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RECENT DEVELOPMENTS OF VARIOUS APPROACHES FOR THE TREATMENT OF ACNE: A SKY-HIGH PERSPECTIVE

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ABSTRACT

Acne vulgaris is a chronic inflammatory human skin condition marked by seborrhoea, comedones, papules, nodules, pimples, and perhaps scarring on the face, neck, and back. The pathogenesis of acne is multifactorial. Traditionally, four distinct processes were believed to play critical roles: increased sebum production, alteration of keratinization processes leading to comedone formation, follicular colonization by *Propionibacterium acnes* (*P. acnes*). The main objective of this project is to highlight the emerging evidence in the complex pathogenesis of acne vulgaris and provide an overview of the novel molecules being evaluated for treatment of acne, with a short focus into relevant pathogenic pathways in relation to mechanisms of action of these novel therapeutic targets like PPAR modulators, anti-androgens, melanocortin receptor, IGF-1 inhibitors, Coenzyme-A Carboxylase Inhibitors, Retinoic acid receptor-γ agonist, Phosphodiesterase 4 inhibitor, Liver X-Receptor (LXR), NMDA antagonist, Stearoyl-CoA desaturase-1 inhibitor, Leukotriene A4 hydrolase inhibitor, Acetylcholine (Ach) inhibitors, Inhibitor of cathelicidin activation and metalloproteinases activity, Specific competitive inhibitor of 5α-reductase etc.

KEYWORDS: Acne vulgaris; *Propionibacterium acnes;* pathogenesis; PPAR modulators; melanocortin receptor; IGF-1; Retinoic acid receptor-γ; LXR; 5α-reductase etc.

INTRODUCTION

Acne vulgaris (commonly known as simply acne) is a chronic inflammatory human skin condition marked by seborrhoea (scaly red skin), comedones (blackheads and whiteheads), papules (pinheads), nodules (big papules), pimples, and perhaps scarring on the face, neck, and back. The swollen glands form pink papules, encircled by comedones from pustules or cysts initiated by anxiety, hereditary factors, hormones, and bacteria that is, *Propionibacterium acnes*.[1]

According to the Global Burden of Disease (GBD) study, acne vulgaris affects ~85% of young adults' aged 12–25 years. The pathogenesis of acne is multifactorial. Traditionally, four distinct processes were believed to play critical roles: increased sebum production, alteration of keratinization processes leading to comedone formation, follicular colonization by *Propionibacterium acnes* (*P. acnes*) and inflammatory mediators around pilosebaceous unit (PSU). The main objective of this project is to highlight the emerging evidence in the complex pathogenesis of acne vulgaris and provide an overview of the novel molecules being evaluated for treatment of acne, with a short focus into relevant pathogenic pathways in relation to mechanisms of action of these novel therapies.[2,3]

Hyperkeratinisation (plugging) of the pilosebacous follicles, elevated testosterone levels, bacterial colonisation with Propionibacterium acnes, and

inflammation are all part of the etiopathogenesis of acne vulgaris. As a result, combination regimens, which usually include an antibiotic and a follicular plugging reducer, have become the standard of care. Despite a scarcity of novel treatments for nearly a decade, recent research has resulted in the development of a number of important oral and topical medicines. Azelaic acid, a naturally occurring dicarboxylic acid analogue, has showed promise, while retinoids such as adapalene, tazarotene, and tretinoin reformulations are among the new and upcoming medicines for acne vulgaris treatment.[4]

Current understanding of acne pathogenesis continues to evolve. Acne is an androgen-dependent disorder of pilosebaceous follicles. There are four primary pathogenic factors that interact to produce acne lesions: (i) increased and altered androgen-dependent sebum production; (ii) altered keratinization leading to comedones; (iii) *Propionibacterium acnes* follicular colonization; and (iv) release of inflammatory mediators into the skin. Although family history and environment factors have an important role in the disease, the exact sequence of events and how they interact remains unclear.[5] Management, therefore, is a multifactorial approach with several treatment options targeted toward the multiple factors contributing to acne pathogenesis. Treatment decisions for patients with acne are compounded by the profusion of available treatments and by the relative paucity of trials with active comparators. Concerns about antibiotic resistance and isotretinoin safety as well as the rise of novel adjunctive treatments bring new perspectives to the treatment of acne. Alternatives to refractory acne, aversion to prescription medications, adverse effects to conventional therapy, and poor adherence to conventional therapy drive interest in novel approaches. This review summarizes the latest developments in the treatment of acne and their rationale and likely place in treatment.[6]

Acne vulgaris is currently treated with either topical benzoyl peroxide, retinoids, and antibiotics like erythromycin or clindamycin, or oral drugs like retinoids and antibiotics from the tetracycline and macrolide groups. In the case of severe acne, however, combined therapies are usually used. Even though antibiotics can reduce acne inflammation and target *P. acnes*, the emergence of antibiotic resistance in *P. acnes* and other acne-causing bacterial species necessitates the development of new treatment drugs. Natural substances such as diverse sections of plants, spices and condiments, and minerals, which have been employed in traditional systems of medicine, could be examined as potent sources for novel antiacne drugs in this regard.[7,8]

Liposomes, niosomes, microsponges, nano-emulsion and micro-emulsion, microspheres, and solid lipid nanoparticles are some of the nanotechnology-based acne treatments that have proven to be effective. Encasing an anti-acne medication molecule in a specific nanocarrier system has been found to improve patient compliance and reduce negative effects.[9] Their efficacy as regulated active component delivery strategies beat standard administration systems' acknowledged limitations, such as low biodistribution, poor efficacy, and toxicity. Nanosystems are also beneficial because they preserve the properties of entrapped active substances (especially labile active ingredients), improve entrapment efficiency (EE), promote penetration, and transport active chemicals to specific sites without causing tissue injury.[10,11] These nanoscale structures also allow for the encapsulation of molecules with a wide range of solubility profiles, accepting both lipophilic and hydrophilic active components. Novel nanotechnology-based acne formulations have been created to transport active chemicals to specific skin localizations, allowing for a reduction in the dose required to achieve the desired effect while causing fewer adverse effects.[12] Furthermore, new information reveals that nanosystems have a high capacity for penetrating hair follicles, a therapeutic skin target that is gaining popularity. The follicular targeting lowers the negative effects of active component administration through the skin. Nanosystems are also removed together with sebum excretion, preventing bioaccumulation.[13]

Concepts in Acne Pathogenesis

Acne pathogenesis is characterised by follicular epithelial hyperproliferation and aberrant differentiation, excessive sebum production, inflammation, and Propionibacterium acnes proliferation and biofilm formation.[14,15] Immunohistochemical investigations reveal that acne patients' skin has larger amounts of CD4 cells, macrophages, and interleukin (IL)-1–alpha than acne-free skin. These findings imply that infammation comes first in the formation of acne, followed by hyperproliferation.[16,17]

Hyperseborrhea and dysseborrhea are the two most common pathogenic conditions in sebocytes. Hyperseborrhea refers to a change in sebum amount, whereas dysseborrhea refers to a change in sebum composition. These metabolomic alterations enhance *Cutibacterium acnes* overgrowth and bioflm production, as well as inflammation, follicular barrier disruption, and comedogenesis.[18] Androgens have the ability to boost lipid synthesis as well as sebocyte proliferation and differentiation. The phosphorylation of mTOR rises after androgens bind to the androgen receptor (AR) in the cell nucleus. When inflammatory sebaceous glands in acne lesions are compared to non-lesional skin, there is a greater cytoplasmic and nuclear expression of mTOR. mTOR is the catalytic core of mTORC1, which activates sterol regulatory element-binding protein-1 to promote lipogenesis (SREBP-1).[19] Endogenous Wnt/β-catenin signalling was likewise negatively influenced by androgen. As a result, Wnt/β-catenin target genes such c-MYC are overexpressed, causing sebocyte differentiation. Nuclear AR and peroxisome proliferator-

activated receptors are abundant in differentiating sebocytes (PPARs).[20,21]

