Role of co-inhibitory molecules in the treatment of psoriasis (Review)

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Abstract. Psoriasis is a common chronic inflammatory skin disease characterized by abnormal activation and infiltration of T-cells and excessive proliferation of keratinocytes (KCs). Its pathogenesis is complex and frequently accompanied by the imbalance of T-cell subpopulations, contributing to its development and further exacerbation. Therefore, the immune system, especially T-cells, is mainly involved in the pathogenesis of psoriasis. While T-cell activation not only requires the first recognition of T-cell receptor and major histocompatibility complex peptide, co-stimulatory and co-inhibitory pathways are reported to promote or dampen T-cell responses through a variety of mechanisms. In recent years, immuno-related agents have been applied in the treatment of numerous clinical diseases, including psoriasis, and are starting to show promising and potential therapy prospects in autoimmune skin diseases. The present review outlined the role of co-inhibitory molecules in the pathogenesis of psoriasis and their application in the treatment of psoriasis.

Contents

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1. Introduction

Psoriasis is a chronic and refractory skin-related autoimmune disease, which is characterized by abnormal differentiation and proliferation of keratinocytes (KCs) and inflammatory cell infiltration. Although the pathogenesis of psoriasis remains to be elucidated, emerging evidence suggests that the aberrant adjustment of immune cells in the skin, especially T-cells, plays a crucial part in the development of psoriasis (1). Studies have mainly focused on the functions of Th17 cells and their related secreted cytokines, namely interleukin (IL)-17 and IL-23, in the pathogenic pathway of psoriasis (2,3). It has been reported that the activation and upregulation of IL-17 create a 'feed forward' inflammatory reaction in KCs, thus resulting in the abnormal proliferation and differentiation of KCs as well as in the recruitment of this subset of leukocytes in the skin, eventually promoting the formation of psoriasis plaques (4).

T-cell activation and expansion require a co-signaling mechanism. One signal can be provided by the antigen peptide/major histocompatibility complex (MHC) on the surface of antigen-presenting cells (APCs) recognized by T-cell receptor (TCR). The other signal can be initialized by the interaction of co-signaling molecules on the surface of T-cells and APCs. To avoid an immune system overreaction, co-inhibitory molecules commonly send feedback inhibitory signals to activated T-cells (5).

The effects of co-inhibitory molecules have been fully studied in patients with types of cancer (6,7). Studies have also led to an awareness of co-inhibitory molecules in autoimmune diseases, including autoimmune glomerulonephritis, multiple sclerosis, atopic dermatitis and systemic lupus erythematosus (8-11). Enthusiasm in the field of co-inhibitory molecules in psoriasis has been aroused by the encouraging results obtained by the application of

immunotherapy with co-inhibitory molecules for treating cancer and other immune-related diseases.

The current treatment approaches for psoriasis mainly include topical agents, phototherapy, traditional systemic drugs and biological agents (12). Compared with traditional therapy, biologic agents have become a mainstay in the treatment of psoriasis. However, there is a tiny subset of individuals who have no response to current biologics or for whom therapeutic efficacy diminishes over time. Furthermore, some patients may still experience notable side effects from presently accessible biologics. Severe adverse events included serious infections, reactivation of hepatitis B and C, tuberculosis, drug-induced lupus and demyelinating central nervous system disorders, with common side effects such as nasopharyngitis, upper respiratory tract infection, headache and fatigue (13). Therefore, in order to develop innovative therapeutics, studies investigating the immunological etiology of psoriasis continue (14).

The current review article mainly focused on the potential roles of co-inhibitory molecules in the pathogenesis of psoriasis and their preclinical studies and clinical applications in the treatment of psoriasis, hoping to provide new potential options for psoriasis treatment (Fig. 1; Table I).

2. Cytotoxic T lymphocyte antigen-4 (CTLA-4)

CTLA-4 is a homologous dimmer of CD28 that binds to B7 molecules. Although CTLA-4 is only expressed on activated T-cells, it has a 20-fold stronger affinity for B7 than has CD28. CTLA-4 has an immunoreceptor tyrosine inhibitory motif in its cytoplasmic domain that activates protein tyrosine phosphatase and inhibits T-cell activation signal transduction and is thereby negatively associated with T-cell activation (15).

