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EDITORIAL

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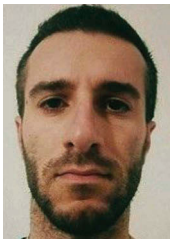
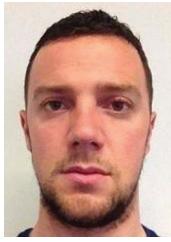
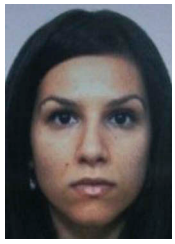
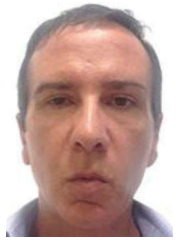

Systemic lupus erythematosus (SLE), a chronic autoimmune disease that can affect multiple organs, is characterized by a dysregulated activation and differentiation of B cells and plasma cells with a massive production of autoreactive antibodies. Overproduction of interleukin (IL)-21, a cytokine with pleiotropic effects on a wide range of cells, occurs in SLE and is supposed to activate detrimental immune pathways in this disorder. Consistently, IL-21 blockade is beneficial in murine models of SLE. We here discuss the available data supporting the involvement of IL-21 in the pathogenesis of SLE and the rationale for the therapeutic targeting of this cytokine.

Evidence supporting the involvement of IL-21 in SLE

SLE is an autoimmune disorder characterized by chronic inflammation that leads to tissue damage in multiple organs. The reported prevalence of SLE in the US population is 52.2 cases per 100,000 and the disease is more common in women of childbearing age [1]. Although etiology of SLE remains unknown, circumstantial evidence supports the hypothesis that interaction between genetic and environmental factors triggers an excessive immune response that promotes the pathological process [2]. The immunological features of SLE include loss of B-cell tolerance, hyperactivation of B cells and plasma cells, enhanced production of autoantibodies against nuclear components, and formation of immunocomplexes (ICs) that deposit in tissues, such as skin, kidneys, and brain, thus resulting in a local inflammatory response and severe tissue destruction [3,4]. ICs can also promote activation of the alternative complement pathway and recruitment of macrophages and dendritic cells to inflamed sites with the downstream effect of upregulating inflammatory cytokine production and activating autoreactive $CD4^+$ T cells [5]. In recent years, the basic mechanisms and factors that promote B-cell dysfunction in SLE patients and lupus-prone mice have been the subject of intense interest and study. This work has contributed to show that interleukin (IL)-21, a cytokine involved in the control of B-cell homeostasis and function, plays a role in the SLE-associated immune alterations [2,6].

Polymorphisms in either the intronal regions of the IL-21 gene or the gene encoding for IL-21 receptor have been associated with SLE and, at least in the Chinese population, the IL-21 rs2055979 A variant allele has been linked to increased circulating levels of IL-21 [7,8]. Plasma levels of IL-21 are higher in SLE patients than in healthy controls [2], but factors that account for such an induction are not fully understood. A possibility is that IL-21 accumulates in the blood as a spillover of the cytokine produced in inflamed sites; indeed IL-21 RNA transcripts are upregulated in skin biopsies of patients with SLE and during the active phases of the disease, IL-21-producing cells (e.g. $CD4^+$ T cells, Vδ2 T cells) are abnormally recruited to tissues [9–11]. Another possibility is that, in the presence of an autoimmune microenvironment, circulating immune cells produce high amount of IL-21. This hypothesis fits with the demonstration that circulating $CD4^+$ T cells of SLE patients synthesize elevated levels of IL-21 in response to 17-β estradiol stimulation [12]. Blockade of IL-21 inhibits induction of antibodies by normal B cells co-cultured with estrogen-stimulated $CD4^+$ T cells from SLE patients [12]. Altogether, these findings provide a link between induction of IL-21 and higher frequency of SLE in women of childbearing age.

IL-21 in lupus-prone mice

A large amount of work has been conducted in mouse models of SLE to explore the role of IL-21 in this disease. BXSB.B6-Yaa +/J mice, a specific strain that displays many of the SLE-associated symptoms (e.g. lymphadenopathy, splenomegaly, hypergammaglobulinemia, and severe immune complex–mediate glomerulonephritis), are characterized by elevated production of IL-21 [13], and IL-21 blockade suppresses activation of effector lymphocytes and reduces circulating levels of antibodies and proteinuria [14]. Consistently, BXSB-Yaa+/J mice lacking IL-21 receptor selectively in B cells exhibited none of the abnormalities characteristic of SLE, thus supporting the role of IL-21 in the accumulation of plasma cells and production of autoantibodies [15]. Blockade of IL-21 with IL-21R/Fc is also beneficial in MRL-Faslpr mice, another murine model of SLE. Treatment of mice with IL-21R/Fc reduces the

circulating levels of autoantibodies and the number of splenic T and B lymphocytes, as well as lymphadenopathy and skin lesions [16]. IL-21R/Fc-treated mice also have reduced levels of IgG deposits in the kidney, no thickening in glomerular basement membranes, and less proteinuria [16].

Further support to the contribution of IL-21 in SLE pathogenesis is provided by studies in the SLE-like *sanroque* mutant mouse model, in which development of lesions is associated with increased production of IL-21 [17].

Therapeutic perspectives

The available data described above suggest that IL-21 can be a promising target for therapeutic interventions in SLE. A randomized, placebo-controlled, double-blind, multiple-dose trial investigating the safety and tolerability of the anti-IL-21 antibody NNC0114-0006 was performed in European and American SLE patients concomitantly treated with stable background therapies [18] but results have not yet been published. A phase 1 study showed that a fully human monoclonal anti-IL-21R antibody, namely ATR-107, was highly immunogenic after a single dose administration in healthy subjects and more than two-third of the ATR-107-treated subjects developed antidrug antibodies, likely precluding further clinical applications [19]. Further work is, therefore, needed to determine whether IL-21 blockade in SLE patients may generate the disease suppressing effects seen in animal models of murine lupus. Meanwhile some critical issue should be taken into consideration in designing future clinical trials with IL-21 blockers. Although the pathogenic pathways involved in SLE are not fully characterized, it is evident that a combination of deregulated processes is necessary for the disease to manifest [4]. Therefore, the targeting of a single molecule/pathway, such as IL-21, could not be sufficient to alter progression of disease and combining of IL-21 inhibitors with other targeted therapeutics can give rise to better outcomes. Time-course studies in the BXSB-Yaa+/J mice revealed a dual role of IL-21 in the initiation and progression of the pathology, as blockade of IL-21 pathway in the early phases exacerbates disease progression while it has beneficial effects at later time points [14]. This finding, which is consistent with studies in other models of immune-mediated diseases, could rely on the divergent role of the cytokine to regulate differently innate and adaptive immunity. Furthermore, IL-21 inhibits response of antigen-presenting cells to microbial stimuli while it has positive effects on B- and T-cell activation [18]. It is, thus, plausible that treatment of SLE patients with IL-21 inhibitors could paradoxically exacerbate SLE course. Since IL-21 is a major inducer and activator of $CD8^+$ T suppressor cells [20], it is conceivable that IL-21 blockade can enhance the risk of malignancy and viral infections.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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