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Review Article

Exploring Systemic Lupus Erythematosus Pathogenesis through Animal Models: A Systematic Review of Humanized and Pristane-Induced Lupus Mice

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Abstract
Studies involving experimental animals to explore the pathogenesis of Systemic Lupus Erythematosus (SLE) which leads to the selection of optimal therapy have been widely conducted. The well-known model used to study SLE includes the pristane-induced mouse model and the more recently developed humanized mouse model that implants human immune cells into immunodeficient mice. The current state of the research has yet to provide a systematic review that analyzes both model and its contribution to our understanding of SLE pathogenesis. This systematic review-based study aims to provide a comprehensive overview of the development and application of pristane-induced and humanized mouse models. We obtained several relevant article sources include: (1) Search Strategy, on databases such as PubMed, MEDLINE, ScienceDirect, and Cochrane by adjusting the protocols listed in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA); (2) Eligibility based on exclusion and inclusion criteria; and (3) Data Extraction. The findings show that 30 articles are relevant to the subject matter. Several strains of mice were used in the model of the 0.5 pristane injection method and the humanized mice model. All studies showed similar patterns in the onset and manifestation of SLE in mice models with slight variations. The purpose of using the pristane injection method and humanized mice model is adjusted to the output of each study. A variety of research preferences can be used as a reason for choosing pristane and humanized cells transplanted methods in making SLE model mice.

Keywords: *animal models; humanized-mice; pristane; systemic lupus erythematosus (SLE)*
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INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that affects millions of people worldwide. Despite extensive research efforts, the pathogenesis of SLE remains poorly understood, leading to suboptimal therapy.[1] The use of animal models plays an important role in advancing the understanding of SLE. Many different models have been developed to study the immune dysregulation and multi-organ involvement that characterize the disease.[2] Animal models of SLE can generally be categorized into spontaneous models, transgenic knockout models, induced models, and humanized mouse models.[2] The focus of each study determines the choice of animal model used. Spontaneous and transgenic models are often used and although they show satisfactory results, they have limitations due to specific SLE manifestations and limited genetic factors.

Spontaneous lupus mice models often do not capture the entire complexity of the disease, including the involvement of specific organs or tissues such as only the kidney. humanized-mice method on creating SLE mice

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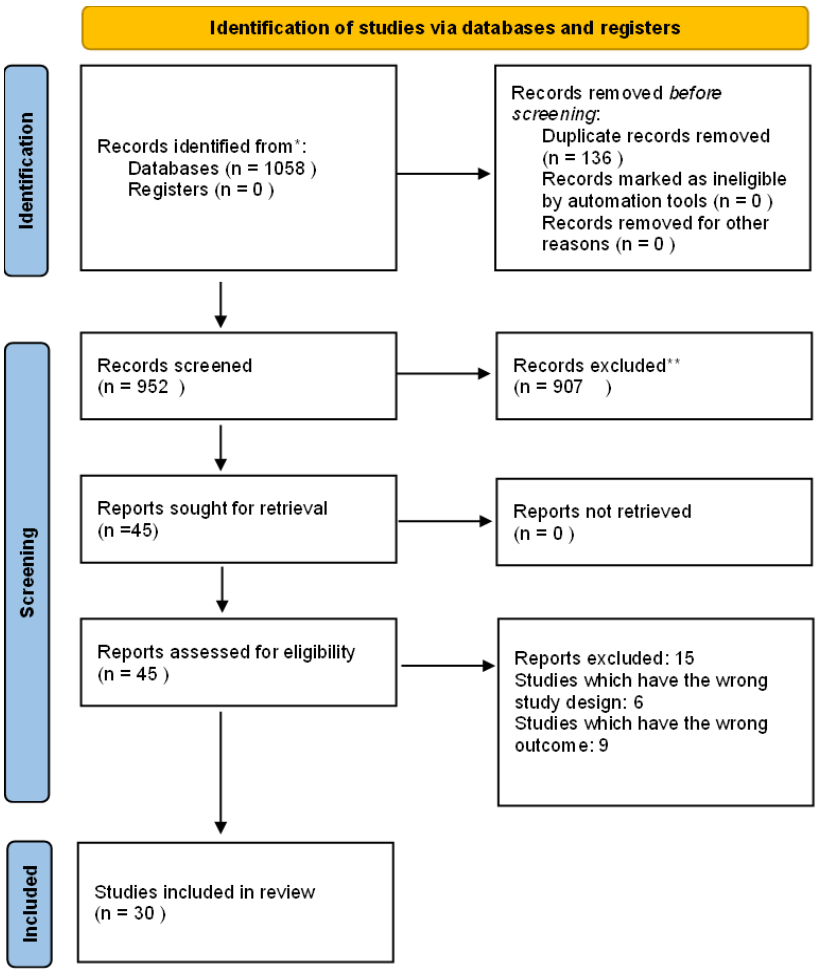

Figure 1 PRISMA flow diagram. There were a total of 1058 articles reviewed from keywords, abstracts, and methods used in research. The types of journals used were original article research and review with a range of years 2013-2023. Based on the flowchart diagram, a final total of 30 articles were included in the review.