Role of CTLA-4 in psoriasis. A previous study revealed that KCs and particular dermal cells in skin with psoriatic lesions expressed CTLA-4 on their surface, while those in skin without lesions expressed very little or no CTLA-4 (16). Liu *et al* (17) indicated that the severity of psoriasis was inversely related to the levels of membrane CTLA-4 (mCTLA-4). In imiquimod-induced mice models, mCTLA-4 alleviated epidermal hyperplasia and inflammation. However, blocking mCTLA-4 resulted in a worsening of psoriasis, demonstrating that mCTLA-4 depletion could aggravate psoriasis.

The relationship between the presence of the CTLA-4 gene variants and the development of different autoimmune diseases has been also studied (18). The -318C>T polymorphism in the CTLA-4 gene works as a powerful promoter to alter the transcription of gene (19). Another study demonstrated that the +49A>G polymorphism in the leader sequence of CTLA-4, could serve a critical role in the binding of CTLA-4 molecule with B7-1 (20). Furthermore, the CT60A>G polymorphism may influence the alternative splicing and the generation of soluble CTLA-4 (21). Dursun *et al* (22) explored the effects of the above three single-nucleotide polymorphisms in the CTLA-4 gene in psoriasis vulgaris patients and healthy volunteers. The results showed that the +49A>G and CT60A>G polymorphisms could be considered as risk factors for the formation of psoriasis vulgaris. In addition, the CGG and CAG haplotypes may play a promoting role in disease progression, while the CAA haplotype displays a protective role.

CTLA-4 in the treatment of psoriasis. Abatacept, a CTLA4Ig, which block the co-stimulation of T-cells via inhibiting the B7-CD28/CTLA4 pathway, is a completely human recombinant soluble fusion protein composed of a human CTLA-4 extracellular domain and an IgG1 Fc fragment. A 26-week phase I, open-label, dose-escalation research proved the efficacy of abatacept in treating patients with psoriasis vulgaris, in which 19/41 (46%) patients receiving medication had a ≥50% improvement in the disease activity index compared with the baseline. The side effects were acceptable and comparatively minor, which mainly included upper respiratory tract infection and temporary headache, each occurring in 16% (23). The efficacy of abatacept was linked with attenuated T-cells activation, KCs and dendritic cells (DCs) in lesions (24).

In the study by Altmeyer *et al* (25), two patients with intractable psoriasis and psoriatic arthritis (PsA) were treated with abatacept. The patients received an initial dose of 10 mg/kg abatacept after failing to respond to conventional therapy and biologic agents such as etanercept, adalimumab and efalizumab. They all experienced a reduction in skin lesions as well as in joint pain and swelling, but eventually both of the patients' responses were not sustained. Because of the severity and drug resistance of the two patients reported in this case report, they may not represent the majority of moderate to severe psoriasis patients who may be benefit from this treatment. No adverse events were reported in either patient.

Recently, abatacept was approved by the American College of Rheumatology/National Psoriasis Foundation to treat PsA (26). In a randomized, double-blind, placebo-controlled phase III study, 20% improvement in American College of Rheumatology score was attained in 39.4% of PsA patients in the abatacept group (n=213) and only 22.3% in the placebo group (n=211) at week 24. Of all participants, ~60% had previously received tumor necrosis factor inhibitor (TNFi) agents, while abatacept showed a maximal effect on TNFi-naïve patients. All participants treated with abatacept tolerated it well and demonstrated favorable outcomes in musculoskeletal manifestations. However, the effect of abatacept on psoriasis lesions was limited (27). In another case study, a 47-years-old Caucasian male with intractable psoriasis and PsA was injected with 125 mg/week s.c abatacept and 25 mg/week s.c. methotrexate. The combined regimen showed a superior effectiveness on musculoskeletal manifestations compared with skin endpoints due to their different sensitivities to abatacept (28). Combination therapy of CTLA-4 molecular agents can be applied for improving the symptoms of psoriasis patients, particularly for those who have peripheral joint involvement, are TNFi-naïve and have limited skin involvement. However, this treatment strategy lacks rigorous experimental support and therefore further studies are needed. A double-blind, randomized clinical trial involving 108 patients with moderate to severe plaque psoriasis demonstrated that abatacept failed to prevent recurrence of psoriasis and was unable to sustain the inhibition of psoriasis-related inflammation factor IL-23 molecule in lesions following ustekinumab withdrawal, which may be attributed to the compensatory mechanism of residuary T-cell activation in lesions (29).

