

### **SFB 680**

# Molecular Basis of Evolutionary Innovations

Molekulare Grundlagen evolutionärer Innovationen

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## DNA Damage Accumulation and Genetic Pathways of Longevity

Genome Instability has been recognized as causal factor of cancer and recently also as a major contributing factor of aging. A number of skin cancer susceptibility and progeroid (premature aging-like) syndromes are linked to defects in nucleotide excision repair (NER). NER thus provides a highly relevant experimental system to study the role of genome integrity both in cancer and in aging. Using the NER system we recently uncovered a novel link between DNA damage accumulation and the regulation of longevity assurance programs and tumor suppressor mechanisms. Based on genome-wide comparative correlation analysis we uncovered similarities between progeroid mouse models and mice with extended longevity. Furthermore, we demonstrated the validity of genome-wide correlation analysis for assessing biological aging. Mechanistically, we identified a response program to persistent DNA damage that is triggered amid increasingly damaged genomes with aging. DNA damage treatment in vitro led to similar gene expression changes as observed in various tissues with aging. Low amounts of persistent lesions that interfere with RNA polymerase II elongation led to attenuation of somatotropic genes that is linked to extended longevity. Functionally, this response program evoked enhanced stress resistance and antagonized hyperplasia. We propose that sensing of low levels of persistent DNA damage by RNAPII comprises a mechanistic basis for hormesis and shifts the organism's resources from growth to somatic maintenance in aging.

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4:30 p. m.

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