Linking the NAD$^+$/SIRT1 signaling to DNA repair

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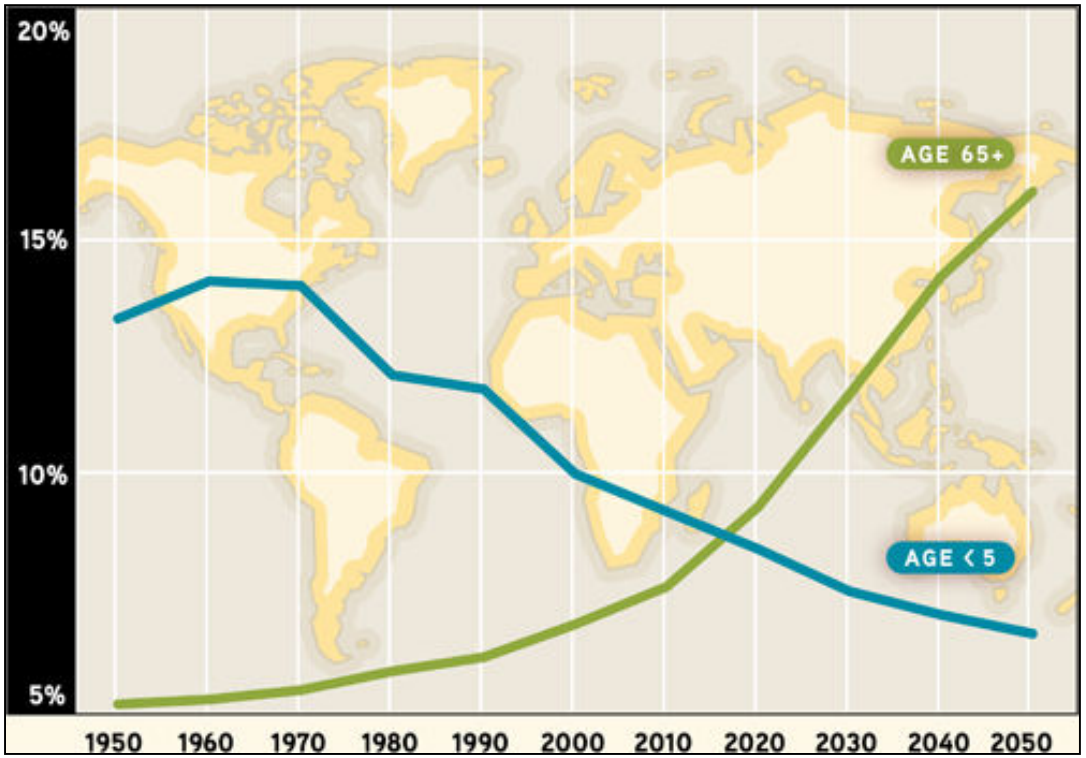
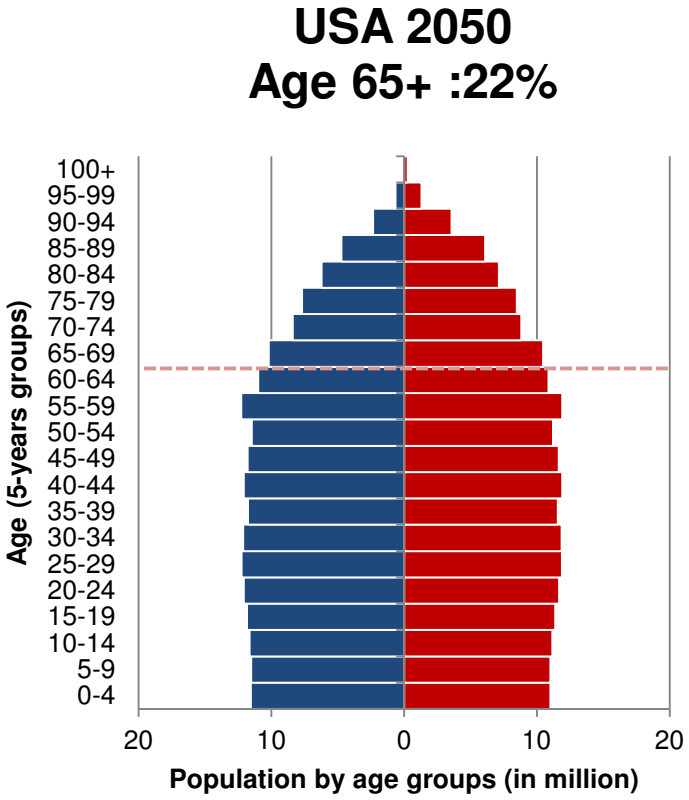
Aging: a universal grand challenge





Fang EF et al., Ageing research reviews 2015.
Data from the United Nations

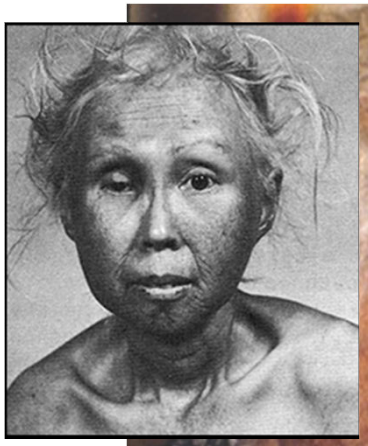
The hallmarks of aging

- Genomic instability
- Mitochondrial dysfunction
- Telomere attrition
- Epigenetic alternation
- Loss of proteostasis
- Deregulated nutrient sensing
- Cellular senescence
- Stem cell exhaustion
- Altered intercellular communication

Lopez-Otin C et al., Cell 2013.

Elite aging and premature aging

14 Years



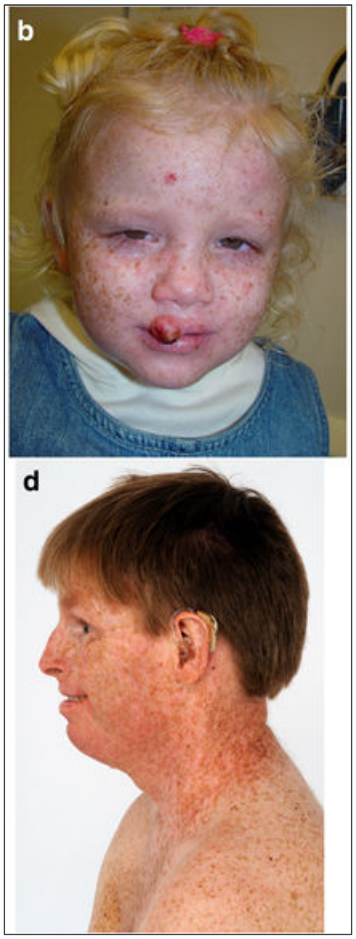
48 Years

The oldest person

Jeanne Calment
122.5 Yrs

Premium model systems for the study of aging

Accelerated aging with DNA damage, neurodegeneration, and mitochondrial dysfunction



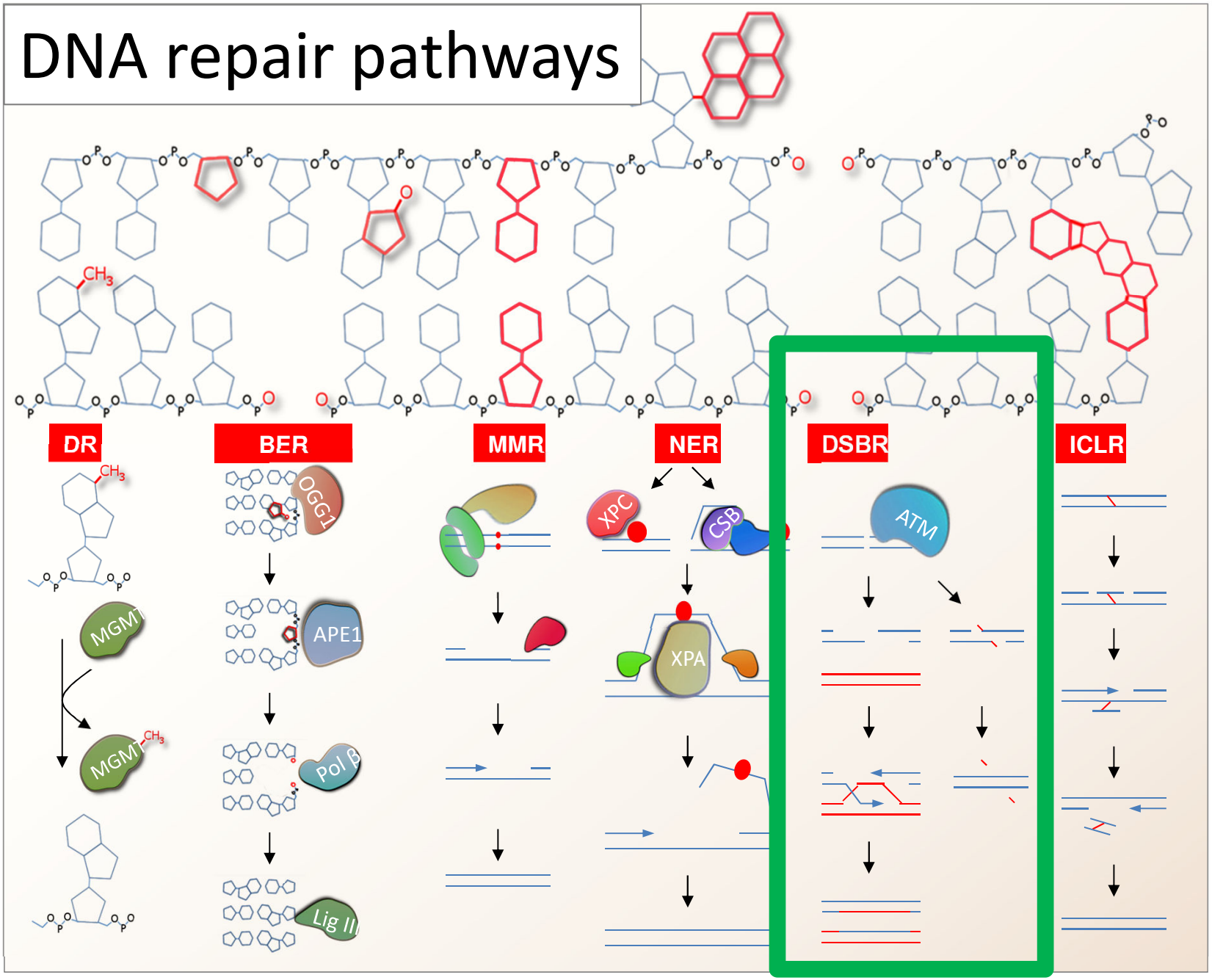
XERODERMA PIGMENTOSUM A (XPA)