Since SLE in humans is not only caused by a single genetic factor but also by the effects of environmental exposures,[2] the induced mouse model was chosen as an alternative. The most commonly used induced mouse model is pristane that represents environmental factors. Pristane is an isopropanol alkaloid that is injected into mice to induce the development of SLE-like symptoms, including autoantibody production, immune complex deposition, and glomerulonephritis.[3,4] Pristane-induced models have been used to study the role of T and B cells in SLE development and environmental factors in disease susceptibility.[3,2] This method has advantages over other methods as an option because of its practicality and the emergence of a more complex spectrum of SLE disease manifestations in different organ systems. Meanwhile, humanized mouse models have also recently been developed by transplanting human immune cells into immunodeficient mice.[5,6] These models provide an opportunity to study the human immune system in vivo and have the potential to advance our understanding of the pathogenesis of SLE, particularly those that are similar to, or close to, the pathogenesis in patients with the disease. This model has also been used to study the role of different immune cell subsets in the development of SLE and to test the efficacy of new therapies.[7,6] Based on these reasons, this article selects pristane-induced and lupus-induced lupus mice, in addition to both methods having advantages over other methods. Such advantages are relevance to human disease, mimicry of environmental factors, suitability for studying neuropsychiatric lupus, ideal lupus mouse model. The problem with the current state of research is that there is no systematic comprehensive review that analyzes the strengths and limitations of each model, which is important to explore between humanized mice and pristane injection methods. In addition, there is still little information to verify the method of humanizing mice as the use of the method to generate SLE mouse models increases and its contribution to our understanding of generating animal models of lupus associated with SLE pathogenesis.

A systematic review would be very useful for researchers in lupus. It would help to guide future investigations and identify potential areas of research that could lead to new therapeutic targets using animal models. This systematic review aims to take a closer look at the existing studies and provide a comprehensive overview of the development and use of pristane-induced mice and humanized mouse models of lupus in SLE research.

Table 1. Summary of results based on the study of research methods in intervening mice to become SLE.

Author and Year of Publication	Animal Models	Method of Induction of Lupus	Research Objective	Result
Aschman *et al*., (2021)	(N= 10) Type III IFN receptor-deficient mice (Ifnlr1-/-) and (N= 10) wild-type mice	0.5 ml i.p. pristane injection		
			Research Objective	**Result**
Delimitreva *et al*., (2021)	(N= 10) Female Balb/c (4 weeks)	0.5 ml i.p. pristane injection	To investigate the function of type III IFN in SLE	Ifnlr1 -/- mice showed a decrease in the number of lipogranulomas, the number of antibody-secreting cells (not significant), natural killer (NK) cells in the kidney, and B cells in the spleen, as well as an increase in survival rate and peripheral CD115+Ly6C+ monocytes compared to wild type mice. Intraperitoneal injections of pristane could show a result in local chronic inflammation and the formation of lipogranulomas.
Dema *et al*., (2017)	(N= 12) Female C57/BL/6 mice with diphtheria toxin-induced basophil depletion and MAR-1	0.5 ml i.p. pristane injection	To investigate the effect of SLE on the oocyte maturation process	Decreased activation and apoptosis of T cells, decreased apoptosis of B cells, increased number of plasma cells secreting IgG anti-dsDNA antibodies, increased levels of IgG, IFN-y, and IL10, the onset of proteinuria, increased mesangial proliferation in the glomeruli. Mice with induced lupus exhibited low egg maturation rate
Gunawan *et al*., (2017)	(N= 61) NOD scid gamma (NSG) mice	fetal haematopoetic stem cell (HSC) transplantation	Analyzing the contribution of basophil cells to pristane-induced lupus nephritis	After pristane injection, basophils were activated and accumulated in SLOs to promote autoantibody production. Basophils contribute to the development of lupus nephritis by increasing autoantibody production. Basophil depletion decreases autoantibodies and immune complex clearance in the glomerulus

Table 1. Cont…

Author and Year of Publication	Animal Models	Method of Induction of Lupus	Research Objective	Result
Kalim *et al*., (2018)	(N= 48) Female Balb/c (8-12 weeks)	0.5 ml i.p. pristane injection	Generation of a human immune system-mediated SLE model induced by pristane injection in humanized mice (hu-mice)	There is a decrease in the number of human lymphocytes in the peripheral blood, hyperactivation of T cells and B cells, an increase in the number of plasma cells and memory T cells, and an increase in pro-inflammatory cytokines and the IFN type 1 gene → resembles lymphopenia in SLE patients. A human immune-mediated SLE model that recapitulates key clinical and immunological features of SLE.
Liou *et al*., (2022)	(N= 90) Mice Balb/c (8 weeks)	0.5 ml i.p. pristane injection	Identify the function of regulatory T cells in the pathogenesis of SLE in pristane-induced mice	Th1 and Th17 in the pristane group were higher than the control group at week 8, the percentage of Th1 and Th17 decreased at week 16, Th1 and Th2 increased in the pristane group at weeks 24 and 32, and there was a positive correlation between IL-6 and Treg in the pristane group.
Pannu *et al*., (2020)	(N= 10) Mice Balb/c (8 weeks)	0.5 ml i.p. pristane injection	Identifying anti-dsDNA IgG and de-SIA IgG antibodies in SLE mice	The spontaneous lupus model in BALB/c mice summaries other spontaneous lupus mouse models driven by toll-like receptor 7 and 9. A low SIA/serum IgG anti-dsDNA ratio indicated a high severity of nephritis in the pristane-induced group. High sialylated anti-dsDNA IgG was able to reduce the severity of proteinuria.
Lee *et al*., (2020)	Female C57BL/6 and IFNAR1-/- mice	0.5 ml i.p. pristane injection	Investigating the status of oxidative stress, inflammation, immune complex, and histopathologic al changes in lupus-affected organs	Pristane injection caused the generation of anti-nuclear antibodies, which were apparent from the different immunofluorescence patterns observed. Immune deposits were evident in all the vital organs stating the similarity this model holds with SLE patients. Pristane injection mimics the two main manifestations of lupus, oxidative stress and inflammation.
Peixoto *et al*., (2019)	(N= 26) female Balb/c (6-8 weeks)	0.5 ml i.p. pristane injection	To understand how inflammation in SLE mice models affects red blood cell (RBC) alloimmunizati on.	Pristine challenge upregulates the secretion of NGAL by macrophages and splenocytes. Pristane induction of a lupus-like phenotype promoted alloimmunization to the KEL RBC antigen in an IFNa/b-dependent manner

