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REVIEW ARTICLE

Pristane-induced lupus: considerations on this experimental model

Eduarda Correa Freitas[1] · **Mayara Souza de Oliveira**[1] · **Odirlei André Monticielo**[1]

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Abstract Systemic lupus erythematosus (SLE) is a multifactorial, autoimmune inflammatory disease with pleomorphic clinical manifestations involving different organs and tissues. The etiology of this disease has been associated with a dysfunctional response of B and T lymphocytes against environmental stimuli in individuals genetically susceptible to SLE, which determines an immune response against different autoantigens and, consequently, tissue damage. The study of different murine models has provided a better understanding of these autoimmune phenomena. This review primarily focuses on that has been learned from the pristane-induced lupus (PIL) model and how this model can be used to supplement recent advances in understanding the pathogenesis of SLE. We also consider both current and future therapies for this disease. The PubMed, SciELO, and Embase databases were searched for relevant articles published from 1950 to 2016. PIL has been shown to be a useful tool for understanding the multiple mechanisms involved in systemic autoimmunity. In addition, it can be considered an efficient model to evaluate the environmental contributions and interferon signatures present in patients with SLE.

Keywords Animal model · Lupus · Pristane · Pristane-induced lupus · Systemic lupus erythematosus

✉ Odirlei André Monticielo
omonticielo@yahoo.com.br

[1] Laboratory of Autoimmune Diseases, Division of Rheumatology, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2350, room 645, Porto Alegre 90035-003, Brazil

Introduction

Systemic lupus erythematosus (SLE) is characterized by multisystem inflammation and the loss of tolerance of T and B lymphocytes to host antigens. The etiology of SLE is still poorly known and is considered multifactorial, involving genetic, hormonal, and environmental aspects. Patients with this disease have various clinical symptoms including renal disease, non-erosive arthritis, serositis, hematological and respiratory manifestations, as well as the production of antinuclear antibodies (ANA). The genetic profile and clinical and laboratory changes of SLE can be studied in experimental models. Animal models of SLE induced in healthy mouse strains by exposure to hydrocarbon oils, such as pristane, have facilitated research into this disease by providing insight into the role of environmental factors that may predispose to SLE [1–3]. Furthermore, they allow study of the initial events that lead to a break in tolerance in the absence of genetic defects, and provide a better understanding of the cellular mechanisms involved in SLE development and progression. In this review, we will discuss what has been learned from the pristane-induced lupus (PIL) model and how this model can be used to supplement recent advances in understanding the pathogenesis of SLE.

Materials and methods

The PubMed, SciELO, and Embase databases were searched for articles published from 1950 to 2016, using the following terms and combinations thereof: "pristane-induced lupus," "tetramethylpentadecane-induced lupus," "pristane-treated mice," "murine lupus," and "hydrocarbon oil pristane." Articles in Portuguese, Spanish, and English were included in this review.

Pristane

Numerous chemicals and drugs have been identified as capable of triggering the production of autoantibodies or inducing a syndrome similar to SLE [4, 5]. However, none of them reproduce completely the spectrum of autoantibodies observed in human SLE. Drugs such as procainamide, hydralazine, quinidine, chlorpromazine, methyldopa, and isoniazid, which act on gene expression, induce a highly restricted and directed response against chromatin antigens (ssDNA, histones) [5, 6]. Pristane, acting differently from the above, is capable of inducing in mice a wide range of autoantibodies specific to or associated with SLE [7–10].

Pristane, also known as hydrocarbon oil (2,6,10,14-tetramethylpentadecane, TMPD), is an isoprenoid alkane. In nature, this oil can be found in small amounts in vegetables [11], in the liver of some sharks [12], and as a byproduct of petroleum distillation [11]. Mice administered pristane into the abdominal cavity develop an ascitic fluid enriched with monoclonal antibodies, local chronic inflammation (lipogranulomas), and a rheumatoid-like erosive arthritis [13], as well as autoantibodies and clinical manifestations similar to those of SLE [7, 14].

The mechanisms by which pristane induces a breakdown in tolerance and intracellular targets become antigenic remain to be defined. Pristane is a membrane-activating compound that interacts with the phospholipid bilayer. It has a cytotoxic effect dependent on concentration and cell lineage, although the mechanism of this cytotoxicity also remains unknown [15]. Apoptosis may explain how autoantigens become available to the immune system [16]. One study demonstrated that pristane induces programmed cell death both in lymphoid cell lines and in peritoneal exudate cells of mice in vitro and in vivo. This suggests that pristane-induced apoptosis provides a sufficient autoantigen substrate for immune tolerance to be broken, causing an immune disorder linked to overproduction of interferon alpha and beta (IFN-α and β), which consequently leads to the development of an autoimmunity similar to SLE [17].