COCKAYNE SYNDROME (C-S)

ATAXIA-TELANGIECTASIA (A-T)

DiGiovanna and Kraemer JID 2012 ; Lindenbaum et al. EJPN 2001

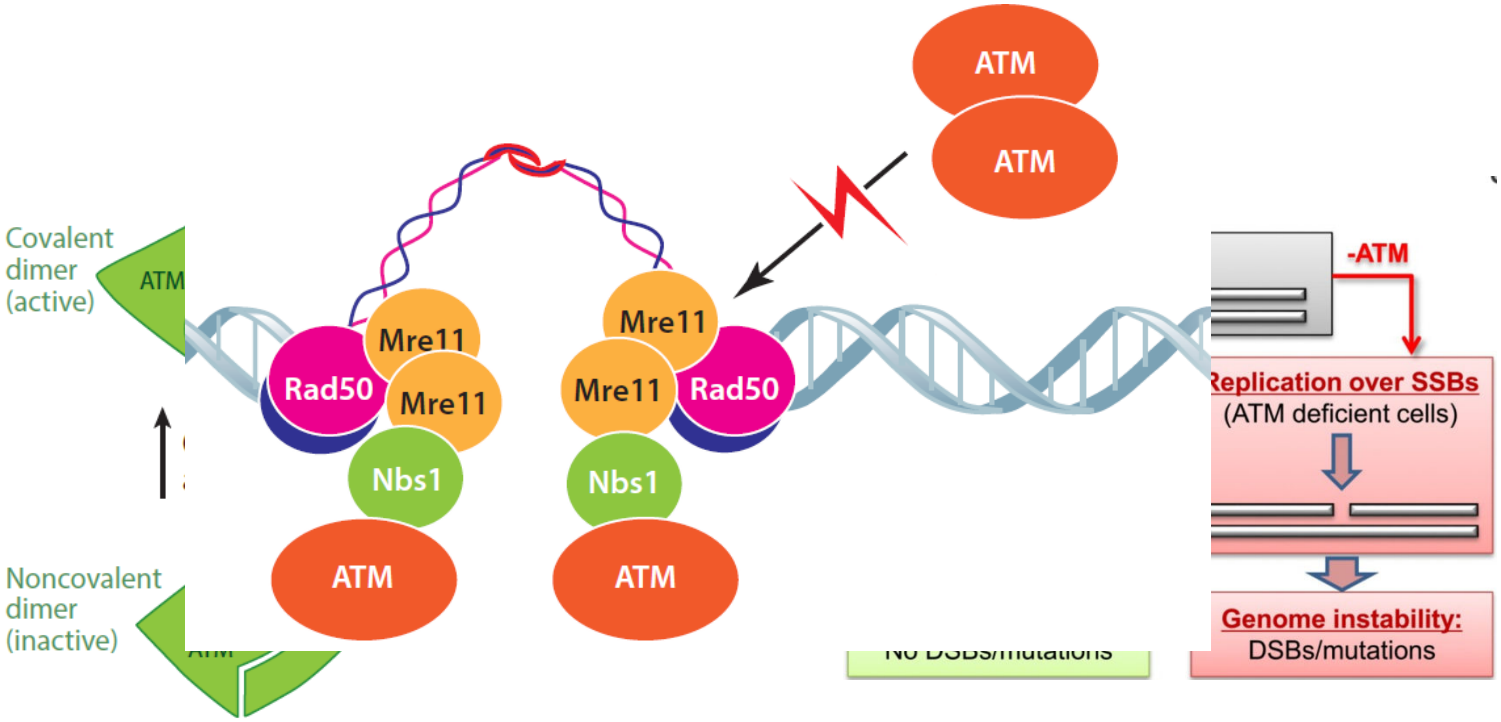
DNA repair pathways



Scheibye-Knudsen, Fang et al., *Trends in Cell Biology, 2015*

ATM is a master regulator of DNA repair

- DNA double strand repair
- Possibly BER and SSB

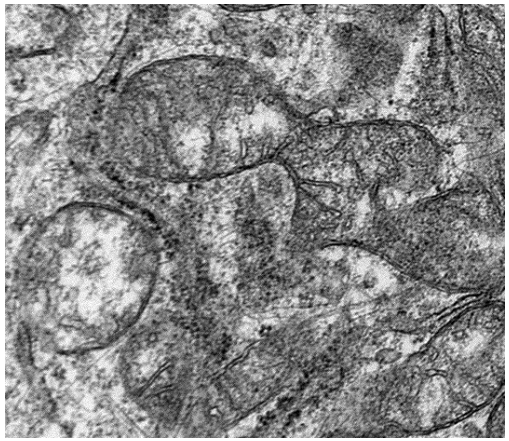


McKinnon PJ, Annu Rew Pathol, 2012
Shiloh Y et al., Nat Rev Mol Cell Biol, 2013
Kastan MB group, Blood, 2012
Paull TT, 2014, Annu Rev Biochem
Dianov GL lab, PNAS 2015

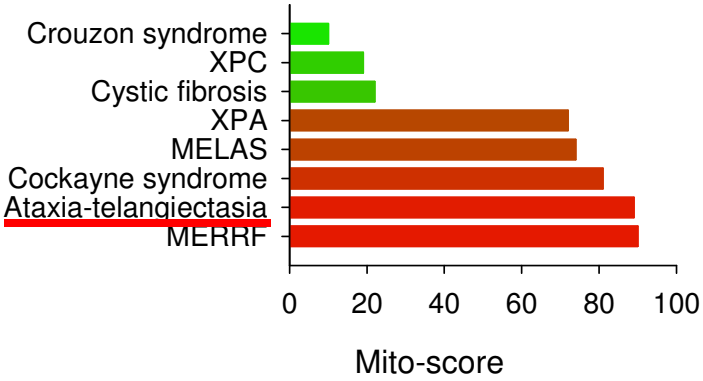
Mitochondrial dysfunction in DNA repair-deficient premature aging disorders

XERODERMA PIGMENTOSUM A (XPA)

COCKAYNE SYNDROME (C-S)



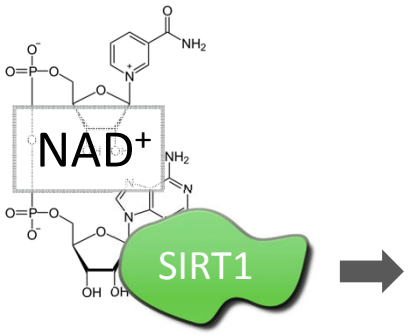
XPA- cells



- **Mitochondrial dysfunction**
- **Defective mitophagy**
- **Depleted NAD^+ due to hyperPARylation**
- **Reduction of NAD^+/SIRT1**

Fang, Scheibye-Knudsen et al, Bohr., ***Cell*** *2014*
Scheibye-Knudsen et al., Bohr, ***Cell Metabolism*** *2014*
Scheibye-Knudsen, Fang et al., Bohr, ***Autophagy*** *2014*
Scheibye-Knudsen, Fang et al., Bohr, ***Trends Cell Biol*** *2015*

