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Inflammatory Markers for Potential Targeted Therapies for Psoriasis: A Review

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ABSTRACT

Psoriasis is characterized by the infiltration of immune cells, epidermal hyperproliferation, and abnormal keratinocyte differentiation. According to recent molecular and cellular research, the key contributors to the pathogenesis of psoriasis are tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin 17 (IL-17), and interleukin 22 (IL-22). Various approaches have been applied to treat psoriasis by suppressing inflammatory expressions, either through conventional therapy or nanotechnology therapy. Conventional therapy shows poor therapeutic effectiveness and requires prolonged treatment durations. These challenges can be overcome with advanced targeted drug delivery systems, which consist of passive targeting and active targeting, offering efficient site-specific delivery. In this review, we discuss the inflammatory markers that contribute to psoriasis and their potential in the development of potent targeted treatment drugs. Moreover, the applications of targeted drug delivery systems for treating psoriasis are summarized.

1. Introduction

Psoriasis is well known as a chronic inflammatory skin disease with a multifaceted cause involving genetic and environmental factors such as trauma and infections [1-3]. It usually appears as elevated, well-defined erythematous oval plaques with silvery scales, which can be found on any part of the skin [4]. The scales are caused by a hyperproliferative epidermis due to early maturation of keratinocytes [4]. This skin disease is characterized by abnormal differentiation of the keratinocytes, neovascularization, and infiltration of inflammatory cells, resulting in a decrease in skin barrier function and an excessive inflammatory response [3, 5, 6].

Keratinocytes regulate skin inflammation and can act as specific targets for a set of cytokines, influencing their biological functions such as the production of cytokines, chemokines, and antimicrobial peptides, as well as their differentiation and migratory capacities [7]. Although the

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causes and mechanisms of psoriasis remain incompletely understood, numerous studies have identified inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-17 (IL-17), interleukin-23 (IL-23), and interleukin-22 (IL-22) as key factors in the development of psoriasis [1, 8-10]. This has led to the development of highly effective targeted therapeutic agents, including cytokine inhibitors (TNF-α, IL-17, IL-23 inhibitors or receptor blockers) and small-molecule inhibitors like Janus kinase (JAK) inhibitors and phosphodiesterase-4 inhibitors (apremilast) [1, 8].

Furthermore, abnormal epidermal thickness reduces skin permeability, necessitating constant administration of drugs, which could result in drug overdose. It has been claimed that nanodelivery approaches significantly enhance topical and transdermal drug delivery [11, 12]. One hallmark of inflammatory skin diseases, which is high reactive oxygen species (ROS), offers an opportunity to develop nanocarrier technology and skin-specific responsive drug release platforms [13, 14].

Targeted drug delivery offers certain benefits, including fewer adverse effects, increased drug absorption, and lower dosages compared to conventional drug delivery [15]. Targeted drug delivery can be classified as passive targeting and active targeting. In passive targeting, the therapeutic agent is encapsulated into nanoparticles that passively enter the target organ. In active targeting, ligand-conjugated nanocarriers bind to overexpressed receptors on specific cells, where these receptors are minimally or not at all expressed on normal cells.

To achieve precise targeting, the inflammatory markers or expressions in psoriasis can be potential targets for creating nanomedicine applications. The main common therapeutic targets are TNF-α, the p40 subunit of cytokines IL-12 and IL-13, IL-17, and the p19 subunit of IL-23 [16] . Recent data showing that immune cells infiltrating psoriatic skin secrete large amounts of several inflammatory cytokines, including IL-22, IL-17A, and IL-23, led to the classification of psoriasis as a paradigm of an inflammatory disease involving the proinflammatory Th17 subset, challenging the previously accepted Th1 theory [7].

Figure 1 summarizes an overview of the pathogenic mechanisms underlying psoriasis, which involves epidermal hyperproliferation, abnormal keratinocyte differentiation, and infiltration of inflammatory cells and cytokines. Among these, TNF-α, IFN-γ, IL-17, IL-22, and IL-23 play key roles in driving chronic inflammation and keratinocyte activation in psoriasis, making them promising therapeutic targets for the development of targeted drug delivery systems. In this review, the role of inflammatory markers in psoriasis and the use of nanotechnology in its treatment will be discussed. This review also focuses on the research progress of targeted drug delivery, including passive and active targeting approaches.

