Thirty Years after the Chernobyl Accident: Molecular Genetic Mechanisms of Carcinogenesis of the Thyroid Gland

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Abstract—The review presents data on the basic molecular genetic mechanisms of formation of papillary thyroid carcinoma. The participation of ionizing radiation in the cancer pathogenesis was analyzed. The role of tumor microenvironment, inflammation, and nuclear transcription factor NF-κB in the initiation and development of papillary thyroid carcinoma was shown.

Keywords: thyroid gland, papillary thyroid carcinoma, oncogenes, ionizing radiation, inflammation, NF-κB
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INTRODUCTION

One of the most serious consequences of the Chernobyl accident is a significant increase in the incidence of thyroid cancer. According to the United Nations Scientific Committee on the Effects of Atomic Radiation, this increase was confirmed by several analytical studies, which demonstrated a statistically significant association between increased incidences of thyroid cancer and received individual doses of radioactive iodine released during the accident. Papillary thyroid carcinoma is the only type of malignant tumors in whose pathogenesis the role of ionizing radiation (IR) was established.

Thyroid cancer is the most common and well-studied type of endocrine tumors. The increased incidence rate of papillary thyroid carcinoma after radiation exposure with radioactive iodine provides an opportunity to study the molecular mechanisms of the pathogenesis of this type of cancer. For comprehensive studies, Chernobyl Tissue Bank (CTB, www.chemobyltissuebank.com) was created at the Institute of Endocrinology and Metabolism, National Academy of Medical Sciences of Ukraine, which has provided a systematic collection of postoperative thyroid tumors from among residents from Ukrainian and Russian regions contaminated by radioactive materials since 1998.

The emergence and development of malignant tumors of the thyroid gland is associated with mutations, deletions, and rearrangements in several important genes—RET, B-Raf, Ras [1]—which are the part of the MAPK cascade controlling cell division. Due to the impaired functions of these genes, this signaling cascade becomes independent of growth factors and constitutively active, which leads to uncontrolled proliferation. In addition, genes encoding c-Met, c-Myc, PTEN, TRK, NF-κB and other factors may be involved in thyroid carcinogenesis [2].

REARRANGEMENTS OF RET/PTC

The appearance of papillary thyroid carcinoma (PTC) is primarily associated with the chromosomal rearrangement of the receptor (nerve growth factor receptor) tyrosine kinase gene RET, as a result of which the promoter and the N-terminal domain of other genes are connected to the C-terminal domain RET (intracellular TK domain). All breakage points for the rearrangement are located within intron 11 of the gene on chromosome 10q11.2. Rearrangements are specific only to PTC and are frequently observed in small carcinomas, that confirms their involvement in early carcinogenesis [3, 4].

The first studies of tumors associated with the release of radioactive materials as a result of the Chernobyl accident revealed a very high percentage of RET-rearrangements (87%), mainly RET/PTC3 (58%). It was suggested that such rearrangements can be a marker of tumors induced by ionizing radiation [5]. Later studies have found that this may be due to the age of patients, since RET/PTC rearrangement with a similar incidence rate and prevalence were observed in sporadic papillary carcinomas of children and young patients [6]. Consequently, these data may reflect the association between RET/PTC3 rearrangements and the age of the patient at diagnosis, as well as the morphology of tumors to a higher extent than with radiation exposure. Furthermore, RET/PTC expression level varies in carcinomas as a result of the nonuniform distribution of the oncogene within a particular...
tumors [7]. The latter fact suggests that such rearrangements cannot be the triggering event and, therefore, the high frequency of this rearrangement is not directly related to the impact of IR. It should be noted that, with the increase of the latency period (time between exposure and operation), the percentage of RET/PTC3 was reduced to 35 and it was in alignment with the number of RET/PTC1 [8].

