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The significance of CYP11A1 expression in skin physiology and pathology

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Abstract

CYP11A1, a member of the cytochrome P450 family, plays several key roles in the human body. It catalyzes the first and rate-limiting step in steroidogenesis, converting cholesterol to pregnenolone. Aside from the classical steroidogenic tissues such as the adrenals, gonads and placenta, CYP11A1 has also been found in the brain, gastrointestinal tract, immune systems, and finally the skin. CYP11A1 activity in the skin is regulated predominately by StAR protein and hence cholesterol levels in the mitochondria. However, UVB, UVC, CRH, ACTH, cAMP, and cytokines IL-1, IL-6 and TNFα can also regulate its expression and activity. Indeed, CYP11A1 plays several critical roles in the skin through its initiation of local steroidogenesis and specific metabolism of vitamin D, lumisterol, and 7-dehydrocholesterol. Products of these pathways regulate the protective barrier and skin immune functions in a context-dependent fashion through interactions with a number of receptors. Disturbances in CYP11A1 activity can lead to skin pathology.

Keywords

CYP11A1; skin; skin barrier function; skin immune activity; neuroendocrine functions of the skin; corticosteroid biosynthesis; hypothalamo-pituitary adrenal axis; steroids; secosteroids; lumisterol

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1. Introduction to CYP11A1

CYP11A1, also known as cytochrome P450scc, is a member of the cytochrome P450 family of heme-containing enzymes and catalyzes the first and rate-limiting step in steroidogenesis (Goursaud et al., 2018; Miller and Auchus, 2011; Rone et al., 2012). It is located in the inner mitochondrial membrane of steroid producing cells (Goursaud et al., 2018; Strushkevich et al., 2011; Tuckey, 2005). CYP11A1 converts cholesterol to pregnenolone through three sequential hydroxylation reactions: hydroxylation at the C22 position of the cholesterol side chain to produce 22R-hydroxycholesterol, hydroxylation at C20 of 22R-hydroxycholesterol to produce 20R,22R-dihydroxycholesterol, and the subsequent oxidative cleavage of the C20-C22 bond in 20R,22R-dihydroxycholesterol to produce pregnenolone (Fig. 1). The two electrons required for each of these reactions are supplied by NADPH. They are initially transferred to the FAD-containing adrenodoxin reductase and then one at a time to the iron-sulfur protein adrenodoxin, which in turn passes them to the CYP11A1 to activate the oxygen substrate. Adrenodoxin reductase and adrenodoxin are located in the mitochondrial matrix (Miller and Auchus, 2011; Strushkevich et al., 2011; Tuckey, 2005).

It is well established that CYP11A1 is expressed at relatively high levels in the classical steroidogenic tissues such as the adrenal cortex (fasciculata, reticularis and glomerulosa zones), testis, ovary and placenta. However, CYP11A1 is also expressed at lower levels in a range of other tissues including the brain, skin, thymus, lung, and even T lymphocytes (Slominski et al., 2004a; Slominski RM et al., 2020a). CYP11A1 has been shown to function as a critical regulator of Th2 and Tc2 cell differentiation and type 2 cytokine production (Gelfand et al., 2017, Wang et al., 2020).

Although cholesterol is the major and best characterized substrate for CYP11A1, CYP11A1 also acts on a range of other sterols and secosteroids including: 7-dehydrocholesterol (7DHC), lumisterol, hydroxysterols, plant and fungal sterols such as camposterol and ergosterol, as well as vitamins D2 and D3 (Slominski et al., 2014a; 2020a; Tuckey et al., 2019). Figure 1 summarizes the various biochemical pathways in which CYP11A1 is involved. These alternative pathways appear to be important in the skin and are further discussed below.

The structure of the *CYP11A1* gene was discovered by Morohashi et al in 1987, and it was found to be at least 20 kb long with 9 exons and 8 introns (Morohashi et al., 1987). Human *CYP11A1* is located on chromosome 15q23–24 (Lara-Velazquez et al., 2017). The gene is only expressed in vertebrates, including fish, birds, amphibians, and mammals (Slominski et al., 2015a).

CYP11A1 activity is stimulated directly by ACTH, LH, and FSH and indirectly by CRH, and proinflammatory cytokines such as IL-1, Il-6, and TNF-α (Guo et al., 2007a; Guo et al., 2007b; Huang et al., 2014; Ruggiero and Lalli, 2016; Slominski et al., 2020a). The steroidogenic acute regulatory (StAR) protein mediates the transport of cholesterol from the outside of the mitochondria to the inner mitochondrial membrane (Chien et al., 207; Issop et al., 203; Manna et al., 2016). ACTH mediates its actions by binding to the melanocortin 2 receptor (MC2R), thereby stimulating adenylyl cyclase and inducing cAMP production

(Ruggiero and Lalli, 2016). Subsequently, cAMP increases the availability of cholesterol via rapid synthesis of the StAR protein and directly increases the *CYP11A1* mRNA and protein levels (Guo et al., 2007b; Miller and Auchus, 2011)

In the adrenals and gonads, *CYP11A1* transcription is regulated by a 2.3 kb promotor containing binding sites for multiple transcription factors including cAMP- response element binding proteins, steroidogenic factor 1 (SF-1), and an Sp-1 (Guo et al., 2007a; 2007b; Ruggiero and Lalli, 2016). SF-1 was discovered nearly thirty years ago by Parker and Morohashi and was shown to play a key role in the regulation of the CYP11A1 gene (Lala et al., 1992; Morohashi et al., 1992; Ruggiero and Lalli, 2016). The two cAMP-responsive sequences (CRS) in CYP11A1: P-CRS and U-CRS contain an SF-1 binding site (Guo et al., 2007a). Both SF-1 and activating protein-1 (AP-1) play a role in the activation of the *CYP11A1* gene (Guo et al., 2007a). Runx2, an osteogenic transcription factor, also plays a role in the regulation of the *CYP11A1* gene regulation (Teplyuk et al., 2009). Teplyuk et al discovered that Runx2 stimulates *CYP11A1* gene expression in osteoblasts (Teplyuk et al., 2009). 1,25$(OH)_2$D3 via binding to the VDR appears to be a negative regulator of *CYP11A1* expression in $CD8^+$ cells (Schedel et al., 2016). Whether this relationship (and hence feedback regulation) also holds for 20(OH)D3, the major product of CYP11A1 action on vitamin D3 that can similarly act through the VDR, remains to be established.

The structure of the CYP11A1 protein displays the typical P450 like folds with a heme group at the protein core (Strushkevich et al., 2011). CYP11A1 has also been found to have a monotopic association with the matrix side of the inner mitochondrial membrane that is mediated primarily via the F-G loop region (Headlam et al., 2003). This forms part of a substrate access channel permitting cholesterol to enter the active site from the membrane phase (Strushkevich et al., 2011).

The CYP11A1 enzyme plays an essential role in steroidogenesis and thus complete loss of expression is incompatible with life. Defects in CYP11A1 are one of the causes of primary adrenal insufficiency (PAI) which can range from classical PAI that is characterized by salt loosing adrenal insufficiency and gonadal insufficiency to more mild cases that present itself as glucocorticoid insufficiency (Maharaj et al., 2019). Congenital lipoid adrenal hyperplasia (CLAH) is primarily due to defects in StAR, which delivers cholesterol to the CYP11A1 in the inner mitochondrial membrane, however, mutations in the *CYP11A1* gene can also cause the disorder (Goursaud et al., 2018; al Kandari et al., 2006). A case study done by al Kandari et al found that a case of adrenal insufficiency, hypogonadism, and agenesis of the corpus callosum was due to a homozygous point mutation in the *CYP11A1* gene (al Kandari et al., 2006). Although rare, mutations in the *CYP11A1* gene can be shown to have clinically significant effects (Kim et al., 2008).

Aberrant/alternative splicing in the *CYP11A1* gene can cause a deficiency in the expression of active enzyme (Goursaud et al., 2018) or production of protein that has a lower molecular weight (MW) that appears to play a different function to the full-length enzyme (Teplyuk et al., 2009; Annalora et al., 2017). An alternatively spliced *CYP11A1* isoform has been detected in human epidermal keratinocytes and melanoma cells (Slominski et al., 2004a).

2. Skin as a stress response organ:

2.1. Overview of the skin:

The skin together with the subcutaneous adipose tissue is the largest organ in the body and plays many roles in preserving the homeostasis of the human body (Slominski et al, 2012a). These roles include, but are not limited to, acting as a physical barrier against microorganisms and physical and chemical insults, regulating body temperature, retaining body fluid, protecting against UV light, and acting as a sensory, immune, endocrine and even steroidogenic organ (Boer et al., 2016; Elias, 2012; Fuchs, 2016; Racine et al., 2020; Slominski et al., 2012a; 2015b; 2018a).

The skin is divided into three layers: the epidermis, dermis, and subcutaneous fat. The epidermis (from the external to internal layers) is subdivided into the stratum corneum, stratum lucidum (only found in thick skin), stratum granulosum, stratum spinosum, and stratum basale. The epidermis contains keratinocytes as well as Langerhans cells, Merkel cells, and melanocytes (Boer et al., 2016; Gallo and Hooper, 2012). The dermis is divided into two layers, papillary and reticular (Brown and Krishnamurthy, 2020). The reticular dermis is thicker than the papillary layer and contains hair follicles, sensory nerves, and sebaceous and sweat glands (Nguyen and Soulika, 2019). Both layers of the dermis are comprised of fibroblasts and myofibroblasts, as well as resident immune cells (Gallo and Hooper, 2012; Nguyen and Soulika, 2019). The immune cells in the dermis play an important role in both innate and adaptive immunity. Dendritic cells, macrophages, mast cells, eosinophils, innate lymphoid cells (ILC), and B and T lymphocytes have all been found in the dermis (Nguyen and Soulika, 2019).

2.2. Skin neuroendocrine system:

The concept that the skin is indeed a neuroendocrine organ was presented for the first time in 2000 (Slominski and Wortsman, 2000; Slominski et al., 2000a), and expanded on in reviews concerning cutaneous CRH signaling, cutaneous serotoninergic and melatoninergic systems, complex local and systemic responses to the UVR and microorganisms, and clinical implications of these properties (Racine et al., 2020; Ramot et al., 2020; Slominski et al., 2005a; 2013a; 2018a; 2018b; 2020b).

The hypothalamic-pituitary axis (HPA) plays a critical role in the stress response as well as being a regulator of glucocorticoid production (Chrousos, 2009). Under stressful conditions, corticotropin releasing hormone (CRH) is released from the paraventricular nucleus (PVN), moves into the anterior pituitary and binds to the type 1 CRH receptors (CRH-R1) (Hillhouse and Grammatopoulos, 2006; Slominski et al., 2001; 2013a; Turnbull and Rivier, 1999; Vale et al., 1981). CRH promotes the expression and processing of proopiomelanocortin (POMC) giving rise to ACTH, endorphins, melanotropins (MSH), and lipotropins (LPH)(Cawley et al., 2016; Slominski et al., 2000a; 2013a; Turnbull and Rivier, 1999). In the adrenal gland, ACTH binds to the melanocortin type 2 receptor (MC-2) resulting in the rapid synthesis of the StAR protein which increases the movement of cholesterol into the mitochondria, and also causes the chronic stimulation of the expression of the steroidogenic enzymes such as CYP11A1.

HPA-like axis behavior has been described in the skin (Slominski and Mihm, 1996; Slominski et al., 2007). The skin has been shown to express CRH, urocortins and CRH receptors (Ito et al., 2004; Pisarchik and Slominski, 2001; Slominski et al., 1996a; 1998a; 1999a; 2000b; 2001e; 2004b; 2006a; Zoubouliset al., 2002; Zbytek and Slominski, 2005) as well as POMC and POMC-derived peptides (Bohm et al., 2006; Luger et al., 1999; Schauer et al., 1994; Scholzen et al., 2000; Slominski, 1998; Slominski et al., 1992; 1993; 1998b) and corticosteroids (Hannen et al., 2017; Ito et al., 2005; Sarkar al., 2017; Slominski et al., 1999b; 2000c; 20002; 2005b; 2005c; 2006b; Vukelic et al., 2011). More details on CRH and POMC involvement in the cutaneous response to stress including those describing the HPA axis in the skin can be found in a number of original reviews (Slominski et al., 2006c; 2013a), with one discussing their possible origin (Slominski, 2007). The elements of CRH-POMC signaling systems can regulate CYP11A1 expression and activity in different cutaneous compartments

In addition to expressing an analog of the HPA axis, the skin plays many neuroendocrine roles (Slominski et al., 2012a). The skin has been shown to produce a number of neurohormones and precursors including catecholamines (reviewed in (Gillbro et al., 2004, Grando et al., 2006, Schallreuter, 1997, Schallreuter et al., 1995)), L-DOPA and L-tyrosine (reviewed in (Slominski et al., 2012c)), serotonin and melatonin (Slominski et al., 2005a,Slominski et al., 2018b,Slominski et al., 2020b), acetylcholine (reviewed in (Grando et al., 2006; Grando, 2006)), histamine (reviewed in (Paus et al., 2006)), cannabinoids (reviewed in (Biro et al., 2009)), and vitamin D including products form non-canonical activation pathways (reviewed in (Bikle, 2020; Bikle and Christakos 2020; Slominski et al., 2020a; 2020c)). This provides strong evidence that the skin plays a critical role in both local and systemic neuroendocrine systems with important implications for steroidogenesis.

2.3. The role of UV in the skin:

UV radiation acts as a two-edge sword in its role of regulating skin functions (Bernard et, 2019; De Silva et al., 2020; Slominski et al., 2018a; Wacker and Holick, 2013; Wondrak, 2007). It can play positive roles in the skin such as stimulating the production of antimicrobial peptides, initiating the synthesis of vitamin D (Bikle, 2011; Holick, 2003; Hong et al., 2008; Wacker and Holick, 2013), and causing the elimination of microbes such as the fungus malassezia furfur (plays a role in seborrheic dermatitis) and the bacterium streptococcus aureus (Abhimanyu and Coussens, 2017; Gontijo et al., 2006; Silva et al., 2006; Wikler et al., 1990). However, UV also stimulates the production of pro-inflammatory cytokines, produces radical oxygen species (ROS) and promotes prostaglandin E2 (PGE2) production, and in high doses damages epithelial keratinocytes in the epidermis and stimulates an inflammatory response (Abhimanyu and Coussens, 2017; Bickers and Athar, 2006; Kabashima et al., 2007). It further accelerates skin aging (Bocheva et al., 2019) and plays a critical role in DNA damage and cutaneous carcinogenesis by acting as a full carcinogen (Athar et al., 2011; Gordon-Thomson et al., 2014; Hocker and Tsao, 2007; Reichrath and Rass, 2014; Schadendorf et al., 2015, Wondrak, 2007; Yang et al., 2020). UV radiation also stimulates the local and systemic HPA axis and the production of corticosterone or cortisol in the skin (Skobowiat et al., 2013a; 2013b; 2017a; Skobowiat and

Slominski, 2015; Tiganescu, Hupe, Jiang et al., 2015). Figure 2 illustrates this concept in both human and mouse skin.

