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Nuclear hormone receptor functions in keratinocyte and melanocyte homeostasis, epidermal carcinogenesis and melanomagenesis

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Abstract

Skin homeostasis is maintained, in part, through regulation of gene expression orchestrated by type II nuclear hormone receptors in a cell and context specific manner. This group of transcriptional regulators is implicated in various cellular processes including epidermal proliferation, differentiation, permeability barrier formation, follicular cycling and inflammatory responses. Endogenous ligands for the receptors regulate actions during skin development and maintenance of tissue homeostasis. Type II nuclear receptor signaling is also important for cellular crosstalk between multiple cell types in the skin. Overall, these nuclear receptors are critical players in keratinocyte and melanocyte biology and present targets for cutaneous disease management.

Mechanisms of action for type II nuclear receptors

Transcriptional control of gene expression is achieved, in part, through protein factors bound to regulatory elements present on the chromatin. The type II nuclear receptors (NR), belonging to the superfamily of steroid-thyroid hormone nuclear receptors, contribute to the cellular responses of physiological demands [1] [2] [3] [4]. Transcriptional modulation is achieved by structural adjustments initiated through ligand binding. Present throughout the animal kingdom, this family of environmental sensors contributes both positively and negatively to gene expression. This differential regulation is useful in organismal development and homeostasis, though it is also implicated in a variety of pathological conditions. The present review will only detail the contributions of type II NRs towards epidermal and follicular development and homeostasis, and in skin diseases. Particular emphasis is given on melanocyte biology and in melanomagenesis arising from altered signaling between keratinocytes and melanocytes, while highlighting the potential therapeutic value of these pliable receptors.

Type II NRs belong to a larger family of steroid hormone receptors, all sharing similarities in domain structure (Fig. 1) [5] [6]. Distinct variations in domain sequence has allowed for the diversification and specialization currently present within the family [7]. The DNA binding domain is highly conserved across the family and contains two zinc finger motifs.

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These domains recognize and bind short response elements, allowing for both homo- and hetero-dimerization combinations. Two activation domains called AF-1 and AF-2 assist the receptors in dimerization and DNA binding. Variability is more evident within the carboxyl terminal ligand binding domain, where individual receptors have evolved to bind a variety of signaling molecules [8]. Receptors for which ligand specificity has yet to be determined are labeled as orphan receptors. Endogenous ligands for NRs known to be expressed in skin include: all-trans retinoic acid (RA) and 9-*cis* RA for retinoic acid receptor (RAR) [9] [10], 9-*cis* RA for retinoid-X-receptor (RXR) [2] [11], 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) for vitamin D receptor (VDR) [12], fatty acids/lipids for peroxisome proliferator-activated receptor (PPAR) [13] [14] [15] [16], oxysterols for liver X receptor (LXR) [17] and triiodothyronine for thyroid receptor (TR) [18].

A distinguishing feature of type II NRs is the promiscuity displayed by RXR. All NRs from this class form heterodimers with an isoform of RXR (α/β/γ) and regulate gene expression in a ligand dependent fashion. RXRα is able to heterodimerize with some 15 NR family members and occupy direct repeat response elements present on the promoters of target genes [19] [20] [21] [22] [23]. The nonsteroidal ligands of RXR/NR heterodimers dictate the organization of complexes associated with the receptors. Serial combinations of regulatory proteins allow chromatin remodeling and recruitment of basal factors to initiate and/or repress transactivation (Fig. 2) [24] [25]. Coactivators include ATP-dependent chromatin remodelers, histone acetyltrasferases and the Mediator complex [26] [27] [28] [29] [30]. Corepressors comprise the N-CoR/SMRT assembly and histone deacetylases [31] [32] [33] [34]. The large numbers of regulatory factors, as well as tissue specific localization, allow NRs to influence a diverse range of gene expression in a cell and tissue specific manner. For example, the PPARγ cofactor PGC-1 is present in adipose tissue but not fibroblasts, allowing a cell-type specific activation of genes related to adaptive thermogenesis [35]. Post-translational modifications of co-factors such as phosphorylation, methylation, sumoylation and ubiquitination are also known to contribute to the extensive specificity of NR regulation [36].

Skin morphogenesis, epidermal homeostasis and hair cycling

Skin is the largest organ in the body and is comprised of multiple cell types such as epidermal keratinocytes, dermal fibroblasts and hypodermal adipocytes, besides Langerhans cells, melanocytes and endothelial cells. It utilizes both autocrine and paracrine signaling for development and maintenance of tissue homeostasis [37]. The outermost epidermal layer provides a protective barrier to environmental and physical stresses and constantly progresses through cycles of proliferation and differentiation. Basal keratinocytes located on the innermost epidermal basement membrane (separating epidermis from the underlying dermis) generate daughter cells, which undergo committed differentiation that give rise to ordered layers of suprabasal early- and late-differentiated keratinocytes. Appendages such as hair follicles and sebaceous glands (SGs) are invaginated into the mesenchymal-derived dermal layer. Different resident multipotent skin stem cell (SC) niches contribute to the renewal, maintenance and repair of the epidermal tissues of the skin, including interfollicular epidermis (IFE), hair follicles and SGs [38]. Epidermal SCs play a crucial role in maintaining tissue homeostasis by supplying new daughter cells to replace those constantly lost during turnover or following injury. Bulge SCs are known to maintain normal follicle homeostasis and can also contribute to the formation of IFE following skin injury and during wound healing. Melanocytes are also located within the hair follicles where they primarily contribute pigmentation to coat color. In humans, IFE melanocyte populations rely on keratinocytic paracrine signaling for assistance in photoprotection from solar ultraviolet irradiation [39].

Type II nuclear receptor signaling contributes to the perpetual renewal of keratinocytic layers, maintenance of the epidermal permeability barrier (EPB) and follicular cycling. Impaired expression or function of these receptors is implicated in aberrant proliferation and/or differentiation of epidermal tissue and alopecia (hair loss). The promiscuous role that RXRs play in type II NR signaling hints to the impact that impaired RXR expression or activity influences receptor signal transduction. Although many of RXRs heterodimer partners are implicated in a wide variety of skin diseases, in many cases these pathologies could instead be associated with compromised RXR mediated gene regulation. Regardless, only studies that have specifically indicated a specific role for RXR function will be discussed here. RXRs play a critical and varied role in epidermal differentiation and EPB maintenance. RXRα, the primary isoform in skin and hair follicles, has stronger expression levels compared to RARs, and RXRα/RARγ heterodimer appears to be the major retinoid transducing element in epidermal biology [40] [41] [42]. RXRα/RARγ heterodimerization is also critical in the development and formation of epidermal lamellar granules by repression of target genes, as RARγ agonists promote lamellar granule defects in murine skin. Similarly, RXRα/PPARβ/δ heterodimers are equally important to stratum corneum homeostasis through activation of gene transcription [43].

