$1.8 Million NIH Grant Supports Head and Neck Cancer Research

Sylvester Comprehensive Cancer Center researchers Lluis Morey, Ph.D., and Ramiro Verdun, Ph.D., have received a $1.8 million NIH R01 grant to study the epigenetic mechanisms that drive head and neck cancers.

Lluis Morey, Ph.D.

“Around 20% of patients who have a head and neck cancer have mutations in the protein histone H3 or the epigenetic enzyme NSD1,” said Dr. Morey, assistant professor in the Dr. John T. Macdonald Foundation Department of Human Genetics at the
University of Miami Miller School of Medicine. “Very little is known about how these mutations affect them. We want to understand how mutations in these genes impact head and neck cancer progression, and potentially find therapeutic targets.”

Histone H3 methylation is an epigenetic tag that changes how genes are expressed, and that plays a significant role in many cancers. Epigenetic mechanisms are molecular software that help regulate gene expression and can have a powerful impact on a cell’s chromatin, which is composed of histones and the DNA that is wrapped around nucleosomes.

Histone H3 mutations block the function of NSD proteins, which under normal conditions methylate an amino acid (protein component) on histone H3. Mutations on histone H3 and NSD1 cause similar gene regulation defects.
The research team is particularly interested in how mutations in chromatin factors, such as histone H3 and NSD1, disrupt the homeostasis (biological balance) in the chromatin environment in cancer and how that might be restored.

**Some Complicated Molecular Relationships**

The mutated histone protein, called H3K36M, loses methylation on one of its amino acid components, a lysine, which can be caused by H3 or NSD1 mutations. Either way, the lost methylation on this lysine is found in many head and neck cancer patients. Drs. Morey and Verdun want to better understand why this is happening and what the potential therapeutic ramifications might be.

“The grant will help us identify the biological function and molecular mechanisms behind these mutations,” said Dr. Verdun, professor in the Department of Medicine at the Miller School. “What happens when a head and neck cancer cell doesn’t have methylation on lysine 36 on histone H3? How does that shift the balance in these cells and what can we do about it?”
To complicate matters even further. There is another histone modification that can further segregate patients. In addition to losing methylation on lysine 36, some patients gain more methylation on lysine 27, which may change their responses to any treatment.

“If lysine 27 is modified, if it's hyper-methylated, we propose one treatment,” said Dr. Morey. “If it's not modified, we would propose another treatment.”

An immunofluorescence of head and neck cancer cells that are positive for markers of DNA damage

Identifying Potential Treatments

At present, head and neck cancer patients receive chemotherapy, but there are no targeted therapies currently approved for them. The researchers believe that some of these patients might respond to PARP inhibitors, which are presently approved to treat ovarian, prostate, and other cancers.
Because these drugs have already been proven safe in previous clinical trials, it's possible they could be fast-tracked for head and neck cancers if the evidence warrants it.

“We think we may have found a new way to treat a significant number of head and neck cancer patients,” said Dr. Morey. “However, first we must do the research to delineate these mechanisms and understand how these epigenetic changes affect cancer patients. Eventually, we hope to work with clinical researchers at Sylvester to set up a trial.”

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