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GRowing an Epidermal Tumor

Wendy B. Bollag[1,2,3,4,5,6] and **Carlos M. Isales**[5,6,7]

[1]Charlie Norwood VA Medical Center One Freedom Way Augusta, GA 30904

[2]Department of Physiology Medical College of Georgia at Georgia Regents University 1120 15th Street Augusta, GA 30912

[3]Department of Medicine (Dermatology) Medical College of Georgia at Georgia Regents University 1120 15th Street Augusta, GA 30912

[4]Department of Cellular Biology & Anatomy Medical College of Georgia at Georgia Regents University 1120 15th Street Augusta, GA 30912

[5]Department of Orthopaedic Surgery Medical College of Georgia at Georgia Regents University 1120 15th Street Augusta, GA 30912

[6]Institute of Regenerative and Reparative Medicine Medical College of Georgia at Georgia Regents University 1120 15th Street Augusta, GA 30912

[7]Institute of Molecular Medicine and Genetics Medical College of Georgia at Georgia Regents University 1120 15th Street Augusta, GA 30912

Abstract

The glucocorticoid receptor (GR), a member of the nuclear hormone family of transcription factors, plays key physiological roles in many organs, including the skin. In this issue, Latorre et al. demonstrate that mice lacking GR in the epidermis exhibit increased vulnerability to chemical carcinogenesis. Evidence supporting an involvement of GR signaling in physiological and pathophysiological processes in skin is discussed.

Glucocorticoids are used pharmacologically to treat multiple diseases, including skin disorders, because of their potent anti-inflammatory properties, but these agents can have significant adverse side effects, such as thinning/atrophy of the skin, impaired wound healing and the development of irreversible striae. However, the physiological and pathophysiological effects of these agents in skin are less well understood.

Glucocorticoids function by binding to the glucocorticoid receptor (GR), a member of the nuclear hormone family of transcriptional regulators. Upon binding their ligands, the nuclear hormone receptors homo- and/or hetero-dimerize and regulate transcription of genes containing response elements in their promoters. Nuclear receptor ligands can also exert

Tele: (706) 721-0698 FAX: (706) 721-7299 WB@gru.edu.

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Anywhere toward the middle:

"non-genomic" (non-transcriptional) effects. These may be mediated through alternate receptors in some cases or via "transcriptional repression" involving interference with other transcription factors. For example, GR can directly suppress nuclear factor-kappa B (NF-κB) signaling to repress NF-κB gene targets.

Accumulating evidence points to an important role for GR in the physiological regulation of epidermal structure and function [reviewed in (Perez, 2011)]. Such support arises from studies investigating the effects of targeted GR overexpression in transgenic mice, as well as global and tissue-specific GR deletion in knockout and conditional knockout mice. For example, Perez et al. (Perez et al., 2001) used the keratin 5 promoter to target GR transgene expression to basal epidermal keratinocytes in a genetically manipulated mouse model, the K5-GR mouse. These mice exhibited defects at birth reminiscent of those observed in patients with ectodermal dysplasia disorders such as aplasia cutis congenita (Perez et al., 2001). Thus, these transgenic mice showed patches of thinning or absent skin, particularly on the cranium, as well as epidermal desquamation and incomplete closure of the fontanella and eyelids. In general, the epidermis was hypoplastic, and in some cases necrotic, with impaired hair follicle development and scarce eyebrows and vibrissae. Upon the application of the phorbol ester tumor promoter, 12-O-tetradecanoylphorbol 13-acetate (TPA), the epidermis of wild-type mice developed hyperplasia and expressed inflammatory cytokines (Perez et al., 2001); this effect was attenuated in K5-GR mice. In addition, by electrophoretic mobility shift assay, these mice also demonstrated reduced basal NF-κB activity, consistent with the ability of GR to induce transcriptional repression. These results suggest that GR has anti-proliferative and anti- inflammatory effects in epidermal keratinocytes in accord with the utility of glucocorticoids in treating hyperproliferative and inflammatory skin disorders. Similarly, Perez and colleagues (Sanchis et al., 2012) also showed decreased keratinocyte migration (*in vitro* and *in vivo*) and delayed cutaneous skin wound healing in the K5-GR mice, as well as a reduced inflammatory response and immune cell infiltration, again in agreement with the impaired skin healing observed with glucocorticoid treatment.

