Retrotransposon Biology: DNA Damage & Repair

Retrotransposon-Mediated DNA Damage & Repair

Almost two thirds of the human genome is composed of repetitive DNA sequences. A fraction of these sequences, called retroelements, can amplify within the genome through a copy-paste-like process. This can lead to insertional mutagenesis and other forms of DNA damage through the enzymatic processes that these elements use to amplify themselves, and is thought to adversely impact human health by facilitating disease states such as cancer and infertility in males.

The lab of **Jeff Han** studies the host factors that are necessary for these genetic entities to amplify themselves within the genome. The lab employs a suite of unique approaches and systems, including yeast and mouse models. By identifying necessary host factors, it may be possible to mitigate the damage these elements can cause to the genome.

Finding Retroelement Host Factors

Early on in his career, Dr. Han identified the ESCRT protein machinery as being essential for retrotransposition. This was unexpected, as these proteins are normally involved in membrane budding and vesicular trafficking. These proteins are among a limited number of known positive regulators of retroelement activity. Normally, screens that identify putative cofactors of retrotransposition rely on immunoprecipitation from animal cells. This normally results in generic nucleic acid binding proteins being identified, along with negative regulators of retrotransposition.

In order to identify positive regulators of retrotransposition, the lab uses two different strains of yeast that overexpress retroelement proteins. In one strain the elements can jump, in the other they cannot. By comparing the yeast proteins that associate with the retroelement proteins between the two strains, positive/necessary regulators of retrotransposition can be identified. The equivalent proteins can then be identified in humans, and their effects on the possible pathological importance of retrotransposition to health can be tested using a mouse model of infertility.

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Retrotransposition & Infertility: Applying Basic Biology

Retrotransposition is thought to contribute to infertility by interfering with the ability of spermatogonial stem cells to mature fully. For example, in the infertile MAELSTROM knockout mouse, males are infertile and retrotransposon activity is markedly elevated. Excessive double stranded DNA breaks appear during spermatogenesis, cells arrest in meiosis, and the cells eventually die. The lab plans on using this model to test the hypothesis that loss of transposon silencing contributes to mammalian infertility.

Spermatogonial stem cells from this mouse model can be isolated, grown in culture and genetically modified using the CRISPR system to be deficient for host factors critical for retrotransposition. These cells can then be transplanted into wild-type mice that have had their own germ cells cleared from the testes. By deleting necessary genes for retrotransposition, they should be able to determine whether loss retrotransposon activity alleviates meiotic catastrophe.

Basic Biology and Blocking Retrotransposon Activity

The lab also focuses on more basic aspects of retrotransposon biology. Most of the structural proteins that retrotransposons rely upon to propagate themselves are found in the cytoplasm. The notable exception to this is in later stage breast cancer, which is known to exhibit nuclear staining for the protein and have increased genetic instability. The lab is currently developing an estrogen receptor fusion protein-based reporter system that will allow them to screen for genes that keep the retrotransposons locked in the cytoplasm under normal circumstances.

Additionally, the lab is also working on developing a yeast system to screen for small circular peptide chains that can inhibit the DNA cutting ability of the retroelement. The data generated by these efforts will ultimately be leveraged to better understand how retroelements contribute to human disease and what could be done to mitigate the genetic damage they are capable of causing.

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