SIRT1 in Aging and DNA repair



Longevity in yeast, *C. elegans*, and mice

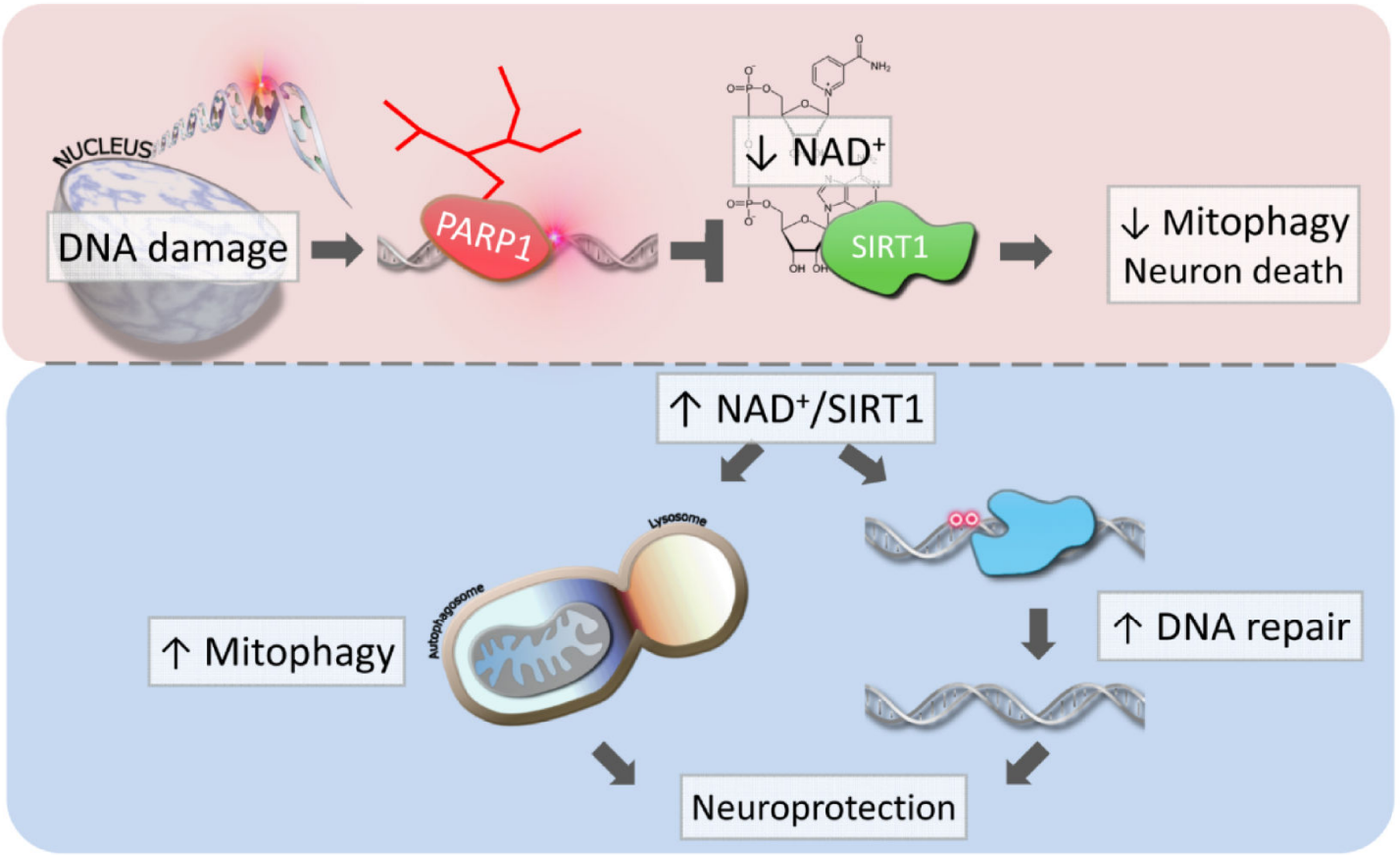
Mitochondrial health: Mito. Biogenesis and mitophagy

Neuroprotection: CREB

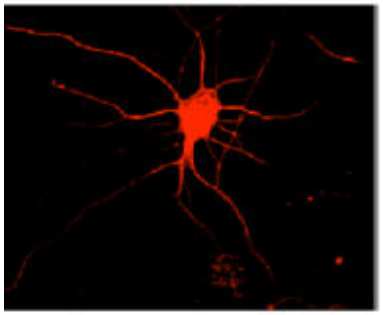
DNA repair:

- BER (APE1, thymine DNA glycosylase)
- DSBR (HDAC1, ATM, WRN, MRN, Ku70)
- NER (XPA)

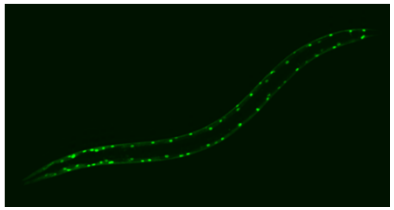
Our question:
Mechanisms of neurodegeneration in AT?



Experimental design



Primary neurons



C. elegans

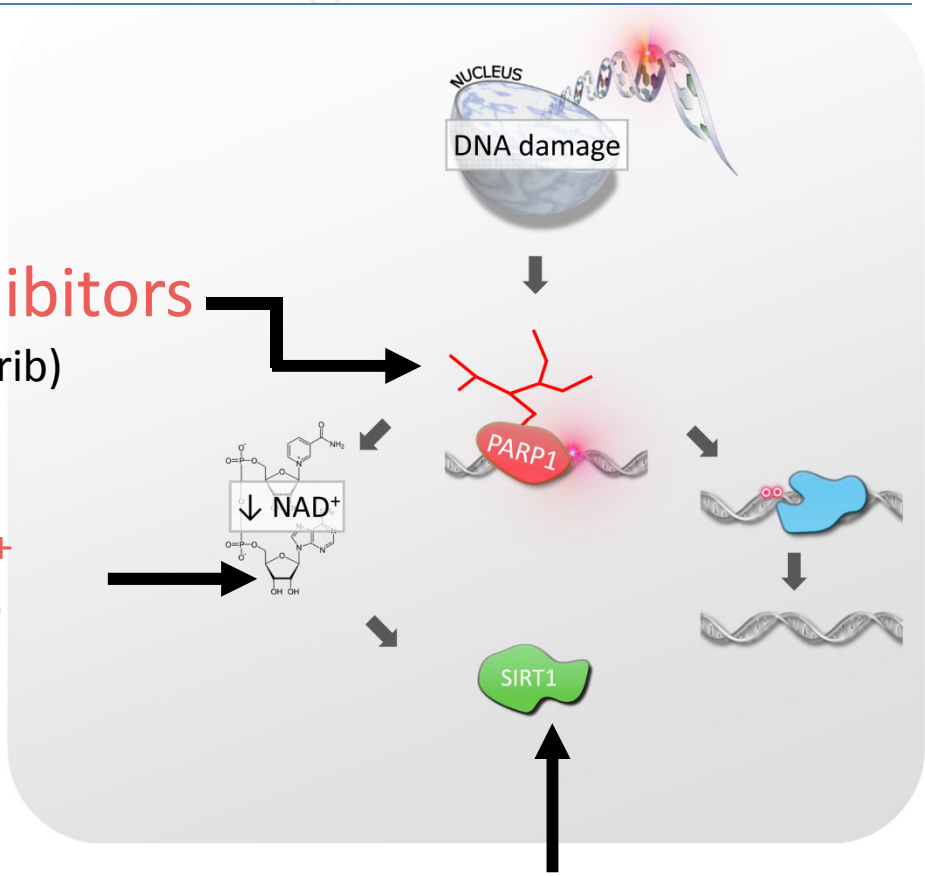
Atm$^{-/-}$ mice

PARP inhibitors

(Olaparib)