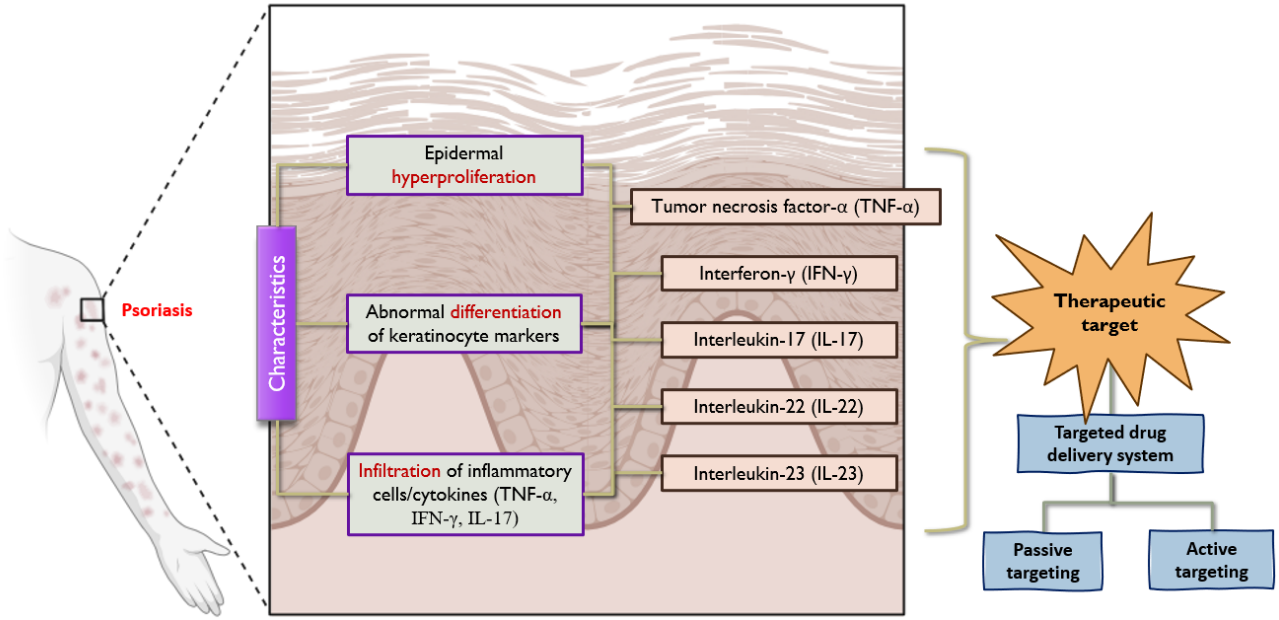

Fig. 1. Overview of psoriasis pathophysiology and its potential therapeutic targets for targeted drug delivery systems

2. Role of Cytokines as Psoriasis Markers

Psoriasis cannot be fully described as a T-cell-dependent disease, as intrinsic changes in epidermal keratinocytes likely play a significant role in initiating and maintaining its chronic phase. [17]. Numerous studies suggested that the interplay between cytokines expressed in psoriasis skin could explain features of psoriasis, such as the hyperproliferation of keratinocytes, increased inflammation, and neovascularization [18]. The most represented cytokines during the chronic stage of psoriasis are tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin 17 (IL-17) and interleukin 22 (IL-22) as key regulators of epidermal activities, and their receptors have been discovered on keratinocytes [19].

2.1 Interleukin-17

IL-17 is produced by T cells, innate lymphoid cells and mast cells [15, 20]. IL-17 activates keratinocytes, which in turn brings out inflammatory cytokines, thereby activating skin-resident T-cells and increasing a vicious circle of inflammatory interaction between the skin and immune system [20]. The IL-17 family consists of six isoforms (IL-17A to IL-17F) [21]. IL-17A is the best known as an important mediator of psoriasis among IL-17 family members and has been linked to the pathophysiology of autoimmune and chronic inflammatory disorders [22] . A study of reconstructed human epidermis (RHE) stimulated with a mixture of IL-17, IL-22 and TNF-α to mimic psoriasis showed destabilization of the epidermis, small pycnotic cells associated with parakeratosis, and a tendency to the disappearance of the granular layer that was caused by IL-17 [23].