Cytokine production

The production of inflammatory cytokines plays an important role in PIL. IFN-α, β and γ, interleukin-6 (IL-6), and interleukin-12 (IL-12) stimulate the formation of autoantibodies in this model. Animals deficient in the production of these cytokines are not able to produce autoantibodies [18, 19]. In the mouse PIL model, IFN-γ deficiency has been shown to have a protective effect on renal disease and production of autoantibodies [20]. The role of IFN will be described in more detail in the next sections, due to its importance in this model. BALB/c IL-$6^{-/-}$ mice do not produce anti-ssDNA, anti-dsDNA, or anti-chromatin antibodies, but continue to produce anti-RNP/Sm and anti-Su (Fig. 1). In the same study, production of anti-dsDNA antibodies in BALB/c IL-$6^{+/+}$ occurred 5 months after intraperitoneal injection of pristane, well after the onset of nephritis, suggesting that this antibody is not responsible for the induction of renal disease. These results suggest that induction of anti-DNA and anti-chromatin antibodies in mice treated with pristane is strictly dependent on IL-6, whereas the induction of anti-RNP/Sm and anti-Su autoantibodies is not [21]. Anti-RNP/Sm antibodies are associated with IL-12 production. IL-$12^{-/-}$ mice exposed to PIL do not develop anti-RNP antibodies or nephritis [22]. In conjunction with interleukin-18 (IL-18), IL-12 promotes differentiation of naive T cells into Th1 cells. IL-12 is produced primarily by antigen-presenting cells (APCs), such as macrophages and dendritic cells. These mice have a relative defect, but are not entirely devoid of Th1 responses [23]. In the absence of IL-12, IFN production can be induced by IL-18 signaling [24], although this process is believed to require the presence of other cytokines, such as interleukin-2 (IL-2) [25]. These studies demonstrate that the production of autoantibodies can be induced by different cytokine pathways that contribute to pathogenesis.

The role of interferon in pristane-induced lupus

IFN is an antiviral cytokine that plays an important role in SLE. Interferon type I (IFN-I) is composed of IFN-α and β subunits, which bind to the same receptor (IFNAR). Through microarray and quantitative PCR techniques in peripheral blood, it was observed that two-thirds of adults and nearly all children with SLE exhibit overexpression of IFN-I and interferon-stimulated genes (ISGs) [26–28]. Also known as "IFN signature," this phenomenon is closely associated with disease activity, lupus nephritis, and autoantibody production [28–31].

Pristane-treated mice exhibit a robust IFN signature [32]. The ectopic lymphoid tissue formed in PIL increases the expression of ISGs [33]. In IFNAR$^{-/-}$ mice, anti-DNA, anti-

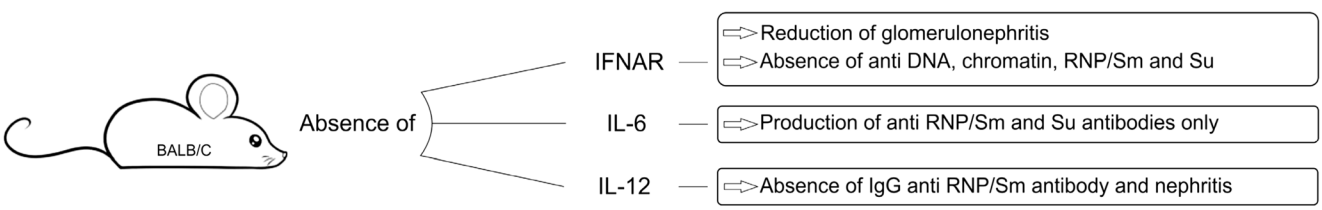

Fig. 1 Cytokines that can modify the production of autoantibodies and clinical expression in pristane-induced lupus

chromatin, anti-RNP, anti-Sm, and anti-Su antibodies are not produced and glomerulonephritis is definitely reduced, demonstrating that IFN-I plays an important role in the pathogenesis of PIL [18, 34]. Although autoantibody production develops around the third or fourth month after induction with pristane, IFN-I production is already detectable as early as 2 weeks after induction [35].

Dendritic cells are the main source of IFN-I production in healthy individuals and in patients with SLE, although their role may be limited in the PIL model [36]. In PIL, Ly6C^{hi} monocytes are the cell type responsible for IFN-I production. In response to intraperitoneal injection of pristane, these cells accumulate in the inflamed peritoneum, where they are triggered to synthesize IFN. Normally absent in the peritoneum, these cells are attracted through CCL2, and represent about 30% of the peritoneal exudate 2 weeks after pristane injection, suggesting that monocytes play an important role in the interferonopathy observed in the PIL model [37].

The mechanism for IFN-I overproduction in SLE cells is known to utilize various innate receptors in response to pathogen-associated molecules [38]. The toll-like receptors 7 (TLR7), 8 (TLR8), and 9 (TLR9) have received considerable attention because of their ability to recognize endogenous nucleic acids [39–41]. TLR7 and TLR9 are expressed intracellularly in dendritic cells, macrophages, and B cells [42, 43], within an endosomal compartment, and trigger IFN-I secretion via the myeloid differentiating factor 88 (MyD88) protein signaling pathway. Indeed, experiments with TLR knockout mice have revealed that production of IFN-I in PIL occurs via the TLR7-MyD88 pathway [44]. There is no production of anti-RNP, anti-Sm, and anti-Su antibodies or accumulation of Ly6C^{hi} monocytes and development of glomerulonephritis in TLR7$^{-/-}$ mice [45]. The Ly6C^{hi} monocytes of the peritoneal cavity express high levels of TLR7 and are considered the main source of IFN-I production. TLR8 is not associated with IFN-I production in humans or in mice, possibly because dendritic cells and B cells do not express this receptor [46].

