Function of molecular switch pinpointed in severe congenital neutropenia

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Researchers have for the first time cleared an important hurdle to clarifying the molecular mechanics behind Severe Congenital Neutropenia (SCN), a deadly disease characterized by a deficiency of neutrophils – a type of mature white blood cell important to fighting infection and disease. A research team led by Cincinnati Children's Hospital Medical Center reports in the March 14 Immunity the first evidence of how a specific genetic mutation found in humans with SCN blocks neutrophil development in mouse bone marrow cells.

The finding is expected to give researchers a way to more effectively study SCN, which puts children at increased risk of developing bacterial and fungal infections and acute myelogenous leukemia.

"Our discovery that humans and mice have a shared pathway for the development of neutrophils should provide new avenues for understanding the molecular basis of SCN associated with other genetic mutations," said H. Leighton Grimes, Ph.D., a researcher in the Division of Immunology at Cincinnati Children's and lead author of the study. "It's important that we find clues for developing possible treatments to help children with this disease."

The research team studied a gene called Growth Factor Independent-1 (GFI1), which is expressed in bone marrow stem cells and known to help control the growth and differentiation of blood cells, including those that become neutrophils. When it works normally, GFI1 promotes the formation of neutrophils by blocking the development of macrophages, the default differentiation pathway. Specifically, GFI1 acts as a molecular switch to moderate the function of another gene, Colony Stimulating Factor-1 (CSF1), which tells marrow stem cells to form macrophage white blood cells instead of neutrophils.

Dr. Grimes and his colleagues discovered that GFI1's ability to act as a rate-limiting molecular switch is compromised by a genetic error found in patients with SCN, a mutation known as GFI1N382S. When the mutant form of GFI1 found in SCN patients interferes with GFI1's switching function, it results in deregulated expression of CSF1, an overproduction of macrophages and blocks to the formation of neutrophils. The researchers also found that blocking the function or expression of CSF1 allowed mutant GFI1cells to become neutrophils.

"In SCN patients with mutations in GFI1, it's as though the switch that allows the formation of neutrophils is always in the off position, and the bone marrow stem cells are constantly receiving the message to become macrophages," said Dr. Grimes. "The ability to produce both types of blood cells is important to fight off infection."

Pursuing the GFI1-CSF1 molecular pathway also led to the study's other milestone, as Dr. Grimes and his co-investigators were able to develop a mouse model for SCN that allows future studies of possible therapies. The most common known genetic mutation found in humans with SCN is in a gene called ELA2, which encodes a protein that cleaves other proteins. Unfortunately, previous research has shown that mice with mutated or deleted ELA2 do not develop SCN, leaving researchers without a workable model of SCN for study. The team used this problem as an opportunity. Because ELA2 is also regulated by GFI1, Dr. Grimes and his colleagues decided to take a step back in the molecular process to further study the influence of GFI1. Their focus on GFI1 also allowed them incorporate their previous research that identified a family of SCN patients, all of whom had the GFI1N382S mutation.

SNC is a rare inherited autosomal recessive disease. The current treatment for SCN includes recombinant Granulocyte-colony stimulating factor (GCSF), which increases the formation and

proliferation of white blood cells for most patients. However, the treatment still fails to correct the underlying gene defects behind the disease and does not work in all patients. There is also concern that GCSF treatment may help induce the development of leukemia, highlighting the need of different treatment options. Besides being prone to infection or acute myelogenous leukemia, children with SCN can contract the bone marrow disorder, myelodysplasia, in which patients have ineffective production of blood cells and are at higher risk of developing acute myelogenous leukemia.

Source: Cincinnati Children's Hospital Medical Center