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Neuroendocrine Controls of Keratin Expression in Human Skin

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Abstract

The human skin serves as a source for a large number of neurohormones and neuropeptides, which affect skin biology on multiple different levels. Intriguingly, this includes the control of keratin expression by neurohormones such as thyrotropin-releasing hormone, thyrotropin, opioids, prolactin, and cannabinoid receptor 1-ligands. While this neuroendocrine regulation of human keratin biology *in situ* is likely to be involved in the maintenance of skin and hair follicle homeostasis and may participate in skin pathology, this regulation remains to be appreciated and explored by mainstream keratin research. Here, we review recent progress in this frontier of neuroendocrine and keratin skin research, define the many open questions in the field, and elaborate how neurohormones may be harnessed to treat selected genodermatoses and other skin disorders accompanied by abnormal keratin expression.

Keywords: keratins, neuroendocrinology, hair, skin, dermatology

1. Introduction

Keratins are the major constituents of the epidermis and skin appendages, which by forming an intracellular structural network provide cellular stability and resilience to the tissue [1]. Furthermore, they exert a surprisingly wide and complex range of additional functions in the skin, including regulating epithelial differentiation and proliferation, migration and wound healing, carcinogenesis and apoptosis, and immunomodulation [2–5]. Taking into consideration the key roles keratins play in the skin, it is of utmost importance to understand and dissect the mediators that affect their expression. One of the key mediators of skin function is the endocrine system, which is also expressed and active in the skin itself.

An important pathway by which the endocrine system controls skin function is by changing keratin expression, and these effects have been described in detail previously [6].

Throughout the last decade, it became clear that the skin reacts and generates not only steroid hormones, but also a large array of neuroendocrine mediators [2, 3, 7–10]. The skin has even formed a hypothalamic-pituitary-adrenal (HPA) neuroendocrine signaling axis, equivalent to the central axis [10–12], and a semi-equivalent hypothalamic-pituitary-thyroid (HPT) axis [13–16]. These neuroendocrine mediators take part in the regulation of many different processes and functions of the skin, both in normal healthy skin and in disease states. These include, for example, regulation of stress response [10, 17], hair follicle (HF) growth [18–22], pigmentation of the skin and HF [18–21, 23, 24], sebaceous gland function [10, 12], proliferation and apoptosis of keratinocytes [9, 10, 25], and mitochondrial activity [16, 26, 27]. They are also involved in controlling the immune privilege of the HF epithelium and the immune response of the skin [24, 28].

Taking into consideration the fact that keratins constitute up to 85% of the cell mass of a terminally differentiated keratinocyte and have such important roles not only in keratinocyte, sebocyte, and trichocyte biology, but also for overall skin physiology [29–31] and the fact that the vast majority of neuroendocrine mediators is expressed in the skin epithelium [11, 12, 17], it is reasonable to ask whether some of the functions exerted by neurohormones in the skin are actually mediated by changing keratin expression. Indeed, in recent years, several studies have demonstrated that keratin expression in human skin and HFs is manipulated by neurohormones and underlies previously ignored, important neuroendocrine controls that invite therapeutic targeting.

In this chapter, we systematically explore the effects of neuroendocrine mediators on keratin expression and connect these changes to physiologically relevant functions of the skin and HFs. We also dissect the ways by which such keratin changes might be harnessed to alleviate different skin conditions.

2. The hypothalamic-pituitary-thyroid axis in the skin and its effects on keratin expression

The fact that skin and HFs are prominent targets for the thyroid hormones, triiodothyronine and thyroxine, is well established [15, 16]. These thyroid hormones also promote cutaneous wound healing [32, 33]. Furthermore, patients suffering from thyroid disorders manifest with significant hair and skin phenotypes [15]. It is possible that some of these changes are due to an effect of thyroid hormones on keratin expression. For example, T3 increases K6, K16, and K17 gene expression in human keratinocytes in culture, keratins that are known to be upregulated during the wound healing process [34], and mice with hypothyroidism have reduced K6 expression [34]. In addition, T3 and T4 stimulate K6 expression and decrease K14 expression in cultured human HFs [15].

However, thyroid hormones can themselves change the production of neurohormones such as prolactin and thyroid-stimulating hormone (TSH, thyrotropin), also in the skin [13, 35].

Indeed, in recent years, it has become evident that the skin expresses receptors for the thyroid hormones and for TSH and thyrotropin-releasing hormone (TRH) [13, 18, 23, 26]. It has also been observed that, just as in the central HPT axis, thyroid hormones decrease intraepidermal TSH expression, while TRH stimulates it in human skin, therefore suggesting that an elementary functional HPT axis also exists in the human skin [36].

Thyrotropin-releasing hormone is expressed by the human HF and can be found in the outer root sheath (ORS). The TRH receptor (TRH-R), on the other hand, is expressed in the inner root sheath (IRS) of the HF [23]. TRH can affect keratin expression: it has been found to upregulate the expression of the hair keratins K31 and K32, while it downregulates the expression of the hair keratins K85 and K86 at the protein level [37]. TRH also has profound effect on the keratins expressed by the ORS in the HF, leading to reduced expression of K6, K14, and K17 [23, 37]. The above-listed keratins have been confirmed to be regulated by TRH at the protein level in the HF, but it should be noted that additional keratins and keratin-associated proteins (KAPs) may be affected by TRH according to microarray results obtained with organ-cultured human HFs [37]. However, further experiments are required to confirm regulation of these keratins and KAPs by TRH. Another important open question is to which extent the TRH-induced changes in keratin expression observed in the HF underlie the complex functional changes exerted by TRH in the HF [2, 16], namely, the stimulation of hair shaft production by TRH [23].

In contrast to the ORS of the HF, TRH stimulated K6, K14, and K17 expression in the epidermis, sweat glands, and sebaceous glands in human skin *ex vivo* at the protein and mRNA levels [37]. The same promoting effect of TRH on human K6 expression was also evident in frog skin *in vitro* [25], and this stimulating effect was suggested to accompany the promotion of wound healing in the frog skin [25]. This suggests that the keratin regulatory effects of TRH are highly conserved in vertebrate skin and underscores the functional importance of this neuroendocrine control of keratin biology. This makes it even more surprising that mainstream keratin research continues to largely ignore this evolutionarily conserved control mechanism, which must have provided significant species survival advantages to have been maintained from frogs to humans. Interestingly, previous studies have found that TRH can also stimulate mitochondrial activity in human epidermis and scalp HFs [26]. This invites the intriguing question whether the part of this TRH-induced increased mitochondrial activity, and thus energy metabolism is actually recruited to promote and support the energy intensive synthesis of selected keratins.