The activation mechanism of TLR7 in the PIL model is still undefined. As the chemical structure of pristane is different from that of TLR7 ligands, this compound cannot directly activate the receptor [44]. It is possible that pristane increases the effects of TLR7 ligands, such as the endogenous U1 RNA Sm and RNP antigen. Furthermore, when incorporated into the cell membrane, pristane can modify the endosomal site, providing access to TLR7 [47]. However, neither TLR7 localization nor phagocytosis is altered by pristane [44]. Pristane also lacks the ability to increase TLR7 expression.

In SLE, an increase in apoptotic and necrotic cells is believed to result in the formation of immunocomplexes (ICs) formed by autoantibodies and autoantigens containing DNA and RNA [48]. In vitro, the Fcγ receptors (FcγR) of dendritic cells have been shown to mediate transport of DNA- or RNA-containing ICs into endosomes, allowing the activation of TLR7, TLR8, and TLR9 by these internalized endogenous nucleic acids [49, 50]. Thus, the production of autoantibodies against autoantigens containing RNA (U1 snRNP) is a prerequisite for the production of IFN-I. However, in the PIL model, IFN-I production precedes the appearance of anti-dsDNA, anti-RNP, or anti-Sm autoantibodies. FcγR$^{-/-}$ animals are able to produce autoantibodies and IFN, thus excluding the role of ICs in initial IFN generation [44, 51].

TLR9$^{-/-}$ BALB/c mice injected intraperitoneally with pristane develop more severe autoimmunity than do their TLR-sufficient cohorts. Early indications include an increased accumulation of TLR7-expressing Ly6C^{hi} inflammatory monocytes at the site of injection, upregulation of ISGs expression in the peritoneal cavity, and an increased production of myeloid lineage precursors (common myeloid progenitors and granulocyte myeloid precursors) in the bone marrow. These mice also develop higher autoantibody titers against RNA, neutrophil cytoplasmic antigens, and myeloperoxidase than do pristane-injected wild-type (WT) BALB/c mice, as well as a marked increase in glomerular IgG deposition and infiltrating granulocytes, much more severe glomerulonephritis, and a reduced lifespan. The BALB/c pristane model recapitulates other TLR7-driven spontaneous models of SLE and is negatively regulated by TLR9 [52].

However, recent research has also suggested that opsonization of dead cells by C3 and IgM in PIL is involved in the pathogenesis of the IFN signature. The data imply that complement receptor-mediated phagocytosis of dead cells opsonized by natural IgM and complement generates IFN-I and other proinflammatory cytokines in PIL. Like C3-deficient mice, C4-deficient lupus patients do not exhibit an IFN signature. This novel pathway, which likely involves the early classical complement cascade, is essential for the IFN signature in PIL and also appears to be relevant in human SLE [53]. Pristane-primed macrophages from C3-deficient mice did not exhibit impaired cytokine production. In contrast, C1q-deficient pristane-primed resident peritoneal macrophages secreted significantly less CCL3, CCL2, CXCL1, and IL-6 when stimulated in vitro with a TLR7 ligand. Furthermore, C1q$^{-/-}$ mice developed lower titers of circulating antibodies and milder arthritis compared with controls. These findings demonstrate that C1q deficiency impairs TLR7-dependent chemokine production by pristane-primed peritoneal macrophages and suggest that C1q, and not C3, is involved in the handling of pristane by phagocytic cells, which is required to trigger disease in this model [54].

Patients with SLE present decreased expression of an estrogen-regulated microRNA, miR-302d, in their monocytes. Its target is the interferon regulatory factor 9 (IRF9), a critical component of the transcriptional complex that regulates the expression of ISGs. Thus, with reduced miR-302d expression, IRF9 levels increase, as does the expression of ISGs. In the PIL model, transfection of miR-302d has a protective effect

against pristane-induced inflammation, suggesting that modulation of miR-302d levels may be protective in SLE. Thus, these findings classify miR-302d as a key regulator of IFN-I-directed gene expression, underscoring the importance of non-coding RNA in the regulation of the IFN pathway both in the PIL model and in patients [55].

In summary, the literature demonstrates that pristane may mimic human SLE by causing synergistic abnormalities in interferon production along with defective clearance of apoptotic cells and overactive B cell signaling. IFN production is essential for development of the disease. PIL may be a good model for studying dysregulation of this cytokine.

