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Gene Profiling Can Single Out the Worst Cases of Multiple Myeloma and Guide Therapy

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Multiple myeloma patients vary widely in how they respond to treatment, but now researchers at the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences have identified a small subset of genes whose activity could predict high-risk cases and potentially guide therapy in the future.

Researchers followed 532 multiple myeloma patients for seven years after blood stem cell transplant to create a genetic profile to chart the severity of the disease. The team determined that the activity of as few as 17 genes could mean the difference between high or low risk for a poor prognosis.

"There are enormous differences between how different people fare with multiple myeloma. While most do very well others have a highly aggressive form of the disease and this is not recognized well with current prognostic variables," said lead researcher John D. Shaughnessy, Jr., Ph.D., a professor of medicine at the Myeloma Institute for Research and Therapy. "If we can categorize a patient's risk early, we can better guide that patient toward therapies that might be more effective for them based on the genetic profile of the disease."

Multiple myeloma is a cancer affecting the blood plasma cells in bone marrow that produce antibodies. Nearly 1,900 new cases of multiple myeloma occur each year in Canada. The disease is most often treated through the use of high dose chemotherapy and peripheral blood--derived stem cell support. While multiple myeloma often responds well to initial treatment, it often becomes drug resistant and patients are prone to relapse.

According to the researchers, survival varies greatly between low-risk and high-risk patients. "At 24 months, about 90 percent of low-risk patients will be alive, whereas about 50 percent of the high-risk patients have succumbed to the disease," said Fenghuang Zhan M.D., Ph.D., of the University of Arkansas for Medical Sciences.

To understand the possible molecular mechanisms driving initiation and progression of multiple myeloma, the researchers launched a large-scale, longitudinal study to categorize the differences in gene expression patterns, that is, which genes are activated and inactivated, in relatively indolent versus aggressive disease.

Using purified tumor cells taken from 532 newly diagnosed patients who went on to receive uniform therapy, the researchers screened over 54,000 genes across the human genome for signs that might relate to multiple myeloma survival estimates. About 13 percent of all the patients they studied exhibited a genetic pattern that fit into the high-risk category, a frequency that rose to 76 percent among relapsed patients.

"The observation of an increase in the gene expression risk score among relapsed patients provides evidence that there are likely to be small subsets of high-risk cells even in patients with low risk disease, and that current therapeutics are sub-optimal in that they kill off the low-risk cells, leaving behind cells that exhibit a high-risk genetic profile," Shaughnessy said. Currently, the researchers have experiments underway to definitively prove this concept.

Initially, the researchers identified 70 genes linked to early cancer-related death, although further analysis narrowed that number to 17. Remarkably, about 30 percent of the genes that predict high risk are found on chromosome 1, enough so that Shaughnessy recognized a trend among the genes, based on where they map on each chromosome in the human genome. The majority of genes that were up-regulated -- or over-produced -- in high-risk patients mapped to the long arm of chromosome 1, while the majority of genes that were down-regulated -- or suppressed -- mapped to the short arm of the same chromosome.

"Together these data suggest that defects in chromosome 1 may be directly related to the acquisition of higher risk in patients with multiple myeloma," Shaughnessy said. "Gene expression profiles have now provided us with signposts that help us risk stratify patients and tailor therapies accordingly."

"Importantly, these data may provide researchers with key insights into molecular mechanisms driving disease severity which might be the target of future therapies," Shaughnessy said.

Researchers presented their data September 18 at the American Association for Cancer Research's second International Conference on Molecular Diagnostics in Cancer Therapeutic Development, in Atlanta, Ga.

Note: This story has been adapted from a news release issued by American Association for Cancer Research.