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BIOCHEMICAL DRIVERS OF SKIN DISEASES AND THE PATH FROM MOLECULAR UNDERSTANDING TO EFFECTIVE CURES

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Abstract

Skin diseases affect nearly one-third of the global population, yet biochemical drivers remain underappreciated in clinical translation. Despite decades of research focusing on genetics and histopathology, the dynamic molecular currencies lipids, proteases, reactive oxygen species, and cytokines that actually govern disease activity have been largely ignored in routine clinical practice. This review addresses this gap by placing biochemistry at the center of dermatologic diagnosis and therapy. Four biochemical pillars drive inflammatory skin diseases. First, lipid barrier defects, including ceramide deficiency and impaired lipid processing, compromise stratum corneum integrity. Second, protease-antiprotease imbalance, particularly involving KLK5 and KLK7 and their inhibitor LEKTI, leads to premature desquamation and inflammation. Third, redox signaling deregulation, characterized by NADPH oxidase-derived reactive oxygen species and depletion of glutathione and thioredoxin systems, amplifies proinflammatory transcription factors. Fourth, cytokine-mediated inflammation, orchestrated by the IL-23/IL-17 axis in psoriasis and the IL-4/IL-13 axis in atopic dermatitis, represents the final common pathway of disease expression Molecular understanding has already yielded transformative therapies. Biologics targeting IL-17A (secukinumab, ixekizumab), IL-23 (guselkumab, risankizumab), and IL-4Rα (dupilumab) have revolutionized treatment of psoriasis and atopic dermatitis. Small molecule inhibitors including JAK inhibitors (upadacitinib, tofacitinib), TYK2 inhibitors (deucravacitinib), and PDE4 inhibitors (apremilast) offer oral alternatives. Gene-targeted approaches for monogenic skin diseases are advancing through preclinical and early clinical development. Biochemical stratification the systematic measurement of lipid profiles, protease activities, redox status, and cytokine signatures in patient skin represents the missing link between descriptive histopathology and mechanism-based curative therapy. Integrating biochemical endotyping into routine dermatologic practice and clinical trial design will accelerate the development of rational, targeted, and ultimately curative treatments for the full spectrum of inflammatory skin diseases.

1. INTRODUCTION

1.1 Burden of Skin Diseases

Despite affecting nearly one-third of the world's population at any given time, the global burden of skin diseases remains staggering, with chronic inflammatory conditions such as psoriasis, atopic dermatitis, hidradenitis suppurativa, and pemphigus posing an escalating challenge to

healthcare systems, dermatologic practice, and patient quality of life (Jain, 2025). Psoriasis alone impacts approximately 60 million people worldwide, driving not only cutaneous inflammation but also systemic comorbidities including psoriatic arthritis, cardiovascular disease, and metabolic syndrome (Felgueiras, 2021). Atopic dermatitis, the most common inflammatory skin disorder, affects 15–20% of children and up to 10% of adults, with severe forms causing intractable pruritus, sleep disturbance, and profound psychosocial morbidity (Mohd Zaid et al., 2023)SS. Hidradenitis suppurativa, a chronic condition of apocrine gland-rich skin, carries one of the highest dermatologic disease burdens as measured by quality-of-life indices, while pemphigus, though rarer, remains a life-threatening autoimmune blistering disease requiring aggressive immunosuppression (Roy et al., 2023). Despite the immense clinical and economic weight of these disorders, conventional therapeutic approaches have historically focused on symptomatic control rather than mechanistic cure, and the fundamental biochemical drivers that initiate, sustain, or resolve these diseases have remained surprisingly underappreciated in routine clinical translation and drug development paradigms (Mamun et al., 2024).

1.2 Why "Biochemical Drivers" Instead of Genetic or Immunological Alone

The central argument of this review is that the concept of "biochemical drivers" offers a more precise and therapeutically actionable framework than genetic or immunological explanations alone (Orzan, 2025). Genetic association studies have identified hundreds of risk loci for psoriasis and atopic dermatitis, yet individual variants typically confer modest effect sizes and fail to explain the dynamic, fluctuating nature of disease activity; a genetic variant does not directly cause inflammation but rather creates a biochemical vulnerability that manifests as disease only when environmental, metabolic, or microbial triggers perturb key molecular pathways (Peña, 2024). Immunological descriptions, while central to understanding psoriasis as an IL-23/IL-17-mediated disease or atopic dermatitis as a Th2-polarized condition, often remain descriptive of cellular populations and cytokine profiles without explaining the proximal biochemical events that initiate immune dysregulation (Parvathy et al., 2025). Biochemical drivers occupy the critical mechanistic space between genotype and phenotype, between trigger and response, and between chronic inflammation and resolution—lipids, proteases, reactive oxygen species, metabolites, and post-translational modifications represent the actual molecular currencies of disease activity, and targeting these biochemical nodes offers the potential for more rapid, direct, and durable therapeutic effects than targeting distal genetic or broad immunological pathways (Kumar et al., 2025).

1.3 Scope of the Review

The scope of this review is deliberately comprehensive yet mechanistically focused, spanning spatial scales from the extracellular organization of stratum corneum lipids to the intranuclear activity of transcription factors, and temporal scales from acute barrier disruption to chronic inflammatory remodeling (Shirley, 2024). The review begins by examining the epidermal barrier as a biochemical entity, analyzing the precise lipid composition of intercellular lamellae, the enzymatic processing of ceramide precursors, and the generation of natural moisturizing factors (Li, 2025). From this structural foundation, the review progresses to protease-antiprotease networks, redox biochemistry, cytokine signaling, genetic and epigenetic regulation, microbiome interactions, and disease-specific molecular mechanisms (Afshari et al., 2024). Current therapeutic strategies, translational research, emerging technologies, challenges, and future directions are critically evaluated (Bieber, 2022). The review concludes with actionable recommendations for integrating biochemical endotyping into precision dermatology, with the ultimate goal of achieving curative, rather than merely suppressive, therapy for the full spectrum of inflammatory skin diseases (Baker et al., 2023).

2. The Epidermal Barrier as a Biochemical Entity

2.1 Rethinking the Epidermal Barrier

The epidermal barrier, long viewed through structural histology as simply a multilayered stratified squamous epithelium, is more accurately understood as a sophisticated biochemical apparatus whose function emerges from the precise composition, spatial organization, and enzymatic regulation of specific lipid and protein species (Afshari et al., 2024).

2.2 Lipid Composition of the Stratum Corneum

The lipid composition of the stratum corneum is fundamentally distinct from any other biological membrane (Puig et al., 2022). Unlike the phospholipid bilayers of most cellular membranes, the intercellular spaces of the stratum corneum contain lamellar sheets composed of three primary lipid classes ceramides, free fatty acids, and cholesterol present in an approximately equimolar ratio of 1:1:1, which is essential for barrier function. Ceramides constitute about 50 percent of stratum corneum lipid mass by weight; they are sphingolipids consisting of a sphingoid base linked to a fatty acid via an amide bond, with over 300 molecular variants existing in human skin, differing in chain length, hydroxylation degree, and sphingoid base structure (He et al., 2024). Free fatty acids, primarily long-chain species with 16 to 28 carbon atoms, provide necessary fluidity and packing properties, while cholesterol modulates membrane permeability and prevents crystallization of other lipid species (Briganti et al., 2024). Together, these three lipid classes self-assemble into highly organized lamellar structures that form the primary diffusion barrier against trans epidermal water loss and the penetration of external irritants, allergens, and pathogens (Tai et al., 2021).

2.3 Enzymatic Processing of Lipids

Ceramides are not synthesized directly within the stratum corneum but are produced from precursor molecules through two essential hydrolases: β-glucocerebrosidase (encoded by GBA1), which cleaves glucose from glucosylceramides to generate mature ceramides, and acid sphingomyelinase (encoded by SMPD1), which hydrolyzes sphingomyelin to produce ceramide and phosphorylcholine (Napolitano et al., 2021). The importance of these enzymes is illustrated by human genetic deficiencies: mutations in GBA1 cause gaucher disease, with the severe neonatal form including an ichthyotic skin phenotype and profound barrier defect, while mutations in SMPD1 cause Niemann-Pick disease type A or B, with cutaneous ichthyosis in severe cases (Nordmann et al., 2024). Partial reductions in enzyme activity due to common polymorphisms or acquired inhibition can compromise barrier function and increase susceptibility to inflammatory skin disease (Huangfu et al., 2023). Both enzymes are pH-dependent, with optima in the acidic range, which explains why the stratum corneum normally maintains a slightly acidic pH of approximately 5.5 (Al-Sadek, 2024). Conversely, alkalinization of the stratum corneum whether from genetic factors, environmental exposures, or topical soaps directly impairs lipid processing and barrier repair (Kawasaki et al., 2023).

2.4 Filaggrin and Natural Moisturizing Factor (NMF)

Profilaggrin, a large polyprotein expressed exclusively in the granular layer, is proteolytically processed into individual filaggrin monomers, which then aggregate keratin filaments into tight bundles, promoting corneocyte flattening and compaction (Condorelli et al., 2021). As corneocytes transition through the outer stratum corneum, filaggrin is progressively degraded by a cascade of proteases including caspase-14 and bleomycin hydrolase into free amino acids and their derivatives, a mixture collectively termed natural moisturizing factor (NMF) (Basurto-Lozada et al., 2021). NMF components include trans-urocanic acid, pyrrolidone carboxylic acid, citrulline, and various neutral amino acids, which function to absorb water from the atmosphere to maintain stratum corneum hydration, contribute to the acidic pH of the skin surface via urocanic acid and pyrrolidone carboxylic acid, and may possess direct immunomodulatory properties. Loss-of-function mutations in the filaggrin gene

(FLG) are among the strongest known genetic risk factors for atopic dermatitis, as affected individuals have profoundly reduced NMF levels, leading to dry, scaly skin and increased allergen penetration (Cerro Chiang, 2023).

