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Mineralocorticoid Receptor Antagonists—A New Sprinkle of Salt and Youth

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Skin atrophy and impaired cutaneous wound healing are the recognized side effects of topical glucocorticoid (GC) therapy. Although GCs have high affinity for the glucocorticoid receptor, they also bind and activate the mineralocorticoid receptor. In light of this, one can speculate that some of the GC-mediated side effects can be remedied by blocking activation of the mineralocorticoid receptor. Indeed, according to Nguyen et al., local inhibition of the mineralocorticoid receptor via antagonists (spironolactone, canrenoate, and eplerenone) rescues GC-induced delayed epithelialization and accelerates wound closure in diabetic animals by targeting epithelial sodium channels and stimulating keratinocyte proliferation. These findings suggest that the use of mineralocorticoid receptor antagonists coupled with GC therapy may be beneficial in overcoming at least some of the GC-mediated side effects.

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Interplay of the glucocorticoid receptor and mineralocorticoid receptor in skin and wound healing

In dermatology, we have long capitalized on the presence of receptors that mediate anti-inflammatory effects. For example, the effects of the glucocorticoid receptor (GR) may be seen in the use of topical and systemic steroids to treat a myriad of inflammatory skin disorders. However, the efficacy of topical glucocorticoid (GC) use does not come without unintended side effects, including skin atrophy and delayed wound healing. For these reasons, it has been the topic of intense scientific inquiry in an attempt to delineate the mechanisms underlying these sequelae of corticosteroid use. Promiscuous activation of cutaneous mineralocorticoid receptors (MR), due to high-affinity binding of excess cortisol, may be one potential driver. However, it has been shown recently that topical inhibition of the MR attenuates glucocorticoid-induced epidermal atrophy (Maubec et al., 2015). Nguyen et al. (2016) propose that cutaneous MR antagonism improves healing in pathological wounds treated with topical corticosteroids by promoting re-epithelialization. Although much is known about GR function in the skin, the importance of competition by activation of the MR and the implications thereof are just beginning to be recognized.

Both GR and MR belong to the steroid hormone nuclear-receptor superfamily of ligand-dependent transcription factors. GR is found in virtually every cutaneous compartment: epidermal and follicular keratinocytes, epithelial cells of eccrine and apocrine glands, sebocytes, melanocytes, immune cells within the epidermis and dermis, dermal fibroblasts, and smooth muscle cells. Cortisol produced systemically and locally, within the epidermal compartment, serves as the primary ligand for GR, thus potentiating its well-known downstream anti-inflammatory properties. Cortisol-bound GR homodimers mediate GC anti-inflammatory effects through a diverse array of mechanisms, including, but not limited to, transcriptional regulation that results in downstream blockade of prostaglandin production and physical interaction and inhibition

Clinical Implications

- Mineralocorticoid receptor antagonists have beneficial effects on corticosteroid-induced delayed wound closure.
- Regulation of the local skin corticosteroid production (11β-hydroxysteroid dehydrogenase type 1 and type 2) can affect mineralocorticoid receptor activation, thus affecting the development of skin atrophy and wound healing.
- Careful manipulation of mineralocorticoid receptor activation in skin may lead to novel approaches to improve elastin content and to reduce aging skin-associated atrophy.

of NF-κB, modulation of mRNA transcript stability, through membrane-associated receptors and secondary messengers (Rhen and Cidlowski, 2005; Stojadinovic et al., 2007, 2013; Vukelic et al., 2011).

In skin, GCs also bind MR with high affinity (Farman and Nguyen, 2016). However, MR are also expressed in the brain, heart, and in the epidermal compartment of skin: keratinocytes, sweat and sebaceous glands, and in the hair follicles. Importantly, the classically appreciated expression pattern of MR is in renal tubules, where it regulates sodium reabsorption (Farman and Nguyen, 2016). Attempts at defining a distinct physiological role for MR in skin were first made using a conditional mouse model in which targeted expression of MR was directed by the use of a keratinocyte specific promoter (K5-MR mice), which ultimately yielded a phenotype reminiscent of GC-induced epidermal atrophy (Sainte Marie et al., 2007). In contrast, more recent knockout mouse models have demonstrated that MR-KO embryos display epidermal hyperplasia (Boix et al., 2016).

