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The Potential Role of Inhibitory Receptors in the Treatment of Psoriasis

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Abstract

Psoriasis is a common autoimmune disorder that affects the skin. Approximately 30% of individuals with psoriasis will develop inflammatory arthritis, often in the setting of human leukocyte antigen B27. Both forms of disease are thought to be the result of prolonged inflammation mediated by T lymphocytes, dendritic cells, and keratinocytes. While there are treatments aimed at immunomodulation, targeting T cell co-inhibitory receptors signaling pathways may provide therapeutic benefit. This review will discuss in detail four T cell co-inhibitory receptors and their potential application for the treatment of psoriasis and psoriatic arthritis.

Psoriasis (Ps) is a common autoimmune skin disorder affecting nearly 2% to 4% of the global population.[1] Despite its broad dispersion in the global population, these conditions are more commonly associated with the American, Canadian, and European populations compared to African, African-American, and Asian populations.[2,3] Men and women are affected with equal frequency. The disease may begin at any age. There are five different types of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic.[4] Plaque psoriasis, also known as psoriasis vulgaris, makes up about 90% of cases. It typically presents with plaques that have an erythematous base and a silvery surface. Areas of the body most commonly affected are the back of the forearms, shins, around the navel, and the scalp. Psoriasis can also cause changes to the nails, such as pitting or onycholysis, hyperkeratosis under the nails, and horizontal ridging. Being multifactorial, psoriasis has both genetic and environmental factors that trigger the onset of disease.[1] Identical twins are three times more likely to be affected compared to non-identical twins. Certain environmental conditions, such as stress, can also trigger psoriasis.[5] Psoriasis has many comorbidities associated with it. These include, but are not limited to, cardiovascular disease, inflammatory bowel disease, nonalcoholic fatty liver disease, and lymphoma.[6,7] Current treatments include topical agents,

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phototherapy, non-biologic systemic agents (e.g., methotrexate, cyclosporine, and retinoids), and biologics (e.g., anti-TNF-α, anti-IL-12/23, and anti-IL-17 monoclonal antibodies).

About 30% of people with Ps develop psoriatic arthritis (PsA). PsA is classified as a seronegative spondyloarthropathy and occurs more commonly in patients with human leukocyte antigen (HLA) type B27. Psoriatic arthritis is characterized by asymmetrical oligoarthritis of the hands and wrists present in most cases as well as dactylitis, a sausage like swelling of the fingers. PsA patients can also develop sacroiliitis or spondylitis, which is present in a majority of cases. Another important clinical feature of PsA is enthesitis frequently affecting the Achilles tendon.

Ps and PsA are autoimmune disorders and according to current view arise as a consequence of the aberrant interplay between T cells, dendritic cells, and keratinocytes, giving rise to a self-perpetuating loop that amplifies and sustains inflammation in the skin and in the joints. In particular, myeloid cell secretion of IL-1, IL-23, and IL-12 activates IL-17-producing T cells (T_H17) and T_H1 cells, leading to the production of additional inflammatory cytokines, such as IL-17, IFN-γ, TNF-α, and IL-22. These cytokines mediate effects on keratinocytes, thus establishing the inflammatory cycle. Additional T cells subtypes, such as the autoreactive CD8 T cells, which were discovered in the 1990s, and the more recent γδ T cells, were also implicated in the disease pathogenesis.

Engagement of T cells requires two signals: antigen recognition through the T cell receptor (TCR) and major histocompatibility complex (MHC); and co-stimulatory or co-inhibitory signals. Chemokine receptors, CD28, CD4, and CD8 are well-known co-stimulatory receptors, while cytotoxic T-cell lymphocyte antigen-4 (CTLA-4), programmed-death receptor-1 (PD-1), T-cell immunoglobulin and mucin domain-3 (TIM-3), and leukocyte activation gene-3 (LAG-3) are co-inhibitory receptors. Several drug therapies utilized today involve antagonists of specific receptors in attempt to down-regulate the immune system. There have also been several suggestions to use agonists of the co-inhibitory receptors in an attempt to treat inflammation. This review will focus on four major co-inhibitory receptors and their respective backgrounds in light of their potential therapeutic application in autoimmunity.