NAD^{+}

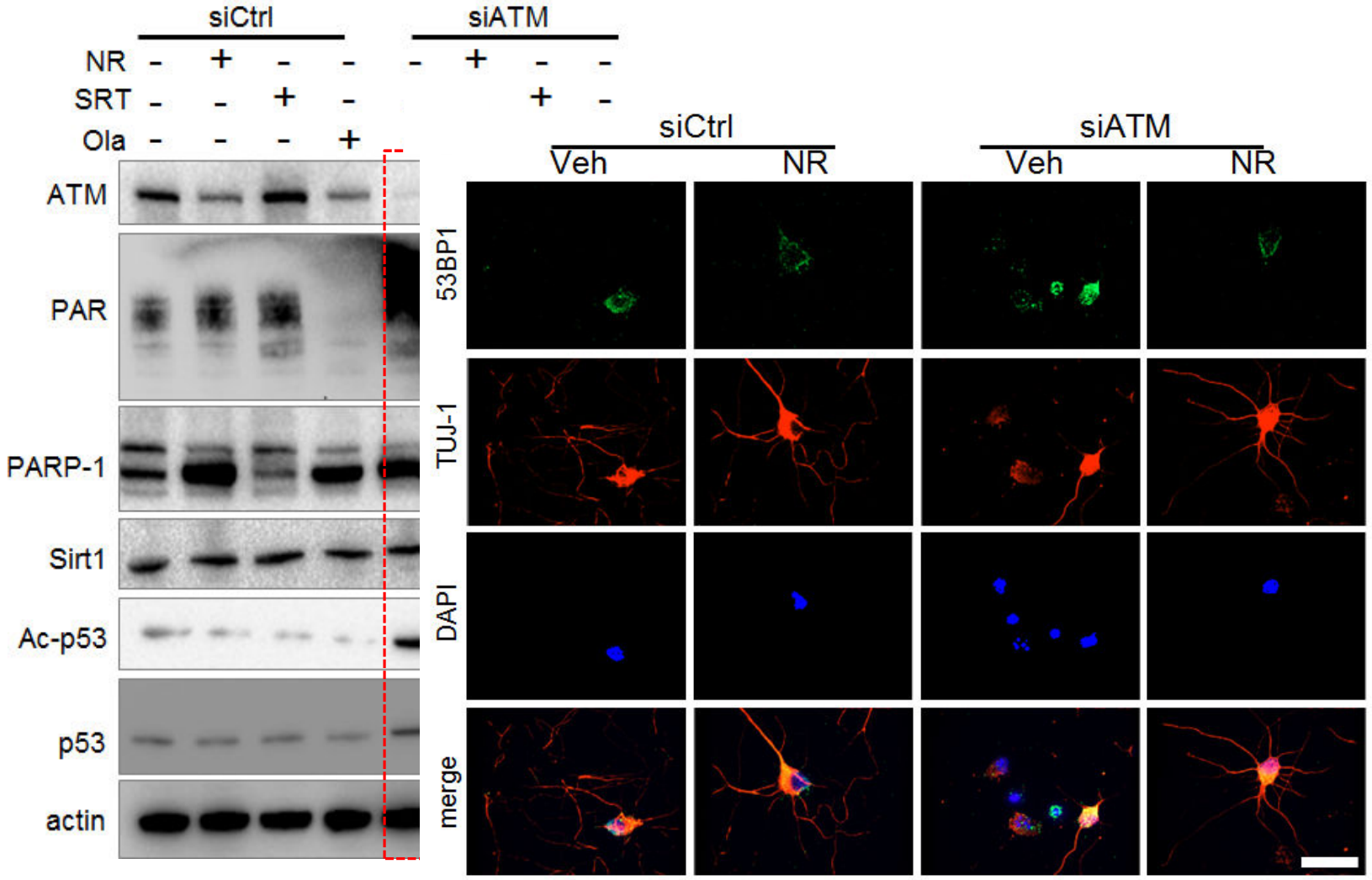
(NR/NMN)



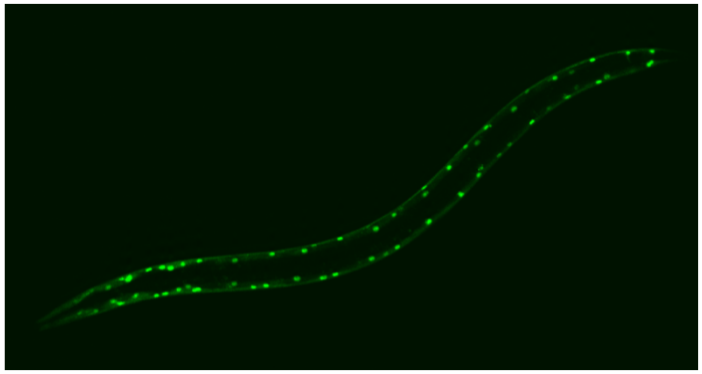
SIRT1 activators

(SRT1720)

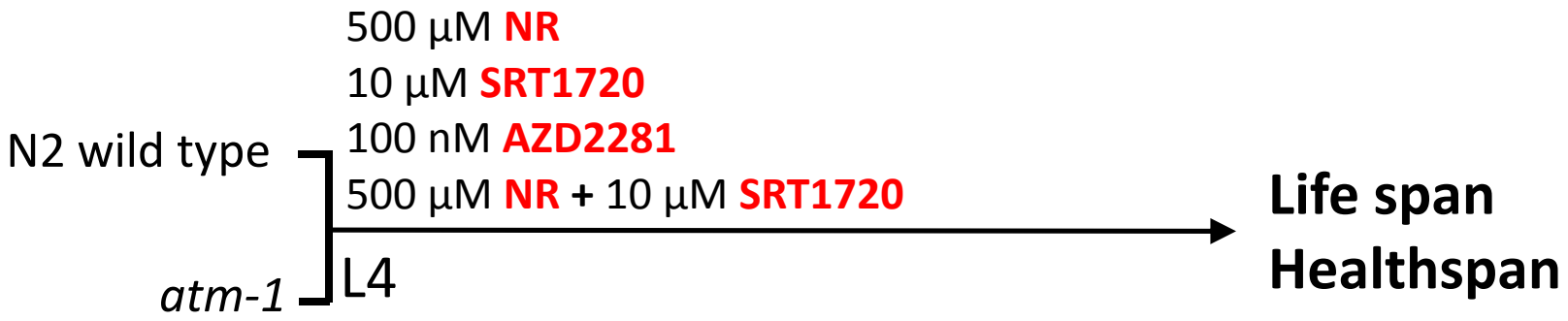
Mitochondrial dysfunction in ATM^{-} neurons via NAD^{+}/SIRT1 reduction



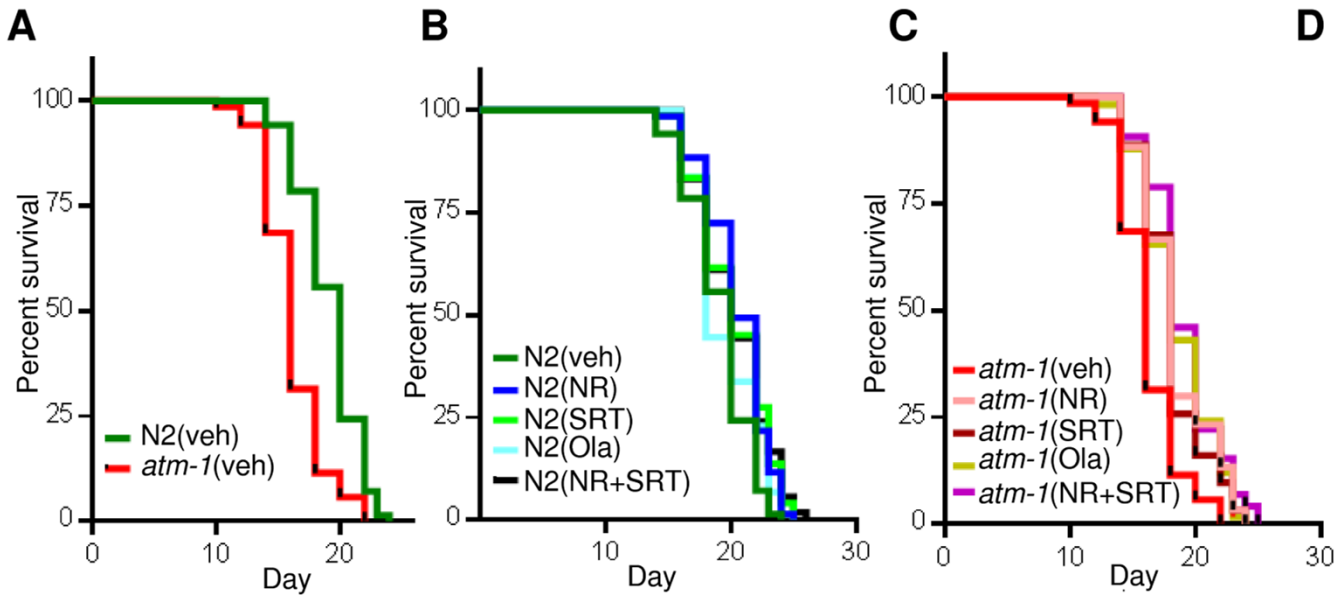
Effects of the NAD+/Sir2.1 signaling in the *atm-1* C. elegans



1. **Short lifespan**
2. **IR sensitivity**
3. **Infertility**
4. **Genomic instability** (small brood size, high male frequency)

