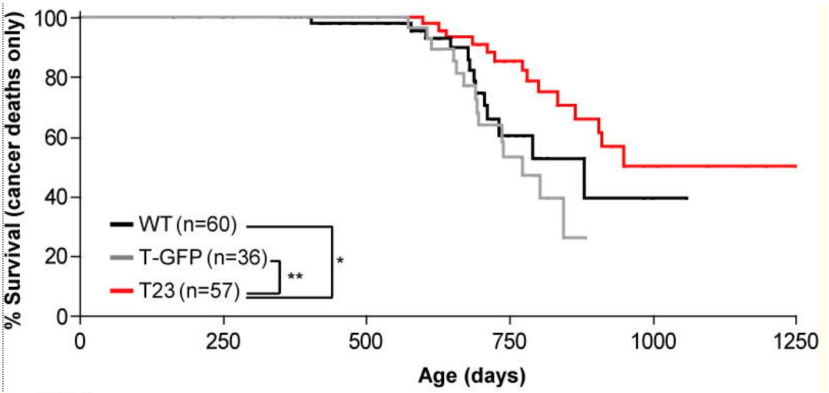
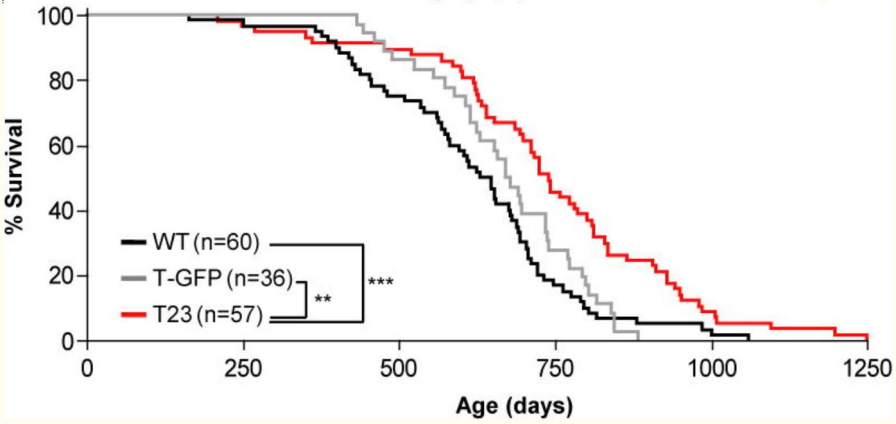
DNA Integrity, DNA Damage Repair and Longevity