2.5 Biochemical Consequences of Barrier Defects

Trans epidermal water loss, the standard biophysical measure of barrier integrity, increases dramatically in all conditions associated with lipid deficiency, protease excess, or filaggrin mutation, but the more insidious consequence is the alkaline shift in stratum corneum ph (Zhao et al., 2022). This shift, caused by loss of free fatty acids, reduced natural moisturizing factor, and impaired lipid processing, raises the pH from the normal range of 5.0–5.5 toward neutrality at 7.0–7.5. Multiple deleterious effects follow: increased activity of serine proteases such as KLK5 and KLK7, which have neutral to alkaline pH optima; reduced activity of β-glucocerebrosidase and acid sphingomyelinase, further compromising lipid processing; and promotion of pathogenic Staphylococcus aurous growth while inhibiting commensal organisms (Anderton, 2022). The result is a self-amplifying cycle of barrier disruption, protease activation, lipid misprocessing, and microbial dysbiosis, which sustains chronic inflammation and provides a biochemical foundation for the clinical exacerbations characteristic of atopic dermatitis and related disorders (Liu et al., 2022).

3. Protease-Antiprotease Networks in Skin Homeostasis and Disease

3.1 Overview of Desquamation and Protease-Antiprotease Balance

The orderly desquamation of corneocytes from the skin surface is a seamless, imperceptible process under physiological conditions, orchestrated by an exquisitely balanced network of proteases and their cognate inhibitors (He, 2022). Any perturbation of this equilibrium rapidly manifests as either excessive scaling or barrier fragility or retention hyperkeratosis, both of which characterize a wide spectrum of inherited and acquired skin diseases (Friedlaender et al., 2024).

3.2 Kallikrein-Related Peptidases (KLK5, KLK7) and LEKTI Inhibition

The central players in desquamation are the kallikrein-related peptidases, a family of fifteen serine proteases highly expressed in the stratum corneum (Korta, 2023). KLK5, which has a neutral to alkaline pH optimum, is synthesized as an inactive zymogen and activated through a complex cascade via auto activation or transactivation by other proteases; once active, KLK5 cleaves and activates downstream proteases such as KLK7 and KLK14, generating a proteolysis cascade that ultimately degrades corneodesmosomes—the intercellular adhesive structures maintaining corneocyte cohesion (Makowska et al., 2023). This protease activity is tightly restrained by LEKTI (lymph epithelial Kazal-type related inhibitor), encoded by the SPINK5 gene, which is a multidomain inhibitor containing 15 potential inhibitory domains, with domains 2–6 and 9–12 specifically targeting KLK5 and KLK7 with high affinity and selectivity (Wu et al., 2022). LEKTI functions as a suicide inhibitor, forming stable complexes with target proteases and irreversibly blocking catalytic activity (Liu et al., 2025). The spatial and temporal coordination of protease activation and LEKTI-mediated inhibition ensures that desquamation occurs only at the outermost layers of the stratum corneum and that the desquamation rate is precisely matched to the production of new corneocytes, with KLK5 and KLK7 being the most abundantly expressed in (Singh et al., 2023).

3.3 Netherton Syndrome as a Biochemical Model

Netherton syndrome is a rare, autosomal recessive disorder resulting from loss-of-function mutations in the SPINK5 gene, leading to complete absence or profound deficiency of functional LEKTI (Rivera-Díaz et al., 2023). Without LEKTI, KLK5 and KLK7 become massively overactive throughout the stratum corneum, with two major biochemical consequences: unchecked KLK5 directly degrades corneodesmosomes, causing premature and widespread desquamation that results in severe scaling and skin fragility, while excessive KLK5 also activates protease-activated

receptor 2 (PAR-2) on keratinocytes, triggering release of proinflammatory cytokines such as thymic stromal lymphopoietin, IL-33, and IL-6 (Guo et al., 2023). The clinical phenotype includes severe, life-threatening inflammatory skin disease with generalized scaling, chronic erythema, profound pruritus, atopic manifestations including food allergies and elevated IgE, and a dramatically increased risk of cutaneous and systemic infections (Zhou et al., 2024). Netherton syndrome thus demonstrates that the LEKTI-KLK axis is a non-redundant, essential regulator of both epidermal barrier integrity and cutaneous immune homeostasis, and the syndrome serves as proof-of-concept for therapeutic strategies targeting KLK5 or KLK7, with topical small molecule inhibitors now advancing through phase 2 clinical trials (Lavalle et al., 2024).

3.4 Matrix Metalloproteinase (MMPs) in Wound Healing and Fibrosis

MMPs (matrix metalloproteinase) constitute a second major family of zinc-dependent end peptidases that collectively degrade all components of the extracellular matrix, shaping skin homeostasis and disease (Mobasheri et al., 2023). In wound healing, MMP-1 initiates degradation of type I and type III collagens, clearing damaged matrix and creating space for migrating keratinocytes and fibroblasts, while MMP-9 degrades denatured collagen and basement membrane components, facilitating tissue remodeling and angiogenesis (Dar et al., 2023). MMP activity is tightly regulated by TIMPs (tissue inhibitors of metalloproteinase), with TIMP-1 and TIMP-2 being most relevant in skin; under normal wound healing, a carefully orchestrated balance between MMPs and TIMPs allows for matrix degradation during inflammatory and proliferative phases, followed by matrix deposition and remodeling during the maturation phase (Raharja, 2021). In chronic wounds such as venous leg ulcers and diabetic foot ulcers, this balance is disrupted, leading to excessive MMP activity and uncontrolled matrix degradation that results in failure to heal. Conversely, in fibrotic skin diseases such as scleroderma and keloids, reduced MMP activity or increased TIMP expression leads to excessive matrix accumulation, causing dermal thickening, tissue rigidity, and impaired function (Chow, 2024).

3.5 Desquamation Failure in Psoriasis and Ichthyoses

Desquamation failure is the pathological opposite of the premature desquamation seen in Netherton syndrome and characterizes a distinct group of skin diseases including psoriasis and congenital ichthyoses (Driver, 2023). In psoriasis, dramatically accelerated epidermal turnover produces parakeratotic scale, yet corneocytes fail to detach properly from the skin surface; this retention hyperkeratosis results from complex dysregulation of the protease-antiprotease network, and although KLK5 and KLK7 activities are elevated in psoriatic lesions, their effects are counterbalanced by increased expression of other protease inhibitors, altered stratum corneum pH, and abnormal lipid composition that physically impedes desquamation (Liu et al., 2023). In autosomal recessive congenital ichthyoses, mutations in genes encoding proteases, protease inhibitors, or their downstream targets directly cause desquamation failure—for example, mutations in the gene encoding KLK7 itself, or genes regulating KLK activation or localization, have been identified in some ichthyosis subtypes (García-Díaz et al., 2021). The therapeutic implications are significant: topical agents that normalize protease activity, such as urea and N-acetyl cysteine, have been used empirically for decades, and the development of more specific protease modulators now offers targeted, rational therapy for these debilitating disorders (Akbarian, 2022).

4. Redox Biochemistry and Oxidative Stress in Cutaneous Inflammation

4.1 Skin as a Unique Redox Interface

The skin is the primary interface with the external environment, constantly exposed to ultraviolet radiation, atmospheric pollutants, mechanical injury, and microbial products, all of which challenge its redox equilibrium (Jin et al., 2024). Under normal conditions, a delicate balance is

maintained between the production of reactive oxygen species (ROS) and the capacity of endogenous antioxidant systems to neutralize them; this balance, termed redox homeostasis, is essential for preventing oxidative damage and for preserving the signaling functions of ROS, which at low concentrations serve as second messengers regulating proliferation, differentiation, and immune responses (Guo et al., 2022). In inflammatory skin diseases, this equilibrium is disrupted, shifting toward oxidative stress characterized by excessive ROS production, depletion of antioxidant reserves, and cumulative oxidative damage to lipids, proteins, and DNA (Klug et al., 2022). Understanding the sources, targets, and consequences of cutaneous oxidative stress is therefore essential for deciphering the biochemical drivers of chronic inflammation and identifying new therapeutic opportunities (Subramaniyan, 2025).

4.2 Sources of Reactive Oxygen Species in Skin

Sources of ROS in skin are both endogenous and exogenous, with relative contributions varying across different disease states (La Cognata, 2021). Endogenous sources include the mitochondrial electron transport chain at complexes I and III, which generates ROS as byproducts of normal aerobic respiration, and the NADPH oxidase (NOX) family, which generates ROS deliberately for innate immunity and cellular signaling—specifically, NOX1 is expressed predominantly in keratinocytes where it contributes to wound healing and antimicrobial defense, and its derived ROS are markedly elevated in psoriatic keratinocytes, driving proinflammatory transcription factors, while NOX4 is more widely distributed and produces hydrogen peroxide rather than superoxide (Ramchatesingh et al., 2022). The primary exogenous source is ultraviolet radiation, particularly UVB, which acts as a potent ROS generator, producing superoxide, hydrogen peroxide, singlet oxygen, and hydroxyl radicals through direct photochemical reactions and indirect mechanisms involving endogenous photosensitizers (Dai, 2025).

