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Steroidogenesis in the skin: implications for local immune functions

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Abstract

The skin has developed a hierarchy of systems that encompasses the skin immune and local steroidogenic activities in order to protect the body against the external environment and biological factors and to maintain local homeostasis. Most recently it has been established that skin cells contain the entire biochemical apparatus necessary for production of glucocorticoids, androgens and estrogens either from precursors of systemic origin or, alternatively, through the conversion of cholesterol to pregnenolone and its subsequent transformation to biologically active steroids. Examples of these products are corticosterone, cortisol, testosterone, dihydrotesterone and estradiol. Their local production can be regulated by locally produced corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) or cytokines. Furthermore the production of glucocorticoids is affected by ultraviolet B radiation. The level of production and nature of the final steroid products are dependent on the cell type or cutaneous compartment, e.g., epidermis, dermis, adnexal structures or adipose tissue. Locally produced glucocorticoids, androgens and estrogens affect functions of the epidermis and adnexal structures as well as local immune activity. Malfunction of these steroidogenic activities can lead to inflammatory disorders or autoimmune diseases. The cutaneous steroidogenic system can also have systemic effects, which are emphasized by significant skin contribution to circulating androgens and/or estrogens. Furthermore, local activity of CYP11A1 can produce novel 7 -steroids and secosteroids that are biologically active. Therefore, modulation of local steroidogenic activity may serve as a new therapeutic approach for treatment of inflammatory disorders, autoimmune processes or other skin disorders. In conclusion, the skin can be defined as an independent steroidogenic organ, whose activity can affect its functions and the development of local or systemic inflammatory or autoimmune diseases.

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Keywords

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1. Skin as an immune organ

1.1. An overview of immune barrier functions of the skin

The primary function of the skin is to protect the body against the external environment, and a hierarchy of systems has developed to fulfill this function (reviewed in [1, 2]). One of the most important is the skin immune system, which is artificially divided into “innate” and “adaptive”, based on the specificity of the offending agent and presence or absence of memory in the system [3] (Fig. 1). Nevertheless, the components of this system interact with one another, are not truly separable and also interact with the cutaneous neuro-endocrine-immune system (reviewed in [1]). Various mediators participate in interactions between these elements (reviewed in [4, 5]) (Fig. 1), and will be discussed further.

1.2. Skin innate immunity

The epidermis is composed of proliferating keratinocytes that differentiate to form the corneal layer. Corneocytes together with intercellular lipids isolate the body from the external environment and also protect it against dehydration [6]. A crucial role in the formation of this layer is played by the lipids and cholesterol derivatives which are synthesized locally from acetate [7, 8]. This structural barrier is complemented by components of innate immunity which are based primarily in the dermis [4]. Neutrophils and macrophages phagocytize non-self cells and organisms and kill them by oxygen-dependent or independent mechanisms. Eosinophils release major basic protein and other substances that inactivate parasites [9]. Mast cells release mediators that enhance local inflammation. Natural killer cells kill abnormal (infected or malignant) cells through antibody-dependent, MHC I-regulated and killer-activating and killer-inhibitory receptors-regulated pathways. The complement cascade kills microbes directly (through the membrane-attack complex), enhances phagocytosis (through binding to antibody-antigen complexes) and inflammation (through anaphylatoxins). Last but not least, keratinocytes and sebocytes produce beta-defensins and other antimicrobial peptides [10, 11]. Toll-like receptors are responsible for the recognition of pathogen-associated molecular patterns (PAMPs) and thus form a basis for the differentiation between self- and non-self in innate immunity [4, 12].

1.3. Skin adaptive immunity

The adaptive immune system is considered to be the more evolved part of the immune response system. Foreign antigens are presented by Langerhans/dendritic cells to T lymphocytes that in turn drive cellular or humoral responses [13]. T cell receptors and B cell/plasma cell-produced antibodies are responsible for specificity of this mode of immune response [4]. Langerhans cells are derived from the bone marrow and express CD (cluster of differentiation) 45, CD1a and CLA (cutaneous lymphocyte-associated antigen) [13]. Foreign antigens are presented in the context of MHC (major histocompatibility complex) II to CD4 positive lymphocytes and in the context of MHC I to CD8 positive lymphocytes. Variability of T cell receptors and antibodies is a function of several mechanisms that recombine and modify genes that code for variable regions [14]. The Th (T helper) 1 lymphocytes response is mediated by cytokines such as interleukin (IL)-2 and interferon (INF)γ. The humoral response is influenced by Th2 lymphocytes in part via the production of IL-4. Abnormal Th1 and Th2 responses play a role in various skin diseases [15]. Th2 lymphocytes additionally stimulate eosinophils (IL-5). CD4, CD25 and Foxp3 positive regulatory T

lymphocytes suppress the immune response [3, 4]. CD4 positive Th17 lymphocytes express RORC (retinoic acid receptor -related orphan receptor C), develop in response to inflammatory cytokines, including IL-23, and release mediators such as IL-17, IL-21, IL-22, GM-CSF (granulocyte-macrophage colony stimulating factor) and CCL20 [chemokine (C-C motif) ligand 20] [16]. Several classes of antibodies are produced. Interaction between CD40 and CD40 ligand is responsible for the Ig (immunoglobulin)M to IgG isotype switch.

1.4. Physiological role of the skin immune system

The above components of the skin immune system are linked in large part by cytokines which serve as mediators connecting different components of innate and adaptive systems within those systems and between them. IL-1α and β, IL-6 and TNF (tumor necrosis factor)α are pro-inflammatory cytokines. INFα and β suppress viral infections. IL-10 inhibits cellular immunity. Transforming growth factor β (TGFβ) suppresses both Th1 and Th2 modes of immune response [17]. IL-12 facilitates Th1 cellular response. These cytokines have local and systemic effects. Moreover, an adaptive response that is initiated in the skin within Langerhans cells are fully matured in lymph nodes [13]. Lymphocytes, act in the skin in a retrograde manner but also affect other areas of the skin and the body [4]. The skin immune system is integrated into the skin neuro-endocrine system [2] through interaction with multiple pro- and anti-inflammatory neuropeptides, cytokines and hormones [1].

2. Steroidogenesis in the skin

2.1. An overview of steroidogenesis in classical steroidogenic organs

Maintenance of normal reproductive function and bodily homeostasis is dependent on steroid hormones synthesized in steroidogenic cells of the adrenal, ovary, testis, placenta, and brain. Steroid hormone biosynthesis is initiated upon mobilization of cholesterol, the substrate for steroid hormones, from cellular stores in cytoplasmic lipid granules to the mitochondrial inner membrane, the site of cytochrome P450scc (CYP11A1). This enzyme catalyses the cleavage of the side chain of cholesterol [18, 19]. In this reaction cholesterol is sequentially hydroxylated at carbons 22 and 20 producing 20R,22R-dihydroxycholesterol as a reaction intermediate [20]. CYP11A1 then catalyses the cleavage of the C20-C22 bond producing pregnenolone and isocaproic aldehyde. The concentration of cholesterol in the inner mitochondrial membrane of steroidogenic tissues is low [21], thus CYP11A1 normally works under subsaturating (limiting) cholesterol concentrations. Increased provision of cholesterol to the inner mitochondrial membrane by the action of the steroidogenic acute regulatory (StAR) protein causes a corresponding increase in the rate of pregnenolone synthesis [22, 23]. The fate of pregnenolone produced by CYP11A1 varies depending on the particular cell type or tissue, each of which contains a particular set of steroidogenic enzymes.

The biosynthesis of steroid hormones is regulated through the action of trophic hormones, ACTH (or angiotensin II for the zona glomerulosa) acting on the adrenal cortex and LH on the corpus luteum or the Leydig cells of the testis. These hormones bind to their specific receptors, which in turn activate the cAMP/PKA signaling cascade, and results in the phosphorylation of protein(s) involved in steroidogenesis [24, 25]. Hormonal regulation of steroid biosynthesis occurs within minutes (acute response) and hours (chronic response) and is mediated by cAMP/PKA signaling. The mobilization and delivery of cholesterol from the outer to the inner mitochondrial membrane initiates the acute response of steroid biosynthesis to hormonal stimulation that has an absolute requirement for *de novo* synthesis of the StAR protein [18, 19, 26]. On the other hand, chronic effects, associated with long-

term steroid production, involve increased transcription/translation of the genes encoding steroidogenic enzymes [19].

The 30-kDa mitochondrial StAR protein was first purified from MA-10 mouse Leydig tumor cells, and its cDNA was cloned and sequenced [27]. There is now a wealth of information indicating that the StAR protein mediates the rate-limiting and regulated step in steroid biosynthesis, i.e. the delivery of cholesterol from the outer to the inner mitochondrial membrane [28–30]. Regulation of the StAR protein and thus steroid biosynthesis, is predominantly mediated by cAMP/PKA signaling in steroidogenic tissues, although several intracellular events have been demonstrated to be instrumental in this process [30–33]. Studies have demonstrated that a tight correlation exists between the synthesis of the StAR protein and the synthesis of steroids through endocrine, autocrine and paracrine regulation (reviewed in [28, 29, 33]).

