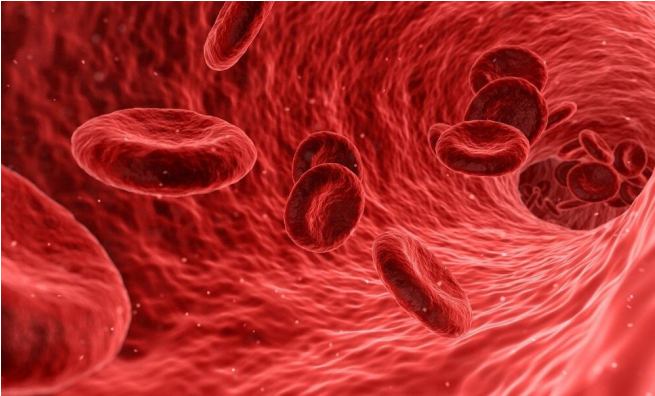


# Too much of a good thing—persistent IFN $\gamma$ depletes progenitor blood cells via BST2

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When a person has an infection, the body activates immune responses to fight it. IFN $\gamma$  is an inflammatory molecule produced by the immune system that helps fight infections. However, long-term exposure to IFN $\gamma$  has undesirable consequences—it irreversibly exhausts blood stem cells, the progenitors of all blood cells, including immune cells, by triggering their proliferation and excessive terminal differentiation. Lacking immune cells, patients eventually are unable to fight infections.

Baylor College of Medicine researchers investigated the mechanism by which IFN $\gamma$  mediates depletion of blood stem [cells](#), which are normally quiescent, meaning they are in a dormant state until activated when stimulated. They showed in the journal *Cell Reports* that IFN $\gamma$  stimulates the production of protein BST2 on these cells, which resulted in their emergence from the quiescent state, persistent proliferation and finally exhaustion. The findings suggest that modulating BST2 expression on blood stem cells may provide a means to regulate these cells' activation and/or persistence during chronic infections.

"We began our investigation by asking, 'What is changing about blood stem cells when they interact with IFN $\gamma$ ?, and how does that influence their reproduction or depletion?'" said co-corresponding author Dr. Katherine King, associate professor of pediatrics-infectious diseases and member of the Dan L Duncan Comprehensive Cancer Center at Baylor.

Blood stem cells reside in the bone marrow, normally in contact with CAR cells that form a sort of a nest. CAR are nurse cells that support stem cell health.

"To investigate the real-time interaction of blood stem cells and CAR cells in [live animals](#), we developed new mouse models designed to express different fluorescent proteins in blood stem cells (red) and CAR cells (green) in the same animals. This model enabled us to visualize and track both cell types individually and simultaneously within intact bones of living animals," said co-corresponding author Dr. Dongsu Park, assistant professor of molecular and human genetics and pathology and immunology at Baylor.

Combining this approach with advanced live-animal imaging technology, the team discovered a tight interaction between blood stem cells and CAR cells in normal bone marrow, but when exposed to IFN $\gamma$ , the stem cells unexpectedly moved away from CAR cells.

"We think IFN $\gamma$  is disrupting the quiescent state of stem cells and promoting cell activity," King said. "Our next experiments looked at how that was happening."

The researchers looked for proteins on the surface of stem cells that were expressed after exposure to IFN $\gamma$ . They hypothesized that probably a surface protein induced by IFN $\gamma$  was promoting the separation of stem cells from CAR cells.

"Think of it as a sticky tag that is on the outside of the stem cells that is pulling them to some other place. That's how we identified this protein called BST2," King said. "In fact, in mice in which we knocked out BST2, the relocalization of stem cells away from the nest and their excessive proliferation and exhaustion did not happen, supporting the role of BST2 in these functions."

## Homing

The researchers also found that BST2 helps cells bind to E-selectin, a protein on the surface of endothelial cells, such as those lining blood vessels. These findings are relevant to homing, a process by which blood stem cells from a bone marrow transplant find their way to their home in the recipient's bone marrow.

"Homing of stem cells improved when we exposed them to IFN $\gamma$ . We propose that having more BST2 may help stem cells stick to E-selectin on endothelial cells, facilitating crossing through [blood vessels](#) to reach the bone marrow," King said.

"BST2 is a fascinating protein that has been mostly studied for its ability to both protect our body from viral infections and its role in cancer. I am most excited that we are the first group to report that BST2 plays an important role in [blood stem cells](#), which are at the top of [immune system](#) hierarchy," said first author Marcus A. Florez, a student in Baylor's Medical Scientist Training Program (M.D./Ph.D.) in the King lab. "This project has important implications in a wide variety of diseases including chronic infections, [bone marrow](#) failure and transplant recipients."

**More information:** *Cell Reports* (2020). [DOI: 10.1016/j.celrep.2020.108530](https://doi.org/10.1016/j.celrep.2020.108530)

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