Apoptosis-derived membrane vesicles drive the cGAS–STING pathway and enhance type I IFN production in systemic lupus erythematosus

Keywords: immunology, autoimmune diseases, allergy internal medicine, cytokine, innate immunity

Objective
Despite the importance of type I interferon (IFN-I) in systemic lupus erythematosus (SLE) pathogenesis, the mechanisms of IFN-I production have not been fully elucidated. Recognition of nucleic acids by DNA sensors induces IFN-I and interferon-stimulated genes (ISGs), but the involvement of cyclic guanosine monophosphate (GMP)–AMP synthase (cGAS) and stimulator of interferon genes (STING) in SLE remains unclear. We studied the role of the cGAS–STING pathway in the IFN-I-producing cascade driven by SLE serum.

Methods
The authors collected sera from patients with SLE (n=64), patients with other autoimmune diseases (n=31) and healthy controls (n=35), and assayed them using a cell-based reporter system that enables highly sensitive detection of IFN-I and ISG-inducing activity. We used Toll-like receptor-specific reporter cells and reporter cells harbouring knockouts of cGAS, STING and IFNAR2 to evaluate signalling pathway-dependent ISG induction.

Results
IFN-I bioactivity and ISG-inducing activities of serum were higher in patients with SLE than in patients with other autoimmune diseases or healthy controls. ISG-inducing activity of SLE sera was significantly reduced in STING-knockout reporter cells, and STING-dependent ISG-inducing activity correlated with disease activity. Double-stranded DNA levels were elevated in SLE. Apoptosis-derived membrane vesicles (AdMVs) from SLE sera had high ISG-inducing activity, which was diminished in cGAS-knockout or STING-knockout reporter cells.

Conclusions
AdMVs in SLE serum induce IFN-I production through activation of the cGAS–STING pathway. Thus, blockade of the cGAS–STING axis represents a promising therapeutic target for SLE. Moreover, our cell-based reporter system may be useful for stratifying patients with SLE with high ISG-inducing activity.

<Article Information>
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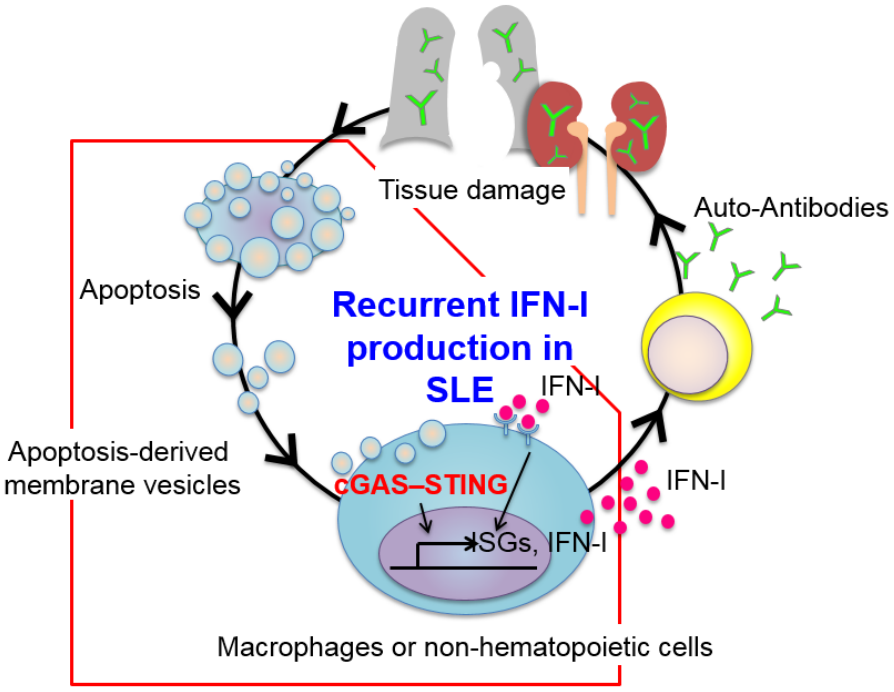
Title: "Apoptosis-derived membrane vesicles drive the cGAS–STING pathway and enhance type-I IFN production in Systemic lupus erythematosus"

Journal: Annals of the Rheumatic Diseases (June 26, 2018 online)



Model of recurrent type I IFN production in SLE patients.

AdMVs stimulate the cGAS–STING signaling pathway in macrophages and non-hematopoietic cells, leading to overproduction of IFN-I. Secreted IFN-I, in turn, activates other immune cells, such as B and T lymphocytes, and promotes secretion of autoantibodies that cause tissue damage in various organs. The tissue damage promotes apoptosis of damaged cells, resulting in further AdMV production, which perpetuates IFN-I production in SLE.