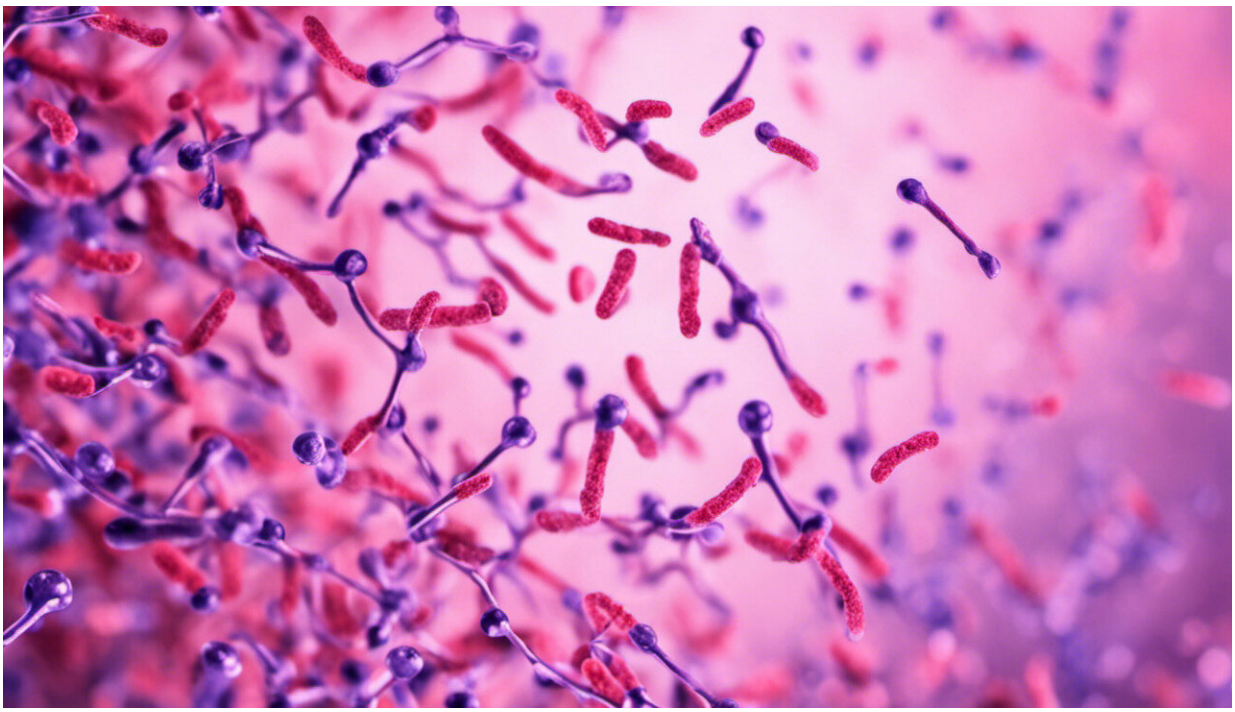
Protein implicated in lupus promotes disease progression by distinct mechanisms in different immune cells

March 13 2013



Credit: AI-generated image (disclaimer)

Patients with systemic lupus erythematosus (SLE) come under attack by their immune system, producing 'autoantibodies' that inflict damage throughout the body. Antibodies normally target foreign proteins, but SLE autoantibodies attack targets contained within the nuclei of host

cells, and immunologists have struggled to untangle how this happens.

Research led by Anna-Marie Fairhurst of the A*STAR Singapore Immunology Network has now uncovered valuable insights into early SLE onset. Part of SLE's complexity arises from the intersecting involvement of multiple genetic factors. Accordingly, one of the primary SLE mouse models that Fairhurst uses contains two clusters of genomic variants, Sle1 and Yaa. Each cluster contains numerous SLE-susceptibility genes.

One of the most interesting genes contained within Yaa is Tlr7, which encodes the TLR7 protein. Fairhurst's team revealed previously that increased Tlr7 expression is an essential contributor to disease severity in Sle1Yaa mice. TLR7 is a cell-surface receptor that recognizes viral RNA , so it is important for the immune response to infection. However, since TLR7 performs different functions in different immune cell types, its potential contributions to disease are ambiguous. One possibility is that TLR7 hyperactivity establishes a 'feedback loop' that drives autoantibody-secreting B cells to overreact to host proteins.

To discern TLR7's role, Fairhurst and co-workers engineered mice whose cells each contain extra copies of its gene. These mice were asymptomatic. When the researchers crossed these mice with Sle1 mice, their offspring produced antinuclear autoantibodies and exhibited severe abnormalities of the kidney and spleen that are typically seen in Sle1Yaa mice.

Fairhurst and her co-workers designed their mouse strain so that the extra Tlr7 copies could be selectively deleted in certain cells via a targeted genetic recombination mechanism (see image). They anticipated that by normalizing TLR7 levels in B cells, they could largely prevent disease onset in animals that still overexpress this receptor elsewhere. Although the researchers observed the expected strong reduction in anti-

RNA autoantibodies in these mice, they were surprised to see only partial mitigation of other SLE symptoms.

This suggests a more complex role for TLR7 in SLE. "TLR7 is required for the initial steps of autoimmunity, meaning autoantibody production," says Fairhurst, "but the [increased expression] of TLR7 in other cells drives the inflammation that leads to tissue destruction and severe disease." Accordingly, she and her co-workers are now actively investigating both how TLR7 drives B cells to attack inappropriate targets in early SLE onset and the cell populations in which it acts to accelerate progression.

More information: Hwang, S.-H., Lee, H., Yamamoto, M., Jones, L. A., Dayalan, J. et al. B cell TLR7 expression drives anti-RNA autoantibody production and exacerbates disease in systemic lupus erythematosus–prone mice. *The Journal of Immunology* 189, 5786–5796 (2012). www.jimmunol.org/content/189/12/5786.abstract

Provided by Agency for Science, Technology and Research (A*STAR), Singapore

Citation: Protein implicated in lupus promotes disease progression by distinct mechanisms in different immune cells (2013, March 13) retrieved 2 May 2024 from https://medicalxpress.com/news/2013-03-protein-implicated-lupus-disease-distinct.html

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