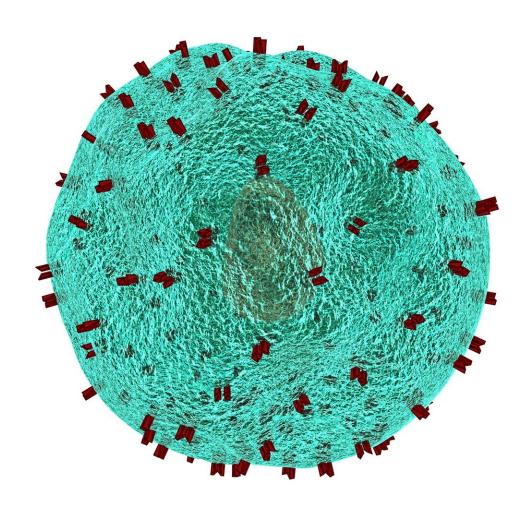


## Striking a balance: a mechanism to control autoimmunity

October 8 2019





Credit: CC0 Public Domain

B cells are white blood cells that generate antibodies against an almost unlimited number of pathogens, a capacity that is vital for any higher organism. However, establishing a diverse repertoire of pathogen recognition comes at a price, as some B cells will inevitably go wild and turn against the organism's own, healthy tissue.

Such autoreactive B <u>cells</u> need to be silenced and are kept within the pool of B cells for emergencies, such as serious infections, for which no specific B cell can be found in the active B cell pool. Scientists from the lab of the IMP Deputy Director Meinrad Busslinger have investigated the two antagonistic mechanisms that silence or awaken autoreactive B cells. Both mechanisms are controlled by the protein Ikaros, thereby controlling autoimmunity—as now reported in the journal *Nature Immunology*.

Remarkably, the starting point of the project was not autoimmunity, but an interest in how the transcription factor lkaros may influence B cell differentiation.

Transcription factors are proteins that bind to specific parts of the DNA to activate or repress certain genes. "When you are interested in how a transcription factor works, you normally start by looking at what it does early or late in B cell development, and you can do so by selectively inactivating the factor", says Meinrad Busslinger in explaining the chosen approach.

In the absence of lkaros in mature B cells of mice, the scientists observed a high degree of autoimmunity. This made them turn to the two mechanisms that switch B cells on and off: "Anergy" of the B cell antigen



receptor (BCR) is a tolerance mechanism that makes auto reactive B cells insensitive to self-antigens, and "Toll-like receptor (TLR)" signalling awakens B cells.

"We could show that in the absence of lkaros, BCR anergy decreases, TLR signalling increases, and B cells become hyperactive leading to systemic autoimmunity in the animals", says Tanja Schwickert, first author of the study, who continued to investigate how Ikaros specifically controls the two mechanisms causing these signalling defects. The results supported the main conclusion of the study: "lkaros acts as a guardian that prevents autoimmunity."

The research project started with the development of a mouse model to study the function of lkaros in mature B cells in 2012. "At this point, nobody could have guessed that we will identify lkaros as a fundamental regulator of autoimmunity", says Meinrad Busslinger. He now considers the establishment of this link to be a case of serendipity: "This is how basic research works—you ask a fundamental question, and you work out mechanisms with unexpected, but very far-reaching implications for all sorts of phenomena". In this case, the two mechanisms through which a single protein is sufficient to control autoimmunity.

In humans, lkaros mutations have been identified as a risk factor for systemic lupus erythematosus (SLE), an autoimmune disease that cannot be cured and drastically shortens the life expectancy of affected patients. The present study will help to bring this condition into context of a basic mechanism that could be involved in the generation of autoimmune disease.

**More information:** Tanja A. Schwickert et al. Ikaros prevents autoimmunity by controlling anergy and Toll-like receptor signaling in B cells, *Nature Immunology* (2019). DOI: 10.1038/s41590-019-0490-2



## Provided by Research Institute of Molecular Pathology

Citation: Striking a balance: a mechanism to control autoimmunity (2019, October 8) retrieved 8 May 2024 from <a href="https://medicalxpress.com/news/2019-10-mechanism-autoimmunity.html">https://medicalxpress.com/news/2019-10-mechanism-autoimmunity.html</a>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.