Results with global GR knockout mice have also suggested the physiological importance of this nuclear hormone receptor in the epidermis. GR knockout mice die perinatally due to a lack of lung surfaction (Perez, 2011), but possibly also in part because of impairment of the permeability barrier in skin. Thus, these mice exhibit an incompetent skin barrier and an abnormal epidermal ultrastructure (Bayo et al., 2008); keratinocytes isolated from these mice demonstrated decreased levels of keratinocyte differentiation markers and increased epidermal keratinocyte proliferation and apoptosis *in vitro* (Bayo et al., 2008). [Interestingly, mice expressing a dimerization mutant GR showed normal embryonic epidermal development and differentiation (Bayo et al., 2008), suggesting that monomeric GR exerts most of the effects of this nuclear hormone receptor in the epidermis.]

Recently, Perez and colleagues have also generated an epidermal-specific conditional GR knockout mouse model (Epi-GRKO) and have begun to characterize its phenotype. These authors found that the Epi-GRKO mice exhibit a thickened epidermis, increased proliferation (BrdU incorporation) in the epidermis and a more pronounced DNA synthetic response to TPA treatment (Sevilla et al., 2010). In addition, loss of the GR in epidermal

keratinocytes results in skin barrier defects and cutaneous inflammation (Sevilla et al., 2013), with features that are characterictic of inflammatory skin diseases such as psoriasis and atopic dermatitis. These features include hyperproliferation, abnormal differentiation, impaired permeability barrier function and infiltration of macrophages and mast cells. In the article reported in the current issue, this same group (Latorre et al., 2013) now reports that the Epi-GRKO mice demonstrate an increased susceptibility to epidermal tumorigenesis in the traditional two-stage model of skin carcinogenesis, in which the epidermis is initiated with topical application of the mutagen 12-dimethylbenz(a) anthracene (DMBA) and promoted using TPA. The effect of the loss of GR in keratinocytes on tumorigenesis appeared to be the result of enhanced proliferation and inflammation and impaired differentiation in these Epi-GRKO mice (Latorre et al., 2013). The results are also consistent with the data of Budunova et al. (Budunova et al., 2003), who showed that K5-targeted overexpression of GR suppressed TPA-promoted tumor formation in mice also possessing the v-Ha-ras oncogene. Together these results suggest that both too little and too much GR activity can result in pathological consequences, indicating the necessity of a precise regulation of glucocorticoids and GR in the skin.

This interpretation is further supported by studies examining the regulation of the expression of enzymes involved in activating or inactivating the physiological glucocorticoid, cortisol (corticosterone in rodents). Cortisol (corticosterone) is produced by the adrenal cortex upon stimulation of the adrenal gland by the hypothalamic-pituitary axis (HPA), although it should be noted that there are reports that the skin also expresses key components of the HPA and can synthesize glucocorticoids [reviewed in (Slominski et al., 2007)]. Active cortisol (corticosterone) can be converted to inactive cortisone (or 11-dehydrocorticosterone in rodents) by the activity of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11HSD2) to decrease GR activity, whereas 11β-hydroxysteroid dehydrogenase type 1 (11HSD1) does the opposite, metabolizing inactive cortisone to active cortisol. Both of these enzymes appear to be expressed in the skin. 11HSD1 is decreased in basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and seborrhoeic keratosis (SK) compared to normal human epidermis, whereas 11HSD2 is increased in BCC and SK but not SCC (Terao et al., 2013). Similarly, 11HSD1 is reduced (concomitant with an increase in mitotic index) in the epidermis upon treatment with TPA. Overexpression of 11HSD2 in keratinocytes *in vitro* stimulates proliferation, as does application of an 11HSD1 inhibitor (Terao et al., 2013). These results are consistent with the idea that cortisol/GR signaling represses tumorigenesis such that the decreased cortisol resulting from reduced 11HSD1 and elevated 11HSD2 would be expected to promote tumor formation.

