The effects of in utero irradiation on mutation induction and transgenerational instability in mice

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It is well known that the developing embryo is especially sensitive to ionising radiation. However, to date little is known about the long-term effects of in utero exposure on mutation rates during adulthood.

To evaluate the effects of in utero irradiation on mutation induction and transgenerational instability, BALB/c pregnant mice (Theiler stage 20, 12 days of gestation) were exposed to 1 Gy of acute X-rays. The in utero exposed 8-week-old males and females were mated to control partners. To evaluate the effects of in utero irradiation on mutation induction in the germline of exposed mice, all parents and offspring were profiled using two mouse-specific expanded simple tandem repeat (ESTR) probes Ms6-hm and Hm-2. The results of our study show that ESTR mutation rates in the germline of in utero irradiated male and female mice remain highly elevated during adulthood. Using single-molecule PCR, the frequency of ESTR mutation was established in DNA samples prepared from sperm, bone marrow and brain taken from the in utero irradiated animals. In all animals, a statistically significant $\sim$2.8-3.7 fold increase in the mean mutation frequency was found in all tissues of the in utero irradiated animals. The results of our study show that the mutagenic effects of in utero irradiation in mice are well manifested during adulthood and therefore suggest that the susceptibility of early stages of mouse development to ionising radiation may be higher than previously thought.

To analyse the effects of parental irradiation on transgenerational instability, the frequency of ESTR mutation was established in DNA samples prepared from sperm, bone marrow and brain taken from the first-generation offspring of in utero irradiated male and female mice. The results of our study show that in the offspring of in utero exposed males the frequency of ESTR mutation is considerably elevated across multiple tissues, whereas in the offspring of irradiated females it does not significantly differ from that in controls. A comparison with the results of our previous studies on transgenerational in stability among the offspring of BALB/c male mice irradiated during adulthood showed that that the magnitude of transgenerational effects is not affected by the stage of paternal exposure. This work has therefore established that an instability signal induced in the germline of in utero irradiated males is manifested during adulthood. The potential implications of our findings to for further understanding of the possible mechanisms of transgenerational genomic instability will be discussed.

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