2.4. The skin immune system:

The skin contains a unique assortment of immunocompetent cells and soluble mediators that play a key role in its protective function against exogenous physical insults, microbes and toxins as well as against endogenous mutations and malignancies (Bernard et al., 2019; Xu, et al.,, 2019). In the stratum corneum of the epidermis, cornified keratinocytes known as corneocytes, contain a lipid envelope and are linked by keratin (Boer et al., 2016; Hoath and Leahy, 2003; Nguyen and Soulika, 2019). The stratum corneum has a pH of around 5.5 that makes it inhospitable to microorganisms (Schmid-Wendtner and Korting, 2006). As part of the rapid innate immune response, epidermal keratinocytes express toll-like receptors (TLRs) and cytosolic nucleotide-binding domain, leucine-rich repeat containing receptors (NLRs) that are receptors for microbial products such as lipopolysaccharides (LPS) from gram-negative bacteria, lipoteichoic acid and peptidoglycans from gram positive bacteria, mannans of yeast and fungi, and nucleic acids from pathogens and the host (McInturff et al.,, 2005; Nestle et al., 2009).

Other components of the cutaneous innate immune response in the skin are the antimicrobial peptides (Schauber and Gallo, 2008) of which cathelicidins and β-defensins are the two best characterized. They are synthesized by keratinocytes, cells of sebaceous and eccrine glands, and mast cells (Gallo and Hooper, 2012; Sanford and Gallo, 2013). The cathelicidins and defensin class of antimicrobial proteins act by disrupting the bacterial and fungal membranes, and viral envelopes (Gallo and Hooper, 2012; Ordonez et al., 2014). Cathelicidin and B-defensin expression is normally low in the skin but is markedly increased when the skin barrier is disrupted (Gallo and Hooper, 2012).

The skin is also a rich source of cytokines and chemokines, which manipulate the extent and characteristics of the immune responses qualitatively and quantitatively (Bernard et al., 2019, Xu et al., 2019; Tan et al., 2015). Cytokines and chemokines also modulate the systemic host response. Their cutaneous production involves several different cell types including keratinocytes, melanocytes, dendritic cells, fibroblasts and mast cells. While cytokines produced by skin cells have similar actions as those secreted by other cell types, they can have distinctive effects on cutaneous tissues. For example, IL-1 stimulates matrix metalloproteinase synthesis in the dermis (Schonbeck et al.,, 1998), while at the same time contributing to wound repair by augmenting collagen production.

Adaptive immunity provides antigen specific protection against intracellular and extracellular pathogens and can be both initiated and expressed in the skin (Nestle et al., 2009; Xu et al., 2019). This is accomplished primarily by a variety of T cell subsets and by IgA, IgM, and IgE antibodies (Debes and McGettigan, 2019). The T cells that carry out these defenses reside within the skin and preferentially recirculate between the skin and regional lymph nodes (Clark, 2015). T-cell mediated immunity is initiated by antigen-presenting myeloid dendritic cells (DCs). There are multiple distinct types of DCs in skin (Clausen and Kel, 2010; Henri et al., 2010). Those that reside within the epidermis are call Langerhans cells (Nguyen and Soulika, 2019; Sanford and Gallo, 2013). The diverse array

of dendritic cells enables a more precise activation of different T-cell subpopulations. Plasmacytoid dendritic cells reside within the dermis and are a potent source of the cytokine interferon-γ (Xu et al., 2019).

Although not specifically made in the skin, IgE antibodies play an important role in host defenses against parasites. IgE antibodies bind to mast cells, which express the high affinity surface receptor for IgE (Longley et al.,, 1995). As a consequence of antigen binding to IgE molecules on mast cells, degranulation occurs with the release of potent prostanoids, histamines and cytokines which help to attract additional inflammatory cells to the skin (Xu et al., 2019).

Aberrant T-cell mediated immunity can result in increased susceptibility to infections and skin cancer if the immune response underperforms, as well as to allergic and atopic dermatitis and autoimmune diseases such as psoriasis, alopecia areata and vitiligo when there is excessive activation. Increased IgE and mast cell activity is considered to be an essential element of urticaria and angioedema, atopic dermatitis, hyperimmunoglobulin E syndrome and bullous pemphigoid.

3. CYP11A1 and the skin

3.1. Classical function

It is now well established that the skin can produce cortisol which can be derived from cholesterol via a complete steroidoidogenic pathway. This starts with the StAR protein that delivers cholesterol to the inner mitochondrial membrane which is subsequently converted to pregnenolone by CYP11A1 (Slominski et al., 2004a; 2013b).The cutaneous rate of steroid synthesis is much lower than in classical steroidogenic tissues such as the adrenal cortex and placenta (Slominski et al., 2013b). Since the initial discovery of *CYP11A1* gene expression in the human skin (Slominski et al., 1996b), a number of papers have documented CYP11A1 enzyme expression in keratinocytes, melanocytes and dermal fibroblasts (Hannen et al., 2011; Skobowiat and Slominski, 2015; Skobowiat et al., 2011; 2013a; 203b; Slominski et al., 2004a; 2013b; 2017; Thiboutot et al., 2003, Tiala et al., 2007; Tongkao-On et al., 2015), as well as in immune cells (Slominski RM et al., 2020a). This indicates that a variety of cell types in the skin are potentially capable of de novo steroid synthesis. CYP11A1 plays several key roles in the skin of which the most important is that it catalyzes the conversion of cholesterol to pregnenolone, which serves as the precursor to cutaneous cortisol, estrogens, and androgens. The pregnenolone is initially converted to either progesterone by 3β-hydroxysteroid dehydrogenase (3-βHSD) or to 17β-hydropregnenolone by CYP17A1. The skin expresses all the downstream CYP enzymes required to convert the progesterone into cortisol (Slominski et al., 2013b; 2015b)(Fig. 3). The skin can also convert the 17β-hydropregnenolone into androgens and estrogens, but these can also be derived from circulating DHEA-sulfate (Nikolakis et al., 2016; Slominski et al., 2013b; 2015b)

The role of steroidogenesis in the skin includes countering the inflammatory responses in the skin and preventing hyperproliferation of keratinocytes (Bigas et al., 2018; Phan et al., 2021; Slominski and Zmijewski, 2017; Vukelic et al., 2011). In fact, dysregulation of steroid synthesis in the skin has been associated with many skin disorders (Hannen et al., 2011;

2017;Nikolakis et al., 2016; Phan et al., 2021; Ramot et al., 2020; Zmijewski, 2017; Slominski et al., 2014c; 2015b; 2017a), which are discussed further below.

3.2. Non-classical functions

CYP11A1 can also use lumisterol, vitamins D2 and D3, ergosterol and 7-DHC as substrates hydroxylating their side chain at different positions, and in some cases cleaving it (Guryev et al., 2003; Slominski et al., 2004a; 2005d; 2005e; 2006d; 2009a; 2011a; 2012c; 2012d; 2017a; Tuckey et al., 2008; 2011; 2014)(Fig. 1). It should be noted that the vitamin D3, lumisterol and tachysterol are derived from UV irradiation of 7-dehydrocholesterol in the skin (Bikle, 2020; Holick et al., 1981; Wacker and Holick, 2013). Thus, the skin is likely to be a primary site of their metabolism to biologically active hydroxyderivatives, supported by the detection of many of these metabolites in the skin (Slominski et al., 2012d; 2013b; 2015d; 2017c). The hydroxyvitamin D products act as biased agonists on the VDR displaying many but not all the effects of 1,25$(OH)_2$D3, and also act to some extent through other receptors expressed in the skin including the retinoic acid-related orphan receptors, RORα and γ (Slominski et al., 2014c; 2017b), and the aryl hydrocarbon receptor (AhR) (Slominski et al., 2018c; 2020a).

The above CYP11A1-derived vitamin D hydroxyderivatives have been proposed to play key roles in the maintenance of skin physiology. At least 10 different CYP11A1-derived vitamin D3 metabolites have been discovered with 20(OH)D3 and 20,23$(OH)_2$D3 being the major ones (Slominski et al., 2014a). In keratinocytes, 20(OH)D3 and 20,23 $(OH)_2$D3 inhibit DNA synthesis and cause cell cycle arrest. The CYP11A1-derived vitamin D hydroxyderivatives have been found to stimulate differentiation and inhibit proliferation and NF-κB activity in human keratinocytes (Chaiprasongsuk et al., 2020a; Janjetovic et al., 2009; 2010; Slominski et al., 2014a; Zbytek et al., 2008). They also show photoprotective properties which are also shared by the CYP11A1-derived hydroxylumisterols (Chaiprasongsuk et al., 2019; 2020a; 2020b; Slominski et al., 2015c; 2017c; 2020; Tongkao-On et al., 2015). Thus, products of CYP11A1 action appear to protect the skin against the harmful effects of UVR with responses that include increased expression of DNA repair enzymes (Slominski et al., 2020a). This is particularly relevant to the photoprotective properties of the hydroxylumisterols, since lumisterol is a product of excessive UV radiation (Holick et al., 1981). Furthermore, UVB is able to upregulate CYP11A1 expression (see Figure 2) which presumably results in increased CYP11A1-mediated hydroxyvitamin D3 and hydroxylumisterol production in the skin to help combat the harmful effects of radiation.

CYP11A1-derived vitamin D metabolites hold therapeutic potential. Besides their photoprotective role, they have been found to inhibit the growth of normal and malignant melanocytes and display anti-fibrotic activity on dermal fibroblasts (Slominski et al., 2011a; 2011b; 2012e; 2013c; 2013d). Treatment with the CYP11A1-derived vitamin D compounds inhibited the growth of the SKMEL-188 melanoma cells *in vivo* as well as downregulating NF-κB activity (Janjetovic et al., 2011; Skobowiat et al., 2017b). Thus, the CYP11A1-derived vitamin D compounds are candidates for the treatment of skin cancers including melanoma (Slominski et al., 2018d; 2020c). Importantly, while showing a lack of (20(OH)D3) or low (1,20$(OH)_2$D3) calcemic effects (Chen et al., 2014; Slominski et al.,

2010; 2013c, Wang et al., 2012), CYP11A1-derived secosteroids also express potent anti-inflammatory effects (Chaiprasongsuk et al., 2020b; Janjetovic et al., 2009; 2010; Lin et al., 2017; 2018; Slominski et al., 2014a; 2014c). Thus, CYP11A1 derived secosteroids are also excellent candidates for treatment of autoimmune or inflammatory disorders of different etiology (Slominski RM et al., 2020a; 2020b).

3.3. Regulation of CYP11A1 expression in the skin

The delivery of cholesterol resulting from the activity of the StAR protein appears to play the most important role in the acute regulation of CYP11A1 activity in the skin (Slominski et al., 2014a; 2014d). Other factors that regulate CYP11A1 including CRH, ACTH, POMC, cAMP, and cytokines IL-1, particularly Il-1β, IL-6, and TNF-α, are likely to operate in the skin, although more detailed studies remain to be performed. Tkachanko et al (2011) found that IL-1α and β stimulate StAR protein, CYP17A1, and 3β-hydroxysteroid dehydrogenase 2 (3βHSD2) expression at the mRNA level in adrenal cells, with increased androgen and cortisol production (Tkachenko et al., 2011). UVB and UVC have been found to stimulate CYP11A1 and cortisol production by skin; however, UVA seems to have no effect on cortisol production (Skobowiat et al., 2011a,; 2013b;). Huang et al (2014) reported that TNF-α suppresses steroidogenesis and CYP11A1 expression in intestinal epithelial cells by activating c-Jun and NF-κB (Huang et al., 2014). When the dominant-negative form of c-Jun amino-terminal kinase 1 (JNK1), an NF-κB inhibitor was injected into mice, steroidogenesis in the intestinal epithelial cells was restored (Huang et al., 2014). Toll-like receptors (TLRs), notably TLR3, can play a role in the regulation of steroidogenesis in the skin. Shimada-Omori et al found that Polyinosinic:polycytidylic acid (Poly(I:C)), a known ligand for TLR3, stimulates glucocorticoid production and CYP11A1 expression in rosacea epidermis (Shimada et al., 2020). Also, other environmental stressors leading to barrier disruption can stimulate epidermal cortisol production (Takei et al., 2013; Zhu et al., 2014).

3.4. CYP11A1 in pathological skin or skin tumors

The synthesis of CYP11A1-derived steroids is a two-edged sword. Although they can play a positive role in maintaining homeostasis, some can also play an enhancing role in certain pathologies. Figure 4 illustrates this concept. CYP11A1 can also be used as an indicator of autoimmune diseases (Slominski RM et al., 2020a). Its expression is decreased in both atopic dermatitis and psoriasis (Hannen et al., 2011; 2017). Metabolomic and transcriptomic profiling of psoriatic skin vs healthy control revealed that deficiencies in cortisol and cortisone production in the psoriatic skin lesions could lead to production of proinflammatory cytokines (Sarkar et al., 2017). These findings support our previous theory that deficient feedback of POMC and glucocorticoids on cutaneous immunity contributes to inflammatory and autoimmune dermatoses, and that restoration of these endogenous deficiencies represents a realistic goal in treating psoriasis and inflammatory disorders (Slominski, 2009; 2013a; 2017a).

CYP11A1 as well as other CYP enzymes can play a role in skin cancer. CYPs such as CYP1A1, CYP1B1, CYP2B6, CYP2E1, and CYP3A5, have been found in keratinocytes (Baronet al., 2001). Keratinocytes play an important role in the most common types of skin neoplasms, such as basal and squamous cell carcinomas (Ratushny et al., 2012; Slominski et

al., 2014d). CYPs in keratinocytes metabolize hazardous materials and carcinogens (Slominski et al., 2014d). Cortisol and cortisone immunosuppression can cause progression of basal and squamous cell carcinoma. However, corticosteroids can inhibit melanoma directly (Horn and Buzard, 1981) or indirectly by inhibiting the production of POMC or NF-κB activity (Bohm et al., 2006; Slominski et al., 2014d). Normal melanocytes and melanoma cells can produce their own cortisol and corticosteroids (Fig 3) (Slominski et al., 1999b;, 2005b; 2005c). This can lead to local immunosuppression allowing tumor cells to escape from immune attack leading to tumor growth and melanoma progression (Slominski and Carlson, 2014). This concept appears to be supported by in vivo experiments in hamsters showing that adrenalectomy significantly inhibited melanoma growth, while use of a synthetic glucocorticoid accelerated it (Stanberry et al., 1982).