The nuclear transcription factor, IGF-1 may play a role in the development of acne through a variety of methods. IGF-1 has been shown to: (1) induce androgen synthesis and increase dihydrotestosterone cutaneous availability; (2) disinhibit the forkhead box O1 (FoxO1) transcription factor, which normally suppresses the androgen receptor; and (3) activate peroxisome proliferator-activated receptor–gamma, liver X receptor–alpha, and sterol regulatory element binding protein-1c (SREBP-1c). The latter actions result in an increase in sebum triglycerides and fatty acid desaturation, resulting in a proinfammatory and comedogenic monosaturated fatty acid profile. Squalene levels rise in response to increased sebum production. UV A–triggered photooxidation of squalene in sebum produces squalene monohydroperoxide, which is comedogenic.[22,23]

Corticotropin-releasing hormone (CRH), -melanocyte-stimulating hormone (-MSH), and substance P are all capable of influencing sebocyte activity. By promoting steroidogenesis and interacting with testosterone and growth hormone, the hypothalamic–pituitary–adrenal (HPA) axis' CRH plays a role in the clinical development of acne. Sebaceous glands in acne-prone skin express a complete CRH system in addition to the HPA axis. In primary cultures of human sebocytes obtained from the face, -MSH exhibits a lipogenic impact and correlates with sebocyte development.[24,25] It can also raise IL-1, IL-6, and tumour necrosis factor (TNF)-related immunoreactivities. By modulating monocyte differentiation and cytokine release, lipids such as oleic acid and linoleic acid can affect the inflammatory response. Leptin, which is secreted by adipocytes, has been found to be a link between lipid metabolism and inflammation in sebocytes.[26,27]

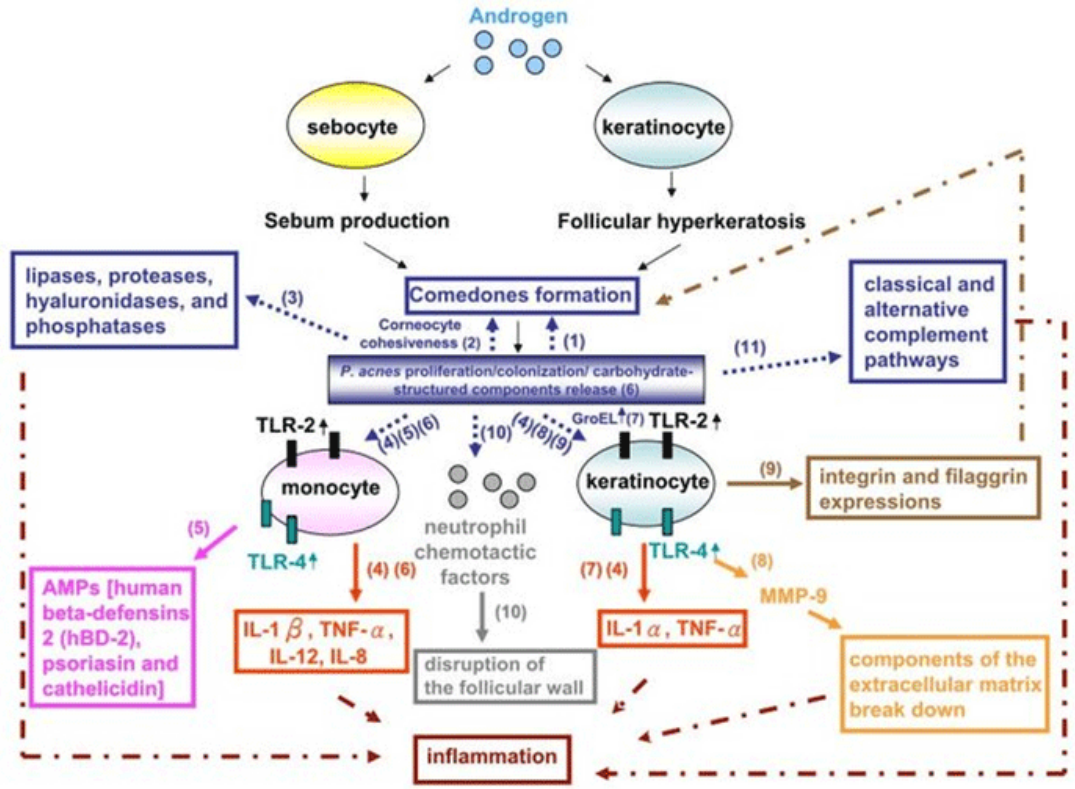

Fig. 1: Pathophysiology of Acne.

Infrainfundibular keratinocytes have been found to have a higher capability for androgen metabolism, suggesting that androgen may be linked to hyperkeratosis. Not only does IL-1 have a role in the immune response, but it also plays a role in the hyperkeratosis of infundibular keratinocytes.[28] The various methods of action are hypothesised to alter signal transduction directly via the IL-1 receptor or increase the production of additional growth factors such vascular endothelial growth factor.[29] Katsuta **et al.** found that N-methyl-d-aspartate (NMDA) receptors increased intracellular concentrations of calcium ions and IL-1α production, which are associated with abnormal follicular keratinization induced by oleic acid.[30] Keratinocytes, like sebocytes, play a role in the inflammatory response. On keratinocytes, *C. acnes* stimulates Toll-like receptors (TLR) -2 and TLR-4, activating signalling pathways such as the NF-kB and MAPK pathways. Keratinocytes then create interleukin-1, interleukin-8, interleukin-6, granulocyte–macrophage colony stimulating factor (GM-CSF), TNF-, matrix metalloproteinases (MMPs), and human -defensin-2.[31,32] Keratinocytes rapidly create reactive oxygen species (ROS), particularly superoxide anions arising from cytosolic enzymes NAD(P)H

oxidase, when C. acnes is identified by CD36. These reactive oxygen species (ROS) are subsequently employed to kill germs and cause inflammation.[33] The anti-acne agents acting against the pathological processes associated with keratinocytes include retinoids, minocycline, azelaic acid and EGCG.

IGF-1 is sufficient to stimulate pro-inflammatory cytokine production in primary human sebocytes, according to previous research. After stimulation with IGF-1, increased expression of NF-kB, IL-1, IL-6, IL-8, and TNF- was seen in cultured sebocytes. However, after IGF-1 therapy, the levels of these inflammatory indicators were lower in NF-kB inhibitor-pretreated sebocytes.[34,35] Androgen, in addition to IGF-1, may have similar effects, as androgen can raise IGF-1 levels in the blood in healthy males. Sebocytes release cytokines and MMPs in response to IGF-1 stimulation, and inflammatory cells are recruited into the pilosebaceous unit. MMPs can breach the follicular membrane, allowing fatty acids to leak into the dermis and the extracellular matrix to dissolve.[36,37] C. acnes also upregulates caspase-1 and NLPR3 gene expression, as well as inducing the activation of the monocyte–macrophage NLRP3-inflammasome, which is dependent on phagocytotic activity, lysosomal breaks with release, and activation of cathepsin B, as well as the generation of ROS and potassium efflux, resulting in abundant IL-1β production.[38] CD4+T cells, specifically T helper (Th) 1 and Th17 cells, are lymphocytes implicated in the C. acnes-induced adaptive immune response. C. acnes stimulates the production of IL-1, IL-6, and TGF- in peripheral blood mononuclear cells (PBMCs), causing naive CD4+CD45RA T cells to differentiate into Th17 cells. This mechanism could be influenced by the presence of the major histocompatibility complex II (MHC II). As a result, the Th effector cytokines IL-17 and interferon (IFN)- production in the same locations of acne biopsies is increased.[39,40]

