Defining the Bone Marrow Microenvironment

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Circulating red and white blood cells derive from resident stem cells found within the bone marrow. Alongside the hematopoietic cells in the bone marrow are stromal cells, including fat cells, blood vessel cells, bone cells, and fibroblasts, which secrete signals to alter the microenvironment. Specific signals maintain hematopoietic stem cells in their immature state, other signals promote the maturation of specific subtypes of blood cells. While the signals that induce blood cell development are well characterized, less is known about which cell types release these signals and how all the cells interact with one another to establish a functioning niche in the bone marrow. Dr. Beverly Torok-Storb and colleagues in the Clinical Research Division recently published a study in *Stem Cells and Development* that defines distinct populations of marrow fibroblasts that can differentially dictate the function of monocytes to modify the molecular composition of niches within the marrow microenvironment.

Lead author Dr. Mineo Iwata and colleagues began their studies by examining the cell lineage of stromal cells isolated from human bone marrow aspirates; specifically, isolating cells that were positive for the surface marker CD146. In previous studies, these CD146+ cells were shown to be necessary for hematopoietic stem cell niches. Iwata *et al*. found the CD146+ stromal cells were fibroblast in origin, using the sensitive digital DNaseI profiling method to compare the chromatin accessibility landscape of the isolated cells to known cell types found in the bone marrow microenvironment. The primary isolated CD146+ cells were compared to HS27a (CD146+) and HS5 (CD146-), two cloned stromal cell lines previously generated in the Torok-Storb laboratory (Roecklein *et al*., 1995) which were also identified as fibroblast in cell origin.

The researchers then examined whether these different stromal cells altered the cell fate of monocytes found in blood circulation and entered the marrow through blood vessels. While both CD146+ and CD146- stromal cells were fibroblast in origin, they induced different cell fates for the monocytes. Conditioned media isolated from both CD146+ primary stromal cells and HS27a cells, which contains secreted factors, promoted macrophage differentiation of monocytes (as determined by morphology and gene expression changes), while HS5-conditioned medium promoted differentiation of the monocytes to dendritic cells. Strikingly, the researchers found that co-culture of monocytes with the HS27a cells, but not the HS5 cells, also significantly altered gene expression when the cells were in direct contact *versus* conditioned medium alone.

Iwata *et al*. then examined the location of the CD146+ stromal cells and resident macrophages in bone marrow biopsies. The two cell types were found in contact with each other, and were located near blood vessels and throughout the marrow, suggesting the cells work in concert to establish the stem cell niche. Dr. Torok-Storb emphasizes that studying "the marrow microenvironment requires that the different cell populations that make up various niches be studied together as a functional unit rather than as isolated cell populations, since their gene expression profiles are significantly different when studied in isolation compared to when they are evaluated in the context of other cells." Furthermore, "this data also explains in part how an abnormally functioning marrow microenvironment can be restored by stem cell transplantation even though the transplant does not replace marrow fibroblasts. If the deficit is caused by abnormal monocyte response to stromal signals, the replacement of resident monocytes with donor stem cell-derived monocytes can restore normal function."

Iwata M, Sandstrom RS, Delrow JJ, Stamatoyannopoulos JA, Torok-Storb B. 2013. Functionally and phenotypically distinct subpopulations of marrow stromal cells are fibroblast in origin and induce different fates in peripheral blood monocytes. *Stem Cells and Development*. Epub ahead of print, doi:10.1089/scd.2013.0300

See also: Roecklein BA, Torok-Storb B. 1995. Functionally distinct human marrow stromal cell lines immortalized by transduction with the human papilloma virus E6/E7 genes. *Blood* 85:997-1005.

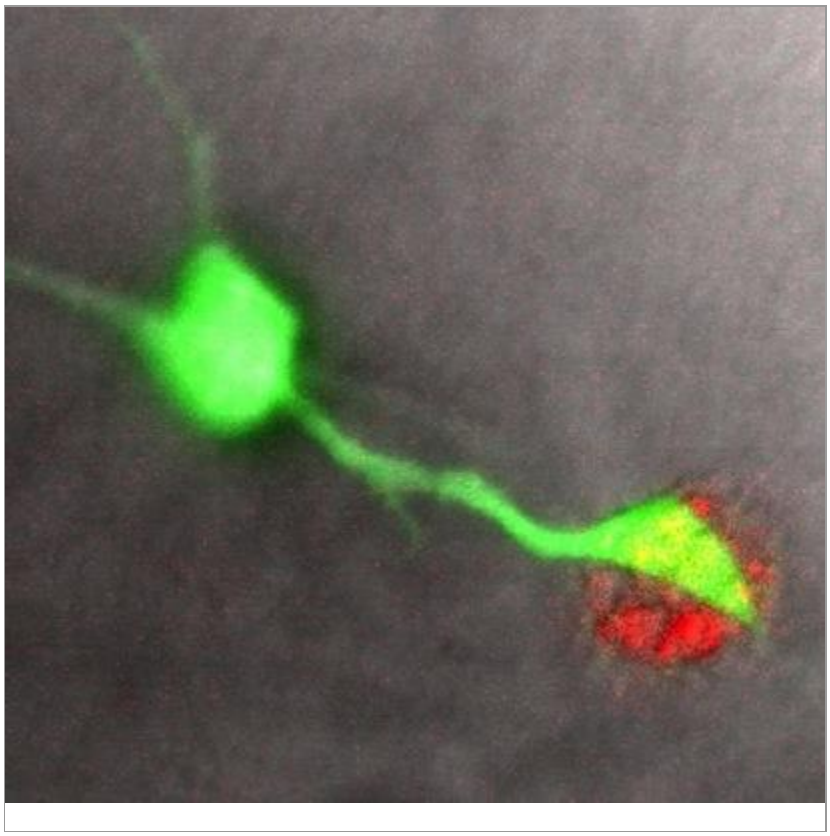

Image provided by Ying Zheng and Dr. Beverly Torok-Storb

A fibroblast cell from the bone marrow (green) reaches out to touch a monocyte (red). Distinct populations of stromal fibroblast cells influence different cell fates for monocytes and can alter the marrow microenvironment.