Thyroid-stimulating hormone is another key neurohormone involved in the regulation of keratin expression in human skin. TSH is expressed in the epidermis, and the gene encoding its receptor reportedly is also transcribed in the epidermis [14], while TSH-R protein is most prominently, if not exclusively, found in the skin mesenchyme, including the dermal sheath of human scalp HFs [18]. However, there is still a debate on the exact location of the TSH-R protein [13, 38]. In whole skin organ cultures, TSH stimulated the expression of K5 and K14, the two prototypic keratins that are expressed in the basal layer of the epidermis, connect to the hemidesmosomes in the basal side of the keratinocytes and are critical for keratinocyte function [6, 29]. Interestingly, TSH did not affect basal epidermal keratinocyte proliferation *ex vivo*, pointing to the fact that the upregulation of K5 and K14 was not just due to enhanced keratinocyte proliferation. Therefore, these findings suggest that TSH effects on

keratin expression are direct and independent of cellular proliferation changes. Just like with TRH, TSH was also found to enhance mitochondrial activity in the epidermis [27] and the HF epithelium [16], again raising the possibility of a coordinated, neurohormone-controlled increase in intraepithelial energy metabolism and keratin synthesis.

As alluded to above, keratin changes following TSH stimulation were also evident in human HFs *ex vivo*. Except for K5 in hair matrix keratinocytes, which was upregulated [18], all the other keratins examined were downregulated following TSH stimulation at the gene and protein levels. These included keratins expressed in the HF ORS, such as K6, K14, and K17, and hair keratins expressed in the hair cortex, such as K31, K32, and K85 [39]. While the exact mechanisms by which TSH changes keratin expression remains unknown, it is noteworthy that TSH also upregulated expression of MSX2 [39], a key transcription factor that controls keratin expression [40, 41]. It is also interesting to note that all these keratin changes were observed in the HF, although TSH itself does not affect hair growth, thus suggesting that these TSH-regulated changes in keratin expression do not translate into altered hair growth [18].

TRH has been found to enhance TSH expression in the human epidermis [13]. Since TSH can change keratin expression as we have just reviewed, it is possible that some of the effects of TRH on keratin expression are indirectly mediated by TSH. Indeed, some of the keratins that are modulated by TRH, such as K14, K17, and K85, are affected in a comparable manner by TSH [39].

3. The hypothalamus-pituitary-adrenal axis in the skin and its effects on keratin expression

Corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), and cortisol form the HPA axis, which has a major role in controlling stress response by producing steroid hormones and regulatory peptides [9]. This axis is also active in human skin and HFs, where, namely, keratinocytes, but also other cutaneous cell populations act as both targets and also as nonclassical producers of these HPA constituents [10–12, 42, 43].

There are plenty of studies that report on the effect of glucocorticosteroids on keratin expression in the skin, effects that accompany physiological processes, such as wound healing [6]. Nevertheless, little is known on the effects of the other components of the HPA axis on keratin expression, and the available information is limited to CRH, which reportedly upregulates K1 and downregulates K14 in HaCaT cells and in human adult epidermal keratinocytes, as part of the induction of the terminal differentiation program [44, 45]. Taking into consideration the fact that the HPA is fully functional in human skin [2, 10–12], it is likely that additional keratins are regulated by these neuromediators, yet have escaped notice so far. Therefore, further research is warranted to explore this neuroendocrine frontier of keratin biology, namely, in human skin.

4. Prolactin effects on keratin expression

Prolactin and its receptor have been found to be expressed at the gene and protein levels in the human skin [19, 35, 46, 47], where they control a large number of functions, such as hair growth [19] and keratin expression (see below). Given the major role of prolactin in the

control of mammary development, growth, and milk production, it is not surprising that the first evidence for an effect of prolactin on keratin expression arose from mammary gland studies [48]. These studies have shown that if the prolactin receptor gene is knocked out, mice do not develop normal mammary buds, accompanied by decreased expression of selected keratins, such as K8, K17, K18, and K19 [48].

Since the mammary gland is basically a sweat gland-like derivative of the epidermis, and a prolactin-like protein has actually been found in human eccrine sweat glands [49], it was reasonable to hypothesize that prolactin may regulate keratin expression also in other skin appendages. Indeed, prolactin administration to organ-cultured human HFs resulted in upregulation of keratins expressed in the ORS, including K5 and K14, while the hair keratin K31 was downregulated *ex vivo* [50].

Perhaps the most interesting observation that emerged from this study was the stimulatory effect of prolactin on K15 and K19, that is, marker keratins for epithelial HF stem cells [51–53]. This stimulatory effect was reversed when a selective prolactin receptor antagonist was added to the culture medium. This effect was further confirmed when prolactin had a stimulatory effect on *KRT15* promoter activity *in situ* [50]. This finding strengthens the importance of prolactin as a stem cell promoting agent, as was also observed later in other classical prolactin target organs, such as the mammary gland [54]. Once again, this underscored the unique instructiveness of HFs as a discovery tool in skin research, namely, in cutaneous neuroendocrinology [2], from which novel, general neuroendocrine principles can be deduced.

Another important observation that emerged from these keratin studies was that the addition of a prolactin receptor antagonist alone also resulted in changes in keratin expression [50]. This shows that endogenous production of prolactin and/or prolactin receptor stimulation is an important element of normal skin physiology and homeostasis and is actually required to maintain the production of keratins in the HF. This is similar to the autocrine/paracrine effects attributed to prolactin also in the pituitary gland, where blocking of the prolactin receptor resulted in changes in cell turnover and prolactin receptor expression [55], and in extrapituitary locations such as the mammary gland, where changes in prolactin receptor patterning resulted in disruption of lobuloalveolar development [56].

It has been previously shown that there is an interplay between the different hormones and neurohormones in the skin and HFs, and that some of these connections are similar to those that exist in the pituitary. As an example, TRH can stimulate prolactin expression in the HF, while it can inhibit expression of the prolactin receptor [35]. Such an interplay is highly likely to also be at play in the regulation of keratin expression, and given that both neurohormones profoundly change the expression of selected keratins in human skin. Obviously, this adds another level of complexity to the challenge of segregating the direct effects of each of these neurohormones from indirect and cross-regulatory ones.

5. The effects of endocannabinoids on keratin expression

Accumulating data show that the endocannabinoid system (ECS) plays a major role in mammalian skin [57, 58]. Indeed, endocannabinoids are being produced by the epidermis and the skin appendages, including the HF, sweat glands, and sebaceous glands [58], and the

cannabinoid receptors CB₁ and CB₂ are prominently expressed on different skin cell populations [58]. Many different skin functions of the skin are now appreciated to be regulated by the ECS. For example, in the epidermis, it controls keratinocyte proliferation and differentiation, thereby affecting the epidermal barrier, and regulates melanogenesis [59–61].

The ECS also affects the skin appendages profoundly. Signaling via CB₁ inhibits hair growth and induces catagen, the regression phase of the HF [22, 62]. In sweat glands, anandamide stimulated sweat secretion of epithelial cells and reduced their proliferation [63]. The ECS can also affect sebaceous gland function, and by acting via CB₂, endocannabinoids positively control sebaceous lipid synthesis [64]. Furthermore, cannabidiol, a CB₁ antagonizing nonpsychotropic phytocannabinoid, reduced sebocyte proliferation and normalized excess sebum production that can be observed in acne lesions [65, 66].