The importance of vitamin A signaling to cutaneous homeostasis has long been observed. Although, comprehensive studies have investigated multiple proteins along this pathway in skin (such as retinoic acid binding proteins), this review will focus primarily on RARs in human and rodent skin, particularly the role of RARγ [40] [44]. RA is widely used as a therapeutic against various skin diseases due to its inhibitory effects on keratinocytic terminal differentiation, besides regulating keratinocyte proliferation and apoptosis, through modulation of RAR target genes [45]. Management of keratin expression, which in turn dictates status of epidermal differentiation, is a known regulatory mechanism of cutaneous RARs [46] [47] [48]. Unfortunately, the use of pan-retinoids is limited due to unwanted side effects such as skin irritation, hypertriglyceridemia, bone toxicity and teratogenicity [49] [50]. In order to utilize these efficacious compounds in a dermatological setting, receptor-selective retinoids in parallel with prophylactic lipid management therapies may provide clinical benefits with decreased risk of toxicities.

Early studies have elucidated the synthesis of pre-hormone 25-hydroxycholecalciferol (calcifediol) by murine epidermal basal cells that acts in a paracrine manner for the CYP27B1 and VDR expressing differentiated keratinocytes [51]. Typical of the type II nuclear receptors, $1,25(OH)_2D_3$-induced VDR activation inhibited proliferation and promoted differentiation of keratinocytes, though VDR/RXRα heterodimers can transactivate keratinocytic genes independent of $1,25(OH)_2D_3$ binding [52]. DeltaNp63alpha, a critical regulator of epidermal biology, is known to directly control VDR expression in murine skin and mediate its function in a ligand-independent manner [53]. Mice bearing a targeted ablation of VDR present a large number of pathological properties in the skin, including progressive alopecia and dermal cysts as well as decreased expression of epidermal differentiation markers [54] [55]. By expressing in discrete epidermal locations, VDR-interacting coactivators contributed divergent roles towards keratinocyte proliferation and differentiation [56] [57]. VDR and its associated cofactors also contributed to lipid production and epidermal barrier formation. Genetic network analysis has implicated VDR as a necessary regulator of skin barrier formation and predicts the phenotype characterized in the VDR-null mice [58]. Many epidermal genes induced by WNT/β-catenin contain VDR response elements and were activated independently of TCF/LEF, implying that it is part of a TCF/LEF-independent aspect of WNT signaling [59]. Likewise, depletion of follicular keratinocyte populations in VDR-null mice was linked to aberration of the canonical WNT pathway [60].

Alopecia is a commonplace in hereditary resistance to $1,25(OH)_2D_3$ and VDR expression is seen in the outer root sheath keratinocytes and dermal papilla of follicles, increasing during late anagen and catagen [61]. The transcriptional repressor hairless (HR) co-localized with VDR in the outer root sheath of hair and has been shown to inhibit target genes leading to hair cycle progression [62]. Another VDR cofactor and critical subunit of the transcriptional coactivator complex Mediator (MED), MED1, has been recently linked to hair cycling and epidermal proliferation and differentiation. Selective ablation of MED1 in keratinocytes presents a similar phenotype to VDR or HR ablation [63]. miR-125b is a known repressor of skin differentiation in the bulge region of the hair follicle and expressing miR-125b in SC progeny significantly downregulated VDR activity [64].

PPARβ/δ expression was seen in both basal and suprabasal layers of the normal human epidermis, while PPARα and PPARγ expression was confined to suprabasal epidermal cells and was linked to squamous differentiation [65]. PPARs are transcriptionally regulated by AP-1, C/EBP family members and p63, the master regulator of epidermal morphogenesis and differentiation [66] [67]. Mechanistically, inhibition of the PKC/MAPK pathway through PPAR-mediated PKCα-ubiqutitination has been implicated in reduction of epidermal proliferation [68]. All PPAR isoforms were expressed in human hair follicle cells while PPARγ ablation in mice mimicked a human scarring alopecia phenotype [69] [70].

The ability of LXRs to act as environmental cholesterol sensors enables them to contribute to consistent epidermal turnover which support a sound EPB. LXRα/β are expressed in all layers of the human epidermis, as well as in the outer root sheath and SG, and the LXR agonists oxysterols act on epidermal keratinocytes by reducing proliferation and inducing differentiation [71]. One proposed mechanism of LXR mediated induction of keratinocytic differentiation is influencing the binding of transcriptional complex AP-1 to target genes. ChIP-on-chip studies investigating LXRβ/RXRα binding in human keratinocytes revealed a strong correlation to AP-1 response elements, with up to 77% of all LXRβ/RXRα binding sites associated with AP-1 motifs [72]. This could indicate LXR involvement in the pathogenesis of certain diseases that present with abnormal keratinocytic differentiation and/or compromised barrier function.

Thyroid-stimulating hormone receptor signaling is commonly associated with cutaneous biology, though TR ligand binding is also known to contribute to epidermal homeostasis. Resistance to thyroid hormones is a syndrome with a wide variety of symptoms and is connected to TRβ mutations in in both mice and humans [73] [74]. Follicular TRβ is the predominant isoform expressed within human skin and one phenotype of the disease linked to aberrant TRβ signaling is alopecia [75] [76]. In support of a role for TRβ in hair cycle homeostasis, thyroid hormones and TRβ-selective thyromimetics are able to induce hair growth in both murine and simian models, as well as stimulate intrafollicular melanin production [77] [78]. TRs bind to conserved keratin response elements located in the promoter region of epidermal keratin genes and can directly control their transcription. One proposed mechanism of these genes involves transcriptional repression in the presence of a liganded TR receptor. In this scenario, proteins typically seen as components of a co-activator/histone acetylase complex display repressive tendencies in the presence of liganded receptors while co-repressors act as activators when unliganded TRs are present on the keratin response element [79]. Transcriptome analyses from epidermal keratinocytes treated with either thyroid hormone or vehicle display only a small number of genes that are differentially expressed. Among the suppressed genes (*integrin β4*, *plectin*, *collagen XVII*, *MMP1/3/14*) there was significant association to the blistering skin disease epidermolysis bullosa, implying an inhibitory role of thyroid signaling to extracellular matrix maintenance [80].

