The National Institute of Environmental Health Sciences: Powerful Techniques for Studying DNA Damage Recognition and Repair

This research project uses very powerful electron microscopic techniques to study DNA repair and DNA damage recognition. The researchers also study telomeres, which are structures of repetitive DNA sequences at the ends of chromosomes.

Lead Agency:

The National Institute of Environmental Health Sciences (NIEHS)/National Institutes of Health (NIH)

Agency Mission:

The mission of the NIEHS is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease.

Principal Investigator:

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General Description:

Powerful Techniques for Studying DNA Damage Recognition and Repair
Single molecule electron microscopy provides a powerful approach for studying the way in which damaged DNA is remodeled by proteins. The focus of this application is to understand how a number of central human DNA repair and telomere binding proteins interact at large, complex DNA structures containing damage, and how they carry out repair or signal the presence of lesions. This is a highly interactive program which represents longstanding fruitful collaborations with Dr. Paul Modrich working on human mismatch factors, Dr. Aziz Sancar working on human repair signaling factors, and with Dr. Titia deLange working on telomere binding proteins. Together from our own work on this topic and through these collaborations we have published over 20 papers in the past 5 years. This is a highly propitious time to carry out these studies since we have developed two powerful new EM methods: nano-scale biopointers that provide a means of identifying the location of proteins within multi-protein complexes and glycerol spray/low voltage EM that provide a more gentle means of preparing samples for EM. Further, as substrates for these studies, we have produced large natural DNAs containing replication forks or Holliday junctions with nearby mismatched bases and a model telomere DNA. Work on the mismatch repair proteins will take advantage of the recent in

vitro reconstitution of nick directed excision repair by the Modrich laboratory. Work on Claspin and the Rad 9- Husl-Radl complex will focus on learning how these proteins interact with replication forks containing damage. Studies of the remodeling of telomeres will take advantage of the recent discovery of discrete multi protein complexes at telomeres. Finally continuing work from our laboratory will focus on p53 as a facilitator of DNA damage recognition. Each system offers a unique window into basic questions of DNA protein remodeling at sites of damage and telomeres and information garnered from one study is immediately applied to the others.

Excellence: What makes this project exceptional?

The research team has discovered a fundamental difference between the telomeres of the roundworm *C. elegans* and those of mammals. Telomeres act like buffers preventing chromosomes from fusing together or rearranging. Those types of abnormalities can lead to cancer. The team found that roundworm telomeres are rich in the compound cytosine as opposed to mammalian telomeres which are rich in guanine.

Significance*:* How is this research relevant to older persons, populations and/or an aging society?

As humans and all higher organisms age, the telomeres at the ends of their chromosomes shorten. Very short telomeres, reached after several cell divisions, signal the cell to go through programmed cell death, thus preventing the chromosomes from rearranging in ways that have been associated with the development of cancer. However, in some forms of cancer, the death signal is not sent and the tumor cells continue to divide allowing the cancer to grow and spread.

Effectiveness: What is the impact and/or application of this research to older persons?

For the most part, cancer is a disease associated with aging. In fact, most people, if they live long enough, will develop some form of cancer in their lives. By identifying methods to prevent or treat cancer, we can extend the healthy years of life for all people.

Innovativeness: Why is this research exciting or newsworthy?

This research team will now search for cytosine-rich telomeres in mammalian cells. If they are found, they could play a role in extending telomere maintenance and in cancer prevention. The research team hopes to exploit these findings in stopping cells from becoming cancerous or killing early stages of cancer by blocking an enzyme critical in telomere synthesis.