The role of DNA repair in healthy aging

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Background

An Aging Population:

Aging is the primary risk factor for most chronic degenerative diseases[1] (Fig 1A)
By 2050, almost 25% of the global population will be over 60 years old[2] (Fig 1B)

Fig 1A

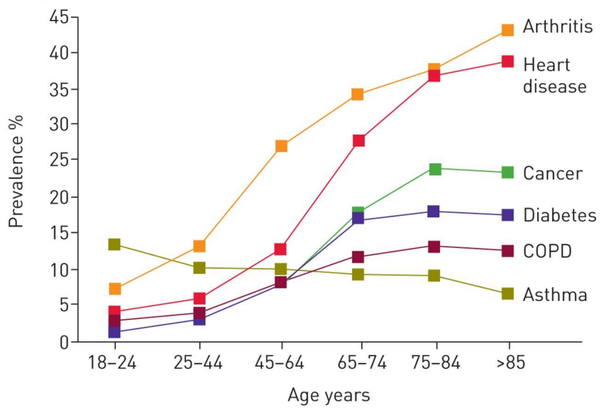
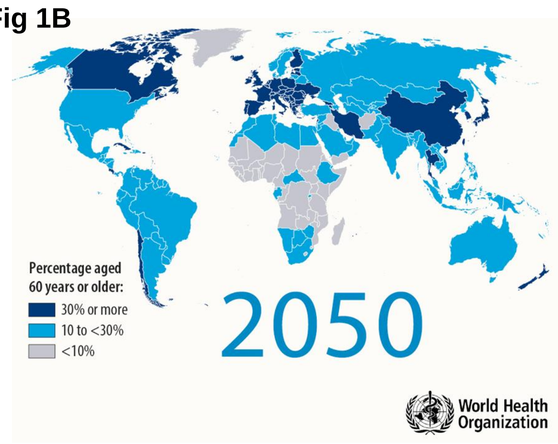


Fig 1B



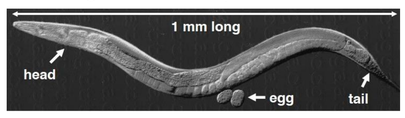
DNA Damage drives aging:

Increased DNA damage and reduced DNA repair is observed with aging[3].
Loss of efficient DNA repair drives age-related pathology[4].
Consistently, effective DNA repair has been linked to longer lifespan and healthspan in animals[5] and humans[3]
However, it is likely that not all DNA repair pathways contribute equally.
AIM: ***Which DNA repair pathways are most important to healthy aging?***

C. elegans as a model organism:

Genetically tractable
Short lifespan (~25 days)
Conserved DNA repair mechanisms with mammals
Easy to experimentally manipulate

C.elegans hermaphrodite adult



Previous Research

Loss of ERCC1-XPF causes accelerates aging in humans, mice[6] and *C. elegans*[7] (Fig 2A, B)

Fig 2A **Healthspan**

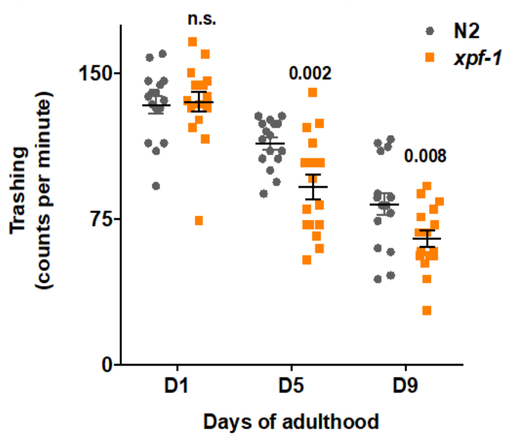
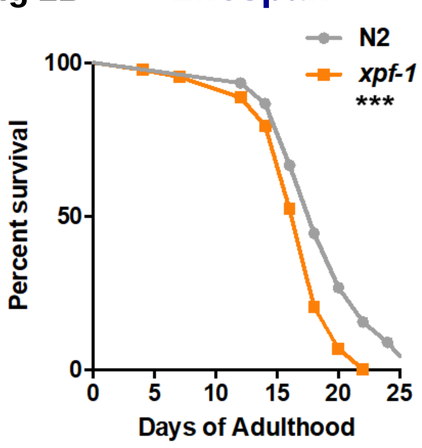


Fig 2B **Lifespan**



ERCC1-XPF is involved in several pathways:

	Strains investigated			
	N2	***xpf-1***	***brc-1***	***fcd-2***
Nuclear excision repair		x		
Homologous Recombination		x	x	
Interstrand Crosslink repair		x		x

x indicates problem in repair mechanism

Expt 1: Confirming DNA repair mutants

DNA repair mutants exhibit an increase in incidence of males (crossover defects) and embryonic lethality in *C. elegans* (Fig 3A, B)

