New Pathogenic Mechanism of Systemic Lupus Erythematosus

(Arase group, in *Arthritis Rheumatol.*)

A research group led by Professor Hisashi Arase (IFReC/RIMD/CiDER, Osaka University) together with Kyoto University, Kobe Central City Hospital, and RIKEN elucidated a new pathogenic mechanism of systemic lupus erythematosus (SLE) [*1].

Although it has been known that a specific HLA[*2] class II alleleis associated with the risk of systemic lupus erythematosus, the functional role of HLA class II molecules in the production of anti-DNA antibodies has remained unclear. The group has previously shown that HLA class II molecules present not only peptides but also misfolded proteins and are involved in the production of autoantibodies in various autoimmune diseases. In this study, they have revealed for the first time that DNA binds to the peptide binding pocket of HLA class II molecules and could be involved in the production of anti-DNA antibodies.

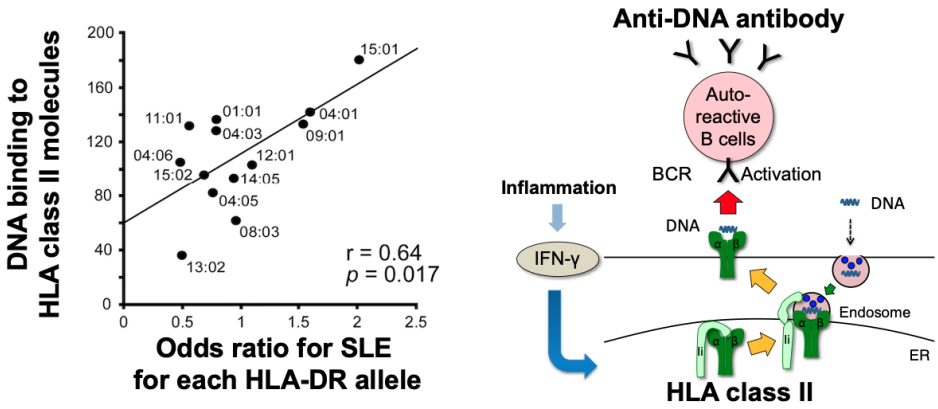

Figure:

In general, immunization of DNA alone does not produce anti-DNA antibodies in mice. The group showed the expression of DNA by HLA class II molecules and stimulation of DNA reactive BCR by DNA/HLA class II complex. Then it may lead the B cell-T cell interaction and production of anti-DNA Abs.

From the analyses of HLA class II transfected cells, we demonstrated that DNA is presented on HLA class II molecules, which have been thought to present only peptides. In particular, DNA was found to bind significantly more strongly to HLA class II molecules with the systemic lupus erythematosus-risk allele than to the resistant allele. In addition, the binding of DNA to HLA class II molecules was inhibited by high-affinity peptides, indicating that DNA binds to the peptide-binding pocked of HLA class II molecules. Furthermore,

analysis using GFP-reporter cells expressing anti-DNA antibodies as B cell receptors revealed that DNA bound to HLA class II transduces activating signals through the anti-DNA B cell receptor. These results suggest that DNA presented on HLA class II molecules could be involved in the production of anti-DNA antibodies in systemic lupus erythematosus.

*1 SLE

Systemic lupus erythematosus (SLE), is the most common type of lupus. SLE is an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels.
(CDC website)

*2 HLA (human leukocyte antigen)

In humans, HLA is synonymous with major histocompatibility complex (MHC). There are two types of molecules, HLA class I and HLA class II. HLA class I molecules are expressed on all cells except red blood cells, while HLA class II molecules are expressed on the surface of specific immune cells. Both HLA class I and class II are involved in antigen presentation to T cells. HLA class II molecules have been considered to present peptide antigens incorporated from outside of cells.

<Article>

Journal: *Arthritis and Rheumatology* 74(1):105-111, 2022.
Title: “Anti-dsDNA antibodies recognize DNA presented on HLA class II molecules of systemic lupus erythematosus risk alleles”
Authors: Hideaki Tsuji, Koichiro Ohmura*, Hui Jin, Ryota Naito, Noriko Arase, Masako Kohyama, Tadahiro Suenaga, Shuhei Sakakibara, Yuta Kochi, Yukinori Okada, Kazuhiko Yamamoto, Hitoshi Kikutani, Akio Morinobu, Tsuneyo Mimori, Hisashi Arase*
(*correspondence)

Link: http://dx.doi.org/10.1002/art.41897