Table I. Biologics targeting co-inhibitory molecules for psoriasis treatment.

Author, year	Name	Type	Targeting	Status	Efficacy	Adverse event	(Refs.)
Abrams *et al*, 1999 Mease *et al*, 2017 Mease *et al*, 2011 Strand *et al*, 2018	Abatacept	Fusion protein	CD80/ CD86	Phase III	Modest impact on psoriasis lesions while beneficial trends overall in PsA	Increased risk of infection, transient headache	(23,27,62,63)
Kim *et al*, 2016 Peng *et al*, 2020 Imai *et al*, 2015	PD-L1-Fc	Fusion protein	PD-1	Preclinical	Alleviated psoriatic inflammation and exhibit additive effects with or without other biologics	/	(43,45,64)
Ellis *et al*, 2021	GSK2831781	mAb	LAG-3	Phase I	LAG-3^+ and $CD3^+$ T-cell counts reduced in peripheral blood and biopsies, reduced pro-inflammatory genes expression, disease activity improved up	Headache, nasopharyngitis, back pain	(56)
Niwa *et al*, 2009	sGal-9	Stable form of galectin-9	TIM-3	Preclinical	Alleviated epidermal thickness and skin inflammation, inhibited STAT3 expression	/	(61)

CD, cluster of differentiation; PsA, psoriatic arthritis; PD-1, programmed death 1; PD-L1/PD-L2, programmed death ligand 1/2; LAG-3, lymphocyte-activation gene 3; sGal-9, stable galectin 9; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3.

3. Programmed death 1 (PD-1)-PD-ligand (PD-L)1/2

PD-1, a type I transmembrane protein, is mainly expressed on activated T-cells and binds to PD-L1 and PD-L2 to prevent T-cells from being overactivated and to inhibit T-cell proliferation, differentiation and cytokine production. Additionally, PD-1 serves a significant role in immune regulation, homeostasis and tolerance (30).

Role of PD-1-PD-L1/2 in psoriasis. Khatery *et al* (31) reported that PD-1 was increased in the serum of patients with psoriasis and in skin lesions and peripheral lesions. In line with these findings, another study found that increased PD-1 expression was related to the severity of chronic plaque psoriasis (32). In addition, a significantly thicker epidermis, more obvious vascular dilation, higher psoriasis area and severity index (PASI) scores and a longer disease course were observed in the PD-1 high expression group compared with the PD-1 low expression group. These results could be attributed to the compensatory upregulation of PD-1 to overcome the Th17 and Th22 pathways (32).

Controversially, a study confirmed that PD-L1 was downregulated in the epidermis of patients with psoriasis in mRNA, protein levels and immunohistochemical staining (33). This study also suggested that PD-L1 expressed on the surface of KCs, rather than PD-L2, is important in the pathogenesis of psoriasis. This finding was in line with the prior conclusion that PD-L1 on the surface of T-cells is the major ligand for PD-1 compared with PD-L2 (34). Tanaka *et al* (35) further confirmed that PD-L1 could exert dominating roles in Th1- and Th17-mediated immunity, whereas PD-L2 was mainly involved in Th2-mediated immunity. Therefore, PD-1 and PD-L1 could interact to inhibit Th17 cell differentiation, while blocking this interaction could induce Th17 cell differentiation. Notably, it has been detected that anti-PD-1/PD-L1 immune checkpoint antibodies might induce or aggravate psoriatic lesions during the clinical treatment of tumors and autoimmune diseases (36-40).

