PERSPECTIVE

Paternal DNA damage is passed down through generations via linker histone H1-mediated DNA repair restriction

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ABSTRACT

One of the most persistent issues in radiation biology relates to how paternal exposure to Ionising Radiation (IR) impacts genetic inheritance and disease risk in the progeny. The transgenerational consequences of Ionising Radiation (IR) exposure have been debated, and the processes remain elusive, despite the fact that 80% of transmitted mutations in humans originate in the paternal germline. Here, we demonstrate that paternal, but not maternal, IR radiation causes transgenerational embryonic mortality in sex-separated *C. elegans* strains. Several manifestations of genomic instability, such as DNA fragmentation, chromosomal rearrangement, and aneuploidy, were seen in the offspring of irradiated males. We found that maternally given error-prone polymerase-theta mediated end joining repairs paternal DNA Double Strand Breaks (DSBs) (TMEJ). We demonstrate the mechanism by which loss of a heterochromatin protein, HPL-1, or a human histone H1.0 ortholog, HIS-24, could significantly reverse the transgenerational embryonic lethality. By enabling the use of error-free Homologous Recombination Repair (HRR) in the germline of the F1 of IR-treated P0 males, removal of HIS-24 or HPL-1 decreased the heterochromatin marker histone 3 lysine 9 dimethylation (H3K9me2) and increased the viability of the F2 generationoverlap.

INTRODUCTION

The impact of parental Ionising Radiation (IR) exposure on the health of the offspring has been hotly contested for many years. IR increases the sperm DNA fragmentation index and lowers fertility in humans by inducing DNA Double-Strand Breaks (DSBs) in the male germline. In response to the epidemiological studies conducted in the previous century, questions about the transgenerational impact of paternal IR exposure were raised. In contrast to children who moved to the area after birth and children who lived in the surrounding areas, the UK government had observed a high incidence of leukaemia and lymphoma in the children living in the vicinity of the Sellafield nuclear plant in the 1980s. According to a case-control research, paternal radiation exposure that took place around the time of conception is associated with a significant chance of malignant illnesses arising in offspring. These reports eventually gave rise to the "Gardner's hypothesis," which put forth a link between a father's exposure to IR and his children's chance of developing cancer.

The "Gardner's hypothesis," however, has recently come under heavy fire and been disproved because no supporting data from studies focusing on the survivors and clean-up crews from the atomic bomb in Japan, the Chernobyl disaster in the Soviet Union, and the workers in other nuclear plants could be found. Furthermore, no biological justification for the transgenerational cancer risk associated with paternal radiation exposure was put out. However, the sample size, the mixed population, and the radiation dosage records often place restrictions on epidemiologic investigations in humans. Therefore, it is unclear whether paternal IR exposure in humans has a transgenerational impact. Two recent studies looking at Chernobyl survivors and cleanup workers found no evidence of a clear increase in DNMs in the offspring, regardless of the maternal or paternal exposure to IR. This is in contrast to some studies that found an increase in minisatellite and microsatellite mutations in children born to parents who lived in highly exposed areas. As a result, past research on the genetic effects of parental radiation exposure have not yet produced a definitive outcome. It is particularly interesting to assess the genome stability in the offspring of the exposed fathers, rather than mothers, given that sperm is responsible for the vast majority of the mutation rate in offspring. Numerous research have

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concentrated on the transgenerational epigenetic impact of parental exposure to IR in addition to the genetic impact. For instance, a connection was found between the heterochromatin mark Histone 3 Lysine 9 Tri-Methylation (H3K9me3) and the parentally inherited DNMs, indicating that epigenetic alterations may be responsible for the parentally inherited genomic instability. Additional proof of transgenerational epigenetic alterations brought on by paternal radiation exposure was found in studies using rats and mice. These modifications in the progeny of the animals exposed to a high dosage of IR include loss of DNA methylation and altered miRNA expression. These results therefore suggest that paternal radiation exposure may possibly alter the epigenetic environment in the progeny. Here, we report a previously unreported mechanism underpinning the transgenerational effect of paternal exposure to IR using sex-separated mutants of the worm C. elegans as a model. We demonstrate that paternal exposure to IR causes transgenerational embryonic mortality and genomic instability in the F1 generation. We found that the polymerase-Theta Mediated End Joining (TMEJ), a maternally provided error-prone DNA repair mechanism that results in a high incidence of chromosomal abnormalities, is the primary mechanism by which the paternal DNA damage is repaired in the zygote. By triggering the error-free Homologous Recombination Repair (HRR) pathway, the removal of histone H1, HIS-24, or the heterochromatin protein HPL-1 may be able to restore the transgenerational embryonic lethality of paternal IR exposure. Our research explains the mechanisms underlying the genetic and epigenetic effects of paternal exposuret to IR on subsequent generations.

CONCLUSION

Because the processes behind this process are still unknown, it has been difficult to determine the transgenerational effects of parental exposure to IR. Here, we demonstrate that paternal radiation exposure causes transgenerational death in the F2 generation using sex-separated C. elegans strains as a paradigm. Additionally, we discovered that maternal POLQ-1 mediates paternal DNA repair by utilising the faulty TMEJ repair machinery, ensuring the viability of the F1 generation despite severe chromosomal rearrangements in both somatic and germ cells. By inhibiting the formation of heterochromatin, deactivating the HRR machinery in the F1's germlines, and knocking down the linker histone H1, HIS24, the embryonic lethality of the F2 generation may be reduced.