Some of the immune cells residing in the skin can affect tumor behavior. Mahata et al used two groups of transgenic mice, mCherry (florescence reporter line) and a conditional CYP11A1 knockout, to prove that T cell steroid biosynthesis could aid tumor growth and progression, and that targeting the rate limiting steps in the steroid synthesis of T cells can prevent tumor metastasis, particularly melanoma (Mahata et al., 2020).

Changes in CYP11A1 levels in cancer tissues relative to normal tissue have been found at several sites in the body. CYP11A1 expression was downregulated in 6 different cancer types, colon adenocarcinoma, kidney renal clear cell carcinoma, liver hepatocellular carcinoma, lung squamous cell carcinoma, prostate adenocarcinoma, and uterine corpus endometrial carcinoma (Fan et al., 2016). In addition, CYP11A1 is expressed in many tumor lines of different lineage including melanomas (Slominski et al., 1996b; 2004a; 2012e; 2014d).

Other steroidogenic enzymes can also contribute to the behavior of skin cancer. Levels of mRNA for 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 (produces cortisol) and 2 (deactivates cortisol) vary between healthy and malignant tissues (Cirillo et al., 2017). Squamous cell carcinoma (SCC) samples showed significantly lower expression of 11β-HSD2 than healthy control cells (Cirillo et al., 2017).

4. Role of steroid signaling in skin physiology and pathology

4.1 Glucocorticoid and mineralocorticoid signaling

Corticosteroids produced endogenously by the skin can affect various signaling pathways. For example, corticosteroids have been shown to influence NF-κB and AP-1, and STAT3 signaling pathways (Sevilla and Perez, 2018). Corticosteroids can also affect gene expression in the skin. Lili et al has found that the synthetic glucocorticoid, clobetasol, upregulates 1607 genes and downregulate 1917 genes from RNA sequencing analysis (Lili et al., 2019). They also found that when given clobetasol, glucocorticoid receptor (GR) targets such as GILZ were more active in African Americans, while females have a stronger shift towards the IFN-α /IFN-γ and IL-6/Jak/STAT3 signaling pathway, which is pro-inflammatory (Lili et al., 2019). Glucocorticoids have been found to activate REDD1, a mTOR inhibitor (Baida et al., 2015). REDD1 mediates many of the adverse effects of glucocorticoids including skin atrophy. Mice that were KO for REDD1 maintained many of

the anti-inflammatory effects of glucocorticoids (Baida et al., 2015). Most recent studies show that keratinocytes control skin immune homeostasis through de novo-synthesized glucocorticoids (Phan et al, 2021).

Many of the actions of glucocorticoids in the skin are mediated by the GR expressed in different cutaneous compartments and involve different mechanisms of action (Aberg et al., 2007; Baida et al., 2015; Chebotaev, Yemelyanov et al., 2007, Jozic et al., 2017; Lili et al., 2019; Nikolakis et al., 2016; Sarkar et al., 2017; Sevilla and Perez, 2018; Slominski and Zmijewski, 2017; Slominski et al., 2017a). Mice in which GR and MC were partially knocked out exhibited more severe inflammation and hyperproliferation of the skin after imiquimod treatment when compared to healthy controls (Bigas et al., 2018). The GR also plays many important roles in skin development. Immunohistostaining on mice embryos that had the GR gene completely knocked out (GR−/−) showed that the skin of these mice had incomplete epidermal stratification as well as significantly less fillagrin and desmosomes, thus incompatible with life (Bayo et al., 2008). In addition, non-genomic actions of GR in the skin have been described concerning the inhibition of wound healing (Jozic et al., 2017; Slominski and Zmijewski, 2017).

Mineralocorticoids mediate their signaling action through the mineralocorticoid receptor (MR). MR antagonism can help counter some of the effects of glucocorticoid-induced skin atrophy and delayed wound healing (Maubec et al., 2015; Nguyen et al., 2016; Stojadinovic et al., 2016). Mice that overexpress MR show skin atrophy and alopecia (Sainte Marie et al., 2007). Thus, research on both GR and MR may yield promising new therapies for treating various skin ailments.

4.2 Estrogen and Androgen signaling

There are two major types of estrogen receptors that have been discovered, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) (Bakry et al., 2014,; Cutolo and Straub, 2020; Hall and Phillips, 2005; Ohnemus et al., 2006; Thornton et al., 2003), with ERβ playing a more important role in the skin (Ahn et al., 2020; Thornton et al., 2003). ERα is barely detectable in the skin, while ERβ was found in the sebaceous glands, hair follicles, epidermis, and dermal fibroblasts (Thornton et al., 2003). Estrogens play several key roles in the skin which include acting as a regulator of the immune system (Cutolo and Straub, 2020; Ohnemus et al., 2006), increasing collagen production in the skin and modulating hair growth (Ohnemus et al., 2006). Patients with estrogen deprivation have symptoms that include dryness, atrophy and wrinkling of the skin, as well as delayed wound healing (Hall and Phillips, 2005). Most recent studies show that photoprotective responses to $1,25(OH)_2D3$ in mice are modulated by the estrogen receptor-β (Tonkgao-on et al., 2021).

Two androgen receptor (AR) isoforms have been identified, AR A and AB (Liegibel et al., 2003). ARs are expressed in epidermal and follicular keratinocytes and melanocytes, dermal fibroblasts, vascular endothelium, and dermal papilla cells (DPC) in hair follicles (Ceruti et al.,, 2018; Chang et al., 2013). Androgens play many roles in skin disorders such as acne, androgenic alopecia, and delayed wound healing (Lai et al., 2012). In castrated mice, accelerated wound healing and decreased inflammation were observed compared to control mice (Ashcroft and Mills, 2002). Thus, androgens show the opposite effect to estrogens and

delay wound healing (Lai et al., 2012). Further research into the role of androgens and estrogens in the skin could pay dividends for treating skin disorders.

5. Conclusions and future directions.

CYP11A1 plays many important roles in maintaining the physiology of the body. It catalyzes the first and rate-determining step in steroidogenesis, the conversion of cholesterol to pregnenolone. It is involved in the production of steroids such as cortisol, pregnenolone, estrogens and androgens. Local production of corticosteroids in the skin, initiated by CYP11A1, appears to play important roles in skin physiology and pathology. CYP11A1 can also metabolize vitamin D and lumisterol into non-calcemic hydroxymetabolites which have potential therapeutic benefits. These reactions appear to occur in the skin, which has a high concentration of these UV-derived substrates, but their exact physiological roles remains to be further investigated. Additional research into cutaneous CYP11A1 derived steroids and secosteroids and their biological effects may yield future therapies for many dermatological and systemic diseases.

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7. References

Aberg KM, Radek KA, Choi EH, Kim DK, Demerjian M, Hupe M, Kerbleski J, Gallo RL, Ganz T, Mauro T, Feingold KR and Elias PM, 2007. Psychological stress downregulates epidermal antimicrobial peptide expression and increases severity of cutaneous infections in mice, J Clin Invest. 117, 3339–49. [PubMed: 17975669]

Abhimanyu and Coussens AK, 2017. The role of UV radiation and vitamin D in the seasonality and outcomes of infectious disease, Photochem Photobiol Sci. 16, 314–338. [PubMed: 28078341]

Ahn S, Chantre CO, Ardona HAM, Gonzalez GM, Campbell PH and Parker KK, 2020. Biomimetic and estrogenic fibers promote tissue repair in mice and human skin via estrogen receptor beta, Biomaterials. 255, 120149. [PubMed: 32521331]

al Kandari H, Katsumata N, Alexander S and Rasoul MA, 2006. Homozygous mutation of P450 side-chain cleavage enzyme gene (CYP11A1) in 46, XY patient with adrenal insufficiency, complete sex reversal, and agenesis of corpus callosum, J Clin Endocrinol Metab. 91, 2821–6. [PubMed: 16705068]

Annalora AJ, Marcus CB and Iversen PL, 2017. Alternative Splicing in the Cytochrome P450 Superfamily Expands Protein Diversity to Augment Gene Function and Redirect Human Drug Metabolism, Drug Metab Dispos. 45, 375–389. [PubMed: 28188297]

Ashcroft GS and Mills SJ, 2002. Androgen receptor-mediated inhibition of cutaneous wound healing, J Clin Invest. 110, 615–24. [PubMed: 12208862]

Athar M, Walsh SB, Kopelovich L and Elmets CA, 2011. Pathogenesis of nonmelanoma skin cancers in organ transplant recipients, Arch Biochem Biophys. 508, 159–63. [PubMed: 21232524]

Baida G, Bhalla P, Kirsanov K, Lesovaya E, Yakubovskaya M, Yuen K, Guo S, Lavker RM, Readhead B, Dudley JT and Budunova I, 2015. REDD1 functions at the crossroads between the therapeutic and adverse effects of topical glucocorticoids, EMBO Mol Med. 7, 42–58. [PubMed: 25504525]

Bakry OA, Samaka RM, Shoeib MA and Maher A, 2014. Immunolocalization of androgen receptor and estrogen receptors in skin tags, Ultrastruct Pathol. 38, 344–57. [PubMed: 24830664]

Baron JM, Holler D, Schiffer R, Frankenberg S, Neis M, Merk HF and Jugert FK, 2001. Expression of multiple cytochrome p450 enzymes and multidrug resistance-associated transport proteins in human skin keratinocytes, J Invest Dermatol. 116, 541–8. [PubMed: 11286621]

Bayo P, Sanchis A, Bravo A, Cascallana JL, Buder K, Tuckermann J, Schutz G and Perez P, 2008. Glucocorticoid receptor is required for skin barrier competence, Endocrinology. 149, 1377–88. [PubMed: 18039792]

Bernard JJ, Gallo RL and Krutmann J, 2019. Photoimmunology: how ultraviolet radiation affects the immune system, Nat Rev Immunol. 19, 688–701. [PubMed: 31213673]

Bickers DR and Athar M, 2006. Oxidative stress in the pathogenesis of skin disease, J Invest Dermatol. 126, 2565–75. [PubMed: 17108903]

Bigas J, Sevilla LM, Carceller E, Boix J and Perez P, 2018. Epidermal glucocorticoid and mineralocorticoid receptors act cooperatively to regulate epidermal development and counteract skin inflammation, Cell Death Dis. 9, 588. [PubMed: 29789551]

Bikle D and Christakos S, 2020. New aspects of vitamin D metabolism and action - addressing the skin as source and target, Nat Rev Endocrinol.

Bikle DD, 2011. Vitamin D: an ancient hormone, Exp Dermatol. 20, 7–13. [PubMed: 21197695]

Bikle DD, 2020. Vitamin D: Newer Concepts of Its Metabolism and Function at the Basic and Clinical Level, J Endocr Soc. 4, bvz038. [PubMed: 32051922]

Biro T, Toth BI, Hasko G, Paus R and Pacher P, 2009. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities, Trends Pharmacol Sci. 30, 411–20. [PubMed: 19608284]

Bocheva G, Slominski RM and Slominski AT, 2019. Neuroendocrine Aspects of Skin Aging, Int J Mol Sci. 20.

Boer M, Duchnik E, Maleszka R and Marchlewicz M, 2016. Structural and biophysical characteristics of human skin in maintaining proper epidermal barrier function, Postepy Dermatol Alergol. 33, 1–5. [PubMed: 26985171]

Bohm M, Luger TA, Tobin DJ and Garcia-Borron JC, 2006. Melanocortin receptor ligands: new horizons for skin biology and clinical dermatology, J Invest Dermatol. 126, 1966–75. [PubMed: 16912693]

Brown TM and Krishnamurthy K, 2020. Histology, Dermis, StatPearls. Treasure Island (FL).

Cawley NX, Li Z and Loh YP, 2016. 60 YEARS OF POMC: Biosynthesis, trafficking, and secretion of pro-opiomelanocortin-derived peptides, J Mol Endocrinol. 56, T77–97. [PubMed: 26880796]

Ceruti JM, Leiros GJ and Balana ME, 2018. Androgens and androgen receptor action in skin and hair follicles, Mol Cell Endocrinol. 465, 122–133. [PubMed: 28912032]

Chaiprasongsuk A, Janjetovic Z, Kim TK, Jarrett SG, D'Orazio JA, Holick MF, Tang EKY, Tuckey RC, Panich U, Li W and Slominski AT, 2019. Protective effects of novel derivatives of vitamin D3 and lumisterol against UVB-induced damage in human keratinocytes involve activation of Nrf2 and p53 defense mechanisms, Redox Biol. 24, 101206. [PubMed: 31039479]

Chaiprasongsuk A, Janjetovic Z, Kim TK, Tuckey RC, Li W, Raman C, Panich U and Slominski AT, 2020a. CYP11A1-derived vitamin D3 products protect against UVB-induced inflammation and promote keratinocytes differentiation, Free Radic Biol Med. 155, 87–98. [PubMed: 32447000]

Chaiprasongsuk A, Janjetovic Z, Kim TK, Schwartz CJ, Tuckey RC, Tang EKY Raman C, Panich C, and Slominski AT, 2020b. Hydroxylumisterols, photoproducts of pre-vitamin D3, protect human keratinocytes against UVB-induced damage, Int J Mol Sci 21(24).