Fig 3A

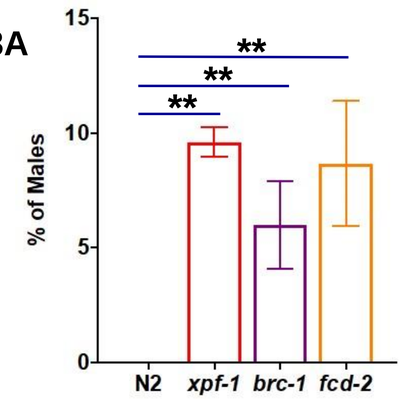
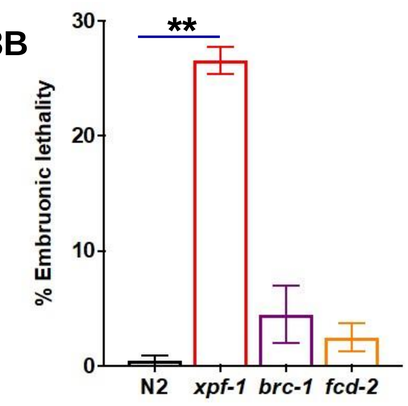


Fig 3B



- *xpf-1*, *brc-1* and *fcd-2* mutants displayed increased incidence of males

Expt 2: Assessing healthspan

Thrashing: Ability to move in liquid declines with age due to deterioration of muscle and motor neurons.
Therefore, thrashing movement in liquid S buffer was compared with age (Fig 4)

Fig 4A

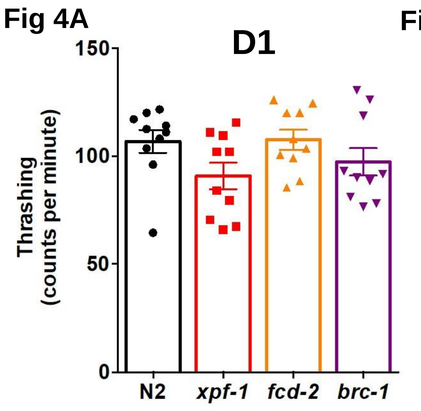


Fig 4B

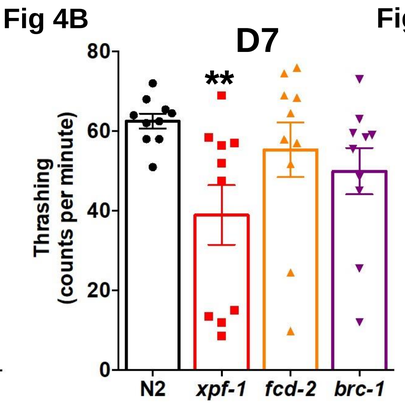
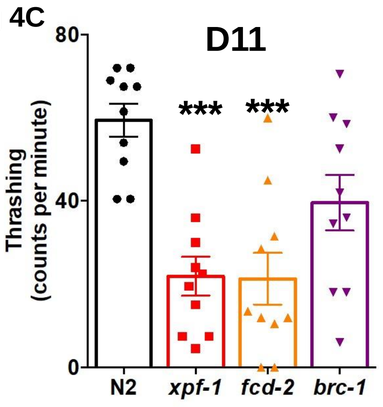


Fig 4C



- Thrashing declined significantly in *xpf-1* and *fcd-2* with age

Stress resistance: Aging significantly reduces stress responses.

Thermorecovery: Ability to respond to heat stress measured by incubating animals at 37℃ for 2 hrs, then allowing to recover overnight. Survival then recorded with age (Fig 5).

Fig 5A

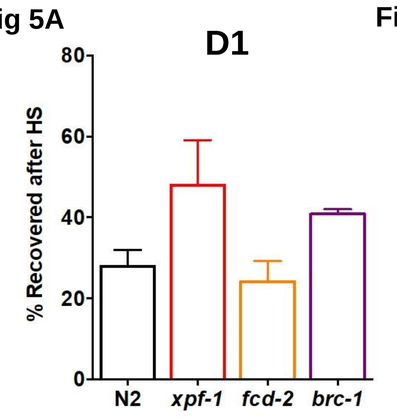


Fig 5B

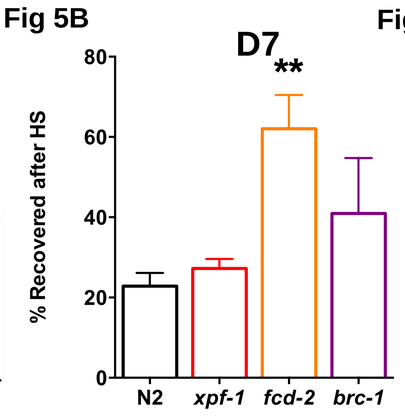
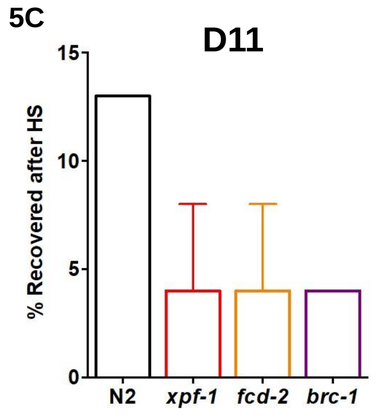