Lymphoid neogenesis and autoantibody production

The production of autoantibodies is a central event in the pathogenesis of SLE [56]. BALB/c, SJL/J, and C57BL/6 mice injected intraperitoneally with pristane develop SLE-specific autoantibodies, including anti-dsDNA, anti-ssDNA, anti-Sm, anti-RNP, and anti-ribosomal P [7, 14, 57, 58]. Antibody production after pristane injection was first described by Satoh et al. in 1995 [59]. Pristane also causes polyclonal hypergammaglobulinemia, which stimulates the production of cytokines. Both the production of antinuclear antibodies and hypergammaglobulinemia are characteristics of human SLE [11], as are the production of antibodies against type II collagen and the presence of rheumatoid factor [60].

In BALB/c mice, a single intraperitoneal injection of 0.5 ml pristane is able to stimulate the production of autoantibodies against the RNA component of U1 small nuclear ribonucleoproteins via TLR7-driven IFN-I production [61]. The increased TLR7 expression may contribute to B cell hyperactivity and autoantibody production in SLE [62]. PIL features an expanded population of B cells with a switched memory-like phenotype and hyperresponsiveness to synthetic TLR7 ligands and apoptotic cells, probably resulting from increased TLR7 expression due to IFN-I production [63]. Also, a build-up of dead cells in lupus tissues may help maintain high serum levels of anti-RNP/Sm autoantibodies [63]. Production of Su autoantigens persists in 50–90% of animals 4–6 months after injection, and production of anti-dsDNA for even longer, between 6 and 10 months [7, 14]. Titers of anti-Su and anti-snRNP/Sm are present in this model at levels as high as 1:25,000–1:250,000 (ELISA). This level of autoantibody production resembles that found in spontaneous autoimmune diseases [59].

Recently, a role for caspase-1 in murine lupus was described, indicating an involvement of inflammasomes in the development of SLE. Nlrp3^{-R258W} mice with PIL were observed to have higher mortality than WT mice following pristane injection. Furthermore, anti-dsDNA and total IgG levels were increased in the serum of Nlrp3^{-R258W} mice compared with those of WT mice. These data indicate that Nlrp3^{-R258W} mutant mice exhibited enhanced autoimmune responses after pristane treatment [64]. Severe glomerular renal damage, characterized by hypercellularity, mesangial expansion, crescent formation, and interstitial mononuclear cell infiltration, was also observed. In PIL, a lack of caspase-1 does not alter the recruitment of inflammatory cells into the peritoneal cavity or change the formation of lipogranulomas, which are considered a nidus of chronic inflammatory mediators for disease development [65]. In caspase-1$^{-/-}$ mice, anti-dsDNA and anti-RNP autoantibody production is attenuated, as is hypergammaglobulinemia. These mice mount intact immune responses, but do not develop an expanded marginal zone B cell population in response to pristane [66]. This may be one explanation for reduced autoantibody production in these mice [66]. Furthermore, levels of circulating inflammatory cytokines, such as IL-6 and IL-17, were lower in control and PIL caspase-1$^{-/-}$ mice, suggesting an overall reduced inflammatory phenotype [65].

Disease induction and production of autoantibodies in the PIL model are independent of exogenous organisms, such as viral, bacterial, and parasitic agents. Experiments with BALB/c mice free of exogenous organisms and treated with pristane showed chronic peritoneal inflammation with lipogranuloma formation, cytokine production, hepatosplenomegaly, and hypergammaglobulinemia similar to those observed in conventionally housed animals. This indicates that stimulation by exogenous agents is not necessary for this inflammatory process to occur [67]. Regarding the origin of the autoantibodies, the literature describes that BALB/c$^{nu/nu}$ (nude) mice [68] or mice deficient in T cell receptors (C57BL6 TcRβ$^{-/-}$, TcRô$^{-/-}$) [69] do not develop IgG or IgM anti-snRNP/Sm/Su autoantibodies after administration of pristane, but produce rheumatoid factor (IgM), which is independent of T lymphocytes [70]. This demonstrates that production of these antibodies occurs through a T cell-dependent immune response, similar to that observed in patients with SLE [68].

Lipogranulomas are inflammatory lesions resembling germinal centers that arise in response to the presence of pristane in the peritoneal cavity, and represent an example of lymphoid neogenesis [33]. This formation of ectopic lymphoid tissue at sites of inflammation [71] is associated with the production of autoantibodies [72]. Ectopic lymphoid tissue resembles secondary lymphoid tissue. It often exhibits B cell, T cell, and dendritic cell zones. The organization of this tissue occurs through the presence of CCL19, CCL21, CXCL12, and CXCL13 lymphoid chemokines. These lymphoid tissues form when the body cannot clear a pathogen, and are also common in autoimmune diseases [72]. Cytokines produced in ectopic lymphoid tissue may play an important role in the production of autoantibodies [33, 73]. Indeed, lipogranulomas exhibit proliferation and interaction of T and B cells [69], and may be a site of antibody production by B cells.

Clinical manifestations of pristane-induced autoimmune disease

Epidemiological studies suggest that occupational exposure to mineral oil or petroleum residue is associated with rheumatoid arthritis (RA) and SLE [74, 75]. Since the first description of PIL in mice, substantial progress has been made in characterizing the relevant immunobiological events. In addition to pristane, other compounds such as incomplete Freund's adjuvant (IFA) and squalene (2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexane) have been reported to induce lupus-related anti-nRNP/Sm and anti-Su autoantibodies in non-autoimmune BALB/c mice. Induction of these autoantibodies appeared to be associated with the hydrocarbon's ability to induce IL-12, IL-6, and TNF-alpha, suggesting a relationship with adjuvanticity. Thus, the potential of hydrocarbon oils to induce autoimmunity has implications for the use of oil adjuvants in basic research [76].

