Directional Genomic Hybridization: An Improved Biomarker for Radiation Exposure

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Cytogenetic biomarkers have been a preferred choice for retrospective estimation of radiation exposure because they are sensitive, quantifiable, and relevant to biological effects of concern. The most commonly used involve the measurement of dicentrics and symmetrical translocations. Both have shortcomings that become increasingly problematic for assays carried out at long times after radiation exposure. Dicentrics in samples from peripheral blood lymphocytes decrease with time after exposure ($t_{1/2}$ 1-2 years), and in the case of more stable symmetrical translocations, background levels are 10-fold higher and increase with age. Another aberration type, inversions, result from exchanges *within* a chromosome that reverse the orientation of the broken segment. We have developed an approach based on directional genomic hybridization (DGH) that facilitates detection of inversions with a greater than 10 fold improvement in resolution over existing techniques, allowing the detection of 1Mb or smaller inversions. Bioinformatics guided design of sequence- and strand-specific probe sets, which when coupled with single-stranded hybridization, produced *chromatid* – rather than chromosome – paints. Inversions register simply as a signal switch from one sister chromatid to the other in the inverted region. Importantly, like chromosome paints, *chromatid* paints also reveal translocations and dicentrics. Modeling suggested that inversions should be more common than translocations after densely vs. sparsely ionizing radiation exposures. We irradiated human cells with high LET heavy ions or low LET gamma rays and, using chromatid painting, compared the dose-response yields for induction of inversions, translocations and dicentrics. As predicted, the slope of the dose-response curve following heavy ion irradiations was steeper, and the yields per unit dose for inversions were higher than for either translocations or dicentrics. In another application, chromatid painting of orangutan cells revealed an inversion that presumably occurred during karyotype evolution of mammals. Together, our results demonstrate that inversion detection is useful for a variety of applications and can be further developed for use as a sensitive tool to measure past exposure to ionizing radiation and/or other clastogens. Funding for this work was provided by NASA (NNX09CE42P; NNX10CB05C) and NIAID (R01AI080486-02).