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Review article

Local cortisol/corticosterone activation in skin physiology and pathology

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ABSTRACT

Cortisol and corticosterone are the endogenous glucocorticoids (GCs) in humans and rodents, respectively. Systemic GC is released through the hypothalamic-pituitary-adrenal (HPA) axis in response to various stressors. Over the last decade, extra-adrenal production/activation of cortisol/corticosterone has been reported in many tissues. The enzyme that catalyzes the conversion of hormonally inactive cortisone/11-dehydrocorticosterone (11-DHC) into active cortisol/corticosterone in cells is 11β-hydroxysteroid dehydrogenase (11β-HSD). The 11β-HSD1 isoform is predominantly a reductase, which catalyzes nicotinamide adenine dinucleotide phosphate hydrogen-dependent conversion of cortisone/11-DHC to cortisol/corticosterone, and is widely expressed and present at the highest levels in the liver, lungs, adipose tissues, ovaries, and central nervous system. The 11β-HSD2 isoform, which catalyzes nicotinamide adenine dinucleotide$^+$-dependent inactivation of cortisol/corticosterone to cortisone/11-DHC, is highly expressed in distal nephrons, the colon, sweat glands, and the placenta. In healthy skin, 11β-HSD1 is expressed in the epidermis and in dermal fibroblasts. On the other hand, 11β-HSD2 is expressed in sweat glands but not in the epidermis. The role of 11β-HSD in skin physiology and pathology has been reported recently. In this review, we summarize the recently reported role of 11β-HSD in the skin, focusing on its function in cell proliferation, wound healing, inflammation, and aging.

Contents

1. Introduction

Cortisol and corticosterone are the endogenous glucocorticoids (GCs) in humans and rodents, respectively. The endogenous GC is

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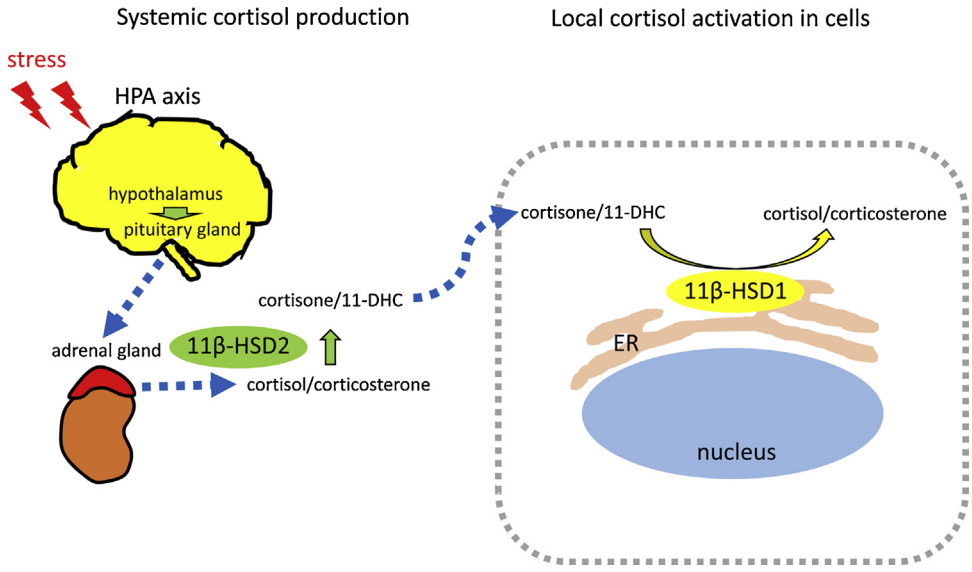

Fig. 1. Systemic cortisol production and local cortisol activation in cells. Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase; ER, endoplasmic reticulum; HPA, hypothalamic-pituitary-adrenal.

released in response to various stressors, such as physical injury and psychological stress. It regulates biological processes including growth, development, metabolism, and behavior [1,2]. Systemic GC is released through the hypothalamic-pituitary-adrenal (HPA) axis. In response to stress, the hypothalamus secretes corticotropin-releasing hormone, which stimulates the release of adrenocorticotropic hormone from the pituitary and cortisol from the adrenal cortex.