4.3 Antioxidant Defense Systems in Skin

The skin deploys an elaborate, multilayered antioxidant defense system to counter pro-oxidant challenges. Glutathione (GSH), a tripeptide of glutamate, cysteine, and glycine, is the most abundant low-molecular-weight thiol, and the ratio of reduced GSH to oxidized GSSG—normally greater than 100:1—serves as a sensitive indicator of cellular redox status (Kolkhir et al., 2023). The thioredoxin system, comprising thioredoxin, thioredoxin reductase, and NADPH, reduces oxidized protein thiols and participates in regenerating other antioxidants including vitamin C (Lin, 2024). Catalase, a heme-containing enzyme localized primarily in peroxisomes, catalyzes the dismutation of hydrogen peroxide to water and molecular oxygen (Li et al., 2022). Superoxide dismutase (SOD) exists in three isoforms: copper-zinc SOD (Cu/Zn-SOD) in the cytoplasm, manganese SOD (Mn-SOD) in the mitochondrial matrix, and extracellular SOD (EC-SOD) in the extracellular space; each SOD isoform converts superoxide anion to hydrogen peroxide, which is then eliminated by catalase or glutathione peroxidase (Dubin, 2021). Although the coordinated activity of these systems normally maintains redox homeostasis, in inflammatory skin diseases sustained immune activation and chronic ROS production overwhelm these defenses (Kim, 2024).

4.4 Oxidative Modification of Biomolecules

Oxidative modification of biomolecules represents the molecular signature of oxidative stress and the mechanism by which ROS propagate tissue injury (Qian et al., 2024). Lipid peroxidation, the oxidative degradation of polyunsaturated fatty acids, generates reactive aldehydes such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which are not inert end products but electrophilic signaling molecules that covalently modify proteins to form advanced lipid peroxidation end products (ALEs) that activate inflammatory pathways. Protein carbonylation, the irreversible oxidation of lysine, arginine, proline, and threonine residues to introduce carbonyl groups, is a hallmark of severe oxidative stress; carbonated proteins lose enzymatic activity,

become more susceptible to proteasomal degradation, and can aggregate, contributing to cellular dysfunction (Nicolay et al., 2021). Both lipid peroxidation and protein carbonylation are markedly elevated in psoriatic lesions, atopic dermatitis, and vitiligo, correlating with disease severity and inflammatory infiltrate density (Kiran et al., 2024).

4.5 Redox-Sensitive Transcription Factors

Redox-sensitive transcription factors provide the mechanistic link between oxidative stress and altered gene expression (Matar et al., 2023). NRF2 (Nuclear factor elytroid 2-related factor 2) serves as the master regulator of the antioxidant response: under basal conditions, NRF2 is bound to its inhibitor KEAP1 in the cytoplasm and targeted for ubiquitin-dependent proteasomal degradation, but upon oxidative stress, critical cysteine residues in KEAP1 are modified, releasing NRF2 to translocate to the nucleus and activate expression of over 200 cytoprotective genes including glutathione S-transferases, NAD(P)H quinone oxidoreductase, and heme oxygenase-1 (Kim et al., 2024). In contrast, NF-κB and AP-1 are proinflammatory transcription factors activated by oxidative stress, with NF-κB activation requiring oxidation of a specific cysteine residue in its inhibitor IκB, and AP-1 (a dimer of JUN and FOS family proteins) being activated through redox-dependent phosphorylation by mitogen-activated protein kinases (MAPKs) (Mackie et al., 2023). The balance between NRF2-mediated cytoprotection and NF-κB/AP-1-mediated inflammation ultimately determines the outcome of oxidative stress (Zouboulis et al., 2021). In disease contexts, for example, NOX1-driven ROS production in psoriasis strongly activates NF-κB, amplifying IL-23 and IL-17 signaling, whereas in vitiligo, melanocytes exhibit intrinsic redox vulnerability due to the pro-oxidant nature of melanin synthesis and relatively low antioxidant capacity, rendering them selectively susceptible to oxidative stress-induced cell death (Bryan, 2022).

Table 1. Redox Parameters: Healthy vs. Inflamed Skin

Parameter	Healthy Skin	Inflamed / Diseased Skin
ROS production	Low, regulated	High (NOX1, UV, immune cells)
GSH/GSSG ratio	> 100:1 (reduced)	Decreased (oxidative stress)
Lipid peroxidation (4-HNE, MDA)	Minimal	Elevated
Protein carbonylation	Low / absent	Increased
NRF2 (cytoprotective)	Basal activity	Dysregulated / exhausted
NF-κB / AP-1 (proinflammatory)	Low activity	Strongly activated
Overall redox balance	Homeostasis	Oxidative stress

5. Cytokine and Chemokine Signaling Networks

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5.1 Overview of Cytokine Signaling as Biochemical Language

Cytokine and chemokine signaling networks represent the biochemical language through which immune cells, keratinocytes, fibroblasts, and endothelial cells communicate to orchestrate cutaneous inflammation (Moingeon, 2023). While often described in immunological terms of cellular sources and targets, these are fundamentally biochemical cascades involving extracellular ligand-receptor interactions, receptor-proximal signal transduction through non-receptor tyrosine kinases, downstream phosphorylation cascades, and nuclear transcription factor activation that reprograms gene expression (Xue et al., 2023). The identification of specific cytokine axes as non-redundant drivers of distinct inflammatory skin diseases has revolutionized dermatologic therapy, enabling the development of biologics and small

molecules that intercept these biochemical signals with remarkable efficacy and safety (Mahmud et al., 2022). Understanding the precise molecular details of these pathways is therefore essential for comprehending disease pathogenesis and for rational therapeutic targeting (Papaccio, 2022).

5.2 The IL-23/IL-17 Axis in Psoriasis

The IL-23/IL-17 axis represents the dominant biochemical driver of psoriasis and one of the most successful therapeutic targets in dermatology (Chen et al., 2022). IL-23 is a heterodimer cytokine composed of a unique p19 subunit and a shared p40 subunit, produced primarily by activated dendritic cells and macrophages in response to microbial stimuli, tissue injury, or innate immune activation (Honkala et al., 2022). The IL-23 receptor, a heterodimer of IL-23R and IL-12Rβ1 expressed on Th17 cells, γδ T cells, and innate lymphoid cells, initiates a downstream signaling cascade: IL-23 binding activates JAK2 and TYK2, which then phosphorylate and activate STAT3; phosphorylated STAT3 dimerizes and translocate to the nucleus, driving expression of RORγt, the master transcription factor for Th17 differentiation (Hasan, 2022). Differentiated Th17 cells produce effector cytokines including IL-17A, IL-17F, and IL-22 (Facheris et al., 2023). IL-17A signals through the heterodimer receptor IL-17RA/IL-17RC, activating the adaptor protein ACT1 and leading to NF-κB, MAPK, and C/EBP pathway activation (Alemu et al., 2025). Importantly, IL-23 also maintains the pathogenic phenotype of Th17 cells; in its absence, Th17 cells lose proinflammatory function or convert to regulatory phenotypes (Thapa et al., 2023).

5.3 Th2 Biochemistry in Atopic Dermatitis

Th2 biochemistry dominates the molecular landscape of atopic dermatitis, with a cytokine hierarchy distinct from the IL-23/IL-17 axis of psoriasis (Wang et al., 2023). The central drivers are IL-4 and IL-13, produced by Th2-polarized CD4-positive T cells, group 2 innate lymphoid cells (ILC2s), basophils, and mast cells (Sasso et al., 2022). Their signaling pathways involve IL-4 and IL-13 sharing either the common gamma chain or the IL-13 receptor alpha 1 chain, activating JAK1/JAK3 or JAK1/TYK2 respectively, with STAT6 serving as the principal downstream transcription factor. The overlapping effects of IL-4 and IL-13 on skin include suppression of terminal differentiation proteins such as filaggrin, loricrin, and involucrin, which directly compromises barrier function, and induction of chemokine's CCL17 and CCL22 that recruit Th2 cells to the skin (Ihim et al., 2022). IL-13 has a specific effect in up regulating periostin, a matricellular protein that contributes to dermal fibrosis and Th2 persistence (Bergqvist, 2021). IL-31, another Th2-associated cytokine, signals through a heterodimer receptor composed of IL-31RA and oncostatin M receptor; transgenic overexpression in mice recapitulates the pruritus and dermatitis of human atopic dermatitis, and IL-31 acts directly on sensory neurons to induce itch (Griffin et al., 2022). Accordingly, anti-IL-31 receptor alpha antibodies have shown substantial antipruritic effects in phase 2/3 clinical trials (Alrumaihi et al., 2024).

5.4 Effects of IL-17A, IL-17F, and IL-22 on Keratinocyte Biochemistry

These effects directly account for many histopathological features of psoriasis. IL-17A is present at concentrations orders of magnitude higher in psoriatic plaques than in non-lesion skin or healthy controls; it potently induces keratinocyte proliferation through NF-κB and MAPK pathway activation, producing acanthosis and elongated rete ridges characteristic of psoriatic histology (Xu et al., 2023). IL-17A also induces expression of antimicrobial peptides including LL-37, S100A7 (psoriasis), S100A8 (calgranulin A), S100A9 (calgranulin B), and human beta defensin 2, which are markedly elevated in psoriatic lesions and contribute to parakeratosis and neutrophil recruitment. IL-22, produced by both Th17 cells and Th22 cells, acts primarily on keratinocytes since immune cells do not express the IL-22 receptor; IL-22 signaling through JAK1 and TYK2 activates STAT3, driving keratinocyte proliferation and antimicrobial peptide expression (Arafah et al., 2023). Unlike IL-17A, IL-22 does not induce proinflammatory cytokine production from keratinocytes, and high levels of IL-22 may

be protective in some contexts by enhancing barrier function and promoting wound healing (Xiao et al., 2023). Notably, the combination of IL-17A and IL-22 produces synergistic effects on keratinocyte proliferation, amplifying the psoriatic phenotype (Afonina, 2021).