Animals subjected to intraperitoneal injection of pristane develop clinical manifestations such as arthritis [60], glomerulonephritis with immunoglobulin and complement deposition, pulmonary capillaritis, anemia, and autoantibody production (Fig. 2). Many of these manifestations are cytokine-driven. As in human SLE, they develop primarily in females, at an approximate female-to-male ratio of 9:1 [77].

Regarding arthritis, BALB/c mice developed synovial hyperplasia, periostitis, and marginal erosions reminiscent of RA [13, 60]. Arthritis in patients with lupus is generally not erosive, although erosions similar to those of RA may develop in some cases. The overlapping characteristics of both autoimmune diseases are known as *rhupus*. The nature of joint disease in animals suggests an arthritis similar to that found in this syndrome [11].

PIL is one of the few inducible models that can progress to glomerulonephritis. Glomerulonephritis is induced in about one-third of BALB/c mice following intraperitoneal administration of pristane, a frequency similar to that of nephritis in humans with SLE [78]. The inflammatory process in PIL nephritis is mediated by the interaction between ICs containing IgG and myeloid effector cells, monocytes/macrophages, with proteinuria beginning 4–6 months after pristane injection [14, 79, 80]. Mice deficient of IL-6 [21] and IL-12 [22] are highly resistant to induction of renal disease. Monocyte influx also appears to play an important role in the pathogenesis of lupus nephritis in humans and mice [81]. Several chemokines involved in recruitment of monocytes are products of IFN, for example, IFN-α and β induce CCL2. The decrease in glomerular cell production in response to immune complexes could modulate the severity of renal disease in IFN-α and β knockout mice.

Despite the important role of IFN-I in the development of several clinical manifestations of this model, the anemia present in PIL animals is TNF-α dependent and IFN-I independent. The bone marrow of animals administered pristane intraperitoneally exhibits high levels of TNF-α, an abnormality also present in patients with SLE [82].

Pristane administration to apolipoprotein E (apoE) knockout C57BL/6 mice led to the development of an experimental model of lupus with atherosclerosis. The animals presented had poor spirit, less activity, obvious hair loss, splenomegaly, and renomegaly. Also, levels of ANA, anti-dsDNA, and anti-Sm antibodies were significantly higher. The same study also evaluated expression of TLRs, and found that pristane induced abnormally high expression of TLR2 and TLR4 in the aorta and TLR2, TLR4, TLR7, and TLR9 in the kidney [83].