In addition to the production of cortisol/corticosterone through the HPA axis, extra-adrenal production/activation of cortisol/corticosterone has been reported in tissues, such as the colon, heart, and lung [3–9] (Fig. 1). Skin is known to have neuroendocrine properties. Skin cells can produce hormones, such as thyroid stimulating hormone, oxytocin, growth hormone, thyroid-releasing hormone, and corticotropin-releasing hormone [10]. In addition, skin is steroidogenic tissue as it expresses CYP11A1, the enzyme that initiates conversion of cholesterol to pregnenolone. Production of cortisol in skin cells was first reported in melanoma cells, and then in melanocytes [11,12]. We and others reported local cortisol/corticosterone activation in the skin via the cortisol-activating enzyme 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) [13].

Skin is exposed daily to various forms of mechanical and chemical stimulation. Chemical stimuli, such as ambient particulate matter, induces barrier disruption [14]. In addition, ultraviolet B (UVB) irradiation, tape stripping, and *Staphylococcus aureus* colonization are known to induce proinflammatory cytokines, such as tumor necrosis factor α and interleukin-6 [15,16]. Thus, we hypothesized that local cortisol/corticosterone activation by 11β-HSD1 in keratinocytes plays a role in regulating local stress to counterbalance repeated stimulation.

In this review, we summarize data recently reported on the role of cortisol/corticosterone-activating enzyme 11β-HSD in the skin, especially focusing on its function in cell proliferation, inflammation, and aging.

2. Local cortisol activation in the skin

11β-HSD catalyzes the interconversion between hormonally active cortisol/corticosterone and inactive cortisone/11-dehydrocorticosterone (11-DHC) in cells. The two isoenzymes of 11β-HSD both reside in the membrane of the endoplasmic reticulum [17]. The 11β-HSD1 isoform is predominantly a reductase, which catalyzes nicotinamide adenine dinucleotide phosphate hydrogen-dependent conversion of cortisone/11-DHC to cortisol/corticosterone, and is widely expressed and present at the highest levels in the liver, lungs, adipose tissues, ovaries, and central nervous system. In some cells, it also acts as a nicotinamide adenine dinucleotide phosphate-dependent dehydrogenase. The 11β-HSD2 isoform, which catalyzes nicotinamide adenine dinucleotide$^+$-dependent inactivation of cortisol/corticosterone to cortisone/11-DHC, is highly expressed in distal nephrons, the colon, sweat glands, and the placenta (Fig. 2). Approximately 90% of the released cortisol is bound to corticosteroid-binding protein. On the other hand, cortisol's inactive form, cortisone, has a lower binding affinity to corticosteroid-binding protein. Circulating cortisone is converted to active cortisol in tissue through 11β-HSD1.

Association of 11β-HSD1 with various diseases has been reported. In 2001, Masuzaki et al. reported that transgenic mice overexpressing 11β-HSD1 in adipose tissue had increased adipose levels of corticosterone and developed visceral obesity that was exacerbated by a high-fat diet [18]. Since then, other studies have reported that 11β-HSD1 is associated with obesity. 11β-HSD1 is also associated with other diseases, including rheumatoid arthritis, inflammatory bowel disease, polycystic ovary syndrome, and lung disease [9,19–22].

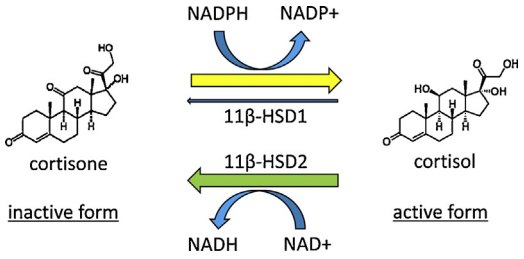

Fig. 2. A schematic of the reactions catalyzed by 11β-hydroxysteroid dehydrogenase (11β-HSD)-1 and −2. Abbreviations: NAD$^+$, nicotinamide adenine dinucleotide$^+$; NADH, nicotinamide adenine dinucleotide hydrogen; NADP$^+$, nicotinamide adenine dinucleotide phosphate$^+$; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen.