Cytotoxic T Lymphocyte Antigen (CTLA)-4

CTLA-4 is a type I transmembrane protein that is part of the immunoglobulin superfamily. It is considered a homologue of CD28 that is capable of binding to both CD80 and CD86 expressed on antigen presenting cells (Fig. 1), but unlike CD28, CTLA-4 is functionally a co-inhibitory receptor.[8] CTLA-4 has a cytoplasmic tail containing an YxxM motif that plays an important role in downstream signaling as well as in its subcellular localization.[9] In resting cells, CTLA-4 is expressed predominately intracellularly in vesicles, the Golgi apparatus, endosomes, and lysosomes.[9–11] CTLA-4 can be detected on the cell surface upon activation downstream of the TCR. Next, the YxxM motif is phosphorylated, and CTLA-4 is stabilized on the surface of T cells. Its surface expression is also based on calcium flux.[12–15] When intracellular calcium levels increase, cell surface expression increases as well. When the YxxM motif is dephosphorylated, it can interact with the clathrin-associated adaptor

protein AP-2, and CTLA-4 becomes endocytosed.[12,13,16,17] While expression on effectors T cells must be induced by activation,[11,18,19] CTLA-4 is constitutively expressed on the surface regulatory T cells (Treg).

The mechanism for CTLA-4-mediated cellular inhibition has not been well defined, but there are a few models for the means of its inhibition. Both CTLA-4 and CD28 can bind to the same ligands CD80 (B7–1) and CD86 (B7–2), but CTLA-4 binds at higher affinity.[11] Thus, due to the competitive binding of B7 to CTLA-4, it can prevent the co-stimulatory signal that is provided by CD28.[15,20–22] Following the engagement of either B7–1 or B7–2 ligands to the MYPPPY binding ecto-motif of CTLA-4, a decrease in T cell proliferation, cytokine production, and overall responsiveness ensue. Intrinsic models for inhibition involve the cytoplasmic tail of CTLA-4. At the molecular level, both proximal TCR signaling events and downstream signaling that are normally enhanced by CD28 and B7–1 or B7–2 are inhibited. Conceptually, there are two proposed modes for CTLA-4-mediated inhibition: threshold and attenuation.[20] In the threshold model, CTLA-4 integration into the immunological synapse raises the threshold level for activation of T cells and by that controls the response in an antigen-dependent manner.[23] In the attenuation model, CTLA-4 essentially reduces the signals delivered by CD28.

Several studies have reported involvement of the CTLA-4/CD28/B7 system in Ps and PsA pathogenesis (Table 1). One study performed by Summers and coworkers examined the expression of both CD80 and CD86 on synovial dendritic cells (DC) isolated from patients with PsA. Low levels of both CD80 and CD86 were found in the majority of patients. The conclusion of this study was that lack of expression of CD80 and CD86 on synovial DC might explain the altered cellular immune responses in these patients.[24] Another prospect is that the low levels of CD80 and CD86 on these cells explain why CTLA-4 itself is not properly engaged to inhibit T cell signaling and functions.

To gain a better understanding of the surface markers expressed on T cells in patients with Ps, Ferenczi and colleagues studied epidermal T cells from skin lesions through flow cytometry. They found that most T cells isolated from Ps patients express CD80 constitutively, along with other activated T cell markers,[25] but there were no significant differences in the levels of CD86 or CTLA-4 expression.

Considering that CTLA-4 could play an important role in the development of Ps vulgaris, Tsunemi and associates[26] looked at polymorphisms in the CTLA-4 gene that could designate susceptibility of developing the disease. One hundred fifty-three unrelated Japanese patients were compared for single nucleotide polymorphisms (SNPs) in the 3’ UTR (318 C/T) and in the first exon (49 A/G), and compared them with 104 healthy control individuals. No significant differences were found between patients diagnosed with Ps vulgaris and the control individuals.[26] A similar study by Kim and coworkers[27] was performed on 137 individuals of Korean descent, compared to a control group of 191 individuals without Ps. The frequency of the CTLA-4 49 A/G variance was slightly higher in Ps patients versus the control group (54.7% vs. 45%), and the CTLA-4 49 G/G homozygous genotype was lower in Ps patients (45.3% vs. 55%).[27] Another similar study by Luszczek and colleagues[28] was performed on Caucasian patients with Ps vulgaris. They compared

additional CTLA-4 SNPs (1147 C/T, 318 C/T, and 49 A/G) from 116 Caucasians diagnosed with Ps vulgaris, and 123 healthy blood donors. Again, no statistically significant difference was found among the two groups. Their study was taken a step further by testing serum for soluble CTLA-4 levels (sCTLA-4). They found that patients who developed Ps before the age of 40 years old had higher levels sCTLA-4. They hypothesized that elevated levels of sCTLA-4 could compete with activated T cells expressing CTLA-4 by blocking its ability to regulate T cell responses.[28]

