A Deeper Look into RNA Splicing

At the forefront of current virology research lies an uncannily evasive virus called human immunodeficiency virus, or HIV. Since its late discovery in the 1980's, the virus has been found to cause Acquired Immunodeficiency Syndrome, or AIDS, a disease of the immune system that can lead to a number of unusual malignancies such as Kaposi's sarcoma, Burkitt's lymphoma, and cervical cancer (Stoltzfus 2009). The CDC estimates that there are currently about 1 million individuals living with HIV in the US, 16% of which are unaware of their infection (Centers for Disease Control and Prevention [CDC]; 2010). Although scientists have developed treatments through "cocktail" anti-retroviral drugs, there still remain many economic and social barriers to achieving therapy around the world. Attempts at singular pharmacological therapies have been for the most part ineffective, for which the nifty biology of HIV is to blame.

In the cells of eukaryotes, including animals, humans, and plants, a large structure called the spliceosome targets specific sequences on RNA (single-stranded copies of DNA) and cuts, or splices, the nucleic acid. The spliceosome removes introns, or regions of RNA that do not code for proteins, and leaves behind a connected strand of genes that will play an active role in protein synthesis. A single RNA transcript can be spliced many different ways to leave behind unique combinations of genes, and through this process of alternative splicing, multiple proteins can be made from a single RNA genome.

Viruses like HIV take advantage of alternative splicing, as it allows them to produce all of the proteins and enzymes needed for viral replication and infection from one efficient strand of RNA (Stoltzfus 2009). In fact, the HIV genome is alternatively spliced to create more than 40 different mRNAs, depending on where the pre-mRNA transcript is spliced (Tazi et al. 2010). Thus, from a single RNA strand, the HIV virion is able to create dozens of unique proteins that are involved in viral replication and targeting cells of the immune system. It is precisely this splicing mechanism that allows the HIV genome to be about 500 times shorter (and thus, more efficient) than the E. coli genome, which does not have the benefit of splicing mechanisms.

Maity's experiment takes a closer look at how seemingly negligible mutations can be utilized to alter the splicing mechanism, effectively deciding the protein structures to be produced. Specifically, Maity has chosen to focus on the Wilms' Tumor gene. This gene plays a differential role in the transcription maintenance, and the production of the associated protein structure is dependent on the proper function of an upstream mRNA segment (Haber et al. 1991; Madden et al. 1991). If this upstream segment is improperly spliced out of the genome, in a similar mechanism to alternative splicing, the individual can develop a severe form of adolescent kidney cancer. As a result, studying this process is important to our understanding of not only the splicing mechanism, but also the origin of a fatal adolescent cancer (Bergmann et al. 1997). For this reason, splicing is often the focus of

of biomedical studies on the pathology and possible treatment of various illnesses.

In her experiment, Maity uses a form of "directed evolution," generating hundreds of pre-mRNA sequences that each has a unique set of mutations. With the help of powerful biomedical algorithms, Maity is able to analyze any changes to the splicing process that result of these mutations. By generating a causal link between the pre-mRNA structure and its functionality downstream from the transcription process, she has taken an important step towards understanding the power of alternative splicing.

References

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