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How red blood cells get so big -- and the bad things that happen when they don't

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Yale researchers have discovered how megakaryocytes — giant blood cells that produce wound-healing platelets — manage to grow 10 to 15 times larger than other blood cells.

The findings, to be published March 13 in the journal *Developmental Cell*, also hint at how a malfunction in this process may cause a form of leukemia.

"A failure of these cells to grow might be an initial trigger for megakaryoblastic leukemias," said Diane Krause, senior author of the paper, who is a researcher for the Yale Cancer Center; professor of laboratory medicine, cell biology, and pathology; and associate director of the Yale Stem Cell Center.

Megakaryocytes grow so large because the DNA within the cell duplicates many times — but without the cell undergoing cell division: a process called endomitosis. A megakaryoblastic can shelter more than 120 sets of nuclear DNA before it eventually becomes the biological equivalent of a supernova, undergoing profound changes to break apart into thousands of platelets needed for normal blood clotting.

The Yale team led by postdoctoral associate Yuan Gao found that two proteins called guanine exchange factors (GEF-H1) put the brakes on endomitosis. They found that without GEF-H1, nuclear DNA couldn't go from two internal nuclei to four. Additional divisions of nuclear DNA within the cell could not take place unless there was decreased

expression of a second factor, ECT2.

The researchers were intrigued by the results because a gene implicated in malignant leukemias, MKL1, also seems to be necessary to promote normal megakaryocyte maturation. The Krause lab is now studying whether mutant forms of MKL1 may keep levels of GEF-H1 high, thereby making it impossible for megakaryocytes to undergo endomitosis and setting the stage for development of cancer.

"These findings reveal another important step toward the formation of functional platelets, which are necessary for normal blood clotting," Krause said. "But they also provide a clue regarding what may go awry to transform normal megakaryocytes into malignant leukemia cells."

Provided by Yale University