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Review article

The dual role of IL-2 in systemic lupus erythematosus: balancing pro-inflammatory and anti-inflammatory effects

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by chronic inflammation and immune dysregulation. Interleukin-2 (IL-2), a central cytokine in T-cell biology, plays a paradoxical role in SLE pathogenesis. On one hand, it promotes effector T cell and natural killer (NK) cell activity, thereby amplifying inflammation; on the other, it supports the expansion and function of regulatory T cells (Tregs), which are essential for maintaining immune tolerance. This dual functionality makes IL-2 a driver of autoimmunity and a potential immunotherapeutic target. This review outlines the molecular mechanisms underlying IL-2's pro- and anti-inflammatory roles in SLE, highlights the regulatory factors that shape its functional balance, such as receptor affinity, dosing, exposure duration, and the immune microenvironment, and discusses recent progress in low-dose IL-2therapy and engineered IL-2 variants. A comprehensive understanding of IL-2 signaling dynamics is essential for the designing development of precision therapies designed to restore immune homeostasis in SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by immune dysregulation, autoantibody production, and widespread inflammation [1–3]. Its pathogenesis involves a complex interplay among innate and adaptive immune cells—including T cells, B cells, and antigen-presenting cells—which culminates in tissue damage and diverse clinical manifestations such as lupus nephritis, arthritis, and cutaneous lesions [1,4].

Among the numerous cytokines implicated in SLE, interleukin-2 (IL-2) plays a central role due to its dual capacity to promote immune activation and maintain immune tolerance [5]. Traditionally recognized for its role in driving T-cell proliferation and effector function, IL-2 also plays a non-redundant role in the development, expansion, and stability of regulatory T cells (Tregs), which are essential for suppressing autoreactive immune responses [6–8].

This duality renders IL-2 a paradoxical but pivotal mediator in SLE pathophysiology—capable of both exacerbating inflammation and restraining autoimmunity. In this review, we examine the molecular and cellular mechanisms underlying IL-2's contrasting immunological roles in SLE, analyze the factors that influence its immunoregulatory balance, and highlight emerging therapeutic strategies that leverage IL-2 biology to restore immune homeostasis in lupus patients.

2. Biological functions of IL-2 in immune regulation

IL-2 is a 15.5-kDa cytokine predominantly secreted by activated $CD4^+$ T cells, although other immune cells, such as dendritic cells, may contribute under specific conditions [9–12]. IL-2 exerts its biological effects through a heterotrimeric receptor complex composed of IL-2Rα (CD25), IL-2Rβ (CD122), and the common gamma chain IL-2Rγ (CD132) [9,11]. Engagement of this receptor complex activates the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway, particularly STAT5, leading to transcriptional programs that regulate the fate and function (Fig. 1) [8,13]. The composition of its receptor determines the strength of IL-2 signaling; the high-affinity trimeric receptor (IL-2Rαβγ), expressed on Tregs and activated effector T cells, is especially responsive to low concentrations of IL-2 [5,14].

A key determinant of IL-2 activity lies in the expression pattern of IL-2 receptor subunits across immune populations. Tregs constitutively express the trimeric high-affinity IL-2 receptor (CD25/IL-2Rα, CD122/IL-2Rβ, CD132/γc), allowing them to respond vigorously to even subphysiological concentrations of IL-2 [15,16]. In contrast, conventional $CD4^+$ and $CD8^+$ effector T cells (Teffs) and natural killer (NK) cells

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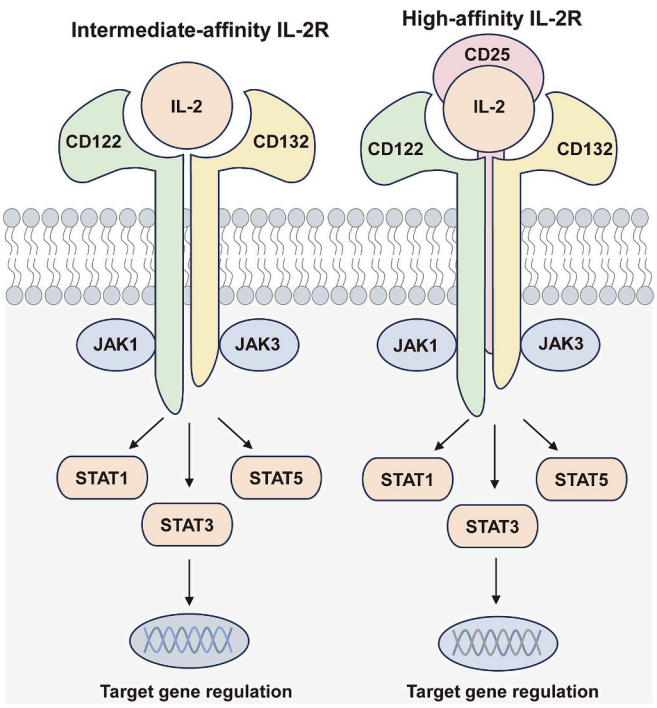

