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Unlocking therapeutic potential: Targeting lymphocyte activation Gene-3 (LAG-3) with fibrinogen-like protein 1 (FGL1) in systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) represents an autoimmune disorder that affects multiple systems. In the treatment of this condition, the focus primarily revolves around inflammation suppression and immunosuppression. Consequently, targeted therapy has emerged as a prevailing approach. Currently, the quest for highly sensitive and specifically effective targets has gained significant momentum in the context of SLE treatment. Lymphocyte activation gene-3 (LAG-3) stands out as a crucial inhibitory receptor that binds to pMHC-II, thereby effectively dampening autoimmune responses. Fibrinogen-like protein 1 (FGL1) serves as the principal immunosuppressive ligand for LAG-3, and their combined action demonstrates a potent immunosuppressive effect. This intricate mechanism paves the way for potential SLE treatment by targeting LAG-3 with FGL1. This work provides a comprehensive summary of LAG-3's role in the pathogenesis of SLE and elucidates the feasibility of leveraging FGL1 as a therapeutic approach for SLE management. It introduces a novel therapeutic target and opens up new avenues of therapeutic consideration in the clinical context of SLE treatment.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder of unknown etiology, characterized by abnormal activation and proliferation of lymphocytes [1]. Recent research has highlighted the multifaceted factors contributing to SLE incidence, encompassing infection, immunity, genetics, and more [2–4]. A prevailing perspective posits that the dysregulation of regulatory T cells (Tregs) and effector T cells (Teffs) disrupts the delicate immune balance, precipitating autoimmune phenomena [5–7].

For many years, the pursuit of targeting specific lymphocyte surface molecules has been a central focus in SLE treatment [8–10]. Within the realm of autoimmunity, lymphocyte activation gene-3 (LAG-3), akin to PD-1, has garnered substantial scholarly attention. LAG-3, an inhibitory co-receptor, serves as a safeguard against autoimmunity and excessive immune responses [11–13]. As a type I transmembrane protein, LAG-3 holds promise as a potential therapeutic target. Studies have demonstrated its capacity to effectively alleviate autoimmune symptoms in murine models of autoimmune diseases and its synergistic potential with PD-1 in mitigating autoimmunity [14,15]. Additionally, Ching-Tai Huang et al. have identified significant upregulation of LAG-3 in Tregs, where it curtails T-cell proliferation [16].

Fibrinogen-like-protein 1 (FGL1), as the principal immunosuppressive ligand of LAG-3, binds stably to p-major histocompatibility complex class II (MHC II), exerting a restraining influence on T cells and immune responses. Building on this unique property, we propose an innovative approach by harnessing FGL1 in conjunction with the emerging checkpoint LAG-3 to function as an "immune brake" through immune checkpoint targeting. This manuscript elucidates the potential of targeting FGL1/LAG3 as the next frontier in immune checkpoint therapy for SLE treatment. Finally, comprehensive coverage is provided regarding biosafety and immunotherapeutic considerations arising from targeted therapy.

2. Structure and biological function of LAG-3

In 1990, Triebel et al. have conducted a cDNA library screening and successfully identified LAG-3 [17–19], a type I transmembrane protein sharing structural similarities with CD4 and playing a crucial role in immune checkpoint regulation. LAG-3's selective expression has been

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observed in three distinct DNA clones [11].

In recent years, a growing body of research has illuminated the dynamic alterations in LAG-3 Treg populations across various autoimmune diseases [16,20,21,22]. It is noteworthy that these changes not only bear relevance to disease pathogenesis but also exhibit close ties to treatment responses in autoimmune inflammatory conditions [23–25]. The development of LAG-3 Tregs as a novel therapeutic approach for managing autoimmune diseases is currently underway, with animal models being designed for this purpose. Such endeavors hold promise in restoring equilibrium to immune-inflammatory responses and regulating associated immune response states [26–28].

The LAG-3 transmembrane protein comprises 525 mature proteins with a molecular weight of approximately 50 kDa. Within this structure, the D1 region serves as a ligand-binding LG-variable domain, capable of selective and stable binding to MHC II. This selective recognition of T cells is a result of this interaction, rendering LAG-3 preferentially inhibitory [29]. Ligand binding occurs within the extracellular domains, designated as D1, D2, D3, and D4. While D1 is distinct, the internal structures of D2, D3, and D4 exhibit homology. Notably, several studies have suggested that LAG-3's functionality extends beyond MHC II binding, as it also transmits information through its cytoplasmic domains, thereby conveying inhibitory signals [29]. However, the specific characteristics of these signals remain an area of ongoing investigation.