Following the StAR-mediated delivery of cholesterol to CYP11A1 in the inner mitochodrial membrane and its conversion to pregnenolone, subsequent pathways are tissue-specific and involve a number of cytochrome P450 family members plus several different steroid dehydrogenases. Unlike the P450 enzymes, there are multiple isozymes for the steroid dehydrogenases catalysing the same reaction, and often varying in the preferred direction of the reaction they catalyse *in vivo* [23]. CYP17A1 plays a pivotal role in steroidogenesis because it is required for the synthesis of cortisol where its 17α-hydroxylase activity is essential, and androgens where both its 17α-hydroxylase and C17-C20 lyase activities are required. High lyase activity is seen when the initial substrate is pregnenolone, but with progesterone essentially only 17α-hydroxylase activity is observed, directing products to the glucocorticoid pathway [23, 34].

The major enzymes in the different classical steroidogenic tissues are listed in Table 1. Thus the glomerulosa zone of the adrenal cortex produces aldosterone, and the zona fasciculata produces cortisol. In the zona reticularis, which is deficient in 3βHSD, the pregnenolone produced by CYP11A1 undergoes complete removal of the remaining two carbons of the side chain by the 17-hydroxylase and C17-C20 lyase activities of CYP17A1, producing DHEA, much of which is sulfated [22, 35]. Cytochrome b5, which is highly expressed in the zona reticularis promotes the lyase activity of CYP17A1.

The corpus luteum produces large amounts of progesterone plus some estradiol [22]. In the ovarian follicle, pregnenolone is produced by the granulosa cells which lack CYP17A1 and cannot convert it to androgens. Conversion to androstendione occurs in the in the thecal cells which do express the required CYP17A1. The androstenedione diffuses back into the granulosa cells for conversion to estrone and estradiol by the aromatase enzyme, CYP19A1, and 17βHSD1 [22, 35]. In the Leydig cells of the testis pregnenolone is converted primarily to testosterone with only minor conversion to estrogens due to only low expression of CYP19A1 [23, 34].

The placenta displays some differences to the other steroidogenic tissues in that pregnenolone synthesis it is not limited by cholesterol availability, but rather by the level of steroidogenic electron transport protein adrenodoxin reductase [20]. The placenta does not express the StAR protein but a related START-domain protein, MLN64, appears to play a role in cholesterol transport o the inner mitochondrial membrane [20, 30]. In the placenta, all pregnenolone is converted to progesterone and cannot be converted to estrogens due to the lack of expression of the CYP17A1 necessary for its initial conversion to androgens. The large amounts of estrogens produced by the placenta are derived from the actions of 3βHSD and CYP19A1 on DHEA derived from DHEA sulfate, produced by the fetal adrenal gland [23].

2.2. Extra-adrenal and extra gonadal steroidogenesis

Several tissues besides the adrenal cortex, gonads and placenta express CYP11A1 and therefore can be considered steroidogenic, with pathways that commence form cholesterol. These tissues and their major products are listed in Table 2. The products most likely play an autocrine or paracrine regulatory role in these tissues [36]. It is noteworthy that steroidogenesis in non-classical tissues is quite modest regardless of the stimulant, usually being less than 1% of that seen with cAMP/PKA mediated StAR expression and steroid synthesis in adrenal and gonadal cells. While the magnitude of StAR-mediated response on steroidogenesis is small, it could be very important in local regulation of steroidogenesis in certain non-classical tissues. One of the first non-classical tissues identified to make steroids from cholesterol is the mammalian brain [23, 37]. Steroids produced include pregnenolone, pregnenolone sulfate, DHEA sulfate, progesterone, 3β and 5α reduced derivatives of progesterone, and corticosteroids [23, 36, 38]. Expression of CYP11A1 and its functional activity in the mouse thymus with the production of corticosterone has also been known for some time, but data for the human is lacking [36, 39]. CYP11A1 is expressed in bone but the predominant form has an N-terminal truncation that is only 30 kDa in size and has a non-mitochondrial localization, and is therefore unlikely to be catalytically active [40]. The expression of CYP11A1, 3βHSD and CYP17A1, as well as the steroidogenic capability of benign and malignant prostate and prostate carcinoma lines, as well as prostate stroma, has been demonstrated [41–47]. CYP11A1 expression has been detected at the mRNA level in both breast tumors and surrounding normal breast tissue [48]. The human gut and colon cancer cells also express glucocorticosteroidogenic activity with production of cortisol and corticosterone and expression of CYP11A1, CYP17A1 and CYP11B1 [49–51]. Other organs which display local steroidogenic pathways in humans are the heart, skin and cells of the immune system (see Table 2) including human basophils [52]. Table 3 shows the expression of steroidogenic genes in different cancers, illustrating their likely capacity to synthesize and/or metabolize steroid hormones as has already been shown with melanoma cells [53, 54].

2.3. Glucocortico-steroidogenesis in the skin

Since the first demonstration that human skin expresses crucial genes of glucocorticosteroidogenesis including CYP11A1, CYP17, CYP21A2, CYP11B1 and MC2 [55], a series of sequential investigations have shown that the skin or skin cells can produce deoxycorticosterone (DOC), 18(OH)DOC, corticosterone and cortisol *in situ* [53, 56–61]. These findings have been firmly confirmed by others [62–69]. Furthermore, skin cells express functionally active CYP11A1 (there are also alternatively spliced isoforms of this enzyme in skin cells [54]), StAR and MLN64, and have the capability of starting the steroidogenic pathway *de novo* from cholesterol [54, 70]. They also express 3βHSD [71, 72] allowing the pathway to proceed with final production of glucocorticoids [73] and sex hormones [74]. Thus, evidence has accumulated classifying skin as an additional extra-adrenal organ with an endogenous steroidogenic capacity that is integrated into the regulatory networks of the cutaneous neuro-endocrine-immune system(s) [1]. The scheme and compartmental distribution of different elements of this steroidogenic pathway, which can start from cholesterol are presented in Figures 2 and 3. The synthesis and metabolism of cholesterol in the skin with phenotypic their phenotypic consequences are the subject of separate reviews [6, 75–77]

It is noteworthy, that steroidogenesis in non-classical tissues is quite modest regardless of the stimulant, and in skin cells the rate of cholesterol conversion to pregnenolone represents 1% of that seen in the placenta [54]. This low rate of production could explain the lack of detection of cortisol formation by keratinocytes in earlier studies by Milevich et al. [78] and later by us [79]. In our studies on HaCaT keratinocytes, we have detected rapid metabolism

of progesterone to DOC with further transformation to several products different from corticosterone, aldosterone and cortisol, some of which were identified by GC/MS as 3β,6α, 21-trihydroxy-5α-pregnan-20-one, 3α,6α,21-trihydroxy-α-pregnan-20-one, and 3α,5α-and 3β,5α-tetrahydrodeoxycorticosterone [80]. Minor metabolites were 3α, 21-dihydroxy-5-pregnen-20-one, 3β, 21-dihydroxy-5-pregnen-20-one, 3α, 21-dihydroxy-4-pregnen-20-one, 6-hydroxy-dihydrodeoxycorticosterone, and two 5-dihydrodeoxycorticosterone species. These studies not only confirmed keratinocytic expression of 5α-reductase and 3α/βHSD but also demonstrated expression of 6α-hydroxylase, and reverse Δ4/Δ5 isomerase enzymes [80]. Other researchers using RIA or ELISA have detected cortisol in follicular [59, 68] or epidermal keratinocytes [63–65]. We have also detected cortisol as well as corticosterone production in epidermal melanocytes and dermal fibroblasts (chemical structure was confirmed by LC/MS) [57, 58, 60]. This latter finding substantiates our previous demonstration of rapid and robust transformation of progesterone and DOC into corticosterone in human malignant melanocytes [53]. So far, production of aldosterone has not been detected in epidermal and dermal cells.

