Clinical, Cosmetic and Investigational Dermatology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Two-Sample Bidirectional Mendelian Randomization Analysis of the Causal Relationship Between Immune Cell Phenotypes and Systemic Lupus Erythematosus

Weilu Niu, Jianwei Li, Huangchao Jia, Liyun Wang, Mengyue Xu, Xuewei Liu

Department of Dermatology, The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou, Henan, People's Republic of China

Correspondence: Xuewei Liu, Email liuxuewei2004@aliyun.com

Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disease. Numerous studies suggest that immune cells play a critical role in the onset and progression of SLE; however, the causal mechanisms underlying these associations remain inadequately defined. This study aimed to systematically evaluate, at the genetic level, the potential causal relationships between 731 immune cell phenotypes and SLE using Mendelian randomization (MR), in order to identify potential pathogenic or protective immune biomarkers.

Methods: We utilized summary statistics from genome-wide association studies (GWAS) involving 3757 individuals of European Sardinian ancestry for 731 immune cell phenotypes and a GWAS for SLE comprising 647 cases and 482,264 controls of European ancestry. Single nucleotide polymorphisms (SNPs) significantly associated with immune phenotypes were selected as instrumental variables. The inverse variance weighted (IVW) method was employed as the primary MR analysis, complemented by the weighted median method, MR-Egger regression, simple mode method, and weighted mode method for validation. Sensitivity analyses included Cochran's Q test, MR-Egger intercept test, MR-PRESSO global test, and leave-one-out analysis to assess heterogeneity, horizontal pleiotropy, and robustness. In addition, reverse MR analysis was conducted to explore the potential causal effects of SLE on immune cell phenotypes.

Results: A total of 24 immune cell phenotypes were identified to have significant causal associations with SLE, of which six showed positive correlations and eighteen showed negative correlations. These associations primarily involved key immune molecules including HLA-DR, CD25, CD45/CD45RA, CD8, BAFF-R, CD24, CD14, CX3CR1, CD28, CD11b, CD4, CD3, CD27, and CD16. Reverse MR analysis revealed that only IgD^+ $CD24^-$ %B cells exhibited a bidirectional causal relationship with SLE.

Conclusion: The findings suggest that immune cell phenotypes may contribute to SLE pathogenesis through mechanisms including immune tolerance regulation, self-antigen recognition, and inflammation amplification. Several phenotypes significantly associated with SLE, such as HLA-DR, CD3, CD24, CD25, CX3CR1, CD8, remain insufficiently investigated at the mechanistic level and may serve as promising targets for future basic and clinical research, with potential therapeutic implications and translational value.

Keywords: immune phenotypes, systemic lupus erythematosus, mendelian randomization, genome-wide association study

Introduction

SLE and Immune Dysregulation

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disease characterized by multisystem involvement, which can lead to damage of multiple organs such as the skin, joints, kidneys, and central nervous system.[1] The overall global incidence of SLE ranges between 1.5 and 11 per 100,000 person- years, and the global prevalence ranges from 13 to 7,713.5 per 100,000 individuals.[2] Both prevalence and incidence have shown an increasing trend in recent years,[3] with females accounting for a significantly higher proportion than males, approximately 80%. Without

https://doi.org/10.2147/CCID.S566075
Received: 20 September 2025
Accepted: 17 January 2026
Published: 29 January 2026

timely diagnosis and treatment, SLE frequently results in irreversible organ damage and, in severe cases, may be life-threatening. Therefore, the exploration of early biomarkers and key pathogenic mechanisms is critical for reducing disease risk and guiding precision therapy.

The pathogenesis of SLE has long been a major focus of investigation. Studies have demonstrated that immune cells play a critical role in the onset and progression of SLE.[4] The immune system aberrations associated with SLE include pathogenic autoantibody production and immune complex deposition, and immune system infiltration and inflammation within damaged organs[5]。 However, most existing studies have focused primarily on observational associations, lacking a systematic analysis of the causal relationship between immune cell phenotypes and SLE, which limits the identification of key targets and their translational applications.

Mendelian Randomization in Autoimmunity

Mendelian randomization (MR) is a causal inference method that exploits genetic variation, using single nucleotide polymorphisms (SNPs) significantly associated with specific exposures as instrumental variables. This method enables the assessment of causal relationships between exposures and outcomes within a framework analogous to randomized controlled trials. Compared with traditional observational studies, the MR approach can better mitigate confounding and reverse causation, thereby enhancing the validity of causal inference.[6] Moreover, bidirectional MR enables causal assessment in both directions—exposure to outcome and outcome to exposure—yielding a more comprehensive understanding of complex causal relationships.

In this study, we conducted a systematic two-sample bidirectional MR analysis to investigate the causal relationships between 731 immune cell phenotypes and SLE, based on publicly available genome-wide association study (GWAS) datasets. The objective was to identify immune cell phenotypes with significant causal associations with SLE, thereby providing theoretical support and a research foundation for elucidating the pathogenic mechanisms of SLE and identifying potential immunological intervention targets. These findings are expected to offer valuable references for subsequent basic research and the development of individualized intervention strategies.

Materials and Methods

Study Design

This study employed a two-sample bidirectional Mendelian randomization (MR) approach, using immune cell phenotypes as exposures and SLE as the outcome, and vice versa. Single nucleotide polymorphisms (SNPs) significantly associated with the exposures were selected as instrumental variables to assess the causal relationships. To ensure the validity of the MR analysis, the chosen SNPs were required to satisfy the following three core assumptions,[7] as illustrated in Figure 1: (1) Relevance: the SNPs must be significantly associated with the exposure variables (ie, immune cell phenotypes); (2) Independence: the SNPs must be independent of confounding factors; (3) Exclusion restriction: the SNPs influence the outcome only through the exposure, with no alternative pathways. The primary analysis was conducted using the inverse variance weighted (IVW) method, supplemented by multiple other methods to comprehensively investigate the causal associations between immune cell phenotypes and SLE, along with sensitivity analyses to enhance the robustness and reliability of the results. The flowchart of this study is depicted in Figure 2.

Data Sources

The GWAS data for immune cell phenotypes were obtained from the IEU OpenGWAS Project database (https://gwas.mrcieu.ac.uk). These data are derived from analyses of 22 million SNPs in 3757 individuals of European Sardinian ancestry. The dataset assesses 731 immune cell phenotypes, representing quantitative traits measured by flow cytometry, including absolute cell counts, immune cell subset frequencies, and surface marker expression levels.[8] The GWAS IDs range from ebi-a-GCST90001391 to ebi-a-GCST90002121, covering 731 phenotypes, including B cells (BC, n = 190), classic dendritic cells (cDC, n = 64), T cell maturation stages (n = 79), monocytes (n = 43), myeloid cells (n = 64), TBNK lymphocytes (T/B/NK cells, n = 124), and regulatory T cells (Tregs, n = 167). Summary statistics for SLE were obtained

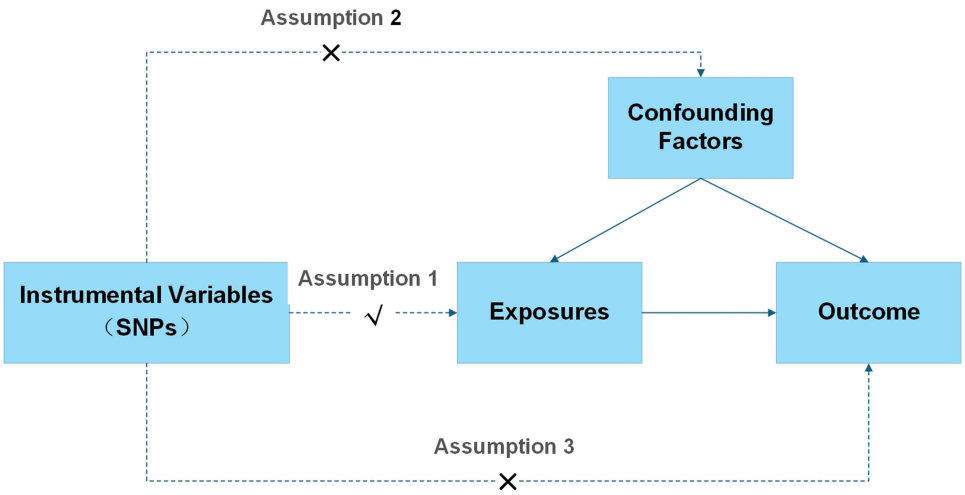

Figure 1 The instrumental variable assumptions in Mendelian randomization analysis. Dashed arrows illustrate the three core assumptions. The tick symbol (✓) signifies that the presence of this association satisfies the assumption, whereas the cross symbol (×) indicates that the presence of this association violates the assumption.