LAG-3 is situated on human chromosome 12, and studies by Maruhashi T et al. have substantiated its stable expression on the surface of both Tregs and Teffs, implicating its pivotal role in T lymphocyte regulation and associated signaling pathways [11,15,30,31]. Upon stimulation by external antigens, LAG-3 maintains a heightened level of expression on the surface of $CD4^+$ and $CD8^+$ lymphocytes. Consequently, this heightened expression correlates with the inhibition of cytokine release, cytolytic activity, and cell proliferation potential [32,33]. Notably, Takumi Maruhashi et al. have observed that LAG-3 is induced on the surface of CD4 and CD8 cells upon antigen stimulation but not on the surface of naïve T cells [11]. Furthermore, the inhibitory function of LAG-3 is closely associated with its surface expression level on T cells, underscoring the potential for therapeutic intervention in human diseases linked to T cells by modulating LAG-3 expression levels [32,34].

Tregs hold a pivotal role in maintaining immune homeostasis by curbing autoimmunity and minimizing cellular and tissue self-destruction. LAG-3, an integral member of the immunoglobulin superfamily, has been demonstrated to modulate T lymphocyte activity. Its fundamental structural components comprise the transmembrane region, the extracellular domain extending beyond the cell surface, and the region containing four Ig-like structural domains, encompassing a total of 498 amino acids [35,20]. Notably, it's worth mentioning that LAG-3 shares 4 % of its amino acids with the extracellular domain of CD20 [36,37].

Furthermore, the interaction between galectin-3 and liver sinusoidal endothelial cell lectins with lactose moieties on LAG-3's surface leads to extensive glycosylation of LAG-3. This glycosylation pattern is associated with the presence of multiple N-glycosylation sites on its surface [38–40]. As a transmembrane protein closely homologous to CD4, LAG-3 possesses the ability to translocate from the cell membrane, facilitated by the metalloproteinases ADAM10/17. This translocation is instrumental in its regulatory function of immunosuppression [41]. The cytoplasmic tail of LAG-3, which primarily mediates the intracellular transmission of negative signals, encompasses three conserved motifs known for their intracellular inhibitory capabilities: a phosphorylated serine residue (S484), a KIEELE motif, and a glutamate-proline dipeptide repeat motif (EP motif) [42–45]. These three motifs can interact with LAG-3-associated proteins, effectively countering the activation pathway of CD3-TCR.

Dr. Ching-Tai Huang and colleagues have conducted an analysis of purified CD4 cells using a microarray chip and initiated minimum threshold PCR amplification of effector/memory T cells utilizing LAG-3 primers. Remarkably, their findings indicate that LAG-3 expression can revert from a heightened level to baseline levels in approximately 20 days [3]. Surprisingly, during the same timeframe, LAG-3 expression on Tregs escalates to 50 times the baseline level and remains elevated for a period of 4 weeks. Concurrently, their *in vitro* experiments have provided compelling evidence that LAG-3 is the pivotal molecule enabling Tregs to achieve maximal activity. Moreover, it emerges as an indispensable molecule for inducing Treg activity *in vivo* [3,46].

3. Mechanism and implications of LAG-3 in SLE

The pathogenesis of SLE is exceedingly intricate, often attributed to factors like infection and environmental elements that lead to cellular damage. This, in turn, triggers the activation of autoimmune responses involving T cells and B cells [47–50]. Whether manifested through the release of cytokines, complement activation, or antibody production, these processes contribute to damage in multiple organs. Consequently, a critical challenge lies in treating SLE by curbing the inflammatory responses of the immune system and mitigating organ damage [51–54].

Recent investigations have unveiled the role of epigenetics and transcriptomics in recognizing the stability of Tregs in the peripheral blood serum of SLE patients. These studies have affirmed the notable plasticity of Tregs under specific conditions, capable of influencing the onset and intensity of inflammatory responses [55]. Building on this foundation, Clemens Scheinecker et al. have underscored the deficiency of Treg expression in autoimmune diseases like SLE. In 2022, Dr. Andreas Mackensen's team has pioneered the use of chimeric antigen receptor (CAR) T cells for expansion in SLE patients, successfully curtailing abnormal B cell proliferation and achieving clinical remission in three severely active SLE patients [56,57]. Collectively, these findings firmly establish the modification and targeted therapy of T cells and T cell surface molecules as an effective and promising approach to alleviate disease activity in SLE patients [58,59].