Fig. 1. Major signaling pathways of intermediate- and high-affinity IL-2 receptors. The intermediate-affinity IL-2R comprises the β-chain (CD122) and the common cytokine receptor γ-chain (γc; CD132), and the high-affinity IL-2R contains the α-chain (CD25), β-chain and γc. Both receptors activate JAK1 and JAK3 kinases, leading to phosphorylation of STAT1, STAT3, and STAT5 transcription factors. The strength of IL-2 signaling is determined by the composition of its receptor. IL-2, interleukin-2; IL-2R, interleukin-2 receptor; JAK, janus kinase; STAT, signal transducer amd actovator of transcription.

generally lack IL-2Rα and predominantly rely on the intermediate-affinity βγ dimer for signaling, which requires higher cytokine availability for activation [17]. This differential receptor expression underpins the dose-dependent selectivity of IL-2 therapies.

In the immune system, IL-2 exerts a context-dependent dual role (Table 1). On one hand, it promotes the proliferation and differentiation of $CD4^+$ and $CD8^+$ effector T cells, as well as the activation of NK cells, thereby enhancing both adaptive and innate immune responses [11,14,18,19]. On the other hand, IL-2 is essential for the survival, expansion, and suppressive function of Tregs, which constitutively express high levels of CD25 [18,20]. These cells play a crucial role in maintaining peripheral immune tolerance by suppressing autoreactive T cells and mitigating inflammatory responses.

This intrinsic duality positions IL-2 as a master regulator of immune homeostasis, with its effects finely tuned by the cytokine milieu, receptor expression profiles, and the concentration and duration of IL-2 exposure.

Table 1
Comparative effects of IL-2 on immune subsets.

Cell type	IL-2R composition	Sensitivity to IL-2	Functional outcome (low dose)	Functional outcome (high dose)
Treg	$CD25^+βγ$	High	Proliferation, tolerance	Stable
$CD4^+$ Teff	βγ	Moderate	Minimal	IFN-γ/IL-17↑
$CD8^+$ Teff	βγ	Moderate	Mild activation	Cytotoxicity↑
NK	βγ	Moderate	NK maintenance	IFN-γ↑

IL-2, interleukin-2; Treg, regulatory T; Teff, effector T; NK, natural killer; IL-2R, interleukin-2 receptor; IFN-γ, interferon-gamma; IL-17, interleukin-17.

3. Pro-inflammatory role of IL-2 in SLE

In SLE, dysregulated immune activation underlies chronic systemic inflammation and organ damage [21]. IL-2 contributes to this pathological process by supporting effector immune responses that exacerbate autoimmunity. IL-2 promotes the proliferation and activation of autoreactive $CD4^+$ T cells [22,23], which in turn facilitate B-cell differentiation and autoantibody production—central features of SLE immunopathology. Additionally, IL-2 enhances the cytotoxic capacity of $CD8^+$ T cells [24–26], further contributing to tissue injury in affected organs such as the kidneys and skin.

Beyond the adaptive immune compartment, IL-2 also acts on innate lymphocytes, particularly NK cells [27–30]. By increasing their proliferation and stimulating the production of pro-inflammatory cytokines such as interferon-γ (IFN-γ), IL-2 amplifies innate inflammatory cascades in target tissues, including the renal parenchyma in lupus nephritis [31–33]. This is supported by studies demonstrating elevated IL-2 expression in renal biopsies and inflamed tissues from patients with active disease.

However, the role of IL-2 in SLE is context-dependent and not uniformly pro-inflammatory. Despite evidence of elevated IL-2 expression in certain tissue compartments during active disease, many patients exhibit reduced systemic IL-2 production, likely due to impaired $CD4^+$ T cell transcriptional programs [4,34–36]. Such deficiency is associated with diminished Tregs function and unchecked immune activation, further complicating the interpretation of IL-2 levels across disease stages and compartments [7,37–39]. These observations underscore the complexity of IL-2's role in SLE pathogenesis, where it may both exacerbate inflammation and reflect a compensatory failure in immune regulation.

4. Anti-inflammatory role of IL-2 in SLE

In contrast to its role in promoting effector immune responses, IL-2 also exerts critical anti-inflammatory effects in SLE by supporting the function and stability of Tregs [7,40]. These cells, characterized by high expression of CD25 and the transcription factor Forkhead box P3 (FoxP3), are essential for maintaining immune tolerance and preventing autoimmunity [9,41,42]. In SLE, Treg numbers are often reduced and their suppressive function impaired, a defect that contributes to unchecked autoreactive T and B cell responses [43,44].

