

Role of immune-regulatory cells in skin pathology

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ABSTRACT

The skin harbors a complex and unique immune system that protects against various pathologies, such as infection and cancer. Although many of the mechanisms of immune activation in the skin have been investigated, it is likewise important to uncover the immune-regulatory components that limit effective immunity or prevent autoimmunity. Several cell populations are involved in this immune-regulatory function, including CD4⁺ T cells that coexpress the transcription factor Foxp3, known as Tregs, and cells with immune-regulatory function known as myeloid-derived suppressor cells (MDSCs). This review focuses on the role that immune-regulatory cells, such as MDSCs and Tregs, play in cutaneous pathology, such as malignancy, psoriasis, dermatitis, burn wounds, and transplantation. Although their depletion may serve to augment immunity, expansion of these cells may be used to suppress excessive immune reactions. These cells are attractive, therapeutic targets for various conditions and thus, deserve further exploration. *J. Leukoc. Biol.* **89**: 000–000; 2011.

The concept that the skin is a unique and important immune organ is certainly not new, and the cellular components that communicate and form a network have been investigated thoroughly [1]. The skin is home to every component of the immune system, as well as some unique cells, such as antigen-presenting LCs, and keratinocytes, which can also produce immune-stimulating factors and present antigens. In normal skin, Langerin-expressing LCs populate the outer epidermis layer and are long-lived, can divide, and replenish themselves. They are inactive in terms of antigen presentation until they receive immune stimulation by an inflammatory signal or pathogen, at which point, they up-regulate their antigen presentation and costimulatory molecules and can migrate to skin-draining lymph nodes, where they present antigen to T cells or other antigen-presenting DCs [2]. Likewise, the dermis is populated

with Langerin⁺ and more recently, identified Langerin⁺ DCs, which also uptake antigen and migrate to draining lymph nodes for antigen presentation. Which subtype of APC takes up antigen in what context is not completely clear and may be critical to the immune reaction that results. Other innate cells, such as mast cells and macrophages, also populate the dermis and respond to pathogens by secreting proteases and inflammatory cytokines and chemokines [3]. In addition to classical $\alpha\beta$ T cells are $\gamma\delta$ T cells in the skin, which provide factors critical for keratinocyte survival and proliferation and also secrete factors critical in recruitment and infiltration of macrophages during inflammation [4]. The complexity of the normal skin-immune system has long been appreciated (cell types in skin, reviewed in ref. [5]), and how these cells act as sentinels and first responders involves multifaceted cellular interactions and products (review and figures in ref. [6]). In addition to the cellular components, a multitude of cytokines, factors, and Igs can be found in the skin, which helps form an impressive defensive system. Although much of the earlier work on the skin-immune system uncovered the mechanisms and factors involved in activating immune responses, it is becoming clear that equally important are the elements that control and limit the immune responses to pathogens and inflammation.

Various immune cells play a role in this negative immune-regulatory function, and 1 such population of cells is known as Tregs. These cells are identified as CD4⁺CD25⁺ T cells, which also express the transcription factor Foxp3. Tregs are deemed responsible for suppressing T cell activation, and their dysfunction or absence in mice has been shown to be greatly detrimental, leading to escape of autoreactive T cells [7]. They can be derived naturally from the thymus [8] or induced by exposing conventional CD4⁺ T cells to TGF- β and IL-2 [9]. These cells regulate immune responses via various mechanisms, such as production of the immunosuppressive cytokines IL-10 and TGF- β [10, 11], and induction of T cell anergy [12]. In addition to suppressing T cells, Tregs can communicate with other immune cells to suppress their immune-activating function. They have been shown to interact with DCs, the critical APCs that bridge innate and adaptive immunity, and

Abbreviations: AD=atopic dermatitis, BCC=basal cell carcinoma, CTCL=cutaneous T cell lymphoma, Foxp3=forkhead box p3, GVHD=graft-versus-host disease, Igs=immunoglobulins, LC=Langerhans cell, MDSC=myeloid-derived suppressor cell, NO=nitric oxide, pDC=plasmacytoid DC, ROS=reactive oxygen species, SCC=squamous cell carcinoma, Treg=T regulatory cell

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to suppress their function leading to a tolerogenic, immature DC phenotype [13, 14]. Tolerized DCs can in turn contribute to further Treg expansion [15]. Furthermore, DCs in various peripheral organs such as the skin have different markers characterizing distinct subsets and have been shown to be capable of induction of Tregs or conversion of T cells to a Treg phenotype [16]. These DCs present antigen and are capable of expansion of antigen-specific Tregs, which have been shown to play a role in immune homeostasis in various organs, and blocking their migration into skin has been shown in mice to result in severe cutaneous inflammation [17].