Fig 5C



- Thermorecovery was not significantly affected in DNA repair mutants

Oxidative stress tolerance: Survival of *C. elegans* in H_2O_2 was recorded at hourly intervals to test oxidative stress resistance (Fig 6).

Fig 6A

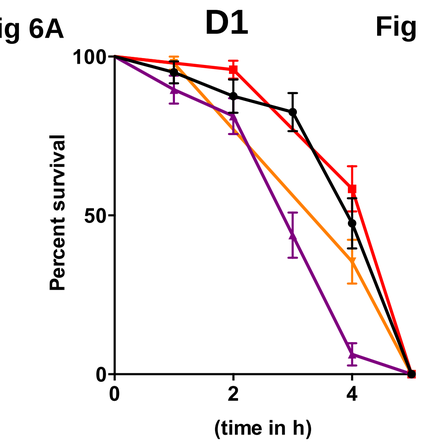


Fig 6B

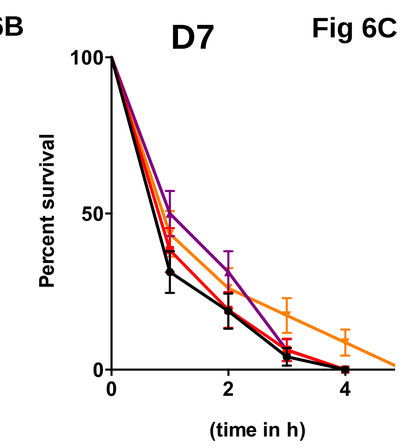
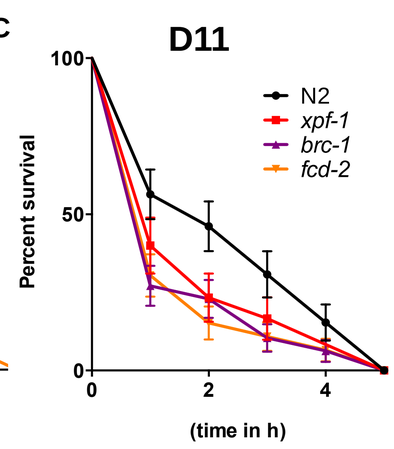


Fig 6C



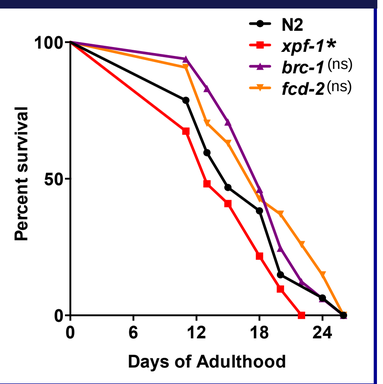
- DNA repair mutants are sensitive to oxidative stress

Expt 3: Assessing lifespan

Lifespan: 100 young adults transferred onto two OP50 plates supplemented with 5-fluorodeoxyuridine (FUDR). Survival was measured at 20℃

- Lifespan was significantly shorter in *xpf-1*

Statistics: One-way ANOVA was performed for most healthspan studies. Log-rank test was performed for oxidative stress and lifespan analysis



Conclusion

brc-1 and *fcd-2* show reduced healthspan, but to a lesser extent than in *xpf-1.*
Only *xpf-1* shows reduced lifespan.
→ *Suggests that all three pathways are necessary for healthy aging*
Loss of different DNA repair processes lead to susceptibility to different stressors
→ *Could be due to different effects on different tissues (similar to human DNA repair conditions)*

Future directions

Investigate the role of DNA repair in a *tissue specific manner,* specifically neuronal and muscular health.

References:
(1) Finkel T. Nat Med 2015 (2) United Nations (2017). World Population Prospects: the 2017 Revision (3) Niedernhofer L., Gurkar A. *et. al.* Annu Rev Biochem 2018 (4) Gurkar A. *et. al.* Exp Geront 2015 (5) Tian X. *et. al.* Cell 2019 (6) Niedernhofer L. *et. al.* Nature 2006 (7) Gurkar A. *et. al.* Redox Biol 2018

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