Inflammatory skin diseases

Cutaneous inflammatory disorders are characterized by inflammation of the skin that can lead to patient discomfort or disfigurement. Psoriasis is a genetic-based cutaneous syndrome that involves epidermal hyperproliferation, compromised EPB and an infiltrative immune response. It is present in up to 5% of the population, affects both sexes equally and is able to manifest within the first two decades of life [81]. As it is currently incurable, primary treatment options focus on the control of symptoms and include the use of topical corticosteroids, phototherapy and moisturizing creams [82]. As proof of concept that type II NR activation is a feasible therapeutic approach, acitretin and calcipotriol are widely utilized for psoriasis. Atopic dermatitis (AD) is another chronic inflammatory skin disease that is characterized by dry and itchy skin, persistent infections and very early onset [83]. AD is linked to other atopic diseases such as asthma and allergic rhinitis, and defective EPB function, environmental insults or genetic background are predisposing factors for this heterogeneous disease [84] [85]. Treatment options are similar to those for psoriasis, while preventing future allergic reactions is also important. Unfortunately, the roots of these diseases may be too deeply embedded in immune functions to be eradicated. Due to early onset and lifelong activity, the use of chronic corticosteroid therapy is discouraged. Knowledge regarding transcriptional regulation by key factors of EPB and epidermal proliferation gene networks enhances our retinue of therapeutic strategies in these diseases. NR ligands may be useful to modulate multiple pathways in order to lessen side effects and/or concentrations of the more efficacious compounds.

Mice with an epidermal-specific ablation of RXRα (RXRα$^{ep-/-}$) presented epidermal hyperplasia, alopecia, dermal cysts and a cutaneous inflammatory response [86] [87]. Likewise, mice lacking both RXRα and RXRβ in keratinocytes (RXRαβ$^{ep-/-}$) developed a chronic dermatitis similar to human AD patients, elevated serum IgE/IgG and cytokine production associated with Th2-type response. Importantly, thymic stromal lymphopoietin (TSLP) was strongly upregulated from the basal keratinocytes, potentially influencing the systemic AD phenotype in these mice [88]. To further support the hypothesis that loss of RXRα contributed to a derepressive mechanism on gene expression leading to inflammatory responses, expression of RXRα has been reported to decrease in human psoriatic lesions, with levels in progressive disease further reduced compared to stable stages [89].

Use of the anti-proliferative, pro-differentiative properties of $1,25(OH)_2D_3$ is not ideal due to harmful calcemic effects. Therefore, synthetic deltanoids represent the best way to initiate VDR activation for therapeutic or investigative purposes. It was previously discussed that keratinocytic *RXRα/β* ablation upregulates production of TSLP leading to an AD-like phenotype in the mouse. Interestingly, topical application of deltanoids also induces TSLP in epidermal keratinocytes, suggesting the role of RXR/VDR heterodimers in regulating *TSLP* expression in this cell type. That evidence suggests a role for VDR antagonists in the treatment of human AD patients [90]. Conversely, deltanoids were shown to significantly improve allergen-triggered eczema in a mouse model through increasing populations of FOXP3-expressing regulatory T cells [91]. Further evidences are needed to determine how VDR transactivation can initiate anti-inflammatory mechanisms if deltanoids are to become accepted therapy for hyperproliferative epidermal disorders in the clinic.

The anti-inflammatory actions of PPARα offer additional treatment modalities for reoccurring skin conditions such as AD and psoriasis. Stimulation of epidermal differentiation and reduction of proliferation can potentially treat these conditions without severe side effects brought on by glucocorticoids (GC). PPARα$^{-/-}$ mice (with a germline deletion of the *Pparα* gene) subjected to antigen sensitization exhibit increased epidermal thickening and inflammatory responses compared to wild-type controls, potentially through

the loss of IL-2-mediated induction of Treg populations [92]. PPARα$^{-/-}$ skin also display heightened levels of both Th2- and Th1-related responses, as well as enhanced NF-κB signaling. Furthermore, PPARα expression is downregulated in lesional skin of human AD patients compared to non-atopic individuals [93]. Topical application of PPARα agonists reduces the hyperplastic response in mouse skin brought on by TPA treatment, in part through the reduction of inflammatory cytokines. Similar results were seen in oxazolone (OX)-induced allergic dermatitis mouse models, and importantly, combination therapy of PPARα agonists and GCs for severe dermatitis prevented GC-induced side effects and inhibited rebound flares [94] [95]. Conversely, activation of PPARβ/δ may trigger psoriasis pathogenesis within the skin and treatment strategies may include antagonism of this signaling pathway. PPARβ/δ is upregulated at both the mRNA and protein level in psoriatic lesions compared to nonlesional skin in human patients and eicosanoid accumulations within the lesions can activate PPARβ/δ [96] [97]. Also, topical antagonists targeted to cutaneous PPARβ/δ demonstrated efficacy in a psoriatic mouse model [98]. Alongside other physiological defects, PPARβ/δ-null mice exhibit an elevated epidermal hyperplastic response after TPA administration and delayed barrier recovery following acute barrier disruption [99] [100]. An increase in the release of inflammatory cytokines after wound healing in murine skin requires upregulation of PPARβ/δ that is otherwise undetected in normal skin. Interestingly, this pro-inflammatory cascade initiates production of endogenous PPARβ/δ ligands, reinforcing the activation of PPARβ/δ after skin injury [101] [102]. PPARβ/δ is also linked to UV-induced premature senescence via upregulation of PTEN that attenuates reactive oxygen species in keratinocytes [103]. Likewise, epidermal PPARγ signaling is also a target for the UV-induced inflammatory response. UV irradiation of human keratinocytes produces potent PPARγ agonistic activity and enhances COX-2 expression in these cells. Furthermore, PPARγ activation was seen as a general consequence to various oxidative stressors in human sebocytes [104] [105].