Skin expresses 11βHSD1 which is primarily involved in the reduction of the 11-keto group to the alcohol, such as in the activation of cortisone to cortisol [23, 54, 66, 81]. Skin also expresses 11βHSD2 which works in the oxidative direction, converting cortisol to the inactive cortisone [23, 64–66, 81]. The type 2 enzyme plays a key role in mineralocorticoid tissues where it protects the mineralocorticoid receptor from cortisol [23]. Both 11βHSD1 and 11βHSD2 have been detected at the protein level in cultured keratinocytes [64, 81]. Keratinocytes with the type 1 isoenzyme silenced with siRNA produced less cortisol from cortisone than control cells. Conversely, the silencing of 11βHSD2 caused an elevation in cortisol levels [64]. It would appear that both the location and relative activities of these two isoenzymes determines the ability of skin to activate/inactivate both locally produced and pharmacologically administered glucocorticoids [64, 66, 81]. In the mouse skin, 11βHSD1 was found by immunohistochemical staining in keratinocytes, dermal fibroblasts and the outer root sheath of hair follicles, and appears to have a similar distribution in humans [66]. In contrast, 11βHSD2 was not detected in these sites by immunohistochemistry, so that the predominant activity was activation of cortisone to cortisol. Cortisol treatment of human dermal fibroblasts increased 11βHSD1 mRNA expression at the mRNA level, and decreased 11βHSD2 expression, providing a positive feedback loop enhancing glucocorticoid activation [66]. The mechanism for this increase in 11βHSD1 remains to be elucidated. In contrast, dexamethasone treatment of human skin was reported to increase 11βHSD2 expression at the mRNA level [65].

In the liver cortisone is mainly converted to cortisol by 11βHSD1 which is then acted on by 5α- or 5β- reductase and 3αHSD producing 5α- and 5β-tetrahydrocortisol, some of which is metabolised by 20αHSD or 20βHSD to α-cortol or β-cortol, respectively. Similar minor pathways are observed for cortisone without the initial action of 11βHSD1. The reduced products are excreted in the urine, predominantly as glucuronides [82, 83]. There is good evidence that these metabolic pathways may occur in skin. As mentioned above, 5-dihydroxycorticosterone and 3α,5α-tetrahydroxycorticosterone are produced by HaCaT keratinocytes incubated with progesterone, along with 5α-reduced pregnanes, indicating that both 3αHDS and 5α-reductase are present in these cells [80] that could potentially act on cortisol or cortisone.

The expression of StAR has been detected by RT-PCR and immunohistochemical analyses in epidermal keratinocytes, sebocytes, outer root sheath of hair follicles (HFs), vascular tissues and eccrine ducts [62, 63, 69, 84]. In addition to StAR, epidermal keratinocytes also express cholesterol transporters TSPO and MLN64 [54, 63]. Expression of positive [adrenal 4-binding protein/steroidogenic factor 1 (SF-1)] and negative (dosage-sensitive sex reversal,

adrenal hypoplasia congenital, critical region on the X chromosome, gene 1) regulators of StAR has also been detected in the epidermis [63, 85–87]. DAX-1 prominent expression has been confirmed in sebaceous and sweat glands, the basal layer of the epidermis and ORSKs, while SF-1 immunoreactivity was detected across all epidermal layers except of the stratum corneum, IRSKs, matrix cells and DPCs [85, 88]. The co-factor, WT-1, modulates androgen sex steroid production by up-regulating DAX-1 and is also present in the skin [89]. It has been reported that the coiled-coil α-helical rod (CCHCR1) protein is involved in epidermal steroidogenesis and that CCHCR1 colocalizes with the StAR protein [62]. Upregulation of CCHCR1, associated with epidermal growth factor receptor expression, has been demonstrated in skin cancer [90]. We observed recently that expression of StAR mRNA was found to be aberrant in several skin diseases, including eczema, intertrigo, and seborrheic keratosis, suggesting acute steroid synthesis is disrupted in these diseased conditions (Manna et al., data not shown). In accordance with the above findings HaCaT cells treated with a cAMP analog, $(Bu)_2$cAMP, significantly elevated StAR mRNA expression and pregnenolone synthesis over unstimulated cells, respectively (Fig. 4). However, levels of StAR mRNA and steroid synthesis in response to cAMP signaling were substantially lower in HaCaT cells when compared to responses for adrenal and gonadal cells. This suggests a slower onset of StAR localization to mitochondria and lower rates of steroid synthesis in epidermal keratinocytes. Moreover, in contrast to the rapid induction of cAMP-responsive steroidogenesis in various endocrine tissues, in HaCaT cells elevations in StAR and pregnenolone levels require a long period of time. These results may suggest differences between the classical steroidogenic organs and the cutaneous system.

2.4 Synthesis of androgens and estrogens in the skin

Plasma dehydroepiandrosterone sulfate (DHEA-S) and lesser free DHEA originate from the adrenal glands, while androstenedione is produced by the adrenal cortex and ovaries, and less by the testes [74]. Testosterone (T) is mainly secreted by the testes in males with the onset at puberty and in premenopausal females from the ovaries and the adrenal cortex. The most potent androgen, dehydrotestosterone (DHT), is mainly synthesized in peripheral tissues, including skin [74]. Since it cannot be further aromatized to estrogens, its action remains exclusively androgenic. The pilosebaceous unit has all the necessary tools to utilize sex steroid precursors for the transformation to more potent sex hormones [91, 92].

Cutaneous formation of DHEA, the main substrate for the more potent androgens T and DHT, proceeds both from endogenous cutaneous cholesterol (see section 2.3) and from DHEA-S of adrenal origin. In support of the latter, T synthesis by SZ95 sebocytes in vitro derives mainly from DHEA [93]. DHEA-S is hydrolysed in the skin to DHEA by steroid sulfatase, detected in sebaceous glands and dermal papilla cells (DPCs) of terminal HFs [94, 95]. Monocytes also exhibit steroid sulfatase activity, thus introducing the variable of “inflammation” to cutaneous androgen production [96].

Addition of pregnenolone, progesterone and 17α-hydroxyprogesterone led to a significant rise of T levels in culture media, reflecting the activity of 3βHSD1 and 17βHSD3 on SZ95 sebocytes [93]. 3βHSD converts DHEA to androstenedione, which is converted in a further step to T by the enzyme 17βHSD. Human skin expresses predominantly the 3βHSD1 isoform [97]. Interestingly, 5 isozymes of 17βHSD were identified, functioning like a “switch on-off” mechanism for the production of more potent sex steroids: Isozymes 3 and 5 catalyze the formation of T from androstenedione, in contrast to isozymes 2 and 4, which oxidize the inactivation of T to its weaker precursor [98–101]. Synthesis of T from androstenedione in skin, similar to other peripheral tissues, is catalyzed by 17βHSD type 5 [102]. 17βHSD is also detected in ORSKs of HFs, mainly type 2 and moderately type 1 in anagen ones, thus inactivating potent androgens [98, 103].

5α-reductase (5αR) type 1 is the predominant isoform detected in the skin [104, 105] and more abundantly expressed in sebaceous and sweat glands [106], keratinocytes [78, 80] and dermal fibroblasts [107]. 5αR2 is detected in genital skin fibroblasts and IRSKs [107]. The 5αR1 inhibitor MK386 blocked completely the conversion of T to DHT in SZ95 sebocytes and HaCaT keratinocytes and reduced T-induced proliferation of sebocytes [108]. The newly found 5αR3 has been detected in prostate cancer and the SZ95 sebocyte line [109]. Sebocytes normally metabolize T mainly to androstenedione, rather than DHT, since low DHT levels are required for skin homeostasis. 5aR2 mRNA levels were minimal in beard and scalp DPCs as well as normal human fibroblasts, while beard DPCs were the ones mainly expressing 5αR1 at the protein level. The formation of DHT in SZ95 sebocytes does not always require T as an intermediate, since 5α-reduction of androstenedione to 5α-androstanedione and subsequent conversion to DHT by 17βHSD provides an alternative pathway [110]. Moreover, the 3αHSD isozymes convert potent androgens to inactive compounds, which do not bind to AR [74, 111]. 3αHSD is strongly expressed in epidermal keratinocytes [80, 91, 112].

E2 derives from T and E1 from androstenedione. Local estrogen synthesis was correlated with aromatase mRNA levels and cutaneous elastic fiber content [69]. mRNA transcripts of the CYP19 gene were reported in dexamethasone-induced human fibroblasts in vitro [113], while aromatase was expressed in anagen and terminal HFs, cultured keratinocytes, melanocytes, sebaceous glands and adipose fibroblasts [114]. Interestingly, 17α-estradiol increases aromatase activity of female HFs [115]. Estrogens are inactivated through sulfation, by the enzyme estradiol sulfotransferase (SULT1E1) [116]. Its activity is higher in differentiated normal human epidermal keratinocytes (NHEKs) in comparison to proliferating ones [117], suggesting a mechanism of attenuation of estradiol-induced keratinocyte proliferation. Aromatase in skin can serve to fine-tune the relative actions of androgens and estrogens in target cells [118].

