NIEHS scientists contribute to advance in urinary bladder cancer research

By Robin Arnette

NIEHS scientists used their expertise to help identify potential therapeutic targets in more than 100 samples of urinary bladder cancer, as part of the Cancer Genome Atlas Research Network, a large international consortium dedicated to studying the causes of, and finding treatments for, cancer.

Dmitry Gordenin, Ph.D., senior associate scientist in the Laboratory of Molecular Genetics, led the NIEHS contingent, which included David Fargo, Ph.D., head of the Integrative Bioinformatics Group; Steven Roberts, Ph.D., Intramural Research Training Award (IRTA) fellow in the Chromosome Stability Group, and Les Klimczak, Ph.D., a contract researcher at NIEHS. They published their results in the March issue of Nature.

Using sophisticated tools developed at the Institute, they determined that 51 percent of the total mutations in urinary bladder cancers were caused by a class of proteins called apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) cytidine deaminases. These proteins normally function in antiviral defense, but can accidentally attack human chromosomes and cause mutations.

One member of this protein family, APOBEC3B, was expressed at high levels in nearly all of the tumor studies, making it the primary suspect for causing mutations. Knowing this, researchers may one day be able to design therapies that prevent the protein from mutating bladder cell DNA.

"We will continue our parallel research of using yeast mutation models and analysis of large cancer datasets to study the complex mix of mechanisms that cause cancer mutations," Gordenin said. "We believe the end results may help develop cancer prevention and therapy strategies."

Citation: The Cancer Genome Atlas Research Network. *(http://www.ncbi.nlm.nih.gov/pubmed/24476821)* 2014. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 507(7492):315-322.

Analysis techniques created at NIEHS

The analytical steps used to determine the frequency of ABOBEC-induced mutations in urinary bladder cancers were employed in earlier research on the causes of cancer.

The method was developed through a collaboration between Gordenin and Roberts, in their hunt for mutations in yeast caused by environmental damage, and Fargo and Klimczak, who took the research one step further by applying bioinformatics approaches.

The method was featured in a 2012 paper published in Molecular Cell and a 2013 article in Nature Genetics.

Gordenin directs several research projects in the NIEHS Chromosome Stability Group, headed by Michael Resnick, Ph.D. (Photo courtesy of Steve McCaw)

Roberts is also a member of the Chromosome Stability Group. (Photo courtesy of Steve McCaw)

Fargo's group promotes and develops bioinformatics tools and resources that empower NIEHS research. (Photo courtesy of Steve McCaw)

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