IL-2 plays a non-redundant role in restoring Treg homeostasis. Due to their constitutive expression of the high-affinity IL-2 receptor (IL-2Rαβγ), Tregs are exquisitely sensitive to low concentrations of IL-2. Even sub-physiologic levels of IL-2 are sufficient to promote Treg proliferation, enhance FoxP3 expression, and preserve their suppressive phenotype [42,45]. Through this mechanism, IL-2 facilitates the re-establishment of peripheral tolerance by attenuating autoreactive lymphocyte activity and dampening chronic inflammation.

Clinical studies have confirmed the therapeutic relevance of this mechanism (Table 2). Low-dose IL-2 (LD-IL-2) therapy has demonstrated efficacy in restoring Treg numbers and function in patients with active SLE [46–49]. In multiple clinical trials, LD-IL-2 treatment was associated with increased circulating Treg frequencies, reductions in disease activity scores such as the SLE Disease Activity Index (SLEDAI), and decreased serum levels of pro-inflammatory cytokines and autoantibodies [48,50]. These findings highlight IL-2's capacity to rebalance the immune system by preferentially expanding Tregs without activating pathogenic effector cells, making it a promising therapeutic strategy for SLE and other autoimmune conditions characterized by Treg deficiency [18,51].

5. Balancing pro- and anti-inflammatory effects of IL-2

At the molecular level, IL-2 engages its receptor in a stepwise fashion. Initial binding to IL-2Rα (CD25) stabilizes the cytokine and

Table 2
Key clinical trials using Low-dose IL-2 in SLE and other AIDs.

Disease	Study design	Groups	IL-2 administration	Endpoint	Clinical response	Immunological response	Safety	Reference
SLE	An open-label, phase I and IIa clinical trial. (ICTRP-DRKS00004858)	IL-2 group (n = 12)	4 cycles of low-dose IL-2 daily for 5 days followed by a 9–16 day rest.	Primary endpoints: safety and the number of patients who achieved at least a 100 % increase in the proportion of CD25hi-expressing cells among circulating $CD3^+CD4^+FOXP3^+CD127lo$ regulatory T cells at day 62. Secondary points: disease activity as measured by SLEDAI and BILAG score. Disease flares as measured by the SLEDAI flare index, auto-antibody and complement concentrations at day 62.	SLEDAI↓, SLEDAI flare index↑	Treg↑; $CD4^+$ Tconv↑; $CD8^+$ T↑; NK↑	IL-2 was safe and well tolerated; AEs: most were transient and mild to moderate. The most common was injection-site reaction and no serious AEs.	[83]
SLE	A randomized, double-blind, placebo-controlled study. (NCT02465580 and NCT02932137)	IL-2 group (n = 30); Placebo group (n = 30)	3 cycles of 1 million IU subcutaneous IL-2 every other day for 2 weeks and followed by a 2-week break	Primary endpoint: the SRI-4 at week 12. Secondary endpoints: other clinical responses, safety and dynamics of immune cell subsets.	SRI-4 response rate↑; SLEDAI↓; C3↑; C4↑	Treg↑; NK↑	AEs: the most common were injection-site reactions, including injection-site pain, redness and swelling. No serious AEs were observed.	[49]
SLE	A multicentre, double-blind, randomized and placebo-controlled phase II trial. (NCT02955615)	ILT-101 group (n = 50); Placebo group (n = 50)	1.5 million IU/day subcutaneous IL-2 for 5 days followed by weekly injections for 12 weeks	Primary endpoint: the SRI-4 response. Secondary endpoints: relative and absolute changes of SLEDAI.	SRI-4 response rate↑; SLEDAI↓	Treg↑; Treg/Tcon↑	ILT-101 was well tolerated and there was no generation of antidrug antibodies.	[84]
SLE	An open-label, phase II, clinical trial. (NCT03312335)	IL-2 group (n = 12)	4 cycles of 5 daily injections of 1.5 million IU over a time period of 68 days (9 weeks)	Primary endpoint: an increase in percentage of Treg cells of total $CD4^+$ T cells. Secondary endpoints: immune cell subsets, cytokines and disease activity.	SLEDAI ↓; BILAG↓; Physician's Global Assessment scores↓; anti-dsDNA↓; C3↑	Treg↑; NK↑; $CD4^+$ Tconv↑; $CD8^+$ T↑	AEs were generally mild and transient, with injection site reactions, flu-like symptoms, and arthralgia reported most frequently.	[51]
SLE	An Open-label, monocentric trial. (ChiCTR-IPR-16009451)	IL-2 plus rapamycin (n = 50)	1 million IL-2 IU subcutaneous 3-5d/month, and oral rapamycin 0.5 mg once every other day	Primary endpoint: SLEDAI. Secondary endpoints: lymphocyte subsets, and $CD4^+$ T subgroup.	SLEDAI↓; The prednisone dosage↓	Treg↑; Th17 ↓; Th17/Treg↓	Not available.	[71]
AIDs	An open-label, uncontrolled phase I-IIa clinical basket trial in 11 AIDs consisting of 46 patients. (NCT01988506)	SLE (n = 6); RA (n = 4); ankylosing spondylitis (n = 10); psoriasis (n = 5); Behcet's disease (n = 2); granulomatosis with polyangiitis (n = 1); Takayasu's disease (n = 1); Crohn's disease (n = 7); ulcerative colitis (n = 4); autoimmune hepatitis (n = 2); sclerosing cholangitis (n = 4)	1 million IU/day subcutaneous IL-2 for 5 days followed by fortnightly injections for 6 months.	Primary endpoint: percentages of Tregs. Secondary endpoints: safety, number of relapse and inflammation marker.	Improvements in most of the diseases.	Treg↑; Treg/Teff↑	IL2 was well tolerated whatever the disease and the concomitant treatments.	[89]
RA	A randomized, double-blind, placebo-	IL-2 plus methotrexate (n = 23); placebo	3 cycles of 1 million IU subcutaneous	Primary endpoints: the proportion of patients achieving ACR20 response and DAS28	The rate of ACR20/50 /70	Treg↑; Treg/Th17↑	IL2 was well-tolerated. AEs: no serious	[85]

