroid Carcinoma

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Abstract. *Thyroid carcinoma represents a leading malignancy among those derived from human endocrine systems. It comprises a variety of different histological subtypes, including mainly papillary carcinoma, follicular carcinoma, anaplastic carcinoma, and medullar carcinoma. A broad spectrum of genetic imbalances, comprising gross chromosomal (polysomy/aneuploidy) and specific gene (mutations, amplifications, deletions) alterations, has been reported. Interestingly, the role of isolated, specific gene polymorphisms, especially of the single nucleotide polymorphism (SNP) type, in thyroid carcinoma is under investigation. SNPs are the most common genetic variations in the genome. The current molecular review focuses on the impact of specific SNPs on the biological behavior of papillary thyroid carcinoma in their carriers.*

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Among endocrine malignancies, thyroid carcinoma is considered the most prominent and frequent (1, 2). Although the exact etiology is under investigation, chronic exposure to ionizing radiation, environmental pollution substances, smoking, hormonal imbalances, and metabolic diseases (obesity) combined with sex (mainly females) have been implicated as critical factors for the onset and progression of the disease (3-5). Thyroid carcinoma demonstrates a variety of different histopathological subtypes, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma, anaplastic thyroid carcinoma, and medullar thyroid carcinoma (6-8). Concerning crucial genetic events detected in the corresponding epithelia, point mutations/amplification negatively affecting RAS proto-oncogene, GTPase/B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) genes, and specific rearrangements in ret proto-oncogene (*RET*) lead to an overactivation of signal transduction pathways, such as RAS/RAF and mitogen-activated protein kinase, respectively (9-13). Epigenetic alterations, including DNA methylation, histone modifications (acetylation), micro-RNAs (miR) imbalances and chromatin re-organization, are also observed in thyroid carcinomas (14, 15). Besides these genetic factors, specific micro-genetic signatures that occur familiarly or heritably (germline mutations) modify the genomic profile of future thyroid carcinoma patients (16, 17). Specific nucleotide

changes in different locations inside the genes can also be responsible for the overactivation or silencing of oncogenes and suppressor genes, respectively (18, 19). In fact, single nucleotide polymorphisms (SNPs) are the most common genetic variations in the genome (20). All of these changes are considered potentially critical for thyroid carcinoma susceptibility and development (21). In the current review, we focus on the impact of specific SNPs detected in PTCs on the biological behavior of tumor in their carriers.

Gene Polymorphisms: Mechanisms and Categories

Since 2002, Human Genome Decoding Project revealed a broad spectrum of gene-based variants due to extended sequencing screening (22, 23). In fact, DNA variants represent focal changes in the corresponding sequences by affecting their nucleotide composition or length (24, 25). Concerning the molecular categorization of them under the term of DNA ''polymorphisms'', *v*ariable number of tandem repeats (VNTRs), single nucleotide polymorphisms (SNPs), restriction fragment length polymorphism (RFLP), and simple tandem repeat (STRs) – microsatellites – have been recognized as prominent (26, 27). The main mechanisms that create these polymorphisms include point mutations/substitutions, deletions and insertions, as well as base-pair multiple repeats (28). Genetic polymorphisms occur randomly across the whole genome at a percentage of at least 1% in the population. The majority are characterized as silent, having no effect on the functionality of the corresponding genes. However, critical nucleotide changes can drive the gene sequence to become a 'malignant' genotype, which leads to the formation of a neoplastic and finally cancerous cell phenotype due to not only a genomic, but also a transcriptomically altered substrate (29, 30). They also lead to aberrant enzymatic activity and abnormal biochemical reactions in a variety of proteins that are involved in specific metabolic and signaling transduction pathways (31, 32). In contrast to this, genetic polymorphisms enhance the diversity of a human population, which is a mechanism of biological evolution regarding all species in ecosystems (33).

