MINI-REVIEW

Getting Under the Skin: Targeting Cutaneous Autoimmune Disease

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Autoimmune diseases of the skin occur when the immune system attacks normal skin. The immune system can be broadly divided into an effector arm responsible for fighting infections and cancer and a regulatory arm that reduces autoreactivity and maintains immune homeostasis. Cutaneous autoimmunity develops when the equilibrium between the effector arm and regulatory arm of the immune system is disrupted. Recent insights into the inflammatory pathways that are overactive in some cutaneous autoimmune diseases have led to therapies targeting the effector arm of the immune system with greater treatment efficacy than previously used broad immunosuppressants. The current paradigm of inhibiting excessive immune activation for treating cutaneous autoimmunity will be discussed including cytokine blockade, cellular depletion, intracellular signaling blockade and costimulatory blockade. Despite the success of this approach many cutaneous autoimmune diseases lack a clearly delineated pathway to target and therefore new strategies are needed. An emerging therapeutic strategy targeting the regulatory arm of the immune system to induce tolerance and disease remission provides new hope for treating cutaneous autoimmunity. Such an approach includes cellular therapy with regulatory T cells and chimeric autoantibody receptor T cells, cytokine therapy with low-dose interleukin-2, immune checkpoint stimulation, tolerogenic vaccines and microbiome biotherapy. This mini-review will discuss the current and emerging therapeutic strategies for cutaneous autoimmune diseases and provide an organizational framework for understanding distinct mechanisms of action.

INTRODUCTION

Cutaneous autoimmune diseases are a major burden of global disease [1,2] and many lack effective treatments. Components of the innate and adaptive immune system can have either effector or regulatory functions and autoimmunity develops when there is an imbalance between the effector arm and the regulatory arm of the immune system. For the purpose of this review, the effector arm of the immune system includes those cellular and molecular components of innate and adaptive immunity responsible for fighting infections and cancer. This includes immunogenic antigen-presenting cells (APCs), effector lymphocytes (B and T cells), proinflammatory cytokines, activating receptors and costimulatory molecules (Figure 1). Aberrant overactivity of these effector components is implicated in cutaneous autoimmune pathogenesis [3]. In contrast, the regulatory arm of the immune system is responsible for maintaining physiologic homeostasis by curtailing excessive immune activation. This includes

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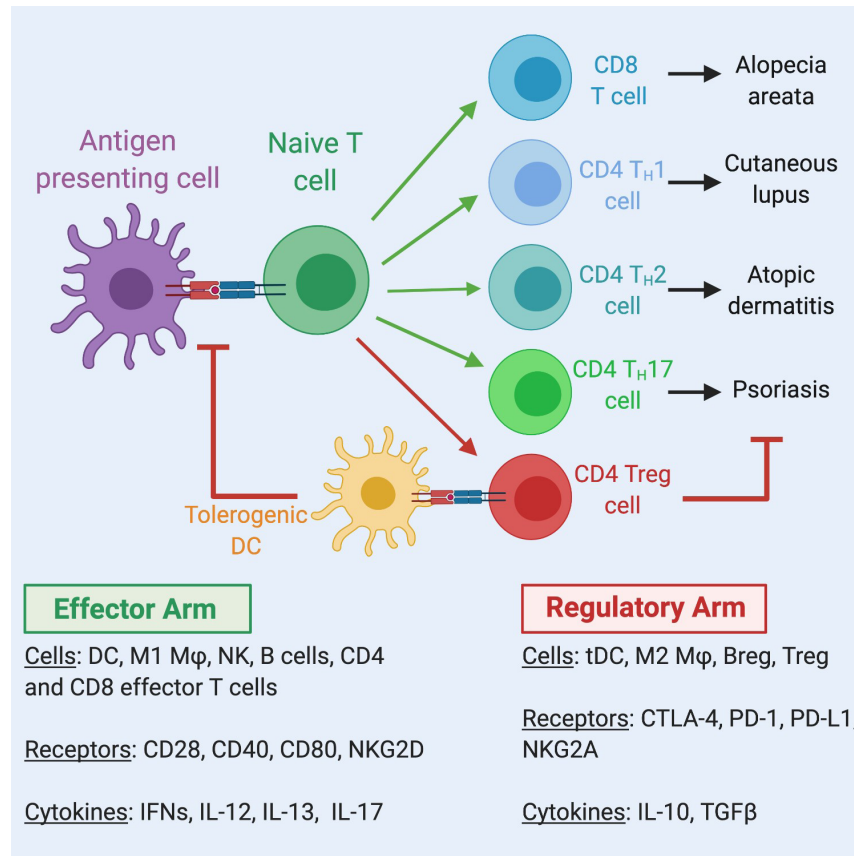
Figure 1. **The effector arm and the regulatory arm of the immune system**. In this simplified schematic, the effector arm of the immune system is represented by antigen presenting cells stimulating naïve T cells to differentiate into distinct effector T cell subsets. Each effector T cell subset plays a role in distinct cutaneous autoimmune disease. The regulatory arm of the immune system feedbacks and reduces T cell activation, thereby limiting autoimmune pathogenesis. Breg, regulatory B cell, CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; IFN, interferons; IL, interleukin; Mϕ, macrophage; NK, natural killer cell, NK2GD/A, natural killer group 2D/A; tDC, tolerogenic DC; TGFβ, transforming growth factor beta; Treg, regulatory T cell.