Table 1. Cont…

Author and Year of Publication	Animal Models	Method of Induction of Lupus	Research Objective	Result
Tang *et al*., (2021)	(N= 5) Female Balb/c (6-8 weeks) mice	0.5 ml i.p. pristane injection	analyzing the expression of CD4+ CD69+ T cells and Treg cells as well as multiple interleukin profiles of SLE model mice	Compared with the controls, SLE-induced animals presented increased numbers of CD4+ CD69+ T cells in the blood on T90 and T120 and in the spleen on T120, but there were decreased numbers in the PL on T120. T90. Increased numbers of CD4 + CD69+ T cells in the PL were positively associated with high IL-2.
Ma *et al*., (2021)	female C57BL/6J (C57), NOD-SCID IL2Rγnull (NSG), B6.SJL-Ptprca Pepcb/BoyJ, Il17rc-/- (IL-17RC KO, with C57), mice MRL/MPJ, and MRL/MpJ-Faslpr/J (MRL/Lpr mice)	Humanized lupus mouse model by transferring Th17 cell-depleted PBMCs from SLE patients	examining changes in the thymus and potential mechanisms responsible for immuno-logical abnormalities in Pristane Induced Lupus (PIL) mice.	The modification in the thymus in PIL and elucidated the immunologic abnormalities of increased B cells, potentially providing insight into the associated molecular mechanisms and facilitating further research.
Leiss *et al*., (2013)	(N= 57) BALB/c mice received pristane (PIL group) and were analyzed for serum autoantibodies (anti-chromatin-, -histone, -Sm, -dsDNA)	injected intraperitoneally (i.p.) with either 0.5 ml of pristane or saline (as a control)	identified a novel function of IL-17 in enhancing plasma cell survival for autoantibody production in SLE pathogenesis	novel function of L-17 in enhancing plasma cell survival for autoantibody production in SLE pathogenesis. IL-17 significantly promoted plasma cell survival via p38-mediated Bcl-xL transcript stabilization.

Table 1. Cont…

Author and Year of Publication	Animal Models	Method of Induction of Lupus	Research Objective	Result
Yun *et al*., (2023)	(N= 12) Female (4 weeks) BALB/c mice	0.5 mL pristane injection intraperitoneally (i.p.)	To characterize the clinical and histological features of arthritis associated with systemic lupus and to compare with models of rheumatoid arthritis (RA)	BALB/c PIL mice developed clinical arthritis within 3 months and correlated with areas of inflammation, erosion, cartilage damage, osteoclast number, and severity. PIL mice with arthritis also showed signs of pulmonary (100%) and renal (46%) lupus.
Luciano *et al*., (2019)	(N= 54) Female BALB/c mice 8–12 weeks old	i.p 0.5 mL pristane injection	To investigate the neuropsychiatric symptoms in the PIL mouse model for the Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) study	Pristane can induce mice to exhibit olfactory dysfunction and an anxiety- and depression-like phenotype, along with increased expression of cytokines, BBB leakage, activation of microglia and astrocytes and aberrant deposition of IgG and lipofuscin in the brain.
Summers *et al*., (2014)	(N= 7) Female wild-type (WT) and (N= 6) IL-17A−/− mice	Injected with 500 µl of pristane	To analyzes the NMDA subunit receptors, finding a downregulation of NR2A subunit related to learning and memory disturbance when were exposed to lipopolysaccharides (LPS).	Pristane-induced lupus BALB/c mice had the downregulation of hippocampal NR2A/2B subunits which related to cognitive impairment i.e., learning and memory disturbance. Moreover, Downregulation of the NR2A subunit was more pronounced when they were exposed to exposed to LPS.
Han *et al*., (2015)	(N= 2-6) BALB/cByJ and BALB/c TLR7−/− mice	Injected with 0.5 mL pristane (i.p.)	To define the role of IL-17A in experimental lupus induced by pristane administration.	Seven months after treatment with Pristane, humoral autoimmunity was reduced in the absence of IL-17A with reduced levels of immunoglobulin (Ig)G and anti-dsDNA antibodies. IL-17A is required for the maximal production of humoral and cellular autoimmunity and IL-17A is even produced early in the disease process, predominantly by innate immune cells.