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3. The expression of 11β-HSD1 in human and murine skin

11β-HSD1 is expressed in all layers of the epidermis and in dermal fibroblasts in healthy human skin[13] (Fig. 3). 11β-HSD1 expression is stronger in the cytoplasm of supra-basal cells and only weakly detected in basal cells of the normal epidermis. In contrast, 11β-HSD2 is expressed in sweat glands but not in healthy epidermis (Fig. 3). 11β-HSD1 is also expressed in cultured normal human epidermal keratinocytes and in normal human dermal fibroblasts.

In murine skin, 11β-HSD1 is expressed in the epidermis and fibroblasts in C57BL/6 mice and Hos: HR-1 (hairless) mice [13]. 11β-HSD1 is also expressed in cultured primary mouse keratinocytes and in cultured primary dermal fibroblasts derived from C57BL/6 and Hos: HR-1 mice.

4. Local cortisol/corticosterone activation and cell proliferation

In addition to its known anti-inflammatory properties, glucocorticoid (e.g., cortisol and corticosterone) regulates the proliferation of keratinocytes and prolongs epidermal turnover time [23–26]. Does cortisol/corticosterone activation by 11β-HSD1 in cells affect cell proliferation? Expression of 11beta-HSD1 decreases cell proliferation, whereas 11beta-HSD2 increases proliferation in the rat osteosarcoma cell line [27]. In skin cells, we found that inhibition of 11β-HSD1 promotes the proliferation of keratinocytes and fibroblasts in vitro. In addition, topical application of 11β-HSD1 inhibitor promotes keratinocyte proliferation; and subcutaneous injection of 11β-HSD1 inhibitor increases the number of fibroblasts [13,28].

These findings suggest that pre-receptor regulation of the cortisol/corticosterone level by 11β-HSD1 modulates keratinocytes and fibroblast proliferation. Topical application or subcutaneous injection of selective 11β-HSD1 inhibitor has the potential to be an effective treatment to stimulate the proliferation of keratinocytes and fibroblasts.

Then, what role does the expression of 11β-HSD1 play in epidermal hyperproliferative conditions? The expression of 11β-HSD1 is decreased in experimentally 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced epidermal hyperproliferation in mouse skin. In this model, the epidermis shows acanthosis; and the number of Ki-67-positive cells is markedly higher in TPA-treated skin compared with ethanol-treated skin as a control [29].

Although we cannot deny the possibility that decreased expression of 11β-HSD1 is the result of hyperproliferation, decreased 11β-HSD1 expression might be affecting cell proliferation in this experimental model. The signal that regulates the expression of 11β-HSD1 in cell proliferation is still unknown.

5. Local cortisol activation and cutaneous wound healing

Delay in wound healing is a clinical problem in the elderly, obese people, and people with diabetes. GC levels increase in response to stress or medical therapy and impair wound healing because they inhibit proliferation of cells and proinflammatory cytokine production [30,31].

Thus, endogenous cortisol/corticosterone activation by 11β-HSD1 is postulated to affect wound healing. Supporting this, one study reported accelerated wound healing in aged 11β-HSD1-knockout mice [32]. As the expression of 11β-HSD1 increases with age (described in the section on aging below), one of the causes of delayed wound healing in the elderly might be increased activation of cortisol in cells.

We showed that 11β-HSD1 inhibitor significantly promotes cutaneous wound healing in C57BL/6 mice [13]. Interestingly, the inhibitor had a stronger effect on wound healing in *ob/ob* mice, a model of impaired wound healing. These mice exhibited severe diabetes and obesity syndromes, phenotypes mediated by the loss of the ob gene product: the 16 kDa cytokine leptin [33,34]. The expression of 11β-HSD1 was elevated in the skin extract of the *ob/ob* mice, and the selective 11β-HSD1 inhibitor promoted wound healing in the *ob/ob* mice, almost to the same level as in the inhibitor-treated group of C57BL/6 mice. Thus, increased expression of 11β-HSD1 in *ob/ob* mouse skin might play an important role in delayed wound healing in *ob/ob* mice.