tolerogenic APCs, regulatory lymphocytes (Breg and Treg cells), inhibitory cytokines, and inhibitory receptors or immune checkpoint molecules (Figure 1). Dysfunction of these regulatory components have also been implicated in cutaneous autoimmune pathogenesis [4].

The first therapies for autoimmunity relied on general immunosuppressive medications that impair the entire immune system, often with high side-effect profiles from broad immunosuppression. For example, corticosteroids, methotrexate, azathioprine, and mycophenolate mofetil are frequently used to treat a variety of cutaneous autoimmune diseases with variable efficacy and medication-related side-effects. Recent insights into pathogenesis, however, have permitted progressively more focused approaches geared toward targeting the mechanisms underlying disease pathogenesis.

The current paradigm for treating cutaneous autoimmune diseases relies on using agents that suppress the effector arm of the immune system. When the specific inflammatory pathway is known for a particular disease, suppressing that pathway can be very effective and safe. For example, monoclonal antibodies (mAbs) targeting the interleukin (IL)-23/IL-17 pathway for psoriasis have dramatically improved efficacy and safety as compared to broad immunosuppressants [5]. This approach can successfully halt disease, but rarely results in long-term remission. A new emerging paradigm for the treatment of cutaneous autoimmunity focuses on targeting the regulatory arm of the immune system to promote tolerance, restore homeostasis, and potentially induce long-term disease remission.

