# Pumping up red blood cell production

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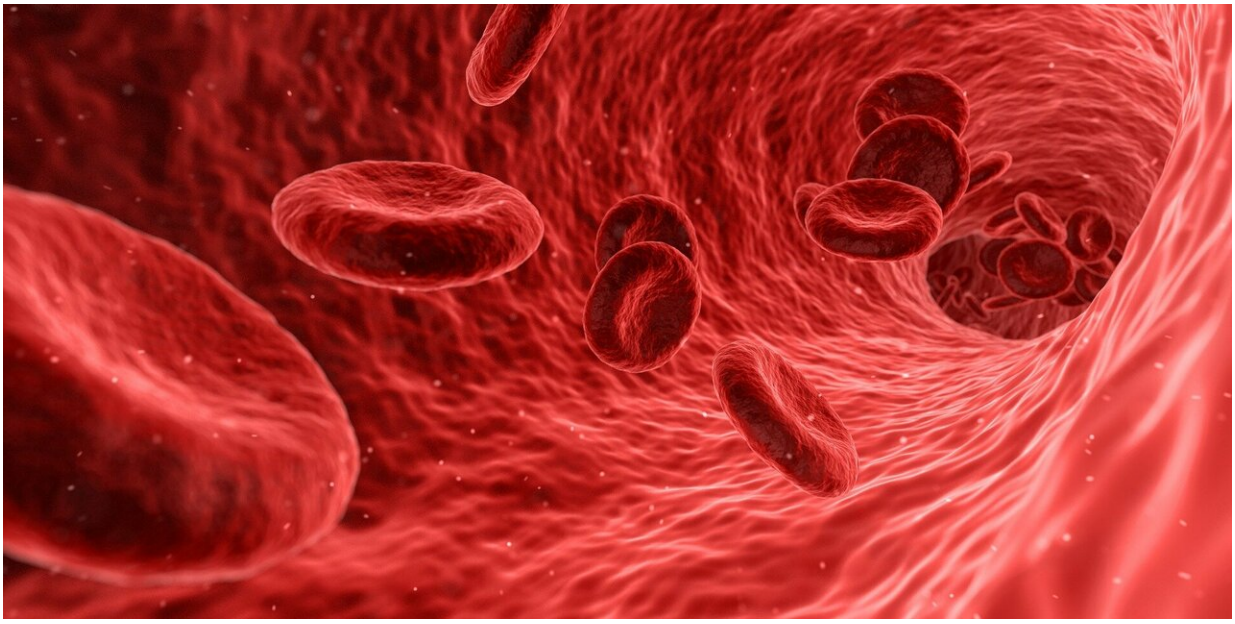

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Red blood cells are the most plentiful cell type in our blood and play a vital role transporting oxygen around our body and waste carbon dioxide to the lungs. Injuries that cause significant blood loss prod the body to secrete a one-two punch of signals – stress steroids and erythropoietin (EPO) – that stimulates red blood cell production in the bone marrow. These signals help immature cells along the path to becoming mature red blood cells. In a healthy individual, as much as half of their blood volume can be replenished within a week. Despite its importance, scientists are still working to unravel many aspects of red blood cell

production. In a paper published online February 28 in the journal *Developmental Cell*, Whitehead Institute researchers describe work that refines our understanding of how stress steroids, in particular glucocorticoids, increase red blood cell production and how early red blood cell progenitors progress to the next stage of maturation toward mature red blood cells.

These findings are especially important for patients with certain types of anemia that do not respond to clinical use of EPO to stimulate the final stages of red cell formation, such as Diamond-Blackfan anemia (DBA). In this rare genetic disorder usually diagnosed in infants and toddlers, the bone marrow does not produce enough of early red blood cell progenitors, called burst forming unit-erythroids (BFU-Es), that respond to glucocorticoids. In both healthy people and DBA patients, these BFU-Es divide several times and mature before developing into colony forming unit-erythroids (CFU-Es) that that, stimulated by EPO, repeatedly divide and produce immature red blood cells that are released from the bone marrow into the blood. But the lack of BFU-Es in DBA patients means that the glucocorticoid signal has a limited target, and the cascade of cell divisions that should result in plentiful red blood cells is contracted and instead produces an insufficient amount.

One of the standard treatments for DBA is boosting red blood cell production with high doses of synthetic glucocorticoids, such as prednisone or prednisolone. But the mechanisms behind these drugs and their normal counterparts are not well understood. By deciphering the mechanisms by which glucocorticoids stimulate red cell formation, scientists may be able identify other ways to stoke CFU-E production – and ultimately red blood cell production – without synthetic glucocorticoids and the harsh side effects that their long-term use can cause, such as poor growth in children, brittle bones, muscle weakness, diabetes, and eye problems.

For more than two decades, Whitehead Institute Founding Member Harvey Lodish, has investigated glucocorticoids' effects on red blood cell production. In his lab's most recent paper, co-first authors and postdocs Hojun Li and Anirudh Natarajan, describe their research, which helps decipher how BFU-Es progress through their maturation process.

For more than 30 years, scientists have thought that glucocorticoids bestowed BFU-Es with a stem cell-like ability to divide until an unknown switch flipped and the cells matured to the CFU-E stage. By looking at gene expression in individual BFU-Es from normal mice, Li and Natarajan determined that the developmental progression from BFU-E to CFU-E is instead a smooth continuum. They also found that in mice glucocorticoids exert the greatest effect on the BFU-Es at the beginning of the developmental continuum by slowing their developmental progression without affecting their cell division rate. In other words glucocorticoids are able to effectively compensate for a decreased number of BFU-Es by allowing those that do exist, while still immature, to divide more times, producing in mice up to 14 times more CFU-Es than BFU-Es lacking exposure to glucocorticoids.

Li and Natarajan's work reveals previously unknown aspects of the mechanism by which glucocorticoids stimulate red blood cell production. With this better understanding, scientists are one step closer toward pinpointing more targeted approaches to treat certain anemias such as DBA.

**More information:** Hojun Li et al. Rate of Progression through a Continuum of Transit-Amplifying Progenitor Cell States Regulates Blood Cell Production, *Developmental Cell* (2019). DOI: 10.1016/j.devcel.2019.01.026