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### *Molecular Carcinogenesis*

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### RESEARCH INTERESTS

My laboratory is interested in mechanisms of DNA replication and cell cycle-dependent induction of mutagenesis and carcinogenesis. Current research is focused on how human S phase cells initiate DNA synthesis and how they replicate DNA containing lesions caused by UV light or chemical carcinogens (post-replication repair). Mechanisms that operate at the level of DNA replication forks to inhibit

synthesis or to promote bypass of unrepaired lesions are being investigated. These studies will help to elucidate the relationship between post-replication repair and S phase checkpoint responses in human cells.

Recent studies have included the biochemical characterization of bypass replication of UV-induced pyrimidine dimers using plasmid DNA carrying the SV40 origin of replication and in vitro replication assays. Fibroblasts derived from normal individuals or from patients with xeroderma pigmentosum (XP) were used in these experiments. XP cells from the variant group are proficient in nucleotide excision repair, but are defective in post-replication repair following exposure to UV light. This defect is associated with UV-induced hypermutability of XP variant cells in culture and a high incidence of skin cancers in XP variant patients. We have established that replication-competent extracts from XP variant fibroblasts are defective in bypass replication of a site-specific pyrimidine dimer. Based on these studies, other groups discovered that the XP variant trait is due to mutations in the gene for a novel DNA polymerase (pol eta) that is capable of efficiently replicating past a thymine dimer.

Analysis of the structure of intermediates of DNA replication demonstrated extended single-stranded regions on the template to the leading strand beyond the site-specific dimer. These single-stranded regions are formed by the polymerization of the lagging strand while the leading strand synthesis is blocked by the dimer. The displacement of the replication fork beyond the lesion and the uncoupling of leading- and lagging-strand synthesis suggested that template switching was a plausible mechanism by which human cells could catalyze the fast and error-free bypass of pyrimidine dimers. Recent data from our laboratory, however, suggest that translesion synthesis is the primary mechanism of bypass replication of thymine dimers in duplex DNA.

Future initiatives will extend our studies of bypass replication to include DNA lesions caused by different genotoxic agents, as well as the characterization of signal transduction pathways involved in DNA damage-induced inhibition of DNA replication. In collaboration with other Cancer Center investigators, we are also involved in the cloning and characterization of DNA sequences where DNA replication initiates at the start of the S phase of normal human fibroblasts. The effects of radiation on the activity of these origins are also under investigation.

### SELECTED PUBLICATIONS

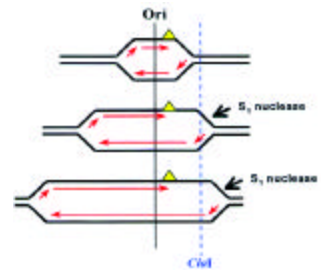
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Uncoupling of leading- and lagging-strand DNA synthesis at a replication fork with a DNA lesion on the leading strand template. The resulting single-strand DNA region is resistant to digestion by the restriction enzyme but sensitive to S<sub>1</sub> nuclease.