This mini-review is not intended to be a compendium of all past, current, and future approaches to treating cutaneous autoimmunity. Rather, the intention of this mini-review is to highlight the most successful current treatment strategies for cutaneous autoimmune diseases, to discuss the emerging shifting paradigm that focuses on modulating the regulatory arm of the immune system and to provide an outlook for future treatment strategies.
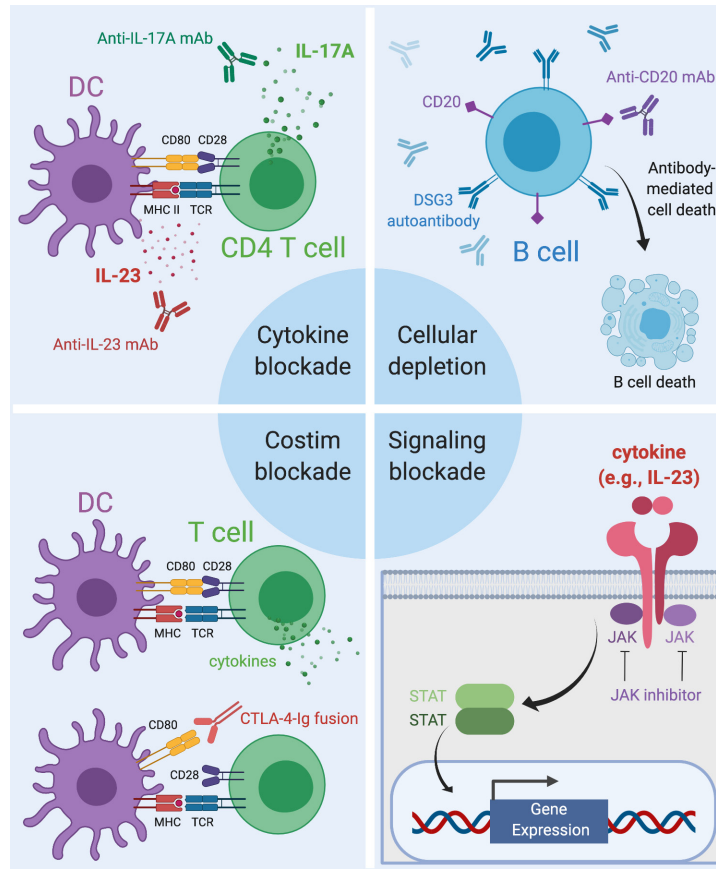
Figure 2. **Current therapeutic approaches for treating cutaneous autoimmunity**. These approaches predominately focus on targeting the excessive immune activation of the effector arm of immunity. For cytokine blockade, monoclonal antibodies bind pathogenic cytokines such as IL-17A and IL-23 for psoriasis and prevent engagement with cytokine receptors. For cellular depletion, monoclonal antibodies directed against CD20 result in cellular destruction of CD20-expressing B cells, including autoreactive B cells specific for DSG3 that drive pathogenesis in pemphigus vulgaris. For signaling blockade, small molecule JAK inhibitors prevent JAK activation of STATs that are downstream of cytokine receptor signaling. For costimulatory blockade, a soluble CTLA-4-Ig fusion protein (abatacept) binds to CD80 on DCs and prevents T cell activation through CD28. CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; DSG3, desmoglein-3; IL, interleukin; JAK, Janus kinase; mAb, monoclonal antibody; MHC, major histocompatibility complex; STAT, signal transducer and activator of transcription; TCR, T cell receptor.

CURRENT PARADIGM: TARGETED BLOCKADE OR INHIBITION OF EXCESSIVE IMMUNE ACTIVATION

Recent advances in biotechnology and insights into disease pathogenesis have moved beyond general immunosuppressant medications to more targeted immunomodulatory medications for autoimmune skin diseases. This current paradigm attempts to more specifically block or inhibit excessive immune activation and has been successfully implemented for a wide variety of autoimmune skin diseases (Figure 2) (Table 1). A new wave of therapies for distinct skin diseases that will become clinically available in the next few years will follow this treatment paradigm. Some of the most successful approaches that use this treatment paradigm of targeting the effector arm of immunity includes cytokine blockade, cellular depletion, intracellular signaling blockade and costimulatory blockade.

Cytokine Blockade

One of the most successful therapeutic strategies for cutaneous autoimmune diseases has been the blockade of cytokines implicated in disease pathogenesis. This approach has revolutionized treatment for psoriasis and atopic dermatitis. Psoriasis is a chronic autoimmune inflammatory skin disease predominately mediated by excessive activation of the IL-23 and IL-17 pathways [5-7]. The success of this approach is evidenced by the seven currently Food and Drug Administration (FDA)-approved mAbs blocking the IL-23/IL-17 pathway for

Table 1. Therapies targeting either the effector arm or regulatory arm of the immune system in cutaneous autoimmune diseases.