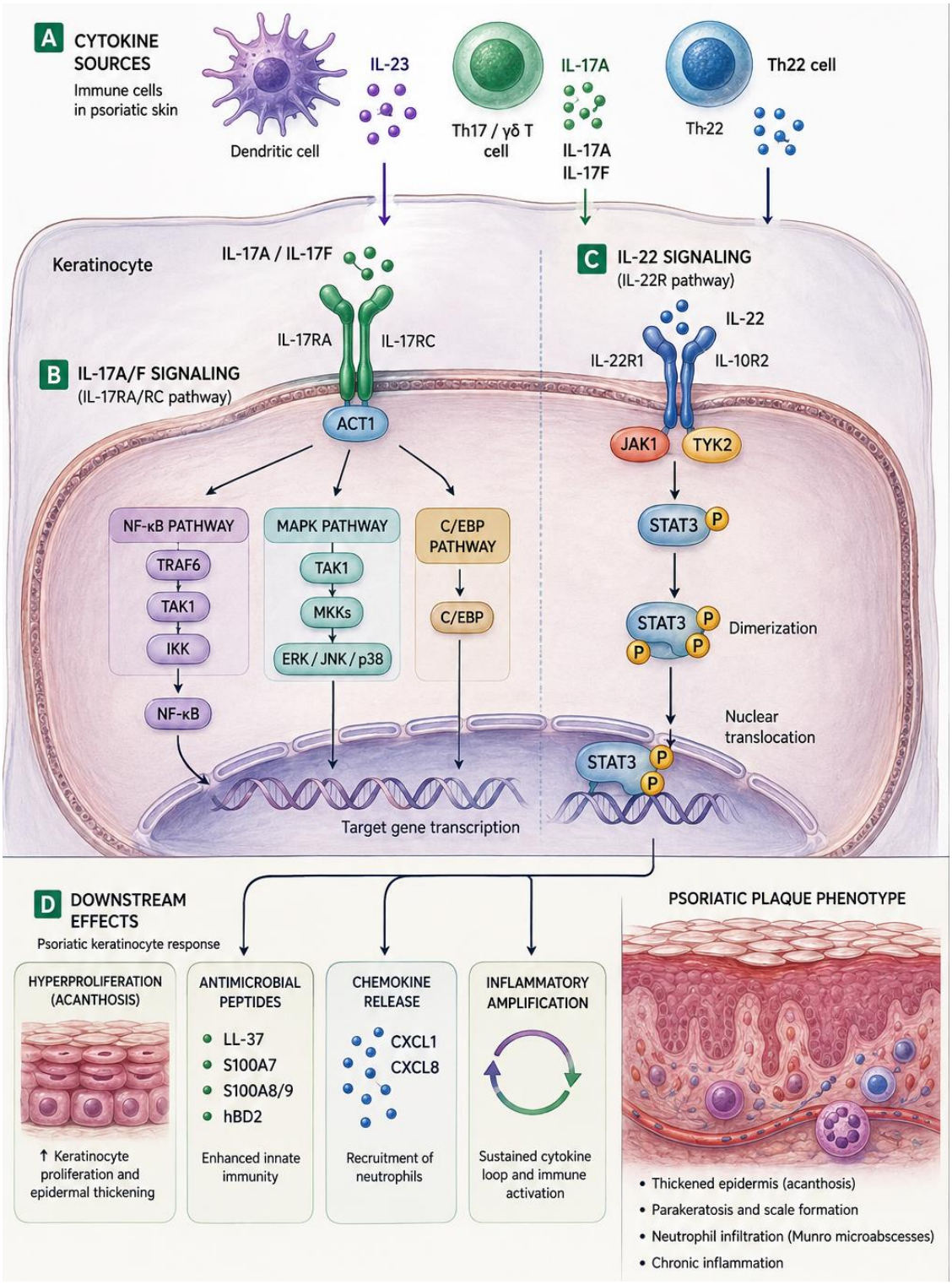

Figure 1. Biochemical signaling pathways in a psoriatic keratinocyte. (A) Immune-cell-derived cytokines (IL-23 from dendritic cells; IL-17A, IL-17F and IL-22 from Th17/γδ T and Th22 cells) bind keratinocyte surface receptors. (B) IL-17A/F signalling through IL-17RA/RC recruits the adaptor ACT1, activating NF-κB, MAPK and C/EBP pathways. (C) IL-22 signalling through IL-22R activates JAK1/TYK2, driving STAT3 phosphorylation, dimerisation and nuclear translocation. (D) Downstream effects include keratinocyte hyperproliferation (acanthosis), induction of antimicrobial peptides (LL-37, S100A7, S100A8/9, hBD2) and chemokine release (CXCL1, CXCL8) recruiting neutrophils—together producing the psoriatic plaque phenotype.

Biochemical signaling pathways in a psoriatic keratinocyte. (A) Immune-cell-derived cytokines (IL-23 from dendritic cells; IL-17A, IL-17F and IL-22 from Th17/γδ T and Th22 cells) bind keratinocyte surface receptors. (B) IL-17A/F signalling through IL-17RA/RC recruits the adaptor ACT1, activating NF-κB, MAPK and C/EBP pathways. (C) IL-22 signalling through IL-22R activates JAK1/TYK2, driving STAT3 phosphorylation, dimerisation and nuclear translocation. (D) Downstream effects include keratinocyte hyperproliferation (acanthosis), induction of antimicrobial peptides (LL-37, S100A7, S100A8/9, hBD2) and chemokine release (CXCL1, CXCL8) recruiting neutrophils—together producing the psoriatic plaque phenotype.

5.5 JAK-STAT Pathways as Biochemical Integrators

JAK-STAT pathways connect extracellular cytokine signals to nuclear gene expression programs, and all cytokine receptors relevant to skin disease lack intrinsic enzymatic activity (Vetrano et al., 2022). Instead, these receptors couple to JAK family members—JAK1, JAK2, JAK3, and TYK2—that are constitutively associated with receptor cytoplasmic domains (Gu, 2024). The activation cascade proceeds as follows: cytokine binding causes receptor dimerization, bringing JAKs into proximity and enabling trans-phosphorylation and activation; activated JAKs then phosphorylate specific tyrosine residues on receptor cytoplasmic tails, creating docking sites for STAT proteins; recruited STATs are phosphorylated by JAKs, dissociate from the receptor, dimerize via reciprocal phosphotyrosine-SH2 domain interactions, translocate to the nucleus, bind DNA response elements, and regulate gene transcription (FitzGerald et al., 2021). Specificity of cytokine responses is determined by the combination of JAKs and STATs recruited—for example, the IL-23 receptor recruits JAK2 and TYK2 leading predominantly to STAT3 activation, whereas the IL-4 receptor recruits JAK1 and JAK3 leading to STAT6 activation (Ma et al., 2021). The therapeutic translation of this understanding has enabled the development of JAK inhibitors that preferentially target specific family members, such as the JAK1-preferring inhibitor upadacitinib, the TYK2 inhibitor deucravacitinib, and the pan-JAK inhibitor tofacitinib (Sarno et al., 2021). These agents provide powerful tools for modulating cytokine signaling at the intracellular level, bypassing the need to identify which specific cytokine is driving disease in each patient (Krautkramer, 2021).

6. Genetic and Epigenetic Biochemical Lesions

6.1 Overview: Three Layers of Molecular Regulation

Biochemical drivers of skin disease are encoded, modulated, and executed through genetic, epigenetic, and post-translational mechanisms (Campanati et al., 2021). Genetic variation provides the inherited template that determines baseline biochemical set points; epigenetic modifications dynamically adjust gene expression in response to environmental cues without altering the DNA sequence; and post-translational modifications expand the functional diversity of the proteome, enabling rapid and reversible regulation of protein activity (Chinemerem Nwobodo et al., 2022). Together, these three layers transform static genetic information into dynamic biochemical outputs that determine health or disease (Li et al., 2024). Understanding each layer is essential for identifying biomarkers of disease risk and activity, as well as for developing

targeted therapies that correct specific molecular lesions (Mills, 2023).

6.2 Monogenic Skin Diseases as Biochemical Lessons

Monogenic skin diseases, though individually rare, reveal essential, non-redundant functions of specific genes in maintaining skin homeostasis (Ali, 2023). Loss-of-function mutations in the filaggrin gene (FLG) provide a clear example: filaggrin is synthesized as a large polyprotein called profilaggrin, then proteolytically processed into multiple filaggrin monomers that aggregate keratin filaments to promote corneocyte compaction and are subsequently degraded into natural moisturizing factor (NMF) components that maintain stratum corneum hydration and acidity (Wagstaff et al., 2022). FLG loss-of-function mutations lead to dramatically reduced NMF levels, resulting in dry, scaly skin, elevated stratum corneum pH, increased trans epidermal water loss, and enhanced allergen penetration; these mutations are the strongest known genetic risk factors for atopic dermatitis, and homozygous or compound heterozygous mutations cause ichthyosis vulgaris (Clark, 2024). In Netherton syndrome, SPINK5 mutations encode a defective LEKTI protein, a multidomain serine protease inhibitor that normally restrains KLK5 and KLK7 activity; loss of functional LEKTI leads to uncontrolled protease activity, premature desquamation, barrier fragility, and a severe inflammatory phenotype with atopic manifestations and elevated IgE (McInnes, 2021). In psoriasis, gain-of-function mutations in CARD14, a scaffolding protein expressed in keratinocytes that activates NF-κB downstream of unknown signals, enhance NF-κB activation and drive expression of proinflammatory cytokines including IL-23 and IL-17 pathway components directly from keratinocytes, bypassing the need for initial immune cell activation and causing psoriasis in some families (Scatena, 2021). The therapeutic implication is that each monogenic disorder defines a specific biochemical vulnerability that can, in principle, be targeted therapeutically (Ma et al., 2024).