(*continued on next page*)

Table 2 (*continued*)

Disease	Study design	Groups	IL-2 administration	Endpoint	Clinical response	Immunological response	Safety	Reference
	controlled trial. (NCT 02467504)	plus methotrexate (n = 24)	infections every other day for 2 weeks and followed by a 2-week break	remission, the change in the CDAI and SDAI at week 24. Secondary points: other clinical responses and safety.	response↑; the DSA28-ESR↓		AEs. There were transient fever and injection-site reactions, but no intervention was needed to resolve these events.	
RA	A randomized controlled trial. (ChiCTR-INR-16009546)	IL-2 group (n = 26); IL-2 plus tocilizumab (n = 9); Control group (n = 15)	0.5 million IU/day subcutaneous IL-2 and/or 8 mg/kg tocilizumab (maximum dose: 800 mg)	Primary endpoint: DAS-28. Secondary points: lymphocyte subsets.	DSA28-ESR↓; tender joint count↓tender joint count↓	CD4+ T↑; Treg↑ ; Th17↑; Th17/Treg↓	No obvious adverse reactions. Slight increase in ALT and BUN levels was observed, but they were all within the normal range and had no special clinical significance.	[86]
RA	A randomized controlled trial. (ChiCTR-INR-16009546)	IL-2 group (n = 26); Non-IL2 group (n = 15)	0.5 million IU/day subcutaneous IL-2 for five consecutive days	Primary endpoint: DAS-28. Secondary points: high-sensitivity CRP and ESR.	DSA28-ESR↓; swollen joint count↓; tender joint count↓	CD4+ T↑; Treg↑ ; Th17↑; Th17/Treg↓	Mild injection-site reactions but no other side effects were observed.	[87]
SS	A randomized, double-blind, placebo-controlled phase II trial. (NCT02464319)	IL-2 group (n = 30); Placebo group (n = 30)	3 cycles of 1 million IU subcutaneously every other day for 2 weeks and followed by a 2-week break	Primary endpoint: Improvement on ESSDAI by week 24. Secondary points: other clinical responses, safety, and changes of immune cell subsets.	ESSDAI↓; VAS↓; ESSPRI↓	Treg↑; Treg/Teff↑	IL2 was well-tolerated. AEs: no serious AEs.	[88]
SSc	A multicentre, open-label phase I and phase IIa study. (NCT01988506)	IL-2 group (n = 9)	1 million IU /day subcutaneously from day 1 to day 5 (induction period), and then every 2 weeks from day 15 to month 6 (maintenance period)	Primary endpoint: the change of Tregs. Secondary endpoints: other immune subsets.	stable measurement in mRSS and Valentini scores	CD4+ T↑; Treg↑; NK↑; Treg/Teff↑	IL-2 was well tolerated. AEs: no serious AEs.	[93]

