ARTHRITIS & RHEUMATOLOGY
Vol. 0, No. 0, Month 2018, pp 1–13
DOI 10.1002/art.40467

Role of *Lgals9* Deficiency in Attenuating Nephritis and Arthritis in BALB/c Mice in a Pristane-Induced Lupus Model

Sonia Zeggar,[1] Katsue S. Watanabe,[1] Sanae Teshigawara,[1] Sumie Hiramatsu,[1] Takayuki Katsuyama,[1] Eri Katsuyama,[1] Haruki Watanabe,[1] Yoshinori Matsumoto,[1] Tomoko Kawabata,[1] Ken-ei Sada,[1] Toshiro Niki,[2] Mitsuomi Hirashima,[2] and Jun Wada[1]

Objective. **In systemic lupus erythematosus (SLE), an autoimmune disease associated with multiple organ involvement, the development of lupus nephritis determines prognosis, and arthritis impairs quality of life. Galectin 9 (Gal-9, *Lgals9*) is a β-galactoside–binding lectin that has been used for clinical application in autoimmune diseases, since recombinant Gal-9, as a ligand for T cell immunoglobulin and mucin domain–containing protein 3 (TIM-3), induces apoptosis of activated CD4+TIM-3+ Th1 cells. This study was undertaken to investigate whether deficiency of *Lgals9* has beneficial or deleterious effects on lupus in a murine model.**

Methods. **Gal-$9^{+/+}$ and Gal-$9^{-/-}$ female BALB/c mice were injected with pristane, and the severity of arthritis, proteinuria, and levels of autoantibody production were assessed at several time points immediately following injection. At 7 months after pristane injection, renal pathologic features, the severity of joint inflammation, and formation of lipogranulomas were evaluated. Subsets of inflammatory cells in the spleen and peritoneal lavage were characterized, and expression levels of cytokines from peritoneal macrophages were analyzed.**

Results. ***Lgals9*** **deficiency protected against the development of immune complex glomerulonephritis, arthritis, and peritoneal lipogranuloma formation in BALB/c mice in this murine model of pristane-induced lupus. The populations of T cell subsets and B cells in the spleen and peritoneum were not altered by *Lgals9* deficiency in pristane-injected BALB/c mice. Furthermore, *Lgals9* deficiency protected against pristane-induced lupus without altering the Toll-like receptor 7–type I interferon pathway.**

Conclusion. **Gal-9 is required for the induction and development of lupus nephritis and arthritis in this murine model of SLE. The results of the current investigation provide a potential new strategy in which antagonism of Gal-9 may be beneficial for the treatment of nephritis and arthritis in patients with SLE through targeting of activated macrophages.**

Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease that is characterized by a wide array of clinical manifestations and multifactorial pathogenic pathways. The disease process of SLE involves genetic, epigenetic, hormonal, and environmental factors, all of which ultimately lead to a disturbance in the pathways of both innate and adaptive immunity. Despite notable progress in the understanding of this disease, its etiology remains unclear and is still to be unraveled. Kidney involvement in SLE is known to be associated with poor clinical outcomes, with 10–30% of young patients developing end-stage renal disease (ESRD) (1,2). Despite the wide availability of different regimens involving treatment with immunosuppressant agents, many of which have undoubtedly improved the prognosis and survival of patients with SLE, an increased risk of ESRD in SLE has been observed since the late 2000s (3).

In contrast to lupus nephritis, lupus arthritis is one of the frequently encountered manifestations in

Supported by the Japan Society for the Promotion of Science (Grant-in-Aid for Scientific Research grants 26293218, 17K09976, 16K19600, and 16K09896).

[1]Sonia Zeggar, MD, Katsue S. Watanabe, MD, PhD, Sanae Teshigawara, MD, PhD, Sumie Hiramatsu, MD, Takayuki Katsuyama, MD, PhD, Eri Katsuyama, MD, PhD, Haruki Watanabe, MD, Yoshinori Matsumoto, MD, Tomoko Kawabata, MD, PhD, Ken-ei Sada, MD, PhD, Jun Wada, MD, PhD: Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [2]Toshiro Niki, MD, PhD, Mitsuomi Hirashima, MD, PhD: Kagawa University, Takamatsu, Japan.

Dr. Wada has received speaking fees and/or honoraria from Astellas, Boehringer Ingelheim, Novartis, and Tanabe Mitsubishi (less than $10,000 each) and grant support from Astellas, Bayer, Chugai, Daiichi Sankyo, Kissei, Kyowa Hakko Kirin, MSD, Otsuka, Teijin, Torii, Pfizer, Takeda, and Taisho Toyama.

Address correspondence to Jun Wada, MD, PhD, Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. E-mail: junwada@okayama-u.ac.jp.

Submitted for publication August 1, 2017; accepted in revised form February 20, 2018.