Another regulatory cell population that plays an integral role in limiting immune responses is the MDSC. These cells were described over 20 years ago and shown to down-regulate polyclonal and antigen-specific T and B cell responses [18, 19]. More recently, they have been recognized in various pathologies and identified as CD11b⁺GR-1⁺ in mice, and in humans, there is less consistent agreement to specific markers as a result of the lack of a GR-1 marker [20]. Many of the studies, however, report human CD11b⁺CD33⁺Lin⁻HLA-DR^{lo} cells, which have the capability to suppress T cell activation. MDSCs have been shown to suppress CD4⁺ and CD8⁺ T cells via several mechanisms, such as arginine depletion, NO production, radical oxide production, CD3 ζ down-regulation, and suppressive cytokine secretion [21]. Additionally, MDSCs block NK cell cytotoxicity [22], modulate macrophages to an immunosuppressive M2 phenotype [23], up-regulate their surface molecules that suppress T cells [24], and can induce the development of Tregs [25]. MDSCs have been found to modulate immunity in various diseases, including most types of cancer [26–31], inflammatory bowel disease [32], traumatic stress [33], burns [34], infection [35], and transplantation [36].

Understanding the immune system of the skin is critical to understanding the pathophysiology of various conditions. This review focuses on the role that cells with cardinal features of immune regulation, such as Tregs and MDSCs, may play in controlling immune responses in various skin pathologies. Other cells, which can have stimulatory or regulatory roles, depending on the context of stimulation, such as DCs and LCs, are mentioned, but more extensive reviews of their plasticity are available [2, 16, 37–39]. Uncovering the function of immune-regulatory cells may also lead to new therapeutic targets or methods to augment current therapies.

CUTANEOUS MALIGNANCY

Tumors have long been known to induce immune responses, and likewise, their growth is shaped by and evolves to escape this defense system [40]. Additionally, the specific assessment of immune cell infiltration for a given tumor has been shown to serve as a better predictor of patient survival than histopathological staging [41]. Furthermore, tumor-infiltrating lymphocytes, expanded from melanoma tumors or genetically engineered to be specific to melanomas, have had some success in treating patients with advanced disease when other modalities have failed [42]. However, these therapies do not work in all patients, which, in part, is likely

a result of immunosuppressive factors produced by the tumors [43] but also, immune-suppressive regulatory cells found in these cancer-bearing patients. In fact, advanced melanoma patients have a significant increase in circulating Tregs and immunosuppressive DCs, and their levels correlate with stage of disease [44]. Tregs have also been found in increased numbers in the dermis and epidermis in mycosis fungoides [45], surrounding BCC nodules [46], and infiltrating SCCs [47]. As there is ample evidence of immunosurveillance against tumors [40], it makes sense that organ transplant patients on chronic immunosuppression have increased rates of SCCs, which recur and are aggressive. Interestingly, kidney transplant patients with SCCs have higher levels of Tregs than patients with SCCs who are not on chronic immunosuppressives, and those patients were also more likely to develop new SCCs [48]. Additionally, it has been suggested that specific subsets of human melanoma cells with tumor-initiating properties, similar to cancer stem cells, have the ability to modulate or preferentially lead to increased abundance of Tregs and immunosuppressive factors [49]. This capacity to expand Tregs provides an immune-escape mechanism allowing the tumor to progress. In CTCLs, the pathogenic T cells can themselves assume a Treg phenotype and contribute to immunosuppression by secreting various factors and inhibiting normal T cell activation [50].