Apart from the aforementioned enzymes involved in the formation of more or less potent androgens or estrogens, tissue-specific ones are responsible for the degradation and subsequent elimination of sex steroids, via their transformation to soluble metabolites, which can be excreted in the urine, bile or feces. Enzymes which play a key role in this procedure are CYP enzymes for the hydroxylation, sulfotransferases (SULT) for the sulfation and UDP glucuronosyl transferases (UGT) for the conjugation of sex steroids with glucuronic acid respectively [119–121]. The three UGT2B enzymes, UGTB7, UGTB15, UGTB17, which are responsible for the glucuronation of DHT and its metabolites, androsterone and 3α-diol are all expressed in the skin [122, 123]. E2 is inactivated by estrogen sulfotransferase SULT1E1 in normal human keratinocytes [117]. The SULT2B1 enzyme, member of the SULT2 family, which catalyzes the sulfation of 3β-hydroxysteroids, such as DHEA and pregnenolone, was also detected in the skin [124, 125]. The isoform SULTB1b is abundantly expressed in ORSKs, sebocytes and differentiated epidermal keratinocytes [125]. The SULT1 family consists of enzymes, which primarily sulfate phenolic groups of estrogens. Its member SULT1A1 are located on the outer sheath of rat HF [126]. Expression of the aldo-keto reductases (AKR) AKRC1 and AKRC2 in keratinocytes and fibroblasts leads to inactivation of progesterone and DHT respectively, which are further metabolized through glucuronosyl transferases or hydroxylases [127]. Skin shows immunohistochemical reactivity for the enzyme CYP7B1, which catalyzes the 7α-hydroxylation of DHEA. Moreover, it turns the DHT metabolites 5-androstene-3β,17β-diol (Aene-diol) and 5-androstane-3β,17β-diol (3-Adiol) in compounds with little or no estrogenic effect [128].

2.5. Regulators of local steroidogenic activity

Steroid production in the skin is controlled by several internal and external factors, and is dependent on local enzymatic activity, substrate availability, and mobilization of signal transduction and gene expression pathways.

The hypothalamic-pituitary-adrenal (HPA) axis—Since all regulatory elements of the hypothalamus-pituitary-adrenal gland (HPA) axis, including proopiomelanocortin (POMC)-derived peptides [129], CRH and related peptides as well as the corresponding functional receptors [130, 131] are expressed in mammalian skin, the concept that skin expresses a homologue of the HPA was introduced 15 years ago [2, 73, 132]. Since then, evidence has accumulated that the cutaneous stress system follows the functional hierarchy of the central HPA with its direct local phenotypic consequences and systemic implications [1, 73, 133]. Most recently, it was proposed that the algorithm of HPA first developed in the primordial integument and then was adopted by central neuroendocrine system [134]. In the skin, induction of steroidogenesis by CRH or ACTH, or factors raising intracellular cAMP levels appears to be cell type dependent because induced corticosterone and cortisol formation has been observed in normal and malignant epidermal melanocytes [53, 58] and dermal fibroblasts [57, 60], but not epidermal keratinocytes. On the other hand HF and follicular keratinocytes were found to produce cortisol after stimulation with CRH and ACTH [59, 68]. The production of steroids in the skin after stimulation by CRH is strongly dependent on the CRH-R1 receptor [57–59]. Another important receptor with a regulatory function on steroids synthesis is the glucocorticoid receptor (GR coded by NR3C1), a ligand activated transcription factor that belongs to the nuclear hormone receptor superfamily that regulates gene expression through DNA-binding–dependent and– independent mechanisms. The wide use of glucocorticoid analogs in clinical practice relies on their great efficacy as anti-inflammatory agents, mostly due to the antagonism between ligand-activated GR and the proinflammatory NF-κB, AP-1, and signal transducer and activator of transcription (STAT) signaling pathways in the skin [135]. Though GR is alternatively spliced and species-dependent differences in aminoacid sequences occur, there are two isoforms, GRα and GRβ. Increased ratios of GRβ/GRα have been shown to correlate with resistance to GCs, and constitutes a big challenge in dermatology[136]. Modern dermatology searches for novel synthetic GR ligands that should display a better therapeutic index than the known classical ones [137, 138].

Cytokines—Cytokines serve as communicators between immunological, endocrine and nervous systems [139]. While the vast majority of both pro- and anti-inflammatory cytokines are involved in cutaneous biology, recognizable effects on steroidogenesis were caused by IL-1β and TNFα [140]. IL-1β is a critical mediator of the adaptive stress response and stress associated psycho- and neuropathology [141]. This cytokine plays a fundamental role in the pathogenesis of many inflammatory and autoagressive disorders in the skin, and its expression is up-regulated by UVB [142]. Furthermore, IL-1β can activate receptors localized on sensory nerve endings, and via a reflex switched in DRG is responsible for release of neuroinflammatory substance P (SP) [143, 144]. IL-1β stimulates components of the HPA axis (c-fos expression in CRH-producing parvocellular neurons in the PVN) to enhance cortisol production [141]. Furthermore, IL-1β can directly stimulate human adrenocortical cells [140], and similar stimulation has been also observed in epidermal keratinocytes [65]. This finding may suggest a possible feedback loop that attenuates the initial proinflammatory responses, preventing excess inflammation that can lead to further tissue damage [65]. TNFα, apart from its well-characterized proinflammatory role, has various antiinflammatory properties; an example of the latter is stimulation of the HPA axis resulting in increased steroid production [145]. Suppressor of cytokine signaling (SOCS)

acts as a potent negative regulator of cytokine signaling and suppresses cytokine-induced POMC expression and ACTH release [146].

11βHSD1 and 11βHSD2—Two key enzymes that regulate the local cortisol availability for the GR are 11βHSD1 and 11βHSD2, which are expressed in many peripheral organs [147]. Recent studies have demonstrated that intracellular conversion, performed by these two enzymes, together with GR activity, represent a key mechanism of tissue-specific regulation of GC action contributing to GC deficiency, which constitutes a big challenge in dermatology [64, 66, 81, 148, 149]. The equilibrium between 11βHSD1 and 11βHSD2 expression in the skin together with sympathetic nerves density can maintain immunological homeostasis [1, 64, 150].

Ultraviolet radiation—Ultraviolet radiation (UVR) represents the electromagnetic energy of solar radiation covering wavelengths between 100–400 nm. UVC (100–280nm), when applied to the skin, stimulates cortisol production with simultaneous GR down regulation and upregulation of CRH, POMC, ACTH, β-endorphin, CYP11A1 and 11βHSD1 [81, 151]. UVB (280–320 nm), a recognized stimulator of melanin pigmentation [152], has similar stimulatory effect on CRH and POMC signaling, production of cortisol and inhibition of the GR [81, 129, 131, 151, 153, 154]. UVA (320–400 nm) had no effect on cortisol, CRH and ACTH production but stimulated β-endorphin and 11βHSD2 expression [81, 151, 155].

The CRH signaling system is highly expressed in mammalian skin (epidermis and dermis), and its expression is up-regulated by UVR [1, 131]. UVB stimulated CREB phosphorylation and the binding of phosphorylated CREB to CRE sites in the CRH promoter [156]. Next, CRH interacts with CRH-R1 stimulating cAMP production with a subsequent increase in POMC gene expression and production of ACTH [57, 60]. Pharmacological inactivation of CRH-R1 by selective inhibitors abrogated the UVB-stimulated induction of POMC production [156]. ACTH stimulates the cutaneously distributed MC2R to start steroidogenesis leading to cortisol/corticosterone production. The paracrine communication in the skin modulated by internal and external stressors can include nerve fibers, keratinocytes, melanocytes, fibroblasts and immune cells to maintain cutaneous homeostasis [1].

2. 6. Non-classical steroidogenesis

A recent review by Shackleton [157] describes in an elegant manner alternative branches in steroidogenesis that are relevant to the skin. Firstly, the 7-Δ reductase deficiency observed in Smith–Lemli–Opitz syndrome (SLOS), in an addition to severe malformations, results in development of skin photosensitivity to UVA [158, 159] and production a series of unusual steroids [79, 160, 161]. 7DHC (7-dehydrocholesterol) can be metabolized by CYP11A1 through hydroxylation at C22 followed by C20, cleavage of the site chain and subsequent metabolism of the 7DHP (7dehydropregnenolone) by existing steroidogenic enzymes [54, 162, 163] (Fig. 5). Interestingly, all of the resulting 5–7 dienes are potential source of vitamin D analogues with short side chain when subjected to UVR [54, 164], while the hypersensitivity of skin in SLOS patients has recently been explained by reactive oxigen species dependent formation of 5, 7, 9(10)-trienes. It was shown that cholesta-5,7,9(11)-trien-3β-ol (9-DDHC) derivative of 7DHC is indeed formed in the skin subjected to UVA irradiation [158]. Such a compound was capable of generating singlet oxygen in the cycle reaction stimulated by UVR [158, 165]. Interestingly, we have recently shown that another 5,7-diene, pregna-5,7-diene-3β,17α,20-triol, when subjected to UVR may also be converted to a triene, namely pregna-5,7,9(11)-triene-3β,17α,20S-triol [166]. The accumulation of unusual steroidal 5,7-dienes in skin subjected to UV irradiation may generate new classes of secosteroids with modified side-chains [166, 167]. It has to be stressed that such reactions

lead not only to formation of vitamin D analogues, but also to other tachysterol- and lumisterol-like derivatives. This photoconversion of 5–7-dienes was demonstrated not only *in vitro* [164, 166, 167] but also *ex vivo* in human skin [166]. In addition, mutation of any gene encoding enzymes involved in steroidogenesis in the skin may result in local formation of unusual steroids, as extensively reviewed recently [157]. Finally, expression of CYP11A1 in the skin is also responsible for the local generation of novel secosteroids with a full-length side chain [168].

