Gene copy number changes in mitochondrial and nuclear genomes of archived samples

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A large collection of paraffin tissues was accumulated from an extensive series of irradiation experiments conducted on 49,000 mice between 1950-1990's at Argonne National Laboratory. At present these tissues are located at Northwestern University and our laboratory has developed websites with digitized information on every animal including radiation exposures (dose, dose rate, etc), pathology, symptoms, and health records. Using a selection of archived tissues we decided to compare effects of long term-fractionated irradiation with acute irradiation, for gamma-rays or fission spectrum neutrons delivered at different dose rates. Our hypothesis was that the mitochondrial gene copy numbers would change differently in response to different qualities and dose rates of radiation. Approximate gene copy numbers were evaluated using quantitative real time PCR. In the case of gamma rays, total dose of approx. 5.5Gy was delivered at different dose rates and fractionation regimens: acute exposure at dose rate of 27.3cGy/min; sixty weekly fractions at dose rate of 0.5cGy/min; and 300 daily exposures with 0.0013cGy/min dose rate. Neutrons were delivered at a total dose of approximately 55 cGy, with a dose rate of 2.8 cGy/min; 24 once weekly fractions with a dose rate of 0.052 cGy/min and 60 once weekly fractions with a dose rate of 0.033cGy/min.

Our hypothesis regarding gene copy number changes was best expressed by fixed effects models, represented by a formula such as this:

Ln(mitochondrial gene) = β0 + β1(dose rate A) + β2(dose rate B) + β3(dose rate C) + β4(ln(nuclear gene)) + β5(dose rate A*ln(nuclear gene)) + β6(does rate B*ln(nuclear gene)) + β7(dose rate C*ln(nuclear gene))

Results from the complete analysis show that: (1) copy numbers of mitochondria and nucleus encoded genes show a relationship modulated by irradiation, different dose rates and qualities of radiation; (2) mitochondria encoded genes and nucleus encoded genes compared within the group show variation that has no dependence on irradiation regimen.

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