Six gene loci have been discovered in current research on genome-wide connections with severe acne: 11q13.1, 5q11.2, 11p11.2, 1q41, 1q24.2, and 8q24. Androgen metabolism, inflammation, and scar formation are all influenced by these genes. In acne lesions, there was a significant increase in Tumor Necrosis Factor (TNF) gene transcripts. In addition, a meta-analysis reveals that the TNF gene's -308 G/A polymorphism relates to acne risk in Caucasians. A variant in the insulin-like growth factor-1 (IGF 1) gene has recently been discovered to predispose Turkish people to acne. Recent research suggests that several molecular pathways (e.g., Lef-1, Blimp1, Wnt, C-myc) regulate sebocyte formation, and that sebocyte activity is regulated by a variety of cellular pathways and hormones other than androgens, such as peroxisome proliferator-activated receptors, substance P receptors, melanocyte-stimulating hormone, insulin-like growth factor, corticotropin-releasing hormone, vitamin D.[41,42]

P. acnes is a major part of the normal cutaneous flora, but only a few studies have indicated that it causes inflammatory reactions in skin parenchymal cells and immune cells. Phylogenetically diverse cluster groups with various pathogenic features, including differing ability to trigger inflammation and differing secretome profiles, were recently discovered using more sophisticated DNA-based typing approaches. This result suggests that, whereas some P. acnes strains may play a role in acne aetiology. P. acnes also produces chemotactic factors, which attract CD4 lymphocytes first, followed by neutrophils and monocytes to the afflicted area. P. acnes activates Toll-like receptor 2 (TLR-2) on monocytes, causing the generation of interleukin (IL)-8, which leads to neutrophil migration into the PSU. P. acnes also interacts with antimicrobial peptides and protease-activated receptors. One of the most important aspects of P. acnes biofilm is that it acts as a protective physical barrier. It further promotes antibiotic resistance of the colonies by production of certain proteins.[43,44]

Management of Acne

Novel insights into the complicated pathophysiology of acne have opened up a slew of new therapy options. due to rising concerns about bacterial resistance, antibiotics will be phased out of acne treatment in the next years in favour of antimicrobial peptides, bacteriophages, sebum-reducing medicines, monoclonal antibodies, and other pharmacological agents, including vaccines against P. Acnes.

Peroxisome proliferator activated receptor (PPAR) modulators

Sebum synthesis is regulated by the peroxisome proliferator-activated receptor gamma (PPAR), a ligand-activated transcription factor found in cells of many tissues, including skin. The expression of PPAR increases in suprabasal and differentiated sebocytes, suggesting that it is involved in the differentiation process.[45,46] When compared to the skin of healthy controls, PPAR expression is lower in the afflicted and unaffected skin of acne sufferers, indicating PPARγ as a possible therapeutic target.[47]

Ottavian et al. looked at the metabolic pathways of insulin-induced sebogenesis in SZ95 cells at various differentiation levels. Low differentiation SZ95 cells were more responsive to the insulin stimulation, resulting in "acne-like sebum" production. NAC-GED0507 (other names N-acetyl-GED0507-levo; GMG-43AC) enhanced cell differentiation, reduced insulin-induced sebogenesis, improved sebum composition, and lowered inflammatory response through activating PPARγ expression. In vivo treatment of acne patients with NAC-GED0507 1 % gel alleviated clinical symptoms and elevated PPARγ expression in sebum by reduction in mTOR activation and inflammatory molecule levels. The researchers discovered that NAC-GED0507 stimulation reduced the inflammatory response induced by several stimuli,

including lipopolysaccharide (LPS), in SZ95 cells and human keratinocytes, counteracting the altered differentiation and proliferation process in these cells[48,49], and it has been suggested that PPARγ may represent a unique target to interfere with all acne pathogenetic mechanisms. As an addendum, the creation of a reliable in vitro model simulating acne conditions, as well as an in vivo method for studying sebocyte biology, is beneficial in our understanding of sebocyte pathophysiology and the efficiency of innovative acne treatments.[50] Insulin-induced proliferation was also influenced by PPAR𝛾 regulation, which slowed cell cycle progression and decreased p21WAF1/CIP1 protein levels (p21). In addition, the expression of inflammatory cytokines produced by insulin or lipopolysaccharide (LPS) was reduced. All of these observed effects were abolished in the presence of a GW9662 antagonist or in PPAR𝛾-deficient cells, indicating that PPAR activation regulates changes in lipogenesis, cell proliferation, and inflammatory signalling, and demonstrating that selective modulation of PPAR𝛾 activity is likely to represent a therapeutic strategy for the treatment of acne.[51]

Certain leukotrienes, such as leukotriene B4 (LTB4), are powerful PPAR𝛾 ligands and are thought to be important in the development of tissue inflammation. The enzyme 5-lipoxygenase regulates LTB4 synthesis (5-LOX). Zileuton, an oral 5-LOX inhibitor that inhibits PPAR-𝛾 mediated lipogenesis and downregulates LTB4 expression in the sebaceous gland and it was tested in a clinical trial for safety and efficacy in the treatment of acne (NCT00098358).[52]

Resveratrol reduced the sebocyte proliferation by inactivation of extracellular signal regulated protein kinase (ERK), Akt, and peroxisome proliferator activated receptor-𝛾 (PPAR𝛾). They showed the antiproliferative effect of resveratrol at the levels of cell cycle regulatory proteins. It also inhibited the formation of cyclin D1 while boosting the production of p21WAF1/CIP1 (p21) and p27KIP1 (p27). In addition, the researchers have discovered that resveratrol-induced cell cycle arrest increased the number of cells in the G0/G1 phase and it has been found that the growth inhibitory effects of resveratrol were increased by treatment with LY294002 [a phosphatidylinositol 3-kinase (PI3-K) inhibitor] better than treating with PD98059 (a MEK inhibitor), which indicates that resveratrol shows its inhibitory effects on sebocyte proliferation through the inhibition of Akt. Linoleic acid (LA) is a well-known sebocyte lipid inducer that has been proven to stimulate sebocyte differentiation by upregulating PPAR𝛾. During LA-stimulated lipogenesis, resveratrol was found to reduce lipid content and PPAR expression.[53,54]

The role of PPAR𝛾 in the pathogenesis of acne vulgaris was validated by Amr **et al**., who targeted at the Pro12Ala polymorphism in acne patients, which is associated with lower PPAR𝛾 transcriptional activity. Pharmacological PPAR𝛾 agonists like pioglitazone and natural PPAR𝛾 ligands like Leukotriene B4 (LTB4) have been proven to increase sebum production.[55,56] Zoubolis **et al.** investigated the effect of the 5-lipoxygenase inhibitor zileuton in the treatment of acne vulgaris. Zeleuton inhibits LTB4, an inflammatory mediator and a natural ligand for PPAR𝛾, which reduced the sebum production indirectly by inhibiting PPAR. PPAR𝛾 inhibitors appear to be the new therapy method for acne control. In a three-month pilot study, zileuton 600 mg taken orally four times a day lowered the papulopustular acne severity index in a time-dependent manner. The study found that the initial acne score had decreased by 41%, and the number of inflammatory lesions had decreased by 29%.[57]