3. Role of local steroidogenic pathways in inflammatory disorders

3.1. Role of local glucocosteroidogenic pathways in inflammatory disorders

Multiple components of innate and adaptive immune systems contribute to pathogenesis of different inflammatory disorders of the skin, including atopic dermatitis, psoriasis, acne vulgaris and alopecia areata. Although described mechanisms typically center on the role of various immune cells and in particular on cytokines, the role of glucocorticosteroids is also emerging. Of note, most treatments for these entities include various analogs of corticosteroids [4]. It has recently been proposed that inflammatory skin diseases may be driven by locally produced CRH that stimulates pro-inflammatory pathways that in turn are not inhibited by glucocorticosteroids [130, 169–172]. These proinflammatory activities can be counteracted by locally produced POMC derived peptides [73, 129, 173] and by locally produced glucocorticoids [1, 73]. Note, that IL-1 affects expression of steroidoigenic enzymes and production of cortisol in the skin [65].

Atopic dermatitis is characterized by extensive pruritus leading to extensive lichenification. Specifically, this is initially a Th-2 entity mediated by IL-4 and IL-5 that with time becomes driven by the cellular mode of immune response mediated by INFγ [174]. Atopic patients demonstrate a blunted response to stress (decreased production of cortisol) compared to normal controls [175]. Production of IL-4 and IL-5 is suppressed by glucocorticosteroids [176]. The absence of GRs in atopic dermatitis leads to impairment of skin permeability function [177]. Psoriatic lesions are sharply demarcated plaques with silvery scale in characteristic distribution including scalp, elbows and knees. The Th1 immune response with increased levels of IL-2 and INFγ occurs in psoriasis. IL-23, IL-17 and Th17 lymphocytes lead to increased levels of IL-22 that stimulates keratinocyte proliferation [16, 178]. Coiled-coil alpha-helical rod protein 1 (CCHCR1) promotes steroidogenesis by interacting with StAR. CCHCR1 expression in psoriatic plaques is decreased [62]. Methylprednisolone inhibits production of IL-17 by lymphocytes [179]. StAR expression has been demonstrated to be decreased or absent in psoriatic and atopic dermatitis when compared to normal skin tissues [62, 63]. Psoriatic patients have lower saliva cortisol levels [138]. Alopecia areata is a non-scarring alopecia that typically presents as well-circumscribed patches of hair loss with exclamation-mark hairs, cadaver hairs and nail pitting [180]. The HF is considered an immune privilege organ that can also be maintained by POMC-derived peptides including melanocyte stimulating hormone (MSH) [129, 180, 181] and perhaps cortisol [59, 182]. The higher elements of the HPA axis are functional within the pilosebaceous unit and provide another important element maintaining the immune privilege of this site [131, 133, 171, 183]. Down-regulation of immune privilege and local activation of the immune system is considered to be operative in alopecia areata [180]. However, in a mouse model of alopecia areata, the basal plasma levels of ACTH and cortisol are higher than in normal mice, although in response to stress the levels are lower [34]. Levels of cortisol change within the HFs, which might reflect its systemic concentration or change in local production [184]. However, it was recently documented that indeed those levels can change locally without central input [68]. In summary, effectors of the HPA and glucocorticoids in particular play significant roles in common inflammatory

skin diseases, and targeted regulation of cutaneous HPA represents an exciting future approach to treat skin pathology [1, 73].

Autoimmune progesterone dermatitis is a cyclic condition of which clinical manifestations are triggered by progesterone surges during luteal phase of the cycle [185]. The symptomatology includes erythema multiforme and urticaria although disease has debatable variety of clinical and histopathological presentations [186]. Progesterone clearly causes this condition only in some women. It is possible that abnormal local cutaneous metabolism of systemically delivered progesterone is responsible for symptomatology. Different defects or levels of expression of enzymes involved in steroidogenesis and steroid metabolism might affect local processes that in turn lead to different clinical and histopathological expressions of this entity.

3.2. Role of sex hormones in inflammatory disorders

In skin, androgens mediate their effects through interaction with the androgen receptors (AR) triggering cascades of networks [91, 106, 187–189]. Higher levels of AR were detected in the balding than non-balding scalp [190], while DPCs from the occipital scalp did not express AR [191] and the expression of AR co-activator was higher in DPCs localized at the beard and frontal scalp than in the occipital scalp [192]. Very high doses of T or DHT induce apoptosis of DPCs through the bcl-2 pathway [193].

Androgens have a central role in acne, since acne onset is correlated with adrenarchal rise of blood DHEA-S levels [194], it manifests in congenital adrenal hyperplasia [195], is seen during hyperadrogenism in women [196], and it develops during anabolic steroid administration [197]. Cutaneous manifestations (SAHA syndrome [198] – seborrhea, acne, hirsutism, male-pattern alopecia) are common in cases of androgen excess. T and DHT promoted sebocyte proliferation *in vitro* at concentrations higher than physiological levels [70, 199], while their synergistic effect with the PPAR ligand linoleic acid resulted in increased lipogenesis [200].

Greater activity of the 17βHSD types 3 and 5 was detected in sebaceous glands of facial skin than in other, non-acne prone skin areas, suggesting the *in situ* more potent androgen formation in these areas [74, 101]. Strong expression of steroid sulfatase was detected in sebaceous glands of acne lesions [74]. 17βHSD2 (which can inactivate potent androgens) and was found mostly in sebaceous glands of non-acne prone areas in comparison to facial skin [99]. Although 5αR1 is the main enzyme converting T to DHT in human sebaceous glands, the use of selective inhibitors did not improve acne vulgaris lesions [201]. This might be interpreted to be due to reduced production of DHT by other 5αR isozymes to the minimal quantity required to trigger cellular responses, and/or the idea that T rather than DHT plays the main role in stimulating sebaceous lipogenesis [107, 202].

Of the two intracellular estrogen receptors, ERα and ERβ, ERβ is the predominant ER of human scalp skin [203] and is expressed in NHEKs. ERα expression of foreskin NHEKs was also reported *in vitro* [204, 205]. DPCs, in contrast to normal human fibroblasts, express double mRNA levels for ERα than for ERβ [111]. Both receptors have been immunohistochemically detected in human sebocytes *in situ*, but ERα was restricted in basal sebocytes [206]. Apocrine and eccrine glands also express ERβ, but not ERα [74, 207, 208].

Estrogens stimulate the proliferation of NHEKs [209], increase acid mucopolysaccharides, hyaluronic acid, collagen I and III synthesis [210, 211], promote wound healing [212], protect from photoageing [213] and prevent wrinkle formation and skin dryness of post-menopausal women [214]. Estrogens are believed to stimulate hair growth in men, by prolonging the anagen phase of the HF and postponing their transition to telogen phase

[114]. *In vitro* E2 has an inhibitory effect in hair shaft elongation in female occipital scalp, while it promotes it in fronto-temporal male HFs [213, 215]. E2 stimulates HF vascular endothelial growth factor (VEGF) synthesis [216]. Estrogens suppress lipogenesis and the size of sebaceous glands in both sexes directly and indirectly, through affecting the gonadotropins released from the pituitary [106].

ERRβ and ERRγ, two orphan members of the nuclear receptor superfamily, are expressed in human skin and may also have a role in cutaneous estrogen signaling [217, 218].

Acne is the most common chronic disorder of the pilosebaceous unit, appearing usually during puberty. Its multifactorial pathogenesis includes local cutaneous sex-hormone hyperproduction or hyperresponsiveness of the epithelial cells involved, inflammatory processes and defects of adaptive immunity [219–224]. Human sebocytes express TLR-2 [225], which is activated by *P. acnes,* thus triggering innate immunity mechanisms. Involvement of SP, the CRH signaling system and the MC1 receptor in acne development was also suggested [226–229]. The androgen/AR complex does not only affect sebaceous gland activity, but also its inflammation, by augmenting the inflammatory responses of neutrophils and macrophages [230, 231].

Rosacea is a chronic, progressive disorder of the interfollicular skin, affecting mainly the convexities of the central face [171, 232]. The mechanisms involved in the disease can be triggered by cytokines, hormones, neuropeptides [233–235], and CRH [169, 171]. UV-radiation is considered as an initial stress factor, which triggers the cutaneous inflammatory response [236, 237]. However, UV radiation can also create a local immunosuppressive microenvironment (see 2.5).