Table 1. Cont…

Author and Year of Publication	Animal Models	Method of Induction of Lupus	Research Objective	Result
Liu *et al*., (2022)	(N= 3-5) BALB/c, C57BL/6 mice, and TCR$\alpha^{-/-}$ mice	Injected by 0.5 mL pristane	To address anti-ribonucleoprotein/Smith (anti-Sm/RNP) and other SLE autoantibodies levels are maintained over time.	B cells with a switched "memory-like" (CD19+ CD138- IgM- IgD-) (sMB) phenotype were increased in pristane-treated mice and expressed higher levels of Toll-like receptor 7 (Tlr7) than cells with this phenotype from untreated mice. Also, B cells are hyper-responsive to synthetic TLR7 ligands and apoptotic cells.
Rodriguez *et al*., (2018)	(N= 7-9) Cd38−/− and Art2−/− mice	intraperitoneal injection of pristane	To investigate the manners of CD4+ T cells in antibody production in a lupus-like mouse model by pristane injection	CD4+ T cells in pristane-treated mice play important roles in IgG production, which implies the critical roles in the induction of pathological autoantibodies in MHC-independent and ICAM-1-dependent manners.
Kienhöfer *et al*., (2017)	Both Ncf1-mutated and PAD4-deficient mice	Injected i.p. alkane pristane	To investigate the role of CD38 in a pristane-induced murine model of SLE.	Reveal a new role for CD38 in promoting aberrant inflammation and lupus-like autoimmunity via an apoptosis-driven mechanism
McClung *et al*., (2021)	(N= 14) female C57BL/6 mice	Pristane 0.5mL injection (i.p.)	To investigate the functional impact of neutrophils and NETs on a mouse model of SLE triggered by intraperitoneal injection of the cell death–inducing alkane pristane.	Hydrocarbon oil pristane induces chronic peritonitis by the production of autoantibodies directed against DNA- and RNA-associated autoantigens and chronic inflammation, resulting in a disease closely resembling and meeting the classification criteria of SLE. The aberrant NET is one of the factors that promotes experimental lupus-like autoimmunity through the uncontrolled release of inflammatory mediators.
Bossaler *et al*., (2013)	Wild-type BALB/c and C57Bl/6 mice as well as B6gld/gld and BALB/c Rag2−/	single i.p. injection of 0.5 ml of pristane	The pristane-inducible model of SLE would develop hypertension and vascular dysfunction as the disease progressed.	Seven months after pristane administration, mice developed various autoantibodies (including anti-dsDNA IgG, anti-ssDNA IgG, and anti-nRNP IgG, as well as hypergammaglobulinemia) and immunological changes (increased circulating neutrophils and increased CD4−CD8−)

Table 1. Cont…

Author and Year of Publication	Animal Models	Method of Induction of Lupus	Research Objective	Result
Bossaler *et al*., (2016)	(N= 29) Tlr92/2 BALB/c mice	injected i.p. with TMPD (pristane)	evaluated the effect of FasL-deficiency, as well as FasL overexpression, on TMPD-injected BALB/c mice.	FasL-deficiency significantly reduced the early inflammatory exudate induced by TMPD injection. In contrast, ΔCS mice developed a markedly exacerbated disease profile, associated with a higher frequency of splenic neutrophils and macrophages, a profound change in ANA specificity, and a more pronounced
Kanno *et al*., (2020)	Male wild type (α2AP+/+) and α2AP−/− mice	Injected 500 µl of pristane (i.p.)	To evaluate the negative regulatory role of TLR9 in murine SLE	Develop more severe autoimmunity than do their TLR-sufficient cohorts (increased production of neutrophils, anti-neutrophil Abs, and the development and progression of renal disease). Thus, the BALB/c Pristine model recapitulates other TLR7-driven spontaneous models of SLE and is negatively regulated by TLR9.
Amarilyo *et al*., (2014)	(N= 12-16) Wild-type (WT) C57BL/6 (B6) and syngeneic IL-17–deficient (IL-172/2) mice	one i.p. injection of 500 ml pristane	identification functions of Alpha2-antiplasmin (α2AP) and to be associated with immune and inflammatory responses in Lupus Nephritis (LN).	The levels of plasmin-α2AP complex and α2AP were elevated in the lupus model mice. In addition, α2AP deficiency attenuated pristane-induced glomerular cell proliferation, mesangial matrix expansion, collagen production, fibrin deposition, immunoglobulin G deposition and pro-inflammatory cytokine production in the model mice. This also correlated with the function of pristane known to induce LN.
Smith *et al*., (2018)	(N= 8) C57BL/6 (B6) mice	i.p. injection of 500 ml pristane	Identification the role of IL-17 in SLE mice that were genetically deficient of this cytokine.	Pristane-treated IL-172/2 mice had significantly reduced titers of IgG and low anti-ssDNA, anti-nRNP, and anti-chromatin Autoantibodies. Pro-inflammatory IL-17 after Pristane administration. administration, it appeared to involve multiple immune cell populations.