As mentioned, CTLA-4 is constitutively expressed on Tregs. T cell activation plays a critical role in the development of Ps, but $CD4^+CD25^+$ Treg effector dysfunction could be another possible explanation for their uncontrolled phenotype. In a study by Sugiyama and associates,[29] the group successfully revealed that Ps $CD4^+CD25^+$ Treg are dysfunctional when compared to cells isolated from normal individuals. Ps $CD4^+CD25^+$ Treg showed only 60.6% inhibition of $CD4^+CD25^-$ Teff proliferation compared to 87.8% in normal individuals. An 8-fold increase in the ratio of Treg:Teff was required to achieve a 50% proliferation inhibition in $CD4^+CD25^-$ Teff cells. Ps $CD4^+CD25^-$ Teff also showed increased proliferative response with allogenic APCs compared to normal $CD4^+CD25^-$ Teffcells. The investigators indicated that the source of the dysfunction could be associated with a proliferative functional deficit in the Ps Treg compartment.[29]

Ryder and coworkers[30] suggested that Treg may be dysfunctional in PsA patients. They found that Foxp3 (Treg transcription factor) expression in $CD4^+$ Treg was elevated in both synovial fluid and peripheral blood of PsA cells compared to healthy individuals. Interestingly, CTLA-4 mRNA expression was not increased in synovial fluid $CD4^+$ Treg and was decreased in peripheral blood $CD4^+$ Treg for arthritis patients. These findings may indicate that synovial fluid and peripheral blood Treg are induced locally or selectively recruited to the sites of inflammation in joints.[30]

Moving to interventional patient data, Abrams and coworkers performed phase I drug testing on Ps patients. They used previous knowledge that activated T cells plays a critical role in the development of Ps. Toward that end, they treated the patient with CTLA-4-Ig (abatacept), a fusion protein that contained an extracellular domain of human CTLA-4 and a fragment Fc portion of human IgG1. This soluble chimeric protein could bind B7 proteins on APC and effectively block co-stimulatory signals to CD28. They found that 46% of patients had a total of 50% or greater improvement in their disease activity indexes compared to the baseline upon drug treatment. The efficacy of the drug was further proved in another study published by the same group in the year 2000. During administration of the drug intravenously, they noticed a decrease in mature DCs and replacement with immature DCs, which could be due to a decreased co-stimulation provided by T cells that was blocked through the administration of the CTLA-4-Ig.[31] CTLA-4-Ig has also been used to treat PsA. In a randomized double-blind study, 48% of PsA patients administered CTLA-4-Ig at 10 mg/kg for 6 months showed improvement in their clinical disease activity compared to only 19% in the placebo group. The study also showed that patients receiving CTLA-4-Ig at 10 mg/kg without prior anti-TNF agents achieved ACR20 of 56% compared to 31% for those previously treated with anti-TNF agents. However, when evaluating its effectiveness for treatment for Ps, the results were inconsistent.[32,33]

Another study utilizing CTLA-4-Ig by Davenport and colleagues[34] exploited immunocompromised mice and transplanted them with $CD45RB^{hi}$ T cells and staphylococcal antigen. None of the mice treated with CTLA-4-Ig developed clinical or histological skin lesions, while all mice left untreated developed skin lesions. This study demonstrated that immunocompromised mice treated with CTLA-4-Ig were able to successfully inhibit the development of induced Ps.[34]

Anti-CTLA-4 based immune therapies have also been extensively used in cancer treatment. Administration of ipilimumab, a mouse anti-CTLA-4 blocking monoclonal antibody, has shown to have adverse side effects in the treatment of melanoma with patients who have baseline autoimmune disorders. A study by Johnson and associates[35] showed that up to 27% of the patients who had previously been diagnosed with an autoimmune disorder showed recurrent manifestations of their symptoms, which included worsening plaques in psoriasis. This study concluded that that anti-immune suppressive therapy has the potential to exacerbate autoimmune disorders such as Ps.[35]