Obesity is a global problem, and systemic administration of 11β-HSD1 inhibitor is now under research and development. In addition to systemic administration of 11β-HSD1 inhibitor, topical application of 11β-HSD1 inhibitor could potentially be effective for the treatment of the chronic wounds in obese and diabetic patients as well as in the elderly.

6. Local cortisol activation and skin cancer

In general, the expression of cortisol/corticosterone-inactivating enzyme, 11β-HSD2, is associated with cancer. For example, in one study, 11β-HSD2 was present in 66% of the breast tumor samples analyzed and associated with cell proliferation [35]. In osteosarcoma, high 11β-HSD2 expression correlates with poor response to therapy [36].

In benign and malignant skin tumors, the expression of 11β-HSD1 is decreased in basal cell carcinoma, squamous cell

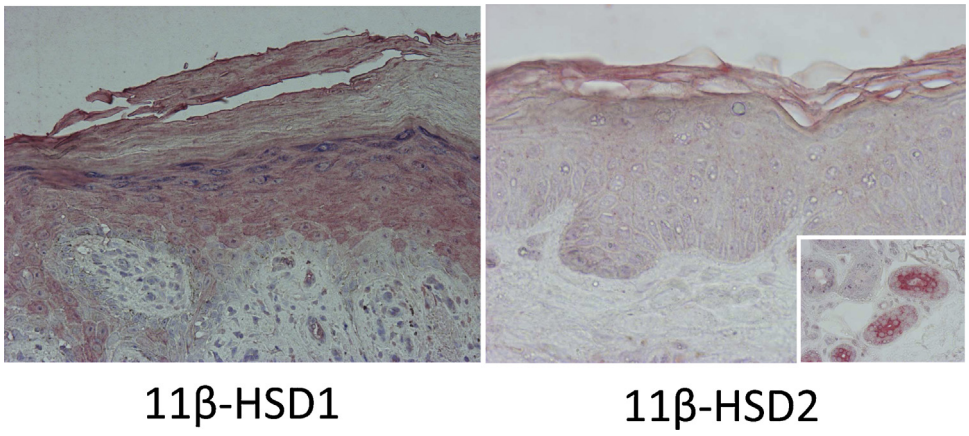

Fig. 3. The expression of 11β-HSD-1 and −2 in skin. Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase.

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carcinoma, and seborrheic keratosis. On the other hand, 11β-HSD2 is increased in basal cell carcinoma and seborrheic keratosis but not in squamous cell carcinoma [29] (Fig. 4).

The markedly reduced staining of 11β-HSD1 in all basal cell carcinoma, squamous cell carcinoma, and seborrheic keratosis tissue sections might be due to the hyperproliferative condition in these tumors as 11β-HSD1 expression is known to be decreased in the experimentally-induced hyperproliferative state [29]. The expression of 11β-HSD2, which is not observed in healthy skin, is increased in basal cell carcinoma and seborrheic keratosis. As basal cells are proliferative in these two tumors, 11β-HSD2 might be associated with basal cell proliferation and/or differentiation. Assessing 11β-HSD1 and 11β-HSD2 expression could be a useful tool for diagnosing and characterizing skin tumors.

7. Local cortisol activation and psoriasis

The expression of 11β-HSD1 in the inflammatory skin disease psoriasis was investigated as psoriasis is representative of epidermal hyperproliferation. The expression of 11β-HSD1 is decreased in psoriasis vulgaris epidermis as evaluated by immunohistochemistry and western blotting. In addition, 11β-HSD1 expression is lower in lesional psoriasis vulgaris skin than in marginal skin [37]. As the 11β-HSD1-staining score is significantly lower in psoriasis vulgaris than in healthy skin and correlates negatively with epidermal thickness in psoriasis vulgaris, expression of 11β-HSD1 might be decreased due to increased epidermal thickness, similar to the findings in skin cancer.

8. Local cortisol activation and aging

The association of 11β-HSD1 and aging skin has been reported. In skeletal muscle, 11β-HSD1 expression is increased 2.72-fold in women over 60 years of age compared to those aged 20–40 years, but no similar age association was found in men. 11β-HSD1 expression is associated with reduced grip strength, insulin resistance, and an adverse body-composition profile [38]. The expression of 11β-HSD1 within bone increases with age and might be associated with age-related osteoporosis [39]. Impairments of spatial memory have been shown to be associated with increases in hippocampal 11β-HSD1 in mice [40].