Table 1. Cont

Author and Year of Publication	Animal Models	Method of Induction of Lupus	Research Objective	Result
Lu *et al*., (2017)	*Nlrp3*$^{-R258W}$ mouse	one i.p. injection of 500 µl of pristane	Identification a role for IL-16/mir-125a in SLE pathology and show not only that IL-16 is a target for miR-125a but that reduced miR-125a expression in SLE patients is associates with lung involvement.	In the pristane model of acute "SLE-like" lung inflammation and alveolar hemorrhage, there is reducing pulmonary miR-125a, neutrophil infiltration was markedly reduced, and enhanced IL-16 expression. miR-125a/IL-16 in the regulation of lung inflammation and suggest that this axis may be a may be a therapeutic target for the treatment of acute lung injury in SLE.
Kluger *et al*., (2016)	(N= 12) Foxp3^{Cre} × Stat3$^{fl/fl}$ mice	one i.p. injection of pristane	Explore the role of NLRP3 in the development of SLE using the pristane-induced experimental lupus model.	Nlrp3^{-R258W} mutant mice exhibited significantly higher mortality upon pristane challenge because developed a much more severe lupus-like syndrome in the pristane-induced SLE model. NLRP3 functions to drive kidney inflammation in lupus are primarily myeloid cells, including macrophages, neutrophils and some dendritic cells. This can be confirmed in the future using conditional NLRP3 knockout mice.
Zhang *et al*., (2018)	BALB/c and C57BL/6 Female (6–8 weeks old) mice	Injected by 0.5 ml pristane (i.p.)	To identify the function of the newly defined Stat3-dependent Th17-specific regulatory T cells (Treg17).	Establishes a role of Treg17 cells for the control of Th17 responses and tissue protection during acute inflammatory and chronic autoimmune-mediated stages of pristane-induced SLE.
Zhou *et al*., (2021)	Balb/c WT mice and BALB/c nude mice (CAnN.Cg-Foxn1nu/CrlVr),	Mice were prepared to be immunodeficient by UVB exposure. Then, PBMC cells from cutaneous lupus patients and healthy controls were transplanted.	to investigate whether MDSCs are involved in the process of podocyte injury in the development of Lupus Nephritis (LN)	MDSCs induce podocyte injury by ROS and were involved for the first time in the subsequent development of proteinuria in LN of pristane-induced lupus mice. Furthermore, TLR-7-activated MDSCs enhanced podocyte injury by activating p-38MAPK and NF-kB pathways through ROS.

Table 1. Cont…

Author and Year of Publication	Animal Models	Method of Induction of Lupus	Research Objective	Result
Zhuang *et al.*, (2016)	(N= 4-8) C57BL/6 (B6), B6 (mu;MT), B6 (C3-/-), and B6 (CD18-/-) mice	Injection of Purified human IgM or murine IgG (200 mu;g/mouse) i.v. into mu;MT mice. Then 0.5 ml pristane injection i.p.	Establishment of humanized mice (hu-mice) model for the development of rapid onset induction murine against cutaneous lupus	Humanized mice develop lupus-like cutaneous lesions under UVB radiation, present cutaneous lupus lesions of Hu-LE mice show B cell clusters and CD11b+ B220+ cell infiltration exhibits prominent expansion

- PIL : Pristane Induced Lupus
- hu-mice : humanized mice
- LN : Lupus Nephritis
- NPSLE : Neuropsychiatric Systemic Lupus Erythematosus

Table 2. List of clinical manifestations that emerged or were the focus of studies with SLE mice model

Disease Manifestation	Pristane-Induced Model (N = 27)	Humanized Model (N = 3)
	N (%)	**N (%)**
Onset		
- < 8 weeks	2 (7%)	1 (33%)
- 8-16 weeks	15 (55%)	1 (33%)
- >16 weeks	8 (31%)	1 (33%)
N/A	2 (7%)	-
Clinical		
- Proteinuria/lupus nephritis	17 (63%)	2 (67%)
- Arthritis	4 (15%)	N/A
- Lung (i.e., pleuritis, vasculitis, alveolar hemorrhage	3 (11%)	1 (33%)
- Skin lesion and/or alopecia	2 (7%)	1 (33%)
- Behavioural/neuronal	2 (7%)	N/A
- Cardiovascular (i.e., hypertension)	1 (4%)	N/A
Serological		
- ANA and/or Anti-dsDNA	20 (74%)	3 (100%)
- Anti-RNP/Anti-Sm	10 (37%)	1 (33%)
- Anti-histone	2 (7%)	N/A
Immunohistochemistry		
- Kidney and/or other organs (i.e., spleen, liver)	20 (74%)	3 (100%)

N/A: not mentioned in the article

Table 3. Summary of the advantage and the disadvantage of pristane induced lupus model and humanized lupus model

Model	Advantage	Disadvantage
Pristane Induced Lupus	● Pristane Induced Lupus (PIL) mice are relatively easy to generate and maintain in the laboratory. ● The development of lupus-like symptoms in PIL mice is highly reproducible, allowing researchers to conduct consistent experiments. ● Pristane triggers the autoimmune response seen in lupus-like symptoms, including the production of autoantibodies and kidney damage. ● PIL mice develop lupus-like symptoms within a predictable timeframe, which is advantageous for studying disease progression and assessing the effects of experimental interventions.	● PIL mice do not spontaneously develop SLE, but rather exhibit lupus-like symptoms and thus do not fully capture the complexity and heterogeneity of human disease. ● The autoimmune response in PIL mice is induced by pristane, which is different from the human lupus trigger. ● PIL mice lack the genetic disorders characteristic of human SLE. ● PIL mice often show kidney disease as a manifestation of lupus-like symptoms, whereas human SLE can affect multiple organs.
Humanized Lupus	● Mice models transplanted with human immune cells allow researchers to study SLE in a more human-relevant context ● Humanized mice can display a variety of disease manifestations, including autoantibody production, tissue damage and organ involvement, reflecting the multifaceted nature of human SLE. ● This model provides a platform to evaluate the efficacy and safety of potential therapeutic interventions for SLE prior to human clinical trials. ● Humanized mice models can be created using immune cells from SLE patients, facilitating the investigation of individualized treatment approaches.	● The creation and maintenance of humanized mice will be technically challenging and time consuming due to the need for human cell transplantation and subsequent maintenance. ● Other physiological and genetic differences between mice and humans may limit the applicability of findings from this model to human SLE. ● Use of humanized mice models raises ethical concerns