Chang C, Yeh S, Lee SO and Chang TM, 2013. Androgen receptor (AR) pathophysiological roles in androgen-related diseases in skin, bone/muscle, metabolic syndrome and neuron/immune systems: lessons learned from mice lacking AR in specific cells, Nucl Recept Signal. 11, e001. [PubMed: 24653668]

Chebotaev D, Yemelyanov A, Zhu L, Lavker RM and Budunova I, 2007. The tumor suppressor effect of the glucocorticoid receptor in skin is mediated via its effect on follicular epithelial stem cells, Oncogene. 26, 3060–8. [PubMed: 17146443]

Chen J, Wang J, Kim TK, Tieu EW, Tang EK, Lin Z, Kovacic D, Miller DD, Postlethwaite A, Tuckey RC, Slominski AT and Li W, 2014. Novel vitamin D analogs as potential therapeutics: metabolism,

toxicity profiling, and antiproliferative activity, Anticancer Res. 34, 2153–63. [PubMed: 24778017]

Chien Y, Rosal K and Chung BC, 2017. Function of CYP11A1 in the mitochondria, Mol Cell Endocrinol. 441, 55–61. [PubMed: 27815210]

Chrousos GP, 2009. Stress and disorders of the stress system, Nat Rev Endocrinol. 5, 374–81. [PubMed: 19488073]

Cirillo N, Morgan DJ, Pedicillo MC, Celentano A, Lo Muzio L, McCullough MJ and Prime SS, 2017. Characterisation of the cancer-associated glucocorticoid system: key role of 11beta-hydroxysteroid dehydrogenase type 2, Br J Cancer. 117, 984–993. [PubMed: 28797028]

Clark RA, 2015. Resident memory T cells in human health and disease, Sci Transl Med. 7, 269rv1.

Clausen BE and Kel JM, 2010. Langerhans cells: critical regulators of skin immunity?, Immunology and cell biology. 88, 351–60. [PubMed: 20351747]

Cutolo M and Straub RH, 2020. Sex steroids and autoimmune rheumatic diseases: state of the art, Nat Rev Rheumatol. 16, 628–644. [PubMed: 33009519]

De Silva WGM, Abboud M, Yang C, Dixon KM, Rybchyn MS and Mason RS, 2020. Protection from Ultraviolet Damage and Photocarcinogenesis by Vitamin D Compounds, Adv Exp Med Biol. 1268, 227–253. [PubMed: 32918222]

Debes GF and McGettigan SE, 2019. Skin-Associated B Cells in Health and Inflammation, J Immunol. 202, 1659–1666. [PubMed: 30833422]

Elias PM, 2012. Structure and function of the stratum corneum extracellular matrix, J Invest Dermatol. 132, 2131–3. [PubMed: 22895445]

Fan Z, Wang Z, Chen W, Cao Z and Li Y, 2016. Association between the CYP11 family and six cancer types, Oncol Lett. 12, 35–40. [PubMed: 27347096]

Fuchs E, 2016. Epithelial Skin Biology: Three Decades of Developmental Biology, a Hundred Questions Answered and a Thousand New Ones to Address, Curr Top Dev Biol. 116, 357–74. [PubMed: 26970628]

Gallo RL and Hooper LV, 2012. Epithelial antimicrobial defence of the skin and intestine, Nat Rev Immunol. 12, 503–16. [PubMed: 22728527]

Gelfand EW, Joetham A, Wang M, Takeda K and Schedel M, 2017. Spectrum of T-lymphocyte activities regulating allergic lung inflammation, Immunol Rev. 278, 63–86. [PubMed: 28658551]

Gillbro JM, Marles LK, Hibberts NA and Schallreuter KU, 2004. Autocrine catecholamine biosynthesis and the beta-adrenoceptor signal promote pigmentation in human epidermal melanocytes, J Invest Dermatol. 123, 346–53. [PubMed: 15245435]

Gordon-Thomson C, Tongkao-on W, Song EJ, Carter SE, Dixon KM and Mason RS, 2014. Protection from ultraviolet damage and photocarcinogenesis by vitamin D compounds, Adv Exp Med Biol. 810, 303–28. [PubMed: 25207373]

Goursaud C, Mallet D, Janin A, Menassa R, Tardy-Guidollet V, Russo G, Lienhardt-Roussie A, Lecointre C, Plotton I, Morel Y and Roucher-Boulez F, 2018. Aberrant Splicing Is the Pathogenicity Mechanism of the p.Glu314Lys Variant in CYP11A1 Gene, Front Endocrinol (Lausanne). 9, 491. [PubMed: 30233493]

Grando SA, 2006. Cholinergic control of epidermal cohesion, Exp Dermatol. 15, 265–82. [PubMed: 16512874]

Grando SA, Pittelkow MR and Schallreuter KU, 2006. Adrenergic and cholinergic control in the biology of epidermis: physiological and clinical significance, J Invest Dermatol. 126, 1948–65. [PubMed: 16912692]

Guo IC, Huang CY, Wang CK and Chung BC, 2007a. Activating protein-1 cooperates with steroidogenic factor-1 to regulate 3',5'-cyclic adenosine 5'-monophosphate-dependent human CYP11A1 transcription in vitro and in vivo, Endocrinology. 148, 1804–12. [PubMed: 17218410]

Guo IC, Shih MC, Lan HC, Hsu NC, Hu MC and Chung BC, 2007b. Transcriptional regulation of human CYP11A1 in gonads and adrenals, J Biomed Sci. 14, 509–15. [PubMed: 17594537]

Guryev O, Carvalho RA, Usanov S, Gilep A and Estabrook RW, 2003. A pathway for the metabolism of vitamin D3: unique hydroxylated metabolites formed during catalysis with cytochrome P450scc (CYP11A1), Proc Natl Acad Sci U S A. 100, 14754–9. [PubMed: 14657394]

Hall G and Phillips TJ, 2005. Estrogen and skin: the effects of estrogen, menopause, and hormone replacement therapy on the skin, J Am Acad Dermatol. 53, 555–68; quiz 569–72. [PubMed: 16198774]

Hannen R, Udeh-Momoh C, Upton J, Wright M, Michael A, Gulati A, Rajpopat S, Clayton N, Halsall D, Burrin J, Flower R, Sevilla L, Latorre V, Frame J, Lightman S, Perez P and Philpott M, 2017. Dysfunctional Skin-Derived Glucocorticoid Synthesis Is a Pathogenic Mechanism of Psoriasis, J Invest Dermatol. 137, 1630–1637. [PubMed: 28359725]

Hannen RF, Michael AE, Jaulim A, Bhogal R, Burrin JM and Philpott MP, 2011. Steroid synthesis by primary human keratinocytes; implications for skin disease, Biochem Biophys Res Commun. 404, 62–7. [PubMed: 21094146]

Headlam MJ, Wilce MC and Tuckey RC, 2003. The F-G loop region of cytochrome P450scc (CYP11A1) interacts with the phospholipid membrane, Biochim Biophys Acta. 1617, 96–108. [PubMed: 14637024]

Henri S, Guilliams M, Poulin LF, Tamoutounour S, Ardouin L, Dalod M and Malissen B, 2010. Disentangling the complexity of the skin dendritic cell network, Immunology and cell biology. 88, 366–75. [PubMed: 20231850]

Hillhouse EW and Grammatopoulos DK, 2006. The molecular mechanisms underlying the regulation of the biological activity of corticotropin-releasing hormone receptors: implications for physiology and pathophysiology, Endocr Rev. 27, 260–86. [PubMed: 16484629]

Hoath SB and Leahy DG, 2003. The organization of human epidermis: functional epidermal units and phi proportionality, J Invest Dermatol. 121, 1440–6. [PubMed: 14675195]

Hocker T and Tsao H, 2007. Ultraviolet radiation and melanoma: a systematic review and analysis of reported sequence variants, Hum Mutat. 28, 578–88. [PubMed: 17295241]

Holick MF, 2003. Vitamin D: A millenium perspective, J Cell Biochem. 88, 296–307. [PubMed: 12520530]

Holick MF, MacLaughlin JA and Doppelt SH, 1981. Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator, Science. 211, 590–3. [PubMed: 6256855]

Hong SP, Kim MJ, Jung MY, Jeon H, Goo J, Ahn SK, Lee SH, Elias PM and Choi EH, 2008. Biopositive effects of low-dose UVB on epidermis: coordinate upregulation of antimicrobial peptides and permeability barrier reinforcement, J Invest Dermatol. 128, 2880–7. [PubMed: 18580964]

Horn D and Buzard RL, 1981. Growth inhibition by glucocorticoids in RPMI 3460 melanoma cells, Cancer Res. 41, 3155–60. [PubMed: 7248973]

Huang SC, Lee CT and Chung BC, 2014. Tumor necrosis factor suppresses NR5A2 activity and intestinal glucocorticoid synthesis to sustain chronic colitis, Sci Signal. 7, ra20. [PubMed: 24570488]

Issop L, Rone MB and Papadopoulos V, 2013. Organelle plasticity and interactions in cholesterol transport and steroid biosynthesis, Mol Cell Endocrinol. 371, 34–46. [PubMed: 23246788]

Ito N, Ito T, Betterman A and Paus R, 2004. The human hair bulb is a source and target of CRH, J Invest Dermatol. 122, 235–7. [PubMed: 14962114]

Ito N, Ito T, Kromminga A, Bettermann A, Takigawa M, Kees F, Straub RH and Paus R, 2005. Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol, FASEB J. 19, 1332–4. [PubMed: 15946990]

Janjetovic Z, Zmijewski MA, Tuckey RC, DeLeon DA, Nguyen MN, Pfeffer LM and Slominski AT, 2009. 20-Hydroxycholecalciferol, product of vitamin D3 hydroxylation by P450scc, decreases NF-kappaB activity by increasing IkappaB alpha levels in human keratinocytes, PLoS One. 4, e5988. [PubMed: 19543524]

Janjetovic Z, Tuckey RC, Nguyen MN, Thorpe EM Jr. and Slominski AT, 2010. 20,23-dihydroxyvitamin D3, novel P450scc product, stimulates differentiation and inhibits proliferation and NF-kappaB activity in human keratinocytes, J Cell Physiol. 223, 36–48. [PubMed: 20020487]

Janjetovic Z, Brozyna AA, Tuckey RC, Kim TK, Nguyen MN, Jozwicki W, Pfeffer SR, Pfeffer LM and Slominski AT, 2011. High basal NF-kappaB activity in nonpigmented melanoma cells is

associated with an enhanced sensitivity to vitamin D3 derivatives, Br J Cancer. 105, 1874–84. [PubMed: 22095230]

Jozic I, Vukelic S, Stojadinovic O, Liang L, Ramirez HA, Pastar I and Tomic Canic M, 2017. Stress Signals, Mediated by Membranous Glucocorticoid Receptor, Activate PLC/PKC/GSK-3beta/beta-catenin Pathway to Inhibit Wound Closure, J Invest Dermatol. 137, 1144–1154. [PubMed: 28017831]

Kabashima K, Nagamachi M, Honda T, Nishigori C, Miyachi Y, Tokura Y and Narumiya S, 2007. Prostaglandin E2 is required for ultraviolet B-induced skin inflammation via EP2 and EP4 receptors, Lab Invest. 87, 49–55. [PubMed: 17075575]

Kim CJ, Lin L, Huang N, Quigley CA, AvRuskin TW, Achermann JC and Miller WL, 2008. Severe combined adrenal and gonadal deficiency caused by novel mutations in the cholesterol side chain cleavage enzyme, P450scc, J Clin Endocrinol Metab. 93, 696–702. [PubMed: 18182448]

Lai JJ, Chang P, Lai KP, Chen L and Chang C, 2012. The role of androgen and androgen receptor in skin-related disorders, Arch Dermatol Res. 304, 499–510. [PubMed: 22829074]

Lala DS, Rice DA and Parker KL, 1992. Steroidogenic factor I, a key regulator of steroidogenic enzyme expression, is the mouse homolog of fushi tarazu-factor I, Mol Endocrinol. 6, 1249–58. [PubMed: 1406703]

Lara-Velazquez M, Perdomo-Pantoja A, Blackburn PR, Gass JM, Caulfield TR and Atwal PS, 2017. A novel splice site variant in CYP11A1 in trans with the p.E314K variant in a male patient with congenital adrenal insufficiency, Mol Genet Genomic Med. 5, 781–787. [PubMed: 29178636]

Lee-Robichaud P, Wright JN, Akhtar ME and Akhtar M, 1995. Modulation of the activity of human 17 alpha-hydroxylase-17,20-lyase (CYP17) by cytochrome b5: endocrinological and mechanistic implications, Biochem J. 308 (Pt 3), 901–8. [PubMed: 8948449]

Liegibel UM, Sommer U, Boercsoek I, Hilscher U, Bierhaus A, Schweikert HU, Nawroth P and Kasperk C, 2003. Androgen receptor isoforms AR-A and AR-B display functional differences in cultured human bone cells and genital skin fibroblasts, Steroids. 68, 1179–87. [PubMed: 14643880]

Lili LN, Klopot A, Readhead B, Baida G, Dudley JT and Budunova I, 2019. Transcriptomic Network Interactions in Human Skin Treated with Topical Glucocorticoid Clobetasol Propionate, J Invest Dermatol. 139, 2281–2291. [PubMed: 31247200]

Lin Z, Chen H, Belorusova AY, Bollinger JC, Tang EKY, Janjetovic Z, Kim TK, Wu Z, Miller DD, Slominski AT, Postlethwaite AE, Tuckey RC, Rochel N and Li W, 2017. 1alpha,20S-Dihydroxyvitamin D3 Interacts with Vitamin D Receptor: Crystal Structure and Route of Chemical Synthesis, Sci Rep. 7, 10193. [PubMed: 28860545]

Lin Z, Marepally SR, Goh ESY, Cheng CYS, Janjetovic Z, Kim TK, Miller DD, Postlethwaite AE, Slominski AT, Tuckey RC, Peluso-Iltis C, Rochel N and Li W, 2018. Investigation of 20S-hydroxyvitamin D3 analogs and their 1alpha-OH derivatives as potent vitamin D receptor agonists with anti-inflammatory activities, Sci Rep. 8, 1478. [PubMed: 29367669]

Longley J, Duffy TP and Kohn S, 1995. The mast cell and mast cell disease, Journal of the American Academy of Dermatology. 32, 545–61; quiz 562–4. [PubMed: 7896943]

Luger T, Paus R, Lipton J and Slominski A, 1999. Cutaneous Neuromodulation: the Proopiomelanocortin System, Ann NY Acad Sci. 885, 1–479. [PubMed: 10816638]

Maharaj A, Buonocore F, Meimaridou E, Ruiz-Babot G, Guasti L, Peng HM, Capper CP, Burgos-Tirado N, Prasad R, Hughes CR, Maudhoo A, Crowne E, Cheetham TD, Brain CE, Suntharalingham JP, Striglioni N, Yuksel B, Gurbuz F, Gupta S, Lindsay R, Couch R, Spoudeas HA, Guran T, Johnson S, Fowler DJ, Conwell LS, McInerney-Leo AM, Drui D, Cariou B, Lopez-Siguero JP, Harris M, Duncan EL, Hindmarsh PC, Auchus RJ, Donaldson MD, Achermann JC and Metherell LA, 2019. Predicted Benign and Synonymous Variants in CYP11A1 Cause Primary Adrenal Insufficiency Through Missplicing, J Endocr Soc. 3, 201–221. [PubMed: 30620006]

