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“A Novel *RET* Rearrangement (*ACBD5/RET*) by Pericentric Inversion, inv(10)(p12.1;q11.2), in Papillary Thyroid Cancer from an Atomic-bomb Survivor Exposed to High-dose Radiation”

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Study Findings

Our analysis has shown that a novel type of *RET* rearrangement (*ACBD5-RET* fusion gene) that was identified in papillary thyroid cancer (PTC) cells of an atomic bomb survivor constitutively activates the MAPK-signaling pathway* and can lead to the development of tumors, as is the case with other types of *RET* fusion genes.

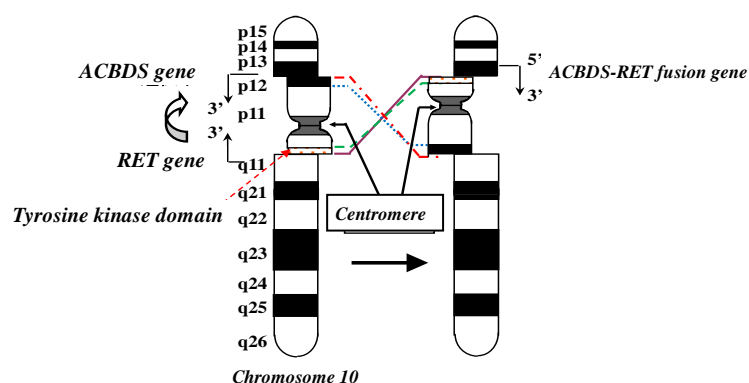
*The term “signaling pathways” denotes the mechanism by which protein kinases phosphorylate (in other words, activate) other protein kinases and cascade signals downstream. The MAPK-signaling pathway is one such pathway.

Explanation

Through chromosomal inversion or translocation, radiation-related PTC cases such as adult PTC among A-bomb survivors and childhood PTC that developed after the Chernobyl nuclear accident often exhibit rearranged *RET* genes, that is fusion genes such as *CCDC6-RET* and *NCOA4-RET*, between the *tyrosine kinase domain* of the *RET* gene and other gene sites. These fusion genes are believed to be significantly involved in papillary thyroid carcinogenesis.

We analyzed the structure and function of a novel *RET* rearrangement (*ACBD5-RET* fusion gene) found in the PTC of an A-bomb survivor exposed to high-dose radiation.

Figure (Inversion)



This figure shows the *ACBD5-RET* fusion gene formed by a pericentric inversion. Inversions occur when a chromosome breaks in two places and the resulting fragment of DNA is inverted and re-inserted into the chromosome. Inversions that involve the centromere (the constricted region of the chromosome) are called pericentric inversions.

1. Objectives

To elucidate, through *in vitro* and *in vivo* experiments, whether the *ACBD5-RET* fusion gene found in the PTC of the A-bomb survivor activates the MAPK-signaling pathway and induces tumor formation.

2. Methods

- (1) Expression vectors, i.e., plasmid DNA with a promoter sequence needed for gene expression, containing cDNA (DNA synthesized from an RNA template by reverse transcriptase and complementary to mRNA) of the *ACBD5-RET* fusion gene were introduced into mouse *NIH3T3* cells (immortalized fibroblasts established from mouse skin cells). This process was undertaken to determine, using Western-blotting*, whether phosphorylation (or, activation) of protein kinase in the MAPK-signaling pathway is enhanced.

*Western-blotting is an analytical technique for detecting specific proteins. It uses gel electrophoresis to separate protein samples, transfers and fixes them to a membrane (filter paper for blotting), and identifies specific proteins based on antigen-antibody reactions.

- (2) We introduced the cDNA of the *ACBD5-RET* fusion gene into *NIH3T3* cells, injected the resultant *NIH3T3* cells subcutaneously into nude mice, and examined tumor formation to evaluate the tumorigenicity of the *ACBD5-RET* fusion gene.

3. Results

- (1) We determined that the *ACBD5-RET* fusion gene is formed via inverse binding between a break point in the *tyrosine kinase* domain of the *RET* gene located in the long arm of chromosome 10 and the 5' end of the *ACBD5* gene located in the short arm of the same chromosome (pericentric inversion) (see Figure).
- (2) Accelerated phosphorylation of protein kinase was observed in the *NIH3T3* cells with an *ACBD5-RET* fusion gene.
- (3) After injection into the nude mice, the *NIH3T3* cells with an *ACBD5-RET* fusion gene continued proliferating and formed tumors.

This study showed that the *ACBD5-RET* fusion gene found in the PTC of an A-bomb survivor is significantly involved in papillary thyroid carcinogenesis, as is the case with other *RET* fusion genes such as *CCDC6-RET* and *NCOA4-RET*. *RET* gene rearrangement induced either directly or indirectly by radiation is therefore suggested to be closely involved in papillary thyroid carcinogenesis among PTC patients exposed to relatively high doses of radiation.

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.

§Oncology Reports is an international journal devoted to fundamental and applied research in oncology, and is published monthly as a comprehensive peer-reviewed journal focusing on oncology, particularly carcinogenesis, metastasis, and epidemiology. (Impact factor in 2013: 2.191)