An increased accessibility of environmental antigens through epidermal tissue can activate cutaneous immune responses that potentially drive inflammation. Creation and maintenance of the EPB is a multistep process involving lipid production and lamellar body formation and LXR activation appears to hold key functions in many of these stages [106] [107]. EPB function is tightly linked to cholesterol levels in the epidermis and LXR has been shown to regulate the storage and efflux of lipid species. Members of the ATP-binding cassette transporter family such as ABCA1, ABCA12 and ABCG1, as well as the glycerol channel AQP3, are transcriptionally regulated by oxysterols [108] [109] [110] [111]. Environmental toxins present in cigarette smoke have been linked to several skin diseases including psoriasis and melanoma [112] [113]. Translocation of LXR to the nucleus in HaCaT cells after exposure to cigarette smoke facilitated an increase in cholesterol trafficking as a result of increased ABCA1 expression [114]. The ability of the synthetic LXR agonist T1317 to prevent physical changes inherent to photoaging and chronological skin aging has been investigated. T1317 inhibited the expression of cytokines and metalloproteinases in cell-based models of skin aging. Furthermore, LXRβ-null murine skin mimics some of the characteristics seen in chronologically aged human skin and the topically applied agonist reduced UV-induced skin thickness and wrinkle formation in a mouse model [115].

The anti-inflammatory actions of LXR activators have been demonstrated in both irritant and oxazolone (OX)-induced allergic dermatitis mouse models, in part through the inhibition of proinflammatory cytokines that are specific to LXRβ [116] [117]. Similarly, global gene expression studies using primary human keratinocytes from psoriatic lesions, non-affected skin of the same patients and healthy control subjects, indicates a role for LXRα in regulating inflammatory response. Along the same line, knocking down LXRα in human keratinocytes lead to a genomic profile similar to that seen in psoriatic skin lesions [118]. Even if LXRs are not directly involved in disease pathogenesis, the receptors might

still be utilized as therapeutic tools to modulate cellular lipid levels. For example, a human sebaceous cell line treated with LXRα agonists increased lipid synthesis and induced the lipogenic gene SREBP-1, potentially useful for the treatment of seborrhea and acne [119]. Selective LXR agonists that are isoform and tissue-specific could provide localized and specific cutaneous effects that do not influence other LXR receptor pools [120] [121].

Epidermal carcinogenesis

Non-melanoma skin cancers arise from both the basal and squamous cells of the epidermis. Basal cell carcinoma (BCC) is the most common neoplasm related to the Caucasian population and its incidence rate is increasing yearly [122]. Though considered malignant due to its ability to invade deep into tissue, it rarely metastasizes from the primary location. Risk factors include fair skin disposed to freckling, family history of BCC and exposure to ultraviolet radiation. Patients with BCC also tend to be prone to other types of skin cancer including malignant melanoma [123]. Disease progression typically arises from UV-induced actinic keratosis or mutations in the hedgehog signaling pathway. Surgical excision is the treatment of choice though pathway specific compounds such as vismodegib provide additional therapy options [124]. Cutaneous squamous cell carcinoma (SCC) is the second leading cause of skin cancer, yet unlike BCC it tends to exhibit metastatic behavior [125]. Again, exposure to ultraviolet radiation is the predominant risk factor for this disease, though immunosuppressed patients are at increased risk for metastatic spread [126]. Treatment options include surgical removal, radiation therapy and in certain cases chemotherapeutics such as 5-fluorouracil or imiquimod [127]. Investigations into pathways regulating keratinocytic proliferation and differentiation may lead to additional treatment options useful in treating these disfiguring diseases.

The transcription factor KLF4 is required for proper EPB formation in mice and dysregulated KLF4 activity is shown to be oncogenic [128]. KLF4 regulates expression of RXRα and KLF4-induced malignant transformation is sensitive to retinoids *in vitro*. Importantly, rexinoid application drastically prevented formation of SCC in a KLF4-activated transgenic mouse line [129]. These results suggest existence of a crosstalk between RXR and KLF4 signaling, where KLF4-mediated expression of RXRα contributes to tumor suppressor activity within the epidermis. $RXR\alpha^{ep-/-}$ mice, selectively lacking RXRα in epidermal keratinocytes, subjected to a 7,12-dimethylbenz(a)anthracene (DMBA)/12-*O*-tetradecanolyphoral-13-acetate (TPA) induced two-step chemical carcinogenic protocol developed higher numbers of epidermal tumors compared to control mice [130]. The $RXR\alpha^{ep-/-}$ papillomas progressed towards SCC in a murine model, further validating the role of RXRα as a cutaneous tumor suppressor.

Both keratinocytes and melanocytes downregulated expression of RARs when subjected to UV exposure, potentially initiating cellular responses to ionizing radiation through the removal of repressive transcriptional controls [131] [132] [133]. A similar downregulation of RAR in mouse skin was seen after application of TPA, as well as when normal human skin progresses through premalignant actinic keratosis to invasive SCC [134] [135] [136]. A loss of RARγ expression exacerbated carcinogenic effects of tumor promoters and enhances malignant transformation [137] [138]. Topical application of RA during the promotion stage of carcinogen treatment in mice reduced the yield of papilloma and carcinoma formation [139]. Likewise, the RARβ/γ retinoid tazarotene displayed anti-tumoral activity when topically applied to BCC and may inhibit psoriatic proinflammatory gene networks [140] [141] [142]. Above results indicate important roles of retinoids and retinoid receptors in the control of epidermal homeostasis and prevention of hyper-proliferative diseases and skin cancer.

The regulatory nature of VDR in hair cycle progression and barrier formation is critical to maintain skin homeostasis, therefore defects in the transactivating function of the receptor allow pathological conditions to manifest. Multiple VDR polymorphisms have been associated with a broad spectrum of cutaneous disease, including SCC, BCC and vitiligo [143] [144] [145] [146] [147] [148]. Indeed, inactivation of VDR in mice enhanced sensitivity to both chemical and solar-induced skin carcinogenesis, potentially through activation of the hedgehog pathway [149] [150].

Due to evidence of PPAR signaling in the development of aberrant growths in differing tissue types, studies have investigated the role of these receptors in cutaneous neoplasms. Tumor formation and size were increased after chemical carcinogen application in PPARβ/$\delta^{-/-}$ mice, while those selectively lacking PPARγ in epidermal keratinocytes show an increase in benign tumors, SCC and BCCs [130] [151]. Ligand activation of PPARβ/δ inhibits chemically induced skin tumorigenesis, most likely through induction of keratinocytic differentiation, and the addition of COX-2 inhibitors may result in synergistic efficacy [152] [153].