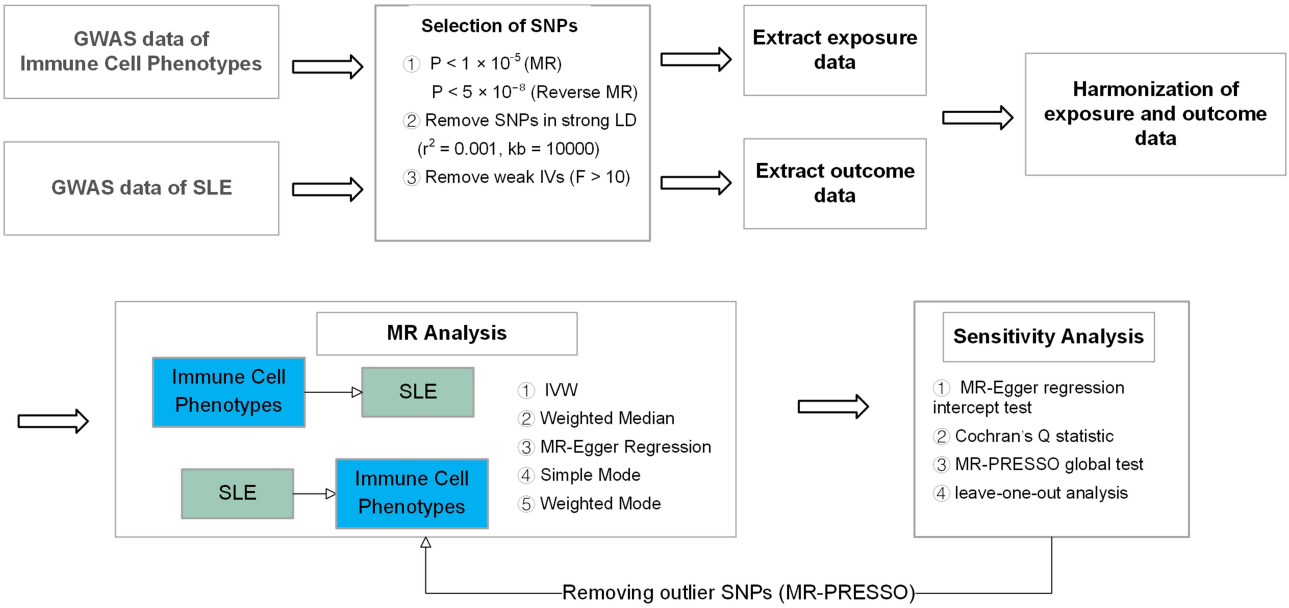

Figure 2 Flow chart of the study.

from the study by Sakaue et al, published in 2021,[9] and are publicly available from the IEU OpenGWAS Project database (https://gwas.mrcieu.ac.uk) under GWAS ID ebi-a-GCST90018917.

This dataset includes 24,198,877 SNPs, comprising 647 SLE cases and 482,264 controls of European ancestry. All data used in this study were sourced from publicly available repositories with prior ethical approval, and therefore no additional ethical approval was required.

Selection of Instrumental Variables

Different selection criteria were applied for instrumental variables depending on the exposure. For immune cell phenotypes, due to the lower GWAS sample size and the need to retain sufficient SNPs for power, the significance threshold for SNP selection was set at a relaxed threshold of $P < 1 \times 10^{-5}$. For the reverse MR analysis with SLE as the exposure, the conventional genome-wide significance threshold of $P < 5 \times 10^{-8}$ was adopted. To ensure the independence of instrumental variables, SNPs in strong linkage disequilibrium (LD) were excluded using an r^2 threshold of 0.001 and

https://doi.org/10.2147/CCID.S566075

the physical distance between any two SNPs was required to exceed 10,000 kb. This criterion effectively minimizes redundancy among SNPs. Furthermore, to minimize bias from weak instruments, the F-statistic was calculated for each SNP ($F = R^2 \times (N - 2) / (1 - R^2)$). Here, N represents the sample size and R^2 represents the proportion of variance in the exposure explained by the SNP, calculated as $R^2 = 2 \times EAF \times (1 - EAF) \times \beta^2$, where EAF is the effect allele frequency and β is the estimated effect size. An F value greater than 10 was considered indicative of a valid instrumental variable,[10] providing sufficient explanatory power and thereby ensuring the stability and reliability of the MR estimates.

Mendelian Randomization Analysis

To systematically evaluate the potential causal relationships between immune cells and SLE, multiple established Mendelian randomization (MR) methods were applied. These included the inverse variance weighted (IVW) approach,[11] weighted median (WM),[12] MR-Egger regression,[13] simple mode,[14] and weighted mode.[14] Among these approaches, the IVW method provides the highest statistical power for estimating causal effects under the assumption that all selected SNPs are valid instrumental variables and no horizontal pleiotropy exists.[15] Accordingly, IVW was employed as the primary analytical method in this study, while the other methods were used as complementary analyses.

Sensitivity Analysis

To enhance the robustness of causal inference and to control for potential bias from by horizontal pleiotropy, several sensitivity analyses were performed. First, the MR-Egger regression intercept test[13] was applied to evaluate horizontal pleiotropy; a significant deviation of the intercept from zero ($P < 0.05$) indicated the presence of systematic horizontal pleiotropy. Second, Cochran's Q statistic[16] was applied to evaluate heterogeneity among the selected SNP instrumental variables, with $P < 0.05$ suggesting potential violations of model assumptions or the presence of invalid instruments. In addition, the MR-PRESSO global test[17] was performed to detect instrumental variables with abnormal residuals. Outlier SNPs were excluded and causal estimates were re-evaluated to minimize potential bias. Finally, a leave-one-out analysis[18] was performed, sequentially excluding each SNP to evaluate its influence on the overall causal estimate. This approach effectively determined whether the results were driven by any single variant, thereby confirming the stability of the findings.

Statistical Analysis

To enhance the rigor of the analysis and the credibility of the findings, we predefined the following criteria to evaluate the significance of causal associations: ① The IVW method was used as the primary reference. Given the exploratory nature of this study and the high correlation among the 731 immune cell phenotypes, a strict Bonferroni correction was not applied to avoid overlooking potential biological signals. Therefore, a P value < 0.05 was considered indicative of a potentially significant causal relationship between the exposure and the outcome; ② The causal effect estimates obtained from multiple MR approaches (including IVW, weighted median, MR-Egger, simple mode, and weighted mode) were required to be consistent in direction, with odds ratios (ORs) pointing toward the same trend. Specifically, an odds ratio (OR) > 1 indicated a positive causal effect (risk factor), implying that the exposure is associated with an increased risk of the outcome, whereas an $OR < 1$ indicated a negative causal effect (protective factor); ③ The Cochran's Q test for heterogeneity yielded a non-significant result ($P > 0.05$), indicating good consistency of effect estimates across instrumental variables; ④ The intercept of MR-Egger regression was non-significant ($P > 0.05$), suggesting the absence of substantial horizontal pleiotropy. Only when an immune cell phenotype satisfied all four criteria was it considered to have a significant and robust direct causal effect on SLE.

All statistical analyses were performed in R software (version 4.3.2), primarily using the TwoSampleMR package (version 0.6.14) for data processing, MR model construction, and sensitivity analyses. Forest plots were generated to visualize the contribution and direction of each SNP instrumental variable to the estimated causal effect.

Results

Results of Instrumental Variable Selection

To identify valid instrumental variables for the bidirectional MR analysis, we conducted an initial screening, applied linkage disequilibrium (LD) clumping, and excluded weak instruments based on the F statistic ($F > 10$). For the

forward analysis (immune cell phenotypes on SLE), a total of 18,195 SNPs that were significantly associated with 731 immune cell sub-phenotypes were retained as valid instrumental variables. The number of instrumental variables varied across phenotypes, with an average of 25 SNPs per phenotype (range: 3–742). In contrast, for the reverse analysis (SLE on immune cell phenotypes), only 5 SNPs meeting the stringent instrumental variable criteria were identified. This limited number reflects the application of the strict genome-wide significance threshold ($P < 5 \times 10^{-8}$) to ensure instrument validity, and we acknowledge that it may constrain the statistical power of the reverse MR analysis.

Causal Relationship from Immune Cell Phenotypes to SLE

In this study, causal associations were identified primarily using the IVW method ($P < 0.05$), supported by concordance in effect direction across complementary MR methods. A positive association (OR > 1) indicates that the immune phenotype is a potential risk factor for SLE (higher immune trait → higher SLE risk), whereas a negative association (OR < 1) suggests a potential protective role (higher immune trait → lower SLE risk).