Taking into consideration its importance in epidermal keratinocyte function, it was not surprising that ECS modulation also affects keratin expression. For example, cannabinoid receptor activation on human HaCaT cells by the prototypic endocannabinoid, anandamide, inhibited cell differentiation, accompanied by reduced transcription of the *KRT1* and *KRT10* genes [67]. When tested in human skin culture and again in HaCaT cells, anandamide also inhibited K6 and K16 expression, independent of its antiproliferative properties [68]. Conversely, administration of the CB₁ antagonist, arachidonyl-2'-chloroethylamide (ACEA), upregulated K10 in human epidermis while decreasing the expression of K1 *ex vivo* [69].

Given its antiproliferative and differentiation-promoting effects in human epidermis as well as its overall largely anti-inflammatory properties (e.g., by reducing mast cell degranulation and maturation *in loco* [70]), CB ligands are coming under scrutiny as potential new therapeutics in the therapy of psoriasis [71]. If this line of research continues to be productive, it will become clinically even more important to dissect the relative contribution of CB-mediated changes in epidermal keratin expression to any beneficial effects observed by therapeutic CB stimulation. The use of ECS antagonists to change keratin expression underscores that, like we have seen in the case of prolactin, blocking the autocrine/paracrine effects of intracutaneously generated neuroendocrine mediators induces functionally relevant changes in human skin, such as altered keratin expression patterns.

6. Opioids and keratin expression

Murine and human skin both express opioid receptors, including the μ -, κ -, and δ -opioid receptors. Stimulation of these receptors participates in the control of melanocyte [72] and keratinocyte functions, such as impeding DNA synthesis and cell differentiation [73, 74]. Therefore, their connection to skin disorders, such as psoriasis, basal cell carcinoma, and wound healing, is currently under scrutiny [73, 75, 76].

As one might expect by now, opioid receptor ligands also induce changes in keratin expression. For example, the key endogenous ligand for the μ -opiate receptor, beta-endorphin, enhances the intraepidermal expression of K16 at the wound margin [77]. In psoriasis, a

hyperproliferative dermatosis, K16 expression is upregulated, and this is accompanied by downregulation of the μ -opiate receptor [75], and treatment of skin organ cultures with beta-endorphin resulted in elevated K16 production [75].

K10 is an additional keratin to be regulated by opioids, as mice knocked out for the δ -opioid receptor had enhanced K10 expression, together with a thinner epidermis [78], and the *Achillea millefolium* extract, a strong inducer of the μ -opioid receptor-1, led to increased differentiation of the cells in the epidermis with stronger K10 expression [79]. Yet, our current understanding of the role of opioid receptor-mediated signaling within the emerging neuroendocrine controls of keratin biology remains even more rudimentary than that of the neuromediators discussed further above.

7. Other neurohormones can alter keratin expression

Parathyroid hormone-related protein (PTHrP) is another important neuroendocrine mediator, which has importance in the normal formation of the mammary gland [80]. Keratin expression was tested in a K14 promoter-driven PTHrP mouse, and an overexpression of K17 in the nipple epidermis was evident in this mouse model [81]. Interestingly, PTHrP signaling affects BMP signaling and *Msx* gene activation, both of which are critical regulators of HF growth and function [80], just like PTHrP itself strongly modulates murine HF cycling [82, 83]. Yet, how PTHrP impacts on intrafollicular keratin remains to be evaluated.

Catecholamines can also change keratin expression, and when evaluated in limbal epithelial cells in culture, isoproterenol, a beta-adrenergic receptor agonist, led to pronounced changes in keratin expression [84]. When tested in HaCaT cells, the same compound stimulated differentiation, which was accompanied by increased K1 and K10 production [85].

In contrast, histamine led to decreased expression of differentiation markers in skin models and human keratinocyte cultures, among others, and also to decreased production of K1 and K10 [86]. The cholinergic system can also affect keratin expression. When tested in skin cultures *in vitro*, blocking of the cholinergic system resulted in decreased expression of differentiation markers, such as K2 and K10 [87]. Although these mediators clearly led to changes in keratin expression in these cases, it remains to be dissected whether these changes were due to a direct effect of the tested compound or reflected secondary events, resulting, for example, from changes in keratinocyte proliferation and differentiation.

8. Possible clinical implications of neuroendocrine-mediated changes in keratin expression

As reviewed in detail above, neuroendocrine mediators can change keratin expression in what appears to be a relatively selective manner. Let us now discuss, therefore, how this phenomenon might be translated into the treatment of several skin and hair conditions. This is

of special clinical relevance since neuromediator analogs, in principle, may be formulated to be topically applicable, thus circumventing or reducing the risk of undesired systemic effects. Some of the possible clinical scenarios for which such analogs may conceivably be used are described briefly below.

8.1. Treatment of keratin-related skin and hair genetic disorders

The list of genetic disorders linked to mutations in keratin genes continues to expand, and more than half of the keratin genes have been linked to a genetic disorder [88–92]. These disorders include ichthyoses, blistering disorders such as epidermolysis bullosa, hair conditions such as wooly hair and sparse hair, and changes in the normal growth of nails. A novel promising approach for the treatment of keratin disorders is the utilization of small molecule drugs to upregulate expression of compensatory keratins or to downregulate the expression of the mutated keratins [89, 93]. Such an approach has already been successful in several autosomal dominant keratin disorders, such as epidermolysis bullosa simplex and pachyonychia congenita [94–96].

It has also been reported to be of potential benefit in epidermolytic ichthyosis, an uncommon genodermatosis caused by mutations in keratins 1 or 10, when Reichelt et al. have shown that increased stability of keratins 5 and 14 could lead to the formation of normal epidermis in K10-null mice [97]. Furthermore, treatment of immortalized cell lines from a *KRT10*-mutated epidermolytic ichthyosis patient with all-trans retinoic acid led to a 200-fold decrease in mRNA expression of K10, accompanied by decreased keratin aggregation [98].

As reviewed above, the CB₁ agonist ACEA increased K10 expression, while reducing K1 production in human epidermis in culture [69]. Such changes could potentially be harnessed in epidermolytic ichthyosis patients to decrease the expression of mutated K1 while upregulating the expression of K10 that can functionally compensate in part for the mutated keratin. Given their differential regulation of distinct human keratins in human skin *ex vivo*, defined neuromediators now need to be systematically explored for their capacity to execute such therapeutically desirable reverse regulation of clinically relevant keratins in selected genodermatoses, perhaps starting with primary keratinocyte cultures derived from affected patients.