In recent years, LAG-3 has emerged as a prominent co-receptor and is poised to become a preferred inhibitory drug target alongside PD-1. Immune cells are subject to immune surveillance at multiple checkpoints to prevent excessive autoimmunity or unwarranted immune reactions, and LAG-3 serves as a pivotal checkpoint in modulating immune responses in autotissues [11] (Fig. 1). Unlike the traditional immunosuppressive checkpoint PD-1, the absence of LAG-3 itself does not trigger autoimmune responses in non-autoimmune mouse models. However, in experimental autoimmune model mice, LAG-3 has been shown to alleviate autoimmune symptoms, suggesting the potential for treating autoimmune diseases by targeting T cells expressing LAG-3. Reports also indicate that the specific agonist (e.g., IMP761) can induce the inhibitory function of LAG-3 *in vivo or in vitro* [11]. Numerous clinical trials have been conducted to substantiate the effectiveness of targeted LAG-3 treatment. Building on these foundations, our aim is to elucidate the mechanism of LAG-3 in the context of the immune disease SLE and explore the feasibility of treating SLE by targeting this specific molecule.

Kubra Yuksel and colleagues have conducted an assessment of immune checkpoint proteins within the plasma of juvenile SLE patients. Their findings reveal a significant correlation between the activity of SLE (measured by SLEDAI) and the presence of immune checkpoint proteins, including LAG-3 [60]. In the realm of autoimmune diseases, other researchers have corroborated these findings by demonstrating that mice lacking LAG-3 develop fatal autoimmune myocarditis [2,61]. Ana C. Anderson and her team propose that the co-suppressor receptor LAG-3 has emerged as an effective target for chronic autoimmune diseases, owing to its pivotal role in T cell regulation [21]. Consequently, the identification and exploration of pertinent regulatory proteins represent vital endeavors that advance the development of therapeutic strategies.

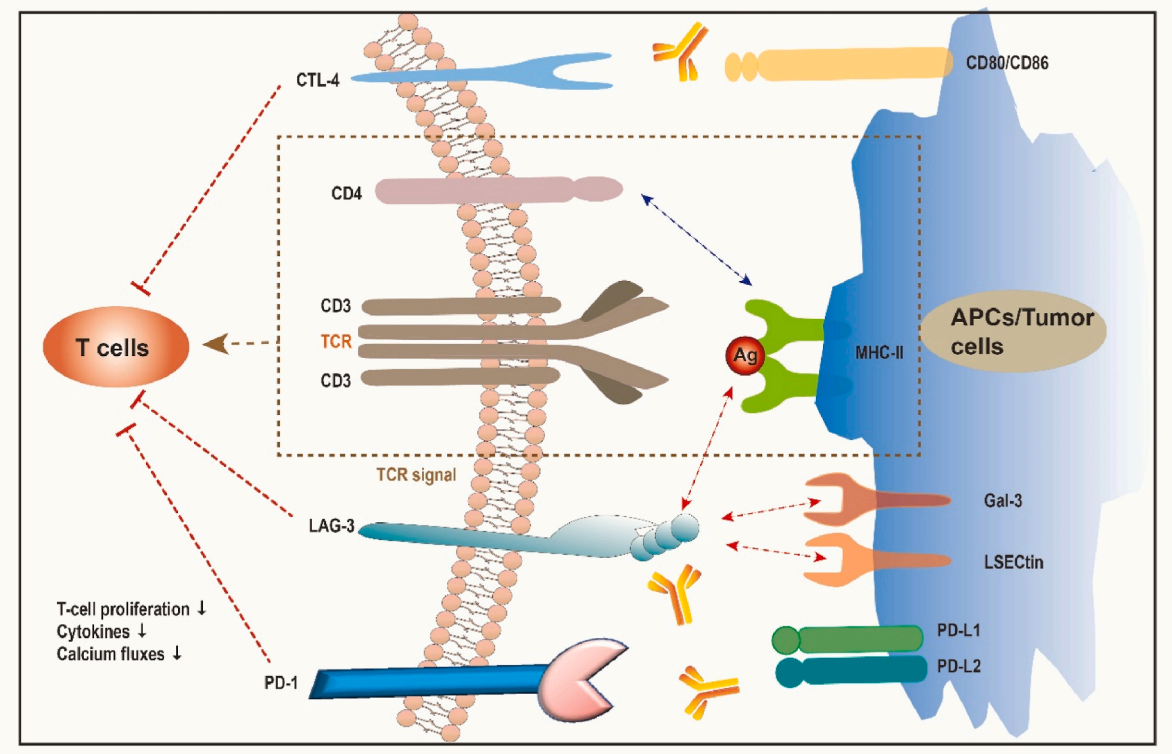

Fig. 1. The function and mechanism of LAG-3 in autoimmune diseases.