Antiandrogens

Sebocyte functions such as lipid production, proliferation, and differentiation are all regulated by endocrine processes. Androgens stimulate the active sebaceous gland by binding to nuclear androgen receptors (ARs). Sebaceous glands have the highest density of ARs. Androgens have a crucial role in acne, especially during sebaceous follicular hyperkeratinization, a common acne symptom.[58] Sebaceous glands produce more sebum when androgens are present. It was believed that androgen levels influenced the entire integument of acne patients.[59] Most antiandrogens examined, including cyproterone acetate, flutamide, 17ct-propylmesterolone, spironolactone, and, more recently, RU882, have been proven to be highly successful in lowering sebum production in such mice.[60] In 20 patients, Califano **et al.** documented their clinical experience with topical treatment of acne with a 5% spironolactone cream. Complete acne regression happened in 30% of the patients in this uncontrolled study, which lasted one month, while improvement occurred in 65% of the patients.[61] Lookingbill and colleagues discuss their findings on the acne-fighting effects of inocoterone acetate (RU882), a novel topical nonsteroidal antiandrogen. In numerous animal models, topical administration of inocoterone acetate has been found to suppress androgen action in the sebaceous tissue.[62] Flutamide, an oral nonsteroidal antiandrogen, has also been studied. It works by attaching to androgen receptors and thereby suppressing testosterone in a competitive manner. In women who used this medicine in conjunction with an oral contraceptive, seborrhea and acne were found to be reduced.[63] Isotretinoin is the recommended medication for recalcitrant severe nodulocystic acne.[64] A comprehensive literature study revealed the role of AR in the skin in the nuclear compartment of the cell. Few studies have found AR positive in the nucleus and cytoplasm. Cytoplasmic androgen receptors are unbound AR receptors that are only internalised or translocated into the nucleus with the help of their ligand.[65] Cortexolone 17α-propionate (CB-03-01) is a new potent topical antiandrogen potentially significant in acne vulgaris. CB-03-01 1% cream was

very well tolerated, and was significantly better than placebo regarding TLC (P = 0·0017), ILC (P = 0·0134) and ASI (P = 0·0090), and also clinically more effective than comparator. The product also resulted in a 50% improvement in all of the above criteria in a shorter period of time. The rationale for using topical antiandrogens in the treatment of acne vulgaris is supported by this pilot trial. CB-03-01 1 percent cream appears to fulfil the profile of a good topical antiandrogen.[66] Carmina **et al.** examined the relative effectiveness of two newer antiandrogens (flutamide and finasteride) with cyproterone acetate (CPA), at both low and high doses in the treatment of acne in hyperandrogenic women. Serum androgens were increased in all 48 women and was similar in each of the four treatment groups. Cook scores were significantly and equally decreased (59–71%) with flutamide and both low and high doses of CPA ($P < 0{\cdot}01$). The decrease with finasteride (-36 ± 2%) was statistically significant but lower than that valued with the other agents. Low doses of various antiandrogens appear to be useful in hyperandrogenic women with moderate to severe acne. The effects of low and high doses of CPA with ethinylestradiol were equivalent to the effects of a low dosage of flutamide and finasteride was shown to be less effective.[67] Clascoterone was the first topical androgen antagonist to be created to treat acne in both male and female patients, and it was also the first such medication to get FDA approval for acne treatment. Androgens drive sebaceous gland development and sebum production directly, providing a fertile environment for anaerobic *Cutibacterium acnes* (*C. acnes*) bacteria to thrive. Androgens may play a direct role in sebaceous gland inflammation. The safety and efficacy of topical clascoterone for acne were verified in a phase III clinical trial, with significant decreases in absolute non-inflammatory and inflammatory lesion counts at week 12. The approval of a first-in-class topical androgen antagonist is indeed a 'game-changer' for acne management. This topical agent is expected to be quickly adopted in clinical practice.[68] Edalatkhah **et al**. compared the efficacy of flutamide-cyproterone compound with flutamide-doxycycline in treating severe acne in women. The mean of the acne severity index at the onset of intervention between the two groups was not significant (p= 0.7). The mean of the acne severity index at the start of treatment in the flutamide-doxycycline group was 306.07±155.46 and at the end of treatment reached to 19.18±19.5, and also in the flutamide-cyproterone compound group, decreased from 293.21±15.21 to 10.5±21.8 at the end of treatment. The difference (p=0.1) was not statistically significant. Both therapy regimens were effective in the treatment of severe acne and might be used as an alternative to traditional acne treatments.

Targeting Melanocortin receptor

Melanocortin receptors influence the activity of the sebaceous gland. Human skin has been found to express the MC1, MC2, MC4, and MC5 receptors, but not the MC3 receptor. The melanocortin MC1 and MC5 receptor is important for skin homeostasis and skin control.[69,70] In sebocyte cultures, NDP-α-MSH caused mild differentiation and enhanced cyclic adenosine monophosphate synthesis, whereas cholera toxin caused higher cyclic adenosine monophosphate growth and increased sebocyte differentiation.[71] The stimulation of the melanocortin receptor 1 (MC1-R) and the melanocortin receptor 5 (MC5-R), both of which are expressed in human sebocytes, causes alpha-melanocyte-stimulating hormone (α-MSH) to promote enhanced sebogenesis in rodents.[72] The physiological function of MC5R in human sebaceous glands was explored by Eisinger **et al.** Primary human sebaceous cells or human skins transplanted onto severe combined immunodeficient (SCID) mice were treated with a new MC1R and MC5R antagonist (JNJ-10229570). The effect of MC5R inhibition on sebaceous gland development and sebum production was studied using transcription profiling, lipid analysis, and histological and immunohistochemical labelling. In cultured primary human sebocytes, JNJ-10229570 reduced the formation of sebum lipids in a dose-dependent manner. Topical treatment of human skins transplanted onto SCID mice with JNJ-10229570 resulted in a significant reduction in sebum-specific lipid synthesis, suggesting that MC1R and MC5R antagonists could be effective sebum suppressive drugs with potential for acne treatment.[73] Malik **et al.** and co-researcher investigated naturally occurring peptides derived from frog skin secretions for selectivity and activity toward melanocortin receptors. Three peptides (ORB, ORB2K, and Ranacyclin-T) were discovered to have melanocortin receptor 5 selectivity (MC5R). At nanomolar concentrations, ORB and ORB2K displayed partial binding affinity, but Ranacyclin-T demonstrated a 57 % binding efficiency at 1.6 M. When ORB and ORB2 backbones were cyclized, their ability to bind to melanocortin receptors was reduced. According to their findings, these frog-skin peptides could be modified to produce melanocortin-specific ligands and possibly future acne treatments.[74] In cultured primary human sebocytes, JNJ 0229570, an MC1-R and MC5-R antagonist, reduces sebaceous gland size and generation of sebum lipids, and its application has been examined in a clinical trial (NCT01492647).[75] α-MSH, apart from its sebotrophic effects in mice, has anti-inflammatory properties. KDPT (a tripeptide derivative of the C-terminal end of alpha melanocyte-stimulating hormone), a tripeptide derivative of α MSH suppressed Il-1β-mediated IL-6 and IL-8 expression and signaling in human sebocytes in vitro, with no melanotropic activity. The α-MSH analog afamelanotide (Nle4-D-Phe7-α-MSH) has been studied for acne (NCT01326780).[76] Afamelanotide 16 mg in a subcutaneous resorbable implant formulation was investigated in a phase 2 trial in three patients with mild-to-moderate facial acne vulgaris.