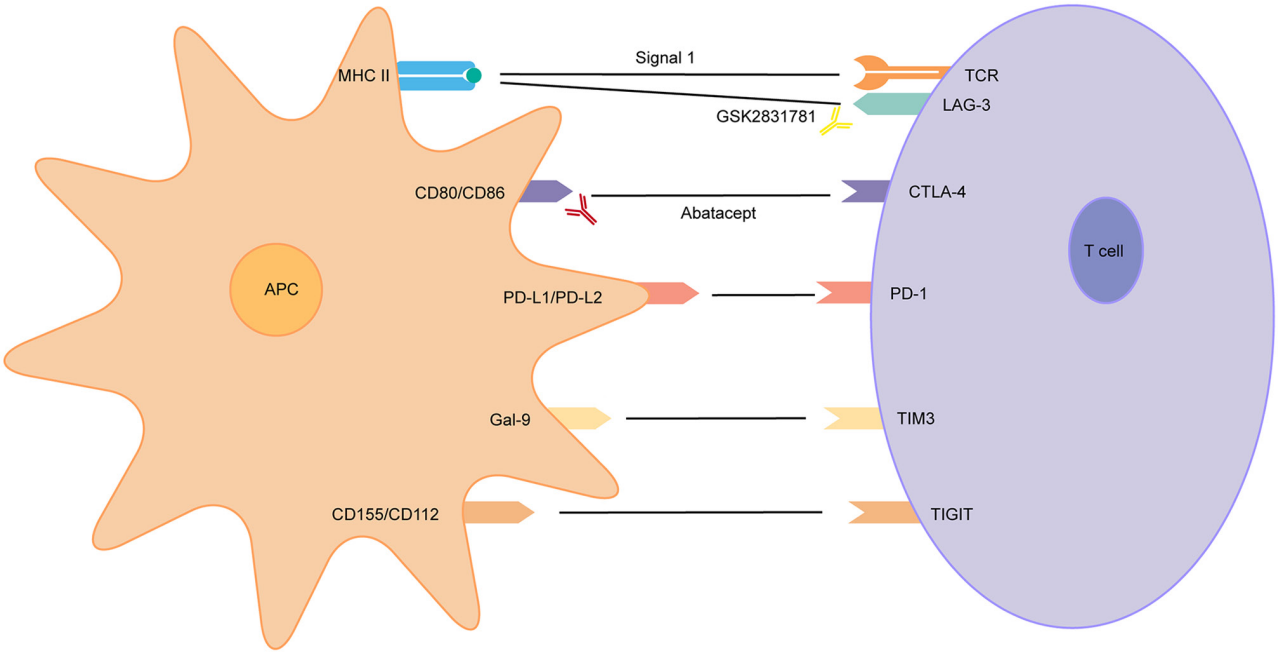

Figure 1. Co-inhibitory molecular targets for the treatment of psoriasis. APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor; LAG-3, lymphocyte-activation gene 3; CD, cluster of differentiation; CTLA-4, cytotoxic T lymphocyte associated protein 4; PD-L1/PD-L2, programmed death ligand 1/2; PD-1, programmed death 1; Gal-9, galectin 9; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains.

Preclinical study of PD-1-PD-L1/2 in treating psoriasis. By interacting with the p40 subunit of IL-23 and IL-12, anti-p40 therapy could prevent IL-23 from inducing the production of Th17 cytokines. It is an approved agent for the clinical treatment of psoriasis and PsA (41,42). However, several patients still have residual lesions following anti-p40 treatment, thus indicating that further treatment strategies are needed for the management of non-IL-23-related psoriasis inflammation. Kim *et al* (43) discovered that PD-L1-Fc could inhibit anti-CD3-induced IL-17A production in CD27-Vγ1-Vγ4-γδ T-cells in imiquimod-induced mice. In addition, combining PD-L1-Fc with anti-p40 therapy was shown to have a cumulative efficacy on psoriatic inflammation in mice, which may be ascribed to the effect of the above two drugs on targeting different IL-17A-secreting γδT-cell populations. Similarly, anti-TNF-α has good efficacy in treating patients with psoriasis and has been licensed for clinical application (44). Peng *et al* (45) indicated that PD-L1-Fc could reduce psoriatic inflammation and show potential synergistic effects with anti-TNF-α treatment in imiquimod-treated mice.