The function and appearance of skin dramatically changes with aging. Collagen fibers in the dermis and keratin fibers in the stratum corneum stiffen with age [41,42]. Local cortisol/corticosterone activation in the skin is associated with skin aging. In human skin tissue explants and in dermal fibroblasts, 11β-HSD1 activity increases with donor age. In addition, 11β-HSD1 expression is higher in photoexposed fibroblasts compared with photoprotected fibroblasts [43].

In mouse skin, expression of 11β-HSD1 is rarely detected by immunohistochemistry and western blotting in newborns but is clearly detected in keratinocytes and fibroblasts of 3-month-old and 1-year-old mouse skin [28]. These findings suggest an association between cortisol/corticosterone activation and skin aging, especially with dermal aging changes.

Collagen content in the dermis is determined by a balance between collagen production, collagen degradation, and the number of dermal fibroblasts. Skin atrophy is a well-known and important side effect of GC treatment. GC-induced skin atrophy is associated with decreased expression of collagen type I and type III [44–46]. All these reports analyzed the effects of a pharmacological dose of GC on skin collagen metabolism. However, 11β-HSD1 is the enzyme that modulates cortisol within physiological levels [47].

We evaluated the effect of 11β-HSD1 in dermal aging and found that subcutaneous injection of a selective 11β-HSD1 inhibitor increases dermal thickness and collagen content. Inhibition of 11β-HSD1 increases dermal collagen content possibly by

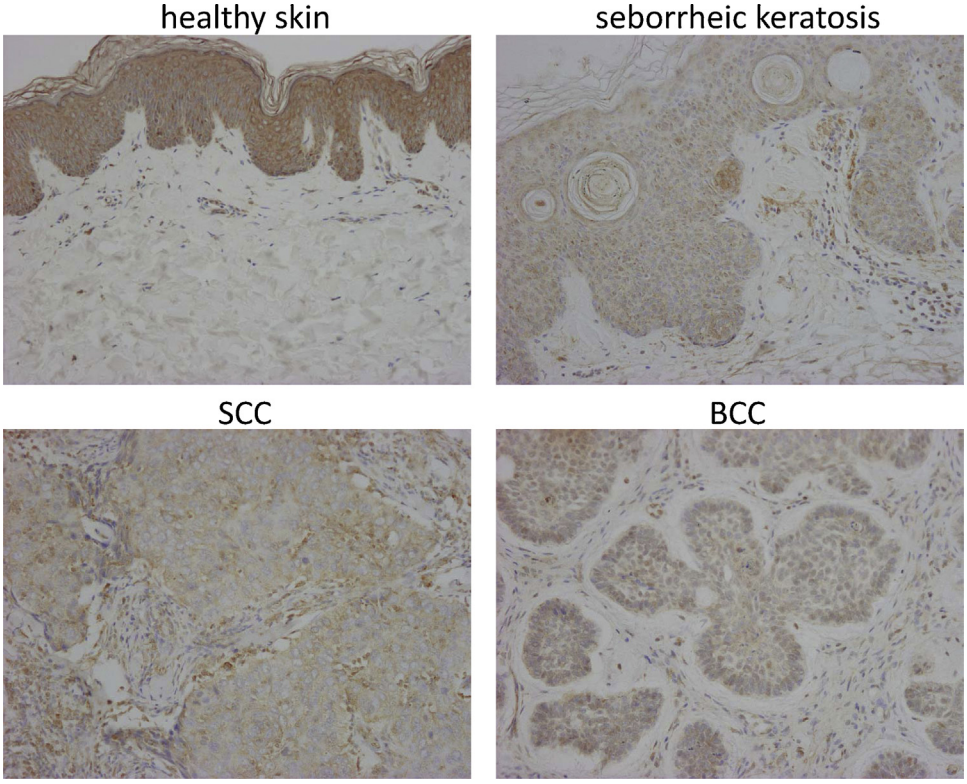

Fig. 4. The expression of 11β-HSD-1 in benign and malignant skin tumors. Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