Another standard dermatological therapy for Ps is utilization of 8-methoxypsoralen plus UVA photochemotherapy (PUVA). A study by Singh and coworkers[36] sought to understand the mechanisms involved in regulating Ps by using K5.hTGF-β1 transgenic mice that develop scaly erythema and skin lesions similar to those of humans with Ps. They found that administration prolonged the survival of mice with Ps-like skin alterations, as compared to similar results with humans that have pustular or erythrodermic Ps. Following PUVA treatment, there was an up-regulation of the number of $CD4^{+}CD25^{+}$ Treg. They were also capable of suppressing the proliferation of Teff cells (unlike normal Ps Treg cells whose suppressive activity is dysfunctional). To understand the suppressive mechanism of these Tregs, K5.hTGF-β1 mice undergoing PUVA treatment were administered anti-CTLA-4 monoclonal antibodies. Following this treatment, PUVA was unable to suppress disease in K5.hTGF-β1 mice, unlike the administration of the isotype control antibodies. While these results are based on mice models, the results were promising due to similarities in Ps development in both the K5.hTGF-β1 murine model and humans.[36]

In conclusion, the CTLA-4/CD28/B7 system has still yet to be explored further as a potential therapy for Ps or PsA. Despite other studies where polymorphisms of CTLA-4 have been linked to autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, Grave's disease, Hashimoto's thyroiditis, and type I diabetes,[37] this has not been the case for either Ps or PsA. While manipulating the pathways has been utilized efficiently by drugs, such as abatacept, this form of treatment takes advantage of its binding capabilities to B7–1 or B7–2 and out-competes CD28. PUVA treatment has also proven to be efficient in murine models, likely by helping improving the function of Treg. To further understand the mechanism of this system in Ps and PsA additional studies using both CTLA-4 agonist and antagonist are needed.

Programmed Cell Death (PD)-1

PD-1 is a co-inhibitory receptor found mainly on the surface of activated T cells, as well as on other hematopoietic cell types, such as B cells, macrophages, natural killer T cells

(NKT), and certain types of dendritic cells (DC).[38,39] Structurally, PD-1 contains an Ig variable-type (V-type) domain, a transmembrane domain, and a cytoplasmic domain. The cytoplasmic domain contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).[38,40–42] Phosphorylated ITSM binds to the phosphatase SHP-2 that in return acts on and deactivates key signaling proteins downstream of the TCR.

PD-1 is first seen on the surface of double negative ($CD4^-$ $CD8^-$) T cells during their thymic development.[40,43] In more mature cells, PD-1 is expressed on single positive $CD4^+$ and $CD8^+$ T cells upon activation in the periphery.[39,40] PD-1 binds to either PD-L1 (B7-H1; CD274) or PD-L2 (B7-DC; CD273),[42,44,45] (Fig. 1) and has a three-fold higher affinity for the later.[40] PD-1 engagement by its ligands causes a decrease in T cell proliferation, cytokine production, cytolytic function, protein synthesis, and overall cell survival.[40,46]

The expression of PD-1 in Ps was first reported in 2014 when skin biopsies were collected from patients with erythrodermic Ps (Table 1). Half of the patients had up to 50% dermal PD-1 expressing T cells. While this study did not make any conclusions on the utilization of PD-1 expression as marker for Ps, it did show that PD-1 is expressed on activated epidermal T cells.[47]

A more recent study has shown that PD-1 can actually play an important role in regulating Ps disease activity. Imai and coworkers[48] tested the effects PD-1 blockade, either by genetic knockout or monoclonal antibodies administration, on a murine imiquimod-induced psoriasis model. At moderate concentrations of imiquimod, there was enhanced psoriaform dermatitis in mice that had PD-1 blockade, suggesting that PD-1 might have a regulatory function in psoriasiform dermatitis. Interestingly, the lesions were characterized by increased neutrophilic infiltration, epidermal hyperplasia, and increased expression of T_H17 cytokines.[48] Another study by Kim and colleagues[49] showed that PD-1 was over-expressed on T cells from an imiquimod-induced Ps model and on human T cells collected from Ps patients. Moreover, the same group reported that IL-17 T cells obtained from Ps patients had higher expression of PD-1 compared to that of normal individuals. Furthermore, imiquimod-induced murine Ps treated with PD-L1-Fc showed decreased inflammation,[49] suggesting that PD-1 may exert an anti-inflammatory effect in this model.