Hidradenitis suppurativa/acne inversa (HS) is defined as “a chronic, inflammatory, recurrent, debilitating skin disease of the terminal HFs with deep-seated, painful and inflamed lesions of the apocrine gland bearing areas of the body, most commonly the axillae, inguinal and anogenital regions” [238–240]. A hypothesis of hyperandrogenism was suggested since premenstrual exacerbations, female preponderance, occurrence after menarche and improvement during pregnancy were observed [241–243]. Altered serum androgen levels [244] are rare in HS patients. Comorbidity with Crohn’s disease and other autoinflammatory Th17-induced diseases [238], subsequent bacterial colonization of the lesions [245, 246] and the response of HS patients to anti-TNFα factors strongly suggest involvement of the immune system.

3.3. Local and systemic autoimmune diseases originating in or involving the skin

Lupus erythematosus (LE) has several cutaneous variants and also a systemic form. The diagnosis is made based, on among other things, on the presence of anti-nuclear antibodies including anti-native DNA (systemic LE), anti-Sm (systemic LE), and anti-Ro (subacute cutaneous LE) [247]. Antigen-antibody complexes are deposited at the dermo-epidermal junction. What triggers production of autoantibodies is still not known, although various genetic and environmental factors are considered [4, 247]. Corticosteroids are one of the main medications used for treatment [4, 247]. Levels of androstenedione, cortisol and DHEA-S are lower in patients with systemic LE than in healthy subjects [248]. ACTH levels do not differ between LE patients and controls [248]. Glucocorticoid treatment seems not to be responsible for these changes but they are possibly due to abnormal cytokine levels or a Th17/Th1 imbalance [248, 249]. In other studies, untreated LE patients had levels of 17-hydroxypregnenolone and cortisol similar to controls, and levels of progesterone, 17-hydroxypogesterone, androstenedione, DHEA and DHEA-S lower than controls [250]. Inhibition of the C17-C20 lyase step of the of CYP17 reaction can also be responsible for decreased levels of steroids in LE patients [250].

Systemic sclerosis (SSc, scleroderma) is an autoimmune disease characterized by a poorly understood vasculopathy, autoimmunity, and extensive deposition of extracellular matrix (ECM) components in skin, lungs, gastrointestinal tract, heart and other body structures [4, 251]. Endothelial damage contributes to ongoing platelet aggregation with release of a member of fibrogenic mediators such as TGFβ1, TGFβ2, IL-4, platelet derived growth factor (PDGF), connective tissue factor, sphingosine 1-phosphate and lysophosphatidic acid [252]. Defective angiogenesis, neointimal proliferation and vascular spasm contribute to tissue hypoxia further stimulating ECM deposition [252]. There is also predominance of Th17 and Th2 cells with release of IL-17, IL-4 and IL-13 at sites of lymphocytic infiltration which contributes to ongoing fibrosis [252]. Basal levels of cortisol, androstenedione, DHEA-S and 17-hydroxyprogesterone in patients with SSc do not differ from healthy controls [253, 254]. Levels of DHEA are lower and of ACTH are higher in SSc patients [254]. They also have a diminished response to a stress test or hypoglycemia, i.e. their level of cortisol does not increase [253, 254]. Apparently, the HPA axis malfunctions in these patients.

4. Systemic implications of cutaneous steroidogenesis and conclusion

Since skin is the largest organ of the human body with powerful neuroendocrine activities (for most recent review see [1]), local production of sex steroids makes a significant contribution to circulating androgens and/or estrogens [255]. Up to half of the total circulating T is produced from skin and other peripheral organs [198]. The stromal cells of adipose tissue express CYP19A1 (aromatase) [256, 257] and provide a source of androgens for both sexes. The skin-located formation of E1 from circulating androstenedione can be the main site of estrogen biosynthesis in postmenopausal women, obese individuals and elderly men. Interestingly, CYP19A1 gene expression is higher in subcutaneous than omental adipose tissue [258–260]. The intracrine production of estrogens in peripheral tissues in women is around 75% in premenopausal and almost 100% in postmenopausal women, with a minor contribution from adrenal and ovarian T and androstenedione [97].

Although it still remains to be tested whether skin produced CRH, urocortin and ACTH can affect pituitary or adrenal functions, it is already well documented that CRH and POMC signaling systems in communication with cytokines can regulate local steroidogenic activity and skin immune activity in a context and compartment dependent manners (for most recent review see [1]). Furthermore, after exposure to UVB human skin in organ culture produces and secretes CRH, POMC derived ACTH, β-endorphin and cortisol [151]. Similarly, *in vivo* studies demonstrate that HF releases cortisol into the hair shaft after local pain stimuli [68]. Thus, it is likely that depending on the type and strength of the stressor(s), cutaneous elements of HPA including POMC-derived peptides and glucocorticoids will be released into the circulation. We have already obtained initial evidence that mice exposed to UVB show increased serum levels of ACTH, β-endorphin and corticosterone (Skobowiat and Slominski, in preparation). Furthermore, locally produced glucocorticoids or POMC-peptides can induce resident and circulating immune cells to express immunosuppressive phenotype with potential systemic implications as suggested previously [1]. The biological significance of novel local secosteroidogenic pathways based on action of CYP11A1 on 7DHC and vitamin D represents a new exciting challenge is skin research [163, 168].

In conclusion, skin is a steroidogenic organ in which local steroidogenic activities can regulate local and systemic immune activities, and dysregulation of cutaneous steroidogenesis may be etiologically linked to inflammatory or autoimmune skin diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS LIST

ACTH	adrenocorticotropic hormone
cAMP/PKA	cAMP-dependent protein kinase A
CD	cluster of differentiation
CRH	corticotrophin releasing hormone
CYP11A1 or P450 scc	cytochrome P450 side-chain cleavage enzyme
CYP11B1	11-hydroxylase type 1
CYP11B2	11-hydroxylase type 2
CYP17A1 or P450c17	cytochrome P450 17α-hydroxylase/17,20-lyase
CYP21	21-hydroxylase
DAX-1	dosage-sensitive sex-reversal-adrenal hypoplasia congenital critical region on the x-chromosome, gene 1
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
DOC	deoxycorticosterone
DPCs	Dermal Papilla Cells
E1	Estrone
E2	estradiol
ECM	extracellular matrix
ERE	estrogen response element
ERR	estrogen-related receptor
F-1	steroidogenic factor 1
GM-CSF	granulocyte-macrophage colony-stimulating factor
HPA	hypothalamus-pituitary-adrenal gland
HF	hair follicle
HS	Hidradenitis suppurativa/acne inversa
3α-HSD	3α-hydroxysteroid dehydrogenase
3β-HSD	3β-hydroxysteroid dehydrogenase
HSD11B1 or 11-HSD 1	11-hydroxysteroiddehydrogenase type 1
HSD11B2 or 11-HSD 2	11-Hydroxysteroiddehydrogenase type 2
17β-HSD	17β-hydroxysteroid dehydrogenase
INF	interferon
IRSKS	Inner root sheath keratinocytes

LE	Lupus erythematosus
MHC	major histocompatibility complex
NFkB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHEKs	normal human epidermal keratinocytes
ORSKs	outer root sheath keratinocytes
POMC	proopiomelanocortin
5αR	5α-reductase
SSc	Systemic sclerosis
SP	substance P
StAR	steroidogenic acute regulatory protein
T	testosterone
TGFβ	Transforming growth factor β
Th	T helper
GR	glucocorticoid receptor
MR	mineralocorticoid receptor
UVR	ultraviolet radiation

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Highlights

- Human skin produces and metabolizes glucocorticosteroids
- Human skin produces and metabolizes sex hormones
- Cutaneous steroidogenesis is regulated by local factors and UVR
- Skin derived steroids regulate activity of skin immune system
- Dysregulation of cutaneous steroidogenesis can lead to inflammatory or autoimmune disorders