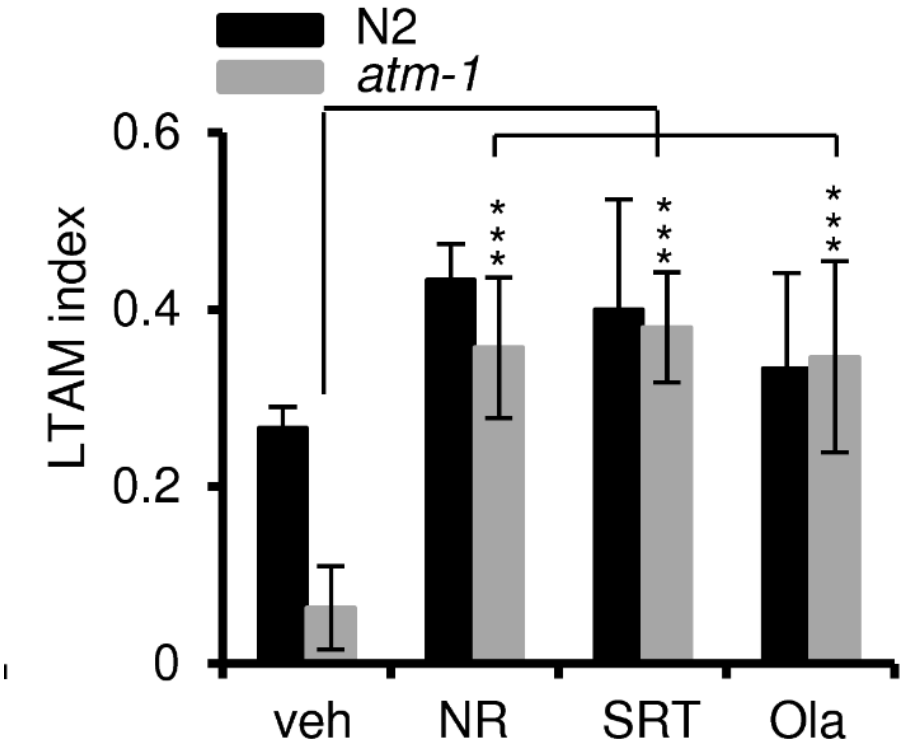


The NAD$^+$/Sir-2.1 signaling increases lifespan in *atm-1* worms



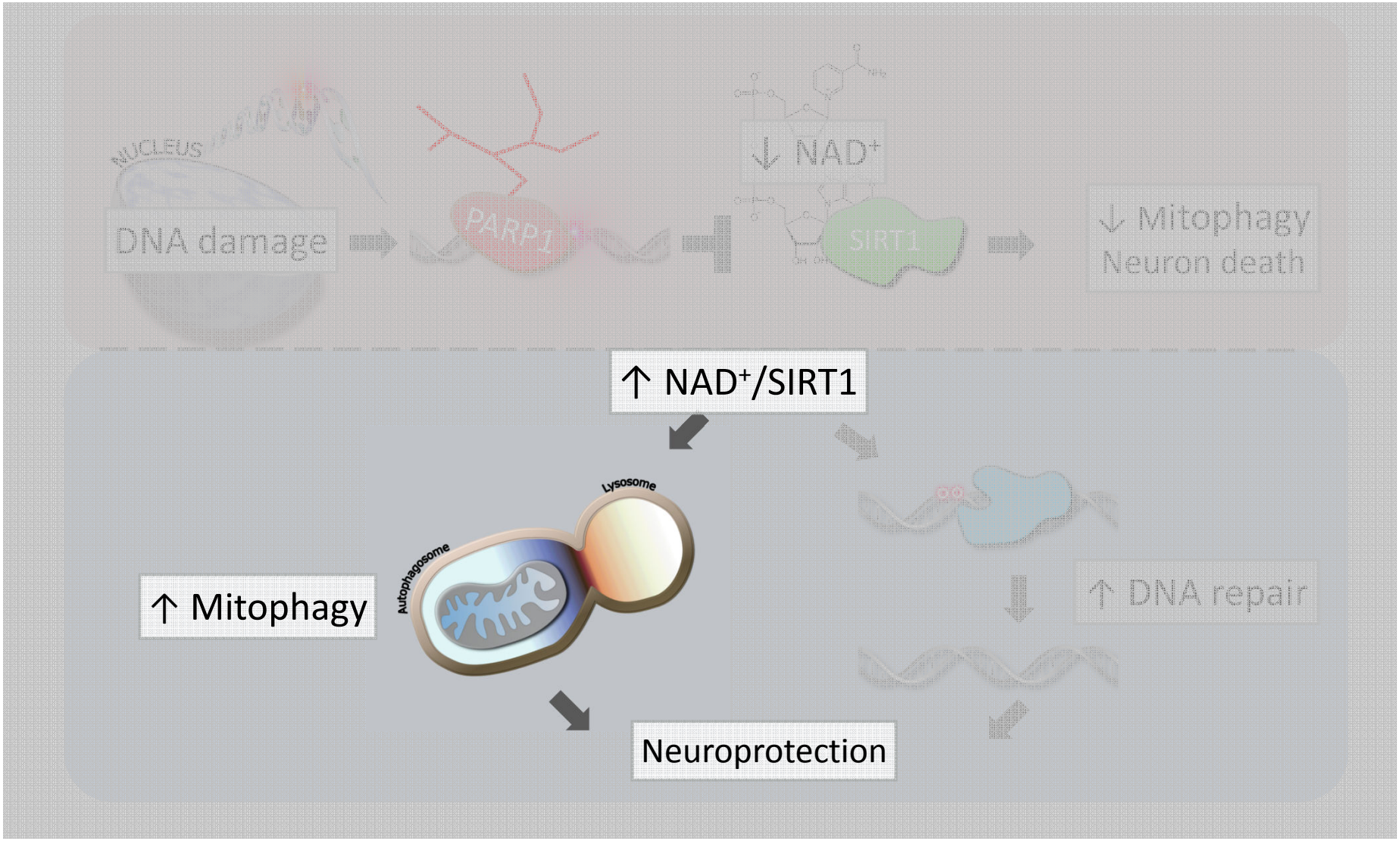
Groups	Life span
N2 (veh)	19.1±0.3
N2 (NR)	20.5±0.3***
N2 (SRT)	20.2±0.3*
N2 (Ola)	19.6±0.5
N2 (NR+SRT)	20.3±0.4*
atm-1 (veh)	16.2±0.2***
atm-1 (NR)	18.3±0.4###
atm-1 (SRT)	18.1±0.3###
atm-1 (Ola)	18.5±0.4###
atm-1 (NR+SRT)	19.0±0.3###

The NAD$^+$/Sir-2.1 signaling increases long term-associated memory in *atm-1* worms