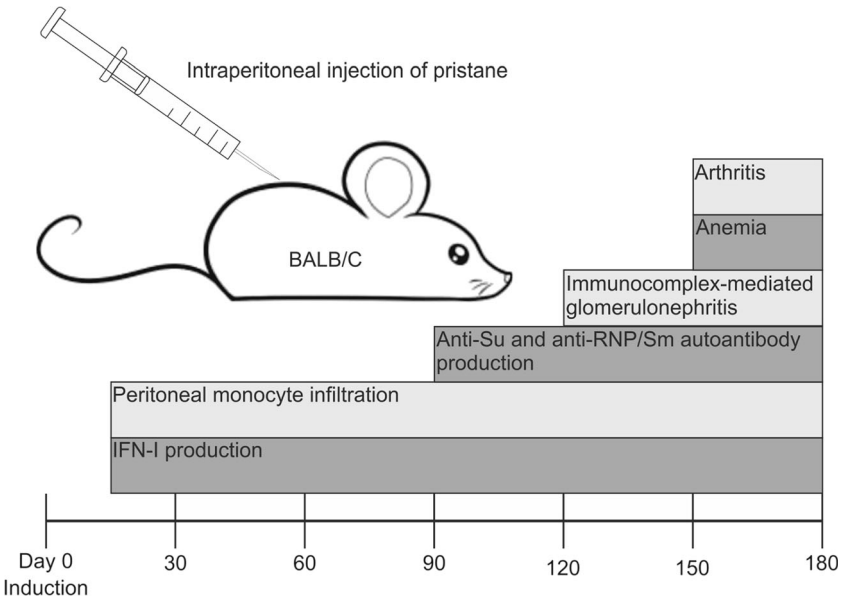

Fig. 2 Clinical manifestations in BALB/c over the trial period

Diffuse alveolar hemorrhage (DAH) is not present in the PIL model in BALB/c mice, but occurs, in a manner similar to that seen in human patients, when this model is developed in C57BL/6 and C57BL/10 mice. Although only 3% of SLE patients develop DAH, this is a significant problem associated with > 50% mortality, and its cause is unknown [84, 85]. In PIL, approximately half of animals die during the experiment [79, 86]. These animals develop pulmonary capillaritis with a perivascular infiltrate of macrophages, neutrophils, lymphocytes, and eosinophils and deposition of ICs, with moderate-to-severe alveolar inflammation [79, 86]. After intraperitoneal injection, pristane migrates to the lung, causing cell death, small-vessel vasculitis, and alveolar hemorrhage similar to that seen in DAH in humans. Anti-neutrophil cytoplasmic antibodies (ANCAs) are absent [79]. The recruitment of macrophages and neutrophils precedes hemorrhage, starting 3 days after pristane injection and peaking at 2 weeks [87]. Furthermore, DAH is independent of MyD88, TLR7, Fcγ receptor, Fas, and T cells, but immunoglobulin-deficient mice are resistant [87]. B cell-deficient animals do not develop DAH [87], possibly because of the lack of production of immunoglobulins or other B cell functions. DAH is also absent in $C3^{-/-}$ and $CD18^{-/-}$ mice [88]. Thus, DAH in PIL is mediated by IgM, C3, and CD18, a component of the C3b receptors CR3 and CR4 [88]. With regard to the underlying mechanism of DAH, pristane was also detected in the lungs of treated $C3^{-/-}$ mice, but not untreated $C3^{-/-}$ mice, indicating that C3 is not necessary for migration of pristane from the peritoneum to lung [88]. As noted earlier, peritoneal pristane injection also causes bone marrow inflammation [82], and pristane was detected in the bone marrow of PIL mice, but not in bone marrow of untreated mice, which suggests that the oil was widely dispersed following IP injection. Examination of lung tissue by the terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay revealed dead cells in pristane-treated mice but not in untreated controls. Dead cells also accumulate in the bone marrow of PIL mice [82], which suggests that pristane might be cytotoxic. Taken together, these data indicate that pristane migrates from the peritoneum to the lungs and other tissues, where it may cause death of certain cell types. Opsonization of these dead cells by IgM and C3 may promote pulmonary inflammation, as also seen in the peritoneum [53]. Lung interstitial macrophages and epithelial cells are anti-inflammatory and secrete IL-10. Although alveolar macrophages are normally anti-inflammatory, when activated via TLRs, IL-10R signal transduction is inhibited and they become proinflammatory [89, 90]. Thus, IL-10 is a crucial regulator of lung inflammation. $IL\text{-}10^{-/-}$ mice had significantly increased mortality from DAH. TLR-activated genes are targeted by IL-10 [91], and pristane induces proinflammatory cytokine production via TLR7 [44]. Unexpectedly, $MyD88^{-/-}$ and $TRIF^{-/-}$ mice developed DAH at a frequency similar to that of WT mice [88]. In summary, induction of DAH is independent of TLR, inflammasomes, and inducible nitric oxide; its mortality is increased in IL-10-deficient mice; and pristane treatment decreases IL-10 receptor expression in monocytes and STAT-3 phosphorylation in lung macrophages [88]. Similar to IFN production in PIL, ischemia-reperfusion injury in mice is mediated by the early classical complement cascade and natural IgM. Thus, the pathogenesis of DAH involves opsonization of dead cells by natural IgM and complement followed by complement receptor-mediated lung inflammation. The disease is macrophage-dependent, and IL-10 is protective. It follows that complement inhibition and/or macrophage-targeted therapies may reduce mortality in lupus-associated DAH.

Relevance of animal models to human SLE

Animal models are advantageous when they reproduce all or some clinical features of the disease in humans. Such models exist for SLE and have contributed significantly to our understanding of its pathogenesis.

SLE in animals may occur spontaneously or be induced. Induction of lupus in animals can be accomplished by a variety of methods, such as genetic manipulation (expression or suppression), autoimmune serum or lymphocyte-lymphocyte injection, dendritic cell vaccination with apoptotic debris, immunization with antigens such as protein complex DNA and RNA, or by hydrocarbons such as pristane [7, 20]. Unlike other autoimmune and inflammatory experimental models, PIL most closely resembles human SLE.

In BALB/c mice, PIL induces mild glomerulonephritis [14], arthritis [13, 60], and the production of several autoantibodies characteristic of SLE, including anti-dsDNA and anti-Sm [7]. However, in this model, animals are not genetically prone to developing the disease as are human patients with SLE. Thus, this model does not provide insight into the genetic abnormalities involved in SLE. Nevertheless, overproduction of IFN-I, which is a core feature of SLE pathogenesis, is present in this model. Moreover, PIL is useful for examining the role of environmental triggers involved in the disease [7, 14]. It is possible to assume that the model induction pathways may be relevant for SLE patients [92, 93]. In addition to BALB/c, almost all other strains of mice are susceptible to pristane induction to varying extents, with production of autoantibodies and other manifestations similar to those of human SLE [58], corroborating the importance of environmental factors in the pathophysiology of this disease.