6.3 Epigenetic Biochemical Modifiers

Epigenetic modifiers represent the interface between the fixed genome and dynamic environment, enabling skin to adapt biochemical outputs to changing conditions (Liu et al., 2023). DNA methylation involves the addition of a methyl group to the fifth carbon of cytosine residues in CpG (Spinelli et al., 2021). dinucleotide and is generally associated with transcriptional repression (Gendrisch et al., 2021). In skin disease, aberrant DNA methylation of the MMP9 promoter has been documented in chronic wounds and scleroderma: MMP9 encodes gelatinase B, which degrades denatured collagen and basement membrane components; hyper methylation in fibroblasts from chronic wounds reduces MMP9 expression, leading to impaired matrix remodeling and failure to heal, whereas hypo methylation in certain inflammatory conditions results in excessive MMP9 activity and tissue destruction (Raufaste-Cazavieille, 2022). Histone deacetylases (HDACs) remove acetyl groups from lysine residues on histone tails, condensing chromatin and generally repressing transcription (Zaino et al., 2023). In scleroderma, HDAC activity is elevated in dermal fibroblasts, causing persistent activation of collagen gene expression, but pharmacological HDAC inhibitors have shown preclinical efficacy in reducing fibroblast activation and collagen deposition, with clinical trials ongoing (Shao et al., 2023). HDAC activity also modulates immune cell function, and HDAC inhibitors are already approved for cutaneous T-cell lymphoma, where they induce cell cycle arrest and apoptosis of malignant T cells (Quan, 2023). Other epigenetic mechanisms—including histone methylation, chromatin remodeling, and non-coding RNAs—further contribute to the regulation of skin biochemistry and represent emerging therapeutic targets (Almatroudi, 2025).

Table 2. Gene → Defect → Disease → Therapy

Gene	Biochemical Defect	Disease	Therapy
FLG	Reduced NMF, high pH	Ichthyosis vulgaris, atopic dermatitis	Barrier repair creams
SPINK5	Uncontrolled KLK5/7	Netherton syndrome	Topical KLK inhibitors
CARD14 (GOF)	Excess NF-κB activation	Psoriasis	Anti-IL-17/IL-23 biologics
MMP9 (epigenetic)	Altered methylation	Chronic wounds, scleroderma	HDAC inhibitors
HDACs	High HDAC activity	Scleroderma	HDAC inhibitors
PAD enzymes	Abnormal citrullination	Atopic dermatitis, autoimmunity	PAD inhibitors (investigational)
OGT	Excess STAT3 O-GlcNAcylation	Psoriasis	O-GlcNAc modulators

6.4 Post-Translational Modifications

Post-translational modifications provide a third layer of biochemical regulation, enabling rapid, reversible, and spatially restricted control of protein function without requiring new gene expression or protein synthesis (Guo, 2021). Citrullination, catalyzed by peptidylarginine deiminases (PADs)—a family of calcium-dependent enzymes—converts arginine residues to the non-coded amino acid citrulline, neutralizing the positive charge of arginine and thereby altering protein structure and function (Adejuyigbe et al., 2023). In skin, PAD enzymes are essential for formation of the cornified envelope and generation of natural moisturizing factor components, with filaggrin serving as a major substrate for PAD-mediated citrullination (Marques et al., 2024). In autoimmune disease, autoantibodies against citrullinated proteins are pathogenic in rheumatoid arthritis, and emerging evidence suggests similar autoimmunity against citrullinated skin proteins may contribute to some inflammatory skin diseases (Schett et al., 2022). O-GlcNAcylation, the addition of a single N-acetyl glucosamine moiety to serine or threonine residues, serves as a nutrient sensor that integrates metabolic status with cellular signaling; unlike phosphorylation which is site-specific and highly regulated, O-GlcNAcylation is dynamic and cycles rapidly in response to glucose availability (Siddiqui et al., 2022). In psoriasis, O-GlcNAcylation of STAT3 enhances its transcriptional activity, amplifying the IL-23/IL-17 axis, and pharmacological manipulation of O-GlcNAc cycling enzymes is being explored for therapeutic potential in inflammatory diseases (Pérez-Gutiérrez, 2023).

7. From Molecular Understanding to Effective Cures

7.1 Overview: Translation of Biochemical Insights into Therapies

Translation of biochemical insights into effective therapies represents the ultimate validation of mechanistic understanding (Bieber et al., 2022). Over the past two decades, identification of specific cytokine axes, signaling pathways and biochemical vulnerabilities has yielded an unprecedented wave of new therapeutics targeting disease mechanisms with increasing precision (Chen et al., 2022). This stands in stark contrast to traditional broad immunosuppressants such as cyclosporine, methotrexate, and systemic corticosteroids, which interfere with fundamental cellular processes and carry substantial toxicity (Xia et al., 2023). Modern mechanism-based therapies, by contrast, intercept specific biochemical signals and achieve high efficacy with improved safety profiles (Kim et al., 2023). The journey from molecular understanding to effective

cure has already transformed the therapeutic landscape of dermatology and provides a roadmap for future drug development (Man et al., 2023).

7.2 Biologics that Neutralize Biochemical Signals

Biologics represent the most successful therapeutic translation of biochemical insights in dermatology (De Pessemier et al., 2021). Anti-IL-17A agents, including secukinumab, ixekizumab, and netakimab, target the IL-23/IL-17 axis the dominant driver of psoriasis—by binding directly to IL-17A to prevent interaction with the IL-17 receptor, thereby blocking downstream activation of NF-κB and MAPK pathways in keratinocytes (Yan et al., 2024). Brodalumab, an anti-IL-17RA agent, blocks signaling of all IL-17 family members that utilize this receptor subunit (Tanaka, 2024). Anti-IL-23 agents act upstream of IL-17 to block differentiation and maintenance of pathogenic Th17 cells; these include ustekinumab targeting the shared p40 subunit, and guselkumab, risankizumab, and tildrakizumab targeting the unique p19 subunit (Moore et al., 2023). Clinical outcomes with these biologics show rapid and substantial improvement in moderate to severe psoriasis, with many patients achieving 90–100% clearance of skin lesions (El-Saadony et al., 2025). For atopic dermatitis, identification of IL-4 and IL-13 as central drivers led to dupilumab, a fully human monoclonal antibody that binds the IL-4 receptor alpha subunit, blocking signaling of both IL-4 and IL-13 simultaneously; dupilumab produces marked improvement in eczema severity, pruritus, and quality of life, and has become standard of care for moderate to severe atopic dermatitis (Zhang et al., 2024). Additional biologics targeting IL-13 alone, such as lebrikizumab and tralokinumab, have also shown efficacy (Andonian et al., 2025).

7.3 Small Molecule Inhibitors

Small molecule targeted therapies offer distinct advantages over biologics, including oral administration, lower manufacturing costs, and the ability to target intracellular signaling nodes not accessible to antibodies (Cutshaw et al., 2023). JAK inhibitors are the most extensively developed class of small molecules for inflammatory skin diseases: tofacitinib, a pan-JAK inhibitor with selectivity for JAK1 and JAK3, was the first approved in this class for psoriasis and more recently for alopecia aerate; upadacitinib and abrocitinib, selective for JAK1, have shown efficacy in both psoriasis and atopic dermatitis, with the JAK1-preferring profile improving safety by sparing JAK2-mediated erythropoiesis (Kim, 2024). Deucravacitinib, a TYK2 inhibitor, targets the JAK family member most specifically involved in IL-23 and type I interferon signaling; it binds to the regulatory domain of TYK2 rather than the catalytic domain, achieving remarkable selectivity and an excellent safety profile, and is now approved for moderate to severe psoriasis (Zhang et al., 2022). Apremilast, a PDE4 inhibitor, increases intracellular cAMP levels, thereby suppressing production of proinflammatory cytokines including TNF-α, IL-17, and IL-23; it is approved for psoriasis and psoriatic arthritis, offering convenient oral administration with a favorable safety profile (Kolkhir et al., 2022). RORγt inverse agonists, which bind to the nuclear receptor RORγt and prevent its activation, block transcription of IL-17 and related cytokines at the level of gene expression, representing a further downstream approach to targeting the IL-23/IL-17 axis, and are currently in clinical development (Jia et al., 2025).

7.4 Barrier Repair Biochemistry

Topical barrier repair therapies have emerged as a complementary therapeutic strategy addressing upstream biochemical defects rather than downstream inflammatory consequences (Chhabra et al., 2022). Ceramide-dominant formulations are designed to replenish specific ceramide species deficient in diseased skin; unlike simple emollients that provide only transient occlusion, these formulations restore the lamellar structure of the stratum corneum, reduce trans epidermal water loss, and normalize barrier function over days to weeks (Davey, 2021). Clinical trial evidence demonstrates that they reduce the need for topical corticosteroids in atopic dermatitis and extend the time between disease flares (Gharibshahian et al., 2024). Sophisticated lipid replacement therapies now

include formulations containing the optimal 1:1:1 molar ratio of ceramides, free fatty acids, and cholesterol, along with cholesterol sulfate necessary for proper lamellar organization (Hu et al., 2021). Some formulations also include lipid precursors that are enzymatically processed by endogenous β-glucocerebrosidase and acid sphingomyelinase to generate mature ceramides, thereby supporting the skin's intrinsic barrier repair capacity (Elshafie, 2023).