The role of Tregs in tumor progression has been confirmed further by evidence of anti-tumor immunity and tumor regression upon their depletion. Treg depletion has been shown in mouse models of melanoma to allow for robust immune-mediated tumor rejection [51, 52]. Likewise, in patients with metastatic melanoma, the use of rIL-2/diphtheria toxin conjugate (denileukin diftitox, Ontak), shown to deplete Tregs, resulted in induction of new, melanoma-specific T cells and therapeutic responses in a significant number of advanced melanoma patients [53]. T cells from Ontak-treated patients regain functional capacity and can be activated by their specific antigen, unlike T cells from patients prior to Ontak treatment [54], and Ontak treatment also proved beneficial in patients with CTCLs who had failed prior therapies, with a 44% response rate and a significant increase in progression-free survival [55]. Imiquimod, a TLR7/8 agonist, has been effective in the treatment of SCCs and BCCs. It has also been shown to augment the effector T cell:Treg ratio in SCCs, reducing the percentage of Tregs but also antagonizing their suppressive function, decreasing their expression of Foxp3, and decreasing their production of suppressive cytokines IL-10 and TGF- β [47]. In some studies, depletion of Tregs has not always proven to affect tumor growth, but the regimen used and the stage of the tumor at initiation are likely an important factor to consider. The importance of this was highlighted in a mouse melanoma study, in which tumor growth was unaffected by Treg depletion; however, although peripheral Tregs were depleted by the regimen used, tumor-infiltrating Tregs were not [56]. Currently, various unique methods are being investigated to deplete or inhibit tumor-induced Tregs. One approach shown to be successful in a mouse model of melanoma depleted Tregs by vaccination using DCs transfected with mRNA for Foxp3

[57]. This led to induction of T cells reactive against Foxp3 and the depletion of Foxp3-expressing Tregs within the tumor and as a result, augmented protective immunity. More studies like these are needed to determine the best method for specific Treg depletion and their clinical implementation.

MDSCs have likewise been shown to play an immunosuppressive role in various mouse and human cancers [26–31]. Furthermore, circulating MDSC levels have been shown to correlate with clinical cancer stage and metastatic burden of various solid tumors [28]. PBMCs from advanced melanoma patients were shown to have an expansion of these myeloid cells, which secrete TGF- β and suppress T cell proliferation [27]. Furthermore, tumor-derived membrane microvesicles circulating in the plasma of advanced melanoma patients have been shown to prevent differentiation of immature myeloid cells, leading to expansion of T cell-suppressive MDSCs among PBMCs of these patients [58]. Interestingly, GM-CSF, which has been used to mobilize myeloid cells in various immunotherapeutic protocols and enhance antigen presentation, can lead to the expansion of MDSCs at high doses [43, 59]. Advanced melanoma patients receiving a GM-CSF-based therapeutic vaccine, have been shown to expand MDSCs following vaccination [27]. Additionally, many mouse and human tumors have been shown to secrete GM-CSF at high levels [43]. This finding may help explain why many vaccines in cancer patients using high systemic levels of GM-CSF, as opposed to local use at low levels, have been met with little success. Interestingly, an oncolytic HSV-1 virus-based vaccine, locally inoculated and expressing GM-CSF locally in the context of infected lysing tumor cells, produced therapeutic responses in some melanoma patients that correlated with a decrease in Tregs and MDSCs [60]. In addition to GM-CSF, various other tumor-derived proteases, cytokines, and chemokines have been associated with MDSC expansion [20, 43, 61]. In addition to aiding tumor escape from immune surveillance, MDSCs have been shown to promote the metastasis of SCC tumor cells from their primary cutaneous site via interaction with a CD200 glycoprotein on metastasized SCCs [62]. This interaction via CD200 likewise induced greater production of GM-CSF and G-CSF from MDSCs, which may contribute further to expansion of MDSCs and immunosuppression, leading to tumor escape. Therapeutic targeting of MDSCs may thus be beneficial for cancer therapy, and various agents have shown some success in preclinical models. Phosphodiesterase-5 inhibitors (Sildenafil) down-regulate suppressive mechanisms of MDSCs, namely arginase and NO production, and enhance anti-tumor immunity [63]. Additionally, synthetic triterpenoids, which activate antioxidant genes aimed at countering the ROS produced by MDSCs, have been shown to limit the MDSC-suppressive potential [64].