Table 1 Major studies using the pristane-induced lupus model

Author (Reference)	Objective	Treatment	Summary	Main treatment effects
Zhou L et al. 2010 [98]	To investigate the effect of melatonin on environmental-related SLE	Melatonin	Female BALB/c mice (age 2 months) were divided into 6 groups (n = 10 animals per group): normal control, PIL, prednisone 5 mg/kg, melatonin 0.01 mg/kg, melatonin 0.1 mg/kg, and melatonin 1.0 mg/kg; daily intragastric treatment with onset after disease induction.	Delayed production of anti-ssDNA and histone IgM antibodies; Decreased IL-6 and IL-13; Increased IL-2; Greater kidney damage
Minhas U et al. 2012 [99]	To investigate the therapeutic effect of *Withania somnifera* pure root powder on pristane-induced lupus in BALB/c mice	*Withania somnifera*	Female BALB/c mice (age 3–4 months) were divided into 6 groups (n = 8 animals per group): normal control, PIL, indomethacin 3 mg/kg treatment, *Withania somnifera* 500 mg/kg, *Withania somnifera* 1000 mg/kg, or 2% gum acacia; daily oral treatment starting 1 month after disease induction.	Reduction of lipogranulomas; Reduction of IL-6 and TNF-α levels in serum and ascitic fluid; Inhibitory effect on proteinuria; Decreased nephritis; Decreased inflammatory markers
Wang Z et al. 2014 [101]	To evaluate the preventive effects of resveratrol on pristane-induced lupus	Resveratrol	Female BALB/c mice (age 2–3 months) were divided into 4 groups (n = 10 animals per group): normal control, PIL, resveratrol 50 mg/kg, and resveratrol 75 mg/kg; oral treatment in daily diet starting on day 2 after disease induction.	Inhibitory effect on proteinuria; Significant reduction in glomerular lesions; Decreased IgG and IgM deposition in the kidney
Li M et al. 2015 [102]	To investigate the potential therapeutic effect of A20 on renal inflammation in pristane-induced lupus	A20	Three months after pristane injection, female BALB/c mice (age 6–8 weeks) were randomized into 3 groups and injected with 1.0×10^9 plaque forming units (PFU) of adenovirus-A20, control adenovirus or PBS (100 μl, n = 6–8 per group) i.p.	Decreased proinflammatory cytokine production; Reduction in anti-dsDNA and anti-nRNP levels in serum; Inhibition of lupus-related renal injury
Bender A et al. 2016 [104]	To determine the therapeutic efficacy of Btk inhibition in two mouse lupus models driven by TLR7 activation and type I interferon	M7583 (Btk inhibitor)	Starting 2 months after pristane injection, female DBA/1 mice (age 11–12 weeks) were fed chow formulated with M7583 at a concentration of 25 mg compound/kg chow.	Reduction in clinical signs of arthritis; Reduction of anti-dsDNA, anti-histone, and anti-Ro/SSA, but not anti-Sm/RNP antibody levels
He Y et al. 2016 [106]	To investigate the potential therapeutic effect of MSL in SLE and explore the underlying mechanisms	Methyl salicylate 2-O-β-d-lactos-ide (MSL)	Female BALB/c mice (age 7–8 weeks), 45 days after PIL induction, were randomly divided into 5 groups: PIL, low-dose MSL (200 mg/kg), medium-dose MSL (400 mg/kg), high-dose MSL (800 mg/kg), or prednisone 5 mg/kg; doses were administered orally once daily.	Reduction in DNA autoantibody titers; Total IgG concentrations in lupus mice were significantly lower at months 4–6; Reduction in IL-6 levels on day 60 after induction; On day 180, IL-17A levels were not significantly reduced.
Lin Y et al. 2017 [107]	To investigate the effects of SAA in pristane-induced lupus in BALB/c mice	Salvianolic acid A (SAA)	60 female BALB/c mice were randomly divided into five equal groups: control, model, SAA, prednisone, or aspirin (n = 12 per group). Mice in the control and model groups were given saline each day by gavage, while mice in the SAA, prednisone and aspirin groups were administered SAA (5 mg/kg/d), prednisone (5 mg/kg/d) or aspirin	Reduction in anti-Sm autoantibody titers; Inhibition of IKK, IκB, and NFκB phosphorylation in renal tissue

Table 1 (continued)

Author (Reference)	Objective	Treatment	Summary	Main treatment effects
			(300 mg/kg/d) by gavage, respectively. Treatment began 1 month after pristane injection.	
Mihaylova N et al. 2017 [109]	To examine the possibility of suppressing autoreactive B and T cells with a monoclonal antibody against ANX A1 in murine pristane-induced lupus	Anti-ANX A1	Female BALB/c mice (age 8 weeks) were randomized into 3 groups (n = 10 each). Pristane-injected mice were immunized every 6 days with 200 ng/mouse of anti-ANX A1 antibody i.p., while the control group of pristane-injected animals was treated with PBS.	Decreased expression of T cell activation markers; Decreased number of anti-dsDNA IgG antibody-secreting plasma cells; Attenuated lupus symptoms in pristane-injected mice

Treatments in pristane-induced lupus

Animal models have been used not only to improve knowledge of the mechanisms involved in SLE, but also to test potential therapies. In addition to assessing possible therapeutic targets, animal models are indispensable before clinical trials. The following section summarizes the main therapeutic studies performed with the PIL model (Table 1). Most of these treatments are preventive.