	Target	Disease	Status
Effector Arm			
Cytokine Blockade	TNFα	Psoriasis, Hidradenitis	FDA-approved
	IL-17A	Psoriasis	FDA-approved
	IL-23	Psoriasis	FDA-approved
	IL-4Rα	Atopic dermatitis	FDA-approved
	IL-13	Atopic dermatitis	Clinical trials
	IL-31	Atopic dermatitis	Clinical trials
	TSLP	Atopic dermatitis	Clinical trials
	IFNAR1	Cutaneous lupus	Clinical trials
	IL-15	Vitiligo	Early stage
Cellular Depletion	CD20	Pemphigus vulgaris	FDA-approved
Signaling Blockade	JAK1	Psoriasis, vitiligo, atopic dermatitis	Clinical trials
	JAK1/2	Psoriasis, atopic dermatitis, cutaneous lupus, alopecia areata	Clinical trials
	JAK1/3	Alopecia areata, vitiligo, sarcoidosis, cutaneous lupus, dermatomyositis	Clinical trials
	JAK2	Psoriasis, vitiligo, atopic dermatitis	Clinical trials
	TYK2	Psoriasis	Clinical trials
Costimulatory Blockade	CTLA-4	Alopecia areata	Clinical trials
Regulatory Arm			
Cytokine therapy	Low-dose IL-2	Alopecia areata	Early stage
Cellular therapy	Polyclonal Treg	Pemphigus vulgaris	Clinical trial
	CAAR T cells	Pemphigus vulgaris	Early stage
Coinhibitory stimulation	PD-1 agonist	Psoriasis	Clinical trials
	BDCA2	Cutaneous lupus	Clinical trials
Tolerogenic vaccines	PI-0824	Pemphigus vulgaris	Clinical trial (no follow-up)
Microbiome biotherapy	TMT lotion	Atopic dermatitis	Clinical trial

This table is not meant to be an exhaustive list of cutaneous autoimmunity treatments targeting the effector or regulatory arm of the immune system. Rather, the intention is to demonstrate that most current and future therapies target the effector arm of the immune system. BDCA2, blood dendritic cell antigen 2; CAAR, chimeric autoantibody receptor; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IFNAR1, interferon alpha receptor subunit 1; IL, interleukin; IL-4Rα, IL-4 Receptor alpha; JAK, Janus kinase; PD-1, programmed death-1; TMT, targeted microbiome transplant; TNFα, tumor necrosis alpha; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; TYK2, tyrosine kinase 2.

psoriasis [5]. Additional mAbs blocking this pathway are in clinical trials that will likely be FDA-approved in the next couple of years. Recently, atopic dermatitis has also been effectively treated by mAbs that block the dominant inflammatory pathway. Atopic dermatitis is thought to be primarily mediated by type 2 inflammation which includes CD4$^+$ T helper 2 cells (T$_H$2) and proinflamma-

tory cytokines IL-4, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP) [8,9]. Currently FDA-approved dupilumab, which prevents IL-4 and IL-13 signaling by binding to the IL-4 receptor alpha (IL-4Ra) subunit has shown to be efficacious in atopic dermatitis [10]. Other type 2 cytokines implicated in atopic dermatitis pathogenesis such as IL-13, IL-31, and TSLP are currently in

clinical trials [8,9] (Table 1). Using cytokine blocking mAbs in autoimmune skin diseases without any FDA-approved therapies are currently under investigation. For example, targeting the type I interferon (IFN) pathway has shown promise in cutaneous lupus with anifrolumab which binds to the interferon-α/β receptor subunit 1 (IFNAR1) [11-13]. Additionally, anti-IL-15 mAb effectively treated vitiligo in a preclinical model [14] and will likely be pursued further in human patients with vitiligo.