Insulin-like growth factor-1 (IGF-1) inhibitors

IGF-1R (insulin-like growth factor 1 receptor) is a multifunctional receptor that mediates cell proliferation, differentiation, and survival signals. Inactivation of IGF-1R in the skin leads in a disordered epidermis, according to genetic research. It has been shown that IGF-1R-deficient skin cocultures have aberrant maturation and differentiation patterns utilising a combined technique of conditional gene ablation and a three-dimensional organotypic model. Furthermore, IGF-1R-deficient keratinocytes differentiate more quickly and proliferate less. Overexpression of insulin receptor substrate 2 (IRS-2) compensates for the loss of IGF-1R, but not of IRS-1, according to research into the signalling cascade downstream of IGF-1R. Researchers further have shown that phosphatidylinositol 3-kinase and extracellular signal-regulated kinases 1 and 2 are engaged in skin keratinocyte differentiation regulation and play a role in mediating IGF-1R's inhibitory signal on differentiation. Furthermore, they demonstrated that the mammalian target of rapamycin is involved in mediating IGF-1R impedance of action on keratinocyte development. In conclusion, these findings show that IGF-1R regulates skin growth and differentiation by acting as an inhibitor.[77] Researchers have established a better understanding of the molecular signalling involved in lipid production in the sebaceous gland, which will help them design therapeutic targets to treat acne. Treatment of 3T3-L1 preadipocytes with methylisobutylxanthine, dexamethasone, and a high dosage of insulin (MDI) has been demonstrated to differentiate them into adipocytes, with an increase in lipid synthesis. The study aimed high doses of insulin will activate the IGF-1 receptor, they examined to test if IGF-1 is capable of recreating the lipogenic impact seen with MDI therapy, and if the sterol response element-binding protein-1 (SREBP-1) pathway drives the rise in lipogenesis. They found that MDI promotes lipogenesis in SEB-1 cells, and that this impact is entirely due to the high-dose insulin. They also discovered that a physiologically realistic dose of IGF-1 or high-dose insulin causes a rise in SREBP-1 mRNA, protein, and total lipid synthesis, whereas 100 nM insulin causes lipogenesis but has no effect on SREBP protein levels. These findings show that IGF-1 receptor activation enhances lipogenesis in SEB-1 cells via both SREBP-dependent and SREBP-independent mechanisms.[78] Insulin and IGF-1 promote lipogenesis in the sebaceous gland. IGF-1 boosts the expression of sterol response element-binding protein-1 (SREBP-1), a transcription factor that controls a slew of lipid biosynthesis genes. Lipogenesis in sebocytes is stimulated by SREBP-1 expression. The purpose of this research was to find the intracellular signalling pathway(s) that transduce the IGF-1-induced lipogenic signal. IGF-1 treatment activated the phosphoinositide 3-kinase (PI3-K) pathway as well as the three major arms of the mitogen-activated protein kinase (MAPK) pathway (MAPK/extracellular signal-regulated kinase (ERK), p38 MAPK, and stress-activated protein kinase/c-Jun-N terminal kinase/c-Jun-N terminal kinase/c The MAPK/ERK and PI-3K pathways were both stimulated by IGF-1. We discovered that the increase in SREBP-1 expression generated by IGF-1 was prevented in the presence of a PI3-K inhibitor but not in the presence of a MAPK/ERK inhibitor when they used specific inhibitors of each pathway. IGF-1-induced transcription of SREBP target genes and sebocyte lipogenesis were likewise suppressed when the PI3-K pathway was inhibited. These data indicated that IGF-1 transmits its lipogenic signal in sebocytes through activation of Akt. Specific targeted interruption of IGF pathway in the sebaceous gland could be a desirable approach to reducing sebum production and improving acne.[79] Hwang et al. studied the effects of a variety of medicinal herbs and discovered that the extract of Ginkgo biloba L. leaves inhibited IGF-1-induced sebum production in sebocytes. They narrowed down the active components and discovered isoginkgetin to be one of the most potent and showed that isoginkgetin decreased IGF-1-induced sebum production in this study, indicating that isoginkgetin could be used to treat acne. IGF-1-induced increases in SREBP-1 and PPAR-γ were considerably reduced by isoginkgetin. Isoginkgetin strongly suppressed IGF-1-induced AKT1 and ERK1/2 activation in sebocytes, confirming recent findings in other systems. These findings imply that isoginkgetin works to suppress sebum production by inhibiting IGF-1 signalling.[80,81] The pharmacological potential of epigallocatechin-3-gallate (EGCG), which has been intensively studied as an anti-proliferative and anti-inflammatory drug, was evaluated by Myung et al. and showed that topical administration of EGCG to rabbit auricles reduced the size of the sebaceous glands in this study. EGCG inhibited cell proliferation and lipogenesis when administered to cultured human SZ95 sebocytes. In IGF-I-differentiated SZ95 sebocytes, EGCG's activities were replicated. To test EGCG's anti-inflammatory potential, researchers measured pro-inflammatory cytokine synthesis in IGF-I-differentiated SZ95 sebocytes and discovered that IL-1, IL-6, and IL-8 expression was reduced. These findings show that EGCG is a promising candidate for acne treatment, with mechanisms of action in IGF-I-differentiated SZ95 sebocytes that include lipogenesis and inflammation suppression.[82] Yoon **et al.** also examined the effects of EGCG, the major polyphenol in green tea, on human SEB-1 sebocytes and in patients with acne. In SEB-1 sebocytes, we found that EGCG reduced sebum by modulating the AMPK-SREBP-1 signaling pathway. EGCG also reduces inflammation by suppressing the NF-κB and AP-1 pathways. EGCG also induces cytotoxicity of SEB-1 sebocytes via apoptosis and decreases the viability of P. acnes, thus targeting almost all the pathogenic features of acne.[83] Lupeol, a pentacyclic triterpene, from the hexane extract of Solanum melongena L. (SM) was identified after instrumental analysis.[84] Lupeol targeted most of the major pathogenic features of acne with desired physicochemical traits. It strongly suppressed lipogenesis by modulating the IGF-1R/phosphatidylinositide 3

kinase (PI3K)/Akt/sterol response element-binding protein-1 (SREBP-1) signaling pathway in SEB-1 sebocytes, and reduced inflammation by suppressing the NF-κB pathway in SEB-1 sebocytes and HaCaT keratinocytes. Lupeol had a minor effect on cell viability and may have influenced epidermal dyskeratosis. Following that, histopathological analysis of human patients' acne tissues after application of lupeol revealed that lupeol significantly reduced the number of infiltrated cells and major pathogenic proteins examined in vitro around comedones or sebaceous glands, indicating that lupeol may have therapeutic potential. These findings show that using lupeol to treat acne is a clinically viable option.[85]

Coenzyme-A Carboxylase Inhibitors

Acetyl-CoA Carboxylase (ACC) is a rate-limiting enzyme in the metabolism of fatty acids. ACC inhibitors have attracted a lot of attention in the past few years as potential therapeutics for a variety of human diseases, including microbial infections, metabolic syndrome, obesity, diabetes, and cancer. The carboxylation of acetyl-CoA to malonyl-CoA is catalysed by acetyl-CoA carboxylase, which is the first committed, rate-limiting step in fatty acid biosynthesis.[86,87] Malonyl-CoA also increases mitochondrial fatty acid uptake and oxidation. Inhibition of malonyl-CoA synthesis offers a means to inhibit de novo fatty acid production in sebaceous glands.[88] Olumacostat glasaretil (OG) (formerly DRM01), a prodrug, is hydrolyzed by esterases in vivo to form the pharmacologically active moiety 5-(tetradecyloxy)-2-furancarboxylic acid, which changes to 5-tetradecyloxy-2-furancarboxylic acid. -2-furoyl-CoA is a fatty acid mimic that competes with acetyl-CoA, preventing malonyl-CoA synthesis.[89,90] Animal models proved that androgenic stimulation of sebaceous glands stimulate the production of acetyl coenzyme-A carboxylase (ACC), which catalyzes the carboxylation of acetyl coenzyme-A (CoA) to form malonyl-CoA[91-93], the first committed, rate-limiting step in saturated fatty acid biosynthesis via the sterol regulatory element-binding protein-1 (SREBP1) pathway. Malonyl-CoA boosts fatty acid absorption and oxidation in mitochondria. Because fatty acids are the building blocks for about 85% of human sebum lipids, pharmacological inhibition of ACC could provide a way to reduce sebum output by inhibiting de novo fatty acid formation in sebaceous glands, making it a potential new target for acne therapy.[94-95]