The availability of active cortisol within the skin is controlled by its local synthesis and the interplay between two enzymes, 11β-hydroxysteroid dehydrogenase type 1 (HSD11B1) and type 2 (HSD11B2). Cortisol is produced locally in skin, and what's more, wounding triggers robust activation of cortisol synthesis (Vukelic et al., 2011). Activation of HSD11B1 results in cortisol production, whereas HSD11B2 functions to metabolize cortisol to its inactive form, cortisone. Moreover, the activity of MR and GR in the epidermis is determined by the availability of ligands, which is largely determined by the presence and activity of HSD11B1/2 and subsequent levels of active cortisol. While the DNA-binding domain of MR has high homology to that of GR, its ligand binding domain is capable of high-affinity binding of its native ligand aldosterone, as well as the GC ligand, cortisol. Thus, in states of cortisol excess, such as those experienced during topical application of

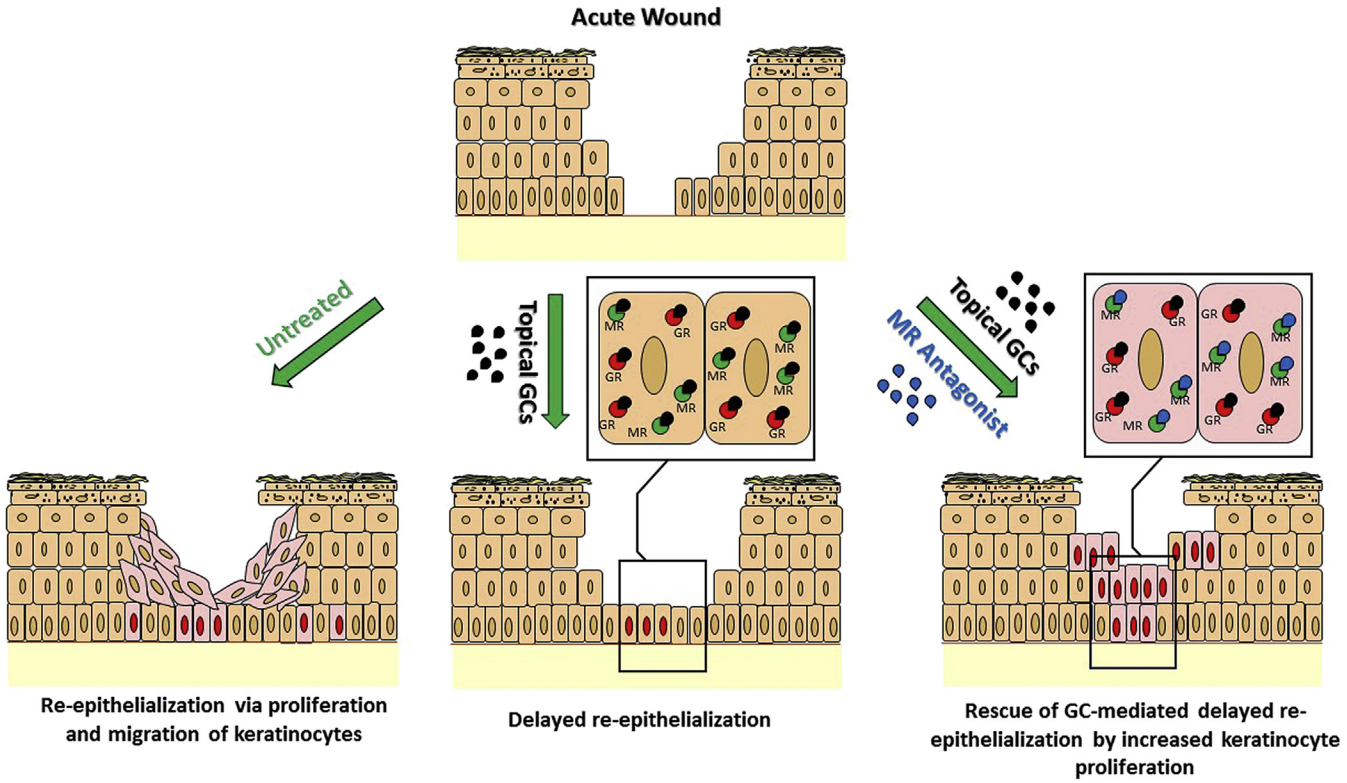

Figure 1. Antagonists of mineralocorticoid receptor rescue glucocorticoid-mediated inhibition of wound healing. After wounding, restoration of the epidermal barrier depends on several essential keratinocyte functions, including proliferation and migration (bottom right), which is inhibited by glucocorticoids (bottom center). Topical application of glucocorticoids leads to excess ligand that may occupy both GR and MR and trigger simultaneous signaling. Nguyen et al. (2016) show that antagonists of MR, when applied with topical glucocorticoids, may diminish this inhibition of healing by stimulating keratinocyte proliferation. GC, glucocorticoid; GR, glucocorticoid receptor; MR, mineralocorticoid receptor.