8.2. Treatment of inflammatory skin conditions (e.g., psoriasis)

Several inflammatory skin disorders are characterized by overexpression of K6. These include, for example, lichen planus and discoid lupus erythematosus [99]. However, the most prominent example is psoriasis, a chronic inflammatory skin condition, which is characterized by increased expression of K6, K16, and K17 [3, 68, 100]. K17 is probably of special importance in psoriasis pathogenesis, since it has been suggested to act as an antigenic target for T lymphocytes in the affected epidermis [101]. Furthermore, mice overexpressing K17 developed an inflammatory reaction and epidermal hyperplasia [102]. Moreover, K6, K16, and K17 expression pattern can impact on the cytokine or chemokine secretion of keratinocytes [102–105] and thus the intraepidermal inflammatory signaling milieu.

Therefore, compounds that can decrease the expression of these keratins might be therapeutically beneficial in these dermatoses, namely, in psoriasis, especially if they can also exert anti-inflammatory effects [106, 107], such as in the case of cannabinoid receptor agonists, which independently decrease the expression of K6 and K16 [68], combined with anti-inflammatory, antiproliferative, and antiangiogenic properties [3, 57, 71, 108, 109].

8.3. Wound healing

In healthy nonglabrous epidermis, K6, K16, and K17 are largely absent and not constitutively expressed by keratinocytes. However, in hyperproliferative states and conditions of epidermal stress, such as during wound healing, these keratins are rapidly upregulated and strongly expressed, since they play a major role in epidermal repair, as they are required for normal migration of keratinocytes from the wound edges and to ensure optimal closure of the wound [29, 110, 111]. Opiate receptor agonists that can boost wound healing are also stimulators for K16 expression, suggesting again the hypothesis of a coordinated neuroendocrine control of both, expression of optimally suited keratins and wound healing as such [77, 112]. Conceivably, therefore, neuroendocrine mediators that upregulate K6, K16, and K17 expression (e.g., catecholamines and endocannabinoids) might become therapeutically useful as promoters of re-epithelialization during wound healing.

8.4. Therapeutic regulation of stem cell-associated keratins

Prolactin increases the expression of the prototypic epithelial stem/progenitor cell-associated keratins, K15 and K19, [48, 50], and a continuous endogenous production of prolactin may be required to maintain normal K15 and K19 expression by these stem cells [50]. This raises the question whether neurohormones such as prolactin or related receptor agonists can be therapeutically recruited to ameliorate or prevent stem cell-based hair diseases characterized by permanent loss of the HF stem cell pool, such as lichen planopilaris or chemotherapy-induced alopecia [51, 113–115], or epidermal atrophy associated with an exhaustion of epidermal stem cell pools, as it occurs, for example, in connection with steroid therapy [116].

8.5. Hair growth

Keratins play a critical role in normal hair growth and structure. This is nicely exemplified by genetic hair disorders caused by keratin mutations [91]. When keratins that are produced in the hair cortex are mutated, the hair shaft is fragile and easy to break, and when the mutations are in keratins expressed in the most proximal part of the hair cortex, this leads to a more severe phenotype of complete hair loss [117, 118]. Instead, when keratins expressed in the IRS are mutated, this leads to a defect in hair curvature, oftentimes evident as wooly hair [90, 92, 119–121]. It is therefore conceivable that neuroendocrine manipulation of hair keratin expression may result in modulation of hair growth and/or hair shaft phenotype. It is therefore not surprising that TRH and prolactin, which both significantly modulate hair growth [2, 3, 23, 50, 122–126], also profoundly modulate hair keratin expression [37, 50].

One additional important aspect when discussing hair keratins is the presence and importance of KAPs. These proteins surround the keratin intermediate filaments in the hair shaft, cross-linking them by disulfide bonds [127], and providing them with rigidity and strength [128]. The number of KAPs is much higher than keratins, and 89 functional KAP genes have been described in humans [128], therefore there is probably a high degree of overlap between these proteins. Nevertheless, changes in KAPs could probably also affect hair structure. On this background, it is interesting to note that preliminary studies using microarrays in cultured HFs have revealed that certain neurohormones, such as TSH and prolactin, appear to alter the transcription of several KAP genes, such as KAP 4-4 and/or KAP 7-1 [18, 50]. These pilot observations deserve systematic follow up and may provide additional targets for therapeutic neuroendocrine intervention.

9. Conclusions

Here, we have reviewed that several neurohormones and neuropeptides generated in human skin as a nonclassical production site profoundly impact on the control of keratin expression. Specifically, we have presented TRH, TSH, opioids, prolactin, and cannabinoid receptor ligands as prominent examples for and indicators of a likely much more widespread and complex, evolutionarily conserved neuroendocrine regulation of human keratin biology *in situ* than we have come to appreciate so far. We have argued that this regulation is critically involved in the maintenance of skin and HF homeostasis and may participate in skin pathology. Thus, it is timely that mainstream keratin and neuroendocrinology research, which traditionally interconnect only rarely, discover the cross-fertilization potential and clinical relevance of systematically exploring the neuroendocrine control of keratin expression and its functional consequences, namely, in human skin and HFs. Besides defining some of the many open questions in the field, we have provided specific examples for how neurohormones may be harnessed to treat selected genodermatoses and other skin disorders accompanied by abnormal keratin expression.

Many obstacles encumber the ongoing journey toward understanding mechanistically how exactly these neuromediators change keratin expression on the molecular level, and in uncovering which of these effects are directly or indirectly mediated (e.g., by affecting other cutaneous functions, which then impact on keratin expression). This situation has been further complicated by increasing insight into the strong interplay between and cross-regulation of different neurohormones within human skin. However, recent advances and refinements of serum-free human skin and HF organ cultures, which permits the silencing of selected neurohormone and receptor genes [70, 129], and the use of selective neurohormone receptor antagonists [50] surely facilitate progress in this exciting, translationally relevant line of investigation.

Conflict of interest

The authors declare they have no conflicts of interest. For the record, however, RP is founder of Monasterium Laboratory, Münster/Germany (www.monasteriumlab.com), a hair and skin research company, and consults for several companies with an interest in skin and hair research.