The small molecule olumacostat glasaretil (OG) inhibits acetyl coenzyme A carboxylase (ACC), the enzyme that controls the first, rate-limiting step in fatty acid production. Because fatty acids make up over 80% of human sebum, inhibiting ACC activity in the sebaceous glands is expected to have a significant impact on sebum production. In primary and modified human sebocytes, OG suppresses de novo lipid production.[96] In OG-treated sebocytes, analysis of the Sebum Panel demonstrated a decrease in saturated and monounsaturated fatty acyl chains throughout lipid species, including di- and triacylglycerols, phospholipids, cholesteryl esters, and wax esters. There was no evidence of a shift toward shorter acyl chain lengths, implying that the fatty acid chain elongation process is unaffected.[97,98] OG is a prodrug of the ACC inhibitor 5-(tetradecyloxy)-2-furoic acid (TOFA) that was developed to improve in vivo administration. Topical application of OG, but not TOFA, reduced the size of hamster ear sebaceous glands, indicating that this pro-drug strategy was necessary to achieve the intended effect in vivo. OG therapy raised ACC levels and the ratio of acetyl-CoA to free CoA in hamster ear extracts, indicating higher fatty acid oxidation in these animals. These modifications are in line with the inhibition of ACC. MALDI imaging demonstrated that OG applied to Yorkshire pig ears accumulated in sebaceous glands compared to the surrounding dermis. Sebaceous gland ACC represents an attractive therapeutic target given its central role in formation of sebum, a key factor in acne pathogenesis.[99] As mentioned above, almost all ACC inhibitors are localized to diabetic and nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), except for Olumacostat Glasaretil, which is used for acne. But researchers from Pfizer Accepted Manuscript Information Classification: General found that compound PF-05175157, which was withdrawn from Phase II trials, had an unanticipated effect on acne control.[100]

Retinoic acid receptor-γ agonist

Location of the gene RARγ is chromosome 12. The key component of the RAR protein, including the binding domains of DNA and ligand, is encoded by seven exons.[101] The current cornerstone of therapy and maintenance in acne treatment is topical retinoids, vitamin A derivatives that normalise keratinization, decrease microcomedone development, and reduce inflammation. They work on the human skin by interacting with the nuclear retinoic acid receptor (RAR), which is divided into three isoforms exists, RAR-α, RAR-β, and RAR-γ[102] One RAR will form a heterodimer with a retinoid X receptor (RXR) and then bind to a retinoic response element (RARE) in the DNA of skin cells to activate the transcription of genes encoding proteins required for keratinocyte development and differentiation, apoptosis, and sebum suppression. RAR-γ accounts for 90% of RARs in the epidermis, hence paired heterodimers formed of RAR-γ and RXR are the primary regulators of human skin.[103]

In the absence of ATRA, the RAR/RXR heterodimer binds to its responsive element constitutively and represses transcription by recruiting corepressors. RAR/RXR dimer binds coactivators and up-regulates transcription of target genes after binding to ATRA.[104] RXRs can serve as heterodimeric partners for other nuclear receptors, such as thyroid hormone receptors, peroxisome proliferator-activated receptors (PPARs),

and nerve growth factor-induced gene B, in addition to serving as a coreceptor for RARs.[105]

Vitamin A and its derivatives are involved in the regulation of a wide range of immunological processes. Members of the retinoic acid receptors (RARs) and retinoid X receptors mediate the effects of these retinoids. Individual retinoid receptors' significance in the pleiotropic effects of retinoids, however, is unknown.[106] Ivan **et al**. studied immune cell formation and function in mice lacking RAR, the third member of the RAR family, to better understand the role of these receptors in the immune system. RAR is not required for T and B lymphocyte growth, humoral immune response to a T-dependent Ag, or in vitro Th cell differentiation, according to the researchers. Infection with Listeria monocytogenes resulted in a poor primary and memory CD8+ T cell response in RAR-γ deficient animals. Surprisingly, RAR-γ deficient macrophages produced less inflammatory cytokine in response to TLR stimulation. These findings imply that RARγ is a positive regulator of inflammatory cytokine production under physiological conditions.[107]

According to Katalin and co-researcher human peripheral T-cells expressed RARα and gamma, but not RARβ. Increasing concentrations of 9-cis RA inhibited phytohaemagglutinin (PHA)-induced proliferation of T-cells, an effect that could be mimicked only by addition of RARγ agonists.[108,109] PHA-induced T lymphocyte proliferation is known to be mediated by interleukin-2 (IL-2). PHA-induced high affinity IL-2 receptor expression was unaffected by RAR ligation, and PHA-induced IL-2 production was marginally reduced, while IL-2-mediated signal transduction was disrupted, resulting in suppression of PHA-induced phosphorylation of retinoblastoma protein and up-regulation of Bcl-2. Janus kinases JAK1 and JAK3 play a determinant role in IL-2-dependent signal transduction. RARγ ligation had little effect on JAK1 levels, but it did reduce IL-2-induced JAK3 production, which inhibited PHA-induced phosphorylation of Stat molecules. Their findings imply that the previously known harmful effect of high retinoid concentrations on the immune system is mediated by the production of 9-cis RA, which not only promotes cell death in immature thymocytes but also suppresses T-cell proliferation via RARγ ligation.[110]

Katheryn **et al.** reviewed clinical trials to assess the efficacy, safety, and clinical application of trifarotene 0.005% cream (Aklief). A systematic review of the literature was performed using the terms trifarotene OR Aklief OR CD5789 in MEDLINE (PubMed) and EMBASE databases. Treatment success rates for face acne (IGA rating of no or nearly no acne) and truncal acne (Physician's Global Assessment [PGA] rating of no or virtually no acne) were 65.1 % and 66.9 %, respectively, in the 52-week phase III trial. Overall success rates (IGA and PGA success in the same patient) were 57.9%, with 52.8 % of patients scoring 0 or 1 on the Dermatology Quality of Life Index, compared to 22.6 % at baseline. Trifarotene was well tolerated, with pruritus, irritation, and sunburn as the most common adverse effects. Trifarotene is a newly Food and Drug Administration–labeled fourth-generation topical retinoid that shows particular promise in the treatment of facial and truncal acne vulgaris. It is an effective and safe addition to currently available retinoids.[111] For the treatment of face and truncal acne, trifarotene is both effective and safe. Future trials should compare its efficacy and tolerability to that of other, more well-known retinoids. Regardless of efficacy, cost may be a deterrent. Trifarotene is a selective RARγ agonist with > 20-fold selectivity over RARα and RARβ. Trifarotene is active and persistent in keratinocytes, but it is rapidly digested by human hepatic microsomes, implying that it is safer. In vivo, trifarotene 0.01% administered topically is extremely comedolytic and anti-inflammatory, as well as anti-pigmenting. After 4 weeks of topical application of trifarotene 0.005% cream, gene expression studies revealed potent activation of known retinoid-modulated processes (epidermal differentiation, proliferation, stress response, retinoic acid metabolism) and novel pathways (proteolysis, transport/skin hydration, cell adhesion) in ex vivo and in vivo models, as well as in human skin.[112]