Using these criteria, we identified 24 immune cell phenotypes with significant causal relationships to SLE (Table 1). Among the protective factors, the most significant association was observed for HLA-DR^+ T cell %T cell, which showed a strong negative correlation with SLE (IVW OR = 0.859, 95% CI: 0.790–0.934, P < 0.001). The protective effect was

Table 1 Results of Mendelian Randomization Analyses from 24 Immune Cell Phenotypes Associated to SLE Using Five Methods

Panel	Trait	nsnp	Method	OR (95% CI)	*P*	β
B cell	BAFF-R on IgD^+ $CD38^-$ unsw mem	21	1	1.022 (0.905 to 1.154)	0.727	0.022
			2	1.068 (0.958 to 1.190)	0.234	0.066
			3	1.089 (1.004 to 1.182)	0.039	0.086
			4	1.191 (0.979 to 1.448)	0.096	0.175
			5	1.065 (0.965 to 1.176)	0.227	0.063
	CD24 on transitional	20	1	0.923 (0.705 to 1.207)	0.565	−0.08
			2	0.875 (0.699 to 1.096)	0.246	−0.133
			3	0.852 (0.728 to 0.997)	0.046	−0.16
			4	0.871 (0.629 to 1.207)	0.417	−0.138
			5	0.898 (0.704 to 1.144)	0.394	−0.108
	CD27 on T cell	21	1	0.942 (0.838 to 1.059)	0.327	−0.06
			2	0.927 (0.817 to 1.053)	0.244	−0.075
			3	0.904 (0.828 to 0.987)	0.025	−0.101
			4	0.968 (0.758 to 1.236)	0.796	−0.033
			5	0.940 (0.833 to 1.060)	0.324	−0.062
	IgD^+ $CD24^-$ %B cell	20	1	1.154 (0.981 to 1.357)	0.101	0.143
			2	1.166 (0.970 to 1.402)	0.102	0.154
			3	1.134 (1.009 to 1.274)	0.035	0.125
			4	1.020 (0.738 to 1.409)	0.905	0.02
			5	1.170 (1.004 to 1.365)	0.059	0.157
cDC	HLA-DR on DC	21	1	0.806 (0.711 to 0.914)	0.003	−0.216
			2	0.836 (0.755 to 0.924)	<0.001	−0.18
			3	0.890 (0.821 to 0.965)	0.005	−0.116
			4	0.827 (0.637 to 1.073)	0.168	−0.19
			5	0.835 (0.752 to 0.926)	0.003	−0.181
	HLA-DR on plasmacytoid DC	23	1	0.932 (0.838 to 1.038)	0.215	−0.07
			2	0.857 (0.784 to 0.938)	0.001	−0.154
			3	0.912 (0.849 to 0.979)	0.011	−0.092
			4	0.828 (0.679 to 1.009)	0.075	−0.189
			5	0.857 (0.783 to 0.938)	0.003	−0.154

(*Continued*)

https://doi.org/10.2147/CCID.S566075

Table 1 (Continued).

Panel	Trait	nsnp	Method	OR (95% CI)	*P*	β
Maturation stages of T cell	CM DN ($CD4^{-}CD8^{-}$) %T cell	16	1	0.877 (0.788 to 0.977)	0.032	−0.131
			2	0.876 (0.774 to 0.991)	0.035	−0.133
			3	0.893 (0.816 to 0.977)	0.014	−0.113
			4	0.982 (0.770 to 1.252)	0.885	−0.018
			5	0.875 (0.786 to 0.973)	0.026	−0.134
Monocyte	CX3CR1 on $CD14^{+}$ $CD16^{+}$ monocyte	34	1	0.890 (0.804 to 0.985)	0.031	−0.116
			2	0.899 (0.796 to 1.015)	0.086	−0.106
			3	0.927 (0.862 to 0.997)	0.04	−0.076
			4	0.921 (0.732 to 1.160)	0.49	−0.082
			5	0.921 (0.830 to 1.022)	0.132	−0.082
	HLA-DR on $CD14^{-}$ $CD16^{-}$	27	1	0.928 (0.820 to 1.049)	0.241	−0.075
			2	0.952 (0.843 to 1.076)	0.432	−0.049
			3	0.915 (0.843 to 0.995)	0.037	−0.088
			4	0.949 (0.772 to 1.167)	0.623	−0.053
			5	0.926 (0.814 to 1.053)	0.252	−0.077
Myeloid cell	CD11b on $CD33^{br}$ HLA-DR^{+} $CD14^{dim}$	20	1	1.064 (0.835 to 1.357)	0.621	0.062
			2	1.199 (1.029 to 1.396)	0.02	0.181
			3	1.136 (1.018 to 1.268)	0.023	0.128
			4	1.179 (0.909 to 1.528)	0.229	0.164
			5	1.272 (1.071 to 1.512)	0.013	0.241
	CD11b on $CD66b^{++}$ myeloid cell	18	1	1.079 (0.871 to 1.337)	0.496	0.076
			2	1.252 (1.051 to 1.493)	0.012	0.225
			3	1.148 (1.018 to 1.295)	0.024	0.138
			4	1.238 (0.937 to 1.637)	0.151	0.214
			5	1.249 (0.970 to 1.609)	0.102	0.223
TBNK	$CD3^{-}$ lymphocyte %lymphocyte	6	1	0.881 (0.102 to 7.568)	0.913	−0.127
			2	0.689 (0.409 to 1.162)	0.163	−0.372
			3	0.633 (0.409 to 0.980)	0.04	−0.457
			4	0.701 (0.350 to 1.403)	0.361	−0.356
			5	0.746 (0.385 to 1.446)	0.425	−0.293
	CD45 on $CD4^{+}$	13	1	1.224 (0.629 to 2.382)	0.563	0.203
			2	1.078 (0.805 to 1.444)	0.614	0.075
			3	1.315 (1.023 to 1.691)	0.033	0.274
			4	1.022 (0.669 to 1.560)	0.921	0.022
			5	1.016 (0.687 to 1.503)	0.938	0.016
	HLA-DR^{+} $CD4^{+}$ %lymphocyte	22	1	0.842 (0.610 to 1.163)	0.31	−0.172
			2	0.747 (0.581 to 0.959)	0.022	−0.292
			3	0.777 (0.657 to 0.919)	0.003	−0.253
			4	0.696 (0.480 to 1.011)	0.071	−0.362
			5	0.765 (0.604 to 0.969)	0.038	−0.268
	HLA-DR^{+} $CD4^{+}$ %T cell	27	1	0.871 (0.654 to 1.160)	0.355	−0.138
			2	0.793 (0.634 to 0.992)	0.043	−0.232
			3	0.785 (0.673 to 0.917)	0.002	−0.242
			4	0.745 (0.514 to 1.080)	0.132	−0.295
			5	0.835 (0.654 to 1.066)	0.159	−0.181
	HLA-DR^{+} $CD8^{br}$ %lymphocyte	32	1	0.974 (0.792 to 1.198)	0.803	−0.027
			2	0.854 (0.723 to 1.009)	0.064	−0.158
			3	0.863 (0.761 to 0.978)	0.021	−0.147
			4	0.870 (0.639 to 1.184)	0.381	−0.14
			5	0.880 (0.714 to 1.085)	0.241	−0.128

(*Continued*)

Table 1 (Continued).

Panel	Trait	nsnp	Method	OR (95% CI)	*P*	β
	HLA-DR^{+} CD8^{br} %T cell	33	1	0.954 (0.843 to 1.080)	0.465	−0.047
			2	0.872 (0.775 to 0.982)	0.023	−0.137
			3	0.908 (0.829 to 0.994)	0.037	−0.097
			4	0.889 (0.728 to 1.087)	0.259	−0.118
			5	0.895 (0.803 to 0.998)	0.054	−0.111
	HLA-DR^{+} T cell%lymphocyte	29	1	0.945 (0.823 to 1.084)	0.424	−0.057
			2	0.883 (0.767 to 1.018)	0.086	−0.124
			3	0.880 (0.804 to 0.964)	0.006	−0.127
			4	0.839 (0.690 to 1.019)	0.087	−0.176
			5	0.889 (0.781 to 1.013)	0.088	−0.117
	HLA-DR^{+} T cell%T cell	33	1	0.901 (0.806 to 1.007)	0.077	−0.104
			2	0.880 (0.782 to 0.990)	0.033	−0.128
			3	0.859 (0.790 to 0.934)	<0.001	−0.152
			4	0.887 (0.750 to 1.050)	0.175	−0.12
			5	0.876 (0.792 to 0.969)	0.015	−0.132
Treg	CD25 on CD45RA^{-} CD4 not Treg	26	1	0.885 (0.794 to 0.986)	0.037	−0.123
			2	0.866 (0.764 to 0.981)	0.023	−0.144
			3	0.897 (0.824 to 0.977)	0.013	−0.108
			4	0.897 (0.731 to 1.099)	0.304	−0.109
			5	0.879 (0.782 to 0.988)	0.04	−0.129
	CD25^{hi} CD45RA^{-} CD4 not Treg %T cell	31	1	1.106 (0.996 to 1.227)	0.07	0.1
			2	1.066 (0.951 to 1.195)	0.27	0.064
			3	1.109 (1.025 to 1.201)	0.01	0.104
			4	1.066 (0.908 to 1.252)	0.442	0.064
			5	1.071 (0.968 to 1.185)	0.196	0.068
	CD28^{-} CD8^{br} %T cell	16	1	0.960 (0.621 to 1.485)	0.857	−0.041
			2	0.858 (0.661 to 1.112)	0.248	−0.153
			3	0.817 (0.668 to 1.000)	0.05	−0.202
			4	0.703 (0.444 to 1.113)	0.154	−0.352
			5	0.815 (0.597 to 1.113)	0.217	−0.205
	CD28 on resting Treg	6	1	0.577 (0.396 to 0.839)	0.045	−0.551
			2	0.749 (0.585 to 0.960)	0.023	−0.289
			3	0.781 (0.632 to 0.965)	0.022	−0.247
			4	0.880 (0.596 to 1.299)	0.548	−0.128
			5	0.729 (0.563 to 0.946)	0.063	−0.315
	CD4 on activated Treg	26	1	0.960 (0.862 to 1.068)	0.459	−0.041
			2	0.922 (0.824 to 1.031)	0.156	−0.081
			3	0.923 (0.851 to 1.000)	0.049	−0.08
			4	0.850 (0.711 to 1.018)	0.089	−0.162
			5	0.920 (0.824 to 1.027)	0.149	−0.083