Other components of the skin-immune system have been found to be defective in tumor-bearers, such as DCs from human SCCs that are not capable of activating T cells [65]. These defects may be attributed to the expansion of regulatory-immune cells, the factors they produce, and those produced by the tumor cells [43, 66]. Additionally, Tregs have been shown to suppress $\gamma\delta$ T cells [67], which are an integral component of the immunosurveillance of cutaneous

tumors such as SCCs [68]. Whether MDSCs also modulate $\gamma\delta$ T cell function is still unclear.

PSORIASIS

There is now ample evidence to suggest that abnormal immune responses in the skin are involved in the pathophysiology of psoriasis, resulting in inflammation and increased epidermal proliferation. Therapies that block cytokines, such as TNF, using a mAb (Etanercept), proved very successful [69]. Subsequently, it has been shown that IL-12 and IL-23, 2 cytokines that share a common subunit, are elevated in psoriatic lesions and could up-regulate TNF and induce epidermal proliferation in mice [70–72]. As with TNF blockade, antibody blockade of IL-12/IL-23 (Ustekinumab) has shown great promise in the treatment of psoriasis [73]. These cytokines are also produced by various immune cells in the skin, including DCs and macrophages [74]. Furthermore, they may be responsible for the recruitment of various inflammatory subsets of T cells to the skin and circulation, such as Th17 cells that produce IL-17 and TNF and Th22 cells that produce IL-22 [75, 76]. In addition to recruitment of inflammatory T cell subsets, there have been reports of elevated levels of Tregs in patients with psoriasis, and increasing levels correlate with disease severity [45, 77]. This seems counterintuitive, as Tregs would be postulated to suppress the inflammatory T cell subsets and prevent disease. On the other hand, it makes sense that a chronic inflammatory response would be followed by an increase in regulatory-immune cells to attempt down-regulation of that response. Several studies provide some evidence suggesting why Tregs are not successful in this regard. One possibility is that in addition to elevated Tregs, there is an increased Th17:Treg ratio correlated with disease severity, suggesting that an imbalance of these T cell subsets may limit Treg effectiveness [77]. Other studies have found that Tregs from psoriatic patients are not as suppressive as those from normal patients, implicating an inherent defect in suppressive capability [78]. Furthermore, although Tregs were increased in psoriatic lesions, they were decreased in the dermis relative to other skin pathologies (AD), which may have an effect on their interaction with other immune cells, such as DCs, in this layer [45, 78]. In a murine model of psoriasis, Treg and DC interactions were critical for suppressive function, showing that reduced expression of the integrin CD18 on Tregs limited this cell–cell interaction, resulting in decreased TGF- β secretion and Treg suppression [79]. Interestingly, a subset of DCs, known as pDCs, has been shown to be recruited early in psoriatic skin lesion development and to secrete high levels of IFN- α , which contributes to expanding pathogenic T cells in psoriasis [80–82]. However, IFN- α has also been shown to suppress generation of Tregs and contribute to activation of effector T cells [83]. The interaction of pDCs and regulatory-immune cells in psoriasis deserves further exploration. Other cytokines, such as IL-6, also shown to be increased in psoriatic lesions by secretion from Th17 cells and DCs, can inhibit immune suppression by Tregs [84]. Furthermore, although Tregs can suppress conventional T cells, it is controversial whether Tregs have the ability to suppress Th17 cells. One study sug-

gested that a CD39⁺ subset of Tregs does have this ability, and in patients with multiple sclerosis, there is a deficit in the proportion of this specific subset of Tregs [85]. The levels of CD18 or CD39 on Tregs in psoriasis have not yet been analyzed. It is also unclear whether Tregs are dysfunctional in all patients with psoriasis, as different forms of the disease may present with a different profile of T cell subsets and cytokine expression [86]. Interestingly, patients with psoriasis that respond to anti-TNF treatment show an increase in Tregs correlating with a clinical response but whether this is an increase in Tregs with greater suppressive function is not known [87]. Likewise, psoriasis patients are also responsive to psoralen and UVA therapy, which increases the level of Tregs, reduces disease severity, and correlates to a greater ratio of Foxp3⁺:CD4⁺ cells [88]. Although many studies have investigated Treg levels and function, the presence and function of MDSCs as immune-regulatory cells in psoriasis have not been investigated. Mechanisms to increase this population may be beneficial to limiting cutaneous inflammation.

