HIGH LET ^{56}FE ION IRRADIATION INDUCES TISSUE SPECIFIC CHANGES IN DNA METHYLATION IN THE MOUSE

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DNA methylation is an epigenetic mechanism that drives phenotype and that can be altered by environmental exposures including radiation. The majority of human radiation exposures occur in a relatively low dose range; however the biological response to low dose radiation is poorly understood. Based on previous observations we hypothesized that *in vivo* changes in DNA methylation would be observed in mice following exposure to doses of high linear energy transfer (LET) ^{56}Fe ion radiation between 10-100 cGy. We evaluated the DNA methylation status of genes for which expression can be regulated by methylation and that play significant roles in radiation responses or carcinogenic processes including apoptosis, metastasis, cell cycle regulation and DNA repair (*DAPK1*, *EVL*, *14.3.3*, *p16*, *MGMT*, *IGFBP3*). We also evaluated DNA methylation of repeat elements in the genome that are typically highly methylated. No changes in liver DNA methylation were observed. While no change in DNA methylation was observed for the repeat elements in the lungs of these same mice, significant changes were observed for the genes of interest as a direct effect and a delayed effect of irradiation 1, 7, 30, and 120 days post exposure. At delayed times, differences in methylation profiles among genes were observed. DNA methylation profiles also significantly differed based on dose, with the lowest dose frequently affecting the largest change. The results of this study are the first to demonstrate *in vivo* high LET radiation induced changes in DNA methylation that are tissue and locus specific, and dose and time dependent.

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