Paper published in *Journal of Thyroid Disorders & Therapy*[§]

"Thyroid Cancer: Molecular Characteristics of Radiation-Associated Papillary Thyroid Cancer, with a Special Reference to Atomic Radiation Exposure"

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J Thyroid Disorders & Therapy 2015 (May); 4(2):1–7
(doi: 10.4172/2167-7948.1000183)

Introduction

It is known that thyroid cancer is radiosensitive and that the onset thereof is associated with malfunction of specific genes. This review will focus on the initiating gene alterations in the development of papillary thyroid cancer (PTC) among individuals exposed to radiation. We considered childhood thyroid cancers in the Chernobyl accident and adult-onset PTCs among A-bomb survivors, addressing the association of those gene alterations with radiation exposure.

Explanation

1. Mitogen-Activated Protein Kinase (MAPK) Signaling Pathway

The MAPK signaling pathway*, one of many intracellular signaling pathways, is activated by an external stimulus and conveys a cell proliferation signal to the cell nucleus. Such signaling is properly controlled in normal conditions. However, in the case of PTC, it is believed that the MAPK signaling pathway is constitutively activated in an early stage of the cancer's development, contributing to the carcinogenesis of thyroid cells. In PTC, rearrangement of *RET** and *NTRK1** genes and point mutations of the *BRAF** and *RAS** genes are widely recognized as gene alterations that cause constitutive activation of the MAPK signaling pathway. Generally, one or the other of those gene alterations is found in individual PTC cases. And, since multiple alterations are rarely found in a single PTC case, those gene alterations are believed to occur in a mutually exclusive manner.

*MAPK signaling pathway: MAPK and other signaling pathways represent a mechanism by which a protein kinase phosphorylates another protein kinase(s), a process that activates downstream signaling cascades.

**RET* rearrangement: Chromosomal rearrangements cause a fusion between the C-terminal side of the *RET* gene, which includes the kinase domain (DNA region that encodes for kinase proteins), and the N-terminal side of a partner gene to generate a chimeric fusion gene composed of parts from two different genes. Researchers believe this duplex-constituting chimeric fusion gene is constitutively activated in PTC and plays a

role in PTC onset.

*_NTRK1_ rearrangement: Chromosomal rearrangements cause a fusion between the C-terminal side of the _NTRK1_ gene, including the kinase domain, and the N-terminal side of a partner gene to generate a chimeric fusion gene. Researchers believe this duplex-constituting chimeric fusion gene is constitutively activated in PTC and plays a role in PTC onset.

*_BRAF_ point mutation: This mutation involves the substitution of thymine with adenine at position 1799 of the _BRAF_ gene, which results in a valine-to-glutamate substitution at amino acid 600. Researchers believe that mutated _BRAF_ genes are constitutively activated and play a role in the onset of certain cancers, including thyroid cancer and melanoma.

*_RAS_ point mutation: This amino acid substitution is caused by single base changes at codons 12, 13, and 61 of the _RAS_ gene. Mutated _RAS_ genes are believed to become constitutively activated and play a role in the onset of various cancers.

2. Characteristics of gene alterations in sporadic PTC

Occurrence of point mutations, especially BRAF point mutations, was evident in sporadic (radiation-irrelevant), adult-onset PTCs. RET rearrangements were found in a portion of these PTCs. PTCs with NTRKI rearrangements are known to be extremely rare.

3. Characteristics of gene alterations in post-Chernobyl childhood thyroid cancers

A majority of post-Chernobyl childhood thyroid cancers are papillary adenocarcinomas. It is well known that childhood PTCs consist mainly of the following: those with typical papillary patterns; those with solid patterns (tumor tissues that do not have either follicular or papillary patterns but are rather packed closely together, showing solid, insular, or trabecular growth patterns); those with follicular patterns (tumor tissues that show single-layer glandular growth patterns); or those with a mixture of the aforementioned histological patterns. In terms of gene alterations, gene rearrangements (especially RET/PTC3 rearrangements*) were observed frequently, instead of the RET/PTC1 rearrangements* often found in sporadic PTC. Furthermore, whereas BRAF rearrangements were not observed in sporadic PTCs, they were detected in a portion of the post-Chernobyl childhood PTCs.

*_RET/PTC1_ rearrangement: one type of _RET_ rearrangement.
*_RET/PTC3_ rearrangement: another type of _RET_ rearrangement.

4. Characteristics of gene alterations in adult-onset PTCs among A-bomb survivors

A majority of adult-onset PTCs among A-bomb survivors display typical papillary patterns, that is, growth patterns of tumor cells that include various levels of papillary projection into the glandular (follicular) cavity. The histologies of these adult-onset PTCs are distinctly different from those in post-Chernobyl childhood PTCs. The frequency of RET/PTC rearrangements were increased in PTCs among A-bomb survivors, compared to the rate in PTCs among those who were not exposed. In contrast, an extremely high frequency of BRAF point mutation was observed in PTCs among the non-exposed, while the rate of these mutations was not as high in PTCs among A-bomb survivors. Furthermore, researchers observed a high frequency of RET rearrangements in PTC cases exposed to relatively high radiation doses (0.5 Gy or more), while the frequency of BRAF point mutations decreased markedly. In post-Chernobyl childhood PTCs, RET/PTC3 rearrangement was a major gene alteration, while RET/PTC1 rearrangement was more frequent in the adult-onset PTCs among A-bomb survivors. The BRAF rearrangements observed in post-Chernobyl childhood PTCs were not detected in A-bomb survivors' adult-onset PTCs. Data also suggested that the frequency of RET/PTC rearrangements in PTCs among A-bomb survivors exposed at a young age was higher than that for those exposed in adulthood.

Consequently, this research seems to demonstrate that gene rearrangements thought to be associated with radiation, especially RET/PTC1 rearrangements, were strongly involved in the development of adult-onset PTC among A-bomb survivors exposed to high radiation doses in childhood.

The Radiation Effects Research Foundation has studied A-bomb survivors and their offspring in Hiroshima and Nagasaki for more than 60 years. RERF's research achievements are considered the principal scientific basis for radiation risk assessment by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and for recommendations regarding radiation protection standards by the International Commission on Radiological Protection (ICRP). RERF expresses its profound gratitude to the A-bomb survivors and survivors' offspring for their cooperation in our studies.