Notes: In the method column, 1 corresponds to the MR-Egger method, 2 to the Weighted Median method, 3 to the IVW method, 4 to the Simple Mode method, and 5 to the Weighted Mode method. nsnp indicates the number of SNPs; and CI denotes the confidence interval.

consistently observed across other TBNK phenotypes, such as HLA-DR^{+} CD4^{+} %lymphocyte (IVW OR = 0.777, 95% CI: 0.657–0.919, P=0.003) and HLA-DR^{+} CD4^{+} %T cell (IVW OR = 0.785, 95% CI: 0.673 to 0.917, P = 0.002). Furthermore, HLA-DR on DC (IVW OR = 0.890, 95% CI: 0.821–0.965, P = 0.005) also demonstrated a robust protective role. Conversely, several phenotypes were identified as potential risk factors. Notable findings included specific myeloid cell phenotypes, such as CD11b on CD66b^{++} myeloid cell (IVW OR = 1.148, 95% CI: 1.018–1.295, P = 0.024) and CD11b on CD33br HLA-DR+ CD14dim myeloid cells (IVW OR = 1.136, 95% CI: 1.018–1.268, P = 0.023). Additionally, the Treg phenotype CD25^{hi} CD45RA^{-} CD4 not Treg %T cell (IVW OR = 1.109, 95% CI: 1.025–1.201, P =

0.010) was significantly associated with increased SLE risk. A complete forest plot visualizing these causal effect estimates derived from the IVW method is presented in Figure 3.

To ensure the robustness of these findings, we performed comprehensive sensitivity analysis (Table 2). The Cochran's Q test (P > 0.05) indicated no significant heterogeneity among the instrumental variables for the identified phenotypes. Furthermore, the MR-Egger intercept test (P > 0.05) and the MR-PRESSO global test (P > 0.05) revealed no evidence of horizontal pleiotropy. Leave-one-out analyses further confirmed that the results were not driven by any single SNP, underscoring the reliability of the study's causal inferences.

Causal Relationship from SLE to Immune Cell Phenotypes

To further investigate potential feedback mechanisms, reverse MR analysis was conducted using SLE as the exposure and the 24 significant immune cell phenotypes from the forward MR analysis as outcomes. It is important to acknowledge that this reverse analysis relied on a limited number of instrumental variables (5 SNPs), which may constrain the statistical power of the analysis.

Remarkably, despite this limitation, the analysis highlighted a unique bidirectional causal relationship involving IgD^+ $CD24^-$ %B cells (Table 3). While the forward analysis identified this phenotype as a risk factor for SLE (IVW OR = 1.134, 95% CI: 1.009–1.274, P = 0.035), the reverse analysis demonstrated that genetically predicted SLE promotes an increase in the frequency of IgD^+ $CD24^-$ %B cells, as indicated by an IVW OR of 1.112 (95% CI: 1.031–1.198, P = 0.006). Integrating these results suggests a complex cyclical mechanism: higher levels of IgD^+ $CD24^-$ %B cells increase the risk of SLE, and SLE in turn promotes the expansion of this specific B cell subset.

Additionally, sensitivity analyses for this reverse finding (Table 4) confirmed the robustness of the result. The P values for Cochran's Q test, the MR-Egger intercept test, and the MR-PRESSO global test were all greater than 0.05, indicating no significant heterogeneity or horizontal pleiotropy. Collectively, these findings imply that IgD^+ $CD24^-$

panel	trait	nsnp	pval	OR(95% CI)
B cell	BAFF−R on IgD+ CD38− unsw mem	21	**0.039**	1.089 (1.004 to 1.182)
B cell	CD24 on transitional	20	**0.046**	0.852 (0.728 to 0.997)
B cell	CD27 on T cell	21	**0.025**	0.904 (0.828 to 0.987)
B cell	IgD+ CD24− %B cell	20	**0.035**	1.134 (1.009 to 1.274)
cDC	HLA DR on DC	21	**0.005**	0.890 (0.821 to 0.965)
cDC	HLA DR on plasmacytoid DC	23	**0.011**	0.912 (0.849 to 0.979)
Maturation stages of T cell	CM DN (CD4−CD8−) %T cell	16	**0.014**	0.893 (0.816 to 0.977)
Monocyte	CX3CR1 on CD14+ CD16+ monocyte	34	**0.040**	0.927 (0.862 to 0.997)
Monocyte	HLA DR on CD14− CD16−	27	**0.037**	0.915 (0.843 to 0.995)
Myeloid cell	CD11b on CD33br HLA DR+ CD14dim	20	**0.023**	1.136 (1.018 to 1.268)
Myeloid cell	CD11b on CD66b++ myeloid cell	18	**0.024**	1.148 (1.018 to 1.295)
TBNK	CD3− lymphocyte %lymphocyte	6	**0.040**	0.633 (0.409 to 0.980)
TBNK	CD45 on CD4+	13	**0.033**	1.315 (1.023 to 1.691)
TBNK	HLA DR+ CD4+ %lymphocyte	22	**0.003**	0.777 (0.657 to 0.919)
TBNK	HLA DR+ CD4+ %T cell	27	**0.002**	0.785 (0.673 to 0.917)
TBNK	HLA DR+ CD8br %lymphocyte	32	**0.021**	0.863 (0.761 to 0.978)
TBNK	HLA DR+ CD8br %T cell	33	**0.037**	0.908 (0.829 to 0.994)
TBNK	HLA DR+ T cell%lymphocyte	29	**0.006**	0.880 (0.804 to 0.964)
TBNK	HLA DR+ T cell%T cell	33	**<0.001**	0.859 (0.790 to 0.934)
Treg	CD25 on CD45RA− CD4 not Treg	26	**0.013**	0.897 (0.824 to 0.977)
Treg	CD25hi CD45RA− CD4 not Treg %T cell	31	**0.010**	1.109 (1.025 to 1.201)
Treg	CD28− CD8br %T cell	16	**0.049**	0.817 (0.668 to 1.000)
Treg	CD28 on resting Treg	6	**0.022**	0.781 (0.632 to 0.965)
Treg	CD4 on activated Treg	26	**0.049**	0.923 (0.851 to 1.000)

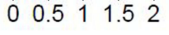

Figure 3 Forest plot depicting the causal effect estimates derived from the IVW method. Bold values in the "pval" column indicate statistically significant results (P<0.05) derived from Table 1.

Table 2 Results of Cochran's Q Test, MR-Egger Intercept Test, and MR-PRESSO Analyses for the Causal Relationships from Immune Cell Phenotypes to SLE

Panel	Trait	Q-*P*	Egger-Intercept-*P*	Global-P
B cell	BAFF-R on IgD^+ $CD38^-$ unsw mem	0.936	0.181	0.932
B cell	CD24 on transitional	0.671	0.482	0.72
B cell	CD27 on T cell	0.408	0.309	0.47
B cell	IgD^+ $CD24^-$ %B cell	0.787	0.761	0.783
cDC	HLA-DR on DC	0.340	0.064	0.317
cDC	HLA-DR on plasmacytoid DC	0.297	0.590	0.255
Maturation stages of T cell	CM DN ($CD4^-CD8^-$) %T cell	0.441	0.547	0.49
Monocyte	CX3CR1 on CD14+ CD16+ monocyte	0.337	0.273	0.294
Monocyte	HLA-DR on $CD14^-$ $CD16^-$	0.263	0.774	0.241
Myeloid cell	CD11b on $CD33^{br}$ HLA-DR^+ $CD14^{dim}$	0.287	0.560	0.185
Myeloid cell	CD11b on $CD66b^{++}$ myeloid cell	0.430	0.499	0.382
TBNK	CD3- lymphocyte %lymphocyte	0.136	0.773	0.176
TBNK	CD45 on $CD4^+$	0.135	0.823	0.207
TBNK	HLA-DR^+ $CD4^+$ %lymphocyte	0.593	0.571	0.642
TBNK	HLA-DR^+ $CD4^+$ %T cell	0.786	0.406	0.82
TBNK	HLA-DR^+ $CD8^{br}$ %lymphocyte	0.081	0.165	0.072
TBNK	HLA-DR^+ $CD8^{br}$ %T cell	0.096	0.261	0.13
TBNK	HLA-DR^+ T cell%lymphocyte	0.722	0.196	0.744
TBNK	HLA-DR^+ T cell%T cell	0.899	0.213	0.934
Treg	CD25 on $CD45RA^-$ CD4 not Treg	0.566	0.684	0.602
Treg	$CD25^{hi}$ $CD45RA^-$ CD4 not Treg %T cell	0.902	0.921	0.924
Treg	$CD28^-$ $CD8^{br}$ %T cell	0.103	0.427	0.124
Treg	CD28 on resting Treg	0.396	0.129	0.45
Treg	CD4 on activated Treg	0.569	0.289	0.609

Notes: Q-P represents the P value from Cochran's Q test; Egger-intercept-P represents the P value from the MR-Egger intercept test; Global-P represents the P value from the MR-PRESSO global test.

