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Epigenetic modifications as a molecular mechanism for transgenerational effects on *Daphnia magna* exposed to radionuclides

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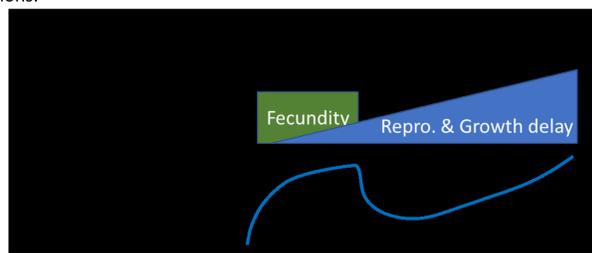
Faire avancer la sûreté nucléaire

Background

In order to assess long term consequences of exposure to ionizing radiation on wildlife, radio-induced effects have to be studied at a multigenerational scale. Multigeneration exposure experiments were performed in *Daphnia magna* exposed to depleted uranium, alpha and gamma radiation^{1,2} and multigenerational DEBtox models were developed. Considering that gamma radiation effects observed on growth and reproduction and DNA alterations shared similar trends across generations³, a multigenerational damage compartment was introduced into the DEBtox models. Damage level in this compartment is transmitted from female to offspring, driving the increase in effect severity observed at organism scale across generations.



Daphnia magna



What is the nature of multigenerational mechanisms at molecular scale?

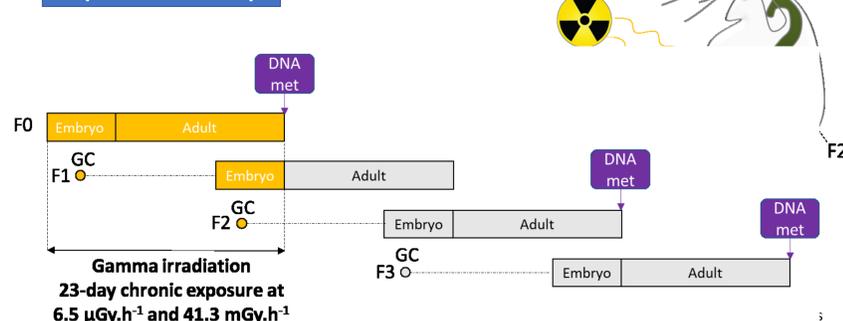
- Several studies suggested that the increase in mutation frequency observed in offspring from irradiated parents in mice would not result from the directed transmission of mutations between generations, but from epigenetic modifications^{3,4}.
- Ionizing radiation are known to induce DNA methylation changes in rodent during laboratory tests (in-vitro and in-vivo <1 generation) and in field studies, but are radio-induced methylation changes transmitted across generations?^{5,6,7,8,9}

Research questions

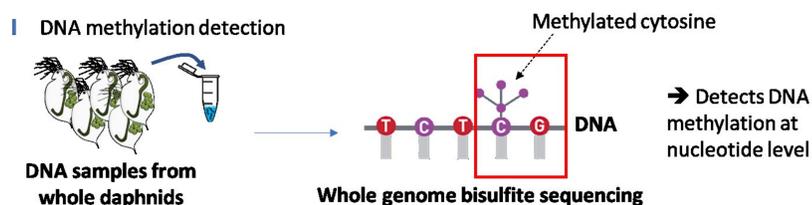
- Are there radio-induced DNA methylation changes in *Daphnia magna* and are they transmitted to non-exposed generations?
- How do they link to radiosensitivity at organism scale?

