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My lab is interested in the molecular biology of aging and cancer. We have been taking a genetic approach to this problem, and have been working to understand how a loss of function of a single gene can cause the human segmental progeroid disorder, Werner syndrome (WS). WS is of interest as it shows many features suggestive of accelerated aging, including an increased incidence of cancers, diabetes and cardiovascular disease. The gene defective in WS, Wrn, encodes a predicted protein with both helicase and exonuclease activities. Our earlier in human cells and in yeast implicated a role of Wrn in telomere processing. In recent years, we have refined a role of Wrn protein in telomere maintenance. We have developed a model of the Wrn protein in unwinding alternative DNA structures that form on replication protein A (RPA) coated filaments. RPA is a protein that is commonly used to “package” single stranded DNA that is generated during multiple processing events, including transcription, replication, and repair. Specifically we demonstrated that WS cells show increased sensitivity to arrest in response to genotoxic stress during the G0 phase of the cells cycle, due to deletion of telomere sequences occurring during repair of telomere breaks by non-homologous end joining.

Alternative mechanisms to remove secondary structures that form on RPA coated single-strand DNA filaments also cause WS to be a “telomere fragility” disorder. Lack of repair of lesions in DNA causes pausing of polymerase, which in turn generates RPA-single-strand DNA filaments secondary to dissociation of the helicase and polymerase activities of the replication complex. When such pausing occurs in telomeres, in WS cells we are demonstrating that the pausing event must be set by a recombination event. This event when it occurs in telomeres (a simple repetitive sequence) also causes deletion of telomere sequences.

Graduate students and post-docs who work in my lab will be trained in a comprehensive approach to the study of mammalian aging and disease. Our goal is to understand how individual gene changes modulate the rate of appearance of age-related phenotypes and disorders. The work we do extends from studies of gene regulation and gene expression up to how alteration of expression of individual genes affects phenotypes in mammals, using mice as a model system for mammalian aging.

