



The Deininger Lab: Retrotransposon-Mediated DNA Damage & Repair

Most of the human genome (~97%) does not code for proteins -- but is made up of regulatory elements and different types of repetitive DNA sequences. Some of these sequences, called retrotransposons, are capable of copy-and-pasting themselves into new genomic locations. This creates the possibility for insertional mutagenesis, which can have adverse effects on human health. With the repetitive nature of these retrotransposons within the genome, they can serve as an inappropriate substrate for DNA repair processes that rely on DNA similarity for accuracy. This can lead to an increase in genomic instability, which is a hallmark of many human diseases, most notably cancer. Dr. Prescott Deininger studies how the short human retrotransposon Alu can affect DNA repair processes and contribute to genomic instability in both normal and cancerous cells.

Inappropriate Recombination DNA Repair and Alu

Alu/Alu recombination occurs when DNA damage arises within close proximity of two Alu elements within the genome. Given that Alu elements are spaced roughly every 3 kb in the human genome, this happens with some frequency. Additionally, Alu elements are enriched in genes, meaning that potential recombination events have a high chance of adversely effecting genes. Reflective of this is that fact that much more human disease has been linked to Alu-Alu recombination than Alu insertional mutagenesis. Human tumors are an especially active environment for this type of inappropriate DNA repair, as it occurs 50 times more frequently in human tumors than in matched normal tissue. Dr. Deininger studies why this happens using a unique cell culture-based assay, in addition to his work developing a unique mouse model.

This approach is unique in the field because it focuses on the substrate (the two nearby Alu elements) of the DNA repair pathways instead of the DNA repair pathways and how this can affect human disease. This allows for different environmental and genetic conditions that are known to be important to cancer development, like DNA repair deficiencies and environmental exposure to heavy metals, to be interrogated in the context of Alu-Alu recombination and the resulting genomic instability.

Cancer Biology: DNA Damage & Repair

Mouse Model Bridging Tissue Culture & Patient Data

This novel mouse model can study the effects of Alu-Alu recombination on genomic instability, as the engineered mouse has two Alu elements flanking an exon of the tumor suppressor gene p53. The repair of any DNA damage between these two elements will be influenced by the two Alu elements, likely leading to the deletion of the p53 exon and carcinogenesis. The resulting tumor will contain enough genetic material to analyze the DNA repair event. This model system provides an until-now absent link between tissue culture models and *post hoc* analysis of patient tumor samples. Additionally, this model system can be integrated with common DNA repair-deficient mouse backgrounds to study DNA repair deficiencies that are both 1) important to cancer and 2) known to influence DNA repair product outcomes.

Second Generation Sequencing Analysis

Current tissue culture-based systems for interrogating Alu-Alu recombination events rely on antibiotic selection. This approach is limited by the fact that only certain repair products can confer antibiotic resistance to cells, meaning that a proportion of repair products are missed during analysis. It is likely that any of these are small deletion- or insertion-inducing Non-Homologous End Joining Events, which are by far the most common DNA repair product in double-strand break repair. The lab has developed a second-generation sequencing-based assay to correct this deficiency.

The application of targeted sequencing to the specific *locus* means that all repair events can be analyzed. This is useful in assessing the impact of different DNA repair deficiencies and pharmacological alteration to DNA repair on Alu-Alu recombination: important to both understanding the genesis of and developing treatments for a variety of cancers. This data can be paired with already available clinical data from patients regarding the frequency of Alu-Alu recombination-mediated genomic instability in genetic diseases like cancer. Through implementing these assays, the lab is well-equipped to study the mechanics and possible health ramifications of Alu-Alu recombination.

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