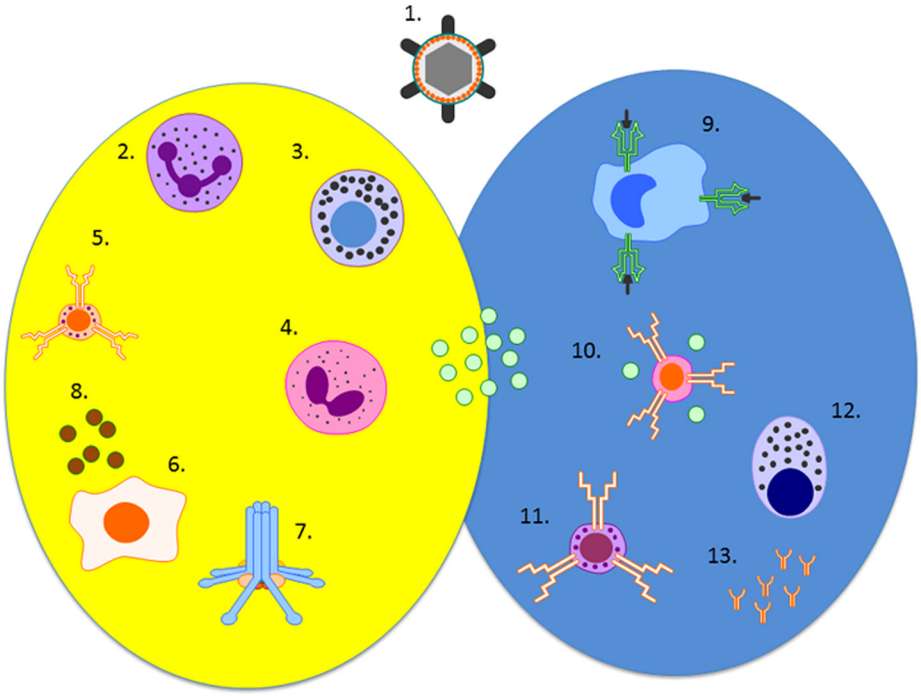

Figure 1. Elements of innate and adaptive immune system

Yellow circle: innate part; blue circle: adaptive part; green dots: cytokines; 1. Microbe; 2. Neutrophil; 3. Mast cell; 4. Eosinophil; 5. NK cell; 6. Keratinocyte; 7. Complement; 8. Antimicrobial peptides; 9. Langerhans cell; 10. T helper 1/2/17 lymphocyte; 11. Cytotoxic lymphocyte; 12. Plasma cell; 13. Antibodies.

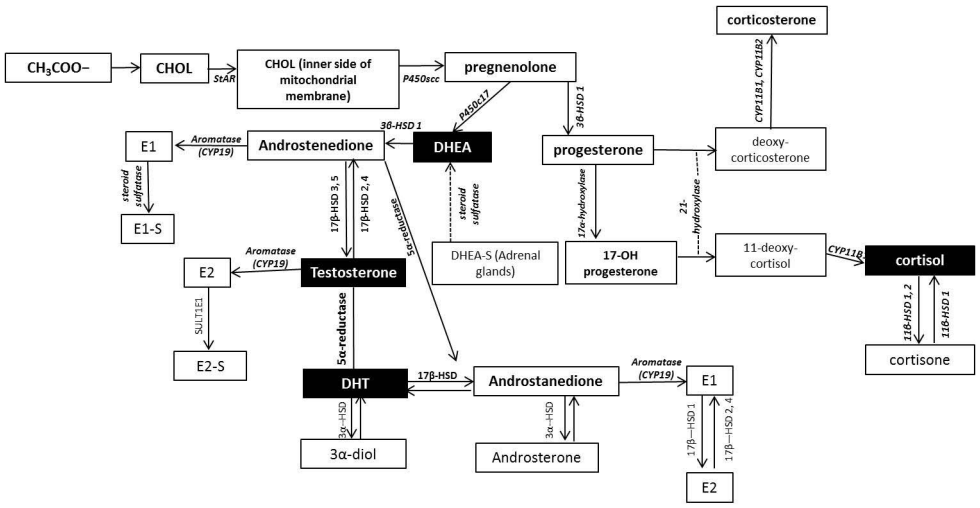

Figure 2. Cutaneous steroidogenic pathways

DHEA: dehydroepiandrosterone, StAR: steroidogenic acute regulatory protein, CYP11A1 or P450scc: cytochrome P450 side-chain cleavage enzyme, CYP17A1 or P450c17: cytochrome P450 17α-hydroxylase/17,20-lyase, 3β-HSD: 3β-hydroxysteroid dehydrogenase, DHEAS: dehydroepiandrosterone sulfate, DHT: dihydrotestosterone, 3α-HSD: 3α-hydroxysteroid dehydrogenase, SF-1: steroidogenic factor 1, E2: estradiol, SULT1E1: estradiol sulfotransferase, E1: Estrone, 5αR: 5α-reductase, HSD11B1 or 11-HSD1: 11-hydroxysteroiddehydrogenase type 1, HSD11B2 or 11-HSD2: 11-hydroxysteroiddehydrogenase type 2, CYP21: 21-hydroxylase, CYP11B1: 11-hydroxylase type 1, CYP11B2: 11-hydroxylase type 2

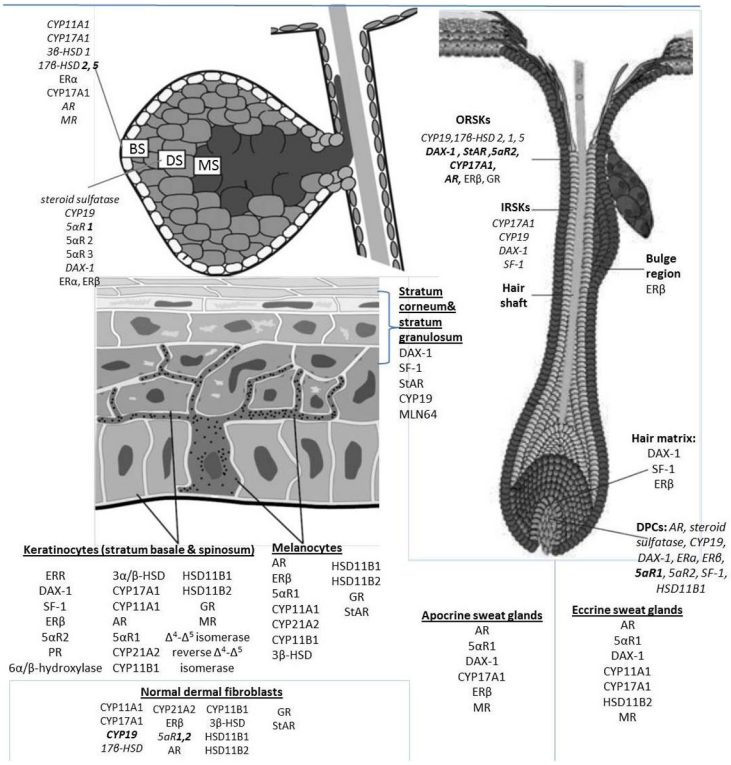

Figure 3. Compartmental expression of enzymes and co-factors involved in cutaneous steroidogenesis

DPCs: Dermal Papilla Cells, ORSKs: outer root sheath keratinocytes, IRSKS: Inner root sheath keratinocytes, BS: Basal Sebocytes, DS: differentiating sebocytes, MS: mature sebocytes, AR: androgen receptor, HF: hair follicle, SF-1: steroidogenic factor 1, SREBP-1: sterol response binding protein-1, DAX-1:dosage-sensitive sex-reversal-adrenal hypoplasia congenital critical region on the X-chromosome, gene 1, ERR: estrogen-related receptor, ERα/β: estrogen receptor α or β, PR: progesterone receptor, GR: glucocorticoid receptor, MR: mineralocorticoid receptor,

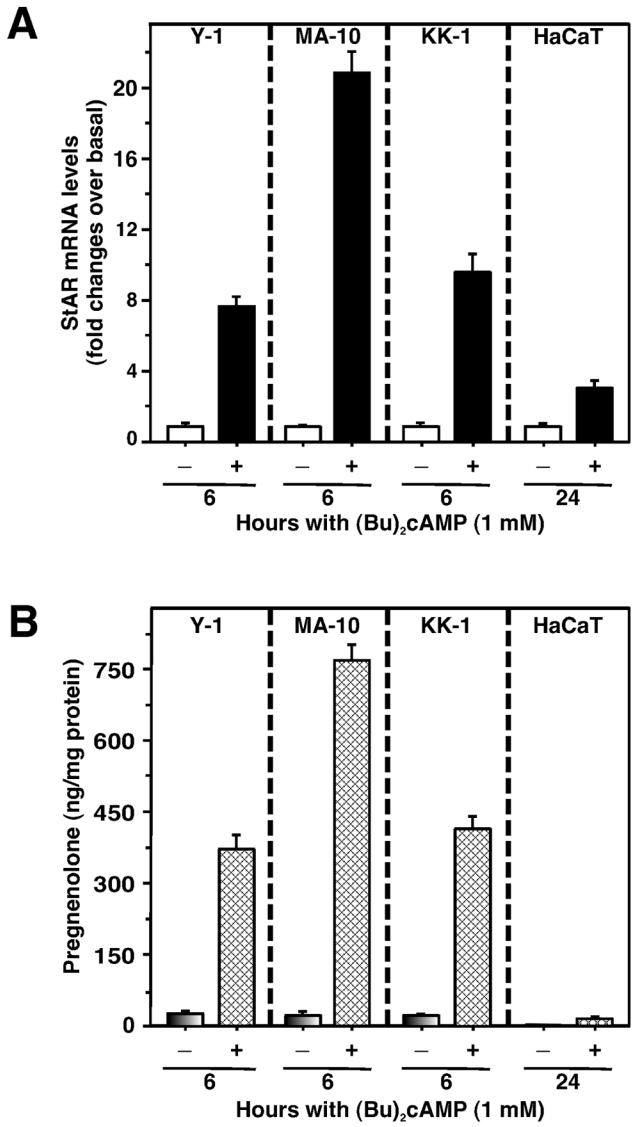

Figure 4. $(Bu)_2$cAMP stimulates StAR gene expression and pregnenolone production

Detailed methodology is in Supplementary Methods. Briefly, mouse adrenocortical (Y-1), Leydig turmor (MA-10), granulosa (KK-1), and human keratinocyte (HaCaT) cells were treated without or with $(Bu)_2$cAMP (1.0 mM) as indicated, in the presence of SU-10603 (20 μM) and cyanoketone (5 μM). StAR mRNA expression (**A**) was measured by quantitative real-time PCR, while accumulation of pregnenolone in conditioned media (**B**) was determined by RIA. Gene expression is shown as fold changes in StAR mRNA levels relative to untreated cells, while levels of pregnenolone are expressed as ng/mg protein. Results represent means ± SE of four independent experiments.

