antiparticle has been studied extensively, and it had a key role in the 1956 discovery of the neutrino[7]. To use reactor-generated electron antineutrinos to investigate neutrino oscillation, it is crucial to know both the flux of antineutrinos emitted in these nuclear reactions and how many antineutrinos are produced at particular energies (the energy spectrum). The precision with which these quantities are measured and theoretically predicted has improved markedly since the 1950s. And in 2011, it was found that the average antineutrino flux detected in these experiments was about 6% less than that predicted[8].

One possible explanation[8] for this reactor antineutrino anomaly is that some neutrinos morph into sterile neutrinos after they leave the reactor core. Dedicated experiments were designed to investigate this possibility by installing detectors close to the reactor, usually at a distance of around 10 metres, where an oscillation into sterile neutrinos might show up in the observed energy spectrum. However, these experiments made the picture only messier: some reported that such a signature was observed[9,10], and others reported a negative result[11,12].

The STEREO experiment settles at least part of this debate with a relative measurement in 6 detector cells that are positioned between 9 and 11 metres from a nuclear reactor generating electron antineutrinos (Fig. 1). If these antineutrinos were to oscillate into sterile antineutrinos, then one would expect to see the 2011 antineutrino flux deficit confirmed, but also to see the antineutrino energy spectrum vary with distance from the reactor. Although the flux measured by the authors was indeed 5.5% lower than the model prediction, the expected oscillation pattern did not show up in their results. Its absence indicates that the reactor antineutrino anomaly cannot be explained by the sterile-neutrino hypothesis.

Because neutrinos are so difficult to detect, signals from sources other than the reactor can be many times more abundant than real neutrino signals if the detector is not well shielded. These false signatures are called background signals, and they can blur or distort the measurements. The authors were able to avoid many uncertainties by using their comparative measurement. The background signals were well controlled with relatively good shielding, and were measured when the reactor was switched off.

In addition to the flux deficit, the authors observed that the energy spectrum was distorted with respect to the model predictions — with a 'bump' between 5 and 6 megaelectronvolts, which was also detected in previous experiments[13–15]. This anomaly in the spectrum is not fully understood, but could be a result of imperfect nuclear data. The STEREO experiment used the uranium-235 isotope, and offers the most precise antineutrino spectrum measured so far for this isotope. The study will therefore be of interest to scientists benchmarking nuclear data for reactor physics, and to those predicting the antineutrino spectrum for other reactor experiments.

The reactor antineutrino anomaly has been confirmed, but its source remains a mystery. However, the impressive precision of the STEREO experiment has ensured that the sterile neutrino is no longer a viable explanation, putting to rest one hypothesis and opening the field for others. The search for an explanation continues.

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Developmental biology

Radiation damage in male worms skips a generation

Ronald Cutler & Jan Vijg

Radiation-damaged paternal DNA has been found to cause embryos of the second generation of nematode worms, but not the first, to die. The proposed mechanisms help to explain the observed lack of such an effect in humans. **See p.365**

Exposure to radiation causes DNA damage that predisposes individuals to mutations and cancer[1]. However, whether this damage, or its effects acquired in adulthood, can be passed on to future generations has remained controversial. There is a lack of evidence in humans for transgenerational effects of radiation from the atomic bombs at the Japanese cities of Hiroshima and Nagasaki in 1945 (ref. 2), or from the 1986 nuclear accident at Chernobyl, Ukraine[3]. Wang *et al.*[4] show on page 365 that exposing male nematode worms (*Caenorhabditis elegans*), but not females, to ionizing radiation results in the death of embryos produced by subsequent generations. The proposed mechanism for these transgenerational effects might explain why similar outcomes are not seen in humans exposed to radiation.

DNA damage is ubiquitous in physiological conditions and is a likely cause of ageing[5]. Most of this damage either is repaired accurately through one of multiple intertwined DNA-repair pathways, or prompts severely damaged cells to undergo a form of programmed cell death known as apoptosis. However, DNA repair is occasionally erroneous, promoting cell survival but resulting in the formation of mutations. Mutations in germline cells (eggs and sperm) are the source of evolutionary variation, but they are also responsible for embryonic lethality and genetic disease[6].

It is now well documented that the main source of genetic variation in humans is mutations in sperm[6]. Germline mutation frequency increases with the father's age, and paternal age at reproduction has been associated with increased risk of genetic disease and a decrease in the lifespan of daughters[6,7]. We would therefore expect that adult exposure to radiation or other known DNA-damaging agents would increase the number of mutations and produce adverse effects in subsequent generations. But, as noted earlier, there is little evidence for such transgenerational effects of radiation in humans[2,3].

Wang and colleagues used nematodes to study how exposing parents to ionizing radiation affects the first (F_1) and second (F_2) generations of progeny. *Caenorhabditis elegans* has two sexes, hermaphrodite and male. In the experiments, male *C. elegans* or 'females' (mutant hermaphrodites that produce only eggs) were irradiated and then immediately mated with healthy worms of the opposite