7.5 Protease Inhibitors (Topical KLK5 Inhibitors)

Protease-modulating therapies target the kallikrein-LEKTI axis, an emerging therapeutic frontier particularly for Netherton syndrome and conditions with excessive KLK activity (Author, 2021). Topical KLK5 and KLK7 inhibitors have shown preclinical efficacy in murine models of Netherton syndrome, reducing desquamation, barrier dysfunction, and inflammation (Swanton et al., 2024). Phase 2 clinical trials of a topical KLK5 inhibitor in Netherton syndrome patients have yielded encouraging results, including reductions in scaling, erythema, and pruritus (Xiong et al., 2025). For more common conditions such as atopic dermatitis, where relative protease excess contributes to pathogenesis, topical protease inhibitors may offer a novel mechanism of action that complements existing anti-inflammatory therapies (Anwar et al., 2024).

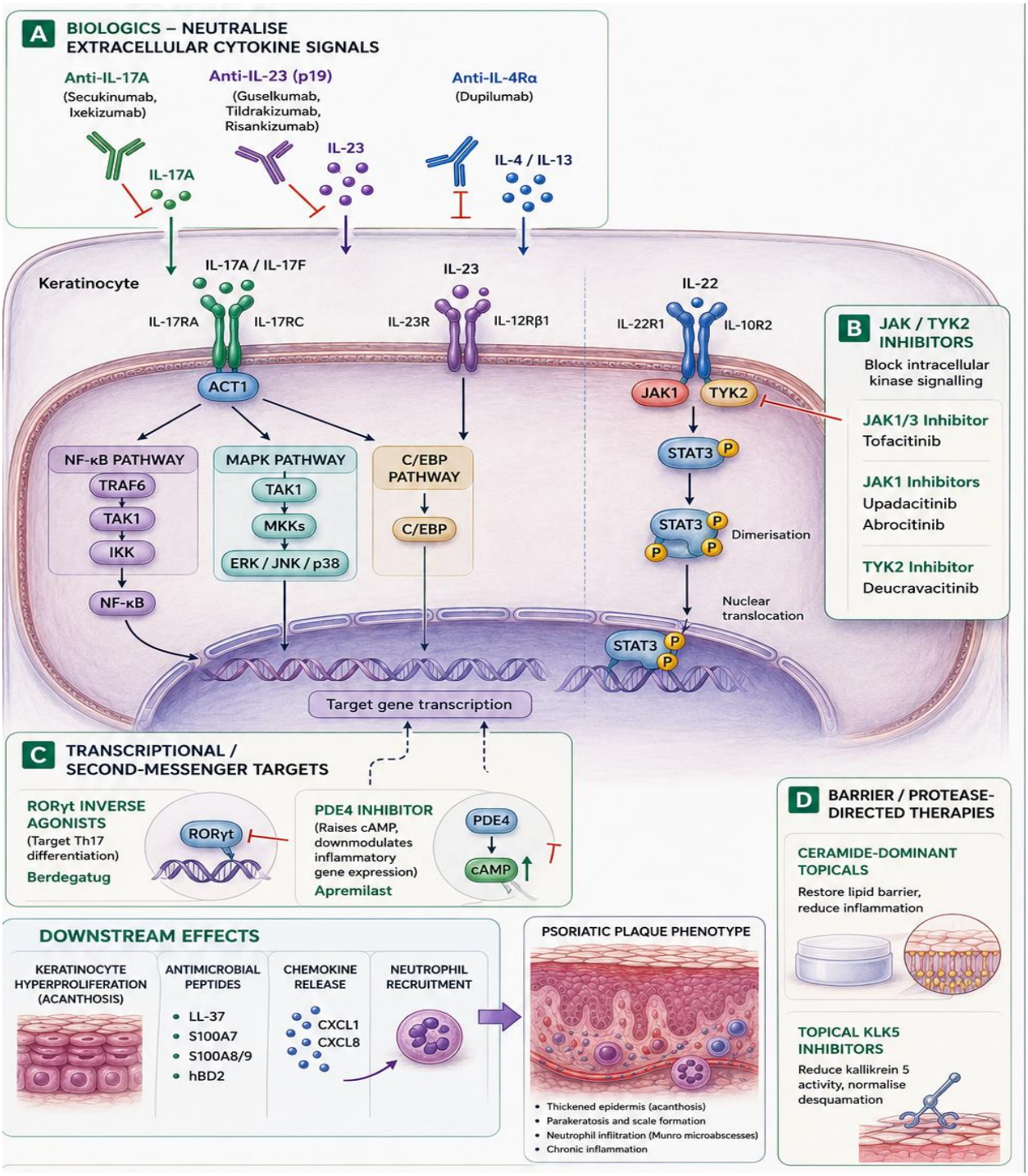

Figure 2. Therapeutic targets mapped onto biochemical pathways. (A) Biologics neutralise extracellular cytokine signals (anti-IL-17A, anti-IL-23 p19, anti-IL-4Rα). (B) JAK/TYK2 inhibitors block intracellular kinase signalling (tofacitinib, upadacitinib, deucravacitinib). (C) RORγt inverse agonists and the PDE4 inhibitor apremilast act at the transcriptional / second-messenger level. (D) Ceramide-dominant creams and topical KLK5 inhibitors correct barrier and protease defects.

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7.6 Antioxidant-Based Therapies

Redox-modulating therapies have proven more challenging to translate effectively (Li et al., 2024). Simple dietary supplementation with antioxidant vitamins such as vitamins C and E has generally failed to demonstrate clinical benefit in large clinical trials, likely because these agents lack sufficient bioavailability in the skin and because oxidative stress is often a consequence rather than a primary driver of inflammation in many settings (El-Tanani et al., 2025). NRF2 activators represent a more sophisticated approach that up regulates the skin's intrinsic antioxidant defenses rather than providing exogenous antioxidants (Kim et al., 2025). For example, topical sulforaphane has shown preclinical therapeutic potential in vitiligo, psoriasis, and ultraviolet-induced skin damage, and clinical trials are ongoing (Fadadu et al., 2023).

8. Challenges and Unmet Needs

8.1 Overview: Success Reveals New Complexity

Despite remarkable therapeutic advances derived from biochemical insights, substantial challenges remain on the path from molecular understanding to effective cures (Gawkrodger, 2025). The very successes of recent years have revealed new layers of complexity previously hidden beneath broad clinical response categories: patients who appear clinically similar by standard dermatologic examination often exhibit divergent biochemical profiles, different responses to the same targeted therapy, and vastly different disease trajectories (Nowak-Perlak et al., 2022). These observations underscore the pressing need for more sophisticated approaches to disease classification, monitoring, and treatment selection, as well as the development of new diagnostic tools, therapeutic modalities, and clinical trial designs (Lyamina et al., 2023).

8.2 Biochemical Heterogeneity within the Same Clinical Diagnosis

Biochemical heterogeneity within a single diagnostic label represents perhaps the most fundamental challenge facing precision dermatology (Castellani et al., 2023). Two patients with psoriasis having identical PASI scores, identical histopathology of acanthosis and parakeratosis, and identical clinical photographs can exhibit dramatically different underlying biochemical profiles: Patient A may show dominant IL-17A expression with minimal IL-23; Patient B elevated IL-23 but relatively low IL-17; Patient C prominent IL-22 signaling with normal IL-23 and IL-17; and Patient D a primarily keratinocyte-intrinsic defect with normal immune cell function (Krueger, 2022). Similarly, in atopic dermatitis, some patients have a pure Th2-dominant profile with high IL-4 and IL-13, others show mixed Th2/Th17 profiles, and still others exhibit Th1 or Th22 predominance (Mu et al., 2024). This heterogeneity matters clinically because anti-IL-17 agents produce dramatic responses in IL-17-dominant psoriasis but may be less effective in IL-22-dominant disease, while dupilumab, which blocks IL-4/IL-13 via IL-4Rα, is highly effective in Th2-dominant atopic dermatitis but shows variable responses in mixed or alternative cytokine profiles (Holl et al., 2021). The current practice problem is that we treat all patients with the same diagnosis identically without biochemical stratification, leading to therapeutic failures, unnecessary exposure to ineffective agents, and prolonged suffering (Liu et al., 2024).

8.3 Lack of Bedside Biochemical Assays

The lack of accessible biochemical diagnostics represents a second major barrier, especially when contrasted with the routine availability of histopathological assessment (Zhou et al., 2021). Histopathology using H&E staining requires less than five minutes to perform, is available in virtually every dermatology clinic and hospital worldwide, and provides diagnostic information within 24 to 48 hours. By contrast, biochemical measurements such as the ceramide-to-free fatty acid ratio, KLK5 activity, GSH/GSSG redox ratio,

and cytokine profiling currently require specialized equipment, expensive reagents, and trained personnel typically found only in research laboratories. Even when technically feasible, such measurements are rarely reimbursed by insurance systems and are not integrated into clinical decision-making algorithms (Duan et al., 2024). There is an urgent need for point-of-care biochemical assays that can be performed in the clinic setting using tape strips rather than biopsies, with real-time results (Schäbitz et al., 2022). Emerging technologies such as paper-based microfluidics, electrochemical biosensors, and portable mass spectrometers show promise but remain largely confined to research (Butler, 2021). Until bedside biochemical assays become as routine as histopathology, the promise of biochemical endotyping will remain unfulfilled (Liu, 2023).