2.2 Interleukin-22

IL-22 is an important cytokine in psoriasis that is released by Th-17 and Th-22 cells, promoting hyperplasia of keratinocytes through the STAT3 signaling pathway [15, 24]. Under inflammatory

circumstances, IL-22 could be one of the mediators that promote keratinocyte migration and wound healing through MMP-3- or S100A8-S100A9-dependent processes [25]. IL-22 has the most dramatic impact on keratinocyte proliferation (based on increased expression of the hyperproliferative marker K16) and differentiation, including hypogranulosis [23, 26]. A study reported that the reconstructed human epidermis (RHE) incubated with IL-22 showed hyperplasia of keratinocytes that caused a rise of thickness in the in the epidermis as well as lowered expression of differentiation-related genes (involucrin, loricrin, and filaggrin) and also increased psoriasis expressions such as keratin 6, CXCL5, and S100A7 [25]. The extreme thickness of the epidermis not only happens because of the impaired keratinocyte differentiation in the upper epidermis layers but it may potentially be contributed by the hyperproliferation of basal layer keratinocyte [27, 28].

2.3 Interleukin-23

Interleukin-23 (IL-23) is a member of the IL-12 cytokine family that is produced by antigen-presenting cells such as macrophages and dendritic cells that are principally responsible for the activation of Th-17 cells for the generation of Th-17 cytokines (e.g., IL-17A and IL-22), which are significant regulators of keratinocyte hyperplasia in psoriasis [15, 20, 29]. It is known as a novel pro-inflammatory cytokine that shares strong similarities to IL-12 has been linked to a number of autoimmune diseases including gastritis, colitis, psoriasis and arthritis [29, 30]. Both IL-23 and IL-12 have similar structures and have the capability of increasing interferon-γ (IFN-γ) production and proliferation by memory T cells. Nevertheless, the ability of IL-23 to produce IL-17 provides a unique or distinct role compared to that of IL-12 in the development and maintenance of autoimmune inflammation [31].

2.4 Tumor Necrosis Factor-α

Tumor necrosis factor-α (TNF-α) is an important inflammatory cytokine in psoriasis disease due to its immunomodulatory properties [32]. TNF-α increases innate immune cell activation and trafficking to the skin, resulting in faster keratinocyte proliferation in psoriasis [33]. TNF-α stimulates keratinocytes to produce intercellular adhesion molecule-1 (ICAM-1) and produces IL-8 in dermal fibroblasts, keratinocytes and endothelial cells [34] . TNF-α is also a strong inducer of inflammatory gene products in human keratinocytes, some of which overlap with IL-17-regulated genes in keratinocytes. TNF-α primarily regulates target gene transcription by activating NF-κB, and TNF-α-induced genes in keratinocytes closely resemble known NF-κB target genes [32]. Besides, TNF-α can work together with the other cytokines present in the lesions and boost its inflammatory activity in psoriasis.

3. Targeted Drug Delivery System for Psoriasis

Numerous studies show that the current approach of targeted drugs in the management of psoriasis provides advantages over conventional therapy. This approach is safe and effective for the delivery of anti-psoriatic drugs and in maintaining local drug concentrations to better treat psoriasis [35]. There are two approaches to targeted delivery systems which are passive targeting and active targeting. Their structural comparisons are shown in Figure 2. In passive targeting, anti-psoriasis drugs are encapsulated within nanocarriers that enter the target site passively. In active targeting, nanocarriers are conjugated with ligands that specifically bind to overexpressed receptors on

psoriasis-affected cells, ensuring precise drug delivery. This approach enhances drug efficacy and reduce side effects by targeting diseased cells while protecting healthy cells.