4. FGL1 is the main immunosuppressive ligand of LAG-3

FGL1, also known as liver fibrinogen associated Gene-1 (LFIRE-1)/heparin (HPS) or hepatocellular derived fibrinogen associated protein-1 (HFREP-1), is a liver-derived protein associated with liver secretion, proliferation, and metabolism [62–64]. It has gained prominence as an emerging checkpoint ligand for LAG-3, playing a significant role in immune checkpoint regulation [62,65,66].

FGL1 has surpassed classical ligands like MHC II and has become a hot topic in research [62]. In humans, FGL1 is situated on chromosome 8 and consists of homologous dimers comprising beta and gamma subunits, which can be detected in plasma during acute reactions [67]. In 2019, Dr. J Wang and colleagues have identified FGL1 as a novel high-affinity ligand for LAG-3. Dr. Katharina Aigner Radakovics' team has used a fluorescent human T-cell reporting system to report FGL1 as an additional binding partner alongside identified LAG-3 ligands such as MHC II [68]. Most fundamental studies have also demonstrated a high-affinity interaction between FGL1 and LAG-3 [4,36,69].

Wan Ting Zhang and colleagues have developed and validated immunoassays based on nanoantibodies to accurately assess FGL1 expression levels. Nanoantibodies offer high affinity, solubility, and stability, enabling the determination of the active state of the FGL1-LAG-3 pathway with increased reliability and accuracy [69]. In addition, Dr. Somaya A Abdel Rahman's team has conducted a high-throughput TR-FRET screening experiment based on the LAG-3/FGL1 interaction this year. They have introduced a time-resolved fluorescence resonance energy transfer (TR-FRET) assay method, which provides insights into small molecule targeted drugs targeting the LAG-3/FGL1 pathway, potentially benefiting a broader range of patients undergoing immune checkpoint blockade therapy [70].

Certain scholars contend that the classical immunosuppressive pathway PD-1/PD-L1 can effectively regulate T cells, thereby mitigating autoimmune diseases [71]. Recent research has unveiled that FGL1 is not only intricately linked to cell proliferation and metabolism but also serves as an emerging focal point for intervening in the inhibition of LAG-3 T cells [2,69]. The FGL1/LAG-3 pathway constitutes an independent immune suppression pathway, and reports indicate that when the inhibitory receptor LAG-3 on T cell surfaces interacts with its ligand FGL1, the blockade of T cell activation and inhibition of inflammatory factor secretion are notably more pronounced [72].

Wen-Wei Lin and colleagues have administered FGL1 protein intraperitoneally to mice with induced arthritis, monitoring tissue levels of inflammatory cytokines. Their findings not only affirm the potential use of FGL1 protein in regulating immune homeostasis but also highlight its promise as a treatment modality for future autoimmune or inflammatory diseases predominantly driven by T cells [73]. *In vivo,* experiments involving FGL1's role in restraining T cell activity and proliferation primarily rely on gene ablation and monoclonal antibody blocking. Dr. Wang's team has further suggested that FGL1 holds promise as a novel anti-inflammatory agent [73].

In light of the above reports and perspectives, it becomes evident that FGL1, as the linchpin in the LAG-3/FGL1 pathway, can be detected with high sensitivity and accurately quantified, a critical facet in advancing our understanding and potential interventions in this context.

5. LAG-3 can serve as a novel biomarker for SLE disease activity

Currently, the biomarkers used to predict the activity of SLE still lack sufficient sensitivity and specificity. This deficiency often results in sudden onset, rapid disease progression, poor prognosis, and the potential involvement of multiple organ systems in many clinical patients. Complications such as lupus crisis, severe lupus encephalopathy, and lupus-related thrombocytopenia are particularly common in this context [74–77]. Hence, the discovery and application of novel biomarkers represent a crucial endeavor to enhance the clinical prognosis of SLE patients [78].

The utilization of CD4-like molecule LAG-3 as a predictor of autoimmune disease activity has been substantiated through numerous clinical trials and can be reasonably applied [20]. Recent research has unveiled that LAG-3 is intricately connected not only to

immunopathology but also to the potential outcomes of inflammatory diseases. Autoimmune disease pathogenesis is closely associated with the activation and proliferation of T cells, and mounting evidence underscores the distribution of inhibitory molecules and their correlations. LAG-3 molecules, being predominantly present on the surface of T cells, can effectively reflect these distributions [20,59].

