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

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Abstract

Among atomic-bomb (A-bomb) survivors of Hiroshima and , incidence of thyroid cancer significantly increased after exposure to nuclear radiation. This review will focus on the initiating gene alterations in the development of adult-onset papillary thyroid cancer (PTC) among A-bomb survivors. The effects of A-bomb radiation on chromosomal rearrangements (*RET and NTRK1 rearrangements*) and point mutations (*BRAF* and *RAS mutations*) after exposure were different. In contrast to PTC cases with point mutations, PTC cases with chromosomal rearrangements were observed more frequently among those exposed to high radiation doses compared to low doses, and these cases developed cancer earlier after exposure than did cases with point mutations. Interestingly, PTC cases with non-detected gene alterations were found more frequently among patients who were exposed to high radiation doses and who developed cancer earlier after radiation exposure than did the cases with *BRAF* point mutation. This suggests that heretofore non-detected gene alterations may also be involved in adult-onset PTC among A-bomb survivors.

Keywords Mutations; Anaplastic lymphoma kinase; Nuclear radiation; Thyroid cancer

Introduction

Thyroid cancer is one of the malignancies most closely associated with radiation exposure. External radiation exposure is related to papillary thyroid cancer (PTC) based on data from atomic-bomb (A-bomb) survivors in Hiroshima and , and also among people exposed to medical radiation sources. Epidemiological studies on the Life Span Study (LSS) cohort of A-bomb survivors have revealed that the excess relative risk (ERR) of thyroid cancer was significantly high and that it linearly increased with radiation dose [1,2]. The patients who received external radiation therapy for either benign or malignant diseases e.g. tinea capitis (Israel), enlarged thymus gland, benign head and neck conditions, lymphoid hyperplasia, childhood cancer, and cervical cancer (USA)showed an increased incidence of thyroid cancer [3,4]. Those radiation-associated thyroid cancers also showed a tendency toward a higher ERR associated with younger age at the time of exposure [1,4]. In addition, cohort studies on subjects who were exposed to ionizing radiation after the Chernobyl nuclear accident in 1986 indicate a very strong association between radiation exposure in childhood or adolescence and the development of thyroid cancer in heavily contaminated areas in Belarus, Northern Ukraine, and [5-7].

Histologically, thyroid cancer among cohorts exposed externally or internally to ionizing radiation is mainly papillary type much like sporadic thyroid cancer. However, there are differences in subtypes of PTC between A-bomb survivors and post-Chernobyl children. Among A-bomb survivors, the thyroid cancers were largely conventional papillary in nature [8], which is also the case for sporadic thyroid cancer in the general Japanese population. In addition, adult-onset PTC among A-bomb survivors included infrequent follicular variants and no solid variants, which are subtypes of PTC. For children internally exposed in Chernobyl, however, malignant thyroid tumors are principally PTC, and include frequent follicular variants and solid variants [9-11], but these morphologic characteristics may have been related to low dietary iodine levels and childhood cancer types [12].

Radiation types and PTC Gene Alterations

Both sporadic PTC and radiation-associated PTC are characterized by the constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway. The major factors involved in the activation of this signaling pathway are *RET/PTC* rearrangements and *BRAF* point mutation [13-17]. It is well known that *RET/PTC* rearrangements were frequently found in PTC among children from areas contaminated by [11,14,18,19]. However, since sporadic childhood PTC with no radiation history shows a high incidence of *RET/PTC* rearrangements [11,14,20-22], it is difficult to distinguish whether the high prevalence of *RET/PTC* rearrangements in PTC from post-Chernobyl children is due to internal radiation exposure or childhood cancer. On the other hand, some reports have found a higher frequency of *RET/PTC* rearrangements in PTC from adult patients who had received external radiotherapy than in those without any radiation history [23,24]; other reports have disputed such findings [22,25]. As seen above, radiation effects on molecular events at an early stage of papillary thyroid carcinogenesis remain undefined. This ambiguity may be due to the different radiation conditions, namely whether internal exposure or external exposure, and whether single exposure or repeated exposures. In addition, radiation effects may differ depending on age at exposure and/or age at onset of PTC. Such differences make comparative analysis difficult and prevent the deepening of our understanding of radiation effects on initiating molecular events in PTC. On the other hand, A-bomb survivors were exposed externally to A-bomb radiation. Cases of PTC developing among LSS cohort members of A-bomb survivors are derived from adult patients with known radiation exposure. Therefore, we believe

that adult-onset PTC among LSS cohort members is a good model for examination of the relationship between radiation dose and gene alterations at early stages of papillary thyroid carcinogenesis. This review will focus on characteristics of early molecular events in pathogenesis of adult-onset PTC among A-bomb survivors (Table 1).