METHODS

Search Strategy

We conducted a comprehensive search on databases such as PubMed, MEDLINE, ScienceDirect, and Cochrane with a publication period from January 2013 to April 2023. The search for published articles in English was conducted with the following keywords: "lupus mouse model"; "lupus mice model"; "humanized mouse model of lupus; "pristane induced mouse lupus"; "Pathogenesis of systematic lupus erythematosus"; and "Pathophysiology of systematic lupus erythematosus". This study followed the protocol listed in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Eligibility

The research criteria included: (1) Studies that used humanized lupus mice models and pristane induction; (2) Studies that successfully induced SLE in mice models; (3) Studies that reported outcomes related to SLE manifestations such as autoantibody production, immune cell disorders, and tissue damage; (4) and studies with statistically significant or non-significant results.

We excluded studies that (1) used spontaneous lupus mice model; (2) used therapeutic interventions that affected improving the condition of the mice; (3) had other autoimmune disorders; (4) did not present primary data; and (5) included reviews, systematic reviews, meta-analyses, commentaries, letters to the editor, books, doctoral dissertations, conference abstracts, and study protocols.

Data Extraction

Data extracted independently using a standardized form that includes the following information: (a) authors and year of publication (b) animal model used, (c) SLE induction method, (d) study objectives, and (e) main results and findings.

RESULTS

Study Selection

Relevant articles were identified based on the database and registers through screening with the Rayyan.ai tool (https://www.rayyan.ai/) resulting in total of 1058 articles (Figure 1). A total of 136 duplicate records were removed to obtain articles that were suitable for the screening process. The 952

articles were separated based on exclusion and inclusion criteria, resulting in 45 articles that met the criteria. A more thorough assessment of reports eligibility excluded studies that had the wrong study design (n = 6) and studies that had the wrong outcome (n = 9). Thus, the final results of articles by the inclusion criteria were 30, which were used as the subject of discussion in the systematic review.

Pristane-induced Lupus Mice Model

Mouse models of lupus induced by intraperitoneal (i.p.) injection of 0.5 ml of pristane cause different onset and clinical manifestations of the disease. Twenty-seven articles are using pristane-induced mice as animal models of SLE. All pristane-model mice showed success in developing lupus-like disease manifestations. The onset of lupus disease in this model most commonly occurred between 8 and 16 weeks after induction, as reported in 15 studies. This was followed by an onset above 16 weeks in 8 studies and 2 studies showing an onset below 8 weeks.[16,20] The most commonly reported or investigated clinical manifestations were the onset of proteinuria and symptoms of lupus nephritis in 17 studies, followed by arthritis (n=4),[1,16,18,19] lung disease (n=3), [18,31,33] skin lesions and/or alopecia (n=2),[1,14] neuronal or behavioral disorders (n=2),[19,20] and cardiovascular disorders (n=1).[26] The most commonly investigated serological signs of SLE were ANA and/or anti-ds-DNA antibody levels (n=20), followed by anti-Rnp/anti-Sm (n=10) and anti-histone (n=2). Immunohistochemistry was used in 20 studies to examine morphological changes in kidney tissue and other organs such as the spleen, brain, and liver.

Humanized lupus mice models

Three articles discuss the use of lupus mice models using humanized mice. This model is obtained by transferring human cells, such as hematopoietic stem cells and PBMC cells, into immunodeficient mice so that human cells can be reconstituted in mice.[7,11,17] All three humanized-modeled mice also showed the progressivity of SLE disease. The onset of lupus and SLE manifestations in each study was different, with an onset of less than 8 weeks,[17] onset between 8 and 16 weeks,[7] and onset more than 16 weeks after stem cell transplantation.[11] Clinical manifestations include proteinuria and lupus nephritis,[11,17] pleuritis,[11] and skin lesions or alopecia.[7] The serological markers used in each study were ANA antibodies, anti-ds-DNA, and anti-RNP/anti-Sm. The use of immunohistochemistry to examine morphological changes in kidney, spleen tissue,[11,17] and skin tissue.[7]

DISCUSSION

The review systematically examines studies based on two methods of making animal models such as mice of various strains into SLE. The two types of methods are pristane induction and transferring cells from SLE patients into immunodeficient mice. Although both have the potential to develop lupus-like disease, the result is that the mice models made humanized lupus have similarities to those suffered by humans. Interestingly, the majority of mice used as animal models are female. Several factors make the selection of female mice as animal models in SLE, including (1) mice have similar characteristics to humans in terms of gene composition, cells, and organs. Lupus in humans often affects women compared to men,[2] (2) high levels of the hormone estrogen in female mice correlate with SLE,[36] (3) in general, women and most female SLE mice models are more susceptible to disease,[37] (4) autoantibodies increase in female mice with SLE which is inversely proportional to male mice.[38]

Regarding the role of estrogen hormones in SLE, the mechanism of action of these hormones, namely through estrogen receptor alpha (ERα), promotes the development of SLE and contributes to female sex bias in the loss of tolerance and immune cell activation caused by the Sle1b lupus susceptibility locus.[39] multiple preferences may serve as reasons for choosing pristane and humanized cells transplanted SLE methods in creating SLE model mice. Pristane injection may be preferred when the study aims to create a widely used murine model for the induced disease, as the pristane-induced model is one of the most widely used SLE models (2). Human cell transplantation may be preferred when studying the pathogenesis of human SLE and testing new therapies, as it can provide a more human-like model of SLE,[6] and transplantation of humanized cells is likely to be chosen when studying the interaction between human immune cells and other cells in the body, such as kidney cells, which are difficult to replicate in pristane-induced models.[11]