AD AND CONTACT DERMATITIS

Dermatitis represents a complex, cutaneous, inflammatory process. Contact dermatitis is believed to result because of toxic injury or allergic response to a chemical or allergen involving a T cell-mediated, inflammatory reaction. AD is a chronic disease involving genetic skin-barrier variations, leading to dry and hyperirritable skin and a complex inflammatory process involving Th2 responses acutely and Th1 responses chronically [89]. Patients with AD have increased susceptibility to skin infections, which exacerbate the inflammatory process further. Various immune cells contribute to this inflammatory reaction, including mast cells, eosinophils, DCs, macrophages, and T cells. Conventional $\alpha\beta$ T cells in mouse models have been shown to be required for induction of spontaneous and contact dermatitis [90]. Furthermore, T cell subsets that have been implicated include Th17 cells with an increase found in the circulation of AD patients [91]. These cells likely contribute to cutaneous inflammation, as in other pathologies such as psoriasis. On the other hand, T cell subsets that can limit dermatitis include Tregs, as seen in melanoma patients who have increased Treg levels and depressed contact hypersensitivity, with reversal of this suppression occurring in these patients following Ontak depletion of Tregs [54]. Furthermore, studies of Tregs from healthy, normal patients relative to nickel-allergic individuals suggest that skin-homing Tregs maintain tolerance to nickel and prevent contact hypersensitivity, whereas Tregs from allergic patients were not capable of immunosuppression [92]. Likewise, the adoptive transfer of Tregs in mouse models can prevent contact dermatitis in an IL-10-dependent, suppressive mechanism [93]. More evidence that Tregs limit cutaneous inflammation comes from patients with X-linked immune dysregulation, polyendocrinopathy, enteropathy syndrome, who harbor a mutation in Foxp3 and develop severe AD with pruritis and hypereosinophilia, among a multitude of other systemic abnormalities [94]. Surprisingly, Tregs have been found to be increased significantly in the circulation of AD patients relative to nonatopic patients [95], and

some studies also indicate an increase in levels within AD skin lesions, albeit along with many more effector T cells [45]. This potential imbalance of activated effector T cells to Tregs may limit Treg-suppressive effectiveness [96]. Furthermore, AD patients are susceptible to skin infections, and bacterial enterotoxins and superantigens have been shown to have inhibitory effects on Treg function [95, 97]. Additionally, TLR2, which can be activated by bacterial lipopeptides and endogenous antigens, has been shown to play a role in sensitization and inflammation and may be required for development of AD and contact dermatitis [98, 99]. It is unclear whether antibacterial treatment can aid in the treatment of AD via preventing activation of this pathway, as this pathway is also activated by endogenous products [100, 101]. Interestingly, bacterial products that activate TLR2 have been shown to block the suppressive function of human Tregs [102]. Thus, TLR2 activation in the pathogenesis of AD, by bacterial products or endogenous products, may involve blocking Treg function. As discussed above for psoriasis, the expression levels of CD18 and CD39 may also play a role in Treg effectiveness in dermatitis [103–105]. Interestingly, probiotic treatment in a mouse model of AD increased Treg levels and repressed cutaneous inflammation [106]. Likewise, cyclosporine A treatment has been beneficial in patients with severe AD and has been shown to increase the levels of Tregs significantly [107].

A variety of other cells has been shown to limit this inflammatory reaction in mice, including $\gamma\delta$ T cells [90] and suppressive B cell subsets [108]. LCs have also been shown to limit contact hypersensitivity, as inflammatory reactions were exacerbated in their absence in mouse models [109]. LCs can limit cutaneous inflammation by down-regulating T cell responses in a contact-dependent manner, requiring IL-10 cytokine secretion [110, 111]. The regulatory role of LCs in contact hypersensitivity is, however, controversial, as their depletion using other mouse models showed a decrease rather than inflammation [112]. Furthermore, their role in presenting antigens for induction of immune responses is well documented [113], and perhaps their role as inducers or regulators of immune reactions depends on the context in which they are exposed to antigen [114]. Additionally, markers, such as Langerins, thought to distinguish LCs from other APCs, such as other DC subsets, may not be completely specific and thus, will require further exploration in these models [115]. The role of MDSCs as another population of immune-regulatory cells, which has been associated with chronic inflammatory states, has not been investigated thoroughly in AD; however, in a mouse model with chronic application of a contact sensitizer, MDSCs were expanded significantly [116]. MDSC levels and function in AD deserve exploration, as they modulate various immune cells in the inflammatory setting.