Phosphodiesterase 4 inhibitor

PDEs are known to reduce cAMP levels in the cytoplasm. Proinflammatory cytokines such as TNF-a, IL-1, IL-8, IL-12, and IL-23 are preferentially expressed when cAMP levels are low. As a result, medicines that inhibit PDEs and so raise cAMP may have a function in chronic inflammatory diseases including acne, rosacea, and atopic dermatitis, which have high levels of IL-1 and TNF-a. Because PDE4 is the main cAMP-degrading isoenzyme, blocking it raises cAMP levels, lowering proinflammatory cytokine activity.[113] PDE4 inhibitors have the potential to expand the anti-inflammatory therapy portfolio in a variety of chronic inflammatory illnesses, including granulomatous skin diseases, several subtypes of chronic dermatitis, and most likely cutaneous lupus erythematosus. The authors of this review explore the mechanism of action of PDE4 inhibitors on skin and joint inflammatory responses, as well as their potential significance in clinical practice.[114,115]

The safety and efficacy of topical E6005, a novel phosphodiesterase 4 inhibitor, in Japanese adults with atopic dermatitis were evaluated.[116] A total of 78 patients were randomized to receive either the 0.2% E6005 ointment or vehicle control (without E6005) at an allocation ratio of 2:1. The randomization phase of 4 weeks was followed by an extension phase of 8 weeks. In the extension phase, all 67 subjects who completed the randomization phase were treated with 0.2% E6005 ointment. The 4-week application of topical E6005 twice daily was safe and well tolerated. For up to 12 weeks, the safety profile was similar to that of the first four weeks. During the 12-week research period, no deaths or other major side effects were detected. Plasma E6005 was

undetectable in all patients at all sample points, while 47 percent of subjects receiving E6005 therapy had very low plasma amounts of an E6005 metabolite. When compared to the vehicle group, the Eczema Area and Severity Index (EASI), Severity Scoring Atopic Dermatitis (SCORAD)-objective, SCORAD-C (visual analogue scales for pruritus and sleep loss), itch Behavioural Rating Scale, and the severity of the targeted eczematous lesions in the topical E6005 group showed trends toward improvement at the end of week 4. However, the group receiving topical E6005 for 12 weeks showed significant score reductions from baselines for EASI ($P = 0.030$), SCORAD-objective ($P < 0.001$) and SCORAD-C ($P = 0.038$). These results further support the development of topical E6005 for the treatment of acne.[117,118]

The PDE4 inhibitor, Apremilast, raises cellular cAMP levels and has been shown to be useful in the treatment of psoriasis and psoriasis arthritis. 6-sulfo LacNAc dendritic cells (slanDCs) were recently described as immature DCs in the blood and as a subpopulation of inflammatory dermal DCs in psoriasis with a strong ability to produce proinflammatory cytokines and programme Th17/Th1 T cell responses. The effects of apremilast on the proinflammatory function of slanDCs and their ability to generate Th1/Th17-biased T cell responses were investigated in vitro. PDE4 inhibition increased cAMP levels in slanDCs, which inhibited the production of IL-12 and TNF-α In line with these findings, co-culture experiments with apremilast-pulsed slanDCs and allogeneic T cells either from psoriasis patients or healthy controls, revealed a significant reduction of IFN-γ production and production of IL-23 and IL-1ß by slanDCs was increased and T cells revealed a largely augmented IL-17 production and an upregulated RORyt expression.[119] Researchers demonstrated anti-inflammatory as well as Th17-promoting effects of apremilast when studying blood precursors of human inflammatory dermal dendritic cells. In the concert of the broad anti-inflammatory effects of apremilast on keratinocytes, fibroblasts and endothelial cells, the dual effect on slan$^+$ inflammatory dermal DCs should be taken into account and may constrain therapeutic responses.[120,121]

An open-label, pilot study to determine the efficacy of 20 mg of apremilast taken orally twice a day for 12 weeks in the treatment of rosacea has already been completed, but results have not yet been published (NCT01045551). In 2010, the University of North Carolina, Chapel Hill, in collaboration with Celgen Corp. started recruiting male and female patients, aged 18 -- 45 years, to participate in a study designed to determine the safety and efficacy of 20 mg apremilast taken twice a day for 12 weeks in the treatment of moderate--to-severe acne (NCT01074502).

Liver X-Receptor (LXR)

Liver X-receptor (LXR) belongs to the nuclear receptor family of transcription factors and closely associated to nuclear receptors like peroxisome proliferator-activated receptors, retinoid X receptors. LXR is differentiated in two different isoforms namely LXRα and LXRβ. LXR-α is highly articulated in liver and is also present in several parts like adipose tissue, macrophages, intestine, and kidney. It is also found in the skin like sebaceous glands, sweat glands as well as hair follicles. LXRα plays a vital role in the regulation of genes implicated in innate immunity, inflammatory response and moreover lipid biosynthesis. While LXRβ are involved in the keratinocyte differentiation as well as epidermal permeability barrier function.[122]

LXRs stimulation induces keratinocyte differentiation and permeability barrier homeostasis through a variety of pathways, including epidermal lipid synthesis activation. The epidermis is a hub for lipid metabolism, and LXR provide a platform for sensing these lipids, which can be used to coordinate downstream events and regulate a number of cellular functions.[123] Furthermore, activation of these receptors improves permeability barrier homeostasis through a variety of mechanisms, including stimulating epidermal lipid synthesis, increasing lamellar body formation and secretion, and increasing the activity of enzymes required for extracellular lipid processing in the stratum corneum, resulting in the formation of lamellar membranes that mediate permeability barrier function. LXR not only has potent anti-inflammatory properties in the skin, but it also regulates epidermal proliferation, carcinogenesis, differentiation, and permeability barrier function, making it an attractive pharmacological target for skin disease treatment.[124]

LXRs may play an important role within the skin. In vivo and in vitro studies showed that LXR ligands share in stratum corneum formation and induce down-regulation of cell proliferation. These ligands stimulate cornified envelope formation through increased transcription of transglutaminase, involucrin, loricrin and filaggrin.[125] It was found that activation of LXR-α induces lipid synthesis in sebocytes. Additionally, it induces Sterol Regulatory Element-Binding Protein 1 (SREBP-1) that regulates genes required for fatty acid and lipid metabolism and production.[126] Researchers have demonstrated that LXRs regulate FAS expression through direct interaction with the FAS promoter as well as through activation of SREBP-1c expression. Induction of FAS expression in HepG2 cells by LXR ligands is reduced, but not abolished, under conditions where SREBP processing is suppressed. Furthermore, LXR ligands increase FAS expression in CHO-7 cells without affecting SREBP-1 expression. It has been shown that the FAS promoter contains a high affinity binding site for the LXR/RXR heterodimer that is conserved in a variety of animal taxa, including birds, rodents, and humans, in addition to tandem SREBP sites. LXR responsiveness on the FAS promoter is conferred independently by the LXR and SREBP binding sites, and optimal induction necessitates both transcription factors.[127] Transient elevation of plasma triglyceride

levels in mice treated with a synthetic LXR agonist correlates with transient induction of hepatic FAS expression. These results indicate that the LXR signaling pathway modulates FAS expression through distinct but complementary mechanisms and suggest that the FAS gene may be a critical target in the control of lipogenesis by LXRs.[128,129] In addition, LXR-α inhibits the expression of macrophage inflammatory genes, including inducible Nitric Oxide Synthase (iNOS), COX-2, interleukin (IL-6), IL-1β, Monocyte Chemo-attractant Protein-1 (MCP-1) and MCP-3, in response to bacterial, Tumour Necrosis Factor-α (TNF-α) or lipopolysaccharide stimulation.[130]

