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Scientists find that persistent infections in mice exhaust progenitors of all blood cells

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Having persistent infections can eventually exhaust the immune cells in charge of fighting disease. In a mouse model, scientists at Baylor College

of Medicine, Texas A&M University Health Science Center and Rice University reveal that long-lasting infections trigger the loss of the progenitors of all blood cells and suggest a strategy that may help prevent or treat this condition in the future. The study appears in *Cell Reports*.

"Over the years I have seen a number of patients with infections that are hard to treat because the patients' blood systems are out of balance," said senior author Dr. Katherine King, who is an assistant professor of pediatrics-infectious diseases at Baylor and an infectious diseases specialist at Texas Children's Hospital. "These patients do not have the ability to produce the immune cells that are naturally in the blood. Their bone marrow, where blood cells originate, has failed them. This motivated me to study how the bone marrow normally regulates the production of blood cells and how patients maintain the normal number of blood cells in order to fight infection."

"In this study, we investigated how the depletion of blood cells is happening by studying mouse models with long-lasting infections of the bacterium Mycobacterium avium," said lead author Dr. Katie Matatall, a postdoctoral fellow of pediatrics-infectious diseases in the King lab. "By understanding the mechanism that leads to the depletion of blood cells we hope to find ways to help these patients recover from bone marrow failure."

A new perspective on how blood cell depletion happens

Animals and people start their lives with a certain number of progenitor cells – stem cells – in their bone marrow. Progenitor cells are ultimately responsible for producing all the blood cells in the body over a lifetime. Blood cells include red blood cells, white blood cells and platelets. The scientists found that long-term infection, about four months, of

experimental animals with M. avium led to the loss of 95 percent of bone marrow progenitor cells.

"This result surprised us," said King, "because bone marrow failure during persistent infection was traditionally attributed mainly to fibrosis, the thickening or scarring of the bone marrow due to infection and accompanying inflammation. In our study, we did not see a high level of fibrosis in the bone marrow of the animals that were tested, instead we found that the progenitor cells were absent. This surprising fact may explain why their bone marrow is failing."

The scientists then investigated what had happened to the progenitor cells.

"We looked at whether the progenitor cells were dying or being displaced to other parts of the body, and for neither of those situations did we find any evidence," said King. "Instead we found evidence that the progenitor cells were differentiating into or becoming other cell types."

"We think that infection and inflammation are driving the pool of progenitor cells to develop into blood cells, instead of self-renewing," said Matatall. "The bone marrow loses the progenitor cells over the course of the infection as they are trying to keep up with the demand of blood cells to help fight the infection."

By depleting the pool of stem cells, the bone marrow loses its ability to produce new blood cells. In time, the individual would not be able to maintain the normal number of blood cells, and, consequently, will be less able to fight disease.

In addition, the researchers identified a gene, BATF2, which seems to play a role in the differentiation of progenitor cells that is triggered by

infection, as observed in the experiments with animal models.

Potential treatments

"We are hoping that by identifying genes such as BATF2, which mediates the depleting effect of inflammation and infection on stem cells, we can design drugs in the future to help preserve the stem cells compartment, even when the individual is having a long-lasting infection or persistent inflammation," said King.

"Currently, there are no preventive treatments for this condition," said Matatall. "But now that we have a better idea of the mechanisms of how this is occurring we can potentially find ways to intervene therapeutically and prevent it from happening."

More information: Katie A. Matatall et al. Chronic Infection Depletes Hematopoietic Stem Cells through Stress-Induced Terminal Differentiation, *Cell Reports* (2016). DOI: 10.1016/j.celrep.2016.11.031

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