Radiation-associated PTC		Chromosomal rearrangements			Point mutations	
	A-bomb survivors (Our study) Non-exposed	RET/PTC 4%	TRK &TRK-T1,2,3 0%	AKAP9-BRAF 0%	BRAFV600E 70%	K, H, N-RAS 4%
	Exposed	18%	2%	0%	56%	0%
	Post-Chernobyl	34-87% [11,14,18,19, 27,52, 53,66,67] [11,14,18,19, 27,52, 53,66,67]	3% [19]	11%* [28]	0-20% [27,28,61,65-67]	0% [52,54,65,73,74]
	Radiotherapy	51-84% [22-25]	19% [56]		4% [68]	40-50% [54,75,76]
Sporadic PTC	Adult-onset	3-61% [13,14,16,17, 20,26, 51,54,55,64]	6-12% [20,26,56,57]	1% [28]	28-83% [15-17,26,28, 61-64,67]	0-58% [16,17,54,64,70, 71,76]
		Childhood	30-71% [11,14,20-22,50,66]	0-11% [20,57]	0-6% [65-67]	0-7% [65,72]

Table 1: Gene alterations in radiation-associated and sporadic PTC (*detected only in PTC developed 5-6 years after radiation exposure).

Constitutive Activation of MAPK Signaling Pathway

A major early molecular event in the development of PTC is believed to be the constitutive activation of the MAPK signaling pathway, which is caused by gene alterations including rearrangement of *RET, NTRK,* and *BRAF* genes, and point mutation of BRAF and RAS genes. Furthermore, those gene alterations are well known to occur in a mutually exclusive manner, and they were found in more than 70% of PTC [16,17,26-28]. Specific activation of *RET/PTC1* or *RET/PTC3* (types of RET rearrangements), *TRK-T1* (one type of *NTRK1* rearrangements), c-*Ha-Ras*, or BRAFV600E in transgenic mice produced thyroid cancer with characteristic papillary features [29-34]. In addition, a part of microscopic PTC (microcarinoma) is known to harbor *RET/PTC* rearrangements, $BRAF^{V600E}$ point mutation, or *NTRK1* rearrangement [35-41], which suggests that a single alteration of these genes involved in the MAPK signaling pathway may be the most important initiating event and may play a causative role in the pathogenesis of PTC. In addition to the MAPK signaling pathway, activation of the phophatydylinositol 3-kinase (PI3K)/AKT pathway through alterations of *PIK3CA* and *PTEN* genes was reported to be implicated in the development of not only follicular carcinoma but also some PTC [42-45].

Chromosomal Rearrangements

Gene rearrangements reported so far in PTC are *RET/PTC, NTRK1*, and *BRAF/AKAP9* rearrangements. Among those, *RET* rearrangements are the most common, especially in PTC developed in subjects with a radiation exposure history, which is supported by several studies indicating the induction of *RET/PTC1* and *RET/PTC3* rearrangements in human thyroid cells by X-ray or γ-ray irradiation, both in vitro and in vivo, as tissue transplants in severe combined immunodeficient mice [46-49].