Mahata B, Pramanik J, van der Weyden L, Polanski K, Kar G, Riedel A, Chen X, Fonseca NA, Kundu K, Campos LS, Ryder E, Duddy G, Walczak I, Okkenhaug K, Adams DJ, Shields JD and Teichmann SA, 2020. Tumors induce de novo steroid biosynthesis in T cells to evade immunity, Nat Commun. 11, 3588. [PubMed: 32680985]

Manna PR, Stetson CL, Slominski AT and Pruitt K, 2016. Role of the steroidogenic acute regulatory protein in health and disease, Endocrine. 51, 7–21. [PubMed: 26271515]

Maubec E, Laouenan C, Deschamps L, Nguyen VT, Scheer-Senyarich I, Wackenheim-Jacobs AC, Steff M, Duhamel S, Tubiana S, Brahimi N, Leclerc-Mercier S, Crickx B, Perret C, Aractingi S, Escoubet B, Duval X, Arnaud P, Jaisser F, Mentre F and Farman N, 2015. Topical Mineralocorticoid Receptor Blockade Limits Glucocorticoid-Induced Epidermal Atrophy in Human Skin, J Invest Dermatol. 135, 1781–1789. [PubMed: 25668238]

McInturff JE, Modlin RL and Kim J, 2005. The role of toll-like receptors in the pathogenesis and treatment of dermatological disease, The Journal of investigative dermatology. 125, 1–8. [PubMed: 15982296]

Miller WL and Auchus RJ, 2011. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders, Endocr Rev. 32, 81–151. [PubMed: 21051590]

Miller WL, 2013. Steroid hormone synthesis in mitochondria, Mol Cell Endocrinol. 379, 62–73. [PubMed: 23628605]

Morohashi K, Honda S, Inomata Y, Handa H and Omura T, 1992. A common trans-acting factor, Ad4-binding protein, to the promoters of steroidogenic P-450s, J Biol Chem. 267, 17913–9. [PubMed: 1517227]

Morohashi K, Sogawa K, Omura T and Fujii-Kuriyama Y, 1987. Gene structure of human cytochrome P-450(SCC), cholesterol desmolase, J Biochem. 101, 879–87. [PubMed: 3038854]

Nestle FO, Di Meglio P, Qin JZ and Nickoloff BJ, 2009. Skin immune sentinels in health and disease, Nature reviews. Immunology. 9, 679–91.

Nguyen AV and Soulika AM, 2019. The Dynamics of the Skin's Immune System, Int J Mol Sci. 20.

Nguyen VT, Farman N, Maubec E, Nassar D, Desposito D, Waeckel L, Aractingi S and Jaisser F, 2016. Re-Epithelialization of Pathological Cutaneous Wounds Is Improved by Local Mineralocorticoid Receptor Antagonism, J Invest Dermatol. 136, 2080–2089. [PubMed: 27262545]

Nikolakis G, Stratakis CA, Kanaki T, Slominski A and Zouboulis CC, 2016. Skin steroidogenesis in health and disease, Rev Endocr Metab Disord. 17, 247–258. [PubMed: 27761789]

Ohnemus U, Uenalan M, Inzunza J, Gustafsson JA and Paus R, 2006. The hair follicle as an estrogen target and source, Endocr Rev. 27, 677–706. [PubMed: 16877675]

Ordonez SR, Amarullah IH, Wubbolts RW, Veldhuizen EJ and Haagsman HP, 2014. Fungicidal mechanisms of cathelicidins LL-37 and CATH-2 revealed by live-cell imaging, Antimicrob Agents Chemother. 58, 2240–8. [PubMed: 24492359]

Paus R, Theoharides TC and Arck PC, 2006. Neuroimmunoendocrine circuitry of the 'brain-skin connection', Trends Immunol. 27, 32–9. [PubMed: 16269267]

Phan TS, Schink L, Mann J, Merk VM, Zwicky P, Mundt S, Simon D, Kulms D, Abraham S, Legler DF, Noti M and Brunner T, 2021. Keratinocytes control skin immune homeostasis through de novo-synthesized glucocorticoids, Sci Adv. 7, doi: 10.1126/sciadv.abe0337.

Pisarchik A and Slominski AT, 2001. Alternative splicing of CRH-R1 receptors in human and mouse skin: identification of new variants and their differential expression, FASEB J. 15, 2754–6. [PubMed: 11606483]

Racine P-J, Janvier X, Clabaut M, Catovic C, Souak D, Boukerb AM, Groboillot A, Konto-Ghiorghi Y, Duclairoir-Poc C, Lesouhaitier O, Orange N, Chevalier S and Feuilloley MGJ, 2020. Dialog between skin and its microbiota: Emergence of "Cutaneous Bacterial Endocrinology", Experimental Dermatology. doi.org/10.1111/exd.14158

Ramot Y, Bohm M and Paus R, 2020. Translational Neuroendocrinology of Human Skin: Concepts and Perspectives, Trends Mol Med.

Ratushny V, Gober MD, Hick R, Ridky TW and Seykora JT, 2012. From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma, J Clin Invest. 122, 464–72. [PubMed: 22293185]

Reichrath J and Rass K, 2014. Ultraviolet damage, DNA repair and vitamin D in nonmelanoma skin cancer and in malignant melanoma: an update, Adv Exp Med Biol. 810, 208–33. [PubMed: 25207368]

Rone MB,Midzak AS, Issop L, Rammouz G, Jagannathan S, Fan J, Ye X, Blonder J, Veenstra T, and Papadopoulos V (2012). "Identification of a dynamic mitochondrial protein complex driving cholesterol import, trafficking, and metabolism to steroid hormones." Mol Endocrinol 26 1868–1882 [PubMed: 22973050]

Ruggiero C and Lalli E, 2016. Impact of ACTH Signaling on Transcriptional Regulation of Steroidogenic Genes, Front Endocrinol (Lausanne). 7, 24. [PubMed: 27065945]

Sainte Marie Y, Toulon A, Paus R, Maubec E, Cherfa A, Grossin M, Descamps V, Clemessy M, Gasc JM, Peuchmaur M, Glick A, Farman N and Jaisser F, 2007. Targeted skin overexpression of the mineralocorticoid receptor in mice causes epidermal atrophy, premature skin barrier formation, eye abnormalities, and alopecia, Am J Pathol. 171, 846–60. [PubMed: 17675581]

Sanford JA and Gallo RL, 2013. Functions of the skin microbiota in health and disease, Semin Immunol. 25, 370–7. [PubMed: 24268438]

Sarkar MK, Kaplan N, Tsoi LC, Xing X, Liang Y, Swindell WR, Hoover P, Aravind M, Baida G, Clark M, Voorhees JJ, Nair RP, Elder JT, Budunova I, Getsios S and Gudjonsson JE, 2017. Endogenous Glucocorticoid Deficiency in Psoriasis Promotes Inflammation and Abnormal Differentiation, J Invest Dermatol. 137, 1474–1483. [PubMed: 28259685]

Schadendorf D, Fisher DE, Garbe C, Gershenwald JE, Grob JJ, Halpern A, Herlyn M, Marchetti MA, McArthur G, Ribas A, Roesch A and Hauschild A, 2015. Melanoma, Nat Rev Dis Primers. 1, 15003. [PubMed: 27188223]

Schallreuter KU, Lemke KR, Pittelkow MR, Wood JM, Korner C and Malik R, 1995. Catecholamines in human keratinocyte differentiation, J Invest Dermatol. 104, 953–7. [PubMed: 7769265]

Schallreuter KU, 1997. Epidermal adrenergic signal transduction as part of the neuronal network in the human epidermis, J Investig Dermatol Symp Proc. 2, 37–40.

Schauber J and Gallo RL, 2008. Antimicrobial peptides and the skin immune defense system, The Journal of allergy and clinical immunology. 122, 261–6. [PubMed: 18439663]

Schauer E, Trautinger F, Kock A, Schwarz A, Bhardwaj R, Simon M, Ansel JC, Schwarz T and Luger TA, 1994. Proopiomelanocortin-derived peptides are synthesized and released by human keratinocytes, J Clin Invest. 93, 2258–62. [PubMed: 8182158]

Schedel M, Jia Y, Michel S, Takeda K, Domenico J, Joetham A, Ning F, Strand M, Han J, Wang M, Lucas JJ, Vogelberg C, Kabesch M, O'Connor BP and Gelfand EW, 2016. 1,25D3 prevents CD8(+)Tc2 skewing and asthma development through VDR binding changes to the Cyp11a1 promoter, Nat Commun. 7, 10213. [PubMed: 26750596]

Schmid-Wendtner MH and Korting HC, 2006. The pH of the skin surface and its impact on the barrier function, Skin Pharmacol Physiol. 19, 296–302. [PubMed: 16864974]

Scholzen TE, Kalden DH, Brzoska T, Fisbeck T, Fastrich M, Schiller M, Bohm M, Schwarz T, Armstrong CA, Ansel JC and Luger TA, 2000. Expression of proopiomelanocortin peptides in human dermal microvascular endothelial cells: evidence for a regulation by ultraviolet light and interleukin-1, J Invest Dermatol. 115, 1021–8. [PubMed: 11121136]

Schonbeck U, Mach F and Libby P, 1998. Generation of biologically active IL-1 beta by matrix metalloproteinases: a novel caspase-1-independent pathway of IL-1 beta processing, J Immunol. 161, 3340–6. [PubMed: 9759850]

Sevilla LM and Perez P, 2018. Roles of the Glucocorticoid and Mineralocorticoid Receptors in Skin Pathophysiology, Int J Mol Sci. 19.

Shimada-Omori R, Yamasaki K, Koike S, Yamauchi T and Aiba S, 2020. TLR3 augments glucocorticoid-synthetic enzymes expression in epidermal keratinocytes; Implications of glucocorticoid metabolism in rosacea epidermis, J Dermatol Sci.

Silva SH, Guedes AC, Gontijo B, Ramos AM, Carmo LS, Farias LM and Nicoli JR, 2006. Influence of narrow-band UVB phototherapy on cutaneous microbiota of children with atopic dermatitis, J Eur Acad Dermatol Venereol. 20, 1114–20. [PubMed: 16987268]

Skobowiat C, Dowdy JC, Sayre RM, Tuckey RC and Slominski A, 2011. Cutaneous hypothalamic-pituitary-adrenal axis homolog: regulation by ultraviolet radiation, Am J Physiol Endocrinol Metab. 301, E484–93. [PubMed: 21673307]

Skobowiat C, Nejati R, Lu L, Williams RW and Slominski AT, 2013a. Genetic variation of the cutaneous HPA axis: an analysis of UVB-induced differential responses, Gene. 530, 1–7. [PubMed: 23962689]

Skobowiat C, Sayre RM, Dowdy JC and Slominski AT, 2013b. Ultraviolet radiation regulates cortisol activity in a waveband-dependent manner in human skin ex vivo, Br J Dermatol. 168, 595–601. [PubMed: 23363016]

Skobowiat C and Slominski AT, 2015. UVB Activates Hypothalamic-Pituitary-Adrenal Axis in C57BL/6 Mice, J Invest Dermatol. 135, 1638–1648. [PubMed: 25317845]

Skobowiat C, Postlethwaite AE and Slominski AT, 2017a. Skin Exposure to Ultraviolet B Rapidly Activates Systemic Neuroendocrine and Immunosuppressive Responses, Photochem Photobiol. 93, 1008–1015. [PubMed: 27716949]

Skobowiat C, Oak AS, Kim TK, Yang CH, Pfeffer LM, Tuckey RC and Slominski AT, 2017b. Noncalcemic 20-hydroxyvitamin D3 inhibits human melanoma growth in in vitro and in vivo models, Oncotarget. 8, 9823–9834. [PubMed: 28039464]

Slominski A, Paus R and Mazurkiewicz J, 1992. Proopiomelanocortin expression in the skin during induced hair growth in mice., Experientia. 48, 50–54. [PubMed: 1737578]

Slominski A, Paus R and Wortsman J, 1993. On the potential role of proopiomelanocortin in skin physiology and pathology., Mol Cell Endocrinol. 93, C1–C6. [PubMed: 8391494]

Slominski A and Mihm MC, 1996. Potential mechanism of skin response to stress, Int J Dermatol. 35, 849–51. [PubMed: 8970839]

Slominski A, Baker J, Ermak G, Chakraborty A and Pawelek J, 1996a. Ultraviolet B stimulates production of corticotropin releasing factor (CRF) by human melanocytes, FEBS Lett. 399, 175–6. [PubMed: 8980146]

Slominski A, Ermak G and Mihm M, 1996b. ACTH receptor, CYP11A1, CYP17 and CYP21A2 genes are expressed in skin, J Clin Endocrinol Metab. 81, 2746–9. [PubMed: 8675607]

Slominski A, 1998. Identification of beta-endorphin, alpha-MSH and ACTH peptides in cultured human melanocytes, melanoma and squamous cell carcinoma cells by RP-HPLC, Exp Dermatol. 7, 213–6. [PubMed: 9758420]

Slominski A, Ermak G, Mazurkiewicz JE, Baker J and Wortsman J, 1998a. Characterization of corticotropin-releasing hormone (CRH) in human skin, J Clin Endocrinol Metab. 83, 1020–4. [PubMed: 9506767]

Slominski A, Botchkareva NV, Botchkarev VA, Chakraborty A, Luger T, Uenalan M and Paus R, 1998b. Hair cycle-dependent production of ACTH in mouse skin, Biochim Biophys Acta. 1448, 147–52. [PubMed: 9824688]

Slominski AT, Botchkarev V, Choudhry M, Fazal N, Fechner K, Furkert J, Krause E, Roloff B, Sayeed M, Wei E, Zbytek B, Zipper J, Wortsman J and Paus R, 1999a. Cutaneous expression of CRH and CRH-R. Is there a “skin stress response system?”, Annals of the New York Academy of Sciences. 885, 287–311. [PubMed: 10816662]

Slominski A, Gomez-Sanchez CE, Foecking MF and Wortsman J, 1999b. Metabolism of progesterone to DOC, corticosterone and 18OHDOC in cultured human melanoma cells, FEBS Lett. 455, 364–6. [PubMed: 10437805]

Slominski A and Wortsman J, 2000. Neuroendocrinology of the skin, Endocr Rev. 21, 457–87. [PubMed: 11041445]

