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Multiple Myeloma Genome Sequenced, Reveals New Therapeutic Targets

Zosia Chustecka, News Editor for *Medscape Oncology*, March 25, 2011

The mammoth undertaking of sequencing the entire genomic multiple myeloma from tissue samples taken from 38 patients has shed light on the molecular mechanisms involved in this disease. It has also revealed some surprising potential therapeutic targets for which there are drugs already available that can be tested.

The study, published in the March 24 issue of *Nature*, unveiled many different pathways involved in the disease, some of which were unknown previously.

"A project of this scale would have been unimaginable a few years ago," said study co-author Todd Golub, MD, from the Dana-Farber Cancer Institute, Boston, Massachusetts. He emphasized the importance of sequencing the genome from many different patients, instead of just one patient, to obtain a complete picture, because some mutations are not found in every patient.

The project has been "very informative," Dr. Golub noted. "We can now see with greater clarity and greater precision how molecular pathways are involved," he said, joking that the study has transformed what was previously a "transistor radio view" of the disease to a "high-definition television view."

Dr. Golub was one of the speakers at a press briefing organized by the Multiple Myeloma Research Foundation (MMRF), which funded the project to the tune of \$12 million. MMRF spearheaded the project by organizing the collection of tissue samples and liaising between the various clinical sites and basic research laboratories that were involved.

Surprising Discovery

One of the surprising discoveries was that *BRAF* mutations are involved in multiple myeloma, but only in about 4% of patients. "No one had been thinking of *BRAF* as a driver or a therapeutic target in multiple myeloma, but this suggests a new hypothesis, and it would be reasonable now to test *BRAF* inhibitors," Dr. Golub said. Such compounds are already available — in fact, a *BRAF* inhibitor has shown significant clinical activity in melanoma, he added.

This compound, PLX0432 (developed by Plexxikon/Roche), showed, in an early clinical trial in patients with melanoma and *BRAF* mutation, responses in "a remarkable 81% of patients," and

was hailed as a "major breakthrough" when these results were published last year (*N Engl J Med.* 2010:363:809-819).

Another surprise was that the genes involved in blood clotting cascades were mutated in some of the multiple myeloma patient samples.

Other mutations that came to light were already on the researchers' radar. For instance, the nuclear factor kappa B (NF- κ B) pathway, when activated, allows cancer cells to grow and divide unchecked. Multiple myeloma researchers had suspected that this pathway was involved in the cancer's development; previous studies have shown an overexpression of NF- κ B. But the new study shows that its role might be broader than was anticipated; 11 different genes involved in this pathway were mutated in at least 1 of the patient samples.

"This is a major finding in that it will provide a roadmap of where to attack the disease," said co-author David Siegel, MD, PhD, chief, multiple myeloma, John Theurer Cancer Center at Hackensack University Medical Center, New Jersey.

Protein Gene Mutations in Half of Patients

Another major finding, described as "striking" in the paper, was that about half of the multiple myeloma patient samples showed mutations in genes involved in protein translation and homeostasis.

This was not such a surprise, because disruption of protein production is one of the hallmarks of this disease. "Multiple myeloma cells are like protein-producing factories," Dr. Siegel explained in an interview with *Medscape Medical News*.

This finding is of clinical significance, the researchers note in the paper, "because of the success of the drug bortezomib (*Velcade*), which inhibits the proteasome and which shows remarkable activity in multiple myeloma," compared with other tumour types.

Another drug active in multiple myeloma, vorinostat (*Zolinza*), is a histone deacetylase inhibitor. "We know that the drug works in this disease, but that was an empirical observation," Dr. Siegel explained. The new study has shown mutations in the genes involved in this pathway, and "so to some extent the story comes full circle," he said.

"It also suggests that we should try different histone deacetylase inhibitors in this disease, from a different chemical class, and that maybe this is a pathway we should be concentrating on more," he said.

"This makes the paper interesting from a practical point of view," he added.

Exciting Times

"We don't really know what causes multiple myeloma," Dr. Siegel said. "What we know has come from studies in cell lines, which has not been that informative about the disease that we actually deal with."

"Now, for the first time, we are able to see on a molecular basis what might be causing this malignancy," he said. "This gives us a window into the biology of the disease."

There has never been a more exciting time.

Another co-author, Kenneth Anderson, MD, program director and chief of the division of hematologic neoplasias at the Dana-Farber Cancer Institute, has been treating patients with multiple myeloma for 30 years. "There has never been a more exciting time. There is now a real possibility for targeted therapies," he said during the press briefing.

There has been a lot of progress in the treatment of multiple myeloma in recent years, he noted, and several new drugs have been approved by the US Food and Drug Administration for this disorder. They have already had an impact on the disease; overall survival has increased from about 4 to 5 years to about 7 to 8 years, and with maintenance therapy that can sometimes be stretched to 10 years or more, he said. "But despite all of this progress, multiple myeloma inevitably relapses and remains an incurable disease."

"The sequencing of the multiple myeloma genome is unprecedented, and it will advance the concept of personalized medicine," he predicted, "so that we can get the right therapy to the right person at the right time."

Nature. 2011;471;467-472. [Abstract](#)