On the role of cholesterol, vitamin D, lumisterol, and tachysterol signaling in psoriasis

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Recent advances in skin omics indicate that increased cholesterol synthesis and downstream cholesterol signaling can play a role in etiology, progression, and presentation of psoriasis through the upregulation of IL-17 signaling and expression of proinflammatory cytokines (Møller et al, 2025; Randon and Ward, 2025). Cholesterol and its downstream oxysterols generated through the action of cytochrome P450 (CYP) enzymes or structural modification by free radicals act as ligands for several nuclear receptors, including retinoic acid orphan receptor (ROR)γ, which have been reported to regulate proinflammatory signaling pathways (Figure 1a) (Jetten and Cook, 2020). Cholesterol and oxysterols through these receptors can contribute to the proinflammatory environment. Therefore, these receptors may represent therapeutic targets for treatment of psoriasis and other inflammatory disorders.

BIOSYNTHESIS AND ACTIVATION OF CHOLESTEROL, VITAMIN D, LUMISTEROL, AND TACHYSTEROL

Postsqualene synthesis of cholesterol follows the Kandutsch—Russel pathway utilizing 7-dehydrocholesterol (7-DHC) as the direct precursor of cholesterol or the Bloch pathway in which 7-dehydrodesmosterol (7-DHD) serves as the 5,7-dienal intermediate leading to the production of cholesterol (Figure 1 in Slominski et al [2015]). Both 7-DHC and 7-DHD have a conjugated unsaturated B ring that can absorb UVB radiation, leading to their intramolecular transformation to either vitamin D, tachysterol, or lumisterol configurations (Figure 1b). Vitamin D3 is metabolically activated to 1,25-dihydroxyvitamin D3 through the canonical pathway or to several hydroxyderivatives ([OH]D3]) through a noncanonical pathway initiated by CYP11A1 (Slominski et al, 2024a; Tuckey et al, 2019). The resulting metabolites lacking a hydroxyl group at C1a act preferentially on nuclear receptors other than the vitamin D receptor (VDR), including the aryl hydrocarbon receptor, liver X receptor, peroxisome proliferator—activated receptor γ, and RORs (Slominski et al, 2024a). Similarly, tachysterol (T_3) and lumisterol (L_3) are activated by either CYP11A1 or CYP27A1 to produce biologically active hydroxyderivatives that also act on these nuclear receptors (Slominski et al, 2024a). Importantly, these novel vitamin D3 and lumisterol (and likely tachysterol) hydroxyderivatives act as inverse agonists on RORγ, inhibiting its transcriptional activity and, subsequently, IL-17 production (Jetten and Cook, 2020; Slominski et al, 2024a). In addition, the (OH)D3 inhibit proinflammatory responses by inhibition of NF-kb through the activation of VDR (Slominski et al, 2024a).

UVB ATTENUATES CHOLESTEROL PRODUCTION/ CONTENT AND STIMULATES SECOSTEROIDAL AND LUMISTEROL SIGNALING

The beneficial role of UVB radiation in several autoimmune and inflammatory disorders through the activation of the central and peripheral neuroendocrine systems is now being appreciated (Slominski et al, 2025, 2024b). The beneficial role of UVB radiation and its use in phototherapy for psoriasis is well-recognized. On the basis of the information mentioned earlier, it is logical to predict that UVB-induced anti-inflammatory effect can be mediated, at least in part, in 3 ways. First, there will be a reduction in cholesterol production through the UVB-induced photolysis of its 5,7-dienal precursors, 7-DHC and 7-DHD. Second, the resulting vitamin D, lumisterol, and/or tachysterol compounds will undergo CYP-dependent activation to hydroxyderivatives that induce anti-inflammatory responses through inverse agonism on RORγ, leading to reduced IL-17 signaling. Third, these hydroxyderivatives will have additional beneficial effects through the activation of the VDR or alternative nuclear receptors (Figure 1b).