Materials and Methods

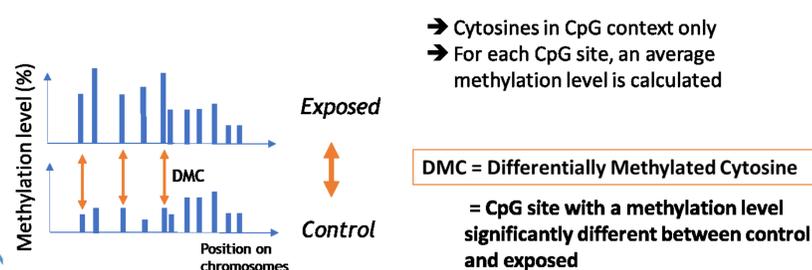
Experimental Setup



DNA methylation analysis



Differential methylation analysis



Results

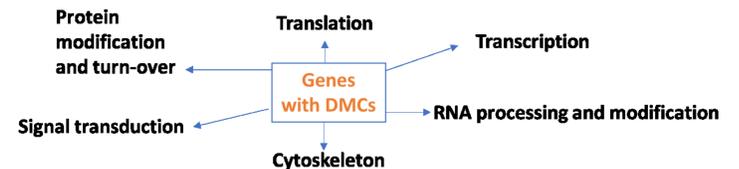
DNA methylation changes detected in all generations

Generation	Number of detected DMCs	
	6.5 µGy h ⁻¹	41 mGy h ⁻¹
F0	209	243
F2	392	413
F3	330	329

- ~5.4 million CpG sites examined (>98% showing no variation)
- ~74 000 CpG sites included in the differential methylation analyses
- Detected DMCs include both hypo- and hyper-methylation, with a slightly greater proportion of hypomethylated DMCs (~55%)

Functional analysis

- Most represented biological functions across the three generations (F0, F2 and F3) are:



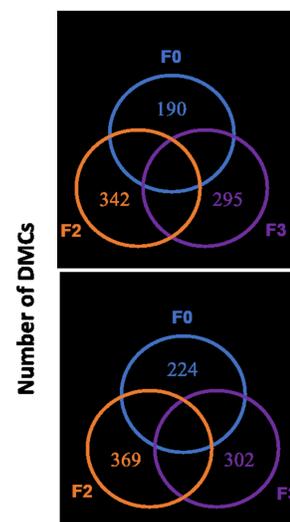
- Examples of genes with DMCs:

- X-box-binding protein (generation F0)¹⁰
- 60S ribosomal protein L28 (generations F2 and F3)¹¹
- "heat-shock" protein (hsp70) (generations F2 and F3)¹²

Cellular response to stress
Protein stability
Cell death prevention

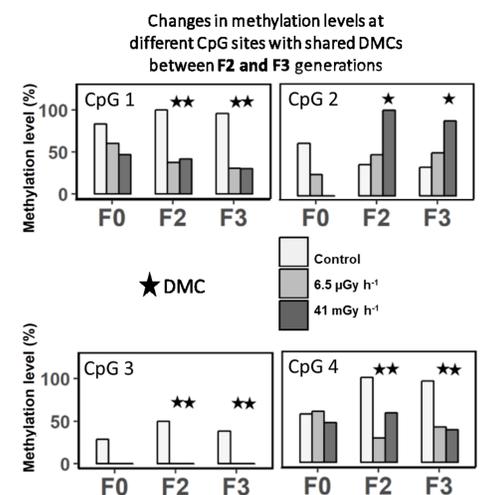
Methylation changes across generations

Comparing DMC positions



- F2 and F3 generations share about 10% of their total DMCs at each dose rate

Comparing methylation levels



- Common DMCs show similar methylation levels between F2 and F3 generations
- Methylation changes were probably transmitted to offspring through the germline and remained visible in unexposed generations

Toxic effects of gamma radiation at organism level

- A decrease in fecundity of 19% was observed in F0 at 41.3 mGy.h⁻¹
- No effect on reproduction or growth were detected in subsequent recovering generations

Conclusions

- DNA methylation changes were detected in *D. magna* exposed during their whole life cycle (F0) and in their offspring exposed as germline cells (F2), even below 10 µGy.h⁻¹
- Common methylation changes were identified between generations F2 and F3, demonstrating a case of transgenerational epigenetic inheritance
- Some of the genes concerned with DNA methylation changes are involved in the biological response to ionizing radiation, but the link with higher biological scales remains unclear