Shp1 protein helps immune system develop its long-term memory

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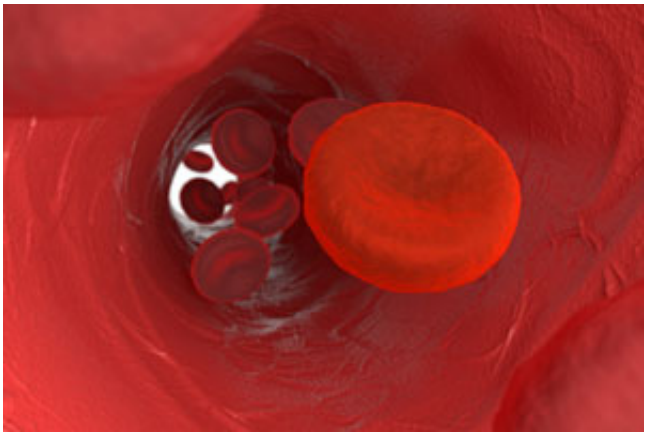

Li, Y.-F., Xu, S., Ou, X. & Lam, K.-P. Shp1 signalling is required to establish the long-lived bone marrow plasma cell pool. Nature Communications 5, 4273 (2014). The protein Shp1 is likely to help plasma cells migrate to the bone marrow, suggesting possibilities for treating debilitating diseases such as multiple myeloma. Credit: Fabian19/iStock/Thinkstock

A protein called Shp1 is vital to the immune system's ability to remember infections and fight them off when they reappear, researchers at A*STAR have found.

In a normal immune response, B cells encounter molecules called antigens, which are markers of foreign pathogens. The B cell swallows up these antigens, and presents pieces of them on its surface, where they are recognized by another type of immune cell called a helper T cell.

That prompts the B cell to differentiate into two new cell types: long-lived memory B cells that hang about in the body waiting for the same infection to turn up again; and plasma cells, which begin producing antibodies to clear the infection by marking the offending antigens for destruction. Some of the plasma cells also migrate to a long-term home in the bone marrow.

Shp1 is known to play a role in this process, because mice that lack the protein in their B cells suffer from skewed B-cell development and from autoimmunity. But immunologist Kong-Peng Lam from the A*STAR Bioprocessing Technology Institute wanted to know exactly how Shp1 was involved in B-cell differentiation into plasma cells and memory B cells. So his team engineered a mouse in which Shp1 was disabled only after the B cell was activated by antigens. What they found was surprising.

Rather than an out-of-control immune system, the loss of Shp1 led to the loss of long-term immunological memory. The memory B cells were not formed, and the antibody producing plasma cells were unable to migrate to their final home in the bone marrow.

"Since Shp1 was generally thought of as a negative regulator of the immune system, we had expected to see enhanced B-cell differentiation into plasma cells and memory B cells upon Shp1 inactivation," says Lam. "Instead we were surprised to see the opposite, in which plasma cells were significantly reduced in the bone marrow."

The role of Shp1 in helping plasma cells migrate to the bone marrow suggests possibilities for treating diseases such as multiple myeloma, in which deformed plasma cells accumulate in the bone marrow to cause bone-debilitating disease, says Lam. A drug that targets and switches off Shp1 could keep the harmful cells out of the bone marrow.

Lam's team is currently studying whether chemical inhibitors of Shp1 could indeed be used to disrupt the migration or retention of plasma cells in the bone marrow.

More information: Li, Y.-F., Xu, S., Ou, X. & Lam, K.-P. "Shp1 signalling is required to establish the long-lived bone marrow plasma cell pool." *Nature Communications* 5, 4273 (2014). dx.doi.org/10.1038/ncomms5273

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