Slominski A, Wortsman J, Luger T, Paus R and Solomon S, 2000a. Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress, Physiol Rev. 80, 979–1020. [PubMed: 10893429]

Slominski A, Roloff B, Curry J, Dahiya M, Szczesniewski A and Wortsman J, 2000b. The skin produces urocortin, J Clin Endocrinol Metab. 85, 815–23. [PubMed: 10690896]

Slominski A, Gomez-Sanchez CE, Foecking MF and Wortsman J, 2000c. Active steroidogenesis in the normal rat skin, Biochim Biophys Acta. 1474, 1–4. [PubMed: 10699483]

Slominski AT, Roloff B, Zbytek B, Wei ET, Fechner K, Curry J and Wortsman J, 2000d. Corticotropin releasing hormone and related peptides can act as bioregulatory factors in human keratinocytes, In Vitro Cell Dev Biol Anim. 36, 211–6. [PubMed: 10777063]

Slominski A, Wortsman J, Pisarchik A, Zbytek B, Linton EA, Mazurkiewicz JE and Wei ET, 2001. Cutaneous expression of corticotropin-releasing hormone (CRH), urocortin, and CRH receptors, FASEB J. 15, 1678–93. [PubMed: 11481215]

Slominski A, Wortsman J, Foecking M, Shackleton C, Gomez-Sanchez C, Szczesniewski A. (2002) Gas chromatography/mass spectrometry characterization of corticosteroid metabolism in human immortalized keratinocytes, J Invest Dermatol. 118, 310–315. [PubMed: 11841549]

Slominski A, Zjawiony J, Wortsman J, Semak I, Stewart J, Pisarchik A, Sweatman T, Marcos J, Dunbar C and R CT, 2004a. A novel pathway for sequential transformation of 7-dehydrocholesterol and expression of the P450scc system in mammalian skin, Eur J Biochem. 271, 4178–88. [PubMed: 15511223]

Slominski A, Pisarchik A, Tobin DJ, Mazurkiewicz JE and Wortsman J, 2004b. Differential expression of a cutaneous corticotropin-releasing hormone system, Endocrinology. 145, 941–50. [PubMed: 14605004]

Slominski A, Wortsman J and Tobin DJ, 2005a. The cutaneous serotoninergic/melatoninergic system: securing a place under the sun, FASEB J. 19, 176–94. [PubMed: 15677341]

Slominski A, Zbytek B, Semak I, Sweatman T and Wortsman J, 2005b. CRH stimulates POMC activity and corticosterone production in dermal fibroblasts, J Neuroimmunol. 162, 97–102. [PubMed: 15833364]

Slominski A, Zbytek B, Szczesniewski A, Semak I, Kaminski J, Sweatman T and Wortsman J, 2005c. CRH stimulation of corticosteroids production in melanocytes is mediated by ACTH, Am J Physiol Endocrinol Metab. 288, E701–6. [PubMed: 15572653]

Slominski A, Semak I, Zjawiony J, Wortsman J, Li W, Szczesniewski A and Tuckey RC, 2005d. The cytochrome P450scc system opens an alternate pathway of vitamin D3 metabolism, FEBS J. 272, 4080–90. [PubMed: 16098191]

Slominski A, Semak I, Zjawiony J, Wortsman J, Gandy MN, Li J, Zbytek B, Li W and Tuckey RC, 2005e. Enzymatic metabolism of ergosterol by cytochrome p450scc to biologically active 17alpha,24-dihydroxyergosterol, Chem Biol. 12, 931–9. [PubMed: 16125105]

Slominski A, Zbytek B, Pisarchik A, Slominski RM, Zmijewski MA and Wortsman J, 2006a. CRH functions as a growth factor/cytokine in the skin, J Cell Physiol. 206, 780–91. [PubMed: 16245303]

Slominski A, Zbytek B, Szczesniewski A and Wortsman J, 2006b. Cultured human dermal fibroblasts do produce cortisol, J Invest Dermatol. 126, 1177–8. [PubMed: 16484985]

Slominski A, Zbytek B, Zmijewski M, Slominski RM, Kauser S, Wortsman J and Tobin DJ, 2006c. Corticotropin releasing hormone and the skin, Front Biosci. 11, 2230–48. [PubMed: 16720310]

Slominski A, Semak I, Wortsman J, Zjawiony J, Li W, Zbytek B and Tuckey RC, 2006d. An alternative pathway of vitamin D metabolism. Cytochrome P450scc (CYP11A1)-mediated conversion to 20-hydroxyvitamin D2 and 17,20-dihydroxyvitamin D2, FEBS J. 273, 2891–901. [PubMed: 16817851]

Slominski A, 2007. A nervous breakdown in the skin: stress and the epidermal barrier, J Clin Invest. 117, 3166–9. [PubMed: 17975659]

Slominski A, Wortsman J, Tuckey RC and Paus R, 2007. Differential expression of HPA axis homolog in the skin, Mol Cell Endocrinol. 265–266, 143–9.

Slominski AT, Zmijewski MA, Semak I, Sweatman T, Janjetovic Z, Li W, Zjawiony JK and Tuckey RC, 2009. Sequential metabolism of 7-dehydrocholesterol to steroidal 5,7-dienes in adrenal glands and its biological implication in the skin, PLoS One. 4, e4309. [PubMed: 19190754]

Slominski A, 2009. On the role of the corticotropin-releasing hormone signalling system in the aetiology of inflammatory skin disorders, Br J Dermatol. 160, 229–32. [PubMed: 19187344]

Slominski AT, Janjetovic Z, Fuller BE, Zmijewski MA, Tuckey RC, Nguyen MN, Sweatman T, Li W, Zjawiony J, Miller D, Chen TC, Lozanski G and Holick MF, 2010. Products of vitamin D3 or 7-dehydrocholesterol metabolism by cytochrome P450scc show anti-leukemia effects, having low or absent calcemic activity, PLoS One. 5, e9907. [PubMed: 20360850]

Slominski AT, Kim TK, Janjetovic Z, Tuckey RC, Bieniek R, Yue J, Li W, Chen J, Nguyen MN, Tang EK, Miller D, Chen TC and Holick M, 2011a. 20-Hydroxyvitamin D2 is a noncalcemic analog of

vitamin D with potent antiproliferative and prodifferentiation activities in normal and malignant cells, Am J Physiol Cell Physiol. 300, C526–41. [PubMed: 21160030]

Slominski AT, Li W, Bhattacharya SK, Smith RA, Johnson PL, Chen J, Nelson KE, Tuckey RC, Miller D, Jiao Y, Gu W and Postlethwaite AE, 2011b. Vitamin D analogs 17,20S(OH)2pD and 17,20R(OH)2pD are noncalcemic and exhibit antifibrotic activity, J Invest Dermatol. 131, 1167–9. [PubMed: 21228816]

Slominski AT, Zmijewski MA, Skobowiat C, Zbytek B, Slominski RM and Steketee JD, 2012a. Sensing the environment: regulation of local and global homeostasis by the skin's neuroendocrine system, Adv Anat Embryol Cell Biol. 212, v, vii, 1–115.

Slominski A, Zmijewski MA and Pawelek J, 2012b. L-tyrosine and L-dihydroxyphenylalanine as hormone-like regulators of melanocyte functions, Pigment Cell Melanoma Res. 25, 14–27. [PubMed: 21834848]

Slominski AT, Kim TK, Chen J, Nguyen MN, Li W, Yates CR, Sweatman T, Janjetovic Z and Tuckey RC, 2012c. Cytochrome P450scc-dependent metabolism of 7-dehydrocholesterol in placenta and epidermal keratinocytes, Int J Biochem Cell Biol. 44, 2003–18. [PubMed: 22877869]

Slominski AT, Kim TK, Shehabi HZ, Semak I, Tang EK, Nguyen MN, Benson HA, Korik E, Janjetovic Z, Chen J, Yates CR, Postlethwaite A, Li W and Tuckey RC, 2012d. In vivo evidence for a novel pathway of vitamin D(3) metabolism initiated by P450scc and modified by CYP27B1, FASEB J. 26, 3901–15. [PubMed: 22683847]

Slominski AT, Janjetovic Z, Kim TK, Wright AC, Grese LN, Riney SJ, Nguyen MN and Tuckey RC, 2012e. Novel vitamin D hydroxyderivatives inhibit melanoma growth and show differential effects on normal melanocytes, Anticancer Res. 32, 3733–42. [PubMed: 22993313]

Slominski AT, Zmijewski MA, Zbytek B, Tobin DJ, Theoharides TC and Rivier J, 2013a. Key role of CRF in the skin stress response system, Endocr Rev. 34, 827–84. [PubMed: 23939821]

Slominski A, Janjetovic Z, Tuckey RC, Nguyen MN, Bhattacharya KG, Wang J, Li W, Jiao Y, Gu W, Brown M and Postlethwaite AE, 2013c. 20S-hydroxyvitamin D3, noncalcemic product of CYP11A1 action on vitamin D3, exhibits potent antifibrogenic activity in vivo, J Clin Endocrinol Metab. 98, E298–303. [PubMed: 23295467]

Slominski A, Kim TK, Zmijewski MA, Janjetovic Z, Li W, Chen J, Kusniatsova EI, Semak I, Postlethwaite A, Miller DD, Zjawiony JK and Tuckey RC, 2013d. Novel vitamin D photoproducts and their precursors in the skin, Dermatoendocrinol. 5, 7–19. [PubMed: 24494038]

Slominski AT and Carlson JA, 2014. Melanoma resistance: a bright future for academicians and a challenge for patient advocates, Mayo Clin Proc. 89, 429–33. [PubMed: 24684870]

Slominski AT, Kim TK, Li W, Yi AK, Postlethwaite A and Tuckey RC, 2014a. The role of CYP11A1 in the production of vitamin D metabolites and their role in the regulation of epidermal functions, J Steroid Biochem Mol Biol. 144 Pt A, 28–39. [PubMed: 24176765]

Slominski AT, Manna PR and Tuckey RC, 2014b. Cutaneous glucocorticosteroidogenesis: securing local homeostasis and the skin integrity, Exp Dermatol. 23, 369–374. [PubMed: 24888781]

Slominski AT, Kim TK, Takeda Y, Janjetovic Z, Brozyna AA, Skobowiat C, Wang J, Postlethwaite A, Li W, Tuckey RC and Jetten AM, 2014c. RORalpha and ROR gamma are expressed in human skin and serve as receptors for endogenously produced noncalcemic 20-hydroxy- and 20,23-dihydroxyvitamin D, FASEB J. 28, 2775–89. [PubMed: 24668754]

Slominski AT, Zmijewski MA, Semak I, Zbytek B, Pisarchik A, Li W, Zjawiony J and Tuckey RC, 2014d. Cytochromes p450 and skin cancer: role of local endocrine pathways, Anticancer Agents Med Chem. 14, 77–96. [PubMed: 23869782]

Slominski AT, Li W, Kim TK, Semak I, Wang J, Zjawiony JK and Tuckey RC, 2015a. Novel activities of CYP11A1 and their potential physiological significance, J Steroid Biochem Mol Biol. 151, 25–37. [PubMed: 25448732]

Slominski AT, Manna PR and Tuckey RC, 2015b. On the role of skin in the regulation of local and systemic steroidogenic activities, Steroids. 103, 72–88. [PubMed: 25988614]

Slominski AT, Janjetovic Z, Kim TK, Wasilewski P, Rosas S, Hanna S, Sayre RM, Dowdy JC, Li W and Tuckey RC, 2015c. Novel non-calcemic secosteroids that are produced by human epidermal

keratinocytes protect against solar radiation, J Steroid Biochem Mol Biol. 148, 52–63. [PubMed: 25617667]

Slominski AT, Kim TK, Li W, Postlethwaite A, Tieu EW, Tang EKY and Tuckey RC, 2015d. Detection of novel CYP11A1-derived secosteroids in the human epidermis and serum and pig adrenal gland, Sci Rep. 5, 14875. [PubMed: 26445902]

Slominski AT, Brozyna AA and Tuckey RC, 2017a. Cutaneous Glucocorticoidogenesis and Cortisol Signaling Are Defective in Psoriasis, J Invest Dermatol. 137, 1609–1611. [PubMed: 28735612]

Slominski AT, Kim TK, Hobrath JV, Oak ASW, Tang EKY, Tieu EW, Li W, Tuckey RC and Jetten AM, 2017b. Endogenously produced nonclassical vitamin D hydroxy-metabolites act as "biased" agonists on VDR and inverse agonists on RORalpha and RORgamma, J Steroid Biochem Mol Biol. 173, 42–56. [PubMed: 27693422]

Slominski AT, Kim TK, Hobrath JV, Janjetovic Z, Oak ASW, Postlethwaite A, Lin Z, Li W, Takeda Y, Jetten AM and Tuckey RC, 2017c. Characterization of a new pathway that activates lumisterol in vivo to biologically active hydroxylumisterols, Sci Rep. 7, 11434. [PubMed: 28900196]

Slominski AT and Zmijewski MA, 2017. Glucocorticoids Inhibit Wound Healing: Novel Mechanism of Action, J Invest Dermatol. 137, 1012–1014. [PubMed: 28411834]

Slominski AT, Zmijewski MA, Plonka PM, Szaflarski JP and Paus R, 2018a. How UV Light Touches the Brain and Endocrine System Through Skin, and Why, Endocrinology. 159, 1992–2007. [PubMed: 29546369]

Slominski AT, Hardeland R, Zmijewski MA, Slominski RM, Reiter RJ and Paus R, 2018b. Melatonin: A Cutaneous Perspective on its Production, Metabolism, and Functions, J Invest Dermatol. 138, 490–499. [PubMed: 29428440]

Slominski AT, Kim TK, Janjetovic Z, Brozyna AA, Zmijewski MA, Xu H, Sutter TR, Tuckey RC, Jetten AM and Crossman DK, 2018c. Differential and Overlapping Effects of 20,23(OH)(2)D3 and 1,25(OH)(2)D3 on Gene Expression in Human Epidermal Keratinocytes: Identification of AhR as an Alternative Receptor for 20,23(OH)(2)D3, Int J Mol Sci. 19.