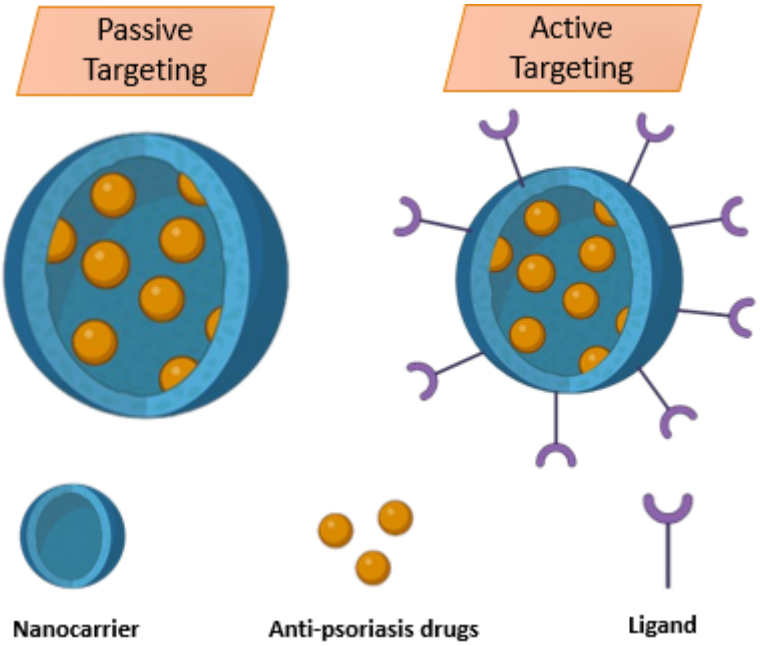

Fig. 2. Comparison structure of targeted nanocarrier systems for psoriasis treatment between passive targeting and active targeting

3.1 Passive Targeting of Psoriasis Markers

Passive targeting occurs when a drug accumulates in a specific location of a targeted area due to its biophysical features, which are based on the enhanced permeability and retention (EPR) effect [35-38]. A particular instance of passive targeting is the site-specific delivery of anti-psoriatic therapies at the nanoscale, where their differential distribution in the skin region is based on the size of the treatment-loaded particles.

The main objective for treating psoriasis is improved skin penetration. A study by Liu *et al*. had created liposomal spherical nucleic acids (SNAs) that are used topically to treat psoriasis. The nanocarriers successfully pass through the epidermal barriers due to excellent fluidity along with the particular interaction that exists between lipids and epidermal lipids. Psoriasis pathogenesis is driven by hyperproliferation, and abnormal differentiation of epidermal keratinocytes induced by IL-23 and IL-17 pathways. With its spherical form, SNAs could successfully target the gene encoding the mouse IL-17A receptor (IL17ra) and reverse psoriasis's growth in imiquimod-treated psoriasis-like mice's skin clinically, histologically, and transcriptionally [39].

Combination therapeutic treatment between psoralen with ultraviolet A radiation (PUVA) for severe recalcitrant psoriasis is an FDA-approved therapy regimen that can alleviate skin cell proliferation [40]. A psoralen-encapsulated liposomal system was created by Doppalapudi *et al*. to increase topical efficacy and safety. The psoralen liposomal system demonstrated a five-fold increase in skin penetration when compared to the psoralen solution. The nanocarrier formulation reduced psoriasis symptoms and inflammatory mediators (TNF-α, IL-22, and IL-17) in an imiquimod-induced psoriatic plaque model [41].

Jain *et al.* formulated the topical administration of thymoquinone via liposphere for psoriasis therapy [42]. In vitro studies revealed a decrease in nitric oxide levels and inflammatory cytokines, including TNF-α, IL-1β, IL-2, and IL-6. Meanwhile, in vivo studies showed lower levels of TNF-α and IL-

17 in psoriatic skin, suggesting enhanced efficacy in psoriasis [42]. Sathe *et al*. successfully prepared nanostructured lipid carriers (NLCs) of dithranol-loaded gel to make application easy for the effective treatment of psoriasis [43]. Topical treatment of dithranol-loaded NLC gel on IMQ-induced psoriatic plaque model decreased psoriasis symptoms and cytokines levels including IL-17, IL-22, IL-23, and TNF-α [43]. NLC gel was efficient at the same drug concentration but resulted in less cloth staining as compared to conventional ointment [15].