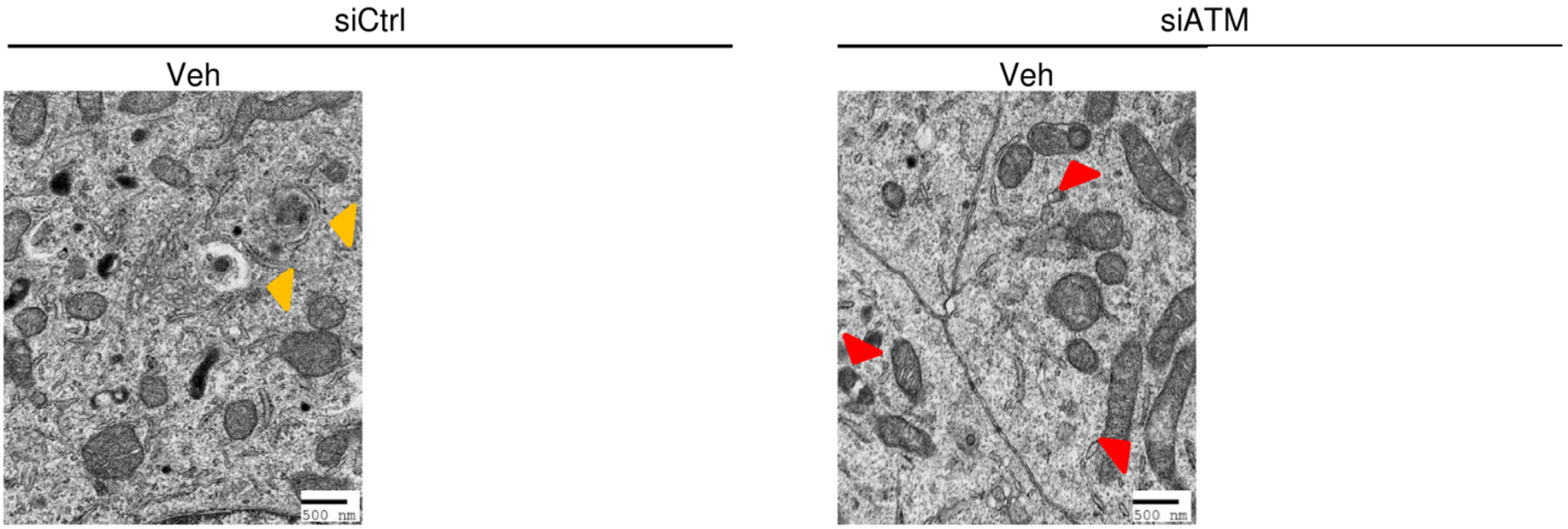


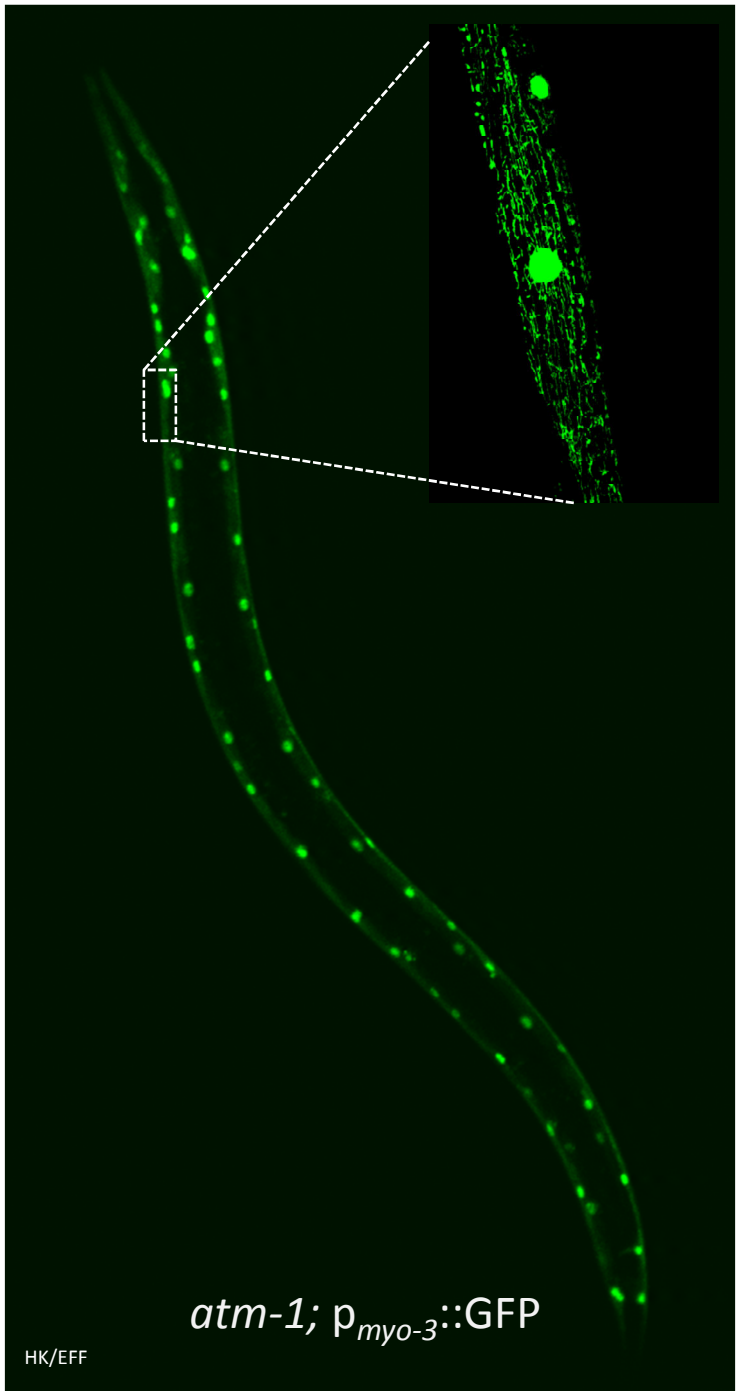
Day 4 adults

What's the role of mitophagy?



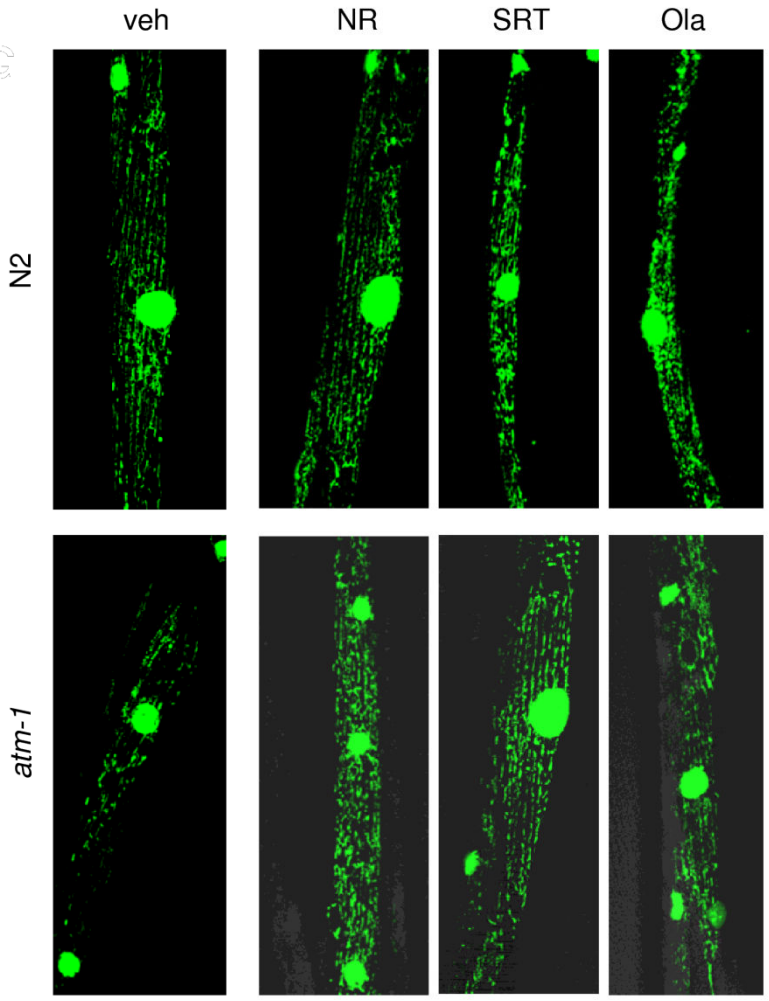
The NAD$^+$/SIRT1 pathway maintains mitochondrial homeostasis in ATM neurons through mitophagy