Slominski AT, Brozyna AA, Skobowiat C, Zmijewski MA, Kim TK, Janjetovic Z, Oak AS, Jozwicki W, Jetten AM, Mason RS, Elmets C, Li W, Hoffman RM and Tuckey RC, 2018d. On the role of classical and novel forms of vitamin D in melanoma progression and management, J Steroid Biochem Mol Biol. 177, 159–170. [PubMed: 28676457]

Slominski AT, Chaiprasongsuk A, Janjetovic Z, Kim TK, Stefan J, Slominski RM, Hanumanthu VS, Raman C, Qayyum S, Song Y, Song Y, Panich U, Crossman DK, Athar M, Holick MF, Jetten AM, Zmijewski MA, Zmijewski J and Tuckey RC, 2020a. Photoprotective Properties of Vitamin D and Lumisterol Hydroxyderivatives, Cell Biochem Biophys. 78, 165–180. [PubMed: 32441029]

Slominski AT, Kim TK, Kleszczynski K, Semak I, Janjetovic Z, Sweatman T, Skobowiat C, Steketee JD, Lin Z, Postlethwaite A, Li W, Reiter RJ and Tobin DJ, 2020b. Characterization of serotonin and N-acetylserotonin syst ems in the human epidermis and skin cells, J Pineal Res. 68, e12626. [PubMed: 31770455]

Slominski AT, Brozyna AA, Zmijewski MA, Janjetovic Z, Kim TK, Slominski RM, Tuckey RC, Mason RS, Jetten AM, Guroji P, Reichrath J, Elmets C and Athar M, 2020c. The Role of Classical and Novel Forms of Vitamin D in the Pathogenesis and Progression of Nonmelanoma Skin Cancers, Adv Exp Med Biol. 1268, 257–283. [PubMed: 32918223]

Slominski RM, Tuckey RC, Manna PR, Jetten AM, Postlethwaite A, Raman C and Slominski AT, 2020a. Extra-adrenal glucocorticoid biosynthesis: implications for autoimmune and inflammatory disorders, Genes Immun. 21, 150–168. [PubMed: 32203088]

Slominski RM, Stefan J, Athar M, Holick MF, Jetten AM, Raman C and Slominski AT, 2020b. COVID-19 and Vitamin D: A lesson from the skin, Exp Dermatol. 29, 885–890. [PubMed: 32779213]

Stanberry LR, Das Gupta TK and Beattie CW, 1982. Biological behavior of MM1 hamster melanoma, Cancer Res. 42, 2238–41. [PubMed: 6280853]

Stojadinovic O, Lindley LE, Jozic I and Tomic-Canic M, 2016. Mineralocorticoid Receptor Antagonists-A New Sprinkle of Salt and Youth, J Invest Dermatol. 136, 1938–1941. [PubMed: 27664711]

Strushkevich N, MacKenzie F, Cherkesova T, Grabovec I, Usanov S and Park HW, 2011. Structural basis for pregnenolone biosynthesis by the mitochondrial monooxygenase system, Proc Natl Acad Sci U S A. 108, 10139–43. [PubMed: 21636783]

Takei K, Denda S, Kumamoto J and Denda M, 2013. Low environmental humidity induces synthesis and release of cortisol in an epidermal organotypic culture system, Exp Dermatol. 22, 662–4. [PubMed: 24079737]

Tan SY, Roediger B and Weninger W, 2015. The role of chemokines in cutaneous immunosurveillance, Immunol Cell Biol. 93, 337–46. [PubMed: 25776847]

Teplyuk NM, Zhang Y, Lou Y, Hawse JR, Hassan MQ, Teplyuk VI, Pratap J, Galindo M, Stein JL, Stein GS, Lian JB and van Wijnen AJ, 2009. The osteogenic transcription factor runx2 controls genes involved in sterol/steroid metabolism, including CYP11A1 in osteoblasts, Mol Endocrinol. 23, 849–61. [PubMed: 19342447]

Thiboutot D, Jabara S, McAllister JM, Sivarajah A, Gilliland K, Cong Z and Clawson G, 2003. Human skin is a steroidogenic tissue: steroidogenic enzymes and cofactors are expressed in epidermis, normal sebocytes, and an immortalized sebocyte cell line (SEB-1), J Invest Dermatol. 120, 905–14. [PubMed: 12787114]

Thornton MJ, Taylor AH, Mulligan K, Al-Azzawi F, Lyon CC, O'Driscoll J and Messenger AG, 2003. The distribution of estrogen receptor beta is distinct to that of estrogen receptor alpha and the androgen receptor in human skin and the pilosebaceous unit, J Investig Dermatol Symp Proc. 8, 100–3.

Tiala I, Suomela S, Huuhtanen J, Wakkinen J, Holtta-Vuori M, Kainu K, Ranta S, Turpeinen U, Hamalainen E, Jiao H, Karvonen SL, Ikonen E, Kere J, Saarialho-Kere U and Elomaa O, 2007. The CCHCR1 (HCR) gene is relevant for skin steroidogenesis and downregulated in cultured psoriatic keratinocytes, J Mol Med (Berl). 85, 589–601. [PubMed: 17221218]

Tiganescu A, Hupe M, Jiang YJ, Celli A, Uchida Y, Mauro TM, Bikle DD, Elias PM and Holleran WM, 2015. UVB induces epidermal 11beta-hydroxysteroid dehydrogenase type 1 activity in vivo, Exp Dermatol. 24, 370–6. [PubMed: 25739654]

Tkachenko IV, Jaaskelainen T, Jaaskelainen J, Palvimo JJ and Voutilainen R, 2011. Interleukins 1alpha and 1beta as regulators of steroidogenesis in human NCI-H295R adrenocortical cells, Steroids. 76, 1103–15. [PubMed: 21600230]

Tongkao-On W, Carter S, Reeve VE, Dixon KM, Gordon-Thomson C, Halliday GM, Tuckey RC and Mason RS, 2015. CYP11A1 in skin: an alternative route to photoprotection by vitamin D compounds, J Steroid Biochem Mol Biol. 148, 72–8. [PubMed: 25448743]

Tongkao-on W, Yang C, McCarthy BY, De Silva WGM, Rybchyn MS, Gordon-Thomson C, Dixon KM, Halliday GM, Reeve VE and Mason RS, 2021. Sex Differences in Photoprotective Responses to 1,25-Dihydroxyvitamin D3 in Mice Are Modulated by the Estrogen Receptor-β, International Journal of Molecular Sciences. 22, 1962. [PubMed: 33669452]

Tuckey RC, 2005. Progesterone synthesis by the human placenta, Placenta. 26, 273–81. [PubMed: 15823613]

Tuckey RC, Cheng CYS and Slominski AT, 2019. The serum vitamin D metabolome: What we know and what is still to discover, J Steroid Biochem Mol Biol. 186, 4–21. [PubMed: 30205156]

Tuckey RC, Li W, Shehabi HZ, Janjetovic Z, Nguyen MN, Kim TK, Chen J, Howell DE, Benson HA, Sweatman T, Baldisseri DM and Slominski A, 2011. Production of 22-hydroxy metabolites of vitamin d3 by cytochrome p450scc (CYP11A1) and analysis of their biological activities on skin cells, Drug Metab Dispos. 39, 1577–88. [PubMed: 21677063]

Tuckey RC, Li W, Zjawiony JK, Zmijewski MA, Nguyen MN, Sweatman T, Miller D and Slominski A, 2008. Pathways and products for the metabolism of vitamin D3 by cytochrome P450scc, FEBS J. 275, 2585–96. [PubMed: 18410379]

Tuckey RC, Slominski AT, Cheng CY, Chen J, Kim TK, Xiao M and Li W, 2014. Lumisterol is metabolized by CYP11A1: discovery of a new pathway, Int J Biochem Cell Biol. 55, 24–34. [PubMed: 25130438]

Turcu A, Smith JM, Auchus R and Rainey WE, 2014. Adrenal androgens and androgen precursors-definition, synthesis, regulation and physiologic actions, Compr Physiol. 4, 1369–81. [PubMed: 25428847]

Turnbull AV and Rivier CL, 1999. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action, Physiol Rev. 79, 1–71. [PubMed: 9922367]

Vale W, Spiess J, Rivier C and Rivier J, 1981. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin, Science. 213, 1394–7. [PubMed: 6267699]

Vukelic S, Stojadinovic O, Pastar I, Rabach M, Krzyzanowska A, Lebrun E, Davis SC, Resnik S, Brem H and Tomic-Canic M, 2011. Cortisol synthesis in epidermis is induced by IL-1 and tissue injury, J Biol Chem. 286, 10265–75. [PubMed: 21239489]

Wacker M and Holick MF, 2013. Sunlight and Vitamin D: A global perspective for health, Dermatoendocrinol. 5, 51–108. [PubMed: 24494042]

Wang J, Slominski A, Tuckey RC, Janjetovic Z, Kulkarni A, Chen J, Postlethwaite AE, Miller D and Li W, 2012. 20-hydroxyvitamin D(3) inhibits proliferation of cancer cells with high efficacy while being non-toxic, Anticancer Res. 32, 739–46. [PubMed: 22399586]

Wang M, Strand MJ, Lanser BJ, Santos C, Bendelja K, Fish J, Esterl EA, Ashino S, Abbott JK, Knight V and Gelfand EW, 2020. Expression and activation of the steroidogenic enzyme CYP11A1 is associated with IL-13 production in T cells from peanut allergic children, PLoS One. 15, e0233563. [PubMed: 32497050]

Wikler JR, Janssen N, Bruynzeel DP and Nieboer C, 1990. The effect of UV-light on pityrosporum yeasts: ultrastructural changes and inhibition of growth, Acta Derm Venereol. 70, 69–71. [PubMed: 1967880]

Wondrak GT, 2007. Let the sun shine in: mechanisms and potential for therapeutics in skin photodamage, Curr Opin Investig Drugs. 8, 390–400.

Xu H, Timares L and Elmets CA, 2019. Host Defenses in the Skin, in: Rich RR et al. (Eds.), Clinical immunology : principles and practice. Elsevier, St. Louis, Missouri, pp. 273–283.

Yang K, Oak ASW, Slominski RM, Brozyna AA and Slominski AT, 2020. Current Molecular Markers of Melanoma and Treatment Targets, Int J Mol Sci. 21.

Yousef H, Alhajj M and Sharma S, 2020. Anatomy, Skin (Integument), Epidermis, StatPearls. Treasure Island (FL).

Zbytek B, Janjetovic Z, Tuckey RC, Zmijewski MA, Sweatman TW, Jones E, Nguyen MN and Slominski AT, 2008. 20-Hydroxyvitamin D3, a product of vitamin D3 hydroxylation by cytochrome P450scc, stimulates keratinocyte differentiation, J Invest Dermatol. 128, 2271–80. [PubMed: 18368131]

Zbytek B and Slominski AT, 2005. Corticotropin-releasing hormone induces keratinocyte differentiation in the adult human epidermis, J Cell Physiol. 203, 118–26. [PubMed: 15468147]

Zhu G, Janjetovic Z and Slominski A, 2014. On the role of environmental humidity on cortisol production by epidermal keratinocytes, Exp Dermatol. 23, 15–7. [PubMed: 24372648]

Zouboulis CC, Seltmann H, Hiroi N, Chen W, Young M, Oeff M, Scherbaum WA, Orfanos CE, McCann SM and Bornstein SR, 2002. Corticotropin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes, Proc Natl Acad Sci U S A. 99, 7148–53. [PubMed: 12011471]

Highlights

- CYP11A1 is expressed and enzymatically active in the skin
- CYP11A1 initiates local steroidogenesis, secosteroidogenesis and 5,7-diene metabolism
- Cutaneous CYP11A1 is regulated by UVB, UVC, CRH, ACTH, c-AMP and cytokines
- CYP11A1 plays a key role in regulation of the protective barrier and immune functions
- Disturbances to CYP11A1 catalytic activity can lead to skin pathology

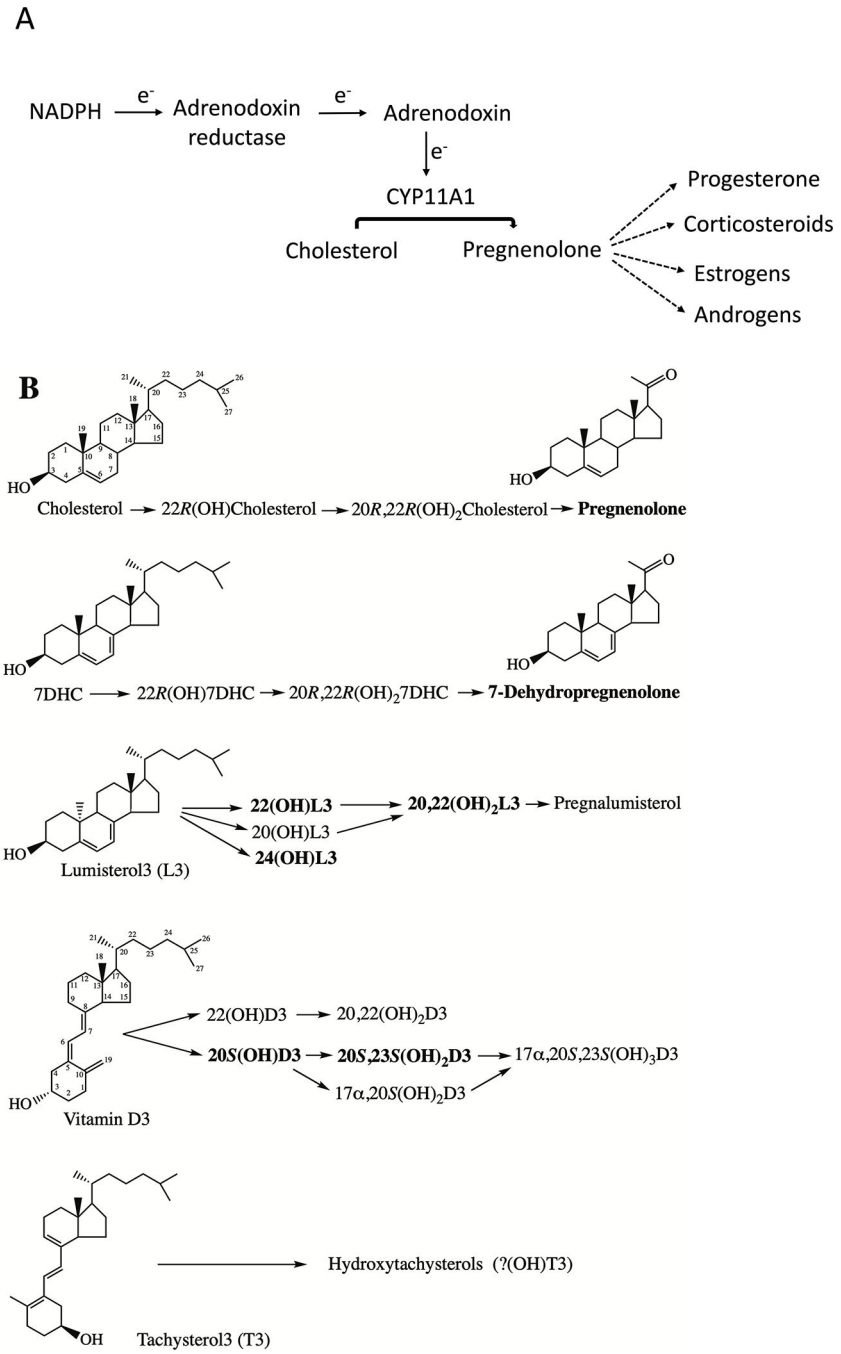

Figure 1.

