Chromatin Folding, Fragile Sites, and Chromosome Aberrations Induced by Low- and High-LET Radiation

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Abstract

We previously demonstrated non-random distributions of breaks involved in chromosome aberrations induced by low- and high-LET radiation. To investigate the factors contributing to the break point distribution in radiation-induced chromosome aberrations, human epithelial cells were fixed in G1 phase. Interphase chromosomes were hybridized with a multicolor banding (mBAND) probe for chromosome 3 which distinguishes six regions of the chromosome in separate colors. After the images were captured with a laser scanning confocal microscope, the 3-dimensional structure of interphase chromosome 3 was reconstructed at multi-mega base pair scales. Specific locations of the chromosome, in interphase, were also analyzed with bacterial artificial chromosome (BAC) probes.

Both mBAND and BAC studies revealed non-random folding of chromatin in interphase, and suggested association of interphase chromatin folding to the radiation-induced chromosome aberration hotspots. We further investigated the distribution of genes, as well as the distribution of breaks found in tumor cells. Comparisons of these distributions to the radiation hotspots showed that some of the radiation hotspots coincide with the frequent breaks found in solid tumors and with the fragile sites for other environmental toxins. Our results suggest that multiple factors, including the chromatin structure and the gene distribution, can contribute to radiation-induced chromosome aberrations.

Introduction

Location of Breaks that Participated in Inter- and Intra-chromosome Exchanges after gamma exposure

Breakpoints in inter-chromosome exchanges are clustered around Band 3p12, 3p11, and 3p1. Most of the rearrangements occur between a break in 3p12 and one in 3p11.

Materials and Methods

Cells

Human epithelial cells (CH184B5F5/M10) were cultured in chamber slides. Upon confluent, the cells in were fixed with methanol/acetic acid.

Interphase chromosome painting with mBAND probes

The interphase cells were hybridized using the XCyto3 mBAND kit from MetaSystems. The 3-D images of chromosome 3 were captured with a laser scanning confocal microscope, and the three dimensional structure of interphase chromosome 3 with six colored regions was reconstructed using 3D analysis software Imaris™. The distances between different regions were measured as well.

The data on the distribution of gene number, gene length, GC content, and fragile sites in various types of cancers, are obtained from various databases.

Results

The Distance between Different Regions of Chromosome 3 and the Center of the Chromosome 3D Domain

The center of Region B is closest to the center of the domain of chromosome 3. Region A (telomere on the p-arm), region C (close to centromere), and region D (proximal) on the q-arm are further away from the chromosome domain center than either region B or region E.

Distribution of Distance between Regions B, 12, and 20, which Involve in Intra-Chromosome Aberrations

The distance between regions 12 and 20 was much longer than the distance from 8 to 12, and from B to 20, indicating that region 12 and 20 may exhibit a lower frequency of intra-chromosome exchanges with each other.

Chromosome 3 and Cancer

Chromosome 3 contains multiple oncogenes and tumor suppressor genes. Chromosome aberrations in the p-arm are known to be associated with various cancer types.

Conclusions

• The regions towards the telomeres are likely to occupy the peripheral area of the chromosome domain. These heterochromatin regions locating in the peripheral of the chromosome domain may provide the structural support, define the chromosome territory, and maintain the chromosome integrity.

• The present results showed that Band 6-8 tends to locate near the interior of the chromosome domain, and are localized closely to Band 12-13 and Band 19-22. This finding is consistent with the frequency of intra-chromosome exchanges between breaks in these regions.

• The non-random breakpoint distribution in chromosome 3 after radiation exposure may be associated with the folding of chromatin in interphase.

• Other factors, including the location of the fragile sites and transcription activities, may also contribute to the distribution of radiation-induced intra- and infra-chromosomal exchange hotspots.

• The distribution of breaks participated in inter- and infra-chromosomal exchanges found in chromosome 3 of solid tumors is in partial agreement with radiation induced chromosome exchange hotspots.

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