Table 3 Results of Mendelian Randomization Analyses from SLE to Immune Cell Phenotypes Using Five Methods

Panel	Trait	nsnp	Method	*OR* (95% *CI*)	*P*	β
B cell	IgD^+ $CD24^-$ %B cell	5	1	1.129 (0.859 to 1.485)	0.448	0.122
			2	1.098 (1.007 to 1.198)	0.035	0.094
			3	1.112 (1.031 to 1.198)	0.006	0.106
			4	1.089 (0.969 to 1.224)	0.224	0.085
			5	1.093 (0.984 to 1.215)	0.174	0.089

Notes: In the method column, 1 corresponds to the MR-Egger method, 2 to the Weighted Median method, 3 to the IVW method, 4 to the Simple Mode method, and 5 to the Weighted Mode method. nsnp indicates the number of SNPs; and CI denotes the confidence interval.

Table 4 Results of Cochran's Q Test, MR-Egger Intercept Test, and MR-PRESSO Analyses for the Causal Relationships from SLE to Immune Cells

Panel	Trait	Q-*P*	Egger-Intercept-*P*	Global-P
B cell	IgD^+ $CD24^-$ %B cell	0.918	0.913	0.92

Notes: Q-P represents the P value from Cochran's Q test; Egger-intercept-P represents the P value from the MR-Egger intercept test; Global-P represents the P value from the MR-PRESSO global test.

%B cells may contribute to the onset and progression of SLE, and that a complex bidirectional biological regulatory mechanism may exist between them, warranting further mechanistic investigation.

Discussion

The onset of systemic lupus erythematosus (SLE) is closely linked to immune system dysregulation, genetic susceptibility, and the loss of immune tolerance. These factors promote the production of pathogenic autoantibodies, leading to the formation and deposition of immune complexes in various tissues and organs, which subsequently trigger acute or chronic inflammatory responses and result in multi-organ damage, including skin, joints, kidneys, and the central nervous system.[1] Therefore, exploring the causal relationships between immune cells and SLE is critical for identifying novel immune-related diagnostic markers and developing targeted interventional therapies.

In this study, we performed a systematic bidirectional two-sample Mendelian randomization analysis using publicly available large-scale genetic data to assess the causal relationships between 731 immune cell phenotypes and SLE. Our results showed that, among the 731 immune cell phenotypes examined, 24 were significantly associated with SLE, with 6 phenotypes positively associated and 18 negatively associated. Furthermore, reverse MR analysis indicated that the B cell phenotype IgD^+ $CD24^-$ %B cells may have a bidirectional causal relationship with SLE.

B Cell Phenotypes

B cells are the primary mediators of immune dysregulation in SLE. Abnormal differentiation and development, dysregulated B cell receptor (BCR) signaling, and excessive activation represent key drivers of disease progression.[19] In this study, we identified four B cell–related phenotypes associated with SLE. Specifically, "BAFF-R on IgD^+ $CD38^-$ unsw mem" and "IgD^+ $CD24^-$ %B cell" were risk factors (positive association), while "CD24 on transitional" and "CD27 on T cell" were protective factors (negative association).

The "unsw mem" subset refers to unswitched memory B cells (NSM), characterized by CD27+ IgD+. Along with switched memory B cells (SM; $CD27^+$ IgD^-) and double-negative B cells (DN B; $CD27^-$ IgD^-), these constitute the three major memory B cell subsets. In healthy individuals, these subsets maintain dynamic equilibrium,[20] whereas in SLE patients, NSM levels often decline while SM and DN B cells are elevated.[21] Notably, memory B cells and T cells in SLE can be co-activated through Toll-like receptor (TLR) and interferon (IFN) signaling, establishing a positive feedback loop that bypasses immune tolerance, amplifies autoantibody production, and positions memory B cells as central regulators of SLE pathogenesis.[22]

We also highlighted key molecular markers involved in B cell regulation. The B-cell activating factor receptor (BAFF-R) is a key component of the BAFF system, which includes two ligands—BAFF and a proliferation-inducing ligand (APRIL)—and three receptors: BAFF-R, B-cell maturation antigen (BCMA), and transmembrane activator and CAML interactor (TACI).[23] These molecules, expressed on B cells and subsets of T cells, regulate B cell survival, autoreactive B cell selection, and plasma cell persistence. BAFF-R primarily governs B cell maturation, while TACI regulates B cell homeostasis and T cell–independent immune responses. The BAFF system is a key participant in autoimmune diseases, with elevated expression observed in SLE. Consequently, it represents an attractive therapeutic target; indeed, belimumab, a monoclonal antibody against BAFF, has been approved for SLE treatment.[24]

Additionally, high expression of Immunoglobulin D (IgD) and CD38 has been linked to SLE disease activity. Immunoglobulin D (IgD), produced during early B cell differentiation, exists as both membrane-bound (mIgD) and secreted (sIgD) isoforms. In SLE, total serum IgD levels are significantly elevated compared to healthy controls and are often accompanied by increased proinflammatory cytokines and reduced circulating basophils.[25] CD38, a type II transmembrane glycoprotein with extracellular enzymatic activity, is a key regulator of nicotinamide adenine dinucleotide (NAD+) metabolism. It is markedly upregulated in SLE and correlates positively with disease activity (SLEDAI). CD38 is most highly expressed in plasma cells and plasmablasts, but is also present in natural killer (NK) cells, plasmacytoid dendritic cells (pDCs), subsets of regulatory T cells, and naïve T cells.[26] Given its pathogenic relevance, CD38 is considered a promising therapeutic target for SLE treatment. CD24, also known as heat-stable antigen, is a glycosylphosphatidylinositol-anchored surface protein. The phenotype "CD24 on transitional" refers to CD24

expression on transitional B cells. Genetic studies have identified associations between CD24 allelic variants and SLE susceptibility,[27] although the mechanistic underpinnings remain incompletely understood.

Dendritic Cell, Monocyte, and Myeloid Phenotypes

Two dendritic cell phenotypes, "HLA-DR on DC" and "HLA-DR on plasmacytoid DC" (the latter classified under the cDC panel in the original GWAS), were both negatively associated with SLE. Notably, plasmacytoid dendritic cells (pDCs) are a distinct subset of dendritic cells; together with classical dendritic cells (cDCs), they play key roles as antigen-presenting cells (APCs). HLA-DR, a class II human leukocyte antigen (MHC class II) molecule, is mainly expressed on the surface of professional APCs such as dendritic cells, macrophages, and B lymphocytes, where it mediates recognition and presentation of exogenous antigen peptides. Previous studies have shown that different HLA-DR genotypes (eg, HLA-DR3, HLA-DR15, HLA-DR2, and HLA-DRB alleles) are associated with SLE in diverse populations,[28] highlighting the critical role of this molecule in infection response, immune activation, and the maintenance of immune homeostasis.

Two monocyte phenotypes, "CX3CR1 on $CD14^{+}$ $CD16^{+}$ monocytes" and "HLA-DR on $CD14^{-}$ $CD16^{-}$", were both negatively associated with SLE. CX3CR1 is the sole known receptor for fractalkine (FLK, also called CX3CL1) and is primarily expressed on monocytes, microglia, NK cells, and T cells. The binding of FLK to CX3CR1 mediates adhesion of these cells to epithelial cells, endothelial cells, and dendritic cells.[29] Previous studies have confirmed the role of CX3CR1 in regulating SLE-associated renal and cardiovascular inflammation.[30] Further mechanistic studies on the link between CX3CR1 and SLE may facilitate the identification of novel pathogenic pathways and therapeutic targets for the severe manifestations of the disease. Cells with the $CD14^{-}$ $CD16^{-}$ phenotype, known as negative low-density granulocytes (nLDGs), have been closely associated with cardiovascular complications and bone deterioration in SLE, suggesting their potential predictive value.[31] Additionally, the proportion of $CD14^{+}$ $CD16^{++}$ monocytes in the peripheral blood of patients with active SLE is significantly decreased, indicating impaired function in immune regulation and apoptotic cell clearance, which may contribute to SLE immunopathogenesis.[32]

Two myeloid cell phenotypes associated with SLE, namely "CD11b on $CD33^{+}$ HLA-DR^{+} $CD14^{dim}$" and "CD11b on $CD66b^{++}$ myeloid cells" were both positively correlated with disease occurrence. CD11b, also known as integrin αM, is broadly expressed on myeloid cells and plays key roles in cell adhesion, migration, and immune regulation. It is also a marker of age-associated B cells (ABCs) and is critical for modulating proinflammatory Toll-like receptor (TLR) signaling, with its gene encoded by ITGAM. Studies in SLE mouse models have shown that $CD11b^{+}$ ABCs are highly expressed in both spleen and peripheral blood, with their proportion positively correlating with lupus nephritis risk.[33,34] CD33, a member of the sialic acid-binding immunoglobulin-like lectins (Siglecs) family, is an inhibitory transmembrane receptor primarily expressed on myeloid cells. By recognizing host sialic acids, CD33 transmits inhibitory signals to restrain innate immune responses. In SLE patients, CD33 expression on peripheral blood monocytes is markedly reduced, suggesting impaired regulatory function and potential immune overactivation.[35,36] CD14, a pattern recognition receptor binding lipopolysaccharide, is expressed on monocytes and macrophages and participates in pathogen recognition and proinflammatory cytokine release.[37] Three CD14-associated monocyte subsets—classical ($CD14^{++}$ $CD16^{-}$), intermediate ($CD14^{++}$ $CD16^{+}$), and non-classical ($CD14^{+}$ $CD16^{++}$)—are associated with SLE progression. In active SLE, decreased classical monocytes and increased intermediate monocytes have been observed, suggesting both monocyte subsets could serve as immune cellular markers for SLE activity.[38] Finally, CD66b is a myeloid activation marker predominantly expressed on neutrophils. Plasma from SLE patients induces higher CD66b expression on neutrophils compared with healthy controls, reflecting enhanced myeloid activation in the disease.[39]

