Researchers sequence multiple myeloma genome in landmark study

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Using new genome sequencing technologies, researchers from the John Theurer Cancer Center at Hackensack University Medical Center joined colleagues from 20 major North American research institutions to publish the first complete genomic portrait of multiple myeloma, a highly aggressive blood cancer. Findings from the study point to new directions for potential myeloma therapies, and begin to unlock the mysteries of what causes this devastating malignancy. The paper will be published in the March 24, 2011 issue of *Nature*.

Multiple myeloma is an incurable malignancy of plasma cells, white blood cells that develop in the bone marrow and make antibodies that help the immune system protect us from pathogens. Myeloma leaves its victims susceptible to infections and other serious complications.

"For the first time, we are able to see on a molecular basis what might be causing this malignancy," said study author David S. Siegel, M.D., Ph.D., Chief, Multiple Myeloma, John Theurer Cancer Center at Hackensack University Medical Center. "We already know what causes many types of cancer, but until now we had few clues to the causes of myeloma."

In cancer, cells develop genetic alterations known as "mutations." These mutations bring with them new and often deadly properties. By sequencing the myeloma genome, the researchers hoped to better understand the underlying mechanisms that lead to the disease's development and spread.

Using new high-throughput technologies that allow scientists to produce multiple sequences at once, the researchers examined genomes for both tumor and normal blood cells of 38 people with multiple myeloma. Other research teams have sequenced the entire genomes of a single person; in the current study, the scientists hoped that by analyzing a number of cases, and comparing normal and abnormal cells, they would be able to identify patterns that would not be clear otherwise.

"We have developed the most comprehensive molecular picture of myeloma to date, which will provide a public resource of genomic information for this disease," said Dr. Siegel. "This is a large step forward in personalized medicine for the treatment of multiple myeloma. My hope is that this will allow us to develop more targeted, effective therapies."

In nearly half of the patients in the study, researchers identified a mutation in genes involved in protein translation. Recent studies have shown that the regulation of protein synthesis is a crucial component of cancer cell survival, transformation, invasion, and metastasis. A better understanding of this regulation may lead to more effective ways to interfere with the disease as it starts and progresses.

Genes involved in blood coagulation and in histone methylation were also identified. Histones are cell-based proteins that help form DNA and are integrated into its structure. Methylation and demethylation are the modification of certain amino acids, which turn the DNA "on" and "off."

"The John Theurer Cancer Center is one only a few facilities in the United States to offer specialized clinical and research expertise in multiple myeloma," said Andrew L. Pecora, M.D., F.A.C.P., C.P.E., Chief Innovations Officer and Professor and Vice President of Cancer Services, John Theurer Cancer Center. "We are proud to play a role in

this milestone study and look forward to taking these discoveries to the next level through translational research and clinical trials."

Another key finding, borne out by mutations in 11 patients, was a broader than anticipated role for NF-Kappa Beta signaling in myeloma. NF-Kappa Beta is a protein that regulates cell division and cell death (apoptosis). Earlier research found that NF-Kappa Beta was over-expressed in multiple myeloma.

"Our study confirms this pathway in myeloma, and points to potential directions for myeloma treatment," said Dr. Siegel. "This is a major finding in that it will provide a roadmap of where to attack this disease and to understand the different species of the disease."

The scientists also found that mutations of BRAF – a protein involved in cell signaling and growth – were present in a number of patients. A number of BRAF inhibitors are currently in development; this finding indicates that these drugs should be evaluated in clinical trials in multiple myeloma.

Provided by John Theurer Cancer Center

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