RET/PTC rearrangements

RET/PTC rearrangements are formed by the fusion of part of the intracellular tyrosine kinase domain with the 5'-end of other genes. *RET/PTC* fusion protein is constitutively expressed by promoter activity of a partner gene, and is then activated by constitutive dimerization. To date, at least 15 different types of *RET/PTC* rearrangements resulting from *RET* fusion to 12 various partner genes have been isolated, of which *RET/PTC1* and *RET/PTC3* are by far the most common [14,50]. *RET/PTC* rearrangements have frequently been found in childhood PTC with and without a radiation exposure history [11,14,18,19-22,51-53]. In post-Chernobyl children with PTC, *RET/PTC3* rearrangement seemed to be strongly associated with solid-variant PTC and/or with a short latent period after exposure, while *RET/PTC1* rearrangement was mainly found in conventional PTC with a long latent period after exposure [11,18,19,53]. In contrast, the frequency of *RET/PTC* rearrangements in adult-onset PTC in the general population was not as high as that in childhood PTC [13,14,54,55] (Table 1). In PTC from patients exposed to therapeutic irradiation, the frequency of *RET/PTC* rearrangements was higher than in PTC from non-exposed patients [23,24], although several papers have reported that no significant difference was detected in the frequency of *RET/PTC* rearrangement for adult-onset PTC with and without a history of radiotherapy [22,25].

NTRK1 and BRAF rearrangements

Rearrangements of the neurotrophic receptor-tyrosine kinase *NTRK* have been observed in a small number of PTC cases in the general population [20,56,57] (Table 1). *NTRK1* rearrangements were also found in a small number of PTC from post-Chernobyl children [19] and patients with a radiotherapy history [56]. Rearrangement of the *BRAF* gene (*AKAP9-BRAF*) was identified in post-Chernobyl childhood PTC [28]: *AKAP9-BRAF* rearrangement was reported to be related to post-Chernobyl PTC that developed shortly after exposure [28].

Point Mutations

BRAF point mutation

Another major early event in the development of PTC is point mutation of the *BRAF* gene. The *BRAF* point mutation identified in PTC so far is almost exclusively in the thymine-to-adenine transversion at nucleotide 1799, resulting in the substitution of glutamate for valine at residue 600 (V600E). The V600E substitution is thought to convert BRAF inactive conformation into its active form by disrupting the residue-residue interaction between the activation loop and the ATP binding site [58-60]. In adult-onset PTC general populations, $BRAF^{V600E}$ mutation has so far been reported as occurring at a high frequency [61-64], although very low frequencies of $BRAF^{V600E}$ mutation were found in PTC among children and adolescents with no radiation history [65-67] (Table 1). In addition, radiation-associated PTC showed a very low frequency of $BRAF^{V600E}$ mutation regardless of the age of patients [27,28,65-68] (Table 1).

RAS point mutations

The RAS point mutations are not restricted to PTC, unlike *RET/PTC* rearrangements and *BRAF* point mutation, and have been found with a wide range of frequency in follicular adenomas, follicular thyroid carcinomas (FTC), PTC, and anaplastic carcinomas (ATC). The prevalence of *RAS* point mutations in PTC among the general populations is not as high as that in FTC and ATC [54,64,69-72]. Furthermore, no RAS point mutations (codons 12, 13, 61) have been observed in post-Chernobyl children PTC [65,73,74]. Some PTC from patients with a radiotherapy history are reported to have *RAS* mutations [75,76] (Table 1).

Gene Alterations in A-bomb Survivors

To clarify the relationship between radiation exposure and development of PTC, we attempted to identify preferentially occurring gene alterations in radiation-associated PTC. Toward this end, we analyzed *RET/PTC, NTRK1*, and *BRAF* rearrangements and *BRAF* and *RAS* point mutations in 73 cases of adult-onset PTC (52 exposed patients and 21 non-exposed patients) among A-bomb survivors. The gene alterations detected in the exposed PTC cases were mutually exclusive, although one non-exposed PTC case had both *RET/PTC1* rearrangement and *BRAF* point mutation.

Chromosomal rearrangements in PTC among A-bomb survivors

Only one non-exposed PTC case showed *RET/PTC1* rearrangement, but among exposed PTC cases, *RET/PTC* rearrangements and a *NTRK1* rearrangement were detected in 11 PTC cases and one case, respectively. In addition to eight PTC cases with only *RET/PTC1* and one with both *RET/PTC1* and *RET/PTC3*, a novel type of *RET/PTC* rearrangement as well as a rare *RET/PTC8* was identified in A-bomb survivors exposed to high radiation doses (1,500 mGy and 2,000 mGy, respectively) [77,78]. The frequency of chromosomal rearrangements composed of *RET* and *NTRK1* rearrangements among exposed subjects was higher than among non-exposed patients, although the significance of this difference was only marginal (Fisher's exact test, P=0.09) (Figure 1A). And, no *AKAP9-BRAF* rearrangement was detected in adult-onset PTC among A-bomb survivors [77].