T Cell and Treg Phenotypes

The T cell phenotype "CM DN ($CD4^{-}CD8^{-}$) %T cell" within the maturation stages of T cells exhibits a negative association with SLE. "CM" refers to central memory T cells, a memory subset generated following antigen stimulation, characterized by rapid proliferation and cytokine secretion, representing a terminal stage of T cell differentiation. Studies have reported a significant reduction of central memory T cells in patients with lupus nephritis, suggesting a protective role in maintaining immune homeostasis.[40] "DN" denotes double-negative T cells. During thymic development, T cells

progress through three stages: double negative (DN: $CD4^{-}CD8^{-}$), double positive (DP: $CD4^{+}CD8^{+}$), and single positive (SP: $CD4^{+}$ or $CD8^{+}$), ultimately giving rise to mature T cells that populate the peripheral circulation. DN T cells account for approximately 1–3% of peripheral $CD3^{+}$ T cells and are a crucial component of the immune system. While DN T cells are generally expanded in SLE patients, potentially contributing to disease immunopathology,[41] the proportion of CM DN T cells ($CD4^{-}CD8^{-}$) within the central memory subset is reduced. This decrease suggests that CM DN T cells may help maintain immune homeostasis, and their reduction could reflect aberrant differentiation or functional impairment of memory T cell populations in SLE.

"TBNK" refers to T cells, B cells, and NK cells, which are key members of the lymphocyte subpopulation and play essential roles in immune regulation. Among them, the phenotype "CD45 on $CD4^{+}$" shows a positive association with the occurrence of SLE. $CD4^{+}$ is a defining marker of helper T cells, representing a major subset of T lymphocytes. CD45, also known as the leukocyte common antigen, is a transmembrane protein tyrosine phosphatase broadly expressed on all nucleated hematopoietic cells and their precursors, except mature erythrocytes and platelets.[42] CD45 molecules are expressed in multiple isoforms, including CD45RA, CD45RB, CD45RC, and CD45RO, and play a crucial role in regulating TCR signal strength and selection of the repertoire in the thymus and periphery.[43] Clinical studies have shown[44] that the ratio of $CD45RA^{+}FoxP3^{low}$ naive Treg cells (nTreg cells) and $CD45RA^{-}FoxP3^{low}$ (non-Treg) cells is significantly elevated in the peripheral blood of SLE patients. Furthermore, the nTreg subset was found to increase when cultured with SLE serum compared to healthy donor serum, suggesting that elevated inflammatory cytokines in SLE serum may drive nTreg proliferation and expansion.

In contrast, seven phenotypes are negatively associated with SLE, with "$CD3^{-}$ lymphocyte % lymphocyte" showing the strongest negative correlation. CD3 is a T cell–specific molecule that forms the TCR–CD3 signaling complex together with the TCR, mediating antigen recognition and downstream signaling. $CD3^{-}$ lymphocytes are primarily B cells and NK cells; thus, a reduction in this phenotype may reflect a relative increase in T cells within the lymphocyte pool or a decline in B or NK cell populations. This shift may indicate an altered lymphocyte composition in SLE, though its functional implications require further clarification in the context of other activation or inhibitory markers. The other six TBNK-related phenotypes negatively associated with SLE include "$HLA\text{-}DR^{+}$ $CD4^{+}$ % lymphocyte", "$HLA\text{-}DR^{+}$ $CD4^{+}$ % T cell", "$HLA\text{-}DR^{+}$ $CD8^{br}$ % lymphocyte", "$HLA\text{-}DR^{+}$ $CD8^{br}$ % T cell", "$HLA\text{-}DR^{+}$ T cell % lymphocyte", and "$HLA\text{-}DR^{+}$ T cell % T cell". Notably, HLA-DR expression appears most frequently among these phenotypes, underscoring its relevance to disease susceptibility. Previous studies have reported that in SLE patients with lupus nephritis, the expression of cytotoxic granules, CD38, and HLA-DR molecules on CD4+ and CD8+ T cells is significantly decreased.[45] This reduction reflects the emergence of exhausted T cell subsets following chronic and sustained immune activation, characterized by functional silencing, impaired cytotoxicity, and diminished antiviral capacity.[46] "$CD8^{br}$" denotes a subset of $CD8^{+}$ T cells with high surface expression of CD8. Under conditions of persistent antigen stimulation or chronic immune activation, certain $CD8^{+}$ T cells transcriptionally downregulate CD8A and CD8B expression, leading to reduced CD8 surface levels.[47] This mechanism may partly explain the significantly decreased proportion of $CD8^{br}$ cells in SLE patients. In addition, T cell exhaustion and immunosuppressive cues within the inflammatory microenvironment likely contribute to further phenotypic alterations and functional impairment of $CD8^{+}$ T cells.

Regulatory T cells (Tregs), a functional subset of T cells, play a central role in maintaining immune tolerance and preventing excessive immune activation. Based on surface markers, Tregs can be classified into resting Tregs (rTregs), activated Tregs (aTregs), and non-suppressive Tregs (nsTregs). They are typically characterized by the expression of $CD4^{+}$, $CD25^{hi}$, and the nuclear transcription factor FoxP3.

The phenotype "$CD25^{hi}$ $CD45RA^{-}$ CD4 not Treg % T cell" shows a positive association with the occurrence of SLE. CD25, the α-chain of the interleukin-2 (IL-2) receptor, is highly expressed on Tregs and plays a critical role in suppressing the activation and proliferation of effector T cells. Clinical studies have shown that $CD4^{+}$ $CD25^{hi}$ Tregs in patients with active SLE display impaired suppressive function, suggesting their dysfunction may contribute to disease pathogenesis. Notably, in vitro activation of $CD4^{+}$ $CD25^{hi}$ Tregs from active SLE patients increased FoxP3 expression and restored their regulatory function, indicating that therapeutic strategies aimed at enhancing Treg activity may offer novel approaches for SLE treatment.[48] Four additional Treg-related phenotypes showed negative associations with SLE: "CD25 on $CD45RA^{-}$ CD4 not Treg", "$CD28^{-}$ $CD8^{br}$ % T cell", "CD28 on resting Treg", and "CD4 on activated Treg".

$CD8^+$ $CD28^-$ T cells have been reported to expand during remission but decline during active disease, suggesting a role in modulating disease activity and highlighting immune dysregulation across disease stages.[49] CD28, an extensively studied co-stimulatory molecule, plays multiple roles during T cell activation, proliferation, and survival. Chronic antigen stimulation and T cell senescence lead to loss of CD28 expression.[50] With regard to $CD28^+$ resting Tregs, direct evidence linking their functional impairment to SLE is lacking; their suppressive activity may be attenuated, but this hypothesis needs to be confirmed by functional assays. Activated Tregs ($CD4^+$ aTregs), derived from Th0 precursors, are potent suppressors of immune responses; however, both total $CD4^+$ Tregs and aTregs are significantly reduced in the peripheral blood of SLE patients, underscoring the loss of their protective role in disease progression.[51] Interestingly, "CD25 on $CD45RA^-$ CD4 not Treg" was negatively associated with SLE, whereas "$CD25^{hi}$ $CD45RA^-$ CD4 not Treg % T cell" was positively associated. The primary distinction lies in CD25 expression levels ($CD25^+$ versus $CD25^{hi}$). Prior studies have reported that $CD4^+CD25^+$ T cells are markedly reduced in SLE,[52] whereas $CD4^+$ $CD25^{hi}$ cells tend to increase during disease remission.[53] These findings suggest substantial functional heterogeneity among $CD4^+$ T cells with partial Treg-like features, and imply that differences in CD25 expression intensity may contribute to stage-dependent immune imbalance in SLE.

Synthesis of Potential Mechanisms

The identified phenotypes implicate several key biological pathways, primarily centered on immune tolerance, antigen presentation, and inflammatory amplification. To summarize the mechanistic links between these genetically predicted phenotypes and SLE pathogenesis, we present the hypothesized mechanisms in Table 5.

Our two-sample bidirectional Mendelian randomization analysis indicates that immune phenotypes with significant causal associations with SLE primarily involve the expression of key molecules, including HLA-DR, CD25, CD45/CD45RA, CD8, BAFF-R, CD24, CD14, CX3CR1, CD28, CD11b, CD4, CD3, CD27, and CD16. Many of these have supporting evidence in prior studies, and our findings provide additional genetic validation of their potential roles. Notably, some molecular signatures significantly associated with SLE such as HLA-DR, CD3, CD24, CD25, CX3CR1, and CD8, while highlighted in our analysis, remain insufficiently characterized at the mechanistic level, warranting further investigation into their contributions to SLE.

