Low LET Radiation Alters the Fetal Epigenome of the A^{vy} Mouse

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Exposure to high levels of ionizing radiation significantly alters the epigenome in somatic cells and gametes (Filkowski and others, 2009), yet it has not been determined if epigenomic modifications occur below 10 cGy. Epigenetic dysregulation during early development is mechanistically linked to the pathogenesis of adult-onset diseases (Jirtle and Skinner, 2007). Thus, we sought to determine whether low doses of ionizing radiation during early gestation affect susceptibility to adult-onset diseases by deregulating the establishment of DNA methylation patterns. *Agouti viable yellow* (A^{vy}) mice were used to test this novel postulate because they are exquisitely sensitive biosensors for environmental agents that alter the epigenome (Dolinoy and others, 2007; Waterland and Jirtle, 2003). Using this model, we have previously demonstrated that low LET X-ray radiation (1.2 cGy/day; 8.4 cGy total) during the first seven days of gestation caused a significant offspring coat color shift towards pseudoagouti (Chi Square Analysis, $p=0.014$) and discordant methylation between radiation and control mice of the same coat color class (ANOVA, Bonferroni corrected, $p<0.01$). Moreover, three CpG sites were significantly hypomethylated in the imprinted gene, *Igf2*. Thus, we postulate that acute radiation exposure *in utero,* when DNA methylation is established at the A^{vy} allele, will significantly alter offspring coat color and methylation at both metastable and imprinted loci in a dose-dependent manner. This exposure timing (GD 4.5) coincides with post-fertilization epigenome-wide reprogramming, a window of vulnerability for exposure to epigenetic toxicants and environmental factors. Our results show that 1.2 cGy of radiation at day 4.5 of gestation (GD 4.5) significantly shifts the coat color of the offspring toward pseudoagouti ($p=0.049$), and significantly hypermethylates the A^{vy} allele ($p=0.012$). Two additional doses (0.6cGy and 2.4 cGy) administered at GD 4.5 are presently being examined along with the $Cabp^{IAP}$ metastable epiallele in tissues from all three germinal layers. To further elucidate the effects of low dose radiation exposure, our laboratory has also defined mouse and human imprintomes, consisting of 29 differentially methylated imprint regulatory regions in mice and 22 in humans. Analysis of these regions will further help define the importance of epigenetic deregulation of gene function in the etiology of diseases.

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