Point mutations in PTC among A-bomb survivors

Among three RAS genes (codons 12, 13 and 61), no RAS point mutations were detected in adult-onset PTC of patients exposed to A-bomb radiation, although only one PTC case among non-exposed patients showed a K-RAS mutation (codon 61). $BRAF^{V600E}$ point mutation was detected in a large number of both non-exposed and exposed PTC cases (Table 1) [77,79], but the frequency of point mutations consisting of $BRAF^{V600E}$ and RAS point mutation in exposed PTC cases was lower than in non-exposed PTC cases (Figure 1A).

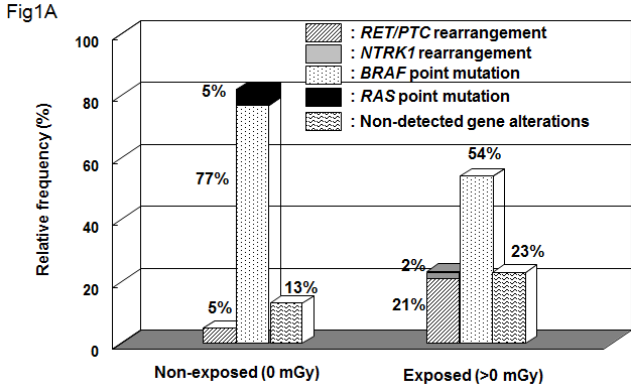

Figure 1A: Chromosomal rearragements.

Relationship between radiation dose and gene alteration

The associations between radiation dose, years elapsed since A-bomb radiation exposure, and age at the time of A-bombing were evaluated. When PTC cases were divided into three groups based on chromosomal rearrangements, point mutations, and non-detected gene alterations, radiation dose (three categories: low, 0+ ~100 mGy; medium, 100+ ~500; high, 500+ ~ 2,760) responses of these groups differed. "Non-detected gene alterations" indicates that alterations for *RET, NTRK1, BRAF* and *RAS* genes could not be detected. Therefore PTC with non-detected gene alterations is thought to carry gene alterations other than those of *RET, NTRK1, BRAF*, and *RAS* genes. The frequency of chromosomal rearrangements in exposed PTC cases increased with increasing radiation dose. The rearrangements were notably more frequent in PTC cases exposed to more than 500 mGy (Figure 1B). The frequency of point mutations in adult-onset PTC among A-bomb survivors decreased with increasing radiation dose, and was especially infrequent for radiation dose more than 500 mGy (Figure 1B). Interestingly, non-detected gene alterations tended to be

more frequent with increased radiation dose (Figure 1B), suggesting that in addition to *RET* and *NTRK1* rearrangements, radiation-associated gene alterations other than rearrangements of *RET, NTRK1,* and *BRAF* might be involved in adult-onset PTC cases among A-bomb survivors exposed to high radiation doses.

Relationship between years elapsed since exposure and gene alterations

Three groups also showed different responses to time from exposure to diagnosis (three categories: short, 11 ~ 20 years; medium, 21 ~30; long, 31 ~ 46) as shown in Figure 2A. Point mutations increased with increased time since exposure, while non-detected gene alterations tended to decrease with increased time since exposure (Figure 2A). On the other hand, chromosomal rearrangements showed a peak around 21-30 years after exposure (Figure 2A). Furthermore, PTC cases with chromosomal rearrangements or non-detected gene alterations developed cancer sooner following exposure than did the cases with point mutations (modified from ref. 77). No *AKAP9-BRAF* rearrangement was detected in adult-onset PTC among A-bomb survivors exposed to high radiation doses. This might be due to the difference in the time from exposure to diagnosis between post-Chernobyl childhood and among A-bomb survivors' PTC (since all tissue specimens were derived from PTC that developed more than 10 years since A-bomb radiation exposure). Therefore, it remains unclear whether *AKAP9-BRAF* rearrangement is involved in adult-onset radiation-associated papillary thyroid carcinogenesis.