Mathieu Angin's team has conducted proliferation assays using peripheral blood from healthy volunteers, employing primary T-cell binding assays to analyze the binding of recombinant human LAG-3Ig protein (IMP200) to captured antibodies at six different concentrations. This approach is taken to assess the binding affinity of LAG-3 [14,15,79,80]. Additionally, the recombinant human LAG-3Ig protein (IMP200) is found to have the potential for gene labeling, inhibiting inflammation induced by tuberculin at DTH sites. Stephanie E. A. Burnell's team has also observed that the regulatory function of LAG-3 involves its lysis. When LAG-3 is removed from the cell surface, soluble LAG-3 is either degraded or secreted, and it ceases to exert further function [81]. Consequently, quantifying the concentration of LAG-3 in serum plays a pivotal role in determining disease activity.

By sorting LAG-3 cells, conducting immunofluorescence staining, and quantifying the results, it becomes evident that LAG-3 cells are enriched in effector memory and central memory T cell populations. Pathway enrichment analysis confirms that LAG-3 cells constitute a heterogeneous group of activated T cells expressing cytokines. Subsequent gene analysis focusing on the clusters of CD8 and CD4 T cells with the highest expression levels reveals enrichment in TCR expression and related cytokine signaling pathways [82,83].

According to reports, quantifying the number of LAG-3 cells can effectively demonstrate a close correlation with endoscopic inflammation. Compared to the normal group, the number of LAG-3 cells in the serum of the control group receiving biological treatment decreases. Interestingly, as tissue inflammation improves and tissue heals, the expression of LAG-3 gradually diminishes or even disappears [84,85]. Conversely, in the population of patients with ongoing disease activity, the expression of LAG-3 remains persistently elevated despite treatment in the control group.

6. Therapeutic potential of targeting LAG-3 by FGL1 in SLE

SLE is an autoimmune disease characterized by multiple tissue damage mediated by autoantibodies. Research has shown that the incidence and clinical course of SLE are closely linked [61,86,87]. While there is no clear inheritance pattern, familial heritability of SLE has been established, and over 100 polymorphic loci have been identified as associated with polygenic SLE [88–92].

Currently, there are 19 drugs targeting LAG-3 molecules undergoing evaluation in clinical trials, and they have exhibited promising results (Table 1) [93–96]. In 2018, the US Food and Drug Administration (FDA) has approved the first clinical development of LAG-3 inhibitors for the treatment of immune diseases, positioning LAG-3 as the most significant next-generation immune checkpoint since PD-1. This finding underscores the significance of molecular targeted therapy in immune disease treatment(Fig. 2) (see Table 2).

Wen Wei Lin's team has discovered that soluble FGL1 can bind to LAG-3 induced expression on T cells using a collagen-induced arthritis mouse model. This interaction effectively inhibits the secretion of interleukin (IL)-2 and interferon-γ (IFN-γ) by T cells in the primary mouse model. Moreover, when FGL1 protein is administered through intraperitoneal injection, the results are highly remarkable: inflammatory cytokines such as IL-1β and IL-6 in tissue cells are significantly reduced, and the progression of joint inflammation and cellular infiltration is significantly attenuated [73].

In a phase I clinical trial focused on autoimmune diseases, specifically psoriasis, conducted by Joanne Ellis and colleagues, it is observed that targeting LAG-3 effectively suppresses the secretion of L-17. Interestingly, FGL1 exhibits the ability to bind to specific domains of LAG-3, inducing T-cell dysfunction. GSK2831781, a collaborative effort between GSK and Immunotep, demonstrated its efficacy in clinical trials by depleting activated T cells expressing LAG-3 in inflammatory diseases. This results in reductions in pro-inflammatory gene expression, including IL-17A, IL-17F, and IFN-γ, with notable pharmacological activity and a substantial safety profile. Remarkably, this clinical trial introduces the innovative concept of FGL1 as a potential novel biomarker associated with autoimmune diseases [4,97–99](Fig. 3).

Dr. Vibha Jha and her team have reported findings from a mouse model of autoimmune diseases induced by heavy metals, drugs, and minerals. Their research indicates that LAG-3-deficient mice exhibit increased susceptibility to mercury-induced autoimmune diseases, marked by elevated levels of inflammatory factors such as IL-4, IL-6, and interferon release. However, this condition can be reversed through the adoption and implementation of transfer technologies [100–102].