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References

- [1] Hsu CK, Lin HH, Harn HI, Hughes MW, Tang MJ, Yang CC. Mechanical forces in skin disorders. *The Journal of Dermatological Science*. 2018;**90**(3):232-240
- [2] Paus R, Langan EA, Vidali S, Ramot Y, Andersen B. Neuroendocrinology of the hair follicle: Principles and clinical perspectives. *Trends in Molecular Medicine*. 2014;**20**(10):559-570
- [3] Ramot Y, Paus R. Harnessing neuroendocrine controls of keratin expression: A new therapeutic strategy for skin diseases? *BioEssays*. 2014;**36**(7):672-686
- [4] Coulombe PA. The molecular revolution in cutaneous biology: Keratin genes and their associated disease: Diversity, opportunities, and challenges. *The Journal of Investigative Dermatology*. 2017;**137**(5):e67-e71
- [5] Coulombe PA. Discovery of keratin function and role in genetic diseases: The year that 1991 was. *Molecular Biology of the Cell*. 2016;**27**(18):2807-2810
- [6] Ramot Y, Paus R, Tiede S, Zlotogorski A. Endocrine controls of keratin expression. *BioEssays*. 2009;**31**(4):389-399
- [7] Slominski AT, Hardeland R, Zmijewski MA, Slominski RM, Reiter RJ, Paus R. Melatonin: A cutaneous perspective on its production, metabolism, and functions. *The Journal of Investigative Dermatology*. 2018;**138**(3):490-499
- [8] Slominski AT, Zmijewski MA, Plonka PM, Szaflarski JP, Paus R. How ultraviolet light touches the brain and endocrine system through skin, and why. *Endocrinology*. 2018;**159**(5):1992-2007
- [9] Slominski AT, Zmijewski MA, Skobowiat C, Zbytek B, Slominski RM, Steketee JD. Sensing the environment: Regulation of local and global homeostasis by the skin's neuroendocrine system. *Advances in Anatomy, Embryology and Cell Biology*. 2012;**212**:v, vii, 1-115

- [10] Slominski AT, Zmijewski MA, Zbytek B, Tobin DJ, Theoharides TC, Rivier J. Key role of CRF in the skin stress response system. *Endocrine Reviews*. 2013;**34**(6):827-884
- [11] Ito N, Ito T, Kromminga A, Bettermann A, Takigawa M, Kees F, et al. Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol. *The FASEB Journal*. 2005;**19**(10):1332-1334
- [12] Slominski A, Wortsman J, Tuckey RC, Paus R. Differential expression of HPA axis homolog in the skin. *Molecular and Cellular Endocrinology*. 2007;**265-266**:143-149
- [13] Bodo E, Kany B, Gaspar E, Knuver J, Kromminga A, Ramot Y, et al. Thyroid-stimulating hormone, a novel, locally produced modulator of human epidermal functions, is regulated by thyrotropin-releasing hormone and thyroid hormones. *Endocrinology*. 2010;**151**(4):1633-1642
- [14] Slominski A, Wortsman J, Kohn L, Ain KB, Venkataraman GM, Pisarchik A, et al. Expression of hypothalamic-pituitary-thyroid axis related genes in the human skin. *The Journal of Investigative Dermatology*. 2002;**119**(6):1449-1455
- [15] van Beek N, Bodo E, Kromminga A, Gaspar E, Meyer K, Zmijewski MA, et al. Thyroid hormones directly alter human hair follicle functions: Anagen prolongation and stimulation of both hair matrix keratinocyte proliferation and hair pigmentation. *The Journal of Clinical Endocrinology and Metabolism*. 2008;**93**(11):4381-4388
- [16] Vidali S, Knuever J, Lerchner J, Giesen M, Biro T, Klinger M, et al. Hypothalamic-pituitary-thyroid axis hormones stimulate mitochondrial function and biogenesis in human hair follicles. *The Journal of Investigative Dermatology*. 2014;**134**(1):33-42
- [17] Paus R, Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the 'brain-skin connection'. *Trends in Immunology*. 2006;**27**(1):32-39
- [18] Bodo E, Kromminga A, Biro T, Borbiro I, Gaspar E, Zmijewski MA, et al. Human female hair follicles are a direct, nonclassical target for thyroid-stimulating hormone. *The Journal of Investigative Dermatology*. 2009;**129**(5):1126-1139
- [19] Foitzik K, Krause K, Conrad F, Nakamura M, Funk W, Paus R. Human scalp hair follicles are both a target and a source of prolactin, which serves as an autocrine and/or paracrine promoter of apoptosis-driven hair follicle regression. *The American Journal of Pathology*. 2006;**168**(3):748-756
- [20] Foitzik K, Krause K, Nixon AJ, Ford CA, Ohnemus U, Pearson AJ, et al. Prolactin and its receptor are expressed in murine hair follicle epithelium, show hair cycle-dependent expression, and induce catagen. *The American Journal of Pathology*. 2003;**162**(5):1611-1621
- [21] Gaspar E, Nguyen-Thi KT, Hardenbicker C, Tiede S, Plate C, Bodo E, et al. Thyrotropin-releasing hormone selectively stimulates human hair follicle pigmentation. *The Journal of Investigative Dermatology*. 2011;**131**(12):2368-2377

- [22] Telek A, Biro T, Bodo E, Toth BI, Borbiro I, Kunos G, et al. Inhibition of human hair follicle growth by endo- and exocannabinoids. *The FASEB Journal*. 2007;**21**(13):3534-3541
- [23] Gaspar E, Hardenbicker C, Bodo E, Wenzel B, Ramot Y, Funk W, et al. Thyrotropin releasing hormone (TRH): A new player in human hair-growth control. *The FASEB Journal*. 2010;**24**(2):393-403
- [24] Paus R. A neuroendocrinological perspective on human hair follicle pigmentation. *Pigment Cell and Melanoma Research*. 2011;**24**(1):89-106
- [25] Meier NT, Haslam IS, Pattwell DM, Zhang GY, Emelianov V, Paredes R, et al. Thyrotropin-releasing hormone (TRH) promotes wound re-epithelialisation in frog and human skin. *PLoS One*. 2013;**8**(9):e73596
- [26] Knuever J, Poeggeler B, Gaspar E, Klinger M, Hellwig-Burgel T, Hardenbicker C, et al. Thyrotropin-releasing hormone controls mitochondrial biology in human epidermis. *The Journal of Clinical Endocrinology and Metabolism*. 2012;**97**(3):978-986
- [27] Poeggeler B, Knuever J, Gaspar E, Biro T, Klinger M, Bodo E, et al. Thyrotropin powers human mitochondria. *The FASEB Journal*. 2010;**24**(5):1525-1531
- [28] Paus R, Arck P. Neuroendocrine perspectives in alopecia areata: Does stress play a role? *The Journal of Investigative Dermatology*. 2009;**129**(6):1324-1326
- [29] Moll R, Divo M, Langbein L. The human keratins: Biology and pathology. *Histochemistry and Cell Biology*. 2008;**129**(6):705-733
- [30] Pan X, Hobbs RP, Coulombe PA. The expanding significance of keratin intermediate filaments in normal and diseased epithelia. *Current Opinion in Cell Biology*. 2013;**25**(1):47-56
- [31] Eckhart L, Ehrlich F. Evolution of trichocyte keratins. *Advances in Experimental Medicine and Biology*. 2018;**1054**:33-45
- [32] Kassem R, Liberty Z, Babaev M, Trau H, Cohen O. Harnessing the skin-thyroid connection for wound healing: A prospective controlled trial in guinea pigs. *Clinical and Experimental Dermatology*. 2012;**37**(8):850-856
- [33] Safer JD, Crawford TM, Holick MF. Topical thyroid hormone accelerates wound healing in mice. *Endocrinology*. 2005;**146**(10):4425-4430
- [34] Safer JD, Crawford TM, Holick MF. A role for thyroid hormone in wound healing through keratin gene expression. *Endocrinology*. 2004;**145**(5):2357-2361
- [35] Langan EA, Ramot Y, Hanning A, Poeggeler B, Biro T, Gaspar E, et al. Thyrotropin-releasing hormone and oestrogen differentially regulate prolactin and prolactin receptor expression in female human skin and hair follicles in vitro. *The British Journal of Dermatology*. 2010;**162**(5):1127-1131
- [36] Paus R. Exploring the "thyroid-skin connection": Concepts, questions, and clinical relevance. *The Journal of Investigative Dermatology*. 2010;**130**(1):7-10

