Study May Lead to New Approaches to Treating Early, Smoldering Myeloma

The findings lay the groundwork for tests that can identify whether the disease is likely to progress rapidly.

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For many people diagnosed with smoldering multiple myeloma—a condition that often precedes myeloma—the shock of the diagnosis can be compounded by the distress of learning they won't receive treatment until physical symptoms of myeloma develop.

Now, Dana-Farber scientists and an international team of researchers have tracked the genomic changes that occur as smoldering multiple myeloma (SMM) advances to myeloma. Their findings lay the groundwork for tests that can identify patients whose SMM is likely to progress rapidly to myeloma, and who could benefit from prompt treatment. Patients with SMM that has a longer lead time to myeloma could be candidates for preventive treatments.

The research, published in Nature Communications, found that SMM can progress by two distinct patterns: one in which the genetic makeup of SMM tissue doesn't change much in becoming myeloma; and one in which the transition is marked by the appearance of new, genetically distinct groups of myeloma cells. The first type, dubbed the static progression model, tends to progress fairly quickly to myeloma. The second, called the spontaneous evolution model, usually takes longer.

The findings may influence how patients with SMM are treated and how multiple myeloma is defined, says senior author Nikhil Munshi, MD, director of Basic and Correlative Science at the Jerome Lipper Multiple Myeloma Center at Dana-Farber.

"Traditionally, a diagnosis of myeloma requires not only the presence of myeloma cells but also the development of symptoms such as anemia, bone disease, too much calcium in the blood, and kidney malfunction," Munshi says. "Our study shows, however, that when the disease follows the static progression model, SMM is, from a genomic standpoint, myeloma. The advance of the disease is solely a matter of an accumulation of diseased tissue. For such patients, it may make sense to begin treatment soon.

"In the spontaneous evolution model, by contrast, SMM is genomically distinct from myeloma," he continues. "It advances toward myeloma only when genetic mutations create new subsets of SMM

cells that develop into myeloma. Treatment for such patients might involve agents that prevent such subsets from arising."

Currently, there is no way of determining whether a patient's SMM is likely to follow the static progression or spontaneous evolution model, but Munshi and his associates are conducting research in that area. Making such distinctions would be crucial to selecting the appropriate treatment for individual patients.

Before and After Analysis

Myeloma originates in plasma cells, which are white blood cells responsible for producing disease-fighting antibodies. As genetic mutations and other molecular derangements accumulate in the cells, they begin to grow out of control and crowd out normal, healthy cells, eventually producing the symptoms associated with myeloma.

The study began with blood samples from 11 patients with SMM, all of whom went on to develop multiple myeloma over the next three-plus years. Researchers took one set of samples when patients had SMM and a second set when they were diagnosed with myeloma, and analyzed the complete genome of the myeloma cells, looking for differences between those in the myeloma set and the SMM set.

They found the genomic composition of cells at the smoldering stage is very similar to that of myeloma cells, and that the course of the disease follows either the static progression or spontaneous evolution model.

The investigators also uncovered some of the processes that alter the genome of myeloma cells at key points in the development of the disease. An enzyme called activation-induced cytidine deaminase, which plays a role in the development of plasma cells, was found to be overactive early in the myeloma process, producing some of the first mutations plasma cells experience. The researchers also found that enzymes known as APOBEC cytidine deaminases become overactive at a later stage—triggering genetic changes as the disease progresses to myeloma.

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