8.4 Drug Delivery across the Biochemical Barrier

The biochemical barrier to topical drug delivery presents a paradox that has frustrated dermatologic drug development for decades (Ojeh et al., 2025). The same stratum corneum lipid organization that provides essential protection also represents a formidable barrier to drug penetration: lipophilic drugs diffuse through intercellular lipid lamellae relatively easily, but hydrophilic drugs, peptides, nucleic acids, and most biologics penetrate the stratum corneum poorly if at all (Dai et al., 2024). Successfully formulated topical drugs have been limited to small, lipophilic molecules such as topical corticosteroids, calcineurin inhibitors, and PDE4 inhibitors (Author, 2024). It remains currently impossible to deliver biologic agents topically because monoclonal antibodies are large, hydrophilic proteins, forcing administration by injection or infusion; topical delivery of siRNA or antisense oligonucleotides for gene targeting faces similar obstacles (Maronese et al., 2022). Various penetration enhancement strategies have been explored, including chemical enhancers like ethanol and fatty acids, physical methods such as microneedles and iontophoresis, and formulation approaches including liposomes, transfersomes, and nanoparticles (Chaudhari, 2021). While each approach shows promise in preclinical studies, few have translated into approved products, and delivery across the biochemical barrier remains a rate-limiting step in developing topical therapies for many diseases (Su et al., 2024).

8.5 Disease Relapse despite Biochemical Remission

The challenge of disease memory despite biochemical remission is a final challenge only now being recognized as clinical experience with biologic and small molecule therapies accumulates (Koushyar et al., 2022). Observations show that patients treated with anti-IL-17 or anti-IL-23 agents for psoriasis, or dupilumab for atopic dermatitis, often achieve complete or near-complete clinical remission with normalized histopathology; however, when therapy is discontinued, the majority relapse within weeks to months, even though the original biochemical drivers may no longer be detectable (Karki, 2021). The proposed explanation is that inflammatory memory of the skin persists long after inciting biochemical signals are neutralized, mediated by resident memory T cells, epigenetic modifications, and structural remodeling of the extracellular matrix (Chaudhary, 2021). A cure, as opposed to sustained suppression, therefore requires not only blocking ongoing inflammatory signals but also erasing this disease memory (Luo et al., 2023). Strategies under active investigation—though none have yet achieved clinical proof-of-concept—include eliminating resident memory T cells using IL-15 blockade or targeted toxins, reversing pathogenic epigenetic modifications using HDAC or DNA methyltransferase inhibitors, and remodeling fibrotic tissue using matrix metalloproteinase modulators (Coll, 2025). The challenge of relapse despite biochemical remission represents the next frontier in the quest for true cures for inflammatory skin diseases (Winge et al., 2023).

9. Future Directions

9.1. Biochemical endotyping for Precision Dermatology

Biochemical endotyping represents the most promising pathway to overcome the challenge of

biochemical heterogeneity, with the goal of moving beyond the current one-size-fits-all diagnostic approach toward a stratified model where each patient's biochemical profile guides treatment selection (Weigelt et al., 2022). A biochemical endotype would be defined by a specific combination of biomarkers—for example, elevated IL-17A, normal IL-23, and low ceramide levels—that predict response to a particular therapy (Xiang et al., 2023). Prospective clinical trials are needed to validate such endotypes, demonstrating that patients assigned to therapy based on their biochemical profile have superior outcomes compared to standard care (Zaripova et al., 2023). Essential for implementation is the development of validated, commercially available assay panels for lipidomic, protease activity, redox status, and cytokine profiling; these assays must be affordable, rapid, and compatible with minimally invasive sampling methods such as tape stripping or microneedle patches (Kychygina et al., 2022). Biochemical endotyping will thus enable personalized treatment selection, matching each patient to the therapy most likely to work for their specific biochemical driver (Jiang et al., 2025).

9.2. Topical RNA Therapeutics Targeting Biochemical Nodes

Topical RNA therapeutics offers a new modality for treating skin diseases at the molecular level (Liu et al., 2022). Small interfering RNA (siRNA) can be designed to silence any gene of interest with high specificity, making it possible to reduce expression of pathogenic proteins such as IL-17, IL-23, or KLK5 directly in the skin, while antisense oligonucleotides (ASOs) can block translation or alter splicing of target mRNAs (Serrano et al., 2024). The primary challenge remains delivery across the stratum corneum, but recent advances in nanoparticle formulation, lipid nanoparticles, and polymer-based carriers have shown promise in preclinical studies (Eyerich et al., 2021). Proof-of-concept has been achieved, as clinical trials of topical siRNA for pachyonychia congenital, a rare keratin disorder, have demonstrated feasibility, and expansion to inflammatory skin diseases is now underway (Maharjan et al., 2021). A key advantage of this approach is the ability to transiently and reversibly modulate gene expression in the skin without systemic exposure, making it particularly well-suited for chronic diseases requiring long-term management (Bou Antoun, 2023).

9.3. Skin Metabolomics and Lipidomics as Routine Diagnostics

Metabolomics and lipidomics will transform the ability to assess biochemical status in individual patients (Alpsoy, 2021). Metabolomics, the comprehensive profiling of small molecule metabolites in a biological sample, can be performed on tape strips or skin biopsy extracts using liquid chromatography-mass spectrometry (LC-MS); its subfield lipidomics provides detailed information on ceramide profiles, free fatty acid composition, and oxidized lipid species (Mlakar et al., 2021). Current limitations are that these techniques remain too expensive and time-consuming for routine clinical use, but advances in high-throughput mass spectrometry, miniaturization of instruments, and rapidly reducing costs and turnaround times are expected to drive future adoption (Holzscheck et al., 2021). In a realistic near-future scenario over the next five to ten years, a skin tape strip sent to a reference laboratory could return a complete biochemical profile including ceramide composition, KLK5 activity, GSH/GSSG ratio, and cytokine levels, at a cost comparable to a standard histopathology report (Holzscheck et al., 2021). Such profiles will enable biochemical endotyping and provide objective measures of treatment response (Donniacuo et al., 2025).