N-methyl-D-aspartate (NMDA) receptor antagonist

Researchers demonstrated that an influx of calcium into epidermal keratinocytes delays recovery of the skin barrier function and induces epidermal hyperplasia. Because unsaturated fatty acids altered the intracellular distribution of calcium both in vitro and in vivo, aberrant keratinization after treatment with unsaturated fatty acids could be due to this disruption in the epidermis. In epidermal keratinocytes, calcium-permeable ionotropic channels exist, and their activation causes barrier-related problems and epidermal hyperplasia. Topical administration of P2X receptor or N-methyl-D-aspartate (NMDA)-type receptor agonists, for example, caused epidermal hyperplasia and delayed barrier healing.[131] Glutamate receptors play an important role in the excitatory synaptic action of the central nervous system. Fuziware and co. researchers studied the effects of glutamate receptor agonists and antagonists on skin barrier homeostasis using hairless mouse. Topical application of L-glutamic acid, L-aspartic acid (non-specific glutamate receptor agonists) and N-methyl-D-aspartate (NMDA, NMDA type receptor agonist) delayed the barrier recovery rate after barrier disruption with tape stripping. Topical administration of D-glutamic acid (non-specific glutamate receptor antagonist), MK 801, and D-AP5, (NMDA-type receptor antagonists), on the other hand, hastened barrier healing. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), a non-NMDA type receptor agonist, had no effect on barrier recovery. Under low ambient humidity, topical use of MK-801 aided in the healing of epidermal hyperplasia caused by acetone therapy. Glutamic acid release from skin was greatly elevated immediately after barrier breakdown on skin organ culture.[132] Katsuta **et al**. investigated the involvement of calcium channel receptors in the influx of calcium after treatment with unsaturated fatty acids. MK801 (dizocilpine; (5S,10R)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5, 10-imine) (NMDA-type glutamate receptor antagonist) (dizocilpine; (5S,10R)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5, In cultured human keratinocytes, MK801 also inhibited calcium influx and cytokine expression.[133]

SUMMARY AND CONCLUSION

Acne is a persistent obstructive and inflammatory condition that primarily affects adolescents' pilosebaceous follicles. The pathophysiology of acne is slowly being uncovered. Sebaceous glands and associated ductal infundibula are not only cutaneous appendageal structures that produce sebum to keep the epidermis moist, but they also act as a stage for essential immunological processes such innate immunity, NP production, antimicrobial peptide synthesis, and stem cell expression.

Receptors play a crucial role in disease pathogenesis. It is difficult to conclude that a single receptor is responsible for the disease because the number of receptors implicated in disease development is increasing. It's always a good idea to cross check the dominant receptor effect and its relationship to other receptors. A formulator's ability to create ligand binding molecules for good therapeutic outcomes is aided by a thorough understanding of this. Drug designers can choose to create an alternative chemical structure design that maintains the optimal binding uniqueness of ligands, ensuring the active moiety's efficacy. Thus, one can exploit these basic findings to design and develop the selective drug that targets the receptors endow with the effectual remedy for acne vulgaris by checking the patient history, dietary habits, hormone levels, ligand levels, lipid profiles etc. Still a lot of research has to be executed to explore this area to come up with the tailor-made medication for acne based on the knowledge of receptors and ligands involved in the disease progression.

Treatment of acne requires proper knowledge on the pathophysiology then only the clinician can come out with a proper therapeutic dosage regimen. Understanding the pathophysiology not only includes the mechanism but also involvement of receptors. Thus, this review is framed in such a way that the authors have focused on the disease acne vulgaris, pathophysiology, transcription factors viz. the Forkhead Box O1 (FoxO1) Transcription Factor, hormones like androgens and receptors such as Histamine receptors, Retinoic receptor, Fibroblast growth factor receptors, Toll like receptor, Androgen receptor, Liver X-receptor, Melanocortin receptor, Peroxisome proliferator-activated receptor and epidermal growth factor receptors involvement in the progression of acne vulgaris.

The combined action of androgens and PPAR ligands on the pilosebaceous unit results in increased sebocyte proliferation according to a recent acne aetiology. Androgenic stimulation is accompanied by aberrant ductal and infundibular hyperkeratinization, which is aided by synergistic growth factors, NPs, and IL-1a. Ectopeptidases and P. acnes proliferation, as well as the resulting increase in bacterial TLR2 ligands in the follicular canal, may increase IL-1 production and secretion, which in turn induces IL-6, IL-8, and IL-12

production in infundibular keratinocytes and macrophages, leading to follicular wall inflammation and rupture, as well as the induction of tissue matrix metalloproteinases that cause acne scar.

The ideal acne treatment would target sebum production, dyskeratosis within the infundibular wall, P. acnes colonisation, and the inflammatory response that follows all at the same time; however, no single treatment has been found to target all four pathogenic factors involved in the appearance of acne lesions. Recent discoveries about the importance of a lipid-rich environment in the overgrowth of P. acnes and the formation of P. acnes biofilms, as well as the role of P. acnes in the formation of microcomedones, have led to the development of new therapeutic molecules that target sebum production, such as topical anti-androgens, CoA carboxylase/desaturase inhibitors, MCR antagonists, IGF-1 inhibitors, and botanical extracts like lupeol and CBD. Currently approved topical retinoids (all dual RAR-β and RAR-γ agonists, are effective in treating microcomedones, comedones, inflammatory lesions and in preventing recurrences and scarring by normalizing follicular dyskeratosis and reducing inflammation, however they commonly cause skin irritation, which limit their use in some patients. RAR-γ agonist, trifarotene, could potentially limit adverse effects linked to RAR agonism and therefore be better tolerated by patients presenting as a better treatment option than currently available therapies. Oral and topical antibiotics have traditionally been used to treat P. acnes colonisation; however, due to rising concerns about bacterial resistance, novel non-antibiotic compounds are favoured. BPO is now suggested for the treatment of acne instead of chronic antibiotic therapy due to its very effective bactericidal capabilities and lack of bacterial resistance; nonetheless, many patients report skin sensitivity. NO-releasing agents, ACPs, M-DDO, and biofilm matrix degradation gels, among other new bactericidal therapies, appear to offer a more bearable treatment alternative for decreasing P. acnes population and biofilm development, without the danger of antibiotic resistance and related adverse effects of BPO. Oral anti-inflammatory agents, such as acebilustat, and subcutaneous monoclonal antibodies, such as Gevokizumab, have shown promising results in clinical trials, but their use in acne remains to be seen.

Prospective new acne treatments may in the future address the normalization of abnormal keratinization in the follicular infundibulum, the inhibition of IL-1α, IL-1α receptor antagonism, the inhibition of inflammatory mediators such as 5-lipoxygenase, the inhibition of leukocyte chemotaxis, the antagonism of pro-inflammatory cytokines, the inhibition of the production of reactive oxygen species, the improvement of anti-androgenic effectiveness, the enhanced production of endogenous antimicrobial peptides and possibly the manipulation of Langerhans cell migration and the expression and activity of TNFα, integrin and TLR2. Nanotechnology may facilitate follicular targeting of such treatments.

Nanomaterials can influence the innate or acquired immune system's response to microorganisms. Although nano-dermatology has begun to dominate the commercial market, the process is sluggish since in-vitro outcomes do not always anticipate the in-vivo outcome. The possible toxicity of certain materials employed to produce these nanostructures is also a source of worry. Clinical translation from the bench necessitates a thorough grasp of the nano-bio interaction, as well as new research to supplement existing expertise in the field of nano dermatology.

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