CYP11A1 activities in the skin. **A**. CYP11A1 receives electrons form its redox partners to cleave the side chain of cholesterol producing pregnenolone which is converted to other steroids by cell/tissue specific pathways. **B**. CYP11A1 can act on endogenous sterols and secosteroids in the skin. The major products from cholesterol and 7DHC have their side chain removed whereas little cleavage of the side chain occurs for lumisterol and no cleavage occurs for vitamin D3. Major products from each substrate are shown in bold font. The stereochemistry of products is shown, where known. 7DHC, 7-dehydrocholesterol;

lumisterol, lumisterol3. More details on these reactions can be found in (Slominski et al., 2015a; 2020a; Tuckey et al., 2011; Tuckey et al., 2019).

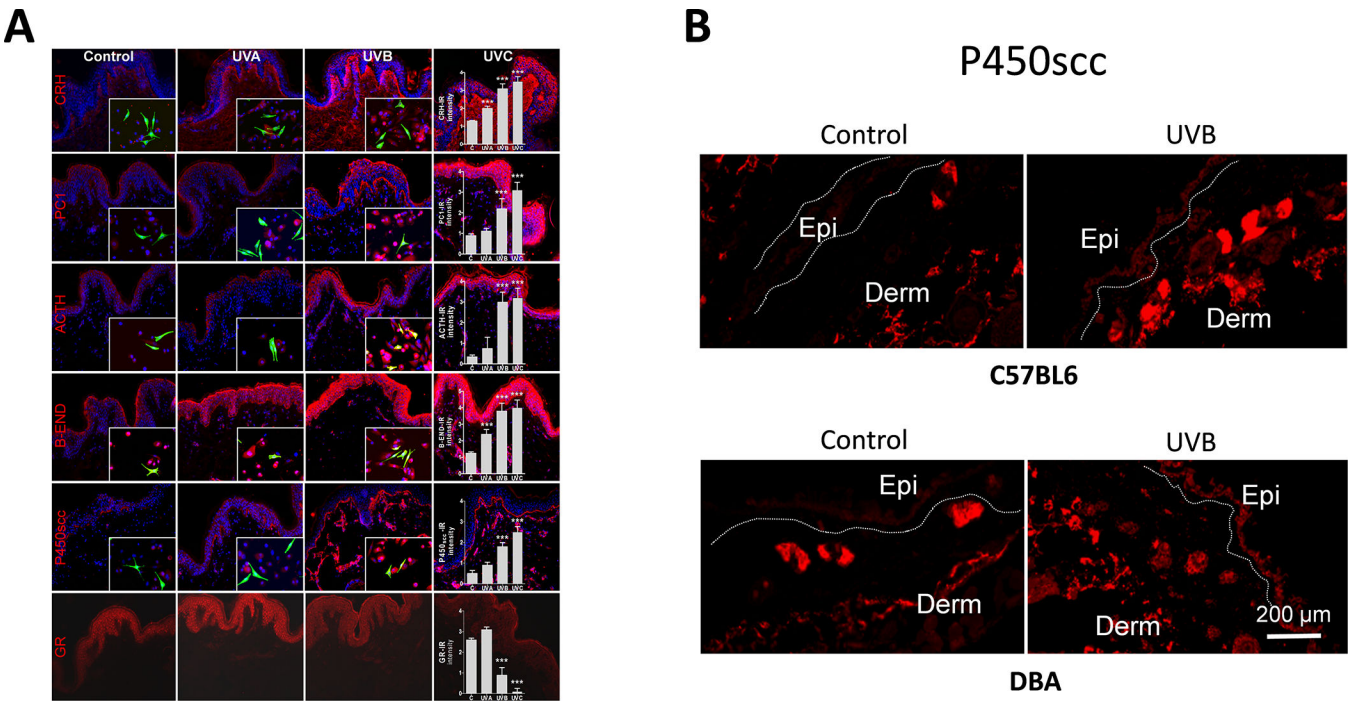

Figure 2.

Immunofluorescent staining of CYP11A1 (P450scc) in skin with and without UV treatment. **A** shows the human skin and the levels of CYP11A1 and its regulators CRH (corticotropin releasing hormone), PC1 (proconvertase-1), ACTH (adrenocorticotropic), B-END (β-endorphin), and GR (glucocorticoid receptor) after treatment with UVA, UVB, and UVC. Image taken from (Skobowiat et al., 2011) with permission from the publisher. **B** shows the CYP11A1 levels in the skin of C57BL6 mice and DBA/2J mice before and after treatment with UVB. Image taken from (Skobowiat et al., 2013a) with permission from the publisher.

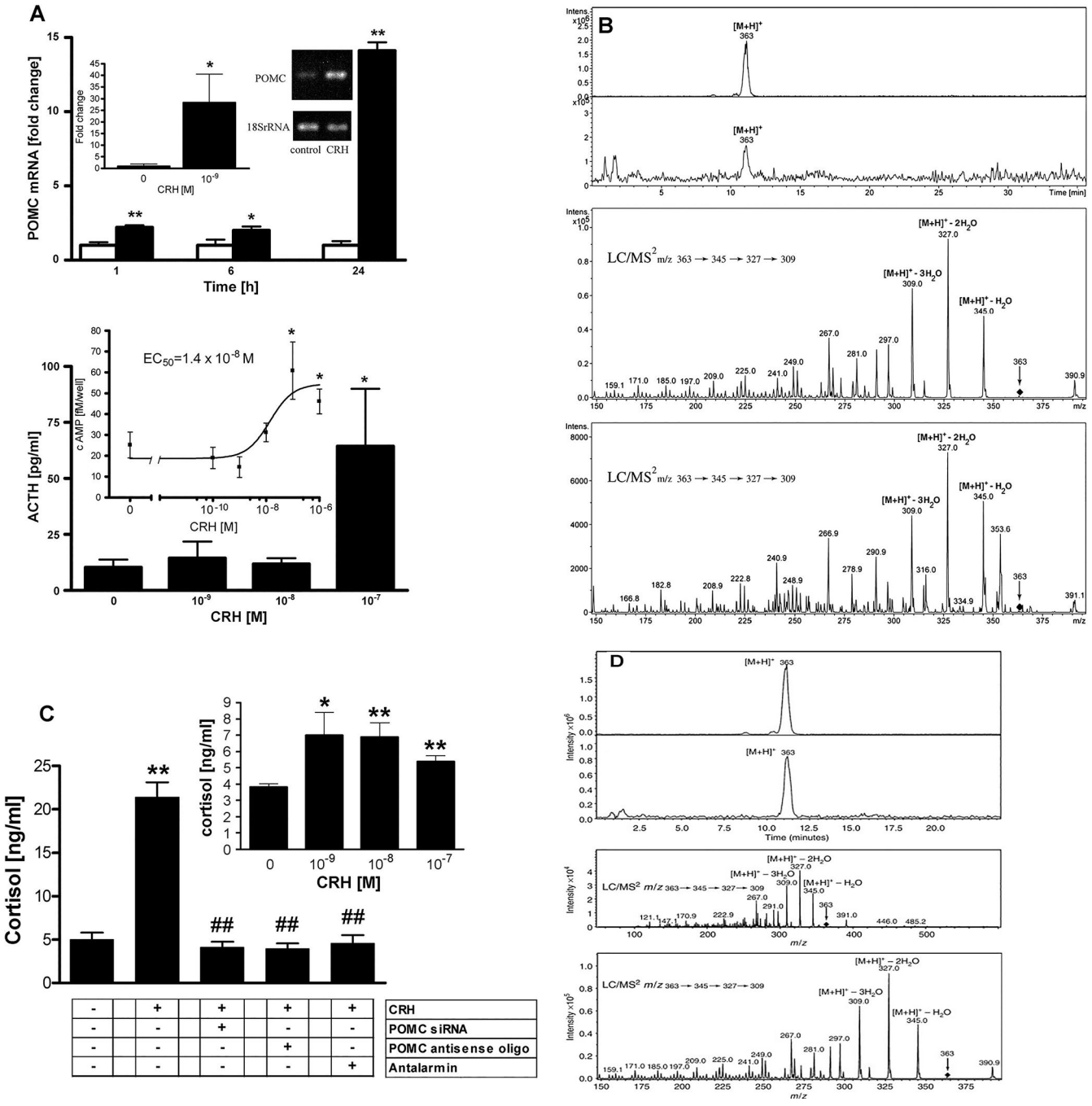

Figure 3.

Production of cortisol in human skin cells. **A.** Corticotropin-releasing hormone (CRH) were shown to stimulate proopiomelanocortin (POMC) in melanocytes in a time dependent manner. The top graph shows CRH stimulating mRNA production of POMC. The white bar shows negative control while the black bar shows treatment with CRH. The bottom graph shows CRH stimulating ACTH production in a concentration dependent manner after 24 hours of treatment. **B.** Melanocytes were shown to produce cortisol. The top graph shows liquid chromatography-mass spectrometry (LC/MS) of cortisol control vs melanocyte

extract. Notice that both of them have a peak of [M+H]+ at mass to charge ratio of 363 with retention time at 11 minutes. The last two graphs come from mass spectrometry fragmentation analysis and shows similarities between melanocytes extract (middle graph) and cortisol standard (bottom graph). **C.** CRH was shown to promote cortisol production in melanocytes in POMC and CRH-R1 dependent manner. **D.** Fibroblasts were shown to produce cortisol. The top graph shows liquid chromatography-mass spectrometry (LC/MS) of cortisol standard vs fibroblasts extract. Notice that both of them have a peak of [M+H]+ at mass to charge ratio of 363 with retention time at 11 minutes. The last two graphs come from mass spectrometry fragmentation analysis and shows similarities between fibroblast containing media (middle graph) and cortisol standard (bottom graph). Panels **A**, **B**, and **C** were taken with permission from the following article (Slominski at al. 2005c) and panel **D** was taken with permission from the publisher (Slominski et al., 2006b).

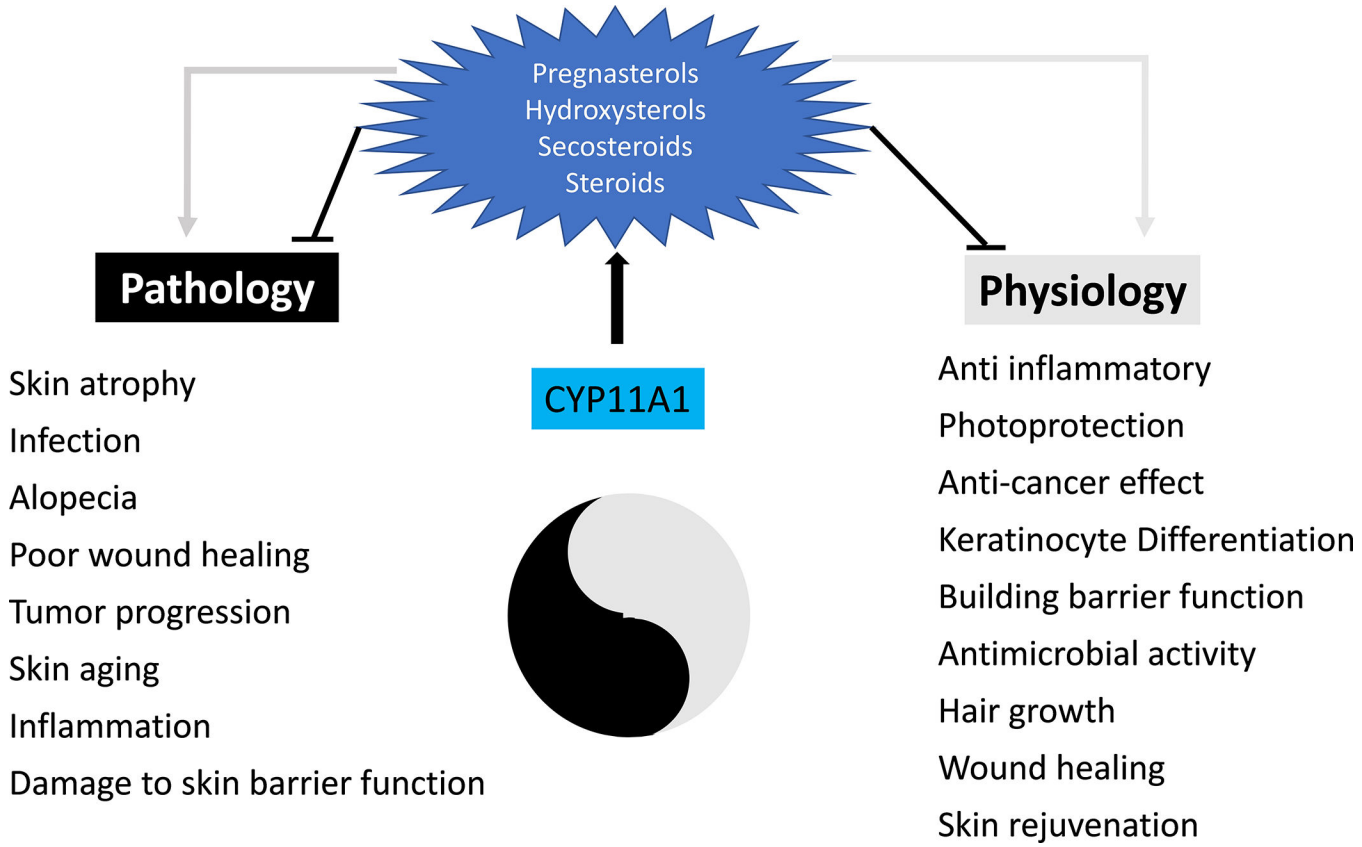

Figure 4.
Summary of the two-edged role that CYP11A1-derived compounds play in the human skin.