IL-2, interleukin-2; AIDs, autoimmune diseases; SLE, systemic lupus erythematosus; IU, International Unit; SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index; BLAG, British Isles Lupus Assessment Group; Treg, regulatory T; T con, conventional T; NK, natural killer; AEs, adverse events; SRI-4, SLE Responder Index-4; C3, complement 3; C4, complement 4; anti-dsDNA, anti-double-stranded DNA; Th, helper T; Teff, effector T; RA, rheumatoid arthritis; ACR20/50/70, the American College of Rheumatology for 20 %/50 %/70 % improvement; DAS28-ESR, erythrocyte sedimentation rate formula; CDAI, clinical disease activity index; SDAI, simplified disease activity index; ESSDAI, the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index; VAS, visual analogue scales; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; mRSS, modified Rodnan skin score.

concentrates it at the cell surface, followed by recruitment of IL-2Rβ and γc, which together form the signaling-competent high-affinity complex [52]. Cells that lack CD25, such as resting Teffs and NK cells, depend solely on the βγ dimer, resulting in markedly lower binding affinity [53,54]. These differences in binding mode and receptor architecture shape the context in which IL-2 exerts either tolerogenic or pro-inflammatory effects.

The dual functionality of IL-2 as both a pro-inflammatory and anti-inflammatory mediator in SLE underscores its complex role in immune regulation [55]. Whether IL-2 promotes immune activation or tolerance in the context of SLE is determined by a dynamic interplay of factors, including cytokine concentration, receptor affinity, exposure duration, the surrounding immune microenvironment, and the phenotypic composition of target immune cells.

Low concentrations of IL-2 preferentially engage the high-affinity IL-2 receptor complex ($CD25^{+}\beta\gamma$), expressed on Tregs, supporting their survival and function [56,57]. In contrast, higher concentrations of IL-2 are more likely to activate conventional effector T cells and NK cells via intermediate-affinity IL-2 receptors (βγ), leading to increased cytokine production and inflammation [58]. The temporal dynamics of IL-2 exposure further modulate these outcomes; sustained low-dose IL-2 favors Treg stability, while transient or excessive IL-2 may potentiate effector responses [55].

This immunological balance is frequently disrupted in SLE. Reduced IL-2 production, altered IL-2 receptor expression, and pro-inflammatory cytokine milieus contribute to skewed IL-2 signaling [23], resulting in inadequate Treg support and heightened effector cell activity [38]. These disturbances promote disease flares, tissue injury, and loss of tolerance.

Understanding the mechanisms that regulate the bifunctional nature of IL-2 is essential for developing precision immunotherapies aimed at restoring immunological equilibrium in SLE [38]. Modulating IL-2 signaling in a context- and cell-specific manner holds considerable promise for attenuating pathogenic inflammation while re-establishing

immune tolerance.

6. Factors influencing IL-2's functional balance and therapeutic optimization

The immunomodulatory outcome of IL-2 signaling in SLE is governed by a confluence of dose, timing, receptor expression, cellular context, and immune microenvironment (Fig. 2). At low concentrations, IL-2 selectively activates Tregs via the high-affinity IL-2Rαβγ complex, promoting immune tolerance [59,60]. In contrast, higher doses are required to activate Teffs and NK cells through intermediate-affinity IL-2Rβγ, resulting in pro-inflammatory responses [45,58,61]. This dose-dependent dichotomy is particularly relevant in SLE, where overall IL-2 production is often diminished due to $CD4^+$ T cell dysfunction, contributing to Treg insufficiency. Conversely, transient spikes in IL-2—such as during disease flares—can activate autoreactive Teffs and exacerbate inflammation. Downstream signaling through IL-2Rβγ subunits also exhibits cell–type–specific consequences. In both Tregs and Teffs, engagement of β- and γ-chain activates JAK1/JAK3, leading to the phosphorylation of STAT5 [62,63]. However, the transcriptional programs diverge: in Tregs, persistent STAT5 activation upregulates FoxP3 and stabilizes suppressive function, whereas in effector T cells and NK cells, βγ-mediated signaling drives proliferation, cytotoxicity, and production of pro-inflammatory cytokines such as IFN-γ and tumor necrosis factor (TNF) [64–66]. These differential outcomes highlight why IL-2 must be carefully dosed and engineered to favor tolerance without provoking pathogenic inflammation in SLE.

Beyond dose, the duration of IL-2 exposure is also critical. Sustained low-level IL-2 supports Treg stability and FoxP3 expression, whereas intermittent or high-intensity exposure favors the activation of inflammatory effector cells [67]. The surrounding immune milieu further shapes IL-2's action: elevated IL-6, TNF, or IL-17 levels in lupus lesions sensitize Teffs and NK cells to IL-2, while immunoregulatory cytokines such as TGF-β promote Treg expansion [68]. Additionally, imbalances in IL-2 receptor expression—such as reduced CD25 on Tregs or increased CD122 on Teffs—can skew IL-2 responsiveness, enhancing inflammation at the expense of regulation [69].