- [37] Ramot Y, Zhang G, Biro T, Langbein L, Paus R. Is thyrotropin-releasing hormone a novel neuroendocrine modulator of keratin expression in human skin? *The British Journal of Dermatology*. 2013;**169**(1):146-151
- [38] Cianfarani F, Baldini E, Cavalli A, Marchioni E, Lembo L, Teson M, et al. TSH receptor and thyroid-specific gene expression in human skin. *The Journal of Investigative Dermatology*. 2010;**130**(1):93-101
- [39] Ramot Y, Zhang G, Biro T, Lisztes E, Funk W, Ingber A, et al. TSH is a novel neuroendocrine regulator of selected keratins in the human hair follicle. *Journal of Dermatological Science*. 2011;**64**(1):67-70
- [40] Cai J, Lee J, Kopan R, Ma L. Genetic interplays between *Msx2* and *Foxn1* are required for *Notch1* expression and hair shaft differentiation. *Developmental Biology*. 2009;**326**(2):420-430
- [41] Cai J, Ma L. *Msx2* and *Foxn1* regulate nail homeostasis. *Genesis*. 2011;**49**(6):449-459
- [42] Skobowiat C, Postlethwaite AE, Slominski AT. Skin exposure to ultraviolet B rapidly activates systemic neuroendocrine and immunosuppressive responses. *Photochemistry and Photobiology*. 2017;**93**(4):1008-1015
- [43] Slominski AT, Zmijewski MA, Plonka PM, Szaflarski JP, Paus R. How UV light touches the brain and endocrine system through skin, and why. *Endocrinology*. 2018;**159**(5):1992-2007
- [44] Zbytek B, Pikula M, Slominski RM, Mysliwski A, Wei E, Wortsman J, et al. Corticotropin-releasing hormone triggers differentiation in HaCaT keratinocytes. *The British Journal of Dermatology*. 2005;**152**(3):474-480
- [45] Zbytek B, Slominski AT. Corticotropin-releasing hormone induces keratinocyte differentiation in the adult human epidermis. *Journal of Cellular Physiology*. 2005;**203**(1):118-126
- [46] Langan EA, Vidali S, Pigat N, Funk W, Lisztes E, Biro T, et al. Tumour necrosis factor alpha, interferon gamma and substance P are novel modulators of extrapituitary prolactin expression in human skin. *PLoS One*. 2013;**8**(4):e60819
- [47] Richards RG, Hartman SM. Human dermal fibroblast cells express prolactin in vitro. *The Journal of Investigative Dermatology*. 1996;**106**(6):1250-1255
- [48] Ormandy CJ, Naylor M, Harris J, Robertson F, Horseman ND, Lindeman GJ, et al. Investigation of the transcriptional changes underlying functional defects in the mammary glands of prolactin receptor knockout mice. *Recent Progress in Hormone Research*. 2003;**58**:297-323
- [49] Walker AM, Robertson MT, Jones CJ. Distribution of a prolactinlike material in human eccrine sweat glands. *The Journal of Investigative Dermatology*. 1989;**93**(1):50-53
- [50] Ramot Y, Biro T, Tiede S, Toth BI, Langan EA, Sugawara K, et al. Prolactin—A novel neuroendocrine regulator of human keratin expression in situ. *The FASEB Journal*. 2010;**24**(6):1768-1779

- [51] Purba TS, Brunken L, Hawkshaw NJ, Peake M, Hardman J, Paus R. A primer for studying cell cycle dynamics of the human hair follicle. *Experimental Dermatology*. 2016;**25**(9):663-668
- [52] Purba TS, Haslam IS, Poblet E, Jimenez F, Gandarillas A, Izeta A, et al. Human epithelial hair follicle stem cells and their progeny: Current state of knowledge, the widening gap in translational research and future challenges. *BioEssays*. 2014;**36**(5):513-525
- [53] Purba TS, Peake M, Farjo B, Farjo N, Bhogal RK, Jenkins G, et al. Divergent proliferation patterns of distinct human hair follicle epithelial progenitor niches in situ and their differential responsiveness to prostaglandin D2. *Scientific Reports*. 2017;**7**(1):15197
- [54] O'Leary KA, Shea MP, Salituro S, Blohm CE, Schuler LA. Prolactin alters the mammary epithelial hierarchy, increasing progenitors and facilitating ovarian steroid action. *Stem Cell Reports*. 2017;**9**(4):1167-1179
- [55] Ferraris J, Boutillon F, Bernadet M, Seilicovich A, Goffin V, Pisera D. Prolactin receptor antagonism in mouse anterior pituitary: Effects on cell turnover and prolactin receptor expression. *American Journal of Physiology. Endocrinology and Metabolism*. 2012;**302**(3):E356-E364
- [56] Grimm SL, Seagroves TN, Kabotyanski EB, Hovey RC, Vonderhaar BK, Lydon JP, et al. Disruption of steroid and prolactin receptor patterning in the mammary gland correlates with a block in lobuloalveolar development. *Molecular Endocrinology*. 2002;**16**(12):2675-2691
- [57] Biro T, Toth BI, Hasko G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: Novel perspectives and therapeutic opportunities. *Trends in Pharmacological Sciences*. 2009;**30**(8):411-420
- [58] Maccarrone M, Bab I, Biro T, Cabral GA, Dey SK, Di Marzo V, et al. Endocannabinoid signaling at the periphery: 50 years after THC. *Trends in Pharmacological Sciences*. 2015;**36**(5):277-296
- [59] Pucci M, Pasquariello N, Battista N, Di Tommaso M, Rapino C, Fezza F, et al. Endocannabinoids stimulate human melanogenesis via type-1 cannabinoid receptor. *The Journal of Biological Chemistry*. 2012;**287**(19):15466-15478
- [60] Pucci M, Pirazzi V, Pasquariello N, Maccarrone M. Endocannabinoid signaling and epidermal differentiation. *European Journal of Dermatology*. 2011;**21**(Suppl 2):29-34
- [61] Roelandt T, Heughebaert C, Bredif S, Giddelo C, Baudouin C, Msika P, et al. Cannabinoid receptors 1 and 2 oppositely regulate epidermal permeability barrier status and differentiation. *Experimental Dermatology*. 2012;**21**(9):688-693
- [62] Srivastava BK, Soni R, Patel JZ, Joharapurkar A, Sadhwani N, Kshirsagar S, et al. Hair growth stimulator property of thienyl substituted pyrazole carboxamide derivatives as a CB1 receptor antagonist with in vivo antiobesity effect. *Bioorganic and Medicinal Chemistry Letters*. 2009;**19**(9):2546-2550