Relationship between age at the time of bombing and gene alteration

Groups with different types of gene alterations also revealed different responses based on age at the time of the bombings (age ATB) (three categories: childhood/adolescence, 0 ~ 19; young adult, 20~39; middle age, 40~47), as shown in Figure 2B. Prevalence of PTC cases with point mutations increased with age ATB, while chromosomal rearrangements showed a small decrease with age ATB (Figure 2B). However, the PTC cases with chromosomal rearrangements showed younger age ATB than did those with point mutations (modified from ref. 77). PTC cases with no detected gene alterations showed no association with age ATB.

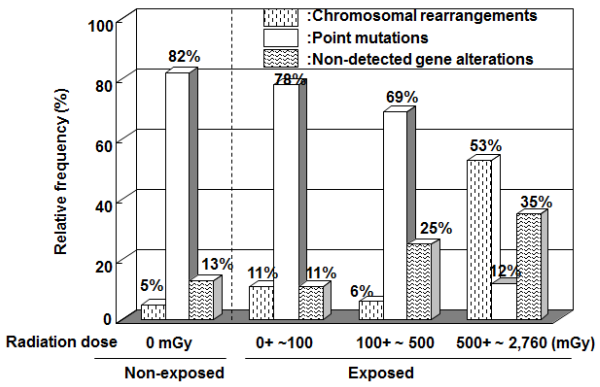

Figure 1B: Chromosomal rearragements.

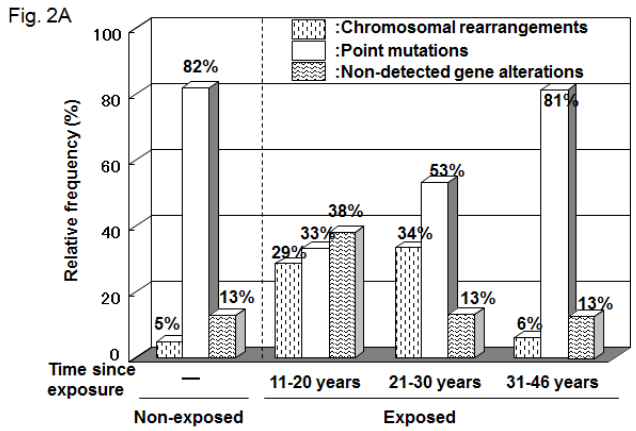

Figure 2A: Chromosomal rearrangements showed a peak.

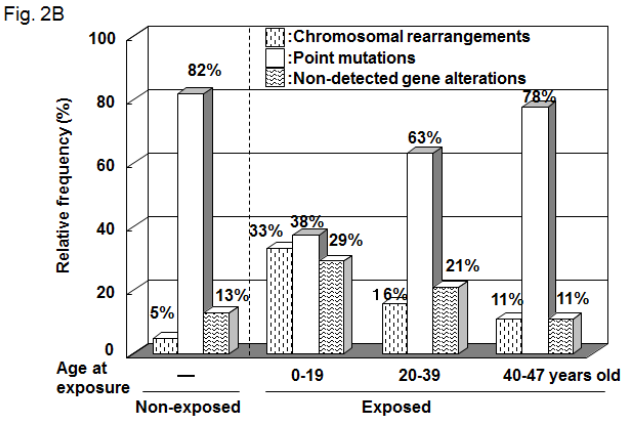

Figure 2B: Different types of gene alterations.

Implications from findings in PTC among A-bomb survivors

Thus, more than 70% of all radiation-exposed PTC cases with *RET/PTC* rearrangements were in the group with >500 mGy, and a *RET/PTC8* rearrangement and a novel type of RET/PTC rearrangement were also identified besides *RET/PTC1* in these high-radiation dose-exposed cases [77]. One *NTRK1* rearrangement was also found in a survivor with a high radiation dose. Interestingly, many *RET/PTC* rearrangements were observed in PTC cases having a relatively short time since radiation exposure. Those findings strongly suggest that chromosomal rearrangements, especially *RET/PTC* rearrangements that were possibly caused by radiation exposure, are strongly involved in adult-onset radiation-associated papillary thyroid carcinogenesis.