Pristane Induced Mice Model

The results of several studies that discuss the effects of pristane injection on animal models of mice are shown in Table 2. According to the summary table, the pristane injection method of 0.5 mL (i.p.) can cause various onset and clinical manifestations of the disease. Pristane (2,6,10,14-tetramethylpentadecane) is a type of isoprenoid alkane commonly found in mineral oil. The mineral oil is injected intraperitoneally into the mice to induce peritoneal irritation and increase the yield of monoclonal antibodies from ascites when hybridomas are injected, which can induce autoimmunity.[2,40] The activation of polyclonal B cells elicited by pristane can lead to autoantibodies and the development of autoimmune diseases. In addition, immunologic factors, such as the development of SLE in mice after pristane injection, are associated with modulation of the immune response, including the expression of activated and inhibited Fc receptors.[41] In summary, the onset of SLE in animal models of mice following injection of 0.5 mL of pristane is a complex process involving multiple factors, including pristane injection, polyclonal B cell activation, and immunological factors. The percentage of success rate by using pristane method varies depending on the study and the strain of mice used. A study has shown that the murine lupus model can be successfully established in female BALB/c mice with a single i.p. injection of 0.5 mL of Pristane, and that the specific autoantibody anti-dsDNA for SLE has appeared in the sera of BALB/c mice.[42] The key features of SLE, including the

production of human anti-nuclear autoantibodies, lupus nephritis and pulmonary serositis, were recapitulated when pristane was injected into immunodeficient mice reconstituted with the human immune system (humanized mice).[42] Overall based on previous study result pristane injection is a well-established method to induce lupus-like disease in mice, it may not fully reflect the complexity of the disease in humans.

Various studies from 27 relevant articles used pristane injection with a dose of 0.5 mL that induced peritoneal irritation and increase monoclonal antibody yield from ascites when hybridomas were injected.[2,43] The dose has been taken as the optimal dose to induce the desired effect of each study. Pristane has the ability to activate membranes through its interaction with the lipid bilayer of cells, as well as trigger programmed cell death in lymphoid cell types through the mitochondrial caspase activation pathway.[3] In the process, this triggers the development of autoimmune conditions similar to systemic lupus erythematosus. Regarding the clinical manifestations that appear in the model mice given pristane induction, most of them develop proteinuria and symptoms of lupus nephritis. The mechanism that occurs behind lupus nephritis due to pristane induction is related to the production of autoantibodies against several polynuclear antigens that can form immune complexes deposited in the kidneys due to inflammation and tissue damage.[11,44] Cytokine dysregulation triggers blood-brain barrier (BBB) disruption, IgG deposition, glial activation in nerves, and nerve damage.[45] Basophil activation can lead to autoreactive B cell expansion and autoantibody production, triggering the development of lupus nephritis.[45] A previous study by Yan *et al.* (2020) explained that coptisine, a natural compound, slowed disease progression in pristane-induced lupus mice by inhibiting the Rho/ROCK pathway.[44] Activation of the Rho/ROCK pathway may contribute to the development of lupus nephritis. Other clinical manifestations include arthritis, pulmonary disorders caused by pulmonary hemorrhage within a few weeks in C57BL/6 mice,[46] the appearance of glaucous lesions and/or alopecia, neuronal and behavioral disorders, and cardiovascular disorders.

Serologically, the clinical manifestations that appear in pristane-injected mice are antinuclear antibody (ANA) levels and/or anti-ds-DNA, anti-Rnp/Anti-Sm, and anti-histone. ANA measurement with Indirect immunofluorescence (IIF) is usually scored as 0 to 4+ or as a titer (referring to the number of times the blood is diluted and still yields a positive result). An ANA of 0, 1+ or 2+, or at a titer of less than 1:80 (diluted 80 times) does not usually indicate a significant problem.[47] ANA titers at higher levels are more likely to indicate the presence of an autoimmune disease. In cases of lupus, ANA is present in approximately 95% of patients with active disease. Specific antibodies that need to be checked and become the hallmark of SLE are anti-Sm/anti-Rnp, which are non-specific antibodies that appear in many patients with lupus and other rheumatic diseases with an incidence percentage of 25%.[48] Anti-histone shows that the characteristics of drug-induced lupus, namely pristane in lupus model mice.[49] The time required to develop mice as SLE model animals after pristane injection (**Table 2**) at a certain dose varies depending on the study and the strain of mice used. Some relevant study results explain that pristane-induced mice (PIL) show olfactory dysfunction accompanied by phenotypic symptoms, such as anxiety and depression at the 2nd or 4th month.[19] There are drawbacks to creating pristane-injected mice as a lupus model animal: exposure to hydrocarbon adjuvants can trigger inflammatory or autoimmune responses in humans,[40] and pristane-induced mice are unlikely to fully replicate the complexities of human SLE.[50] Thus, to produce SLE model mice that are similar to humans, other methods are carried out by humanized-lupus mice.

