Researchers uncover potential target for treating autoimmune disease

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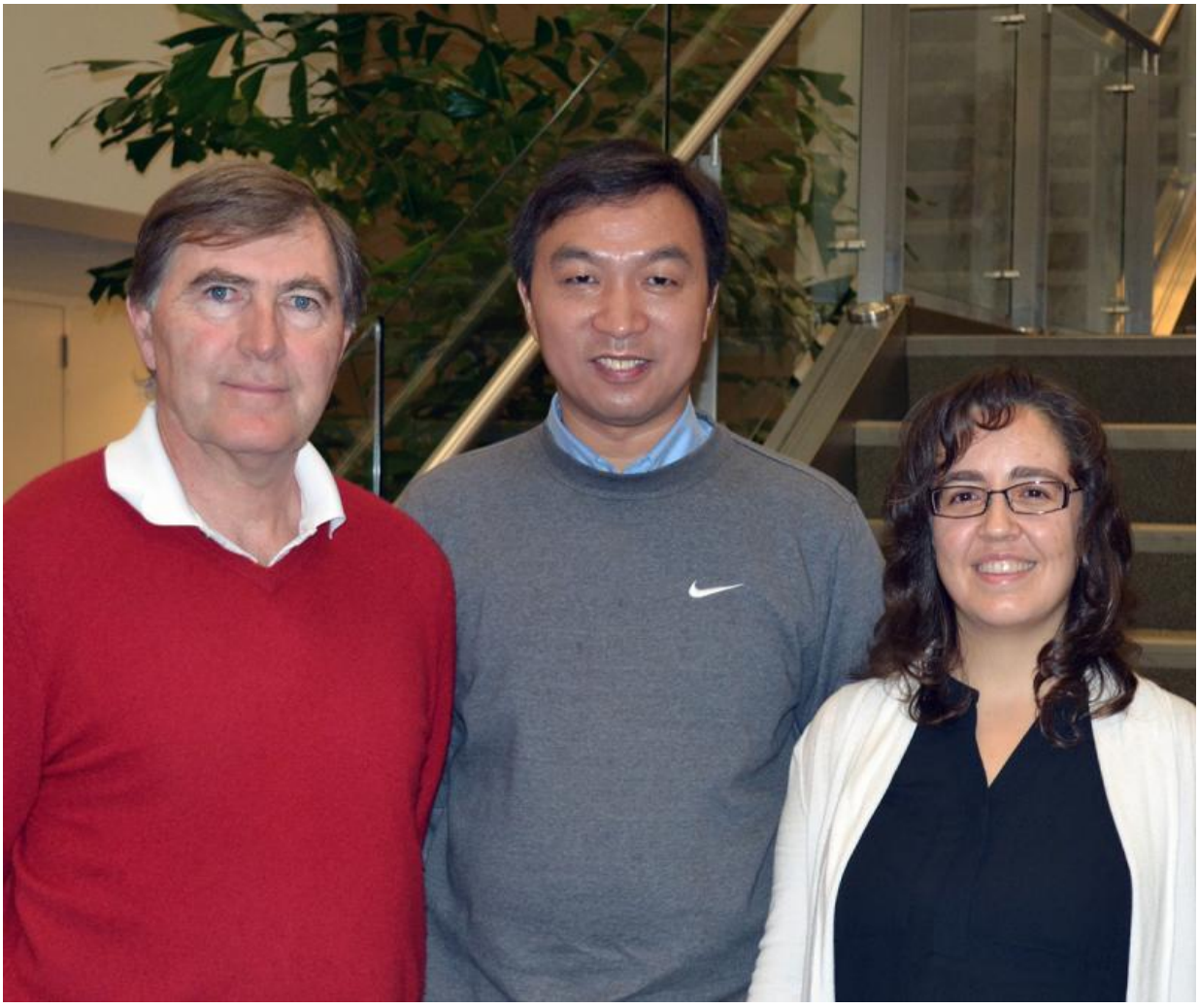

Key authors of the new paper included (left to right) Professor David Nemazee, Associate Professor Changchun Xiao and Research Associate Alicia Gonzalez-Martin. Credit: The Scripps Research Institute.

Scientists from The Scripps Research Institute (TSRI) have identified a molecule that appears to be a cause of autoimmune diseases such as lupus. Elevated levels of the molecule allow self-reactive immune cells to escape into the blood stream and attack the body's own tissues.

"This is a good target for future therapies," said TSRI Associate Professor Changchun Xiao, who was co-senior author of the study with TSRI Professor David Nemazee. "We now know that this is causative—it's not just a side effect."

The research, published February 22, 2016, in the journal *Nature Immunology*, focused on the identification of a specific microRNA (miRNA)—a small non-coding RNA molecule playing a role in regulating gene expression—that affects the immune system.

Alicia Gonzalez-Martin, research associate in the Xiao lab and first author of the new study, was excited by the discovery. "This is the first miRNA implicated in the regulation of B cell tolerance," she said.

Clues in Mouse Models

Immune cells known as B cells develop in the bone marrow and acquire specific receptors in a random assembly process that helps the body prepare to fight different enemies, including a multitude of viruses and bacteria. Xiao compared the assembly process to handing soldiers different kinds of weapons—a rifle for one soldier, a bayonet for another.

Normally, the body also has a system of B cell tolerance checkpoints in place to eliminate self-reactive B cells, which attack not only germs but also the body's own tissues. This process, which relies on apoptosis (programmed cell death), seems to go awry in patients with autoimmune diseases. "For some reason, their self-reactive B cells have not been

purged," said Xiao.

The new research began when Nemazee's lab engineered a mouse model of immune tolerance, which rendered all B cells self-reactive. As a result, the cells continually eliminated themselves by natural self-tolerance processes, leading to an absence of B cells in the body. The researchers, however, noticed a strange phenomenon—as the mice got older, some self-reactive B cells escaped into the blood stream. The phenomenon reminded the researchers of cells seen in autoimmune diseases and suggested a way to search for genes whose dysregulation hindered tolerance and promoted such diseases.

The scientists hypothesized that some of the more than 1,000 known miRNAs might be affecting the gene expression regulating the survival or destruction of self-reactive B cells. The challenge was to pinpoint the exact miRNA responsible.

"This was a risky project because we weren't sure if any miRNA at all would regulate B cell tolerance," explained Gonzalez-Martin.

Setting the Trap

Finding the miRNA culprit meant setting a trap.

The team first generated its own self-reactive B cells by prompting a virus to express select miRNAs in haematopoietic stem cells (stem cells producing blood cells and platelets). The researchers then seeded the bone marrow of the Nemazee lab's mouse model with these cells.

Eventually, some of these self-reactive B cells escaped into the spleens of the mice, where researchers caught and analyzed the miRNAs expressed.

The researchers found elevated expression of a specific miRNA called miR-148a that was responsible for B cell escape. MiR-148a suppressed three genes that control apoptosis. Without apoptosis, self-reactive mutants were not purged.

When the team prompted mouse models of lupus to overexpress miR-148a, the mice developed lupus faster than their counterparts with normal miR-148a expression. Interestingly, miR-148a is also overexpressed in many human lupus patients.

"This brings us to a pathway that we might be able to regulate with a therapeutic," Nemazee said.

The researchers said the next step is to investigate miR-148a's other functions in the body to see if inhibiting its actions would have any negative side effects.

More information: The microRNA miR-148a functions as a critical regulator of B cell tolerance and autoimmunity, *Nature Immunology*, DOI: 10.1038/ni.3385

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