The consequence of the rearrangement is the formation of chimeric forms of the receptor with constitutively active tyrosine kinase. Seventeen rearrangements are currently known, but the most prevalent are RET/PTC1 and RET/PTC3 [4]. RET/PTC1 forms by paracentric inversion of the long arm of chromosome 10, which leads to the fusion of the tyrosine kinase gene with H4 gene (CCDC6, D10S170). RET/PTC3 results from intrachromosomal rearrangement, of which with the fusion with the NCOA4 (RFG, ELE1) gene occurs. Due to these rearrangements, the loss of extracellular and transmembrane parts of the receptor occurs and such truncated form of the receptor transfers into the cytosol. Promoter of the gene from the 5'-end, controlling the part of RET gene, provides the expression of the chimeric gene. For involvement of the chimeric product in signal processes, dimerization is required. The dimerization provided by domain from N-terminal fragment of the partner gene containing elements of coiled helix [1, 9]. The next stage of the activation of tyrosine kinase is the autophosphorylation of specific tyrosine residues, enhancing the interaction of the receptor with the effector proteins. There are three types of RET proteins, formed as a result of alternative splicing—RET9, RET43, and RET51. They are characterized by the same amino acid sequence up to the 1063rd residue and C-terminal sequence next to it [1, 9]. All phosphorylation sites in RET are common for these variants and serve as sites providing interaction with signaling proteins. Phosphorylation of tyrosine residues pY905 provides interaction with adapter proteins Grb7 and Grb10, containing SH2 domain; pY1015 residue promotes association with phospholipase C and the subsequent activation of protein kinase C and pY1062 promotes association with Shc and Frs2. Phosphorylation of tyrosine residue pY1062 activates signaling cascade the Shc-Ras-Raf-MEK-ERK, which initiates DNA synthesis and cell division. The rate of tumor formation is reduced when tyrosine pY905, pY1015, pY1062 was replaced by phenylala-nine, but most significant reduction was detected when tyrosine pY905 was replaced. This fact emphasizes the role of Grb10 and Grb7 adapter proteins in the transformation of thyroid cells, but, at the same time, it shows the importance of all three signaling pathways [1, 9].

In addition to chromosome 10, other chromosomal breakpoints at 1p32-36, 1p11-13, 1q22, 3p25-26, and 7q32-36 and deletions at 11q were identified, but their importance in the pathogenesis of PTC remains unclear [4].

A comparison of the genetic material of children and adults, as well as RET/PTC (+) and RET/PTC (−) cases, showed that deletions occur with a higher frequency than amplification. This is easily explained, since radiation exposure induces chromosome breaks, which may result in deletions, translocations, and inversions. Deletions were found predominantly at chromosomes 1, 6, 7, 9, 10, 11, 12, 13, 16, 19, 20, 22, and amplifications were found at chromosomes 10, 12, 19, 20, 21. RET/PTC (+) cases were significantly different for the site in chromosome 1p, which was absent in adults but not in children. Moreover, RET/PTC (+) cases were significantly different from RET/PTC (−) cases by deletions at chromosomes 1p, 7p, 9, 13q and amplification at chromosomes 3q, 4p, 12q, 21q [10].

These aberrations are more specific for sporadic carcinoma of the thyroid than for IR-induced, and cannot be considered as a specific biomarker of exposure. The study of gene spectrum in changed regions revealed 31 candidate genes involved in tumor progression and 21 tumor suppressor genes specifically mapped in remote chromosomal regions. The identified genes are involved in signaling pathways associated with apoptosis, interleukin-27, angiopeo-tin receptor, and PI3K/MAPK signaling cascades. These findings reflect the heterogeneity of the post-Chernobyl PTC, which suggest different pathways of tumor development [4, 11].

Our studies of sporadic PTC showed that gene copy-number alterations (CNA) were detected with low frequency. Several amplifications were found at chromosome 22 as well as at chromosomes 1 and 12q. Another, less frequent amplification was observed at chromosomes 5p, 9q, 16p, and 21q. Deletions were identified at chromosomes 21q and 14q [12].

There is no direct evidence that the number of chromosomal aberrations in the IR-induced PTC was higher than in the sporadic PTC. Nevertheless, some aberrations are more common after radiation exposure. In particular, changes associated with the tumor aggressiveness in young patients were detected in chromosome 22 of post-Chernobyl patients [13]. The gene expression in these sites was compared with sporadic tumors. It was shown that the expression of 41 genes was increased in the post-Chernobyl pediatric PTC but not in sporadic PTC. The most significant increase was observed for the following genes: TESC, PDZRN4, TRAA/TRA, GABBR2, CA12, MPZL2, SCG5, PDZKI1, AMIG02, NOVA2, and TNIK. The suppression of the expression of 24 genes, especially significant for APTSS2, PDLM3, BEX1, ANK2, SORBS2, PPARGCIA, MTIM, CTGRF, LYVE1, and OGDHL was also observed [4]. Probably, in the future, these genes may be used as markers of radiation exposure.

In these studies, biomarkers specific to radiation exposure could not be reliably identified. This may be partially due to the design of studies and the need to consider a number of different factors during compar-