- [63] Czifra G, Szollosi AG, Toth BI, Demaude J, Bouez C, Breton L, et al. Endocannabinoids regulate growth and survival of human eccrine sweat gland-derived epithelial cells. *The Journal of Investigative Dermatology*. 2012;**132**(8):1967-1976
- [64] Dobrosi N, Toth BI, Nagy G, Dozsa A, Geczy T, Nagy L, et al. Endocannabinoids enhance lipid synthesis and apoptosis of human sebocytes via cannabinoid receptor-2-mediated signaling. *The FASEB Journal*. 2008;**22**(10):3685-3695
- [65] Olah A, Markovics A, Szabo-Papp J, Szabo PT, Stott C, Zouboulis CC, et al. Differential effectiveness of selected non-psychoactive phytocannabinoids on human sebocyte functions implicates their introduction in dry/seborrheic skin and acne treatment. *Experimental Dermatology*. 2016;**25**(9):701-707
- [66] Olah A, Toth BI, Borbiro I, Sugawara K, Szollosi AG, Czifra G, et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. *The Journal of Clinical Investigation*. 2014;**124**(9):3713-3724
- [67] Paradisi A, Pasquariello N, Barcaroli D, Maccarrone M. Anandamide regulates keratinocyte differentiation by inducing DNA methylation in a CB1 receptor-dependent manner. *The Journal of Biological Chemistry*. 2008;**283**(10):6005-6012
- [68] Ramot Y, Sugawara K, Zakany N, Toth BI, Biro T, Paus R. A novel control of human keratin expression: Cannabinoid receptor 1-mediated signaling down-regulates the expression of keratins K6 and K16 in human keratinocytes in vitro and in situ. *PeerJ*. 2013;**1**:e40
- [69] Ramot Y, Olah A, Paus R. Cover image: Neuroendocrine treatment of inherited keratin disorders by cannabinoids? *The British Journal of Dermatology*. 2018;**178**(6):1469
- [70] Sugawara K, Biro T, Tsuruta D, Toth BI, Kromminga A, Zakany N, et al. Endocannabinoids limit excessive mast cell maturation and activation in human skin. *The Journal of Allergy and Clinical Immunology*. 2012;**129**(3):726-738 e8
- [71] Derakhshan N, Kazemi M. Cannabis for refractory psoriasis-high hopes for a novel treatment and a literature review. *Current Clinical Pharmacology*. 2016;**11**(2):146-147
- [72] Kauser S, Thody AJ, Schallreuter KU, Gummer CL, Tobin DJ. Beta-endorphin as a regulator of human hair follicle melanocyte biology. *The Journal of Investigative Dermatology*. 2004;**123**(1):184-195
- [73] Bigliardi-Qi M, Bigliardi PL, Buchner S, Rufli T. Characterization of mu-opiate receptor in human epidermis and keratinocytes. *Annals of the New York Academy of Sciences*. 1999;**885**:368-371
- [74] Tominaga M, Ogawa H, Takamori K. Possible roles of epidermal opioid systems in pruritus of atopic dermatitis. *The Journal of Investigative Dermatology*. 2007;**127**(9):2228-2235
- [75] Bigliardi-Qi M, Bigliardi PL, Eberle AN, Buchner S, Rufli T. B-endorphin stimulates cytokeratin 16 expression and downregulates mu-opiate receptor expression in human epidermis. *The Journal of Investigative Dermatology*. 2000;**114**(3):527-532
- [76] Kohl A, Werner A, Buntrock P, Diezel W, Adrian K, Titov MI. The effect of the peptide dalargin on wound healing. *Dermatologische Monatschrift*. 1989;**175**(9):561-572

- [77] Bigliardi PL, Sumanovski LT, Buchner S, Rufli T, Bigliardi-Qi M. Different expression of mu-opiate receptor in chronic and acute wounds and the effect of beta-endorphin on transforming growth factor beta type II receptor and cytokeratin 16 expression. *The Journal of Investigative Dermatology*. 2003;**120**(1):145-152
- [78] Bigliardi-Qi M, Gaveriaux-Ruff C, Zhou H, Hell C, Bady P, Rufli T, et al. Deletion of delta-opioid receptor in mice alters skin differentiation and delays wound healing. *Differentiation*. 2006;**74**(4):174-185
- [79] Pain S, Altobelli C, Boher A, Cittadini L, Favre-Mercuret M, Gaillard C, et al. Surface rejuvenating effect of *Achillea millefolium* extract. *International Journal of Cosmetic Science*. 2011;**33**(6):535-542
- [80] Hens JR, Dann P, Zhang JP, Harris S, Robinson GW, Wysolmerski J. BMP4 and PTHrP interact to stimulate ductal outgrowth during embryonic mammary development and to inhibit hair follicle induction. *Development*. 2007;**134**(6):1221-1230
- [81] Eastwood J, Offutt C, Menon K, Keel M, Hrcirova P, Novotny MV, et al. Identification of markers for nipple epidermis: Changes in expression during pregnancy and lactation. *Differentiation*. 2007;**75**(1):75-83
- [82] Peters EM, Foitzik K, Paus R, Ray S, Holick MF. A new strategy for modulating chemotherapy-induced alopecia, using PTH/PTHrP receptor agonist and antagonist. *The Journal of Investigative Dermatology*. 2001;**117**(2):173-178
- [83] Schilli MB, Ray S, Paus R, Obi-Tabot E, Holick MF. Control of hair growth with parathyroid hormone [7-34]. *The Journal of Investigative Dermatology*. 1997;**108**(6):928-932
- [84] Ghoubay-Benallaoua D, Pecha F, Goldschmidt P, Fialaire-Legendre A, Chaumeil C, Laroche L, et al. Effects of isoproterenol and cholera toxin on human limbal epithelial cell cultures. *Current Eye Research*. 2012;**37**(7):644-653
- [85] Mammone T, Marenus K, Maes D, Lockshin RA. The induction of terminal differentiation markers by the cAMP pathway in human HaCaT keratinocytes. *Skin Pharmacology and Applied Skin Physiology*. 1998;**11**(3):152-160
- [86] Gschwandtner M, Mildner M, Mlitz V, Gruber F, Eckhart L, Werfel T, et al. Histamine suppresses epidermal keratinocyte differentiation and impairs skin barrier function in a human skin model. *Allergy*. 2013;**68**(1):37-47
- [87] Kurzen H, Henrich C, Booken D, Poenitz N, Gratchev A, Klemke CD, et al. Functional characterization of the epidermal cholinergic system in vitro. *The Journal of Investigative Dermatology*. 2006;**126**(11):2458-2472
- [88] Chamcheu JC, Siddiqui IA, Syed DN, Adhami VM, Liovic M, Mukhtar H. Keratin gene mutations in disorders of human skin and its appendages. *Archives of Biochemistry and Biophysics*. 2011;**508**(2):123-137
- [89] Chamcheu JC, Wood GS, Siddiqui IA, Syed DN, Adhami VM, Teng JM, et al. Progress towards genetic and pharmacological therapies for keratin genodermatoses: Current perspective and future promise. *Experimental Dermatology*. 2012;**21**(7):481-489