Roadmap of Biomedical Research

BUB1B (BUB1R) - mitotic spindle checkpoint kinase

Cancer and overall deaths/survival curves of wildtype, T-GFP, and T23 mice



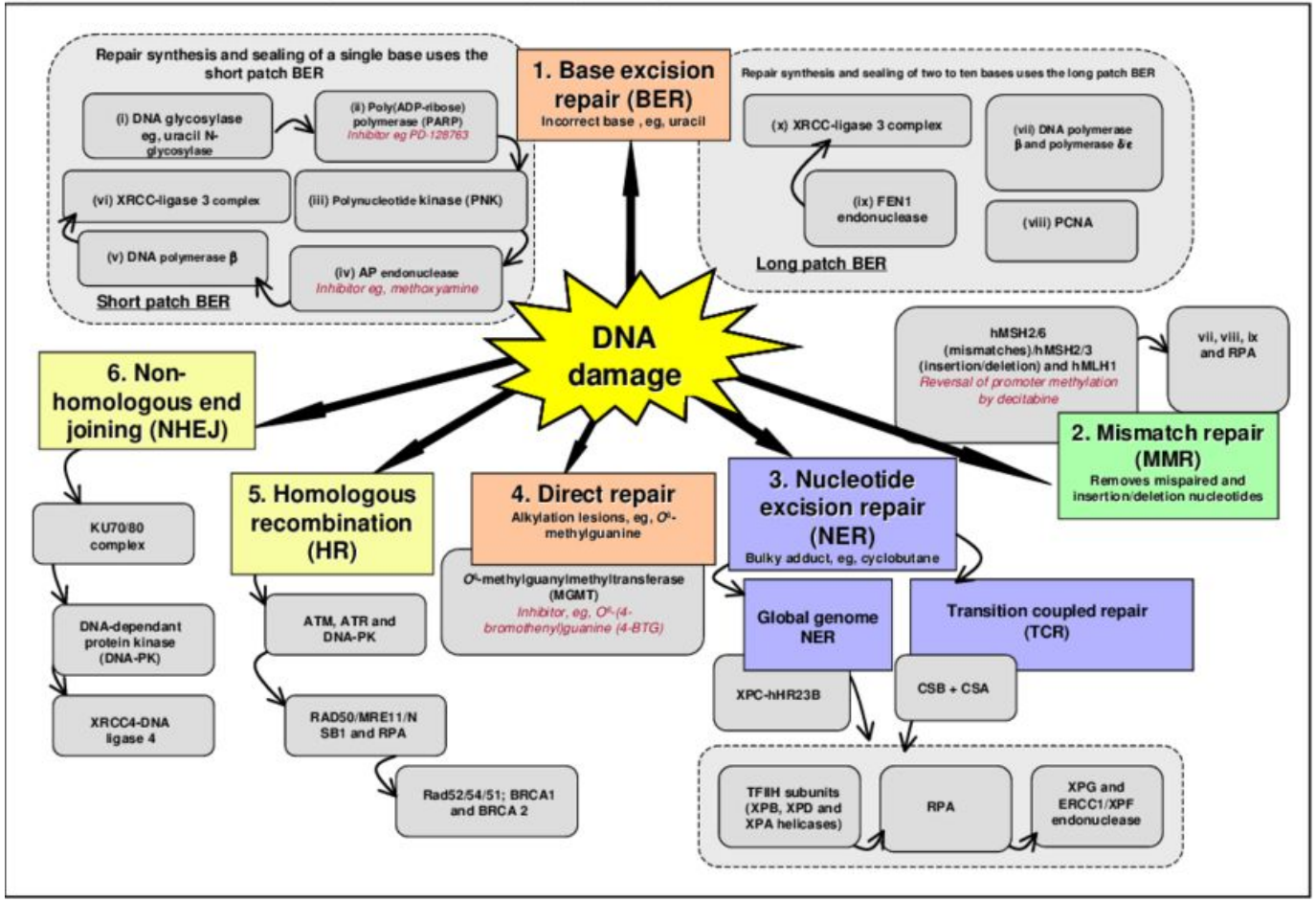


Could increasing Bub1R levels and expression increase longevity and decrease cancer rates in humans?

- Bub1R decreases during aging (Alekseev's calculations)
- Bub1R-activating gene therapy may be risky because Bub1R is increased in some cancers (although decreased in others)
- Pharmacological Bub1R seems like a viable strategy, as it can be easily ceased
- NMN raised SIRT2 and Bub1R in deficient mice and significantly increased lifespan. This is another reason for more clinical research on NMN (in humans)

Baker DJ, et al. Increased expression of BubR1 protects against aneuploidy and cancer and extends healthy lifespan. Nat Cell Biol. 2013 Jan;15(1):96–102.

DNA repair pathways



50.000 - 1.000.000 DNA breaks per cell per day

A number of substances are involved in DNA repair,
but there is not much clinically relevant findings for many of them

DNA repair genes and longevity

Animals

- DNA-PKcs and Ku80 and lifespan across species
- RAD54L and longevity in species
- SNCA gene in long living species
- RAD50 and long-living microbats
- ERCC1, ERCC3 in bowhead whale
- PCNA and longevity in bowhead whale
- HSBP1 in bowhead whale
- XRCC5 in African turquoise killifish
- PARP1 and longevity in mammals
- p53 in long living African elephant