In mice, TRβ expression is detected in normal and TPA-treated hyperplastic skin. Loss of TRβ expression is seen in benign papillomas generated by the DMBA/TPA protocol and completely abrogated in subsequent SCC formation. Importantly, skin tumors from mice lacking both TRα and TRβ were more likely to develop *in situ* carcinoma and SCC than those from wildtype mice, supporting TRs role as a tumor suppressor [154]. In order to determine the role TRs have in the hyperproliferative response, TRα/β-double null mice were subjected to both TPA and RA treatments [155] [156]. Reduced hyperplasia with a decreased expression of cyclin D1 was seen in the TRα/$\beta^{-/-}$ skin after TPA treatment. That profile was correlated with increases in cell cycle inhibitors p19 and p27, as well as induction of proinflammatory cytokines and phosphorylation of p65/NF-κB and STAT3. This phenotype is opposite to that seen in PPARβ/$\delta^{-/-}$ mice and elucidates the combinatorial mechanisms RXR/NR heterodimers regulate within the skin. Similarly, a typical retinoid response requires the presence of ligand-bound TR in mouse skin. Decreases in skin hyperplasia and expression of keratins 5/6, alongside increased transcription of inflammatory and chemotactic cytokines, are also seen in TRα/$\beta^{-/-}$ mice treated with 9-*cis* RA. Since TPA and retinoids are modulating separate signaling cascades, it is possible that TRs are involved in the cellular responses to both these compounds.

Melanocyte homeostasis and melanomagenesis

Melanocytes are neural crest-derived pigment producing cells that contribute photoprotective properties to the skin. Cutaneous melanoma is the deadliest form of skin cancer, with a diagnosis of metastasis indicating a median survival rate of less than a year [157]. Solar ultraviolet irradiation, especially childhood sun exposure, is an important etiological risk factor of melanoma [158]. Surgical excision prevents growth of the primary lesion, yet once transformed melanocytes spread to distal organs and this disease is refractory to current therapeutics. Recent evidence supports the use of MAPK inhibitors and immunomodulatory treatments with the goal of increasing lifespan [159] [160]. Therefore, any research directed towards key regulators of melanocytic activity could potentially open up new avenues for disease management.

Type II NR-mediated signaling via RXR dimerization is essential to melanocyte biology. RXRα and β expression has been detected in B16 and S91 murine melanoma cells, with RXRβ being the predominant isoform [161] [162]. Interestingly, loss of melanocytic RXRα expression was seen in human primary and metastatic melanoma compared to benign nevi, indicating the importance of this signaling pathway to the differentiation of these cell types

[163]. RARβ expression was also downregulated in melanoma and its RA-induced expression was linked to growth inhibition and differentiation in these cells. Sequential occupation of the RA response element located on the *Rarβ* promoter by RXR/RXR and RXR/RAR combinations is believed to be a molecular switch responsible for *Rarβ* transcriptional activation in these cells. Since ligand activation of RXR heterodimeric partners regulates transcriptional activity of target genes involved with differentiation and growth arrest, it is possible that combinatorial activation of both dimer partners may assist in melanoma therapy. Rexinoid treatment alongside glitazones (PPARγ agonists) have displayed efficacy against melanomagenesis in *in vitro* and xenograft models, potentially through the inhibition of matrix metalloproteases and increases in S100A2 calcium binding activity [164] [165] [166].

Our own work has demonstrated the role of keratinocytic RXRα in manipulating melanocyte activation and proliferation through modulation of the cutaneous microenvironment [167]. RXRα/NR heterodimer binding regulates transcriptional repression of soluble mitogens and cytokines, making it a critical factor in the ultraviolet radiation (UVR) induced cellular responses. The loss of keratinocytic RXRα in RXRα$^{ep-/-}$ mice relieves transcriptional repression and allows overexpression of keratinocytic soluble factors that act on melanocytic cell-surface receptors. Higher numbers of epidermal melanocytes were seen after UVR exposure in RXRα$^{ep-/-}$ mice compared to controls, suggesting contribution of soluble factors in the cellular microenvironment for melanocyte activation and migration out of the hair follicle. Indeed, increased expression of *Edn1*, *Fgf2* and *Kitlg*, that are known to be upregulated by keratinocytes and influence melanocyte activation, migration and proliferation, were seen in RXRα$^{ep-/-}$ skin post-UVR [167]. Interestingly, in a two-step carcinogenesis model, RXRα$^{ep-/-}$ mice developed a higher number of dermal melanocytic growths (nevi) compared to control mice, implicating contribution of keratinocyte-derived factors in melanomagenesis. Only nevi from RXRα mutant mice progressed to melanoma-like tumors, suggesting that RXRα-mediated distinct non-cell autonomous actions suppressed nevi formation and melanoma progression in mice [130]. Similarly, VDR$^{-/-}$ mice undergoing identical treatments also developed higher numbers of melanocytic lesions, indicating RXRα/VDR heterodimerization may be the causative factors, at least in part, in these non-cell autonomous events [130]. Finally, the loss of keratinocytic RXRα alongside an activated-CDK4 mutation enhanced the metastatic transformation of cutaneous melanoma after chemical carcinogenesis. Expression of *Edn1*, *Hgf*, *Fgf2*, *Pomc* and *Kitlg* were all upregulated in the skin of RXRα$^{ep-/-}$/CDK4$^{R24C/R24C}$ bigenic mice. Direct binding of RXRα on the promoter of *Edn1* and *Hgf* was also seen in *ex vivo* primary murine keratinocytes. Gene expression analyses on mRNA isolated from melanocytic lesions from the bigenic skin using laser-capture microdissection demonstrated reduced apoptotic and enhanced invasive responses within bigenic melanomas. Loss of epidermal RXRα was also seen in human melanoma progression and could potentially be utilized as a therapeutic biomarker [168]. These results indicated a crucial role of RXRα/NR signaling in melanocytic homeostasis and in cellular responses to tumor promotion.

