Inflammatory Skin Disease Treatment

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Treatment goals of inflammatory skin diseases are mainly symptom control and improving quality of life. The treatment options for inflammatory skin diseases include corticosteroids; vitamin D3 analogues; disease-modifying anti-rheumatic drugs, such as methotrexate and cyclosporine; and newly developed biological-targeted drugs targeting on the IL-23/Th-17 axis, such as brodalumab and risankizumab . Both expensive biologics and systemic treatment may cause serious side effects.

Keywords: skin barrier ; inflammatory skin ; topical treatment ; stratum corneum ; formulation

1. Introduction

Stratum corneum, the epidermis' most superficial layer, serves as a protective barrier against the external environment and protects inner cells from dehydration, infection, and physical, chemical, and mechanical insults [1][2]. Skin barrier integrity can be influenced by various factors such as differentiation, proliferation, and adhesion of epidermal cells and skin lipids. Dysfunction of the skin barrier can cause skin disorders, for example, atopic dermatitis, psoriasis, and eczema. On the contrary, skin disorders can also impair the skin barrier [3][4].

On the other hand, the stratum corneum also works as the first limiting barrier for drugs to be transported into the skin [5]. The skin barrier can resist the penetration of many molecules. The 500 Dalton rule proposes that for skin absorption, a compound must be under 500 Dalton and larger molecules cannot pass the corneal layer [6]. Therefore, different strategies have been developed to overcome this issue and achieve successful topical drug delivery [5].

However, for inflammatory skin disorder treatment, topical delivery strategies must be extremely careful to prevent inducing a further inflammatory reaction whilst achieving effective drug delivery to the target site. Thus, this review focuses on and briefly reviews the available data on these issues whilst providing opinions on strategies to develop a suitable formulation for inflammatory skin diseases treatment.

2. Inflammatory Skin Diseases

Skin barrier, innate immunity and acquired immunity are the three major components of the skin's host defense system. The dysfunction of any of these components may lead to inflammatory skin disorders, unless there is a general response to specific infectious pathogens or internal/external damage [7]. As mentioned in the introduction, the stratum corneum serves as a protective barrier against the external environment and protects inner cells from physical, chemical, and mechanical insults [1][2]. Dysfunction of the skin barrier may lead to a skin inflammation response whereby the signaling molecules are released from the injured stratum corneum, initiating a cytokine cascade and triggering an inflammatory response, which then contributes to the pathogenesis of a variety of dermatoses [8][9].

Physical barriers such as the tight junctions between the stratum corneum, white blood cells such as neutrophils, basophils, eosinophils, monocytes, macrophages, reticuloendothelial system, and natural killer cells, as well as membrane-bound receptors and intracellular proteins, are all parts of innate immunity [10]. Additionally, the acquired immunity can identify the pathogen quickly and creates a faster and more intensive response upon re-contact [10]. An effective skin immune response requires antigen-specific T cells located in the damaged or infected skin area. Among the memory T cells, tissue-resident memory T cells remain in the skin for long periods of time and involve lasting protective immunity as well as the regulation of several inflammatory skin diseases [11].

Based on the involved T cell subtypes, T-cell-mediated diseases can be classified into T helper 1 (Th1) cell-dominated such as vitiligo, T helper 2 (Th2) cell-dominated such as atopic dermatitis, and Th1/T helper 17 (Th17) cell-involved responses such as psoriasis, and regulatory T (Treg) cell-based responses such as melanoma [12].

The estimated prevalence of vitiligo is in about 1% of the global population. (Tc1) cell 1-dominated immune response is well demonstrated in vitiligo. Recent studies reported that vitiligo patients had elevated numbers of circulating Th1/17 cells and Tc1/17 cells [13][14]. This result may imply an unbalanced barrier homeostasis/impaired barrier function in vitiligo.

Increased trans-epidermal water loss value, changes to the skin surface pH, and skin dehydration may lead to severe atopic dermatitis because of the loss of function or mutations in filaggrin. and Th22 cells, which may all contribute to skin barrier disruption and the development of atopic dermatitis. The Th2 cells mediated immune responses may also boost the IgE-mediated hypersensitivity response and facilitate atopic dermatitis development [15][16]. Antibiotic treatment is effective in treating or preventing secondary skin infections, whilst ultraviolet phototherapy is another safe and effective treatment option for moderate to severe atopic dermatitis.

Psoriasis is an immune-mediated genetic disease that causes red, flaky, and crusty skin patches covered with silvery scales. The most frequent histopathological findings in psoriasis are inflammatory cell infiltration, vascular dilatation, absence of the granular layer, regular elongation of rete ridge, elongation of the dermal papillae, and parakeratosis [17]. Genetic, immunological, and environmental factors are related to the pathogenesis of psoriasis. Various predisposing factors may cause psoriasis in genetically susceptible populations.