Table 5 Summary of Immune Cell Phenotypes Causally Associated with SLE and Their Hypothesized Pathogenic Mechanisms

Panel	Immune Cell Phenotypes	Direction	Key Hypothesized Mechanisms	Mechanism Category
B cell	**Risk Factors**: • BAFF-R on IgD^+ $CD38^-$ unsw mem • IgD^+ $CD24^-$ %B cell	↑	B cell hyperactivation: Elevated BAFF signaling promotes survival of autoreactive B cells; TLR/IFN signaling drives a B-T cell feedback loop that bypasses tolerance and amplifies autoimmunity.	Immune Tolerance
	Protective Factors: • CD24 on transitional • CD27 on T cell (B-cell panel)	↓	Maintenance of equilibrium: Proper B cell differentiation and regulatory signaling help preserve balanced memory B cell subsets and limit pathogenic activation.	Immune Tolerance
cDC	**Protective Factors**: • HLA-DR on DC • HLA-DR on plasmacytoid DC	↓	Preserved antigen presentation: Adequate HLA-DR expression supports effective antigen presentation and immune homeostasis.	Antigen Presentation

(*Continued*)

https://doi.org/10.2147/CCID.S566075

Table 5 (Continued).

Panel	Immune Cell Phenotypes	Direction	Key Hypothesized Mechanisms	Mechanism Category
Monocyte & Myeloid cell	**Risk Factors**: • CD11b on $CD33^{br}$ $HLA\text{-}DR^{+}$ CD14dim • CD11b on $CD66b^{+}$ $^{+}$ myeloid cell	↑	Adhesion & Inflammation: High CD11b (integrin αM) mediates leukocyte adhesion/migration to inflamed tissues and TLR-signaling amplification.	Inflammatory Amplification
	Protective Factors: • CX3CR1 on $CD14^{+}$ $CD16^{+}$ monocyte • HLA-DR on $CD14^{-}$ $CD16^{-}$	↓	Immune Regulation: CX3CR1 mediates tissue-specific immune regulation (eg, kidney); functional subsets are critical for apoptotic cell clearance to prevent inflammation.	Inflammatory Amplification
TBNK & Maturation stages of T cell	**Risk Factors**: • CD45 on $CD4^{+}$	↑	TCR signaling modulation: Altered CD45 expression regulates TCR signal strength and T-cell repertoire selection, potentially favoring aberrant T-cell activation.	Immune Tolerance
	Protective Factors: • CM DN ($CD4^{-}CD8^{-}$) %T cell • $CD3^{-}$ lymphocyte %lymphocyte • $HLA\text{-}DR^{+}$ $CD4^{+}$ % lymphocyte • $HLA\text{-}DR^{+}$ $CD4^{+}$ % T cell • $HLA\text{-}DR^{+}$ $CD8^{br}$ % lymphocyte • $HLA\text{-}DR^{+}$ $CD8^{br}$ % T cell • $HLA\text{-}DR^{+}$ T cell % lymphocyte • $HLA\text{-}DR^{+}$ T cell%T cell	↓	T Cell Exhaustion & Homeostasis: Reduced proportions of activated and memory T-cell subsets, together with altered lymphocyte composition, reflect chronic immune activation–induced T-cell exhaustion and disrupted immune homeostasis.	Immune Tolerance
Tregs	**Risk Factors**: • $CD25^{hi}$ $CD45RA^{-}$ CD4 not Treg %T cell	↑	Dysfunctional Regulation: Accumulation of dysfunctional Treg-like cells or activated effectors that fail to suppress autoreactivity.	Immune Tolerance
	Protective Factors: • CD25 on $CD45RA^{-}$ CD4 not Treg • $CD28^{-}$ $CD8^{br}$ %T cell • CD28 on resting Treg • CD4 on activated Treg	↓	Impaired Regulatory Capacity: Reduced proportions of regulatory or senescent T-cell subsets reflect compromised immune regulation and stage-dependent imbalance of peripheral tolerance.	Immune Tolerance

Notes: Direction: ↑Positive association; ↓ Negative association.

Limitations

This study has several limitations. First, the GWAS data for both immune cell phenotypes and SLE were derived from European-ancestry populations. While this ancestry alignment helps minimize population stratification bias, it may limit generalizability. Second, the SLE dataset included 647 cases and 482,264 controls. The relatively limited number of cases may constrain the statistical power of the analysis, potentially leading to the oversight of weaker causal associations. Third, the associations rely on statistical inference without direct experimental confirmation; further validation in cellular and animal models is therefore needed.

Despite these limitations, this study provides genetically informed insights into the immunopathogenesis of SLE and offers a framework for prioritizing immune cell-related biomarkers and therapeutic targets. Future research integrating functional experiments, multi-ethnic cohort validation, and interventional approaches will be essential to clarify the biological and clinical relevance of these phenotypes.

Conclusion

Our findings suggest that genetically predicted immune cell phenotypes contribute to SLE pathogenesis through interconnected mechanisms including immune tolerance regulation, antigen presentation, and inflammation amplification. Notably, phenotypes involving the expression of HLA-DR, CD3, CD24, CD25, CX3CR1, and CD8, while strongly associated with SLE, remain incompletely characterized at the mechanistic level. These molecular and cellular signatures may therefore represent promising priorities for future basic and translational research, with potential therapeutic implications.

Ethics Statement

This study is a secondary analysis of publicly available GWAS data, with no original data collection. According to Items 1 and 2 of Article 32 of the Ethical Review Measures for Life Science and Medical Research Involving Human Subjects of the People's Republic of China (February 18, 2023), research using legally obtained public data or anonymized information is exempt from institutional ethics review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was supported by the National Key Research and Development Program of China, Key Special Project for the Modernization of Traditional Chinese Medicine (2024YFC3505301); the Science and Technology Innovation Guidance Project in the Medical and Health Field of Zhengzhou (2025YLZDJH339); and the 2025 Culture and Tourism Research Project of the Department of Culture and Tourism of Henan Province (No. 7).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kiriakidou M, Ching CL. Systemic lupus erythematosus. *Ann Intern Med*. 2020;172(11):ITC81–ITC96. doi:10.7326/AITC202006020
2. Barber MRW, Drenkard C, Falasinnu T, et al. Global epidemiology of systemic lupus erythematosus. *Nat Rev Rheumatol*. 2021;17(9):515–532. doi:10.1038/s41584-021-00668-1
3. Shim JS, Sung YK, Joo YB, Lee HS, Bae SC. Prevalence and incidence of systemic lupus erythematosus in South Korea. *Rheumatol Int*. 2014;34(7):909–917. doi:10.1007/s00296-013-2915-9
4. Fava A, Petri M. Systemic lupus erythematosus: diagnosis and clinical management. *J Autoimmun*. 2019;96:1–13. doi:10.1016/j.jaut.2018.11.001
5. Herrada AA, Escobedo N, Iruretagoyena M, et al. Innate immune cells' contribution to systemic lupus erythematosus. *Front Immunol*. 2019;10:772. doi:10.3389/fimmu.2019.00772
6. Haycock PC, Burgess S, Wade KH, Bowden J, Relton C, Davey Smith G. Best (but oft-forgotten) practices: the design, analysis, and interpretation of mendelian randomization studies. *Am J Clin Nutr*. 2016;103(4):965–978. doi:10.3945/ajcn.115.118216
7. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet*. 2014;23(R1):R89–R98. doi:10.1093/hmg/ddu328
8. Orrù V, Steri M, Sidore C, et al. Complex genetic signatures in immune cells underlie autoimmunity and inform therapy. *Nat Genet*. 2020;52(10):1036–1045. doi:10.1038/s41588-020-0684-4
9. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet*. 2021;53(10):1415–1424. doi:10.1038/s41588-021-00931-x

