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“*CD14* and *IL18* gene polymorphisms associated with colorectal cancer subsite risks among atomic bomb survivors”

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Study Findings

Our gene structures contain individual differences (called “gene polymorphisms,” based upon which are formulated several genotype classifications), with our basic physical constitutions sometimes being affected by this genetic variation. Dividing colorectal cancer among atomic bomb (A-bomb) survivors into proximal (i.e., in the upper half of the colon) colon cancer and distal (i.e., in the lower half of the colon) colorectal cancer, we examined the association between colon cancer risk and radiation dose by *CD14* and *IL18* genotypes. (*CD14* and *IL18* are genes related to immune response and inflammation.) Our findings suggest that *CD14* gene polymorphisms*¹ may contribute to individual differences in the risk of radiation-related distal colorectal cancer and that *IL18* gene polymorphisms*² may contribute to individual differences in the risk of radiation-related proximal colon cancer.

*¹*CD14* gene polymorphisms are related to innate immunity

*²*IL18* gene polymorphisms are related to elimination of pathogens from the body through a process of inflammation induction

Explanation

Dr. Tomonori Hayashi, Assistant Department Chief, Department of Radiobiology/Molecular Epidemiology, Radiation Effects Research Foundation (RERF), and his colleagues examined the association between colon cancer and immune/inflammatory-related gene polymorphisms using samples collected from immunological studies conducted since 1981 that followed a subset of participants in RERF’s Adult Health Study (AHS), which is a long-term follow-up study of the health of A-bomb survivors in Hiroshima and Nagasaki. The research team published the results in *Human Genome Variation*.

1. Study purpose

Colorectal cancer is one of the cancers regarding which risks of mortality and

incidence are clearly increased for A-bomb survivors. The colorectal cancer incidence in RERF's Life Span Study (LSS) population increased with radiation dose and remains high even today, more than 65 years since exposure. In this study, we specifically examined the association between risk of colorectal cancer (proximal colon cancer and distal colorectal cancer)*³ and radiation exposure by genotype of the *CD14* gene, which is involved in innate immunity, and the *IL18* gene, which is related to elimination of pathogens from the body by inflammation induction, to investigate individual differences in colorectal cancer susceptibility to radiation exposure.

*³Since it was recently discovered that major oncogenic pathways differ between proximal colon cancer and distal colorectal cancer, we investigated in this study individual differences in proximal and distal colorectal cancer susceptibility to radiation exposure.

2. Study methods

We examined *CD14* and *IL18* gene polymorphisms in 4,690 subjects of the AHS, including 222 colorectal cancer cases (81 proximal colon cancer and 131 distal colorectal cancer cases). *CD14* and *IL18* genotypes can be divided into the following three categories: major homozygotes, heterozygotes, and minor homozygotes*⁴. Using statistical models, we assessed risks in, and examined the interaction between, different combinations of radiation doses and the *CD14* or *IL18* genotypes.

*⁴When wild-type gene "A" is prevalent in a population and minor type gene "a" is low, the major homozygote is AA, the heterozygote is Aa, and the minor homozygote is aa.

3. Study results

(1) *CD14* genotype and distal colorectal cancer:

After adjustment for sex, year of birth, city of exposure, smoking status, and radiation dose, the risks of overall colorectal cancer and distal colorectal cancer with *CD14-911 A/A* (major homozygotes of *CD14* polymorphisms, localized on 911 base pairs 5'-upstream of *CD14* gene) were significantly higher compared with those with two other genotypes (*A/C* heterozygotes and *C/C* minor homozygotes). No statistically significant interactions were observed between radiation exposure and *CD14* genotype*⁵. The *CD14-911 A/A* genotype had significantly higher levels of membrane-bound and soluble CD14 protein than the other two genotypes. (Membrane-bound CD14 is joined to the cell membrane, and soluble CD14 is protein originally bound to the membrane that was cleaved by an enzyme and is present in the blood.)

*⁵This study examined whether distal colorectal cancer risk was increased with increasing radiation dose among populations who have the *CD14-911 A/A* genotype. Thus far, no increased risk due to radiation exposure has been observed for rectal cancer among the larger population in the epidemiological study that is not divided by genotype. However, it was impossible to evaluate the risk of rectal cancer alone in-association with radiation exposure due to the small number of cases available for use in this study. Separate analysis by genotype of distal colon cancer and rectal cancer among all distal colorectal cancer cases remains an important task to be tackled in the future.

(2) *IL18* genotype and proximal colon cancer:

After adjustment for sex, year of birth, city of exposure, smoking status, and radiation dose, the risk of proximal colon cancer with *IL18-137 G/G* (major homozygotes of *IL18* polymorphisms localized on 137 base pairs 5'-upstream of *IL18* gene) was significantly higher compared with the other two genotypes (*G/C* heterozygotes and *C/C* minor homozygotes). No statistically significant interactions were observed between radiation dose and *IL18* genotype. The *IL18-137 G/G* genotype had lower levels of IL18 in the plasma than did the other two genotypes.

Study Significance

These findings suggest the potential involvement of CD14-mediated inflammatory responses in distal colorectal cancer and IL18-mediated inflammatory responses in proximal colon cancer in atomic bomb survivors.

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.

[§]***Human Genome Variation***, an official monthly journal of the Nature Publishing Group of the UK, features original articles and reviews on the human genome and newly discovered variability and mutations in human genes. (Impact factor in 2014: 2.684)