About 75% of all psoriasis patients can be appropriately treated with topical glucocorticosteroids, vitamin D derivatives, or combinations of both [17][18]. However, the practicability, convenience, and adverse effects such as skin irritation may limit the use of topical drugs [17]. Phototherapy and systemic treatments are other effective methods of psoriasis management. However, the cumulative toxicity potential of individual therapy limits the duration of treatment [19].

The recently developed and approved biological drugs targeting TNF-α, IL-23, and IL-17 provide another choice for psoriasis treatment. The inflammatory response induced by the IL-23/Th17 axis can be blocked by either directly or indirectly inhibiting IL-17-producing cells or their receptors. However, the use of biological drugs has dramatically changed the treatment and management of psoriasis [20]. At this present time, there is still no curative treatment for psoriasis.

Compared with the normal un-lesion skin site, amounts of active macrophages, dendritic cells, mast cells, and natural killer cells were redistributed at the melanoma lesion site [21][22]. Langerhans cells, melanocytes, and Merkel cells are three main resident dendritic morphology cells in the skin. Langerhans cells are known to have the capacity to present antigens and are essential for initiation and maintenance of specific T-cell-mediate responses in the skin [21][23]. Ultraviolet light exposure might also lead Merkel cell mutations to progress as Merkel cell carcinoma [24].

Naive T cells can be differentiated into several different types of effectors and regulatory T cells. Specific cytokines and transcription factors contribute to the differentiation and expansion of these effectors and regulatory T cell populations. Their differential activation plays an important role in determining whether the immune response contributes to either host protection or pathological inflammation [15][16][25].

Unlike Th1, Th2 and Th17 cells, which may mediate harmful skin inflammation processes, Treg cell are involved in the down-regulation immune response. Th2 cells produce a panel of cytokines such as IL-4 and IL-13, which also contribute to abnormal keratinocyte proliferation. In response to IL-4 and IL-13, B cells produce high amounts of IgE. Cutaneous resident and infiltrated cells release Th2-related chemokines such as cc chemokine ligand 17 (CCL17), CCL22, and CCL26. Th2 cells also release IL-31, which may stimulate sensory nerves, triggering the itch sensation.

In the IL-23/Th17 axis, the activated Th17 cells product cytokines IL-17A and IL-17F stimulate keratinocytes. The stimulated keratinocytes lead to abnormal differentiation and proliferation as well as an elevated production of proinflammatory cytokines such as IL-1 and TNF-α, antimicrobial peptides, and chemokines such as CCL20. The immune responses and abnormal keratinocyte differentiation and proliferation lead to a dysfunctional skin barrier and skin dehydration. The impaired skin barrier and dysregulated or misdirected immune response may result in chronic inflammatory skin.

To provide a global view of the relationship between T cells and the inflammatory skin barrier, Figure 1 illustrates the T cells involved in immune responses and the mechanisms of barrier dysfunction.

Treatment goals of inflammatory skin diseases are mainly symptom control and improving quality of life. Both expensive biologics and systemic treatment may cause serious side effects. Therefore, topical treatment for local inflammatory skin diseases is considered safer to use. As such, a suitable topical delivery formulation is necessary for appropriate selection and development to improve therapeutic effects and treatment adherence, as well as to reduce side effects.

3. Skin Microbiota

With the advances of computing and high-throughput bacterial 16S rRNA genes sequencing technology, scientists in microbiology and dermatology can now analyze, identify and characterize different microbiota compositions in depth. The new subject of the role/functionality of skin microbiota in cutaneous disorders and the cross-talk network with immune responses and skin barrier functions can now discover significantly more than it could last decade. Different, healthy skin sites have different diverse microbe communities. Allergic or inflammatory status may arise when changes in steady microbiome occur [26][27][28].

The term “commensal-epidermal homeostasis” means the homeostatic interactions between normal skin commensal microbiota and the epidermis physical barrier. For example, the natural moisturizing factors and metabolites from skin commensal microbiota contribute to acidic skin may alert the diversity of skin microbiota [27]. External stimulus and pathogens may then further impairer the skin barrier and result in inflammatory skin diseases.

Decreased commensals abundance may contribute to the progression and exacerbation of inflammatory skin diseases, such as atopic dermatitis [27]. However, studies reported that the richness and diversity of skin microbiota could be reversed by topical emollients [29][30][31][32]. Thus, topical treatment to restore the skin barrier function is the primary prevention for developing inflammatory skin disease; however, selecting suitable topical formulation ingredients to maintain commensal-epidermal homeostasis is necessary.

4. Topical Formulation Development Strategies

Solvents such as ethanol, propylene glycol and both dimethyl sulfoxide and ointments are the most common topical vehicles for lipophilic substances, yet solvents are limited as they are too fluid to be adsorbed on the skin surface. Experimental data demonstrates that solvents such as polyethylene glycol, propylene glycol, alcohols, dimethyl sulfoxide, and dimethyl acetamide may cause dehydration of the horny layer of the epidermis [33][34]. The therapeutic approach to inflammatory skin is directed at restoring the skin barrier function and reducing dehydration, for example, atopic dermatitis [29]. Unlike other delivery vehicles, the ointment base affects the active compound’s bioavailability due to its occlusion effect on the stratum corneum, which then increases drug penetration/diffusion across the skin [35].