Beyond antibodies, a new approach is under development by Bioniz therapeutics to block cytokines using peptides that bind the common gamma chain (γ$_c$). The common gamma chain (γ$_c$), referred to as the IL-2 receptor subunit gamma (CD132), is a receptor subunit used by six different cytokines including, IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [15]. One peptide (BNZ-1) currently in clinical trials for alopecia areata (NCT03532958) is designed to selectively target IL-2, IL-9, and IL-15 which has been implicated in alopecia areata disease pathogenesis [16,17]. The use of immunomodulatory peptides that bind to cytokine receptors may open a new avenue for targeting cytokines in cutaneous autoimmunity that does not require the high cost of antibody manufacturing.

Cellular Depletion

In rheumatology, cellular depletion of B lymphocytes has successfully been used for decades for the treatment of inflammatory arthropathies such as rheumatoid arthritis. Cellular depletion of autoreactive B cells is accomplished by a mAb targeting the cell surface marker CD20 on B cells. Once the antibody is bound to CD20, the cell is targeted for destruction by antibody- or complement-dependent cellular cytotoxicity [18]. Pemphigus vulgaris is a mucocutaneous autoimmune blistering disease driven by autoantibodies directed against cell adhesion molecules desmoglein-1 (DSG1) or DSG3 on keratinocytes and has a high rate of mortality if untreated [19]. The depletion of mature CD20$^+$ B cells with anti-CD20 rituximab has become a significant advancement in the treatment of pemphigus [20] and has shown some efficacy in recalcitrant cases of dermatitis herpetiformis [21]. A limitation of rituximab is that it depletes all mature B cells expressing CD20, resulting in loss of humoral immunity, but does not deplete B cell precursors or plasma cells that are also implicated in disease pathogenesis due to lack of CD20 expression on these B cell subsets.

Signaling Blockade

A class of small molecule inhibitors targeting the Janus kinase (JAK) family members have provided a lot of excitement for the treatment of multiple autoimmune diseases of the skin. After cytokines bind their cellular receptors, JAKs are activated which in turn activate signal transducer and activator of transcription (STAT) proteins to induce gene expression [22]. JAK inhibitors (JAKi) are FDA-approved for several rheumatologic conditions including rheumatoid and psoriatic arthritis and have also shown promise in treating cutaneous autoimmune conditions such as alopecia areata, vitiligo, sarcoidosis, and dermatomyositis among others [23-25]. Approximately 60 cytokines transmit molecular instructions through the JAK-STAT pathway, using a unique combination of JAKs and STATSs to induce unique gene expression profiles [22]. In addition to targeting cutaneous autoimmune diseases that lack effective therapies, JAK inhibitors are efficacious for the treatment of psoriasis and atopic dermatitis [26,27].

Costimulatory Blockade

Another approach to limit autoimmunity is to block costimulatory molecules expressed on T cells. Costimulatory molecules are necessary for T cell activation when the T cell receptor (TCR) engages major histocompatibility complex (MHC) on antigen presenting cells such as dendritic cells (DCs) [28,29]. Costimulatory receptor CD28 on T cells engages with CD80 or CD86 on DCs to activate T cells. Immune checkpoint molecule cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expressed on DCs and Tregs binds to CD80 or CD86 and prevents CD28 engagement, thereby decreasing T cell activation. Costimulatory blockade with a soluble CTLA-4-Ig fusion protein is FDA-approved for rheumatoid arthritis (abatacept) [30,31]. Currently, abatacept is in clinical trials for the treatment of alopecia areata (NCT02018042) and may be a useful therapeutic strategy for other cutaneous autoimmune diseases.