Additionally, it has been observed that patients treated with anti-PD1 immunotherapy in the treatment of malignancy develop psoriatic lesions. This was first discovered in a patient with metastatic melanoma treated with nivolumab, who developed Ps plaques scattered over the trunk and extremities.50 Subsequently, this was also reported in a patient with metastatic non-small cell lung cancer undergoing treatment with pembrolizumab who developed diffuse erythematous and scaly plaque-like psoriasis lesions in his upper and lower limbs, trunk, and back.[51]

Our group has investigated the role of the potential role of PD-1 as a treatment modality for PsA. Due to PsA being a T cell mediated autoimmune disorder, we analyzed the expression levels of PD-1 in T cells isolated from patients with PsA and from healthy controls. PD-1 was expressed in 11% ± 2% of the $CD3^+$ T cells isolated from the patients, compared to

1.2% ± 5% of the cells collected from the healthy population. Furthermore, the disease activity scores inversely correlated with PD-1 expression levels, suggesting insufficient PD-1 signaling might contribute to disease pathogenesis.[52] Clearly, more data about PD-1 biology (e.g., polymorphism, signaling, and function) is absolutely needed prior to any attempt to engage the PD-1 receptor aimed at treatment of Ps and PsA.

T cell Immunoglobin and Mucin Domain-3 (TIM-3)

Previously known as a receptor for galectin-9 and phosphatidylserine, TIM-3 is a 33 Kd type I transmembrane protein. It is expressed on terminally differentiated T_H1 cells, T_H17 cells, DC cells, macrophages, natural killers cells, and some cancer cells.[53–58] Like other inhibitory receptors, it mediated exhaustion T_H1 responses by regulating the interaction with APCs. It consists of an IgV and mucin extracellular domains, a single transmembrane domain, and a cytoplasmic tail. The IgV domain is capable of binding phosphatidylserine molecules that are found on the surface of APCs.[59]

Differential functions are the results of interaction with different ligands. Some inhibitory effects are shown following engagement with galactin-9 (Fig. 1). One study showed that binding induces an intracellular calcium influx and cell death for T_H1 cells[60] while another study also suggested that Bat3 is released from the cytoplasmic tail of TIM-3 and activates the cell death pathway.[61] Overall binding to galactin-9 leads to immune suppression of T cells, and following injection of galactin-9, there has been an upregulation of Treg cells.[59,62–64]

Due to its immunosuppressive capabilities, TIM-3 has been studied for potential therapeutic use in Ps (Table 1). It has been shown that TIM-3 is expressed in activated T_H1 cells but is also expressed in murine T_H17 cells.[65] Considering that galactin-9 was found in skin lesions of Ps patients, Kanai and associates[66] studied if T_H1 and T_H17 cells in blood expressed TIM-3, and whether its capabilities of immunosuppression were impaired. They found that Ps patients' T_H1 and T_H17 cells had lower levels of TIM-3 expression compared to healthy patients. They also hypothesized that despite high levels of expression of galactin-9 in fibroblast cells of skin lesions, the lowered expression of TIM-3 could impair the function of T_H1 and T_H17 cells. The cause of the impairment was suggested to occur during cell differentiation or expansion of T cell clones in Ps patients.[66]

Another study by Niwa and coworkers[67] sought to use a stable form of galactin-9 (sGal-9) that is resistant to proteolysis and to engage T_H1 and T_H17 cells to induce T cell apoptosis in IL-23 based Ps murine models. Following induction of disease, administration of sGal-9 reduced epidermal hyperplasia in the ear lobes of mice. They also found that administration of sGal-9 increased the numbers of $Foxp3^+CD25^+CD4^+$ Treg. The sGal-9 resistance of proteolytic inactivation of sGal-9 properties make it a potential therapeutic tool to engage T_H17 cells that can potentially alleviate autoimmune disorders, such as Ps.[67]

In conclusion, while research in TIM-3 biology and signaling is still ongoing, its ability to suppress the autoimmune responses of T cells has therapeutic potential for both Ps and PsA. T_H17 cells are the main mediators of Ps and PsA, and the fact that they are capable of

expressing TIM-3 is promising. By engaging this receptor and inducing apoptosis, we can potentially reduce T cell mediated inflammation. Possible side effects of reducing neutrophil recruitment during a bacterial infection may occur, since T_H17 cells secrete IL-17, a potent neutrophil chemo-attractant. The preliminary studies mentioned above provide insight into utilizing this inhibitory receptor to our advantage, but further investigations still need to occur before a drug is developed for human trials.