Researchers tested the regulatory effect of melatonin at concentrations of 0.01, 0.1, and 1.0 mg/kg/daily for 6 months via intragastric administration. Melatonin slowed the increase in anti-ssDNA and histone IgM antibody levels, decreased IL-6 and IL-13, and increased IL-2 production in the splenocyte supernatant of pristane-treated mice. In addition, melatonin decreased the renal damage caused by pristane. These results suggest that melatonin has a beneficial effect on PIL through cytokine regulation [94].

In 2012, the therapeutic effect of the herb *Withania somnifera* in PIL was tested. Treatment with root powder at concentrations of 500 and 1000 mg/kg was administered orally once daily, starting 1 month after disease induction. Animals treated with the 1000 mg/kg concentration exhibited reduced lipogranuloma formation compared to the untreated disease group. Furthermore, treatment was associated with a reduction in IL-6 and TNF-α levels in both serum and ascitic fluid, and was shown to have a potent inhibitory effect on proteinuria, nephritis, and inflammatory markers. However, the production of autoantibodies in serum appeared to be unchanged in both groups treated with *W. somnifera*, demonstrating the same pattern of nuclear fluorescence [95].

Resveratrol (3,5,4-trihydroxystilbene) is a natural antimicrobial compound found in various plants and fruits [96]. It has anti-inflammatory and immunoregulatory properties and was recently tested in the PIL model. In this study, resveratrol was added to the animals' diet at concentrations of 50 and 75 mg/kg and administered for 7 months. The results obtained with resveratrol treatment included decreased proteinuria, immunoglobulin deposition in the kidney, glomerulonephritis, and serum levels of IgG1 and IgG2a treatment. At the end of the experiment period, IFN-α levels in mice in the resveratrol groups were lower than those of control mice, but the difference was not statistically significant. This suggests that resveratrol has protective effects in murine PIL and may represent a novel approach for the treatment of SLE [97].

Considering the development of new therapies for the control of systemic inflammation in patients with SLE, treatment with A20 has been proposed [98]. A20, also known as tumor necrosis factor alpha-induced protein 3 (TNFAIP3), is an anti-inflammatory factor induced by TNF [99]. A20 overexpression significantly mitigated pristane-induced systemic inflammation and renal injury in mice. The therapeutic effect of A20 may be associated with inhibition of the NLRP3 inflammasome and NFκB activation in macrophages. Because of this dual inhibitory effect, A20 may be a promising new candidate for the treatment of SLE [98].

Likewise, Bender et al. found that Bruton's tyrosine kinase (Btk) inhibition treats TLR7/IFN-driven murine lupus [100]. Btk is expressed in a variety of immune cells, and previous work has demonstrated that blocking this protein is a promising strategy for treating autoimmune diseases. In PIL, Btk inhibition suppressed arthritis, but neither autoantibodies nor the IFN gene signature was significantly affected, suggesting efficacy was mediated through inhibition of Fc receptors [100].

Methyl salicylate 2-O-β-d-lactoside (MSL) is a novel salicylic acid analogue, extracted from the traditional Chinese herbal medicine *Gaultheria yunnanensis* that has been widely used for treatment of swelling and various inflammatory responses in the southern regions of the People's Republic of China [101]. In PIL, MSL was found to antagonize the increasing levels of antibodies and cytokines, suppressing joint swelling, and having an inhibitory effect on arthritis-like symptoms. It also significantly decreased the

spleen index and expression of inflammatory markers, and protected the kidneys of PIL mice from injury by inhibiting expression of inflammatory cytokines and reducing IgG and C3 immunocomplex deposition [102].

Lin Y et al. demonstrated that treatment with salvianolic acid A (SAA), isolated from the dried roots of *Salvia miltiorrhiza* Bunge, alleviates renal injury in PIL. The NFκB pathway may be implicated. SAA treatment caused a significant reduction in the level of anti-Sm autoantibodies (including IgG and IgM) and reduced total IgG levels. SAA inhibited phosphorylation of IKK, IκB, and NFκB in renal tissues, possibly accounting for its renoprotective effects [103].

Studies have also suggested anti-annexin A1 (ANX A1) monoclonal antibodies as a potential therapy. Annexin A1 (ANX A1) is a member of the annexin superfamily which, in the presence of Ca^{2+}, binds acid phospholipids with high affinity [104]. The administration of anti-ANX A1 monoclonal antibody resulted in inhibition of T cell activation and proliferation, suppression of IgG anti-dsDNA antibody-secreting plasma cells and proteinuria, decreased disease activity, and prolonged survival compared to control animals [105].

Conclusion

SLE is a complex disease that involves several immune dysfunctions. Experimental models have provided useful insight into its etiology and pathogenesis. The PIL model in particular has shed light on the role of environmental factors that may predispose to development of SLE. In addition, this model is associated with excess production of IFN-I and expression of ISGs and, thus, may be a good tool for studying the dysregulation of this cytokine observed in SLE patients.

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Compliance with ethical standards

Disclosure None.

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