Study of gene mutations in aplastic anemia may help optimize treament

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Scientists have identified a group of genetic mutations in patients with aplastic anemia, which likely will help doctors optimize treatment for this rare and deadly blood condition. The study, appearing in the *New England Journal of Medicine*, could lead to tailor-made treatment plans for aplastic anemia patients as part of the emerging precision medicine movement. It is the largest study of its kind to examine gene mutations in aplastic anemia, the scientists note.

The work involved researchers from the National Institutes of Health, the Cleveland Clinic, Cleveland, OH, and Kanazawa University, Kanazawa, Japan. Neal S. Young, chief of the hematology branch at the NIH's National Heart, Lung, and Blood Institute, was the study's co-leader. Almost 1,000 new cases of aplastic anemia occur each year in the United States alone. Although the disease can affect anyone, children and young adults make up the majority of cases. Stem cells in the bone marrow are normally responsible for producing blood. In aplastic anemia, the body's immune system appears to destroy these stem cells.

Historically, severe aplastic anemia was almost always fatal due to infections and bleeding. Today, bone marrow transplantation can cure the condition, but it is not widely available and requires hard-to-find donors. Doctors generally treat aplastic anemia effectively using immunosuppressives—drugs that prevent the immune system from attacking bone marrow—allowing recovery of the patient's own marrow and long-term survival. However, about 15 percent of patients on immunosuppressives develop cancer of the blood—acute leukemia and

myelodysplastic syndromes—months or years following treatment.

For the current study, researchers used next-generation DNA sequencing, a way of rapidly analyzing genes, to examine the genomes of blood samples from more than 400 patients with aplastic anemia, enrolled from centers specializing in the treatment of bone marrow failure. Within bone marrow, stem cells can differentiate into mature blood cells or self-renew, meaning make more stem cells. In about a third of patients with aplastic anemia, stem cell "clones" appear with mutations in a few specific genes (DNMT3A and ASXL1), genes previously identified as mutated also in blood cancers. Patients with these mutations do not fare as well long term as those without mutations, or, patients with mutations in a few other apparently favorable genes (BCOR and PIGA, for example).

In the future, genomic screening at diagnosis should allow care providers to choose the best treatment option or monitor for the emergence of clone stem cells. The unfavorable genes, DNMT3A and ASXL1, are frequently mutated in myeloid leukemia and myelodysplastic syndromes, and they are also mutated in a substantial number of older individuals without a blood disease.

Using specimens collected annually in patients seen at Dr. Young's bone marrow failure clinic at the NIH Clinical Center, the investigators show that patients can support good blood cell production for many years from only a few stem cell clones, which can contain many unfavorable mutations. Potential scientific questions from this research relate to the origin and function of stem cell clones and to whether they could be used to predict future outcomes.

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