The clinical and preclinical implications of this hypothesis are as follows. Noncalcemic and nontoxic CYP11A1-derived $(OH)_nD3$ (Slominski et al, 2024a), such as 20(OH)D3 and $20,23(OH)_2D3$, which are natural products (Kim et al, 2024), can potentially serve as therapeutics for psoriasis, acting through the mechanisms outlined earlier. Similar mechanisms could apply to lumisterol and/or tachysterol hydroxyderivatives; however, this requires further experimental

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Clinical Implications

- UVB attenuates cholesterol production and stimulates generation of vitamin D, lumisterol, tachysterol, and cutaneous expression of CYP11A1.
- Cholesterol and oxysterols are proinflammatory in part through the activation of retinoic acid orphan receptor (ROR)γ.
- Vitamin D, lumisterol, and tachysterol hydroxyderivatives exert anti-inflammatory activities through the activation of the vitamin D receptor and inverse agonism on RORγ.
- Stimulation of local vitamin D, lumisterol, and tachysterol signaling represents a realistic strategy for the therapy of psoriasis.

investigation, particularly with respect to their interaction with RORγ.

It has already been shown that 7-DHD is present in rat skin, representing 22% of the total provitamin D3 content, and that UVB radiation converts it to 24-dehydroprevitamin D3 and, by inference, to 24-dehydrovitamin D3 (Δ^{24}-D3) (Holick et al, 1985). Photochemical conversion of 7-DHD to 24-dehydrolumisterol and 24-dehydrotachysterol, as proposed in Holick et al (1985), requires experimental verification. It remains to be established how much the Bloch pathway, which generates the 7-DHD, contributes to cholesterol synthesis in human skin. On the basis of the similar structures of 7-DHD and 7-DHC, we expect that the photoderivatives of 7-DHD, including Δ^{24}-D3, would serve as substrates for hydroxylation by CYP enzymes, leading to the production of new intermediates (Figure 1b) (Slominski et al, 2015). If this is so, it would increase the panel of the endogenous steroidal and secosteroidal metabolites contributing to the regulation of epidermal homeostasis, with potential use as therapeutics. Furthermore, but still to be experimentally verified, such photoproducts may be generated across different species (Figure 2 in Kim et al [2024]).

CONCLUSION

In summary, recent concepts on the role of cholesterol in psoriasis (Møller et al, 2025; Randon and Ward, 2025) allow us to hypothesize that part of the therapeutic effect of UVB radiation in the treatment of this disease is related to both attenuation of cholesterol synthesis, and local production of vitamin D3, L3, and T3 and their activation to hydroxyderivatives. The latter opens new perspectives for educated photo and/or chemotherapeutic approaches for the treatment of this common hyperproliferative inflammatory disorder.

KEYWORDS
7-Dehydrocholesterol; 7-Dehydrodesmosterol; Nuclear receptors; Secosteroids; UVB radiation