NEW EMERGING PARADIGM: PROMOTING TOLERANCE AND RESTORATION OF HOMEOSTASIS

A new emerging paradigm for treating autoimmunity includes promoting tolerance and restoration of homeostasis by targeting the regulatory arm of the immune system [3,4,32]. Many of the approaches discussed in this section have been adapted and modified from cancer immunotherapy including cellular therapy, cytokine therapy, and targeting immune checkpoints (Figure 3). Not all of these emerging therapeutics directly target the regulatory arm of immunity, but they all attempt to restore immune equilibrium and have the potential to induce long-term disease remission. These treatment strategies are in its infancy and may be several years or longer before they are developed for clinical use.
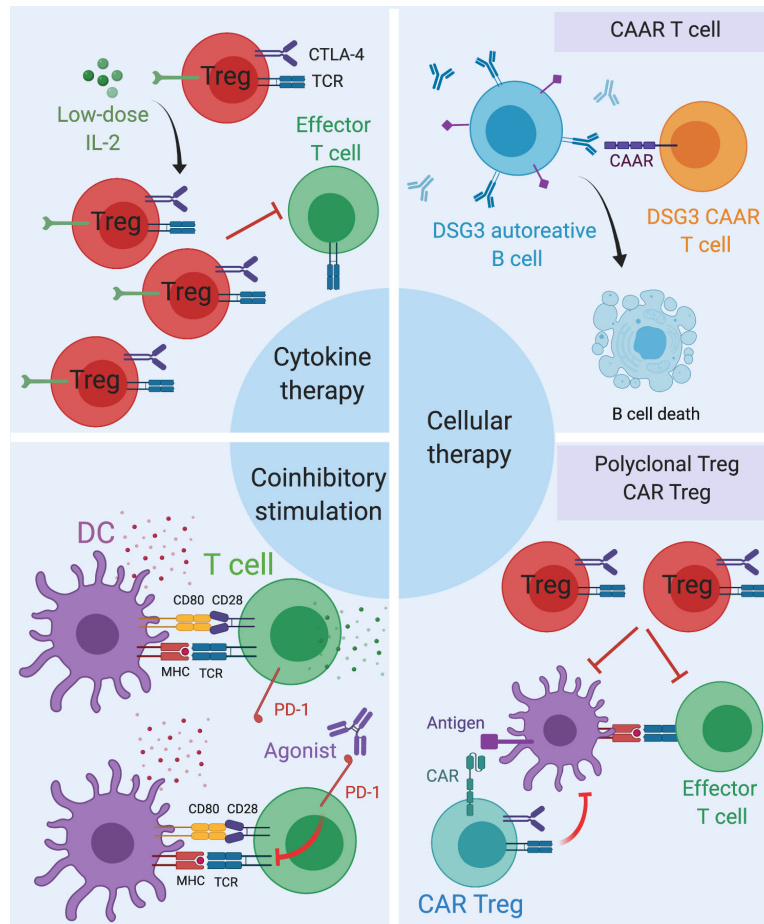
Figure 3. **New emerging therapeutic approaches for treating cutaneous autoimmunity**. These approaches predominately focus on targeting the regulatory arm of the immune system. For cytokine therapy, low-dose IL-2 preferentially expands Tregs which subsequently inhibit effector T cells. For cellular therapy, three distinct approaches may be used, including polyclonal Tregs that inhibit effector responses, CAR-Tregs that recognize autoantigens displayed on antigen presenting cells or other tissues to induce tolerance, and CAAR T cells that recognize autoreactive B cells and target them for destruction. One example is DSG3 CAAR T cells that recognize B cells expressing anti-DSG3 autoantibodies. For coinhibitory stimulation, agonist monoclonal antibodies bind to PD-1 on activated T cells and inhibit downstream TCR signaling. CAAR, chimeric autoantibody receptor; CAR, chimeric antigen receptor; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; DSG3, desmoglein-3; IL, interleukin; MHC, major histocompatibility complex; PD-1, programmed death-1; TCR, T cell receptor; Treg, regulatory T cell.