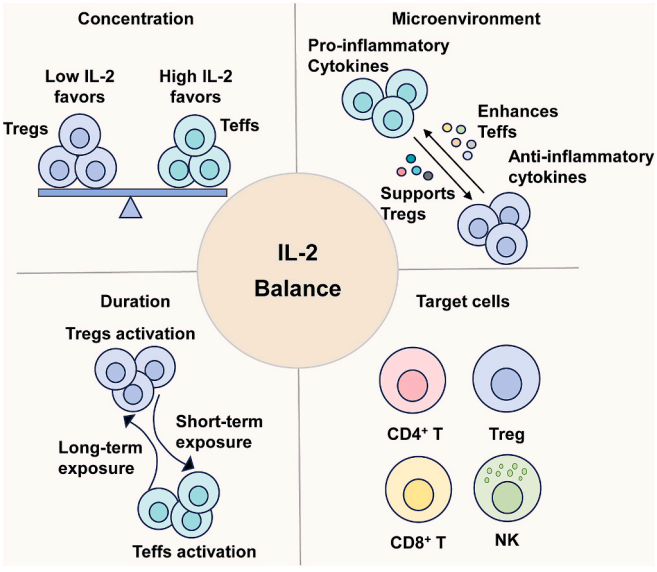

Fig. 2. Factors influencing IL-2's functional balance. Low IL-2 concentration preferentially promotes the survival and function of Tregs, while high IL-2 levels favor the activation of Teffs. The immune microenvironment influences IL-2 activity, with pro-inflammatory cytokines enhancing Teffs and anti-inflammatory cytokines promoting Tregs. In addition, the duration of IL-2 exposure determines its effects: sustained low-level exposure favors Treg activation, while short-term or high-dose exposure drives Teff activation. Target cells of IL-2 include $CD4^+$ T cells (Tregs), $CD8^+$ T cells, and NK cells, highlighting its dual role in balancing immune responses. IL-2, interleukin-2; NK, natural killer; Treg, regulatory T; Teff, effector T.

These mechanistic insights inform therapeutic approaches aimed at restoring the balance of IL-2. LD-IL-2 therapy has emerged as a promising strategy that selectively expands Tregs without stimulating pathogenic Teffs or NK cells [40,70]. Clinical trials have shown that LD-IL-2 enhances Treg numbers, reduces disease activity (e.g., SLEDAI), and lowers autoantibody titers [47].

Personalized IL-2-based immunotherapy is an emerging goal. Factors such as genetic polymorphisms in IL-2/IL-2R genes, Treg/Teff ratios, disease stage, and cytokine profiles may all influence treatment efficacy [71–73]. Biomarkers such as CD25 expression, serum IL-2 levels, or transcriptional signatures of Treg function are being explored to guide patient selection and dosage refinement [74,75]. Adjunctive strategies, such as combining IL-2 with cytokine inhibitors (e.g., IL-6 or TNF blockade) or standard immunosuppressants like belimumab and hydroxychloroquine, may further enhance therapeutic outcomes [3,76]. The therapeutic landscape has been broadened by the development of engineered IL-2 variants with altered receptor affinities [77]. Recombinant wild-type IL-2 can bind both αβγ and βγ complexes, thereby expanding Tregs at low concentrations but also stimulating effector subsets at higher doses [78–80]. In contrast, IL-2 muteins and partial agonists have been designed to preferentially engage CD25 while reducing affinity for IL-2Rβ, thereby enhancing Treg selectivity and minimizing the activation of autoreactive Teffs and NK cells. These receptor-biased modifications exemplify rational strategies to harness IL-2's immunoregulatory capacity in autoimmunity [14,77,81].