Lymphocyte Activation Gene −3 (LAG-3)

LAG-3 is a co-inhibitory receptor that is expressed on the cell surface of hematopoietic cells.[68] More specifically, it is expressed on the surface of B cells, NK cells, NKT cells, plasmacytoid DC, γδ T cells, activated T cells, and Tregs.[69–76] It represented a homologue of CD4, and it is capable of binding to MHC class II molecules but with higher affinity.[68] It is also expressed intracellularly in close vicinity to microtubule-organizing centers (MTOC).

LAG-3 has different regulatory roles in different cell types. Effector CD4 T cells are capable of expressing MHC class II molecules upon activation. The molecular mechanism of LAG-3 downstream signaling is unclear, but ligand engagement can inhibit T cell proliferation, cytokine production, and calcium influx.[77,78] Furthermore, LAG-3 can outcompete CD4 for binding to MHC class II molecule for activation. LAG-3 has a unique cytoplasmic tail that contains three domains. One of those, the KIEELE motif, has been shown to have an important role in the suppressive capabilities of CD4 T cells. Naïve CD8 T cells also express LAG-3 but at very low levels. Following activation, LAG-3 is upregulated,[73] but the exact biologic meaning of that is not clear.

Currently, the data is limited in regard to the therapeutic potential of LAG-3 in the treatment of Ps or PsA. Due to its immunosuppressive function, it may serve as an additional therapeutic target to consider.

Conclusions

Most of the targeted therapies for Ps and PsA have been geared toward immunosuppression; while utilization of the natural suppressive capabilities of the immune system have been rarely used or poorly understood (Table 1). CTLA-4 has been the most widely studied receptor for Ps and PsA treatment therapy but still requires further studies. Other agonists targeting the receptors PD-1, Tim-3, and LAG-3 have the potential to be powerful treatments for Ps and PsA as well. Another potential therapeutic option is to combine therapies that would utilize multiple co-inhibitory receptors to enhance the suppression of dysfunctional T cells. There is a fine balance between immunosuppression against autoimmune disorders and controlled regulation against malignancy. Again there needs to be more basic and clinical research geared toward the co-inhibitory receptors in order to understand their potential as treatment modalities against Ps and PsA.

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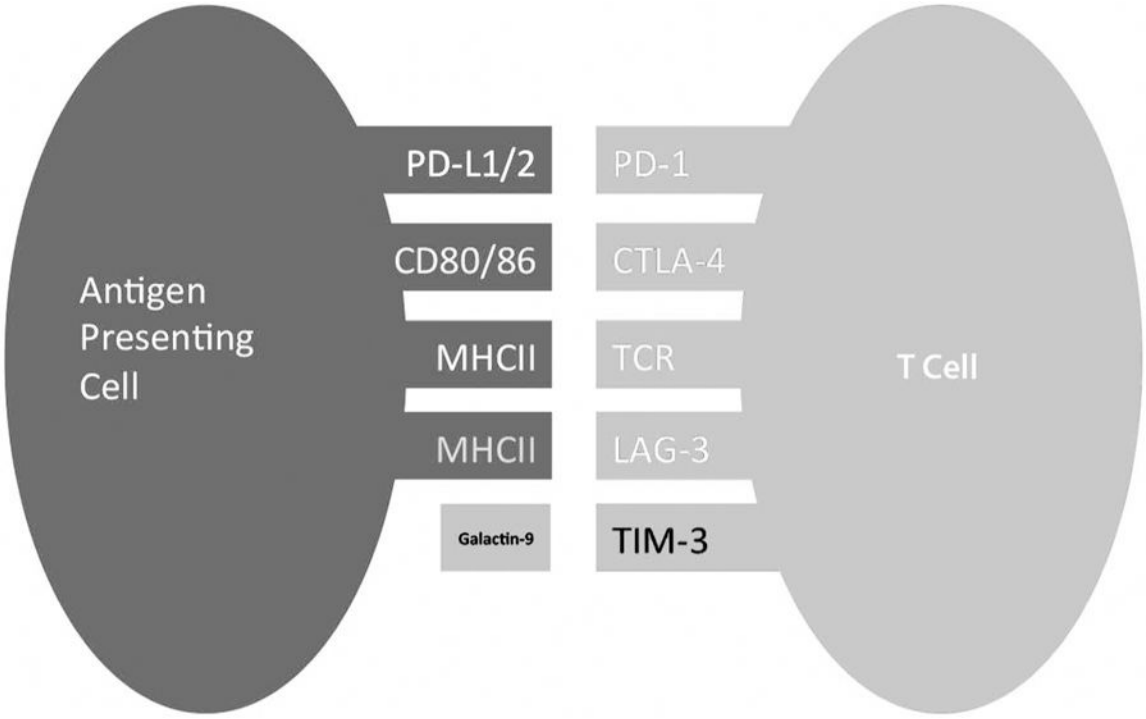

Figure 1.
Inhibitory receptors expressed on T cell and their counter ligands.