All RAR isoforms were expressed in melanocytes and treatment of retinoids, particularly RARγ-specific agonists, inhibits growth and initiates apoptosis in melanoma cells [169] [170] [171]. RA treatment increases expression of RARβ and PKCα while stimulating AP-1 transcriptional activity in melanoma cells. RARα specific agonists were most effective in upregulating RARβ levels and combinatorial RAR/RXR activation demonstrate the strongest induction of both PKCα and AP-1 function in murine melanoma cells [172] [173] [174]. Loss of RARs, especially RARβ and its tumor suppressor activities, was observed during melanomagenesis and could account for RA resistance in this disease [163] [175] [176]. That disruption of RARβ or RARγ signaling in benign nevi may predispose a lesion towards malignant transformation. Co-treatment of retinoids with histone deacetylases also

counteracted the epigenetic silencing of RARβ often seen in RA resistant melanoma cell lines and provides increased antitumor activity [177]. Another mechanism implicated in RA-resistant melanoma cells is an increase in intracellular reactive oxygen species (ROS) that is inversely related to RAR activity. RA-sensitivity was restored when ROS levels were lowered, potentially through improved RXR/RAR promoter binding activity [178]. RA treatment in combination with polyl:C synergistically increased the toll-like receptor 3 chemokine responses in human melanoma cells and induced migration of antigen-presenting cells [179]. Decreased expression of collagenolytic-enzymes and alterations in mobility-associated cell surface receptors were consequences of RAR activation in melanoma cells [180] [181]. Further evidence of RARγ-mediated inhibition of melanoma invasion came from microarray analysis of murine melanoma cells treated with RARγ agonists, which identified the sulfotransferase CHST10 as being directly regulated by RARγ through RA response elements located in its promoter region. CHST10 synthesizes a HNK-1 carbohydrate that was involved with cell adhesion in the nervous system and RA-mediated embryonic plasticity [182]. Altogether, RAR-specific agonists present a potential therapeutic candidate for the treatment of metastatic melanoma if mechanisms of RA resistance can be elucidated and exploited.

Skin is both a target and producer of $1,25(OH)_2D_3$, the secosteroid ligand of VDR and regulation of melanocyte homeostasis is a physiological role that is attributed to VDR signaling. The use of vitamin D analogs to combat vitiligo depigmentation has been well reviewed [183]. It is hoped that Vitamin D agonists might protect melanocyte loss in this disease through inhibition of immune response and modulating calcium flux. VDR activation may also promote re-pigmentation processes by upregulating melanogenic cytokines that drive pigment production. Due to insufficient knowledge on what drives the etiology of this disease, any research implicating driver mutations is important for developing effective therapeutics. Genomic DNA isolated from vitiligo patients, as well as age and sex-matched controls, demonstrated the TaqI VDR polymorphism is a risk factor for the disease. Haplotype BsmI/ApaI/TaqI/FokI/Cdx2 was also overrepresented in those patients [148].

The use of low-calcemic deltanoids for treatment of melanocytic lesions is another potential candidate for future therapies. Sunlight generates DNA damage within melanocytes yet also produces anti-proliferative $1,25(OH)_2D_3$ ligands. This physiological dichotomy provides endogenous regulation of melanomagenesis and may offer directions on how to manage cutaneous melanoma. Human melanoma cell lines have been shown to posses different expression levels of VDR and different growth inhibitory responses to $1,25(OH)_2D_3$. Importantly, melanoma cells demonstrate increased sensitivity to deltanoids compared to normal melanocytes [184]. Similar to some other type II NRs, a loss of VDR expression was seen during the progression of melanocytic lesions and that attenuated VDR signaling was linked to decreased overall survival time [185]. Likewise, a retrospective cohort study of large numbers of melanoma patients associated higher serum $1,25(OH)_2D_3$ levels with thinner presenting melanomas and improved survival from melanoma [186]. In addition to investigations associating VDR polymorphisms to keratinocytic pathologies, extensive studies have shown VDR mutations as a critical contributing factor towards melanoma susceptibility and outcome, in particular the BsmI, FokI and TaqI polymorphisms [187] [188] [189]. Not all melanoma cell lines were sensitive to $1,25(OH)_2D_3$ treatment though. Resistance to $1,25(OH)_2D_3$ treatment may be attributed to epigenetic mechanisms that abrogate VDR signaling in those cell lines. An inverse relationship has been shown to exist between VDR mRNA expression and level of microRNA miR-125b, most likely through posttranscriptional regulation of VDR by miR-125b interacting with a recognition element in the 3′-UTR of human VDR mRNA. Treatment of these cells with a DNA methyltransferase inhibitor reduces expression of miR-125b and may prove efficacious

alongside other chemical therapies [190] [191]. In short, aberrant VDR signaling appears to contribute significantly to the development of melanoma in humans and $1,25(OH)_2D_3$ analogs may provide additional targeted chemotherapeutics in the treatment of that disease.

Due to importance of lipid metabolism in skin homeostasis, PPAR signaling in skin has been thoroughly investigated, including its role in melanocyte homeostasis. All PPAR isoforms are expressed in human melanocytes, though PPARγ signaling appears to be a primary possible drug target for melanoma. Two common PPARγ polymorphisms implicated in susceptibility of the malignant disease were evaluated as influences in melanoma risk, though it appeared that inactivating mutations do not appear to be a significant risk factor for the disease [192]. Recently a link was shown between α-MSH signaling and PPARγ nuclear translocation that reduced proliferation rates and increased melanogenesis through the $Pi(4,5)P_2$/Plcβ pathway [193]. Glitazones are known to activate PPARγ and promote melanocyte differentiation. One mechanism to induce melanocyte differentiation is through β-catenin mediated upregulation of MITF levels. Phenotypic changes that occured in melanoma cells post-ciglitazone treatment include dendritic morphology and increased tyrosinase functions, possibly linked to large increases of *Mitf* promoter activity. β-catenin protein levels in ciglitazone-treated murine melanoma cells followed the same trend of transient increase followed by gradual decrease pattern as seen with MITF, suggesting that depleted levels of nuclear β-catenin was influencing the downregulation of MITF activity in these cells [194]. In addition to its pro-differentiative properties, inhibition of proliferation was seen in melanoma cells after ciglitazone treatment and is also associated with induction of apoptosis [195]. PPARγ agonists regulate the WNT3A/β-catenin signaling pathway and inhibits human melanoma cell proliferation through direct inhibition of β-catenin activity [196]. Though PPAR functions as a tumor suppressor at times, two studies screening large numbers of melanocytic lesions determined that both PPARγ and COX-2 expression was increased during progression from benign nevi to metastatic melanoma and may indicate therapy response levels of this disease [197] [198]. That conflicting role of PPARγ in tumorigenesis has yet to be elucidated but provides an exciting investigative target in the treatment of metastatic melanoma.

