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Review

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.

1. 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 [1–4]. 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. 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-

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Fig. 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.

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) [13–16], 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 [19–23]. 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 [26–30]. Corepressors comprise the N-CoR/SMRT assembly and histone deacetylases [31–34]. 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].

2. 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 [40–42]. RXRα/RARγ heterodimerizationis 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/PPARβδ heterodimers are equally important to stratum corneum homeostasis through activation of gene transcription [43].

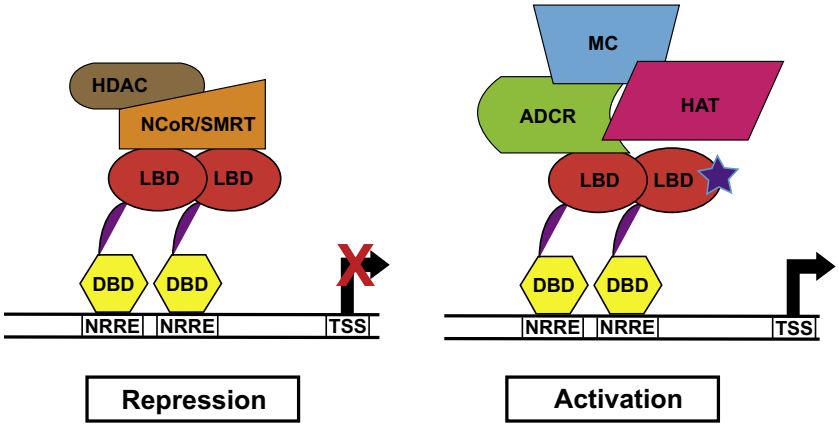

Fig. 2. Putative mechanisms of transcriptional regulation by type II nuclear receptors. Repression of gene expression by nuclear receptor heterodimers involves association with co-repressor protein complexes, including NCoR/SMRT and histone deacetylases (HDAC). Positive transactivation occurs after ligand 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.