Modeling aging and degenerative disease in DNA repair-deficient *Drosophila*

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As cells age, they accumulate DNA damage that can lead to genomic instability, mutations, and cancer. DNA repair proteins, such as Werner (WRN), have essential roles preventing and repairing DNA damage caused by stress from the environment, DNA replication errors, and free radicals. In humans, mutations in *WRN* lead to Werner syndrome (WS), a heritable disease characterized by patients' early onset of aging, increased risk of cancer and other age-related pathologies. My lab uses *Drosophila* mutant in the fly homolog of *WRN*, *WRNexo*, to elucidate its role in DNA repair and aging. While human WRN has both an exonuclease and helicase domain, the *Drosophila* homolog, *WRNexo,* only contains an exonuclease domain, providing us with a unique model to study exonuclease-specific functions largely uninvestigated in human cells. Previous studies have shown that *WRNexo* has exonuclease activity and acts on similar DNA substrate as human WRN. Similarly, flies with *WRNexo* mutations, (*WRNexo*$^{\Delta}$) are sensitive to reagents that cause DNA replication stress demonstrating that *WRNexo* is important in maintaining normal DNA replication.

We have recently found that compared to age-matched wild type controls, *WRNexo*$^{\Delta}$ flies exhibit increased physiological signs of aging. *WRNexo*$^{\Delta}$ adults have higher tumor incidence and shorter lifespans. Compared to wild-type controls, aged *WRNexo*$^{\Delta}$ flies display degeneration of their flight muscles, reduced climbing ability, decreased activity, and altered behavioral patterns. *WRNexo*$^{\Delta}$ larvae have lower body fat compared to wild-type controls, suggesting that metabolic differences in this developmental stage may influence the observed aging phenotypes. Interestingly, these effects are more pronounced in females suggesting sex-specific differences in the role of WRNexo in aging.

Because accumulation of damaging free radicals is commonly associated with aging, we hypothesize that age-related pathologies observed in *WRNexo*$^{\Delta}$ flies are caused by free-radical damage. *WRNexo*$^{\Delta}$ adults have higher total antioxidant activity that declines with age indicating a larger free radical burden. Additionally, *WRNexo*$^{\Delta}$ adults show altered behavior and shorter lifespans when subjected to stress via high temperature and starvation. Interestingly, exposure to either vitamin C (antioxidant) or alcohol (free radical generator) restored body fat in *WRNexo*$^{\Delta}$ larvae to wild-type levels. These data suggest that that some free radical damage may increase antioxidant defenses and equip *WRNexo*$^{\Delta}$ mutants to better respond to oxidative stress. Furthermore, this response may indicate a role of *WRNexo* in maintaining normal metabolism. This and future studies will contribute to our knowledge of DNA repair mechanisms and their role in aging.