SNPs in PTC

Extensive molecular, especially microgenetic, analyses have revealed a broad spectrum of SNPs in subgroups of patients diagnosed with thyroid carcinoma. Interestingly, specific SNPs characterize thyroid carcinomas of different histological subtypes, including mainly PTC, follicular carcinoma, anaplastic carcinoma, and medullar carcinoma (34). Implementing a high-resolution melting technique, one study group reported multiple detection of SNPs produced by inherent/germline or sporadic mutations in a series of PTC, correlating or not with the biological behavior of the malignancies in the patients (35). Similarly, another genetic study focused on the analysis of a specific population (Egyptians) in order to identify the potential impact of new SNPs on patients with PTC. In fact, they examined the role of SNPs of glucagon-like peptide-1 receptor (*GLP1R*) as a potential risk factor for carcinoma development. Based on a combination of immunohistochemistry and real-time polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP), they observed that rs1042044 and rs6923761 SNPs in the *GLP1R* gene were most frequently detected in patients with PTC (36). Besides this, *GLP1R* overexpression correlated with lymph node metastasis and tumor stage was also associated with the presence of these SNPs. Another study group explored the role of the G allele of rs8101923 SNP in terminal differentiation-induced non-coding RNA genotyping of a series of PTCs by a PCR-RFLP protocol (37). They reported a higher risk of PTC in carriers of the rs8101923 G allele. Furthermore, another multi-SNP-based analysis in patients with PTC focused on the BTG anti-proliferation factor 3 (*BTG3), caspase 9 (CASP9)* and LDL-receptor related protein 4 (*LRP4)* genes. The study group observed that the concurrent presence of *BTG3* rs9977638 CC, *CASP9* rs884363 AC and *LRP4* rs898604 AG SNPs significantly increased the risk of PTC susceptibility (38). In contrast, other detected SNPs, including the rs9977638 TC and CC, rs884363 CC and rs898604 GG genotypes, were not implicated in the carcinogenetic process. Another study group analyzed the role of SNPs detected in BCL3 transcription coactivator (*BCL3*), arachidonate 5-lipoxygenase-activating protein (*ALOX5AP*), and ferroptosis-related genes apolipoprotein E (*APOE*) genes (39). They genotyped a variety of polymorphisms including rs429358/rs7412 in *APOE*, rs34698726/8100239 in *BCL3*, and rs4076128/ rs4073259 in *ALOX5AP*, respectively. Among them, rs429358-TC, rs34698726-TA/TT, and rs8100239-AT/AA, respectively, were correlated with a high risk of developing PTC, whereas the other genotypes seemed to provide a level of protection in their carriers (normal-control group). Focused on a target population, another study examined the impact of a specific SNP (rs9939609) affecting fat mass and obesity-associated protein (*FTO*) gene on a PTC series in Iranian patients (40). They also explored the role of potential genetic variations in exon 3 of serpin family A member 5 (*SERPINA5)* gene. Based on a PCR-RFLP assay, they found that *SERPINA5* rs6115G>A and rs6112T>C SNPs were potentially implicated in PTC onset, whereas *FTO* rs9939609 polymorphism was not associated with that risk.

Involvement of SNPs detected in apoptosis-related genes are also under investigation. Concerning the BCL2 apoptosis regulator-associated X, apoptosis regulator *(BAX)* gene, one study group reported a high prevalence in Brazilian patients with PTC due to a specific polymorphism (-248 G>A) that down-regulates *BAX* gene transcription leading to its reduced expression (41). Interestingly, the GG genotype seems to be a protective factor for the corresponding carriers. Similarly,

analyzing SNPs in a Chinese population, Hao *et al*. focused on a specific gene, pecanex 2 (*PCNXL2)* (42). The study group considered the rs10910660 SNP in *PCNXL2* to be a major microgenetic marker for increased PTC susceptibility. In contrast, another polymorphism (rs12129938) may potentially be a protective factor in the corresponding carriers. Analyzing the status of the X-ray repair cross-complementing group 1 (*XRCC1*) gene, which is implicated in DNA repair process, another study group reported a high prevalence of its Arg280His GA genotype in patients with differentiated PTCs (43). In contrast, PTC cases showed absence of the Arg280His AA genotype. Interestingly, the GA genotype was frequently identified in familial thyroid carcinoma cases. Analyzing specific short non-coding functional RNAs (miRNAs), Khan *et al*. focused on the role of *miRNA-149*-based SNPs and forkhead box E1 (*FOXE1)* gene (44). They concluded that SNP rs2292832 in *miRNA-149* was associated with a high risk of PTC onset, whereas rs3758249 in *FOXE1* demonstrated no correlation. Concerning new histotype variants of PTC, there is a specific SNP that is considered critical for its carriers. A molecular study applying PCR-RFLP in a series of micro-papillary PTCs reported that 1562C/T functional polymorphism is a crucial variant of matrix metalloproteinase-9 (*MMP9*) gene involved in this histological form of PTCs (45).

In conclusion, genetic polymorphisms occur randomly across the whole genome at a percentage of at least 1% in the human population overall. SNPs particularly implicated in thyroid carcinomas represent critical markers for identifying subgroups of patients based on molecular criteria. A broad spectrum of functional polymorphisms in a variety of genes affect their activity (overexpression in oncogenes/low expression in suppressors, respectively), driving normal epithelia to their neoplastic and progressively malignant phenotypes. Patients with PTC are carriers of many specific SNPs that modify the expression of the corresponding gene. Extensive SNP-based analyses in patients with PTC may provide useful molecular data for future targeted therapeutic approaches.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

ET, AC, ET, and VP: Design of the study, article writing; NM, DP, VR, and DP: Academic advisors; SK, GP, AM, SP, and PP: Collection and management of references and published data. All Authors read and approved the final article.

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