Study finds monocytes replenish the bone marrow's supply of infection-fighting monocytes

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Infection-fighting immune cells known as monocytes consist of two distinct subpopulations in the bone marrow, an A*STAR investigation has found. One of these acts as a reservoir for the other in order to maintain a stable pool of monocytes circulating through the bloodstream, a discovery that could inform future drug development.

"We discovered a new population of bone marrow monocytes, debunking the popular view that monocytes constitute a homogenous population," says Lai Guan Ng of the A*STAR Singapore Immunology Network (SIgN), who led the research. "Since monocytes are increasingly being recognized as attractive therapeutic targets, our findings provide critical biological knowledge that could form the basis for improved therapeutic treatments of disease."

Ng and his colleagues used a cell sorting technique called flow cytometry to categorize monocytes in the bone marrow on the basis of six surface receptor proteins. One of these proteins, CXCR4, stood out because its expression levels on the cells clearly demarcated two subsets of monocytes—one with high CXCR4 activity that serves as a kind of transitional pre-monocyte, and a more mature monocyte with low CXCR4 levels.

Gene activity analyses and experiments in mice showed that the CXCR4-expressing cells were actively proliferating and slowed their

division as they matured to replenish supplies of monocytes that were ready to move from the bone marrow to the bloodstream. As Ng explains, "This newly defined transitional phase is believed to act as a regulatory checkpoint to maintain a stable pool of circulating monocytes throughout the body."

The SIgN team, in collaboration with scientists from the A*STAR Institute of Molecular and Cell Biology and around the world, went on to define a number of other novel functions of CXCR4 in monocyte biology. Aside from CXCR4's role in retaining transitional pre-monocytes in the bone marrow, the researchers found that CXCR4 activity also continues to affect migration and localization of mature monocytes after they have left the bone marrow and entered the rest of the body.

In fact, by inhibiting CXCR4, Ng and his colleagues showed that they could reduce the number of monocytes that congregate in the blood vessel walls of the lungs of endotoxin-exposed mice, thereby limiting lung injury and the risk of sepsis-induced death. "These findings may pave the way for future CXCR4-based therapies," says Ng, noting that monocytes are increasingly being recognized as critical mediators of inflammation in conditions such as heart disease, multiple sclerosis, and liver fibrosis.

More information: Shu Zhen Chong et al. CXCR4 identifies transitional bone marrow premonocytes that replenish the mature monocyte pool for peripheral responses, *The Journal of Experimental Medicine* (2016). DOI: 10.1084/jem.20160800

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