A cell-free carrier called PD-L1 overexpressed mesenchymal stem cell (MSC)-derived extracellular vesicles (MSC-sEVs-PD-L1) has been developed to treat autoimmune diseases. Therefore, MSC-sEVs-PD-L1 could target and repair tissue damage via inhibiting immunoinflammatory cells through the PD-1-PD-L1 pathway. Due to its simplicity of preparation, cheap cost, practicality and biosafety, the MSC-sEVs-PD-L1 technology may have strong clinical application potential (46).

The aforementioned studies indicated that PD-L1-Fc alone or in combination could be considered as a therapeutic approach for treating psoriasis. However, no research has proved the efficacy of PD-L1-Fc in treating human psoriasis. Since the T-cell subsets generating IL-17 in psoriasis animal models and human patients differ, future studies are needed to determine whether this variation could affect the efficiency of PD-L1 protein on inhibiting psoriasis-related inflammation. In any case, PD-1 or PD-L1 targeted treatment for psoriasis remains worthy of exploration.

4. Lymphocyte-activation gene 3 (LAG-3)

LAG-3 (CD223) belongs to the superfamily of immunoglobulins and negatively regulates the proliferation, activation and homeostasis of T lymphocytes (47). To date, MHC-II, galectin-3, liver sinusoidal endothelial cell C-type lectin (LSECtin), a-synuclein and fibrinogen-like protein 1 (FGL1) have been identified to interact with LAG-3 (48). It has been reported that galectin-3 and LSECtin are involved in T-cell regulation (49,50), while a-synuclein is involved in the neurological function of LAG3s (51). FGL1 is a key LAG-3 immune inhibitory ligand (52).

Role of LAG-3 in psoriasis. A previous study revealed an inverse association between the PASI score and the level of CD4+CD49b+LAG-3+Type 1 Tregs in the blood of patients with psoriasis (53). Reduced LAG-3 levels were also found in patients with PsA (54). For psoriasis, the production of interferon (IFN)a by plasmacytoid DCs is the initial event in the innate cascade to pathologic inflammation. The anti-LAG-3 mAb can activate LAG-3-mediated signaling in pDCs in psoriatic lesions, thus attenuating IFNa production and hindering the activation of dermal DCs and the onset of pathogenic Th1 responses. Additionally, cytotoxic anti-LAG-3 mAb could also decrease the number of autoreactive LAG-3^{+} T-cells (55).

LAG-3 in the treatment of psoriasis. GSK2831781, a humanized IgG1 monoclonal antibody, has a strong affinity with Fc receptors and LAG-3 and can therefore deplete LAG-3 expressing cells. A phase I/Ib, double-blind, placebo-controlled clinical study assessed the safety, tolerability and therapeutic effect of GSK2831781 on patients with psoriasis. The results showed that there were no safety or tolerability concerns associated with GSK2831781. In addition, the treatment of patients with GSK2831781 reduced the number of LAG-3$^+$ and CD3$^+$ T-cells in peripheral blood and psoriasis plaque biopsies. Furthermore, a 5 mg/kg dosage of GSK2831781 decreased the expression of pro-inflammatory genes, such as those of IL-17A, IL-17F, IFN and S100A12, and enhanced those associated with epidermal barrier function, including cadherin-related family member 1. All GSK2831781 dosages (0.5, 1.5 and 5 mg/kg) improved the activity of psoriasis compared with a placebo group up to day 43 (56). To the best of our knowledge this was the first time that LAG-3 antibodies were used in clinical practice to treat psoriasis. Single doses of >5 mg/kg were well tolerated and could reduce the number of LAG-3$^+$ T-cells in the blood and psoriatic lesions in a dose-dependent manner. GSK2831781 was also related with reduced disease activity in patients with mild-to-moderate, possibly due to its downstream effects on pro-inflammatory and epithelial integrity genes in psoriatic plaques.