10. Burgess S, Thompson SG. Avoiding bias from weak instruments in mendelian randomization studies. *Int J Epidemiol*. 2011;40(3):755–764. doi:10.1093/ije/dyr036
11. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658–665. doi:10.1002/gepi.21758
12. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. doi:10.1002/gepi.21965
13. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through egger regression. *Int J Epidemiol*. 2015;44(2):512–525. doi:10.1093/ije/dyv080
14. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. 2017;46(6):1985–1998. doi:10.1093/ije/dyx102
15. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing mendelian randomization investigations: update for summer 2023. *Wellcome Open Res*. 2023;4:186. doi:10.12688/wellcomeopenres.15555.3
16. Bowden J, F DGM, Minelli C, et al. Improving the accuracy of two-sample summary-data mendelian randomization: moving beyond the NOME assumption. *Int J Epidemiol*. 2019;48(3):728–742. doi:10.1093/ije/dyy258
17. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698. doi:10.1038/s41588-018-0099-7
18. Corbin LJ, Richmond RC, Wade KH, et al. BMI as a modifiable risk factor for type 2 diabetes: refining and understanding causal estimates using mendelian randomization. *Diabetes*. 2016;65(10):3002–3007. doi:10.2337/db16-0418
19. Rubin SJS, Bloom MS, Robinson WH. B cell checkpoints in autoimmune rheumatic diseases. *Nat Rev Rheumatol*. 2019;15(5):303–315. doi:10.1038/s41584-019-0211-0
20. Kaminski DA, Wei C, Qian Y, Rosenberg AF, Sanz I. Advances in human B cell phenotypic profiling. *Front Immunol*. 2012;3:302. doi:10.3389/fimmu.2012.00302
21. Kosalka J, Jakiela B, Musial J. Changes of memory B- and T-cell subsets in lupus nephritis patients. *Folia Histochem Cytobiol*. 2016;54(1):32–41. doi:10.5603/FHC.a2016.0005
22. Dörner T, Lipsky PE. The essential roles of memory B cells in the pathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol*. 2024;20(12):770–782. doi:10.1038/s41584-024-01179-5
23. Mackay F, Schneider P. Cracking the BAFF code. *Nat Rev Immunol*. 2009;9(7):491–502. doi:10.1038/nri2572
24. Ahmed S. Belimumab in kidney transplantation. *Lancet*. 2019;393(10174):874. doi:10.1016/S0140-6736(18)33074-5
25. Liang P, Huang Q, Xu Y, et al. High serum immunoglobulin D levels in systemic lupus erythematosus: more to be found? *Clin Rheumatol*. 2023;42(4):1069–1076. doi:10.1007/s10067-022-06457-9
26. Burns M, Ostendorf L, Biesen R, et al. Dysregulated CD38 expression on peripheral blood immune cell subsets in SLE. *Int J Mol Sci*. 2021;22(5):2424. doi:10.3390/ijms22052424
27. Lee YH, Bae SC. Association between functional CD24 polymorphisms and susceptibility to autoimmune diseases: a meta-analysis. *Cell Mol Biol*. 2015;61(8):97–104. PMID: 26718436.
28. Yen CY, Wang PY, Chen KY, et al. HLA-DR genotypes in patients with systemic lupus erythematosus in Taiwan. *J Chin Med Assoc*. 2023;86(12):1060–1065. doi:10.1097/JCMA.0000000000001009
29. Imai T, Hieshima K, Haskell C, et al. Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. *Cell*. 1997;91(4):521–530. doi:10.1016/S0092-8674(00)80438-9
30. Cabana-Puig X, Lu R, Geng S, et al. CX3CR1 modulates SLE-associated glomerulonephritis and cardiovascular disease in MRL/lpr mice. *Inflamm Res*. 2023;72(5):1083–1097. doi:10.1007/s00011-023-01731-1
31. Suárez A, Tobío-Parada U, Rodríguez-Carrio J, et al. Circulating levels of low-density granulocytes and cell-free DNA as predictors of cardiovascular disease and bone deterioration in SLE patients. *Thromb Haemost*. 2025;125(9):859–870. doi:10.1055/a-2467-6826
32. Burbano C, Vasquez G, Rojas M. Modulatory effects of $CD14^{+}CD16^{++}$ monocytes on $CD14^{++}CD16^{-}$ monocytes: a possible explanation of monocyte alterations in systemic lupus erythematosus. *Arthritis Rheumatol*. 2014;66(12):3371–3381. doi:10.1002/art.38860
33. Ma K, Du W, Wang X, et al. Multiple functions of B cells in the pathogenesis of systemic lupus erythematosus. *Int J Mol Sci*. 2019;20(23):6021. doi:10.3390/ijms20236021
34. Villanueva V, Li X, Jimenez V, Faridi HM, Gupta V. CD11b agonists offer a novel approach for treating lupus nephritis. *Transl Res*. 2022;245:41–54. doi:10.1016/j.trsl.2022.03.001
35. Thornhill SI, Mak A, Lee B, et al. Monocyte Siglec-14 expression is upregulated in patients with systemic lupus erythematosus and correlates with lupus disease activity. *Rheumatology*. 2017;56(6):1025–1030. doi:10.1093/rheumatology/kew498
36. Son M, Diamond B, Volpe BT, Aranow CB, Mackay MC, Santiago-Schwarz F. Evidence for C1q-mediated crosslinking of CD33/LAIR-1 inhibitory immunoreceptors and biological control of CD33/LAIR-1 expression. *Sci Rep*. 2017;7(1):270. doi:10.1038/s41598-017-00290-w
37. Furukawa D, Yamanaka Y, Kasai H, Urushibara T, Ishiwata T, Muranishi S. Temporal characteristics of aspiration pneumonia in elderly inpatients: from resumption of oral intake to onset. *PLoS One*. 2022;17(4):e0267119. doi:10.1371/journal.pone.0267119
38. Oehadian A, Ghozali M, Kusuma S, et al. Peripheral classic and intermediate monocyte subsets as immune biomarkers of systemic lupus erythematosus disease activity. *Acta Med Indones*. 2024;56(4):469–475.
39. Wang T, Kuley R, Hermanson P, et al. Immune complexes-mediated activation of neutrophils in systemic lupus erythematosus is dependent on RNA recognition by toll-like receptor 8. *Front Immunol*. 2024;15:1515469. doi:10.3389/fimmu.2024.1515469
40. Wu L, Guan Z, Zhang X, et al. Bifidobacterium ameliorates lupus nephritis and modulates aberrant differentiation of lymphocyte subsets. *Rheumatology*. 2025:keaf271. doi:10.1093/rheumatology/keaf271
41. Poddighe D, Dossybayeva K, Kozhakhmetov S, Rozenson R, Assylbekova M. Double-negative T (DNT) cells in patients with systemic lupus erythematosus. *Biomedicines*. 2024;12(1):166. doi:10.3390/biomedicines12010166
42. Cheng G, Cox J, Wang P, et al. A C-type lectin collaborates with a CD45 phosphatase homolog to facilitate West Nile virus infection of mosquitoes. *Cell*. 2010;142(5):714–725. doi:10.1016/j.cell.2010.07.038
43. Wu Z, Yates AL, Hoyne GF, Goodnow CC. Consequences of increased CD45RA and RC isoforms for TCR signaling and peripheral T cell deficiency resulting from heterogeneous nuclear ribonucleoprotein L-like mutation. *J Immunol*. 2010;185(1):231–238. doi:10.4049/jimmunol.0903625

44. Pan X, Yuan X, Zheng Y, et al. Increased CD45RA^{+} FoxP3^{low} regulatory T cells with impaired suppressive function in patients with systemic lupus erythematosus. *PLoS One*. 2012;7(4):e34662. doi:10.1371/journal.pone.0034662
45. Wang CM, Jan Wu YJ, Zheng JW, Huang LY, Tan KP, Chen JY. T cell expressions of aberrant gene signatures and co-inhibitory receptors (Co-IRs) as predictors of renal damage and lupus disease activity. *J Biomed Sci*. 2024;31(1):41. doi:10.1186/s12929-024-01024-7
46. Draborg AH, Jacobsen S, Westergaard M, et al. Reduced response to Epstein-Barr virus antigens by T-cells in systemic lupus erythematosus patients. *Lupus Sci Med*. 2014;1(1):e000015. doi:10.1136/lupus-2014-000015
47. Hedrich CM, Rauen T, Crispin JC, et al. cAMP-responsive element modulator α (CREMα) trans-represses the transmembrane glycoprotein CD8 and contributes to the generation of CD3^{+}CD4^{-}CD8^{-} T cells in health and disease. *J Biol Chem*. 2013;288(44):31880–31887. doi:10.1074/jbc.M113.508655
48. Valencia X, Yarboro C, Illei G, Lipsky PE. Deficient CD4+CD25high T regulatory cell function in patients with active systemic lupus erythematosus. *J Immunol*. 2007;178(4):2579–2588. doi:10.4049/jimmunol.178.4.2579
49. Minning S, Xiaofan Y, Anqi X, et al. Imbalance between CD8^{+}CD28^{+} and CD8^{+}CD28^{-} T-cell subsets and its clinical significance in patients with systemic lupus erythematosus. *Lupus*. 2019;28(10):1214–1223. doi:10.1177/0961203319867130
50. Weng NP, Akbar AN, Goronzy J. CD28(-) T cells: their role in the age-associated decline of immune function. *Trends Immunol*. 2009;30 (7):306–312. doi:10.1016/j.it.2009.03.013
51. Kälble F, Wu L, Lorenz HM, Zeier M, Schaier M, Steinborn A. Impaired differentiation of highly proliferative ICOS+-Tregs is involved in the transition from low to high disease activity in systemic lupus erythematosus (SLE) patients. *Int J Mol Sci*. 2021;22(17):9501. doi:10.3390/ijms22179501
52. Yang XY, Lu XY, Xu DH, Lu QH, Wang QH, Wu HX. Clinical significance of CD4^{+}CD25^{+} T cells in peripheral blood of patients in systemic lupus erythematosus. *Zhonghua Nei Ke Za Zhi*. 2005;44(8):570–572.
53. Miyara M, Amoura Z, Parizot C, et al. Global natural regulatory T cell depletion in active systemic lupus erythematosus. *J Immunol*. 2005;175 (12):8392–8400. doi:10.4049/jimmunol.175.12.8392