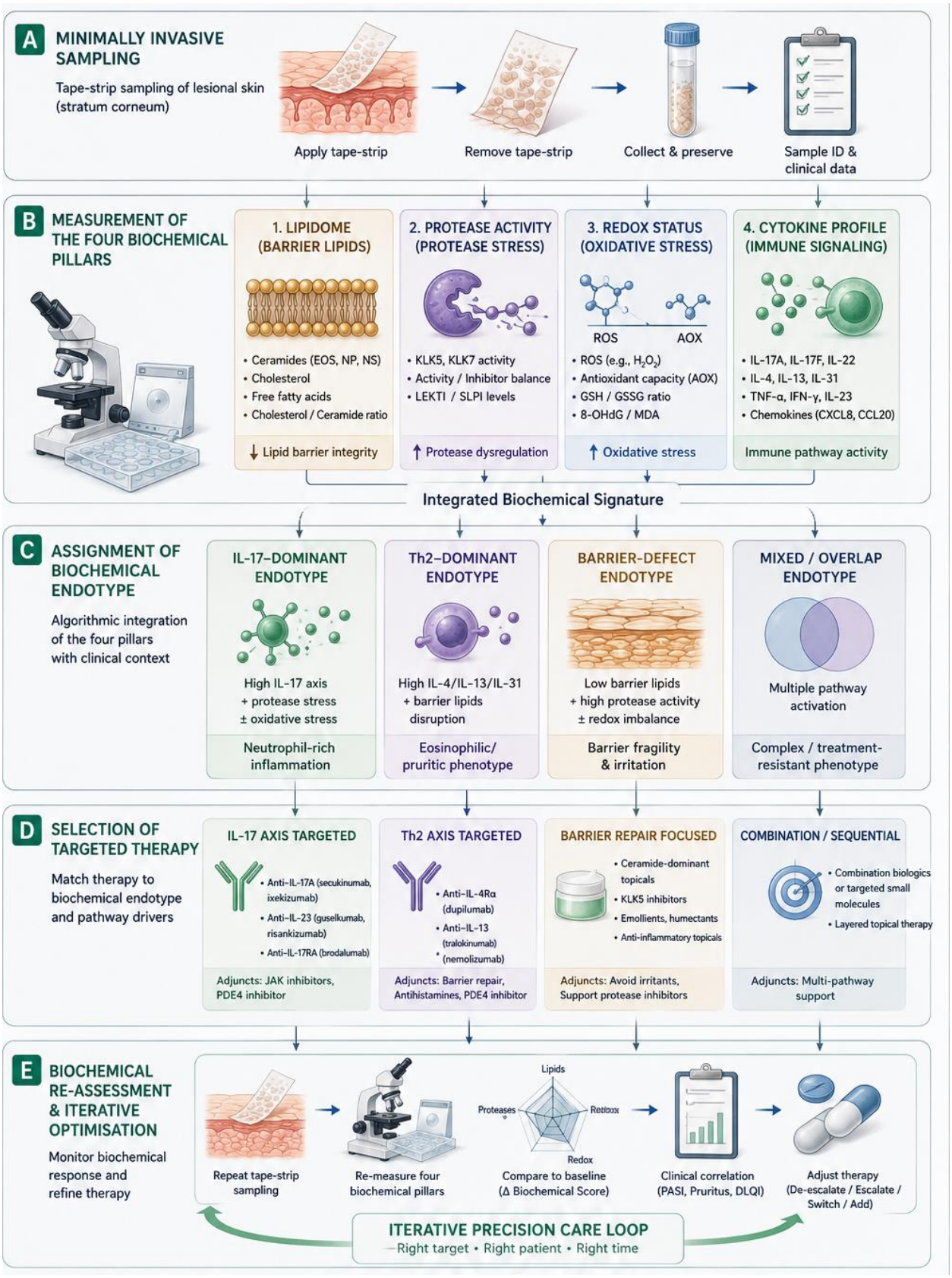
A
MINIMALLY INVASIVE SAMPLING
Tape-strip sampling of lesional skin (stratum corneum)
Apply tape-strip
Remove tape-strip
Collect & preserve
Sample ID & clinical data
B
MEASUREMENT OF THE FOUR BIOCHEMICAL PILLARS
1. LIPIDOME (BARRIER LIPIDS)
• Ceramides (EOS, NP, NS)
• Cholesterol
• Free fatty acids
• Cholesterol / Ceramide ratio
↓ Lipid barrier integrity
2. PROTEASE ACTIVITY (PROTEASE STRESS)
• KLK5, KLK7 activity
• Activity / Inhibitor balance
• LEKTI / SLPI levels
↑ Protease dysregulation
3. REDOX STATUS (OXIDATIVE STRESS)
ROS
AOX
• ROS (e.g., H_2O_2)
• Antioxidant capacity (AOX)
• GSH / GSSG ratio
• 8-OHdG / MDA
↑ Oxidative stress
4. CYTOKINE PROFILE (IMMUNE SIGNALING)
• IL-17A, IL-17F, IL-22
• IL-4, IL-13, IL-31
• TNF-α, IFN-γ, IL-23
• Chemokines (CXCL8, CCL20)
Immune pathway activity
Integrated Biochemical Signature
C
ASSIGNMENT OF BIOCHEMICAL ENDOTYPE
Algorithmic integration of the four pillars with clinical context
IL-17–DOMINANT ENDOTYPE
High IL-17 axis + protease stress ± oxidative stress
Neutrophil-rich inflammation
Th2–DOMINANT ENDOTYPE
High IL-4/IL-13/IL-31 + barrier lipids disruption
Eosinophilic/ pruritic phenotype
BARRIER-DEFECT ENDOTYPE
Low barrier lipids + high protease activity ± redox imbalance
Barrier fragility & irritation
MIXED / OVERLAP ENDOTYPE
Multiple pathway activation
Complex / treatment-resistant phenotype
D
SELECTION OF TARGETED THERAPY
Match therapy to biochemical endotype and pathway drivers
IL-17 AXIS TARGETED
• Anti-IL-17A (secukinumab, ixekizumab)
• Anti-IL-23 (guselkumab, risankizumab)
• Anti-IL-17RA (brodalumab)
Adjuncts: JAK inhibitors, PDE4 inhibitor
Th2 AXIS TARGETED
• Anti-IL-4Rα (dupilumab)
• Anti-IL-13 (tralokinumab)
• (nemolizumab)
Adjuncts: Barrier repair, Antihistamines, PDE4 inhibitor
BARRIER REPAIR FOCUSED
• Ceramide-dominant topicals
• KLK5 inhibitors
• Emollients, humectants
• Anti-inflammatory topicals
Adjuncts: Avoid irritants, Support protease inhibitors
COMBINATION / SEQUENTIAL
• Combination biologics or targeted small molecules
• Layered topical therapy
Adjuncts: Multi-pathway support
E
BIOCHEMICAL RE-ASSESSMENT & ITERATIVE OPTIMISATION
Monitor biochemical response and refine therapy
Repeat tape-strip sampling
Re-measure four biochemical pillars
Lipids
Proteases
Redox
Compare to baseline (Δ Biochemical Score)
Clinical correlation (PASI, Pruritus, DLQI)
Adjust therapy (De-escalate / Escalate / Switch / Add)
ITERATIVE PRECISION CARE LOOP
Right target • Right patient • Right time

Figure 3. Biochemical endotyping algorithm for precision dermatology. (A) Minimally invasive tape-strip sampling. (B) Measurement of the four biochemical pillars—lipids, protease activity, redox status and cytokine profile. (C) Assignment of a biochemical endotype (IL-17-dominant, Th2-dominant, barrier-defect or mixed). (D) Selection of targeted therapy matched to the endotype. (E) Biochemical re-assessment and iterative adjustment of therapy.

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9.4. Combination Therapy Based on Biochemical Synergy

Combination therapy represents the logical extension of biochemical endotyping, based on the rationale that the four biochemical pillars—barrier defects, proteases, reactive oxygen species (ROS), and cytokines—are interconnected: barrier defects activate proteases, proteases generate ROS, ROS amplify cytokines, and cytokines further impair barrier function (Slack et al., 2022). The implication is that targeting a single node may be insufficient for patients with multiple concurrent biochemical abnormalities (Wang et al., 2023). For example, a patient with low ceramides, high KLK5 activity, and elevated IL-17 might benefit from triple therapy comprising a ceramide-dominant moisturizer for barrier repair, a topical KLK5 inhibitor for protease inhibition, and an anti-IL-17 biologic for cytokine neutralization (Marrakchi, 2022). Preclinical studies and early clinical trials suggest such combinations may produce additive or synergistic effects, allowing lower doses of each agent and reducing toxicity (Chang, 2021). The challenge lies in identifying which combinations are most effective for which biochemical endotypes, requiring large, well-designed clinical trials with biochemical stratification (Swaney, 2021). Ultimately, the future of dermatologic therapy lies not in a single blockbuster drug for all patients with a given diagnosis, but in rationally designed, biochemically guided combination regimens tailored to the individual patient (Naveed et al., 2024).

10. Conclusions

10.1 Recap of Four Major Biochemical Drivers

This review has synthesized the current understanding of biochemical drivers of inflammatory skin diseases across four major pillars (Jain, 2025). The first pillar, lipid barrier defects, encompasses ceramide deficiency, abnormal free fatty acid and cholesterol ratios, impaired enzymatic processing by β-glucocerebrosidase and acid sphingomyelinase, and filaggrin mutations leading to reduced natural moisturizing factor, with consequences including increased trans epidermal water loss, alkaline pH shift, and enhanced allergen penetration (Felgueiras, 2021). The second pillar, protease-antiprotease imbalance, involves kallikrein-related peptidases KLK5 and KLK7 and their inhibitor LEKTI—with Netherton syndrome serving as the classic biochemical model—as well as matrix metalloproteinase MMP-1 and MMP-9 and their TIMP inhibitors in wound healing and fibrosis, and desquamation failure in psoriasis and ichthyoses (Liu et al., 2022). The third pillar, redox signaling dysregulation, includes sources of ROS such as mitochondria, NADPH oxidases (NOX1, NOX4), and UV radiation; antioxidant systems including glutathione, thioredoxin, catalase, and superoxide dismutase; oxidative damage through lipid peroxidation (4-HNE, MDA) and protein carbonylation; redox-sensitive transcription factors NRF2 (cytoprotective), NF-κB, and AP-1 (proinflammatory); and disease examples such as vitiligo with melanocyte redox vulnerability and psoriasis with NOX-driven inflammation. The fourth pillar, cytokine-mediated inflammation, covers the IL-23/IL-17 axis as the dominant driver of psoriasis, Th2 biochemistry (IL-4, IL-13, IL-31) in atopic dermatitis, JAK-STAT pathways as biochemical integrators, and the effects on keratinocyte proliferation, antimicrobial peptides,

and barrier function. Each pillar represents a distinct but interconnected biochemical vulnerability that can be measured, monitored, and therapeutically targeted (Serrano et al., 2024).

10.2 The Path to Cure Requires Targeting Biochemistry, Not Just Histology or Genetics

Histopathology describes structure and is valuable for diagnosis, but it does not capture dynamic molecular activity; genetics describes inherited risk and provides susceptibility information but does not explain current disease activity or guide acute therapy; biochemistry describes function, which is the most proximal to disease activity and the most directly modifiable by therapy (Bou Antoun, 2023; Mlakar et al., 2021). A cure—as distinguished from sustained suppression—requires neutralizing ongoing inflammatory signals, erasing disease memory (including resident memory T cells and epigenetic modifications), restoring normal barrier function, rebalancing protease-antiprotease networks, and normalizing redox homeostasis. The remarkable success of biologics and small molecule inhibitors targeting cytokine signaling validates the central premise: understanding biochemistry at the molecular level leads directly to effective therapies (Di Paolo, 2021).

10.3 Call for Integration of Biochemical Monitoring in Clinical Trials

For routine clinical practice, every patient with a chronic inflammatory skin disease should have the opportunity to have their biochemical profile characterized—just as they currently have their histopathology characterized—necessitating the development and deployment of point-of-care biochemical assays using tape strips with real-time results, and insurance systems should reimburse biochemical testing as a standard diagnostic procedure (Donniacuo et al., 2025). For clinical trials, every trial of a new therapeutic agent should include biochemical endpoints that measure target engagement and pathway modulation, not just clinical response scales such as PASI, EASI, or IGA, and biochemical data should explain which patients are most likely to respond. For regulatory approvals, every approval should be accompanied by biochemical data identifying the patient subgroups most likely to benefit, and biochemical stratification should become a requirement for precision medicine approvals. The ultimate goal is to place biochemistry at the center of dermatologic research and practice, thereby achieving curative, rather than merely suppressive, therapy for the full spectrum of inflammatory skin diseases (Slack et al., 2022).

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