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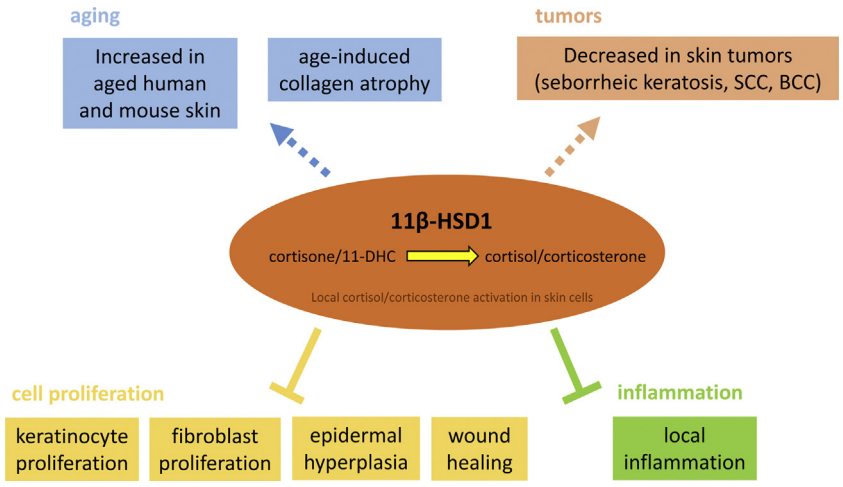

Fig. 5. The role of 11β-HSD-1 in skin cells. Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

increasing the number of dermal fibroblasts, as cell proliferation is significantly increased in dermal fibroblasts derived from *Hsd11b1*$^{-/-}$ mice compared with wild-type mouse fibroblasts [28]. In addition, collagen density is higher in aged 11β-HSD1 knockout mouse compared with aged wildtype mice [32].

These findings suggest that 11β-HSD1 expression increases with age and regulates collagen metabolism, at least in mouse skin. An 11β-HSD1 inhibitor may have the potential to reverse the decreased collagen content that is observed in intrinsically and extrinsically aged skin and in the skin atrophy that is induced by GC treatment.

9. Local cortisol activation and inflammation

Skin is exposed daily to various forms of mechanical and chemical stimulation. A local stress-regulatory mechanism might exist in keratinocytes to counterbalance this repeated stimulation.

Various stimuli, such as UVB irradiation and hapten application, increase the level of 11β-HSD1 in skin and in keratinocytes [37,48–50]. To address whether this increase of 11β-HSD1 in keratinocytes modulates local inflammation, we created keratinocyte-specific *Hsd11b1* knockout (*K5-Hsd11b1-KO)* mice. We found that low-dose-hapten (oxazolone, trinitrochlorobenzene, and dinitrofluorobenzene)–induced irritant dermatitis is augmented in *K5-Hsd11b1-KO* mice. However, we found no difference in irritant dermatitis induced by high-dose haptens between wild-type and *K5-Hsd11b1-KO* mice [37]. UVB-induced dermatitis is also augmented in *K5-Hsd11b1-KO* mice [49].

These data suggest that a local immunosuppressive effect through the action of 11β-HSD1 in keratinocytes is only limited to mild inflammation. This may be so because 11β-HSD1 regulates cortisol concentration between these physiological doses. Although the cortisol production pathway is reported to be a minor one in keratinocytes compared with those of other steroids, we believe it plays an important role in regulating skin inflammation locally.

10. Conclusions

In this review, we present the current findings on local cortisol/corticosterone regulation in the skin (Fig. 5). The expression of cortisol/corticosterone activating enzyme, 11β-HSD1, is increased with age and obesity, and it suppresses cell proliferation and wound healing. 11β-HSD1 in keratinocytes modulates mild skin inflammation induced by haptens and UVB. In skin diseases, 11β-HSD1 might also be associated with skin tumors, such as basal cell carcinoma and squamous cell carcinoma, and with inflammatory skin diseases, such as psoriasis.

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Conflicts of interest

The authors have no conflict of interest to declare.

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