Humans

- RAD52 and longevity in Danish people
- RAD23B and longevity in Danish people
- XRCC5 and longevity in humans
- ATM and longevity in humans
- XRCC5 and longevity in humans
- POLB and longevity in Danish people
- WRN and longevity in Danish people
- EGFR and longevity in Koreans
- ASF1A and longevity
- EXO1 and longevity in Germans
- PARP1 activity and longevity in people, but the relationship is not clear

ATM as the key DNA repair enzyme (DSB repair, HR, NHEJ, SSA)

About

- ATM plays major role in double-strand break repair
- ATM is associated with longevity in humans
- ATM improves mitophagy
- Maintaining youthful ATM levels may be beneficial for longevity
- ATM expression is decreased in aging
- ATM can be elevated or decreased in different cancer
- Estradiol may induce ATM. Can ATM be reduced due to menopause in women?

Pro-longevity treatment strategies

- Why ATM decreases with age?
- Is higher ATM level associated with health and longevity in older people?
- What is optimal ATM level/expression?
- Are there safe ways to maintain youthful ATM levels which are also cancer-preventive?
- Chloroquine increases ATM and reduces against atherosclerosis in ATM+/+apoE-/- mice. Low dose Chloroquine and hydroxychroloquine are beneficial for CVDs, blood pressure, lipid profile, ROS, improve cancer survival. Explore low doses in healthy individuals?

BRCA (HR, FA)

About

- BRCA is reduced during aging
- Mutant BRCA is associate with breast and ovarian cancer
- BRCA loss during aging is associated with ovarian aging
- Sedentary behaviour decreases BRCA1
- Are high BRCA levels associated with health and longevity?
- What are the optimal BRCA levels?

Pro-longevity treatment strategies

- Should BRCA levels be increased in aging humans? How?
- BRCA gene therapy increased survival in ovarian cancer
- 3,3'-diindolylmethane increases BRCA1 mRNA (increase by Brassica vegetables consumption). It may work against endometriosis, cervical intraepithelial neoplasia, pancreatic cancer, neurological deficits after intracerebral hemorrhage. Yet, it has anti-estrogenic effects (or not). Can it be explored in eligible individuals in terms of anti-aging effects? It is strong enough inducer of BRCA?

PAPR-1 (NHEJ, BER, including mitochondrial BER)

About

- PARP1 activity is associated with longevity in mammals
- It is decreased during aging but high in centenarians
- PAPR forms PARs (polymeric ADPr units) formed from NAD+ by PARPs, reducing NAD+
- PAPR1 induces NF-Kb, inflammation, may lead to cell apoptosis
- High PARP1 levels are associated with poor health outcomes
- PARP1 inhibition by olaparib cures BRCA-mutant cancers, increases NAD+, SIRT, protects against kidney, liver damage, post-stroke damage
- Resveratrol, nicotinamide activate PARP1 (both do not increase lifespan)

Pro-longevity treatment strategies

- What is trajectory of PARP1 during aging?
- What is the healthy levels of PARP1, PAR? What are unsafe PARP1 levels?
- Could XPA deficiency in aging cause PARP1 activation?
- Should PARP1 hyperactivation/PAR be prevented?
- Should PARP1 by activated?
- Hydroxyfasudil, fisetin, Ginsenoside Rd, thymidine, 3,5,3'-triiodothyronine (T3), zinc chloride, taurine reduce PARP1/2
- Is this clinically important in terms of anti-aging? Is this due to reduced DNA damage?

SIRT1 (DSB repair, including HR, NHEJ)

About

- SIRT1 gene is not related to human longevity
- SIRT1 is increase in poor aging
- SIRT1 activation increase lifespan in animal models including SRT1720 and epicatechins, but not resveratrol
- SRT2104 failed as it increased glycated haemoglobin
- SRT1720 a more promising SIRT1 inhibitor is not being developed. It increases lifespan in mice, reduced atherosclerotic plaques, reduced arterial stiffness and hypertension
- cAMP inducers/PDE inhibitors increase SIRT1 and may increase lifespan in humans