7. Clinical potential and ongoing challenges

Humrich et al. first reported the case of a 36-year-old patient with SLE who received four treatment cycles each with human IL-2 recombinant (aldesleukin), each with 1.5 or 3.0 million IU subcutaneous injections daily for five days. The regimen was effective in both improving clinical manifestations and increasing $CD25^+$ $Foxp3^+$ Treg cells [82]. Clinical evidence for IL-2–based therapies in SLE and related autoimmune diseases derives from both open-label trials and rigorously conducted randomized controlled studies (Table 2). An open-label study found that LD-IL-2 therapy is safe and well tolerated (four cycles of low-dose aldesleukin daily for 5 days followed by a 9–16 day rest.) and selectively promotes the expansion of functional regulatory T cells in patients with moderate-to-severe systemic lupus erythematosus [83]. These exploratory studies provided critical proof-of-concept and safety data. Increasing placebo-controlled trials have validated these findings, showing statistically significant improvements in composite endpoints such as SLE Responder Index-4 (SRI-4) response and SLEDAI. Differentiating between these trial designs underscores the progressive maturation of IL-2 research from exploratory to confirmatory evidence. A double-blind, placebo-controlled clinical trial was conducted with 3 cycles of IL-2 (1 million IU) or placebo subcutaneously injection every other day for 2 weeks (seven injections), followed by a 2-week break, as one treatment cycle of 4 weeks [49]. Patients were evaluated at screening, every 2 weeks to week 12, and every 4 weeks thereafter to week 24. The primary endpoint was the SRI-4 at week 12, and the secondary endpoints were other clinical responses, safety, and dynamics of immune cell subsets. The study reported better response in SRI-4 between two groups (IL-2, 55.17 % vs. placebo, 30.00 %, $p = 0.052$). The endpoint was not met, however, in week 24, participants were found to have a significant difference (IL-2, 65.52 % vs. placebo, 36.67 %; $p = 0.027$). The most common adverse events (AEs) were injection-site reactions, manifested as injection-site pain, redness, and swelling in the IL-2 group, but no serious AEs were observed. In immunological parameters, IL-2 upregulated Treg and NK cells. Another multicentre phase II trial demonstrated the efficacy and safety of low-dose IL-2 in SLE therapy [84]. The experimental group was injected with 1.5 million IU/day

subcutaneous IL-2 for 5 days, followed by weekly injections for 12 weeks. This trial evaluated the safety, clinical efficacy, and biological responses of ILT-101 (aldesleukin) in patients with moderately to severely active SLE. The SRI-4 response rate is 68 % in the ILT-101 group, while 59 % in the placebo ($p = 0.3439$), and ILT-101 was well tolerated with no generation of antidrug antibodies. Due to placebo patients of 2 sites having a 100 % SRI-4 response, the endpoint was not met. However, a post hoc per-protocol analysis on a prespecified population that excluded patients from these two sites showed a statistically significant difference for the SRI-4 response rate (ILT-101, 83.3 % vs. placebo, 51.7 %; $p = 0.0168$), and was accompanied by differences in several secondary exploratory end points. These findings provide strong support for IL-2 treatment for SLE.

Additionally, therapeutic strategies with IL-2 have expanded beyond monotherapy. LD- IL-2 therapy has demonstrated consistent efficacy in normalizing Treg/Teff ratios and lowering disease activity in SLE, rheumatoid arthritis [85–87], and Sjögren's syndrome [88]. A basket trial enrolled 11 varied autoimmune diseases including SLE and RA [89]. Patients all received LD-IL2 (1 million IU/day) for 5 days, followed by fortnightly injections for 6 months, evaluated by deep immunomonitoring and clinical evaluation. The results showed that dose of IL-2 and treatment scheme used selectively activate and expand Tregs and are safe across different diseases and concomitant treatments with good tolerance. In combination settings, IL-2 plus rapamycin has been shown to restore the Th17/Treg balance in refractory SLE in a synergistic manner and lowered glucocorticoid dosage [71]. Meanwhile, IL-2 combined with tocilizumab or rituximab is being investigated to enhance immunomodulation and potentially prolong remission [86,90]. These approaches reflect a growing recognition that IL-2 may serve as a backbone therapy, adaptable to different pathogenic pathways by rational combinations with existing biologics or immunosuppressants.

The dual role of IL-2 in SLE presents a unique therapeutic opportunity. LD-IL-2 and IL-2–based biologics offer the potential to correct immune dysregulation by re-establishing the balance between effector activation and immune suppression (Fig. 3). However, several challenges remain [9]. These include optimizing dosing regimens, managing interpatient variability in IL-2 responsiveness, and ensuring long-term safety—particularly the risk of inadvertently stimulating autoreactive effector cells [47]. Moreover, the heterogeneity of SLE pathogenesis across tissues and disease stages necessitates individualized treatment strategies informed by immunological profiling.

Even though low-dose IL-2 expands Tregs, its frequent short half-life in human serum (5–7 min) leads to the requirement of frequent injections. Thus, engineered IL-2 muteins are entering clinical translation [91]. These receptor-biased variants are designed to preferentially engage CD25 on Tregs while minimizing IL-2Rβγ binding, thereby reducing off-target stimulation of effector T cells and NK cells via a prolonged half-life in vivo [55]. Many studies have demonstrated that IL-2 muteins have better effects in animals than normal IL-2, but there is a lack of confirmed clinical evidence in humans [91]. Fanton et al. reported NKTR-358, a polyethylene glycol-interleukin-2 conjugate composition, which can extend the half-life of IL-2. Their Early-phase trial had shown promising immunoselectivity and durable Treg expansion with fewer adverse events [92]. These advances indicate that next-generation IL-2 therapeutics may overcome some of the limitations of conventional low-dose IL-2, providing safer and more precise options for long-term disease control.

