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Commentary on Updated Insight into the Role of Th2-Associated Immunity in Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a common autoimmune disease caused by multiple factors. The pathogenesis of SLE remains unclear. Helper T cell 2 (Th2 cell) is essential for humoral immunity, which participates in regulating type 2 immune response by producing typical cytokines of interleukin (IL)-4, IL-5, and IL-13. It is well known that Th2-associated immunity plays a vital role in autoimmune diseases, including SLE. However, current progress on the role and potential mechanism of Th2-associated immunity in SLE remains largely unknown. The work by Wang et al. have provided an in-depth association of Th2-associated immunity with SLE and the clinical application perspectives. We provide a more comprehensive and up-to-date commentary on Th2-associated immunity in regulating SLE to explore new therapeutic targets.

Keywords: Systemic lupus erythematosus, Th2-associated immunity, Cytokine, Targeted therapy

Commentary

Systemic lupus erythematosus (SLE) is a common autoimmune disease, which is more frequent in women at childbearing age. The typical characteristics are the apoptotic debris removal defect and abundant autoantibody production, resulting in abnormal immune response, chronic inflammation, and tissue damage. Cytokines have been fully demonstrated to participate in the pathogenesis of SLE by regulating inflammation and immune homeostasis. The imbalance of pro- and anti-inflammatory cytokines leads to Th1/Th2 bias. In particular, Th2-associated immunity has drawn more and more attention in SLE. It is crucial to investigate the potential molecular mechanisms and key checkpoint molecules involved in Th2-associated immunity in SLE.

In the paper by Wang et al. [1], the key role and potential mechanisms of T cell-mediated immune reaction in SLE have been fully reviewed, which provided a theoretical basis for the diagnosis and targeted therapy of SLE, with special emphasis on the latest progress of Th2-related immunity. The immune disorders mediated by Th2 bias contribute to autoimmune diseases, including SLE. Type 2-related immune response is common in more than 50% of SLE patients [2]. Abnormal Th2-associated immunity is more frequent in elderly and male SLE patients [3], while the detailed molecular mechanism for this discrepancy has not been verified. Identifying new strategies targeting checkpoint molecules involved in Th2-related immunity is urgent for the targeted treatment of SLE. The role of Th2-associated immunity in the pathogenesis of SLE is the focus of the review by Wang et al. [1]. This review has detailed summarized most currently available studies regarding the mechanisms involved in Th2 cell differentiation and polarization, such as IL-4-related signal transduction (IL-4/JAK/STAT6 pathway), Th2-related transcription factors (Gata3), epigenetic modifications (DNA methylation, ubiquitination, and degradation), and regulatory effects of mesenchymal stem cells (MSCs) (**Table 1**). By searching the latest literature in PubMed and Web of Science databases, we found that glycolysis and lipid metabolism reprogramming driven by mTOR signal also confer modifying effects on Th2 cell differentiation and function (**Table 1**). MTORC2 pathway participates in regulating glucose reprogramming and Th2 immune response by activating c-MYC and RhoA [4]. Besides, a recent study has shown that growth differentiation factor 15 (GDF-15) was highly expressed in SLE patients, which inhibited the production of autoantibodies and inflammatory cytokines [5]. The percentage of Th2 cells in lupus mice was significantly reduced after GDF-15 treatment, implicating the protective role of GDF-15 in suppressing type 2 immune response [5]. In

Table 1. Th2 mediated therapeutic targets.

Classification	**Indirect target**
epigenetic modifications	mTOR [4]
	GDF-15 [5]
	miRNA [6-8]
	BDH2 [9]
	E4BP4 [10]
	PPAR-γ [11]
transcription factors	CEBPβ [12]
regulatory effects of mesenchymal stem cells	MSCs [1,2,13,14]
cytokines and various cell signaling pathways	IL-4-STAT6-GATA3-αvβ3 pathway [1,15,16]
	IL-4-CNS2-Notch-RBPJ pathway [17]
	IL-5-JAK-STAT [1] and IL-5-Ras/Raf-ERK pathway [1]
	IL-6-STAT3 pathway [1,18]
	IL-6R -JAK-STAT pathway [19]
	IL-6- CRIF1 [22]
	IL-9-IRF4 pathway [1]
	IL-10-E2F2-miR-175p pathway [1]
	Il-10-CNS9-NFAT1-IRF4 pathway [17]
	IL-13-rs20541 CT/TT gene polymorphism [1]
	IL-4/IL-13- Monoclonal antibody Dupilumab [21]
	TLR9-TGF-1-PDGF-B pathway [1]
	IL-25-JAK-STAT [1] and IL-25-MAPK pathway [1]
	IL-33-ST2 axis [20]