Pro-longevity treatment strategies

- Is SIRT1 activation effective to increase DNA repair?
- Is long-term SIRT1 activation safe? Can it increase lifespan in humans?
- Promote clinical trials of SRT1720, find out about the progress on it
- NAD+ activators increase SIRT1, including NMN, NR, AICAR, PARP1 inhibitors
- Caloric restriction, NAC, magniferin, berberin, hydroxytyrosol, isoflavones, baicalein, wogonin, epigallocatechin-3-gallate, astragaloside IV, cAMP inducers/PDE inhibitors increase
- increase SIRT1
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SIRT6 (DSB repair, including NHEJ and BER)

About

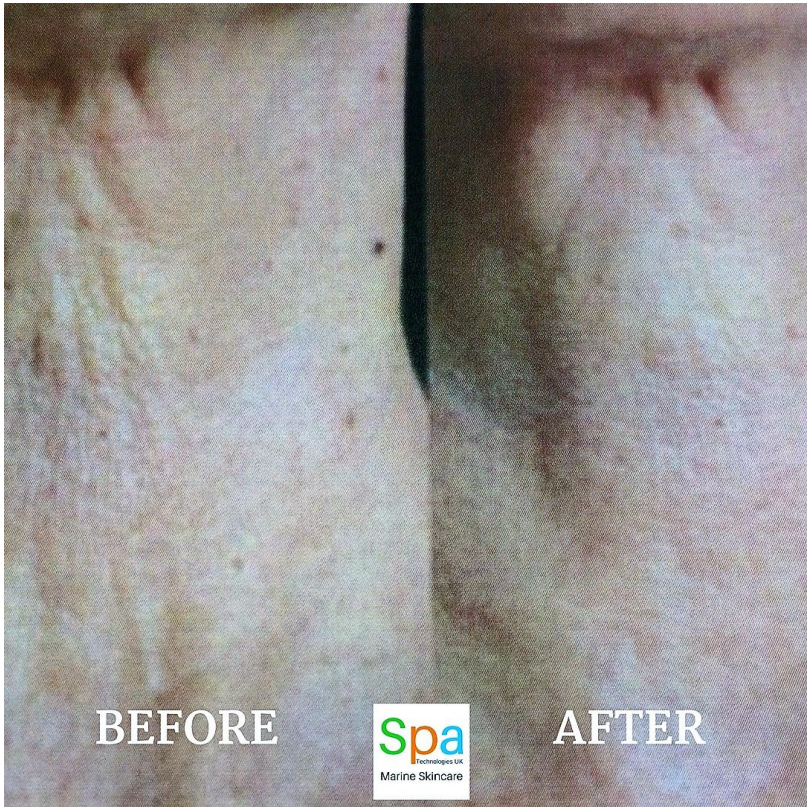
- SIRT6 may be related to evolution of longevity in mammals
- SIRT6 overactivation increased lifespan in male mice
- SIRT6 LINE1 overactivation
- Yet, it may activation inflammation

Pro-longevity treatment strategies

- Is SIRT6 activation safe and clinically relevant?
- Minimally invasive bipolar fractional radiofrequency ^ SIRT6 in the skin
- Cyanidin ^ may increase SIRT6. Can cyanidin inducers be developed pharmacologically?
- Nicotinamide riboside increase SIRT6

DNA repair enzymes (NER) in skin care

- NER DNA repair enzymes T4 endonuclease (T4E), photolyase, and 8-oxoguanine-DNA glycosylase 1 (OGG1) are used in sunblocks or aftersun lotions
- Their use prevents UV irradiation damage, actinic keratosis and basal cell carcinomas
- Should these enzymes be widely used against photoaging?



General questions

- We need to develop and test pharmacological BUB1R activation
- Why ATM decreases with aging?
- Will activating DNA repair increase human lifespan? How it can be done safely without promoting existing cancers?
- Should DNA repair biomarker panels be developed?
- What about all other DNA repair enzymes for which will do not have putative interventions?
- What is behind PARP1 overactivation in aging and disease?