Table 1

Summary of Clinical Studies of Inhibitory Receptors

Targeted Receptor and Focus of Study	Descriptive Findings	Study
CTLA-4		
Synovial dendritic cells	Expression and function of CD80 and CD86 costimulator molecules on synovial dendritic cells in chronic arthritis.	Summers K, et al., 1996
T cells	HLA-DR and IL-2R identify persistently activated T cells in psoriasis vulgaris lesional skin: blood and skin comparisons by flow cytometry.	Ferenczi L, et al., 2000
Genetic polymorphisms of CTLA-4	CTLA-4 polymorphisms in Japanese patients with psoriasis vulgaris.	Tsunemi Y, et al., 2003
	Lack of associations of CTLA-4 and ICAM-1 polymorphisms with psoriasis in the Korean population.	Kim Y, et al., 2003
	CTLA-4 gene polymorphisms and natural soluble CTLA-4 protein in psoriasis vulgaris.	Luszczek W, et al., 2006
Regulatory T cells (Tregs)	Dysfunctional blood and target tissue $CD4^{+}CD25^{high}$ regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation.	Sugiyama H, et al., 2005
	FoxP3 mRNA splice forms in synovial $CD4^{+}$ T cells in rheumatoid arthritis and psoriatic arthritis.	Ryder L, et al., 2000
CTLA-4-Ig (Abatacept)	Abatacept in the treatment of patients with psoriatic arthritis: results of a 6-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial.	Mease P, et al., 2011
	Inhibition of pro-inflammatory cytokine generation by CTLA-4-Ig in the skin and colon of mice adoptively transplanted with $CD45R^{high}$ $CD4^{+}$ T cells correlates with suppression of psoriasis and colitis.	Davenport CM, et al., 2002
Anti-CTLA-4 in cancer therapy	Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders.	Johnson DB, et al., 2016
8-methoxypsoralen plus UVA photo chemotherapy (PUVA)	8-methoxypsoralen plus ultraviolet A therapy acts via inhibition of the IL-23/Th17 axis and induction of $Foxp3^{+}$ regulatory T cells involving CTLA-4 signaling in a psoriasis-like skin disorder.	Singh TP, et al., 2010
PD-1		
PD-1 expression	PD-1 signaling in primary T cells.	Riley JL, 2009
	Expression of programmed death-1 in skin biopsies of benign inflammatory vs. lymphomatous erythroderma.	Cetinozman F, Jansen PM, Willemze R, 2014
	Analysis of programmed death-1 in patients with psoriatic arthritis.	Peled M, et al., 2015
PD-1 blockade	PD-1 regulates Imiquimod-induced psoriasiform dermatitis through inhibition of IL-17A expression by innate gamma $delta^{Low}$ T cells.	Imai Y, et al., 2015
	Programmed cell death ligand 1 alleviates psoriatic inflammation by suppressing IL-17A production from programmed cell death 1^{high} T cells.	Kim JH, et al., 2016
Anti-PD-1 in cancer therapy (Nivolumab and Pembrolizumab)	Exacerbation of psoriasis during nivolumab therapy for metastatic melanoma.	Matsumura N, et al., 2016
	Severe psoriasis flare after anti-programmed death ligand 1 (PD-L1) therapy for metastatic non-small cell lung cancer (NSCLC).	Chia PL, John T, 2016

Targeted Receptor and Focus of Study	Descriptive Findings	Study
TIM-3		
Expression	Impaired expression of Tim-3 on Th17 and Th1 cells in psoriasis.	Kanai Y, et al., 2009
Soluble galactin-9	Stable form of galectin-9, a Tim-3 ligand, inhibits contact hypersensitivity and psoriatic reactions: a potent therapeutic tool for Th1- and/or Th17-mediated skin inflammation.	Niwa H, et al., 2009
LAG-3		
No published studies		

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