Cytokine Therapy

The cytokine IL-2 is critical for T cell growth and expansion. High-dose IL-2 therapy was approved in 1998 by the FDA for the treatment of metastatic melanoma [33], but its use was limited due to toxicity [34]. Recent insights into Treg biology reveal that Tregs express the high-affinity IL-2 receptor subunit constitutively and expand in the presence of low-dose IL-2 [35]. Regulatory T cells have important functions in multiple autoimmune diseases of the skin and suppress autoreactive lymphocytes [36]. Proof-of-concept studies have been performed for systemic lupus erythematosus and chronic graft versus host disease [37]. One study demonstrated that low-dose IL-2 was efficacious in a subset of patients with alopecia areata and that Tregs expanded at the hair follicle [38]. Currently, low dose IL-2 therapy is being investigated for the treatment of alopecia areata in a Phase 3 clinical trial (NCT02557074) with results pending. Cytokine modifications including mimics or mimetics are also being engineered for preferential Treg expansion [39].

Cellular Therapy

One innovative approach for autoimmunity treatment is the use of adoptive cell transfer (ACT) with Tregs to induce immune tolerance. The use of ACT of effector T cells has successfully been used to treat a subset of cancer patients for decades [40]. Recently, a patient with cutaneous and systemic lupus was treated with autolo-

gous polyclonal Tregs [41]. The infused Tregs infiltrated the inflamed skin and suppressed the IFNγ pathway [41] suggesting that this approach may be feasible. Currently a phase 1 clinical trial has been initiated to treat pemphigus vulgaris with polyclonal Tregs (NCT03239470) and results are pending. The next-generation of ACT uses virally transduced T cells to express a chimeric antigen receptor (CAR) with greater affinity and antigen-specificity [42]. The successful treatment of hematopoietic malignancies by CAR-T cells is driving development of CAR-T cells to detect solid malignancies, including melanoma [43]. This concept has been used in preclinical models of autoimmunity by developing CAR-Tregs to suppress inflammation [44,45].

A modification of this cellular therapeutic approach is the development of autoantigen specific chimeric autoantibody receptor (CAAR) T cells to attack and deplete autoreactive B cells [46,47]. In this approach, effector T cells are engineered to recognize B cells expressing anti-DSG3 and eliminate these anti-DSG3 autoantibody expressing B cells driving pemphigus vulgaris without depleting other B cell subsets [46,47]. Currently, a phase 1 trial is planned to explore the safety and efficacy of DSG3 CAAR T cells for pemphigus vulgaris. Although, this approach does not directly target the regulatory arm of the immune system, it is discussed as a new emerging paradigm given its potential to completely eliminate autoreactive lymphocytes and induce long-term disease remission or immune homeostasis. A limitation of this technological approach is that it requires the identification of autoantigens which are known for only a minority of cutaneous autoimmune diseases.

Coinhibitory Stimulation

Blocking coinhibitory receptors, often referred to as immune checkpoints, such as programmed death-1 (PD-1) or CTLA-4 have helped usher in a new era in cancer immunotherapy [48]. For the treatment of autoimmunity, immune checkpoints may be stimulated with agonist antibodies in an attempt to rebalance homeostasis [32]. These coinhibitory receptors represents an attractive target in autoimmune diseases as inflamed tissues have increased expression of inhibitory molecules in an attempt to restrain ongoing inflammation and tissue damage [29,49-52]. For example, an agonist against PD-1 is currently in clinical trials for psoriasis (NCT03337022) as PD-1 expression is increased on pathogenic IL-17A-producing CD4$^+$ T cells [53].

The plasmacytoid DC-specific receptor blood DC antigen 2 (BDCA2) functions as an inhibitory receptor that upon engagement is internalized and reduces production of type I interferons, cytokines, and chemokines [54]. Recently, a phase 1 clinical trial using an anti-BDCA2 mAb (BIIB059) which results in BDCA2 internalization and

plasmacytoid DC inhibition demonstrated a reduction in cutaneous lupus and clinical improvement correlated with normalization of the type I interferon response in the skin [55]. A phase 2 clinical trial of BIIB059 in cutaneous lupus patients is currently in progress (NCT02847598).