BURN WOUNDS

Cutaneous burn injuries are associated with an immense inflammatory reaction involving various cytokines and a concurrent immunosuppression of T cell activation [117]. Additionally, the damage to the barrier function of the skin and immunosuppression in burn injuries likely leads to the increased

susceptibility to infection and sepsis. Burn injuries in mouse models lead to massive myelopoiesis, including CD11b⁺GR-1⁺ subsets, likely to be MDSCs, which suppress lymphocyte proliferation [34, 118]. Additionally, MDSCs are found infiltrating the burn wound itself, and these and other wound cells contributed to greater levels of various cytokines, such as IL-6, IL-10, keratinocyte chemoattractant, and MCP-1 [119]. MDSCs at the burn site have also been shown to prevent keratinocyte production of murine defensins, which normally prevent infection, and thus, augment susceptibility to infection with *Pseudomonas aeruginosa* [120]. Tregs likewise play a role in suppressing the inflammatory reaction to burn injuries, and their depletion leads to increased cytokines and innate cell activation post-burns [121]. Burn injury in rats leads to increased expansion of Tregs and inflammatory high mobility group box 1 protein secretion, which may be responsible for an increase in IL-10 production by Tregs following injury [122]. This injury has also been shown to augment Treg function by increasing IL-10 secretion and surface expression of TGF- β [123]. Thus, although MDSCs and Tregs likely expand to limit tissue damage as a result of increasing inflammation following a burn injury, this may also lead to immunosuppression and increased susceptibility to infection. Additionally, in patients with burn injuries, the levels of circulating DCs were found to drop to low levels relative to normal patients and do not recover in those who develop sepsis [124]. Whether immune-regulatory cells, such as MDSCs or Tregs, may play a role in this DC depression remains to be investigated.

TRANSPLANT

In transplantation, a complex immune reaction between donor- and recipient-immune cells occurs, which can lead to donor tissue rejection and/or a GVHD, leading to attack of the recipient's tissues by donor-immune cells. It is thought that these immune reactions can involve a direct pathway of activating, allogeneic-reactive T cells, which recognize foreign MHC

molecules, and an indirect pathway, in which APCs take up and present foreign peptides to their syngeneic T cells [125]. Critical in this inflammatory reaction are donor and recipient DCs, which can migrate into lymph nodes and activate alloreactive T cells by the direct or indirect pathway [125]. However, this reaction is complex, and some subsets of DCs may actually be beneficial in inducing T cell anergy or tolerance. Skin allografts, like other transplanted tissues or organs, thus require immune tolerance to prevent rejection. Immune-regulatory cells can play an important role in this process to prolong graft acceptance and survival. In a mouse model of skin grafting, it has been shown that the i.v.-adoptive transfer of Tregs is protective of skin grafts that are immunologically matched to the donor Tregs [126, 127]. Additionally, a study using a skin-explant model showed that human Tregs, if present during priming of alloreactive T cells, could prevent a graft-versus-host immune reaction [128]. Other cells, such as mast cells, have also been shown to play a role in inducing skin-allograft tolerance, recruited by and interacting with Treg cells [129]. Likewise, adoptive transfer of MDSCs also results in prolonged allogeneic skin-transplant survival [130]. MDSCs are capable of suppressing rejection of skin allografts in a mechanism that was found to require IL-10 and heme oxygenase-1 expression [131]. Additionally, other immune cells, such as LCs, within skin grafts may contribute to immunosuppression of T cells in an IL-10-dependent manner [111]. Although donor DCs are thought to be involved in the alloreaction in transplantation, the depletion of donor LCs in 1 mouse model indicates that LCs are not necessary for the induction of graft rejection, and rather, their depletion led to a break in tolerance to minor antigens in skin grafting [132]. Aside from skin grafting, the skin is also a common site for GVHD following bone marrow transplantation protocols used in the treatment of leukemia. Interestingly, the trafficking of alloreactive cells into the skin and their subsequent attack of local tissue appears to require an initial inflammatory reaction in the skin, which signals their recruitment [133]. Furthermore, Th17 do-