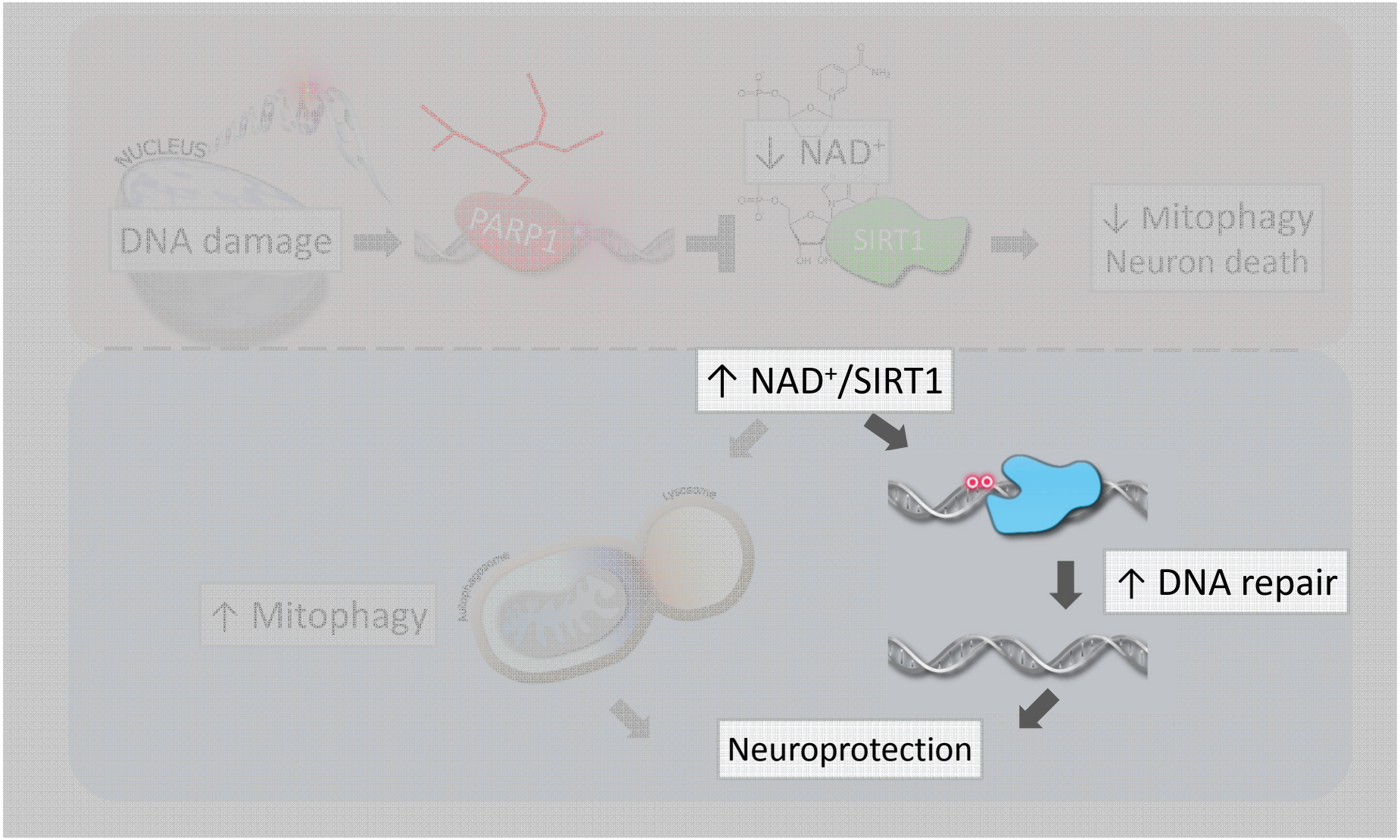


Myo-3 encodes the minor isoform of myosin heavy chain which is muscle-specific

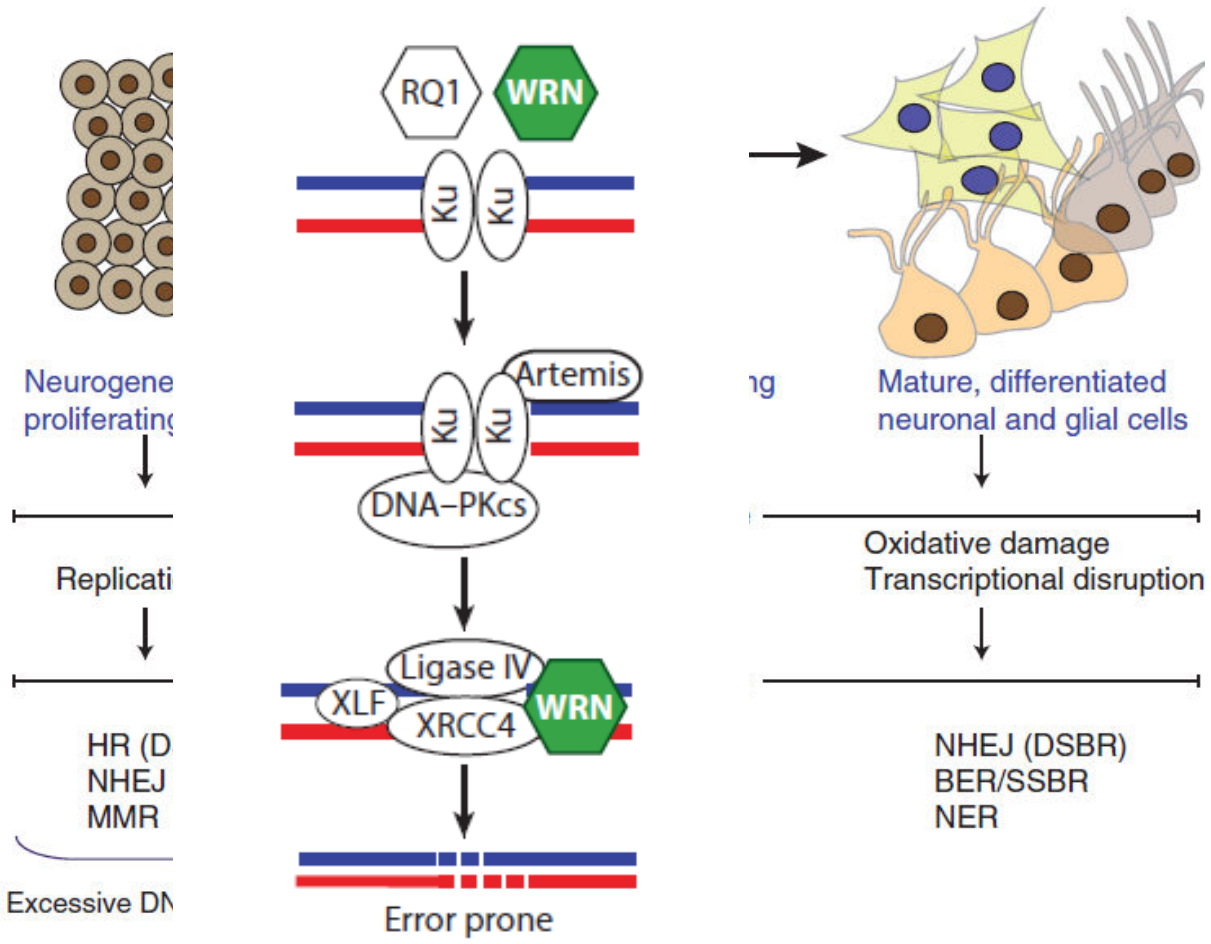
The NAD$^+$/Sir-2.1 signaling reverts impaired mitochondrial networking in *atm-1* muscle cells



Can SIRT1 signaling restore NHEJ in ATM?