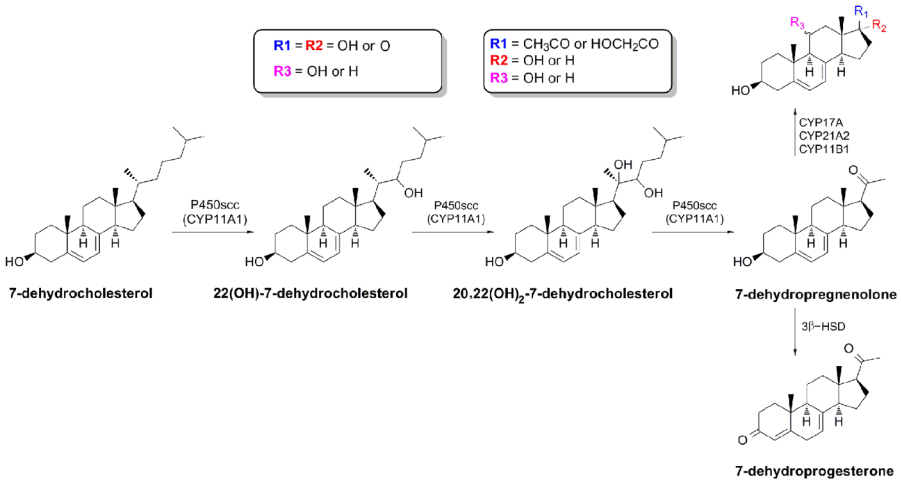

Figure 5.
Production of 7-Δ-steroids in the skin.

Table 1

Expression of CYP enzymes involved in steroid biosynthesis and the major steroid products in classical steroidogenic tissues.

Organ/tissue	CYP enzymes	Other Steroidogenic proteins	Major Steroid products
Adrenal cortex, zona glomerulosa	11A1, 17A1, 21A2, 11B2	StAR protein, 3βHSD2	aldosterone
Adrenal cortex, zona fasciculata	11A1, 17A1, 21A2, 11B1	StAR protein, 3βHSD2	cortisol
Adrenal cortex, zona reticularis	11A1, 17A1, 11B1	StAR protein, cytochrome b5, sulfotransferase	DHEA-S
Ovary, corpus luteum	11A1, 17A1, 19A1	StAR protein, 3βHSD2,	progesterone,
Ovary, follicle, granulosa cells	11A1, 19A1	StAR protein, 17βHSD1	estradiol
Ovary, follicle, thecal cells	17A1	3βHSD2	androstendione (converted to estrogen in granulosa)
Testis, leydig cells	11A1, 17A1,	StAR protein, 3βHSD2, 17βHSD3	testosterone
Placenta, syncytiotrophoblasts	11A1, 19A1	MLN64, 3βHSD1, 17βHSD1, steroid sulfatase	progesterone, estradiol, estrone, estriol

See [23] for further details of steroidogenesis in the tissues listed.

Table 2

Extra-adrenal and extra-adrenal steroidogenesis in humans.

Tissue	CYP Enzymes	Other Steroidogenic proteins	Major Products from cholesterol	References
Brain	11A1, 17A1, 11B1, 11B2, 2D6 (21-hydroxylase)	StAR, 3βHSD, sulfotransferase, 5α-reductase 3αHSD	pregnenolone sulfate, DHEA-S, corticosteroids	[23, 36, 38]
Gut	11A1, 17A1, 21A2, 11B1	3βHSD	cortisol	[36, 49]
Heart	11A1, 21A2, 11B1,11B2	StAR, 3βHSD	aldosterone	[36]
Mammary Gland	11A1, 19A1		Unknown	[36, 48]
Prostate (including tumors)	11A1, 17A1	StAR, MLN64, 3βHSD, 17βHSD, 11βHSD, 5α-reductase, cytochrome b5	progesterone, androgens	[41–47].
Skin	11A1, 17A1, 21A2, 11B1, 19A1	StAR, MLN64, adrenodoxin, adrenodoxin reductase, 3βHSD1, 17βHSD, 11βHSD	glucocorticoids, androgens, estrogens	[65, 69, 73, 151, 255] Also see Sections 2.3 and 2.4.
Thymus* (mouse)	11A1, 11B1, 21A2	StAR, 3βHSD	corticosterone	[36, 39]

*Steroidogenesis in thymus is for mouse species.

Table 3

Relative expression of genes coding steroidogenic enzymes in various cancers.

Cell Line	7DHCR	CYP11A1	3βHSD	CYP21A2	CYP11B1	CYP17A1	HSD11B1
Osteosarcoma (MG63)	14.14±0.26	10.07±0.01	21.20±0.19	22.38±0.01	20.16±0.38	7.16±0.26	10.18±0.04
Glioblastoma (U87)	9.44±0.37	15.57±0.05	16.7±0.17	22.1±0.02	22.1±0.02	6.57±0.03	16±0.04
Breast carcinoma (MCF7)	8.05±0.32	20.59±0.26	20.74±0.03	20.74±0.03	20.74±0.03	14.34±0.03	11.17±1.76
Breast carcinoma (MDA-MB 231)	13.6±0.06	20.59±0.26	18.33±0.18	0.47±0.48	18.19±0.3	18.57±0.4	16.74±0.13
Breast carcinoma (MDA-MB 453)	9.57±0.23	14.80±0.11	21.88±0.1	10.24±10.08	20.22±0.32	6.61±0.36	17.77±0.14
Melanoma (WM164)	16.36±0.08	13.18±0.04	18.34±0.07	9.28±0.48	21.6±0.18	19.49±0.12	10.51±0.06
Melanoma (WM1341)	11.44±0.26	19.84±0.17	17.25±0.08	8.7±0.06	21.9±0.34	7.68±0.02	22.81±0.49
Melanoma (WM98D)	15.93±0.19	13.18±0.04	15.93±0.19	−19.07±0.0	15.93±0.19	15.93±0.19	13.84±0.22
Melanoma (YUROB)	17.83±0.98	19.84±0.17	21.41±0.51	−13.290.0	19.33±0.41	21.71±0.04	18.08±0.21
Melanoma (YULAC)	0.03±0.0	20.21±0.48	23.36±0.33	−11.64±0.0	22.14±0.49	22.87±0.54	23.16±0.48
Oral squamous cell carcinoma (SCC15)	10.26±0.0	11.03±0.0	21.35±0.0	22.42±0.0	21.84±0.0	15.1±0.0	15.1±0.0
Oral squamous cell carcinoma (SCC25)	9.88±0.41	10.07±0.01	17.49±0.34	5.47±0.37	17.19±0.46	18±0.46	12.92±0.38
Promyelocytic leukemia (HL-60)	8.42±0.34	19.64±0.13	18.64±0.31	21.54±0.03	19.07±0.35	12.99±0.04	21.54±0.03
Myelogenuous leukemia (K562)	17.91±0.26	14.80±0.11	21.02±0.13	15.97±0.16	21.02±0.13	18.18±0.31	19.86±0.19
Promonocytic leukemia (U937)	14.09±0.23	11.03±0.0	19.07±0.08	−15.93±0.0	17.30±0.22	14.07±0.09	18.58±0.43
T-cell leukemia (Jurkat)	13.44±0.32	19.64±0.13	19.41±0.16	8.18±0.29	20.90±0.14	15.03±0.15	20.75±0.42
Embryonic kidney (HEK293)	11.55±0.33	15.57±0.05	16.03±0.1	21.26±0.06	19.28±0.09	15.17±0.08	21.26±0.06

Lower the number the higher is gene expression level. Detailed methodology is in Supplementary Methods.

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