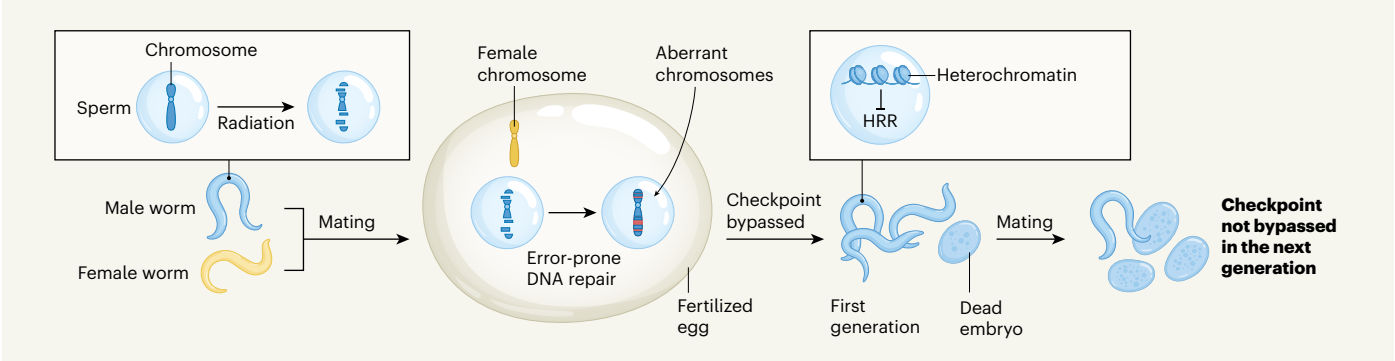

Figure 1 | Transgenerational inheritance of radiation-induced DNA damage from male nematode worms. Wang *et al.*[4] exposed male nematodes (*Caenorhabditis elegans*) to ionizing radiation, damaging the DNA in the animals' sperm cells. The worms were immediately mated with healthy 'females' (mutant hermaphrodite worms that produce only eggs). The authors found that the damaged paternal DNA is repaired by an error-prone mechanism in fertilized eggs. This results in the formation of aberrant chromosomes that nevertheless bypass biological checkpoints in the resulting embryo — thereby enabling most of the embryos to develop into adult worms. However, the DNA in the germlime cells (eggs and sperm) of this first generation of worms adopts a compacted form (known as heterochromatin), which blocks further DNA repair by an error-free pathway (homologous recombination repair; HRR). When these worms mate with healthy worms, their DNA does not bypass the checkpoints in the resulting embryos, most of which therefore die.

sex. In females, this treatment caused high embryonic lethality in the F_1 generation but had little effect on the F_2 generation, which was obtained by mating the surviving F_1 worms with healthy worms.

By contrast, embryonic lethality was low in the F_1 generation produced from irradiated males, but was greatly elevated in the F_2 generation (Fig. 1). This striking observation of embryonic lethality that skips a generation (being present mostly in F_2) from the irradiated males provides evidence of the transgenerational effect that was expected in people exposed to radiation in Hiroshima, Nagasaki[2] and Chernobyl[3]. However, these transgenerational effects in worms were seen only when irradiated males were immediately mated with healthy females, and not when mating was delayed. Sperm are produced continuously in *C. elegans*, so this finding indicates that only mature sperm are affected by irradiation. The finding might also explain the absence of such effects in radiation-exposed humans[2,3], given that male humans also produce sperm continuously.

To gain more insight into how embryonic lethality skips the F_1 generation, Wang *et al.* studied the progeny of the irradiated males. The authors found chromosomal defects in the embryos and in adult intestinal cells of these worms, indicating that DNA damage in the paternal germ line had somehow bypassed the biological checkpoints that would normally have halted embryonic development.

Usually, DNA damage caused by ionizing radiation is fixed by one of the two main DNA-repair pathways: homologous recombination repair (HRR) and non-homologous end joining. However, when these pathways are not available, a highly error-prone pathway known as DNA polymerase theta-mediated end joining (TMEJ) is used instead. This pathway results in the formation of mutations, including structural variation of the genome caused by the exchange of sections of DNA between chromosomes.

Wang and colleagues' whole-genome sequencing of the affected F_1 generation of worms uncovered an unusually large number of such genome structural variants, the signature of TMEJ repair. The authors therefore conclude that TMEJ repair prevents embryonic lethality of the F_1 worms by making their DNA resistant to the damage checkpoints that abort the embryonic development of the F_1 progeny of irradiated females. Remarkably, the authors observe the same mutational signature of TMEJ repair in human whole-genome sequences, indicating that the processes identified in *C. elegans* are evolutionarily conserved and might contribute to genetic diversity in evolution.

The authors' final set of experiments sought to explain how embryonic lethality is markedly increased in the F_2 generation produced from irradiated males. Wang *et al.* focused on the molecular changes in the F_1 generation, and observed high expression of certain proteins that have a role in the formation of compacted DNA (heterochromatin), including heterochromatin protein-1 (HPL-1) and some 'histone linker' proteins[8]. Strikingly, when HPL-1 or the histone linker protein HIS-24 was depleted in irradiated parental male worms, transgenerational embryonic lethality was prevented. By contrast, no such prevention occurred when the F_1 generation also lacked the relatively error-free HRR repair pathway. These findings led the authors to conclude that paternally inherited DNA damage is associated with elevated heterochromatin formation, which prevents germline cells from using accurate DNA-repair machinery (Fig. 1). This, in turn, leads to structural mutations in the genome that result in embryonic lethality in the F_2 generation.

Taken together, Wang and colleagues' findings establish a mechanism for the transgenerational inheritance of DNA damage. They also offer a potential explanation for the lack of transgenerational effects of radiation in humans, which can now be explained by delayed conception after exposure[9]. Interestingly, the work also raises the possibility that transgenerational embryonic lethality could be prevented by inhibiting heterochromatin formation. Future research should investigate whether similar processes do indeed occur in humans, and whether HRR can be promoted to increase genome stability.

Finally, Wang and colleagues observed a delay in the embryonic development of the F_1 progeny of irradiated males, but did not analyse the traits of these animals more deeply — for example, by measuring their lifespans. An interesting avenue for future work will be to investigate whether the accumulation of ageing-related mutations and DNA damage has other effects on these progeny and on subsequent generations. The answers could have implications for male reproductive health in humans.

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