Interestingly, GR signaling may also participate in the aging process in skin. Thus, the K5-GR mice exhibit features similar to those observed in aged skin (e.g., atrophy and decreased proliferation); together with the ability of exogenous glucocorticoids to induce skin atrophy, this result suggests the possibility that skin aging could be related to excess glucocorticoid/GR activity. Indeed, Stewart and colleagues (Tiganescu et al., 2013) have shown that blocking 11HSD1, either with an inhibitor or by deleting the gene in 11HSD1 knockout mice, prevents age-related defects in skin structure and function. Thus, the 11HSD1 knockout mice show less dermal atrophy and more dermal collagen with age, as

well as accelerated wound healing. An 11HSD1 inhibitor also enhances skin wound healing in wild-type mice. In addition, aged human and rodent skin both demonstrate elevated 11HSD1 levels and activity; the latter is also increased in photo-exposed relative to photo-protected skin (Tiganescu et al., 2013). These results suggest a possible involvement of cortisol/GR signaling in age- and ultraviolet irradiation-induced changes in skin.

Finally, it should be noted that the effects of glucocorticoids in the skin may not be solely related to GR signaling. Thus, cortisol (or corticosterone) can also bind to and activate the mineralocorticoid receptor (MR), another member of the nuclear hormone receptor family. Indeed, serum cortisol (or corticosterone) levels are actually much higher than the levels of circulating aldosterone, the physiologic mineralocorticoid. In classical mineralocorticoid-responsive tissues such as the kidney, the MR is protected from activation by cortisol by attendant 11HSD2. However, without 11HSD2's conversion to inactive cortisone, cortisol is capable of activating MR signaling. MR is known to be expressed in the skin [reviewed in (Farman et al., 2010)], and targeted overexpression of this receptor in the epidermis produces epidermal thinning, premature permeability barrier formation and alopecia (Sainte Marie et al., 2007). Interestingly, in a metabolic syndrome mouse model characterized by insulin insensitivity, the accumulation of visceral fat and lipid metabolic changes, a single exposure to ultraviolet light results in increases in epidermal oxidative stress and inflammatory markers similar to those changes observed with aging (Nagase et al., 2013). In these mice not only are MR levels up-regulated but also antagonism of this receptor with spironolactone blocks the ultraviolet-induced aging-like skin alterations (Nagase et al., 2013).