Tolerogenic Vaccines

Vaccines to prevent infections is perhaps the greatest triumph of modern medicine. In contrast to vaccines used for the prevention of infectious diseases, therapeutic vaccines to treat active disease have been less successful. In the case of autoimmunity, peptides to induce antigen-specific tolerance in animal models of autoimmune diseases has been successful [4]. For example, the hCDR1 peptide reduced lupus in mice and resulted in expanded Tregs [56,57]. In patients with systemic lupus erythematosus treated with hCDR1 there was some clinical benefit [58], suggesting that tolerogenic peptides have some potential for treating autoimmunity in humans. In dermatology, a vaccine (PI-0824) using a synthetic peptide of DSG3 was developed for pemphigus vulgaris (NCT00063752), but no further development of this therapeutic approach has been pursued [59]. There are some limitations in the use of tolerogenic vaccines. To develop a tolerogenic vaccine, the autoantigens and initiators of autoimmune skin diseases must be known. However, autoantigens that initiate and drive cutaneous autoimmune diseases have to yet to be defined. Once a tolerogenic vaccine is developed, its efficacy may wane over time due to epitope spreading whereby the autoimmune response spreads to different epitopes on the same protein [60]. Therefore, the future of tolerogenic vaccines for the treatment of cutaneous autoimmunity is uncertain.

Microbiome

As a barrier tissue, the skin is colonized by trillions of microorganisms that make up the skin microbiome. The functions of the microbiome are myriad and include educating the immune system and tolerance induction [61]. Alterations of the skin microbiome (dysbiosis) contributes to cutaneous autoimmunity, including atopic dermatitis [62,63]. Using coagulase-negative *Staphylococcus aureus* as biotherapy to treat atopic dermatitis has demonstrated efficacy in animal models [64] and is currently under investigation in human patients with atopic dermatitis (NCT03151148). In addition to the skin microbiome, the gut microbiome can also affect cutaneous autoimmune diseases such as atopic dermatitis, cutaneous lupus, and alopecia areata [65-69]. In two recent reports, a total of three patients with alopecia areata undergoing fecal microbiota transplant for *Clostridium difficile* infection had substantial hair regrowth [68,69]. Restoration of gut dysbiosis through fecal microbiota transplant may

improve the fitness of Tregs via increase short-chain-fatty acid production by the healthy microbiota [70]. Thus, the approaches of both skin and gut biotherapy may improve cutaneous autoimmune diseases.

CONCLUSIONS AND OUTLOOK

In summary, advances in understanding disease pathogenesis have led to more targeted and effective treatments for cutaneous autoimmune diseases. The current success is predominately due to therapeutic approaches that target the excessive overactivity of the effector arm of immunity. The emerging paradigm of boosting a dysfunctional immunoregulatory system will hopefully provide a new set of therapeutic approaches for difficult to treat autoimmune diseases. Combinatorial therapies using treatment strategies that target both effector and regulatory arms may be needed for maximum efficacy.

A critical issue remaining is how to localize these treatment strategies to specific tissues. None of the treatments discussed in this review specifically target the cutaneous autoimmune ecosystem. Advances in technologies for single cell analysis have revealed a unique immune microenvironment within tissues comprised of resident immune cells that perform unique homeostatic functions [71]. Within the skin, resident memory T cells appear to be key drivers of autoimmune diseases such as psoriasis and vitiligo [72,73]. One future approach could be targeting these pathogenic resident memory T cells in the skin either for deletion or convert them to skin-resident regulatory T cells. Perhaps wearable bioadhesives could locally deliver drugs that promote skin-resident Treg development, resulting in tissue-specific disease remission.

As many new therapeutic strategies emerge for treating cutaneous autoimmunity, it is important to understand whether the treatment is targeting the effector or regulatory arm of the immune system as outlined in this review. The highest chance of success will likely come from combinatorial treatments targeting both effector and regulatory arms of the immune system. Future research should focus more on drug development targeting the regulatory arm of the immune system in an attempt to induce long-term disease remission.

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