Mao *et al*. developed curcumin-loaded nanoparticles (CUR-NPs), where curcumin was encapsulated into the cationic RRR- α-tocopheryl succinate-grafted-ε-polylysine conjugate (VES-g-ε-PLL) which was developed and self-assembled to become polymeric nanoparticles [44]. Curcumin, a polyphenol derived from turmeric, exhibits antioxidant, antimicrobial, and anti-inflammatory properties, making it a potential treatment for reducing psoriasis symptoms [45-47].The formulation allowed for a deeper absorption into the skin [15]. Silk fibroin was employed as a hydrogel-based matrix to extend the retention period of the NPs in the skin and improve the drug's topical distribution. Inflammatory cytokines such as TNF-α, NF-κB, and IL-6 were effectively suppressed [44].

Wang *et al.* effectively synthesized flexible liposomes co-loaded with transretinoic acid and betamethasone. The formulation showed that application in gel form can reduce the thickness of the epidermis and decrease psoriasis cytokine levels such as TNF-α and IL-6 [48]. Freag *et al*. reported that the formulation of berberine oleate loaded liquid crystalline nanoparticulates (Brb-OL-LCNPs) was efficient for a topical regimen for psoriasis management [49]. Lyotropic liquid crystalline nanoparticles are promising carriers for skin administration and have the potential to modulate the stratum corneum barrier. *In vivo* study revealed that Brb-OL-LCNPs significantly reduced the expression of inflammatory cytokines such as IL-17 and IL-23 [49].

Meng *et al*. created an innovative topical niosome loaded with celastrol and demonstrated its efficacy in reducing symptoms of psoriasis such as scaling and erythema in a mouse model [50]. In addition, noisome treatment also reduced spleen size and cytokine levels (IL-22, IL-23, and IL-17), indicating that it has promising therapeutic potential in psoriasis [50]. Fan *et al*. prepared a polymer-based nanocarrier that is modified c-Rel specific siRNA (siRel) loaded poly (ethylene glycol)-b-poly(L-lysine)-b-poly(L-leucine) (PEG-PLL-PLLeu) micelles [51]. The proposed formulation effectively lowered the expression of c-Rel, a susceptibility locus for psoriasis. Besides, the modified polymeric micelles decreased IL-23 expression, a major cytokine associated with the development of psoriasis [51].

Sharma *et al*. designed a squalene-incorporated nanostructured lipid carrier (NLC)-based gel of tamoxifen citrate to boost the lipid and water content of the skin and form a local depot in the skin for enhanced efficacy in psoriasis [52]. The analysis of the in vivo study revealed improved efficacy in suppressing PASI scores, pro-inflammatory cytokine levels, and reinstating splenomegaly and other histological abnormalities to normal [52]. Desmet *et al.* evaluated 'DDC642' as a novel liposomal carrier, that is capable of operating on the epidermis of compromised and intact human skin, transferring siRNA molecules without damaging the blood capillaries or dermis [53]. The DDC642 delivering or carrying siRNA was also evaluated on a psoriasis tissue model, resulting in the downregulation of the human beta-defensin 2 psoriasis markers [53].

3.2 Active Targeting of Psoriasis Markers

Targeted drug delivery systems in the management of psoriasis are an excellent way to deliver loaded therapies to specific cells in the skin, which results from a combination of inflammatory and immunological responses in psoriatic skin. [35]. Several targeting ligands, including folic acid,

carbohydrates, peptides, aptamers, and antibodies, have recently been used in targeted drug delivery systems. Active targeting technique allows drugs to get into tissues at the molecular level [36]. In fact, nanoparticles offer promising applications in diagnosing and treating diseases. In active targeting process, ligand nanoparticle conjugation will recognize their receptor or target cells to link via ligand-receptor interactions [37]. Then, the conjugated nanoparticles are internalized before the drug is released within the cell. As a result, less off-target drug release compared to a passive targeting approach.