Humanized Mice Model of Lupus

The humanized mice model (hu-mice) is a mice model in which human cells are transplanted into immunodeficient mice. The term "humanized" is used to indicate that these mice can produce cells that have characteristics similar to humans. For example, by transplanting human immune cells, it is expected that the mice will exhibit characteristics of the human immune system. The use of this humanized mice model can assist researchers in conducting human immune system and stem cell research in vivo.[5] The development of humanized mice models is still carried out in limited numbers and involves mice that have been designed to experience immunodeficiency, followed by the transfer and transplantation of human cells.[6] From the findings of related articles, only three articles were relevant to the topic of this systematic review. There is a great opportunity for researchers to use this method as it can provide a platform to study the pathogenesis of SLE and test potential therapeutic agent interventions.[4] In addition, using the hu-mice model can also help identify genetically susceptible loci and targets for future drug development.[51] Thus, this model can further clarify the pathogenesis of SLE and provide new strategies for the prevention and treatment of SLE, especially the development of new drugs for which there are still very few challenges in the form of biological therapies for SLE.

In general, there are currently two main methods used to create hu-mice lupus models. The first method involves the transfer of human peripheral blood mononuclear cells (PBMCs) or peripheral blood lymphocytes (PBLs) from SLE patients to immunodeficient mice. The second method involves the transfer of human hematopoietic stem cells (HSCs) to immunodeficient mice, followed by intraperitoneal administration of pristane to induce SLE.[6,11] The difference between the two characteristics of the PBMC cell transfer method and HSC cells followed by pristane administration according to Chen *et al.* (2022) is that the PBMC method from the patient's blood cells is injected intravenously (i.v.) or intraperitoneally (i.p.) into immunodeficient mice,[6] while in the HSC method, blood stem cells are injected i.v. into immunodeficient mice followed by i.p. pristane administration. The purpose of giving pristane in the HSC method is to stimulate SLE in mice so that it is expected that animal models will produce human anti-nuclear autoantibodies, lupus

nephritis, and pulmonary serositis.[11] Based on the immune cells involved, the HSC + pristane method involves various immune cells in the body, such as T cells, memory B cells, NK cells, Human CD19+ CD20- CD27hi CD38hi plasma blasts/plasma cell, Human CD27+ memory B cells and CD27- IgD- B cells, and human CD27- IgD + naive compared to the PBMC method, namely Human CD45+ cells, CD4+, T cells and CD8+ cells, and IL-17+.[6] In terms of survival rate, mice given PBMCs are more vulnerable than HSCs which can survive up to 13 weeks.[11]

The clinical manifestations that appear in Table 2 are similar to the pristane-injected mice model, among others: Clinical manifestations include proteinuria and lupus nephritis,[11,17] pleuritis,[11] and skin lesions or alopecia.[52] Serological signs in each study studied were ANA antibodies and anti-ds-DNA and anti-RNP/anti-Sm. Each strain of mice used gives rise to the onset of SLE with different times. Some factors may cause differences in onset, namely genetic, environmental and immunological. According to Chen *et al.* (2022), genetic studies in susceptible human or mouse populations show that disease susceptibility is multifactorial, involving complex interactions between several genes along with environmental factors, especially the importance of non-MHC loci that play a role in increasing or suppressing susceptibility to SLE.[6] Environmental factors, such as infections, medication-induced, and UV exposure can be genetically triggered in at-risk individuals.[53] Other immunologically related factors due to T and B cell activation, autoantibody production, and immune complex formation may contribute to the development of SLE in different mouse strains.[2]

There are some advantages (Table 3) of using human stem cells transplanted into mice as an animal model. Cells with cellular defects in SLE humans can provide a SLE model that is more similar to humans, as they are derived from SLE patients and can mimic the complexity of human SLE.[6,11] Transplanted cells from the patients can be used as a method of studying the pathogenesis of SLE and testing new therapies, and the interactions between human immune cells and other cells in the body, such as the kidney that are difficult to replicate in pristane-induced models, can be studied through this method.[11] However, the use of transplanted human SLE cells also has some limitations, such as difficulties in establishing and characterizing models, cell variability among patients, and the cost and ethical considerations associated with using human cells in animal models.

Considering the advantages and disadvantages of both models, it is important to consider the synergy between them. SLE is a complex autoimmune disorder characterized by a multifaceted pathogenesis, which includes an elaborate immune response, autoantibody production and tissue damage. Humanized mouse models of lupus offer a unique opportunity to study disease mechanisms in a more human-like context. This allows researchers to explore the interaction of genetic and environmental factors that contribute to the development of SLE. By contrast, pristane-induced lupus models, which mimic the disease through chemical triggers, provide insights into the immune dysregulation and autoantibody production that are central to SLE pathology. By combining these models, we can attain a deeper understanding of SLE, bridging the gap between fundamental immunological processes and environmental influences. This integrative approach not only improves our understanding of SLE pathophysiology, but also offers a promising path to evaluate potential therapeutic strategies from a more comprehensive point of view.

CONCLUSION

Pristane-induced lupus mice offers simplicity, reproducibility, and a predictable time course for studying lupus-like symptoms and autoimmune responses. However, they lack genetic predisposition, relevance to human SLE triggers, and comprehensive organ involvement. On the other hand, humanized mice models with engrafted human immune cells provides a more human-relevant context, complex disease manifestations, and opportunities for drug testing and personalized medicine. Nevertheless, technical challenges, heterogeneity, species differences, and ethical concerns limit their applicability. Choosing between these models depends on the research goals, aspects of the disease being studied, and available resources, while a combination of models can offer a more comprehensive understanding of SLE.

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