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Scientists identify progenitor cells for blood and immune system

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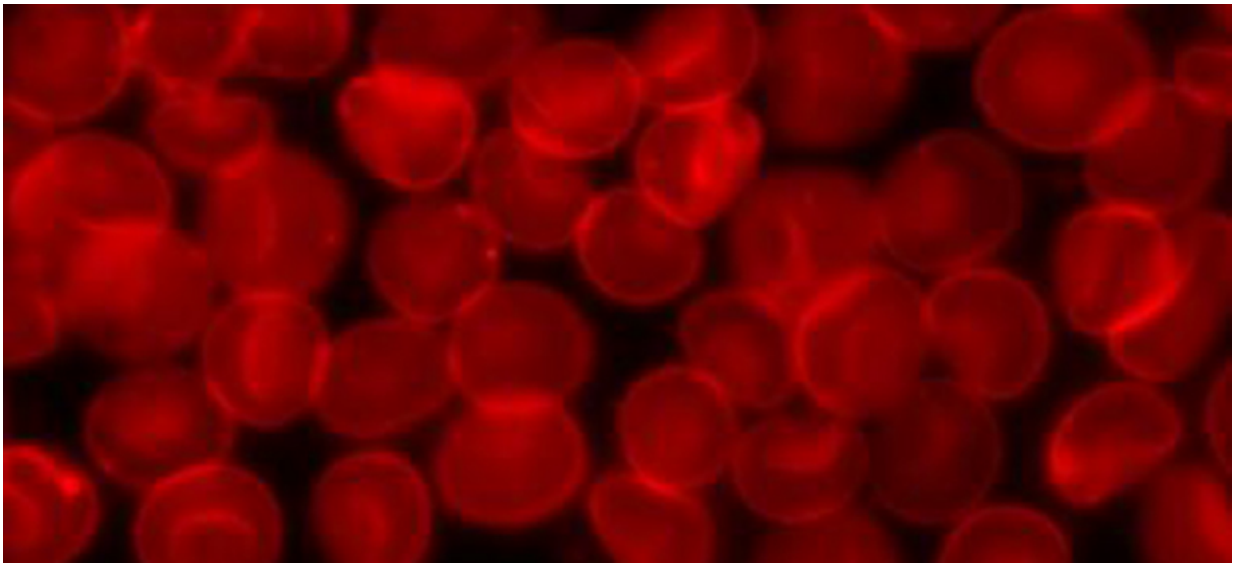

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University of California San Francisco scientists have identified characteristics of a family of daughter cells, called MPPs, which are the first to arise from stem cells within bone marrow that generate the entire blood system. The researchers said the discovery raises the possibility that, by manipulating the fates of MPPs or parent stem cells, medical researchers could one day help overcome imbalances and deficiencies that can arise in the blood system due to aging or in patients with specific types of leukemia.

Similar imbalances can render patients vulnerable immediately following bone-marrow transplants, especially following transplants of umbilical cord blood stem cells, said Emmanuelle Passegué, Ph.D., professor of medicine and member of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF, and the senior scientist for the study. Such patients often need red-blood-cell and platelet transfusions, as well as antibiotics to fight infections, until their grafted stem cells kick in and they produce an adequate balance of different types of blood cells.

Passegué's lab group determined that adaptation to the body's need to produce different mixes of blood cells at different times starts at the top of this hierarchy, with the hematopoietic stem cell (HSC). 'What we show is that the stem cell is making very educated decisions,' Passegué said. 'Previously, researchers thought that the developmental paths of daughter cells were randomly specified by the HSC, but we conclude that the HSC normally responds appropriately to signals in the environment, making the different MPPs in parallel, but at different speeds and in different amounts to meet the body's needs.'

Passegué's research team investigated in mice the patterns of gene expression and cell signaling that determine which developmental paths are favored when relatively rare HSCs spin off daughter cells, leading to the development of all of our red blood cells, white blood cells and platelets needed for blood clotting—hundreds of billions of new cells each day.

In the new study, published online in *Cell Stem Cell* on June 18, Passegué also used mice to explore the responses of HSCs during transplantation. HCSs are the only cells known to be able to engraft in bone marrow and to regenerate the entire blood system. Among all blood cells, only HSCs are immortal. Each one can self-renew, spinning off new HSCs with each successive cycle of cell division. Alternatively, HSCs can instead

divide into progenitor cells that cannot self-renew or engraft in bone, but which can give rise to generations of ever-more-specialized cells.

The UCSF team's experiments, many performed by postdoctoral fellows Eric Pietras, Ph.D., and Damien Reynaud, Ph.D., revealed that the first daughter cells that arise from HSCs already are distinct, favoring the development of different specialized cell lineages. The scientists identified two types of daughter cells, called MPP2 and MPP3, which under normal conditions are rare. They work together with more common daughter cells, called MPP4 cells, to control blood production.

MPP2 cells favor production of platelets and red blood cells, while MPP3 cells favor production of inflammatory cells. MPP4 cells are the main producers of lymphocytes that fight specific disease pathogens, but the study team showed that MPP4 cells can easily be re-educated to make many inflammatory cells when regenerative needs are high, as they are following transplantation. They found that during transplantation regenerating HSCs limit their own self-renewal, and instead go to work overproducing MPP2 and MPP3 cells that quickly produce needed red blood cells, platelets and inflammatory cells. Only later does MPP4 production return to normal, enabling the immune system to replenish lymphocytes.

In humans it's clear that imbalances often arise during aging, Passegué said, with production of disease-fighting immune cells lagging far behind youthful levels.

'It will be compelling to test whether the developmental pathways leading to cell specialization can be manipulated to favor production of specific lineage-biased MPPs in order to optimize blood recovery following hematopoietic injury, or to rebalance the output of various cell lineages in an aging or deregulated blood system,' she said.