addition, some disease-specific microRNAs (miRNAs) are well documented to promote DNA hypomethylation of $CD4^+$ T cells and affect Th2 cell differentiation and Th2-type cytokine generation by targeting DNA methyltransferase 1 (DNMT1) in SLE, such as miR21, miR25, miR186, and miR146a [6]. Therefore, the epigenetic modification mediated by miRNAs also plays an indispensable role in Th2-associated immunity. Previous studies have found that ferroptosis drives DNA hydroxymethylation and demethylation, which thus promotes $CD4^+$ T cell differentiation and activation in lupus [7,8]. The deficiency of 3-hydroxybutyrate dehydrogenase 2 (BDH2) is associated with the dysregulation of iron homeostasis in $CD4^+$ T cells [8]. Yang et al. have found that inhibition of BDH2 expression but promotion of CD40L ligand demethylation in SLE mice not only increased the level of oxidative stress, but significantly reduced the Th1/Th2 ratio [9]. The suppression of CD40L expression through epigenetic modification of CD40L promoter by E4BP4 leads to CD40L signal pathway inactivation, which thus negatively regulates type 2 immune response in SLE [10,11]. CCAAT/enhancer-binding protein β (CEBPB) is a newly discovered transcription factor, which regulates NLRP3 inflammasome and participates in the pathogenesis of SLE [12]. CEBPB directly targets the promoter of Pim kinase (Pim-1), which promotes its expression and lupus nephritis progression [12]. In addition, Th2-related immunity can influence basophils- and mast cells-mediated immune and inflammatory response via IgE, IgG4 and other bioactive factors. A recent study has shown the cortical role of IgE in SLE [2]. IL-33 and self-IgE can activate dendritic cells and basophils in SLE. These cells migrated to the secondary lymphoid organs and promoted the Th2 and Tfh2 cell differentiation. Taken together, the imbalance of Th1/Th2 promotes the progression of SLE, and targeting key molecules, such as BDH2, E4BP4 and PPAR-γ, in the signaling network will provide new insight into exploring biological strategies for the targeted therapy of SLE.

Wang H et al. [1] have shown that mesenchymal stem cells (MSCs) exert anti-inflammatory and immunomodulatory effects by promoting the polarization of Th2 and Treg cells [2]. Recent studies have found that adipose-derived mesenchymal stem cells (ASCS) can directly alter Th cell differentiation and the secretion of related cytokine, which transform Th cells from Th1 cells to Th2 cells, and induce Treg cell polarization indirectly [13]. Xie et al. have proposed that MSCs alleviated SLE by inhibiting $CD19^+$ B cells, but not conferred significant effect on Th2 cells [14]. The above findings would be complementary to the theory that MSC regulates T cell response in SLE.

With regard to Th2-related cytokines, the authors have summarized the latest insights of IL-4, IL-5, IL-6, IL-10, IL-13, transforming growth factor β1 (TGF-β1), IL-9, IL-25, and the molecular targets currently evaluated in clinical trials (**Table 1**). Targeting cytokines, cytokine receptors and the key signal transduction pathways, is promising for the treatment of SLE, such as IL-4-STAT6-GATA3-αvβ3 pathway [1,15-16], IL-4-CNS2-Notch-RBP-J pathway [17], IL-5-JAK-STAT [1,16], IL-5-Ras/Raf-ERK pathway [1,15-16], IL-6-STAT3 [1,18] and IL-6R-JAK-STAT pathway [19], IL-9-IRF4 pathway and IL-2-JAK-STAT5 signal pathway [1], IL-10-E2F2-miR-175p pathway [1], IL-10-CNS9-NFAT1-IRF4 pathway [17], IL-13-rs20541 CT/TT gene polymorphism [17], TLR9-TGF-1-PDGFB pathway [1], IL-25-JAK-STAT and IL-25-MAPK pathway [1], and IL-33-ST2 axis [20]. Monoclonal antibody Dupilumab has been found to specifically inhibit the signal transduction of IL-4 and IL-13 in SLE [21]. Recent studies have found that targeting IL-6-related transcription factors (CRIF1) [22] was associated with lupus development and progression. Nevertheless, it has also been suggested that IL-6-targeted therapy does not provide therapeutic benefits for the treatment of SLE [23]. Accordingly, the application of bioreagents by targeting Th2-related cytokines should fully consider the clinical practice and the individualized needs of SLE patients.

To be summarized, Wang H et al. [1] have summarized the explorations of the underlying mechanisms of Th2-related immunity in SLE, which provides the latest insights for the pathogenesis and biotargets of this disease. We have also made an updated review of Th2-associated immunity in SLE and commented on the paper by Wang H et al. The above findings will provide an updated insight into exploring new strategies for the diagnosis and biological treatment of SLE.

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Conflicts of Interest

All authors declare no conflict of interest.

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