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Role of the 26S Proteasome in Regulation of DNA Repair

[Our goal is to elucidate the role of the 26S proteasome in regulating eukaryotic nucletide excision repair *invivo* by determining the rates of nucleotide excision repair and the stability and abundance of NER proteins in yeast strains with conditional proteasomal mutations.]

Maintaining the integrity of genetic material is critical for the survival of an organism and for species. All organisms are exposed to a large number of physical and chemical agents that can damage their DNA. Essential cellular processes of transcription, DNA replication, and the cell cycle are extremely sensitive to DNA damage. Perturbation of these processes can lead to altered function or cell death. At lower, non-lethal levels of DNA damage, unrepaired or misrepaired DNA can cause mutations, perhaps leading to cancer, genetic defects, and cellular aging. Connections between defects in DNA repair and cancer were shown for the cancer-prone diseases *xeroderma pigmentosum* and human nonpolyposis colon cancer (Lynch syndrome). Therefore, it is imperative that most of the DNA damage be correctly repaired. A major pathway dealing eith removal of DNA damage is nucleotide excision repair.

One way that the levels of proteins in cells can be controlled is by their destruction. The 26S proteasome is responsible for degrading many cellular proteins. Our goal is to determine the role of the 26S proteasome in nucleotide excision repair in living cells. To this end we will determine the roles of the proteasome on transcription-coupled repair and overall nucleotide excision repair. The significance of DNA repair deficiencies in human diseases is well documented and the studies we propose will clarify the role of protein degradation in controlling repair. Our preliminary studies with proteasomal mutants have already pointed to a direct role for the 26S proteasome I controlling DNA repair. Our approach may lead to clinical treatments that modulate protein degradation and prevent mutagenesis or improve DNA repair, therby reducing the incidence of cancer.