Few reports demonstrate a role of LXR activation in melanocytes, though known LXR target genes are important in melanocyte biology. LXRα appears to be the predominant isoform and could provide LXR-oriented strategies of melanoma therapy. LXRα expression was also localized adjacent to the follicular dermal papilla, suggesting a contribution to hair follicle melanocyte activity [199]. LXRα expression was seen in both human melanocytes and in melanoma cells. Moreover, LXRα mRNA and protein levels were increased in melanocytes present in the skin surrounding vitiligo lesions compared to normal skin, suggesting LXRα is modulating the melanocytic response to this disorder [200] [201]. Interestingly, LXRα has been linked to immunoevasion of melanoma through inhibition of dendritic cell (DC) migration to lymphoid organs. Production of LXR ligands from both human and mouse tumors were shown to hinder CCR7 expression on DCs that is required for lymphoid homing. Conditioned media from the human melanoma cell line MSR3 was shown to inhibit CCR7 expression in DCs, though not affecting other aspects of DC activation. Also, the media from MSR3, as well as from another melanoma cell line MR255, was able to activate LXRα reporter constructs, suggesting the presence of ligands expressed in the media. Use of the sulfotransferase enzyme SULT2B1b, which inactivates natural oxysterols, was able to protect CCR7 inhibition from the conditioned media. Similarly, mice receiving bone marrow transplants from an LXRα-null line demonstrated an enhanced ability of tumor rejection [202]. Altogether, studies indicate an important immuno-modulatory role of LXR signaling in melanocytic lesions and in melanoma primarily mediated by LXRα. Additional studies are required to establish the receptor functions in melanocyte homeostasis and in melanomagenesis.

Evidence for a role of TR in melanocyte biology is limited, though thyroid-stimulating hormone expression is seen in epidermal melanocytes. Of note, one study involving patients with uveal melanoma demonstrated that 60% of the cohort contained a loss of heterozygosity in the TRβ alleles in both the ciliary body and choroidal melanomas [203]. Further *in vivo* studies are needed to determine how TR signaling is impaired in epidermal diseases and in skin cancer, as well as the severity of any non-autonomous actions that affect the malignant transformation of melanocytic cells.

Conclusion

RXR/NR signaling makes important contributions to both the development and homeostasis of keratinocyte and melanocyte biology (Table 1). The ability of epidermal tissue to maintain a rigorous cycle of proliferation and differentiation utilizes complex transduction pathways that rely on tight transcriptional control of key target genes. Ligand activated regulation of gene transcription and/or repression by type II NR heterodimers is one example of how skin is able to continually replenish itself while at the same time inhibiting neoplastic transformation. Extensive research presents a scenario where type II NRs are critical tumor suppressors that regulate the sequential differentiation of maturing keratinocytes. With the exception of TR, which does not appear to play a major role in skin biology, loss of RXR/NR activity through inactivating mutations or epigenetic silencing leads to hyperproliferation and immune responses. Likewise, activation of NR heterodimers through endogenous ligand binding, or exogenous topical application of synthetic agonists, typically provides anti-inflammatory actions. Modulation of these receptors could provide supplemental therapy for inflammatory skin disease that is usually treated with potent GCs. The development of tissue specific NR ligands may provide additional relief for diseases such as psoriasis and AD that are not currently curable. RXR/VDR regulation of genes such as *TSLP* provides strong drug targets that could significantly alter the micro-environmental milieu that drives skin inflammation. Abolishing keratinocytic derived paracrine signaling utilized by melanocytes and immune cells may provide additional options in curative techniques for skin diseases including melanoma. Overall, RXR/NR signaling has evolved as extensive and dominant signaling networks within skin, the largest organ and most important barrier to environmental damages and insults. Utilizing these regulatory checkpoints through the use of synthetic ligands will be an important focus of cutaneous research in the immediate future.

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Figure 1. Schematic representation of functional domains in type II nuclear receptors

Transcriptional activation function 1 (AF-1) domain initiates at the amino terminus, followed by the DNA-binding domain (DBD). A flexible hinge region (H) assists in DNA binding, dimerization and transactivation functions. Variable ligand-binding domains (LBD) and a second activation function (AF-2) are present at the carboxyl terminus.

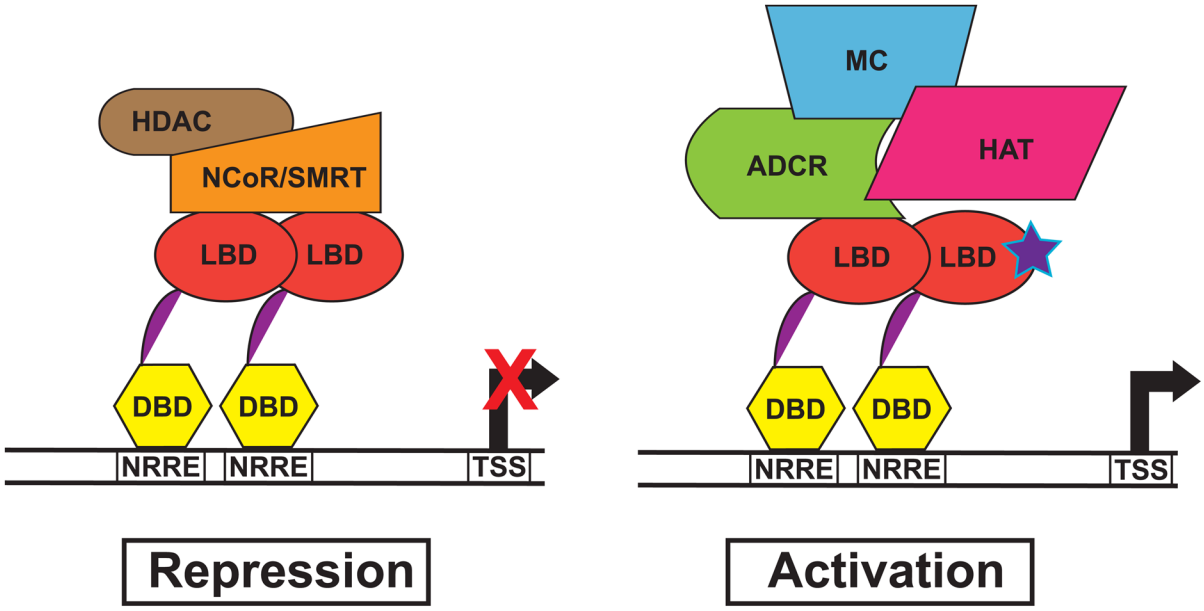
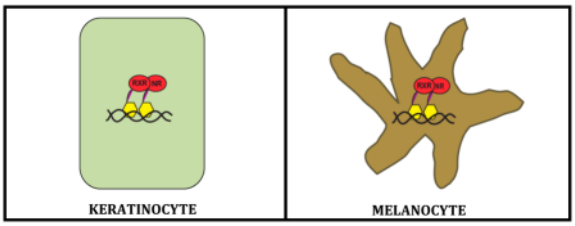


Figure 2. Putative mechanisms of transcriptional regulation by type II nuclear receptors

Repression of gene expression by nuclear receptor heterodimers involves association with co-repressor protein complexes, including NCoR/SMRT and histone deacetylases (HDAC). Positive transactivation occurs after ligand binding when co-repressor complexes are replaced by co-activator proteins such as ATP-dependant chromatin remodelers (ADCR), histone acetyltransferases (HAT) and the Mediator complex (MC). DBD, DNA-binding domain; LBD, ligand-binding domain; NRRE, nuclear receptor response element; TSS, transcriptional start site.