All initiating gene alterations occurring in PTC cannot be categorized with only the rearrangements of *RET, NTRK1,* and *BRAF* genes, and point mutations of *BRAF* and *RAS* genes. Interestingly, adult-onset PTC without any gene alteration of *RET, NTRK1, BRAF,* or *RAS* among A-bomb survivors was marginally more frequent in cases who were exposed to high radiation dose (>500 mGy) and in the cases with shorter time since exposure (<20 years), compared with

non-exposed cases. Those results raise the possibility that there are radiation-related gene alterations other than rearrangements of *RET, NTRK1*, and *BRAF* genes in radiation-associated PTC. To understand the mechanism of adult-onset radiation-associated PTC, it is essential to identify gene alterations occurring in such PTC cases. Figure 3 indicates a model of initiating molecular events in radiation-associated adult-onset papillary thyroid carcinogenesis in A-bomb survivors exposed to high radiation doses. Recently, echinoderm microtubule-associated protein-like 4 *(EML4)*- anaplastic lymphoma kinase *(ALK)* fusion gene was discovered in some PTC cases among atomic bomb survivors that carried no alterations in *RET, NTRK1, BRAF,* and *RAS* genes [80].

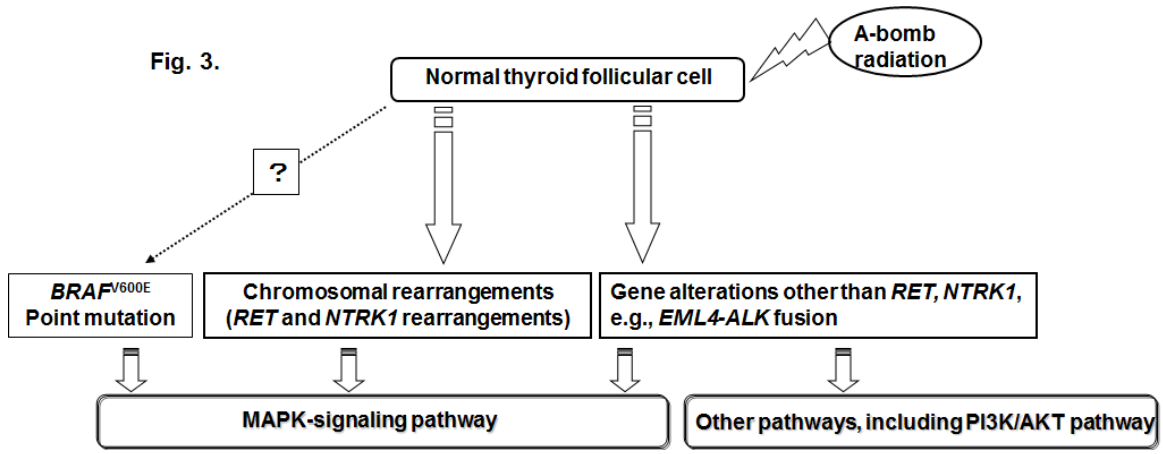

Figure 3: Molecular events in radiation-associated adult-onset papillary thyroid carcinogénesis.

Future Prospects

The molecular oncology study of PTC in A-bomb survivors suggests that, in addition to the important roles of *RET/PTC* and *NTRK1* rearrangements in adult-onset radiation-associated papillary thyroid carcinogenesis, gene alterations other than *RET/PTC, NTRK1* and *AKAP9-BRAF* rearrangements are involved in development of some radiation-associated PTC of adult patients who were exposed to high radiation or whose cancer developed in a relatively short time since exposure. *EML4-ALK* fusion gene may be one of candidates. Identification of gene alterations in PTC besides *RET, NTRK1, BRAF,* and *RAS* genes is crucial for understanding the mechanisms of the development of PTC, not only among A-bomb survivors but also for other adult patients who were externally exposed to radiation. If the molecular analysis of adult-onset PTC in patients exposed in childhood to Chernobyl is conducted and integrated with the analyses of A-bomb survivors' PTC, the mechanism of radiation-associated adult-onset papillary thyroid carcinogenesis should become clearer.

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