In conclusion, glucocorticoids are routinely used pharmacologically in dermatology to treat several skin diseases, with their therapeutic use limited by adverse effects like skin atrophy. On the other hand, multiple and accumulating lines of evidence suggest the importance of the glucocorticoid cortisol and its target receptor GR (and/or possibly MR) in regulating normal skin structure and function. In addition, data also point to a possibly key role of cortisol/GR signaling in the pathophysiology of various skin disorders, including hyperproliferative inflammatory skin disorders such as atopic dermatitis and psoriasis, genetic skin diseases such as ectodermal dysplasia/aplasia cutis congenital and the changes associated with metabolic syndrome and chronological and photo-aging. Thus, it seems likely that sustained research into this important signaling system will continue to provide insights into physiological and pathological processes in the skin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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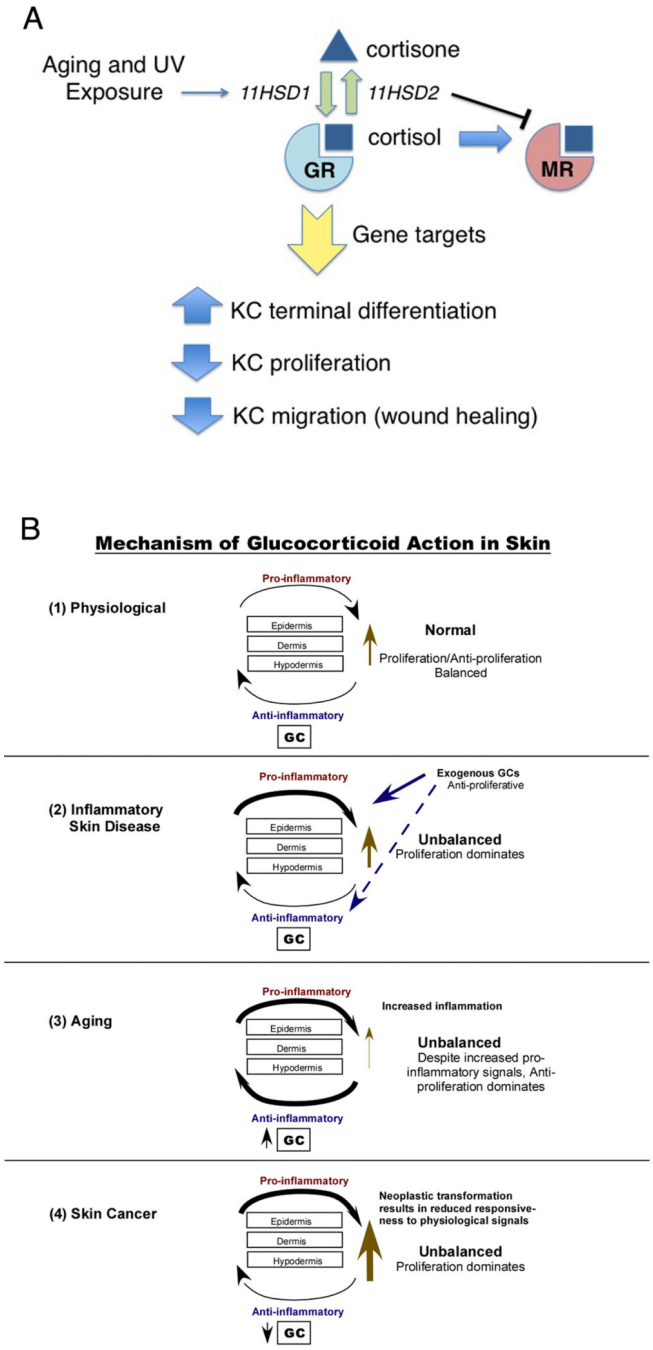

Figure 1. Glucocorticoid Receptor Signaling and Epidermal Function

(A) The glucocorticoid (GC) cortisol (corticosterone in rodents) binds to the glucocorticoid receptor (GR) to stimulate keratinocyte (KC) terminal differentiation and inhibit KC proliferation and migration through the modulation of various gene targets with GC response elements in their promoters. Cortisol (corticosterone) can be converted by 11β-hydroxysteroid dehydrogenase 1 (11HSD1) to inactive cortisone (11-dehydrocorticosterone); the activity of 11HSD1 can be increased by chronological and photo-aging. The reverse reaction resulting in activation of cortisol is catalyzed by 11β-

hydroxysteroid dehydrogenase 2 (11HSD2). Cortisol can also bind to and activate the mineralocorticoid receptor (MR), a process that can be inhibited by the action of 11HSD2. **(B)** This panel depicts the role of GR and GCs in the skin under various conditions. (1) Under normal physiological conditions there is a balance between pro-inflammatory, proproliferative mediators and anti-inflammatory, anti-proliferative (pro-differentiative) factors in the skin. One such anti-inflammatory/anti-proliferative factor is GC/GR signaling, since loss of GR in a genetically manipulated mouse model results in basally elevated skin inflammation (Sevilla et al., 2013). (2) In inflammatory skin diseases such as atopic dermatitis and psoriasis, pro-inflammatory (and pro-proliferative) mediators predominate. In this case, treatment with exogenous GCs enhances anti-inflammatory, anti-proliferative effects to restore balance and help to resolve disease. (3) With aging, despite the fact that pro-inflammatory mediators are often elevated, other changes (e.g., augmented activity of 11HSD1 activity to increase endogenous active cortisol/corticosterone levels) lead to a predominance of anti-inflammation and anti-proliferation. (4) In the case of skin cancer, neoplastic transformation results in non-responsiveness of cells to normal anti-proliferative signals. Nevertheless, even under this condition, the anti-inflammatory, anti-proliferative action of GC/GR continues, such that epidermal deletion of GR (in a genetically manipulated mouse model) leads to increased susceptibility to tumor development (Latorre et al., 2013).