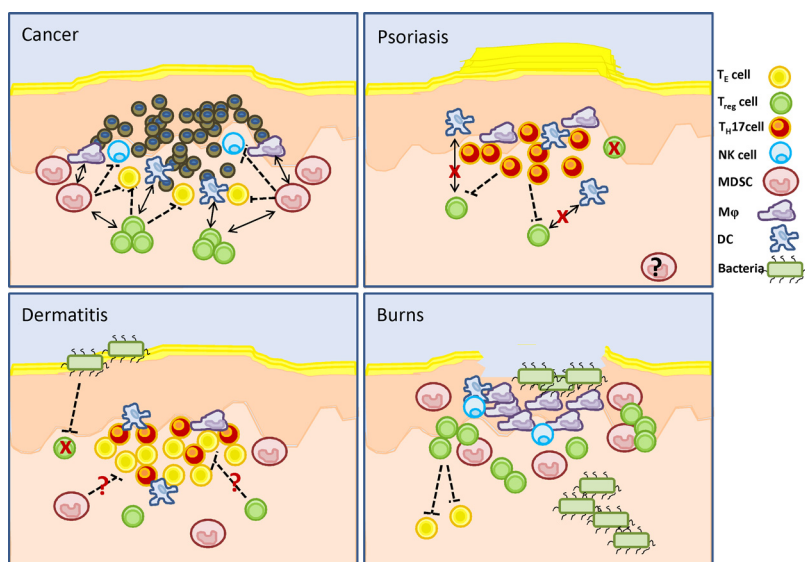


Figure 1. Proposed role of immune-regulatory cells in skin pathology. In cutaneous malignancies, Tregs and MDSCs are expanded and are able to suppress various arms of the immune system, including NK and T cells, and modulate macrophages to allow tumor escape from immune surveillance. In this environment, DCs and Tregs have been shown to interact and lead to their further expansion and suppressive function. In psoriasis, Tregs are outnumbered by the pathogenic Th17 cells, which produce various factors that can exacerbate the disease and inhibit Tregs. Furthermore, Tregs may not be able to interact effectively with other immune cells that are critical for their suppressive activity. The role of MDSCs in psoriasis has not been investigated. In AD and contact dermatitis, Tregs may also be outnumbered, and their suppressive function may be inhibited by various mechanisms, such as bacterial-produced toxins. In burn wounds, there is a great expansion of inflammatory cells, Tregs, and MDSCs, which can contribute to the inflammation and also suppress immune defense against infections. T_E, Effector T cell; M ϕ , macrophage. Arrows, Interaction; dashed lines, suppression; "X", a block in communication or suppressive function; "?", unknown function.

nor cells may be critical in the process of cutaneous GVHD [134], and regulatory cells, which are capable of suppressing this population, need to be analyzed. Thus, a better understanding of how to suppress alloreactive cell expansion and recruitment into organs, such as the skin, deserves more exploration. Determining methods to increase regulatory populations and their effectiveness may enhance skin grafting and also, provide a long-lasting method of tolerance in various transplantation protocols.

CONCLUSION

It is clear that immune-regulatory cells, such as Tregs and MDSCs, play a role in the immune response accompanying various skin pathologies. These cells may prevent or contribute to the pathophysiology of various cutaneous conditions (Fig. 1). In malignancies, these cells suppress anti-tumor immunity by NK cells and effector T cells and alter macrophages to a suppressor M2 phenotype, allowing the tumor to escape immune surveillance. In psoriasis, Tregs may not be able to suppress the pathogenic T cells, as they are outnumbered, or their suppressive function is inhibited. Likewise, in AD or contact dermatitis, the suppressive capability of Tregs and MDSCs may be inhibited as a result of being outnumbered or suppressed by various mechanisms, such as bacterial-produced toxins. Additionally, these immune-regulatory cells may produce various factors that exacerbate the inflammatory environment. This has been shown for burn wounds, in which these cells contribute to inflammation and also prevent immune defense against bacterial infection. On the other hand, their immune-suppressive function is beneficial in maintaining tolerance in transplantation. Elucidating how these immune-regulatory cells are expanded and their function, enhanced or inhibited, can benefit therapeutic design. These cells are thus attractive therapeutic targets that deserve further exploration in the various skin pathologies described.

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