Nevertheless, there are few studies on the relationship between LAG-3 and psoriatic immunity, the molecular mechanism and the compensation mechanism of its synergistic action with other immune checkpoints. Therefore, further research is urgently needed.

5. T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3)

TIM-3 belongs to the Tim family and is mainly expressed on Th1 and Th17 cells. It has been reported that TIM-3 is involved in mediating cell apoptosis or inhibiting cell differentiation, while it suppresses the IFN-γ- and IL-17-triggered immune responses via adversely regulating their expression. The currently known TIM-3 ligands include galectin 9 (Gal-9), phosphatidylserine, high mobility group protein B1 and carcinoembryonic antigen cell adhesion molecule 1 (57). The immune regulation mediated by TIM-3 and Gal-9 has been widely explored in various immunological-related diseases.

Role of TIM-3 in psoriasis. Kanai *et al* (58) determined the expression levels of TIM-3 in peripheral blood IL-17- or INF-γ-secreting T-cells through flow cytometry to evaluate if T-cells have functional disorders in psoriasis patients. In psoriasis, IL-17- or INF-γ-secreting T-cells seem to have defective TIM-3 expression, which causes Th17/Th1 immunity to act more actively since Tim-3 could not provide braking signals. Additionally, a markedly high expression of Gal-9 was determined in the dermal fibroblasts isolated from patients with psoriasis vulgaris. This finding was also verified in *in vitro* experiments, indicating that IFN-γ could also stimulate fibroblasts form the human dermis, thus successfully inducing Gal-9 expression (59).

Preclinical study of TIM-3 in the treatment of psoriasis. Nishi *et al* (60) constructed a stable type of Gal-9 (sGal-9) by selectively deleting the linker peptide, which was extremely resistant to proteolysis and kept its biological activity. In a IL-23-induced psoriatic mouse model, sGal-9 administration ameliorated epidermal thickness and dermal cell infiltration. At the same time, the levels of IL-17, IL-22, IL-6 and TNF-α in psoriatic lesions were reduced. Moreover, sGal-9 inhibited the expression of activated phosphorylated STAT3 in epidermal KCs. Therefore, inhibiting the proteolysis of Gal-9 could be considered as a potential therapy for Th1 or Th17 cell-mediated autoimmune diseases, including psoriasis (61). However, no clinical trials or case reports have been published on the effect of TIM-3 checkpoint agents in the treatment of psoriasis at present.

6. Summary and scope

Psoriasis, a common but challenging disease in dermatology, is a long-lasting autoimmune disease characterized by abnormal skin patches. Co-inhibitory molecules are natural targets for the immunotherapy of autoimmune diseases. Over the last few decades, great progress has been made in the identification of alternative targets and development of innovative targeted medicines for the treatment of autoimmune disorders. In particular, the successful clinical application of CTLA-4, PD-1 and PD-L1 targeting therapies has produced interest in identifying novel therapeutic targets. When traditional therapy and biologics are unresponsive or adverse reactions are intolerable, targeting co-inhibitory molecules agents can be considered. In order to maximize the efficacy of immunotherapy in treating psoriasis, there are some noteworthy problems that still need to be solved. First, a more in-depth and detailed understanding of these areas is required to create and improve therapeutic approaches to these novel targets. For example, TIM-3 has multiple ligands whose functions have not been fully elucidated. Therefore, increased understanding of the mechanisms of co-inhibitory molecules and their ligands in psoriasis may contribute to their clinical application. Second, how to transform the research on immune targets into clinical fields is still a large challenge. It is hoped that more drug candidates can be translated into clinical applications through rigorous evidence-based studies, thus bringing new options for the treatment of patients with psoriasis.

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Authors' contributions

LW and GZ contributed to the study conception and design. Material preparation, data collection and analysis were performed by YY, LZ, XH and JZ. The draft of the

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Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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