The greater targeting ability of nanocarriers can help to improve drug bioavailability and psoriasis treatment outcomes [14]. Zhang *et al.* combined hyaluronic acid (HA) with propylene glycol-based ethosomes for topical administration of curcumin, targeting CD44 in the inflammatory epidermis of psoriatic lesions [6]. CD44 expression is upregulated in the epidermis of inflamed psoriatic skin but the distribution of HA which is a natural ligand for CD44 showed a significant decrease [54, 55]. This suggests that overexpressed CD44 protein could be a suitable target for nanocarriers to increase skin medication retention and improve treatment efficacy. Nanocarriers containing HA as targeting ligands demonstrated higher anti-inflammatory effects than the ethosomes and propylene glycol solution (PGS) groups [6].

Xi *et al.* designed celastrol-loaded mannose-modified liposomes (CEL-MAN-LPs), where mannose was grafted onto liposomes to bind with the mannose receptors on dendritic cells for psoriasis treatment [56]. Surface-specificity modified nanoparticles, which can be identified by receptors on the surface of dendritic cells, have been used in cancer as well as inflammation therapies [57]. High expression of mannose receptors on dendritic cells makes them ideal targets for receptor-mediated delivery methods. The formulation of CEL-MAN-LPs was found to be more effective than CEL and CEL-LPs in reducing psoriasis symptoms and suppressing inflammatory cytokines (IL-1β, IL-6, IL-17A, IL-23 and TNF-α) in this study [56].

4. Potential Receptors for Targeted Therapies for Skin Disease

The targeting of potential receptors in any skin disorder might be helpful to treat psoriasis, as it shares similar inflammatory expression. Besides, it might be helpful and useful in systemic or topical therapy by enabling drug formulation to deal specifically with pathogenic molecular targets.

Numerous studies reported that intercellular adhesion molecule-1 (ICAM-1; CD54) is upregulated in epidermal keratinocytes under inflammatory skin conditions such as psoriasis, allergic contact eczema, exanthema, and others [58, 59]. The selective expression of ICAM-1 in inflammatory skin conditions allows for the targeting of certain drugs using active targeting nanocarriers. Jaafari *et al*. prepared a liposome that was bound to peptides derived from P0 protein to investigate the ability of the modified liposome to specifically interact with interferon-(IFN-)-stimulated keratinocytes [60]. It showed that peptides derived from the P0 protein that linked with the liposome able to specifically target ICAM-1 expression and suggested applying them topically as the action site would be directly accessible [60]. Another study by Jaafari *et al*. reported that the reconstitution of P0 protein with liposome bilayer can induce binding to melanoma cells with high levels of ICAM-1 expression and might be an effective targeting strategy [61].

The use of PEGylated liposomes is a drug delivery method that is usually used for systemic and transdermal drug delivery [62]. Knudsen *et al*. designed calcipotriol that was encapsulated into liposomes with the lipopolymer poly (ethylene glycol)-distearoylphosphoethanolamine (PEG-DSPE) to study the effect or modified liposome for topical delivery of calcipotriol [63]. The utilization of PEGylated liposomes allows for active targeting approaches to certain cell types in the skin by conjugating receptor-specific ligands to the distal ends of the PEG chains. A current instance is the

discovery and conjugation of a new 12 amino acid peptide ligand generated from the Jararhagin protein to the distal ends of PEG chains on the surface of PEGylated gel-state liposomes [64, 65]. This ligand targets liposomes to the integrin $\alpha_2\beta_1$ receptor, a collagen I receptor found on keratinocytes in the basal layer of the skin [66].

5. Conclusions

Psoriasis is an inflammatory skin condition recognized as a serious dermatological problem globally. Many studies show that targeted drug delivery is gaining significant attention since it provides new opportunities and aspects for an outstanding delivery method. Therefore, new discoveries and an enhanced understanding of inflammatory pathways could contribute to improved treatment methods for psoriasis therapy. These findings are expected to aid in understanding the functions of cytokines as psoriasis markers, the current targeted drug delivery systems for psoriasis treatment, as well as the potential receptors that could be found in psoriasis for future and ongoing research in the development of drug delivery systems.

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