Clinical practice has embraced a design aimed at mitigating immune rejection and treating autoimmune diseases: the development of extracellular vesicles as dual-targeted delivery systems for FGL1 and PD-L1 [103]. These extracellular vesicles, composed of miRNA and proteins, possess excellent membrane-transmitting capabilities and can effectively inhibit the activity of CD8 T cells [104–106]. As is well-recognized, IL-6 plays a pivotal role in mediating inflammatory cascades in the pathogenesis of SLE. FGL1 exerts its inhibitory effect on autoimmunity by disrupting AKT signal transduction through IL-6-mediated JAK2/STAT3 signal activation [65].

7. Biosafety issues and future prospects

LAG-3 currently stands as a significant novel lymphocyte activation gene, ranking second only to PD-1, and serves as a suppressive immune checkpoint protein [20,107–109]. While the advantages and feasibility of targeting FGL1 to modulate LAG-3 in the treatment of SLE have been discussed previously, it is essential to acknowledge potential biological issues and clinical application risks.

FGL1, functioning as the principal inhibitory receptor of LAG-3, can facilitate stable binding with pMHC II, effectively dampening T-cell activation both *in vivo* and *in vitro*. Notably, this stable binding remains unaffected by the FGL1 protein itself [2].

FGL1, secreted during acute liver injury, has been shown to promote liver cell proliferation [110–112]. However, evaluating its long-term systemic use in clinical practice poses challenges to assessing safety. Inappropriate FGL1 dosing may lead to dyslipidemia and disruptions in energy utilization, potentially affecting normal physiological functions [113]. Furthermore, there remains a dearth of adequate clinical evidence and treatment cases to comprehensively evaluate adverse events and potential risks associated with FGL1-targeted LAG-3 therapy for SLE [73,97].

It is crucial to note that although targeting LAG-3 via FGL1 can partially inhibit T-cell activation and proliferation, dampen inflammatory responses, and maintain relative autoimmune response stability, it can also result in excessive T-cell depletion, rendering individuals vulnerable to infections, weakened immune surveillance, compromised defense mechanisms, and even an elevated risk of tumor development [11,14,46].

8. Conclusions

Over the years, the use of immunosuppressants and cytotoxic drugs in the clinical treatment of SLE has been associated with side effects such as nephrotoxicity, infections, bone marrow suppression, and gastrointestinal reactions [93]. While biological agents targeting specific molecules have exhibited strong specificity, the variety of available drugs remains relatively limited. Hence, the development of new targeted drugs based on novel mechanisms is of paramount importance. Such drugs not only serve as a valuable addition to clinical treatment but also enhance the overall survival rates of lupus patients [103].

Table 1
Preclinical and clinical development of targeted LAG-3 therapy.

Study	Autoimmune Disease	LAG-3 Target	Results	Drug	Phase	Number of trials	Intervention model assignment	R&D institutions
Smith et al.	Rheumatoid Arthritis	LAG-3 on T cells	Increased LAG-3 expression in synovial T cells; correlation with disease severity	BMS-986016	Early phase I Phase I Phase I/II Phase II Phase II/III Phase III	1 8 8 23 1 1	Parallel (65 %) Single group (25 %) Sequential (9 %) Crossover (1 %)	Bristol-Myers Squibb
Garcia et al.	Multiple Sclerosis	Soluble LAG-3 in serum	Higher levels of soluble LAG-3 in MS patients compared to controls; correlation with disease activity	IMP321	Early phase I Phase I Phase I/II Phase II Phase II/III Phase III	– 9 2 3 – –	Parallel	Immutep
Chen et al.	Type 1 Diabetes	LAG-3 blockade	Reduced incidence of diabetes in LAG-3 knockout mice	MK-4280	Early phase I Phase I Phase I/II Phase II Phase II/III Phase III	– 1 4 1 – 1	Sequential	Merck KGaA
Patel et al.	Systemic Lupus Erythematosus	LAG-3 on regulatory T cells	Decreased expression of LAG-3 on Tregs in SLE patients; association with impaired immune regulation	MGD013	Early phase I Phase I Phase I/II Phase II Phase II/III Phase III	– 3 1 1 – –	Parallel	MacroGenics
				LAG525	Early phase I Phase I Phase I/II Phase II Phase II/III Phase III	– 1 1 3 – –	Single group	Innovent Bio
				Sym022	Early phase I Phase I Phase I/II Phase II Phase II/III Phase III	– 3 – – – –	Parallel	–
				GSK2831781	Early phase I Phase I Phase I/II Phase II Phase II/III Phase III	– 2 – 1 – –	Parallel	GlaxoSmithKline
				RO7247669	Early phase I	– 1	Parallel	Roche