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CONFLICT OF INTEREST

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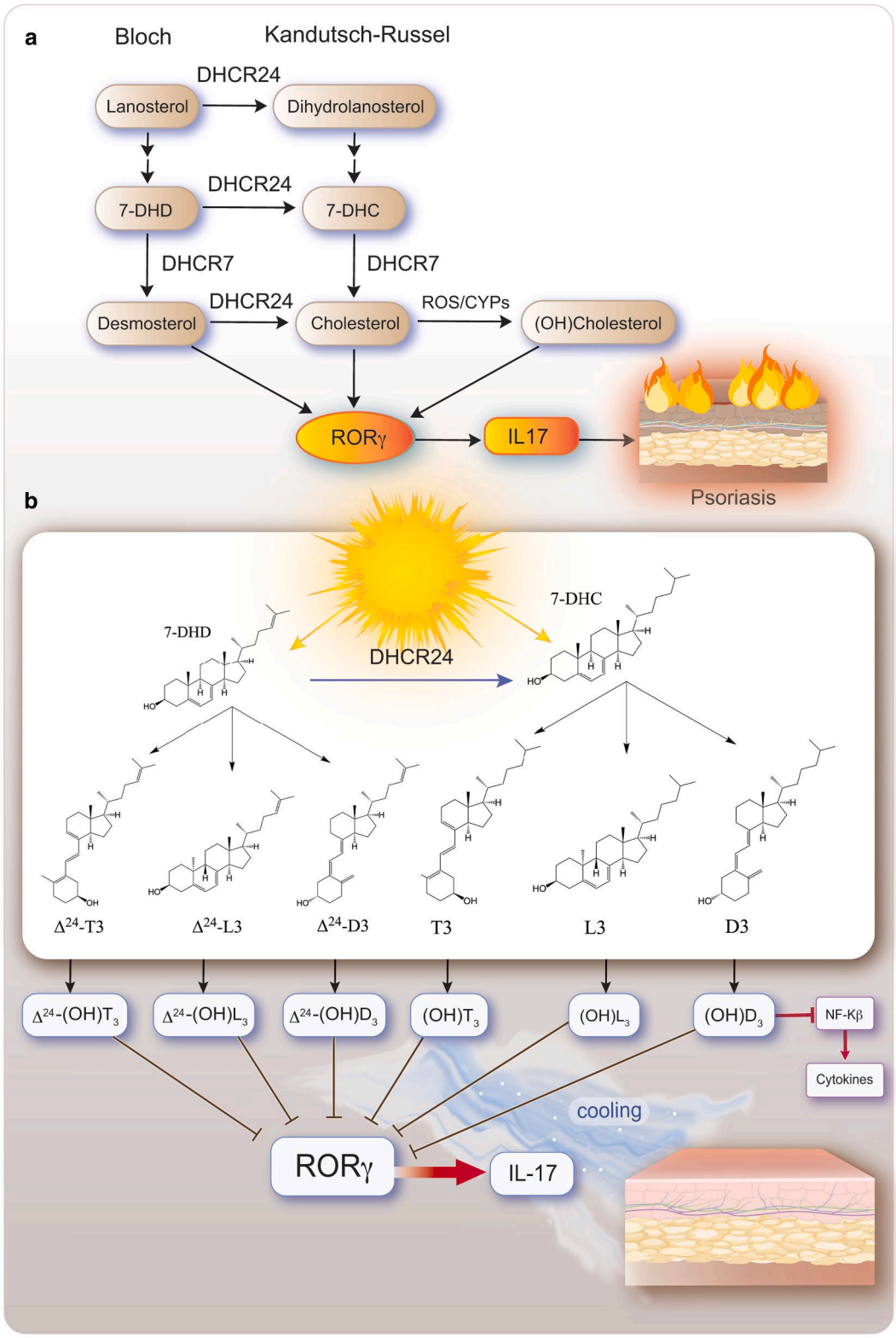

Figure 1. Cholesterol, vitamin D, lumisterol, and tachysterol signaling in psoriasis. (**a**) Outlines the role of cholesterol signaling in psoriasis. Briefly, 7-DHD produced in the Block pathway can either be transformed to 7-DHC by DHCR24 or reduced to desmosterol by DHCR7. Desmosterol can act on RORγ or be transformed by DHCR24 to cholesterol, another ligand for this receptor. The 7-DHC produced in the Kandutsch–Russel pathway is reduced to cholesterol, which can be transformed to oxysterols ([OH]Cholesterol) either by the action of ROS or CYP enzymes. All of the indicated sterols, including oxysterols generated from desmosterol (not shown), can activate RORγ, causing stimulation of IL-17 signaling, with a net proinflammatory effect contributing to psoriasis development and/or progression. Image was created in https://BioRender.com. **(b)** Shows how UVB attenuates psoriasis through the depletion of 7-DHD and 7-DHC precursors of desmosterol and cholesterol, respectively, and generation of vitamin D3, lumisterol, and tachysterol compounds. The latter acting either directly or after hydroxylation by CYPs, including CYP11A1, CYP2R1, and CYP27A1, serve as inverse agonists on RORγ terminating the proinflammatory IL-17 signaling. In addition, vitamin D3 hydroxyderivatives acting through other nuclear receptors (VDR or AhR/LXR/PPARγ) can inhibit the production of other

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proinflammatory cytokines through the inhibition of NF-kb activity "cooling down" psoriatic flares. Image was partially created in https://BioRender.com. 7-DHC, 7-dehydrocholesterol; 7-DHD, 7-dehydrodesmosterol; AhR, aryl hydrocarbon receptor; CYP, cytochrome P450; DHCR24, 3β-hydroxysterol Δ^{24}-reductase; DHCR7, 3β-hydroxysterol Δ^{7}-reductase; LXR, liver X receptor; PPARγ, peroxisome proliferator-activated receptor γ; ROR, retinoic acid orphan receptor; VDR, vitamin D receptor.