The function of mature B cells is regulated by a small genomic cluster called mir-17-92

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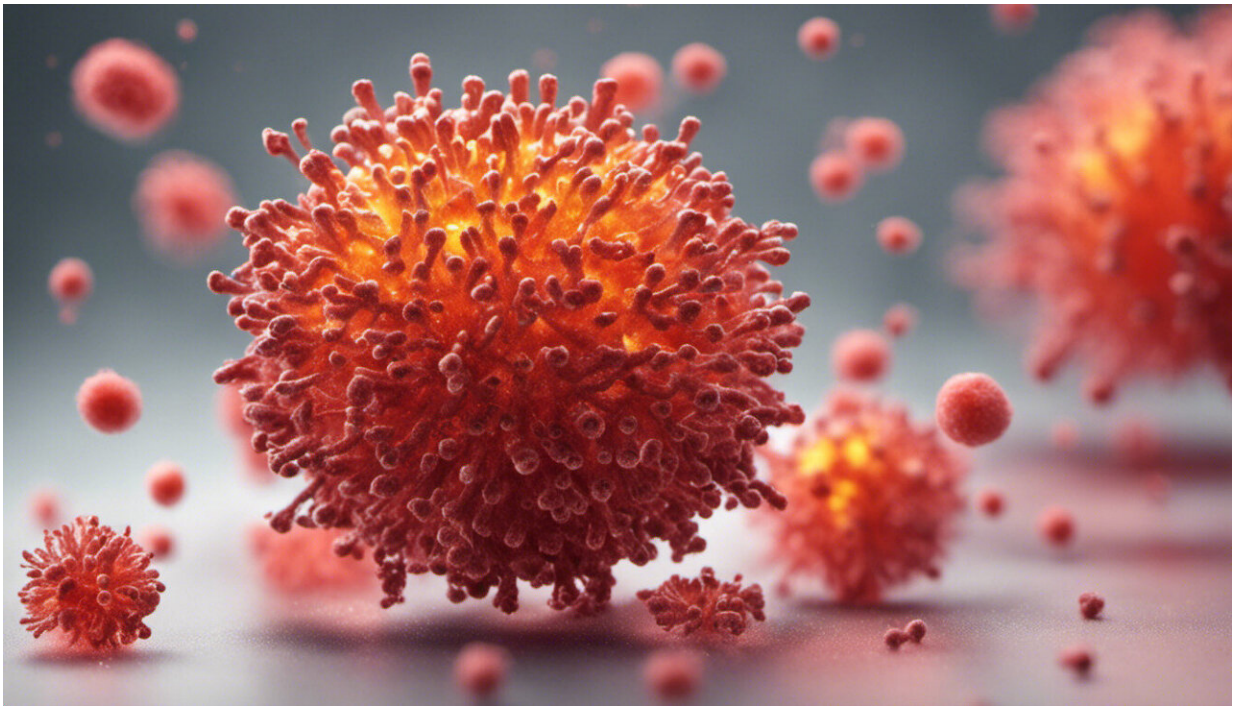

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B cells are immune cells that generate antibodies against foreign antigens and play an important role in fighting pathogens. The overproduction of antibodies is a cause of the autoimmune disease lupus, leading to kidney dysfunction. Now A*STAR researchers have identified a small cluster of RNAs that regulate antibodies in mice, shedding light on how B cells are

regulated.

The team, including Shengli Xu from the Bioprocessing Technology Institute at A*STAR, identified a genomic cluster of six short noncoding RNAs, called mir-17-92, that regulates the function of mature B cells.

Short noncoding RNAs modulate the expression of a number of target genes by binding specifically to complementary mRNA transcripts and affecting their stability, or their ability to be translated into protein. While the mir-17-92 genomic cluster was known to influence the early development of B cells, its role in mature B cells was not understood.

Xu and colleagues produced a mouse that lacked mir-17-92 only in mature B cells, and observed that more antibody-producing plasma cells—derived from B cells—ended up in the bone marrow during immune responses than in normal mice. They showed that this was because mir-17-92 normally reduced the expression of a receptor called sphingosine 1-phosphate receptor 1 (S1PR1) that is known to drive bone marrow homing by plasma cells. The absence of mir-17-92 meant S1PR1 expression went up, leading to increased plasma cell homing to bone marrow.

The mice lacking mir-17-92 also produced less of a certain class of antibody called IgG2c, which is the most prevalent type of antibody against self molecules in mouse models of lupus. The researchers identified the mir-17-92 gene target responsible for supressing the production of IgG2c in mice is the protein IKAROS. Levels of this protein are elevated in mir-17-92-deficient mice: bringing its levels back to normal also brought IgG2c production back to normal levels.

Because of the significance of IgG2c antibodies in mouse models of lupus, the team also wanted to know if reducing mir-17-92 could affect disease in the mice. By deleting mir-17-92 in the mouse model of lupus,

they found diminished autoantibody production and kidney injury in mice lacking mir-17-92 compared with controls.

"These findings lead to better understanding of the role of mir-17-92 for normal B cell function, and also pave the way for development of new treatments for some B cell-related diseases in humans, such as multiple myeloma and lupus," explains Xu.

More information: Shengli Xu et al. Mir-17–92 regulates bone marrow homing of plasma cells and production of immunoglobulin G2c, *Nature Communications* (2015). DOI: 10.1038/ncomms7764

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