(*continued on next page*)

Table 1 (*continued*)

Study	Autoimmune Disease	LAG-3 Target	Results	Drug	Phase	Number of trials	Intervention model assignment	R&D institutions
					Phase I	1		
					Phase I/II	1		
					Phase II	–		
					Phase II/III	–		
					Phase III			
				REGN3767	Early phase I	–	Parallel	Regor
					Phase I	–		
					Phase I/II	1		
					Phase II	1		
					Phase II/III	–		
					Phase III	–		
				89Zr-DFO-REGN02385	Early phase I	1	Single group	Regor
					Phase I	–		
					Phase I/II	1		
					Phase II	–		
					Phase II/III	–		
					Phase III	–		
				INCAGN02385	Early phase I	–	Parallel	Incyte Biosciences International Sàrl
					Phase I	1		
					Phase I/II	1		
					Phase II	–		
					Phase II/III	–		
					Phase III	–		
				TSR-033	Early phase I	–	Sequential	GSK
					Phase I	2		
					Phase I/II	–		
					Phase II	–		
					Phase II/III	–		
					Phase III	–		
				FS118	Early phase I	–	Sequential	–
					Phase I	–		
					Phase I/II	1		
					Phase II	–		
					Phase II/III	–		
					Phase III	–		
				EMB-02	Early phase I	–	Sequential	EpimAb
					Phase I	–		
					Phase I/II	1		
					Phase II	–		
					Phase II/III	–		
					Phase III	–		
				XmAb841	Early phase I	–	Sequential	Xencor
					Phase I	1		
					Phase I/II	–		
					Phase II	–		

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Table 1 (*continued*)

Study	Autoimmune Disease	LAG-3 Target	Results	Drug	Phase	Number of trials	Intervention model assignment	R&D institutions
				IBI323	Phase II/III Phase III Early phase I Phase I Phase I/II Phase II Phase II/III Phase III	– 1 – – – –	Crossover	–

Table 2
Key points for FGL1 and LAG-3 participating in SLE.

Aspect	FGL1	LAG-3
Prevalence	Elevated levels observed in SLE patients	Expression increased in SLE
Expression	Upregulated in serum and tissues	Increased expression on T and B cells
Cell Types	Expressed by immune and non-immune cells	Predominantly expressed on T cells
Animal Models	Not extensively studied in SLE models	LAG3 knockout exacerbates lupus in mice
Function	Modulates immune response, promotes tolerance	Inhibits T cell activation and proliferation
Therapeutic Target	Potential therapeutic target in SLE	Investigated for immunotherapy in cancer

LAG-3, functioning as a novel suppressive immune checkpoint molecule on T cells, represents a next-generation immunotherapy target [114,115]. Precise targeted therapy can be achieved by leveraging the high binding affinity of the ligand FGL1. Although our understanding of its functions is still evolving, the development of therapies targeting this pathway has gained substantial momentum. Currently, the advantages of this innovative approach are apparent: traditional cytotoxic drugs or immunosuppressants do not possess the capacity to directly block or eliminate T-cell activation, whereas this targeted strategy can promptly halt new immune activation without resorting to widespread cytotoxicity.

Currently, at least 15 new molecules and biological agents targeting LAG-3 as a therapeutic target are in various stages of preclinical and clinical development. In the realm of autoimmune disease treatment, immune regulation through LAG-3 targeting has demonstrated promising therapeutic effects in conditions such as psoriasis and ulcerative colitis [12,14,38,116]. Therefore, employing FGL1 to target LAG-3 in the treatment of SLE represents a highly promising treatment paradigm

