Genotoxic stress resistance and cellular senescence in the blind mole rat cells

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The subterranean mole rat, *Spalax*, is a long-lived rodent (~20 years) that tolerates hypoxia and resists cancer, which implies molecular adaptations to prevent genomic instability underlying cancer and aging. We question whether *Spalax* cells resist genotoxic, accumulate less genotoxic lesions, and maintain enhanced repair capacity. Since persistent DNA damage response triggers senescence, we also addressed cellular senescence program in *Spalax* cells. Cellular senescence is an important program evolved to stop the division of damaged cells. Yet such cells also express an inflammatory signature. Accumulating with aging, these cells induce chronic inflammation and support cancer-promoting microenvironment. In this context we investigated whether cellular senescence in *Spalax* cells is associated with inflammatory responses known in human and other animals' cells. In contrast to mouse and human, senescent *Spalax* cells did not accumulate DNA damage and showed undetectable expression of inflammatory cytokines, indicating the uncoupling of the inflammatory response from cellular senescence as a unique feature of *Spalax* senescent cells. Our results strongly support that this species has evolved efficient mechanisms to maintain DNA integrity and to avoid age-related maladies as prerequisites of survival and fitness under the stressful conditions in its subterranean habitat.

Research questions:

- What are mechanisms standing behind the longevity and cancer resistance in this mammalian group?
- What are the driving forces for such uncommon features in rodents?

References:

Resistance to DNA damage and enhanced DNA repair capacity in the hypoxia-tolerant blind mole rat Spalax carmeli. J Exp Biol. 2018 Apr 20;221

Genome maintenance and bioenergetics of the long-lived hypoxia-tolerant and cancer-resistant blind mole rat, Spalax: a cross-species analysis of brain transcriptome. Sci Rep. 2016;6:38624

Pronounced cancer resistance in a subterranean rodent, the blind mole-rat, Spalax: in vivo and in vitro evidence. BMC Biol. 2013.