Emulsions including lotion, cream, nano-/micro-emulsion and liposomes are alternative approaches for the topical delivery of both hydrophilic and lipophilic compounds. The compositions of the selected phospholipid type, surface charge and phase transition temperatures have been shown to affect the topical delivery of liposomes [36]. Emulsifying agents and oil-in-water emulsions may also lead to dehydration of the horny layer of the epidermis and can cause damage to the barrier [36][37][38]. Our ongoing study has also demonstrated that generic desoximetasone cream containing too many emulsifying agents such as Span 60 and Tween 60 results in a poor therapeutic outcome in the imiquimod induced psoriasis-like animal model (Figure 2).

On the other hand, a penetration enhancer is one of the most common and useful strategies to overcome natural defects, such as achieving the molecular weight of over 500 Dalton of the selected compound, or to increase the skin deposition/permeation amounts on the target site [37][39]. Chemicals such as short-chain fatty acids and surfactants called skin penetration enhancers, percutaneous absorption promoters or accelerants produced a shift in the C-H2 asymmetric/symmetric stretching vibration of the stratum corneum lipid, resulting in increased wavenumbers and a disordered intercellular lipid structure between corneocytes in the stratum corneum. As a result, the impaired inflammatory skin barrier treated by a drug containing penetration enhancers may lead to increased barrier damage severity and a greater inflammatory response. To avoid the damaging effect caused by the formulation excipients such as emulsifying agents, alcohols, and chemical enhancers, the addition of moisturizers/humectants, such as glycerol and urea, is recommended [40][41].

Due to high specificity and potency, proteins and peptides have become increasingly considered as therapeutic methods for serious and complex diseases such as cancer or autoimmune diseases. Because of their unique structure and unstable physical-chemical properties, proteins and peptides require more attention during manufacture/formulation and the administration process. The topical application of proteins and peptides is an attractive option and highly recognized by patients compared with conventional systemic injections [42]. Transdermal delivery of proteins and peptides could be more effective by using chemical penetration enhancers, transfersomes, nanoparticles delivery system, or cell-penetrating peptide

For instance, oleic acid, which works as a penetration enhancer, reduced the order of stratum corneum lipids, which then induced phase separation. The surfactant, such as Tween 20, then interacted with the stratum corneum lipids [43][44]. The compositions of the formulation may alter the skin integrity, increasing the permeability of drugs; however, such

manipulations may lead to more serious barrier damage and a greater inflammatory response in inflammatory skin. Thus, reducing the amounts of skin lipid bilayer perturbation ingredients is recommended for inflammatory skin formulation.

The transport of drugs through the skin may be carried out through three potential pathways: (1) the transepidermal route, which reaches across the continuous stratum corneum and can then be divided into (a) the intercellular route between the corneocytes and (b) the transcellular route through the corneocytes and interleaving lipids; (2) the trans-appendageal route, including sweat ducts, hair follicles, and associated sebaceous glands; (3) the micro-scale route, which stratum corneum is removed from by tape stripping, ablation, abrasion, or micro-needles, for instance. The compound may use more than one absorption/penetration route regarding the physicochemical properties of the selected compounds. For example, the transcellular route is suitable for transporting hydrophilic compounds, while the intercellular and trans-appendageal route is for lipophilic compounds [40][45][46].

Formulation may increase the epidermis or dermis deposition amounts of selected compounds due to the limit of nature physicochemical properties. For example, an oil-in-water microemulsion gel enhances one and a half folds of the epidermis deposition amounts of curcumin compared with the conventional delivery system in the mice skin model [47]. Try et al. reported that small polymeric nanoparticles (below 100 nm) loaded fluorescein can easily penetrate and accumulate selectively in the deep epidermis and hair follicles, while larger polymeric nanoparticles (around 300 nm) and fluorescein solution remain at the epidermis surface in two atopic dermatitis animal models [48]. Although using the formulation may increase drug skin deposition amounts, the ultimate goal of suitable topical formulation development should provide a safe and effective therapeutic approach for the management inflammatory skin diseases.

However, the barrier function between untreated normal healthy skin and inflammatory skin is quite different. This means that a small quantity of irritants may not achieve the minion concentration required to induce the redness and inflammation response in normal skin. In contrast, a very small quantity of irritants may evoke severe trans-epidermal water loss, skin erythema, and an inflammation response in inflammatory skin. Here, mice dorsal skin was applied with imiquimod for six consecutive days to induce inflammation of the skin, followed by the application of only selected formulation bases for another five days.

On the other hand, satisfaction with therapy, cosmetic acceptability, and complexity of the treatment regime may also affect treatment compliance [49]. Several studies have reported that cosmetic moisturizer generally appears well-tolerated and suitable for topical use on sensitive skin [50][51][52]. Moisturizers are standard adjuvant therapy for anti-inflammatory skin disorders in dermatology. Some moisturizers or skin care products may induce barrier disruption in sensitive skin [53].

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