Researchers reveal how receptor TLR-9 protects against lupus

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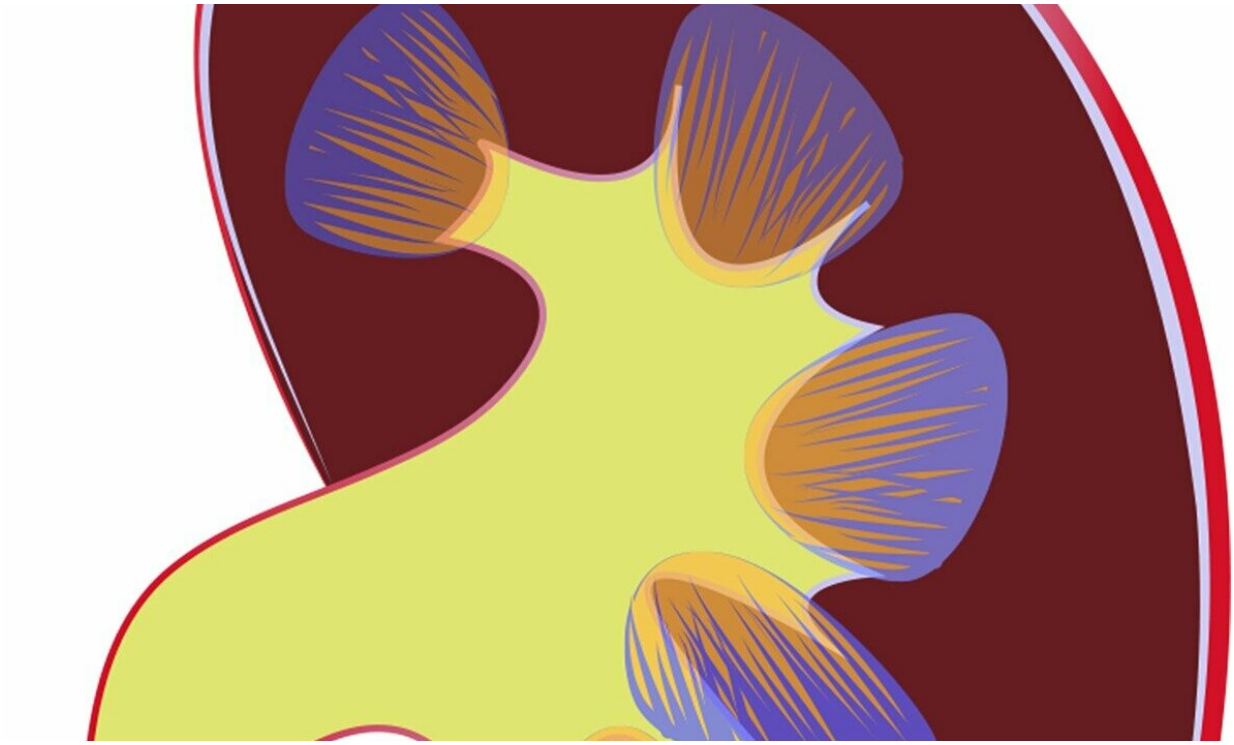

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When the pathogen-sensing intracellular receptors TLR-7 and TLR-9 were implicated in systemic lupus erythematosus (SLE), it was suspected that their removal would lessen the severity of the disease. However, while this held true for TLR-7, removing TLR-9 in mice unexpectedly caused severe SLE with an inflammatory kidney disease called

glomerulonephritis.

"Everyone was scratching their heads: all the signs of autoimmunity were there but no-one had any idea why it happened," recalls A*STAR's Anna-Marie Fairhurst. The two receptors share similar expression and signaling patterns, and their aberrant expression is implicated in SLE, but their absences caused opposite effects.

Fairhurst's team at A*STAR's Singapore Immunology Network has now revealed the stabilizing action of TLR-9, and how its depletion boosts pathogenic levels of TLR-7 which leads to the production of antibodies that act against the body's own genetic material.

SLE is an autoimmune disease—a condition in which a person's immune system turns on its host's own cells and tissues. SLE's exact causes aren't fully understood, however, it is thought that a combination of inherited risk factor genes and a trigger—such as an infection—could precipitate it.

In their paper, published in *Arthritis and Rheumatology*, Fairhurst and her team explain that, in SLE, complexes of host-attacking antibodies and genetic material embed in organs and cause irreversible damage. When these complexes activate infection-sensing toll-like receptors (TLRs), the result is an exacerbating and damaging inflammatory response.

The researchers bred lupus-prone, TLR-9 deficient mice to establish the impact. The mice exhibited a systemic increase in TLR-7, including within the immune system's dendritic cells. Dendritic cells with increased TLR-7 expression infiltrated the kidneys, where TLR-7 played an initiative role in the development of glomerulonephritis.

Mice lacking TLR-9 also developed increased autoantibodies that

targeted a form of genetic material known as RNA, a nucleic acid involved in carrying instructions from DNA to control protein synthesis. Fairhurst's team report in their paper that this loss of 'tolerance' to a host's own RNA is thought to be a key stage in the transition to active autoimmune disease.

"It's really two things coming together. It's the anti-RNA antibodies, and then also TLR-7 and dendritic cells. These two are coming together to really drive inflammatory events that slowly, but surely, destroy the kidney," says Fairhurst.

"This research points to targeting this pathway for patients with lupus," she adds. "It paves the way to further understand and tells us we need to do more research and develop targets in these two pathways."

More information: Teja Celhar et al. Toll-Like Receptor 9 Deficiency Breaks Tolerance to RNA-Associated Antigens and Up-Regulates Toll-Like Receptor 7 Protein in Sle1 Mice, *Arthritis & Rheumatology* (2018). DOI: 10.1002/art.40535

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