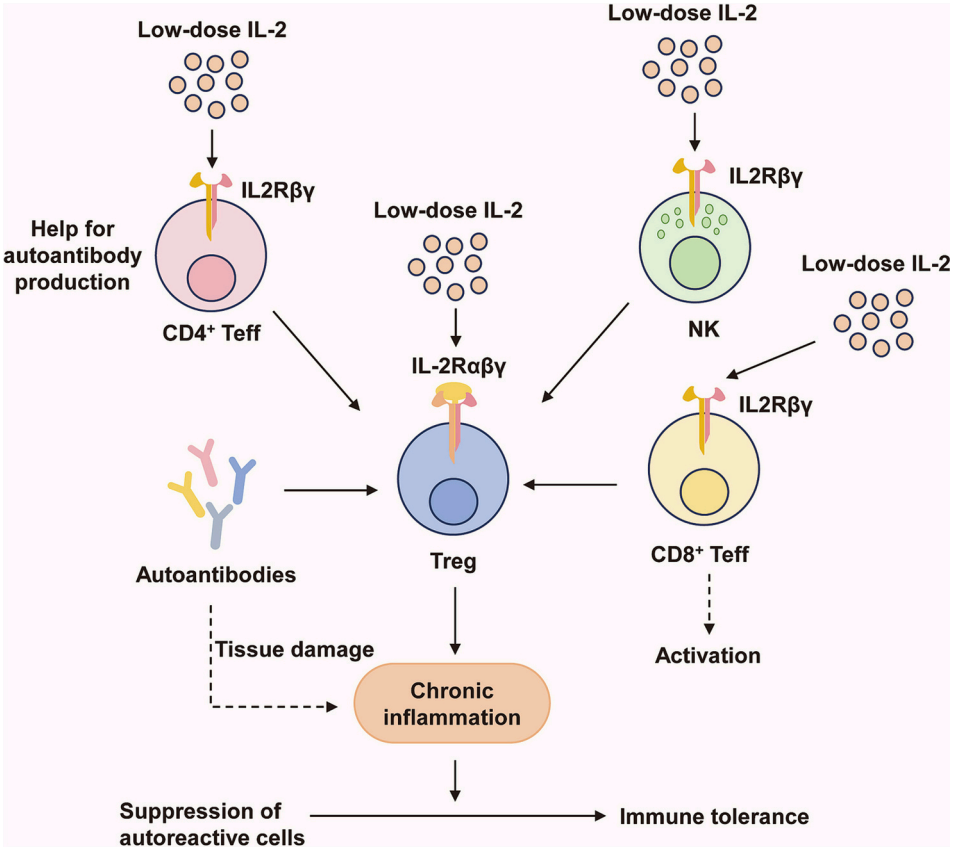

Fig. 3. Immunomodulatory effects of low-dose IL-2 therapy in autoimmune diseases. Low-dose IL-2 signals through different IL-2 receptor complexes: IL-2Rβγ on $CD4^+$, $CD8^+$ Teffs and NK cells promotes their activation, autoantibody production, and tissue damage, while IL-2Rαβγ on Tregs enhances immune tolerance by suppressing autoreactive cells. The dynamic balance between pro-inflammatory pathways (chronic inflammation, autoantibody generation) and regulatory mechanisms (Treg-mediated suppression) ultimately shapes disease outcomes in autoimmune conditions. IL-2, interleuin-2; IL-2R, interleukin-2 receptor; NK, natural killer; Treg, regulatory T; Teff, effector T.

8. Conclusion and future directions

Interleukin-2 occupies a central, context-dependent position in SLE immunopathology, capable of driving inflammation or restoring tolerance depending on how it is delivered and to which cell populations it is directed. Precision targeting of IL-2 signaling—through low-dose administration, receptor-selective biologics, and biomarker-guided personalization—represents a promising path forward in the treatment of SLE. Future research should focus on refining Treg-selective IL-2 analogs, elucidating the influence of the immune microenvironment on IL-2 responses, and developing rational combination regimens. As these strategies mature, IL-2-based therapies may offer transformative, mechanism-driven interventions to achieve long-term immune remission in patients with SLE.

CRediT authorship contribution statement

Hao Li: Writing – review & editing, Writing – original draft, Visualization. **Xiang Lin:** Writing – review & editing. **Jing He:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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