Table 1

Description of pathologies associated with alteration of skin keratinocytes and melanocytes homeostasis and mechanisms influenced by type II nuclear receptor signaling. Summary of references from the primary literature reviewed regarding keratinocyte or melanocyte-associated NR signaling. AD, atopic dermatitis; BCC, basal cell carcinoma; EPB, epidermal permeability barrier; Hh, hedgehog; SC, stratum corneum; SCC, squamous cell carcinoma; TSLP, thymic stromal lymphopoietin; UVR, ultraviolet radiation.



RXR		
Pathology	**Mechanism**	**Ref.**
EPB defects	Lamellar granule formation in epidermis	43
Alopecia	Follicular destruction and hair cycling defects, epidermal hyperplasia	86, 87
AD	TSLP derepression and Th2-type inflammation	88, 90
Psoriasis	Stage-related loss of expression	89
SCC	Cell-autonomous suppression of epidermal tumorigenesis and progression	130
	Stage-related loss of expression	136
Melanoma	Stage-related loss of expression	163, 175
	Growth and invasion arrest by NR ligands	164
	Growth arrest by NR ligands	165, 166, 172
	Keratinocyte-derived paracrine effects in melanomagenesis	130, 167, 168

RAR		
Pathology	**Mechanism**	**Ref**
EPB defects	Lamellar granules formation in epidermis	43
Aging	UVR-induced loss of expression	131, 132
AD	TSLP derepression and Th2-type inflammation	90
Psoriasis	Negative gene regulation via retinoids	140
SCC	Stage-related loss of expression induces malignant progression	136, 138
BCC	Anti-proliferative and pro-apoptotic effects of retinoids	141
BCC	Tumor suppressor activities of basal RAR signaling	142
Melanoma	Stage-related loss of expression	163, 175
	Epigenetic silencing of RARβ	176
	Anti-proliferative and pro-differentiative properties	165, 169, 172, 174
	Induction of apoptosis by retinoids	170, 171
	Regulation of cell surface receptors	180, 182
	Modulates HLA-DR expression on melanoma	169
	Increase in chemokine and IFNβ secretion	179

VDR		
Pathology	**Mechanism**	**Ref**
EPB defects	VDR genetic network linked to EPB function, inflammation	58
Alopecia	$VDR^{-/-}$ mice display progressive hair loss	55
Alopecia	VDR drives mammalian hair cycle through gene repression	62
AD	TSLP derepression and Th2-type inflammation	58, 90
AD	Low-calcemic VDR agonist improves allergen-induced eczema	91
SCC	VDR polymorphisms linked to SCC development, tumor susceptibility	58, 143, 147
SCC	$VDR^{-/-}$ mice susceptible to carcinogen-induced SCC through Hh pathway	149, 150
BCC	VDR polymorphisms linked to BCC development	146, 147
BCC	$VDR^{-/-}$ mice susceptible to carcinogen-induced BCC through Hh pathway	150
Vitiligo	VDR polymorphisms linked to vitiligo susceptibility	148
	VDR targets the epidermal melanin unit	183
Melanoma	Stage-related loss of expression of VDR	185, 186
	miRNA associated epigenetic silencing	190, 191
	Anti-proliferative and pro-differentiative properties of vitamin D analogs	184
	VDR polymorphisms linked to melanoma development	187, 188, 189

PPAR		
Pathology	**Mechanism**	**Ref**
EPB formation	Lamellar granules formation	43
	PPAR agonists regulate involucrin and CD36 expression	65
	PPARβ/δ is required for EPB homeostasis	100
	Activators stimulates lipid synthesis and processing	107
	Regulate expression of cholesterol and water transporters	109, 110, 111
Alopecia	PPARγ ablation in hair follicles displays a scarring alopecia phenotype	69
Aging	PPARδ/γ provides resistance to UV-induced cellular senescence through PTEN upregulation	103
	PPARγ is necessary for production of UV-induced epidermal prostaglandins	104
AD	PPAR regulates IL-2-mediated Treg induction	92
	PPAR negatively regulates skin inflammation through TH1 and TH2 responses	93
	PPAR agonists as therapy in murine AD models	94, 95, 117
Psoriasis	Activation of epidermal PPAR linked to psoriatic gene regulation	96, 97
	Inhibition of PPAR signaling as therapy for psoriasis	98
SCC	Loss of expression induces malignant progression	130
	Inhibition of PPAR signaling as therapy for SCC	152, 153
BCC	Loss of expression during progression	130
Melanoma	Growth and invasion arrest by PPARγ ligands	164
	Growth arrest by PPARγ, RAR and RXR agonists	165, 166
	PPAR-mediated downregulation of β-catenin downregulates MITF	194
	Growth arrest and induction of apoptosis by PPARγ ligands	195
	PPARγ agonists inhibit proliferation and modulate Wnt/β-catenin mediated signaling	196

LXR		
Pathology	**Mechanism**	**Ref**
EPB defects	LXR/AP-1 crosstalk in lipid production and barrier formation	72
EPB formation	Acidification of SC	106
EPB formation	Activators stimulates lipid synthesis and processing	107
EPB formation	Regulate expression of cholesterol and water transporters	108, 109, 110, 111
Aging	Cigarette smoke inhibits LXR translocation	114
Aging	Phenotype of chronically aged skin	115
AD	LXR agonists display anti-inflammatory effects	116, 117
Psoriasis	Loss of LXRα expression stimulates psoriatic gene profile	118
Vitiligo	Increased expression in vitiligo perilesional skin	201
Melanoma	LXR ligands inhibit CCR7 expression on maturing DCs and their migration to lymphoid organs	202

TR		
Pathology	**Mechanism**	**Ref**
Alopecia	Hair follicles are direct targets of thyroid hormone	76, 77, 78
SCC	TRs inhibit tumor progression and suppress metastasis	154