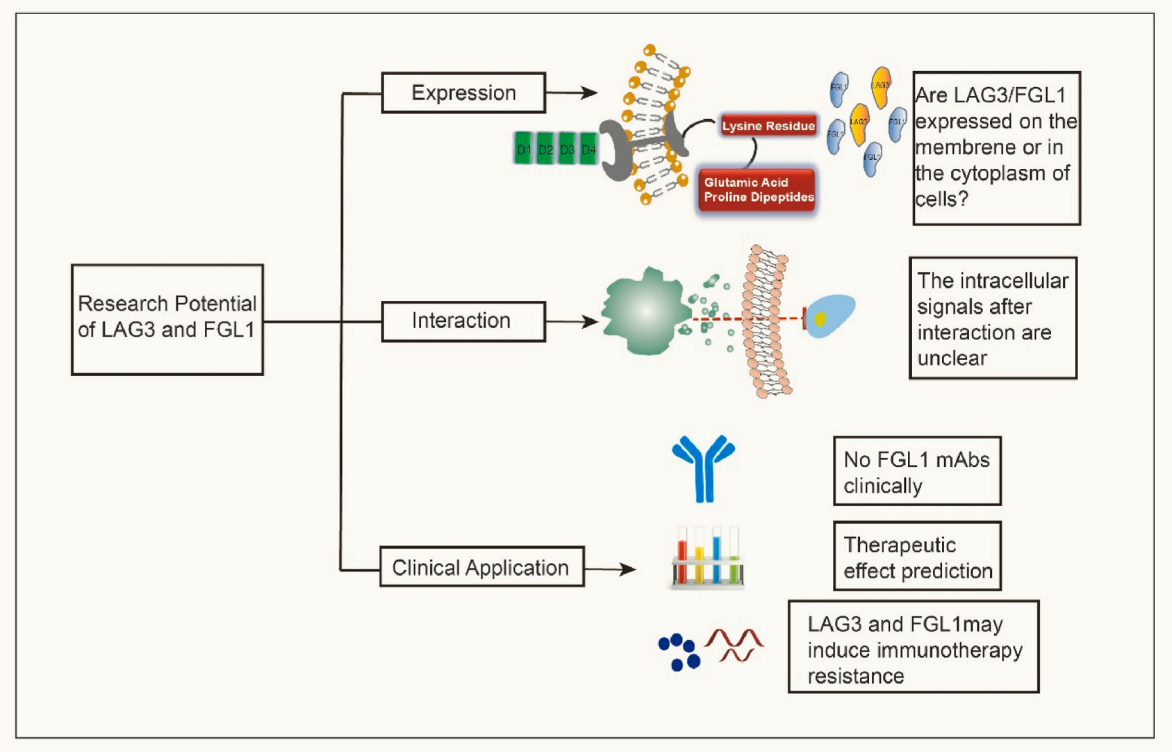

Fig. 2. Research potential of LAG-3 and FGL1 in autoimmune diseases.

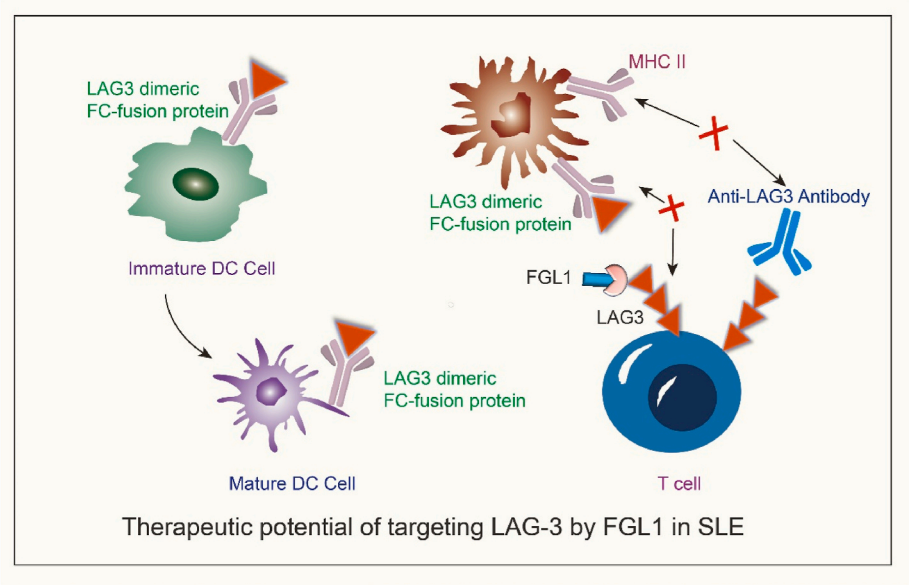

Fig. 3. Therapeutic potential of targeting LAG-3 by FGL1 in SLE.

that can significantly enhance the clinical outcomes of patients and expand the treatment options available to healthcare practitioners.

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CRediT authorship contribution statement

Bing Wang: Writing – review & editing, Writing – original draft. **Biqing Zhang:** editing. **Min Wu:** Yue Jiang, Validation. **Ting Xu:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

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

Data availability

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

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