Cancer Biology: Environmental Influences

The Belancio Lab: DNA Damage & Repair

Protein-Coding genes make up a minority (~3%) of the human genome. The rest is comprised of assorted regulatory sequences and different types of repetitive DNA, some of which have the ability to copy-paste themselves into new genomic locations. One of these so-called retroelements, Long Interspersed Element 1 or L1, relies on two proteins to do this. L1 can cause DNA damage through insertional mutagenesis when it copies itself into a new genomic location. More commonly, the enzymatic activities of the L1 ORF2 protein (ORF2p) cause various types of DNA damage.

Dr. Victoria Belancio studies how the L1 elements and its proteins 1) cause DNA damage, 2) are regulated by the host cell, and 3) may be involved in carcinogenesis. The techniques employed allow for the study of all aspects of L1 biology, from mechanistic biochemistry work to tissue culture models; and animal models to patient data. This is important because the real-life impact of L1 has yet to be definitely demonstrated beyond correlative data in patient tumor samples.

Environmental Modulation of L1 Activity

A principal focus is how known carcinogenic conditions impact L1 biology. Recently, light exposure at night has gained recognition as a probable carcinogen – as it is known to disrupt production of the hormone melatonin, a central player in the circadian system. The lab has shown that L1 is likely regulated by melatonin (probably through the L1 structural protein ORF1p), and is studying the effects of circadian disruption on L1 biology in the whole animal context of a rat model.

Additionally, data is being analyzed from a survey of more than 600 pediatric and adolescent patients regarding their exposure to light at night. This is notable as this population is understudied, despite a wealth of literature noting their special sensitivity to circadian disruption. By integrating these different models and data sets, this research paints a holistic picture of the interplay between L1, the circadian system, and its possible impact on human health. Lastly, there is a focus on studying the effects of environmental heavy metal exposure on L1 activity to determine the associated implications for human health and cancer risk.

Tulane
SCHOOL OF MEDICINE

Modeling Aging & Carcinogenesis Using Rodent Models

L1 is known to be active in both tumor cells and (to a much lesser extent) normal human cells, but the specific relevance to human health remains unclear. Animal models are being used to fill this gap in knowledge, so a rat model with a transgenic L1 copy is used to study the interplay between aging, the circadian system, and DNA repair. The lab has also generated a novel mouse model with a transgenic human L1, that is employed to study DNA repair deficiencies common in a variety of cancers (*i.e.* breast, prostate, & lung) and how they affect tumor formation and progression. This work bridges the gap between studies of basic L1 biology conducted using cell lines and the observed increase in L1 retrotransposition in a spectrum of human cancers.

Basic Protein Biology

In addition to the study of global L1 regulation and the impact of L1 on human health, the lab also focuses on the basic biology of the L1 proteins, ORF1p (the structural protein of L1) and ORF2p (the enzymatic machinery necessary for L1 to amplify itself within the genome). Most copies of L1 are non-functional and cannot amplify due to mutations in the two proteins of truncations, but it has been learned that defunct L1 copies can produce L1 ORF1p that can affect currently active copies and possibly influence human health. These *loci* could be useful as prognostic biomarkers for diseases in which L1 activity has a key role.

Additionally, the lab studies both how the ORF2p is regulated and its potential for causing DNA damage. This led to a patented monoclonal antibody to the DNA-cutting domain of the L1 ORF2p. This antibody may be able to reduce L1-induced DNA damage, which is important as there are currently no known small molecule inhibitors of this protein domain. These efforts to understand the basic biology of the L1 proteins will ultimately feed back into animal studies and inform both future *in vivo* experiments and patient data collection. This comprehensive approach to L1 biology and its relevance to human health, using such a wide array of model systems and strategies, is a tremendously innovative method for unraveling the unknown details behind this understudied source of genomic instability.

Contact & Further Info:

James R Zanewicz, RTTP
Chief Business Officer
zanewicz@tulane.edu
504.919.3800 (m)

Claiborne M Christian, PhD
Business Development Assoc.
christian@tulane.edu
504.909.3905 (m)

engage.tulane.edu
t: @engagetulane

Tulane
SCHOOL OF MEDICINE