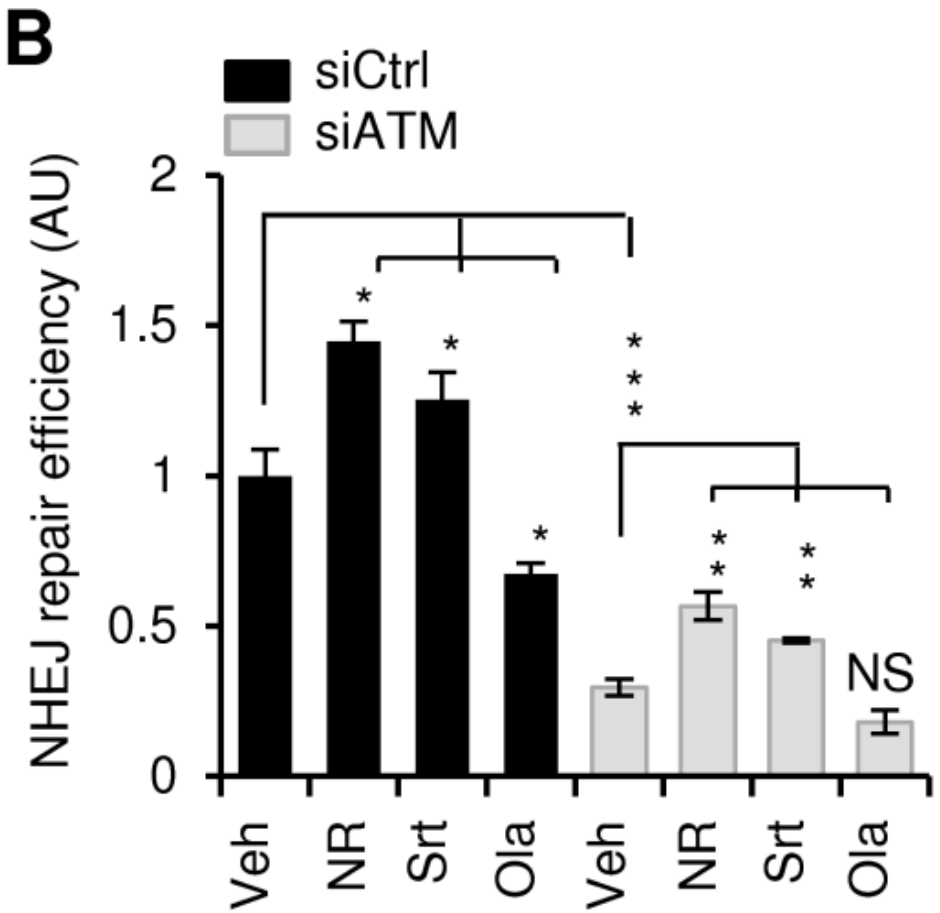


NHEJ is the only DSBR in neurons

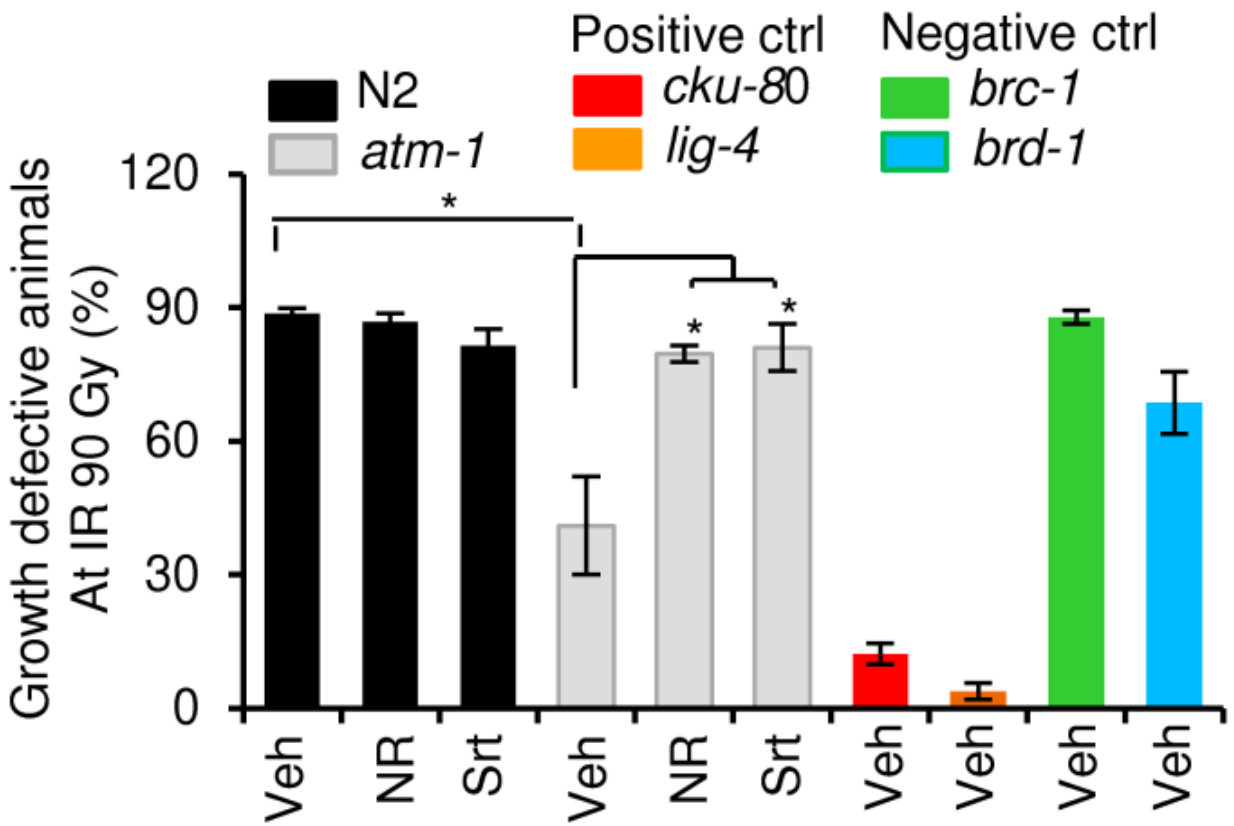


Peter J McKinnon, Nature Neu, 2013
Croteau… Bohr, Annu Rev Biochem, 2014

The NAD$^+$/SIRT1 pathway reverts NHEJ



The NAD$^+$/SIRT1 pathway reverts NHEJ in *atm-1* worms



The NAD$^+$ precursors ameliorates pathological features in *Atm*$^{-/-}$ mice

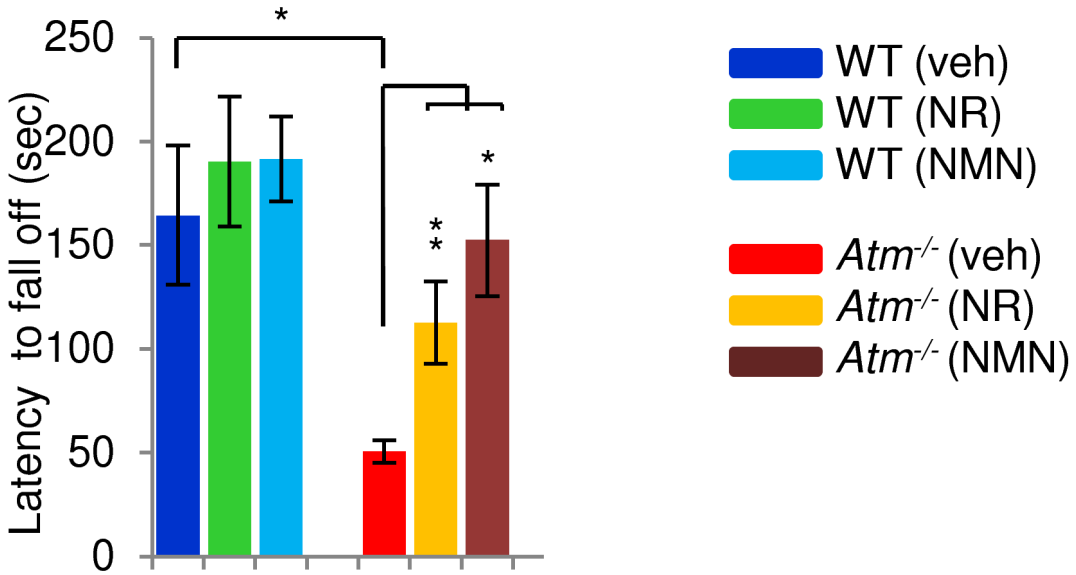
B6;129S4-*Atm*^{tm1Bal}/J

4- 6 males/group, 1 month old

NR: 3.5 mg/ml (12 mM)

NMN: 4.02 mg/ml (12 mM)

14-day with NR/NMN in drinking water (570-590 mg/kg/day)



Summary

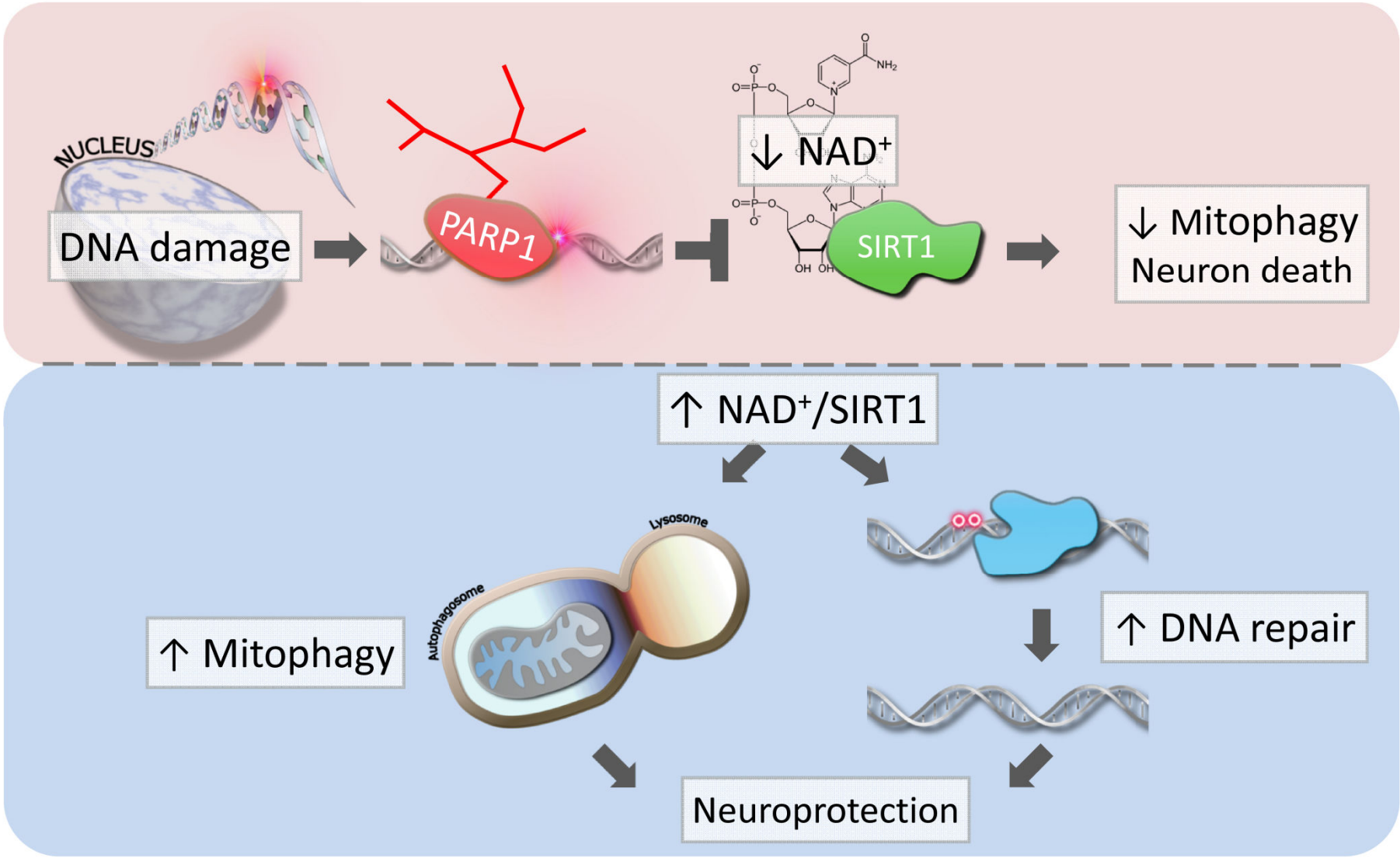
Conclusions

1. Mitochondrial dysfunction in ATM neurons due to NAD^+/SIRT1 reduction
2. Restoration of the SIRT1 pathway ameliorates neuronal pathology of A-T across species
3. Neuroprotection of the SIRT1 pathway may operate via mitophagy and DNA repair

Future Perspectives

1. Molecular mechanisms of sirtuins (1, 3, 6, 7) in DNA repair
2. Exploring the mechanism of nuclear DNA damage to mitochondria signaling
3. Pharmacological intervention in premature aging disorders

Graphical Abstract



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Mark Mattson

Henok Kassahun
Hilde Nilsen

David Sinclair

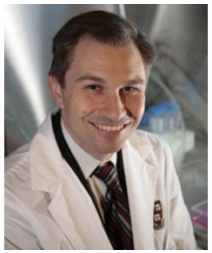
Chromadex
Johan Auwerx
Ann Rose
Yosef Shiloh
Peter J. Mckinnon


Bohr


Croteau


Nilsen


Mattson

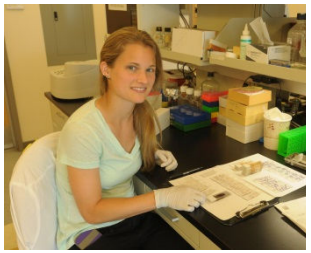

Sinclair


Scheibye-Knudsen


Kassahun


Marosi


Wollman


Froetscher


Iser


Wilson