- [90] Ramot Y, Zlotogorski A. Molecular genetics of alopecias. *Current Problems in Dermatology*. 2015;**47**:87-96
- [91] Ramot Y, Zlotogorski A. Keratins: The hair shaft's backbone revealed. *Experimental Dermatology*. 2015;**24**(6):416-417
- [92] Ramot Y, Zlotogorski A. The twisting tale of woolly hair: A trait with many causes. *Journal of Medical Genetics*. 2015;**52**(4):217-223
- [93] Wally V, Lettner T, Peking P, Peckl-Schmid D, Murauer EM, Hainzl S, et al. The pathogenetic role of IL-1beta in severe epidermolysis bullosa simplex. *The Journal of Investigative Dermatology*. 2013;**133**(7):1901-1903
- [94] Hickerson RP, Leake D, Pho LN, Leachman SA, Kaspar RL. Rapamycin selectively inhibits expression of an inducible keratin (K6a) in human keratinocytes and improves symptoms in pachyonychia congenita patients. *Journal of Dermatological Science*. 2009;**56**(2):82-88
- [95] Kerns ML, DePianto D, Dinkova-Kostova AT, Talalay P, Coulombe PA. Reprogramming of keratin biosynthesis by sulforaphane restores skin integrity in epidermolysis bullosa simplex. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;**104**(36):14460-14465
- [96] Zhao Y, Gartner U, Smith FJ, McLean WH. Statins downregulate K6a promoter activity: A possible therapeutic avenue for pachyonychia congenita. *The Journal of Investigative Dermatology*. 2011;**131**(5):1045-1052
- [97] Reichelt J, Bussow H, Grund C, Magin TM. Formation of a normal epidermis supported by increased stability of keratins 5 and 14 in keratin 10 null mice. *Molecular Biology of the Cell*. 2001;**12**(6):1557-1568
- [98] Li H, Torma H. Retinoids reduce formation of keratin aggregates in heat-stressed immortalized keratinocytes from an epidermolytic ichthyosis patient with a KRT10 mutation. *Acta Dermato-Venereologica*. 2013;**93**(1):44-49
- [99] Ichikawa E, Watanabe S, Takahashi H. Keratin and involucrin expression in discoid lupus erythematosus and lichen planus. *Archives of Dermatological Research*. 1997;**289**(9):519-526
- [100] Ramot Y. Psoriasis and osteoporosis: The debate continues. *The British Journal of Dermatology*. 2017;**176**(5):1117-1118
- [101] Gudmundsdottir AS, Sigmundsdottir H, Sigurgeirsson B, Good MF, Valdimarsson H, Jonsdottir I. Is an epitope on keratin 17 a major target for autoreactive T lymphocytes in psoriasis? *Clinical and Experimental Immunology*. 1999;**117**(3):580-586
- [102] Depianto D, Kerns ML, Dlugosz AA, Coulombe PA. Keratin 17 promotes epithelial proliferation and tumor growth by polarizing the immune response in skin. *Nature Genetics*. 2010;**42**(10):910-914

- [103] Chung BM, Arutyunov A, Ilagan E, Yao N, Wills-Karp M, Coulombe PA. Regulation of C-X-C chemokine gene expression by keratin 17 and hnRNP K in skin tumor keratinocytes. *The Journal of Cell Biology*. 2015;**208**(5):613-627
- [104] Hobbs RP, Batazzi AS, Han MC, Coulombe PA. Loss of keratin 17 induces tissue-specific cytokine polarization and cellular differentiation in HPV16-driven cervical tumorigenesis in vivo. *Oncogene*. 2016;**35**(43):5653-5662
- [105] Hobbs RP, Lessard JC, Coulombe PA. Keratin intermediate filament proteins - novel regulators of inflammation and immunity in skin. *Journal of Cell Science*. 2012;**125**(Pt 22):5257-5258
- [106] Chang T, Sun L, Wang Y, Wang D, Li W, Li C, et al. Inhibition of keratin 17 expression with antisense and RNAi strategies: Exploring novel therapy for psoriasis. *Experimental Dermatology*. 2011;**20**(7):555-560
- [107] Fu M, Wang G. Keratin 17 as a therapeutic target for the treatment of psoriasis. *Journal of Dermatological Science*. 2012;**67**(3):161-165
- [108] Norooznejhad AH, Norooznejhad F. Cannabinoids: Possible agents for treatment of psoriasis via suppression of angiogenesis and inflammation. *Medical Hypotheses*. 2017;**99**:15-18
- [109] Toth BI, Dobrosi N, Dajnoki A, Czifra G, Olah A, Szollosi AG, et al. Endocannabinoids modulate human epidermal keratinocyte proliferation and survival via the sequential engagement of cannabinoid receptor-1 and transient receptor potential vanilloid-1. *The Journal of Investigative Dermatology*. 2011;**131**(5):1095-1104
- [110] Pastar I, Stojadinovic O, Yin NC, Ramirez H, Nusbaum AG, Sawaya A, et al. Epithelialization in wound healing: A comprehensive review. *Advances in Wound Care (New Rochelle)*. 2014;**3**(7):445-464
- [111] Rotty JD, Coulombe PA. A wound-induced keratin inhibits Src activity during keratinocyte migration and tissue repair. *The Journal of Cell Biology*. 2012;**197**(3):381-389
- [112] Stein C, Kuchler S. Targeting inflammation and wound healing by opioids. *Trends in Pharmacological Sciences*. 2013;**34**(6):303-312
- [113] Harries MJ, Jimenez F, Izeta A, Hardman J, Panicker SP, Poblet E, et al. Lichen planopilaris and frontal fibrosing alopecia as model epithelial stem cell diseases. *Trends in Molecular Medicine*. 2018;**24**(5):435-448
- [114] Ramot Y, Mastrofrancesco A, Camera E, Desreumaux P, Paus R, Picardo M. The role of PPARgamma-mediated signalling in skin biology and pathology: New targets and opportunities for clinical dermatology. *Experimental Dermatology*. 2015;**24**(4):245-251
- [115] Paus R, Haslam IS, Sharov AA, Botchkarev VA. Pathobiology of chemotherapy-induced hair loss. *The Lancet Oncology*. 2013;**14**(2):e50-e59
- [116] Chebotaev DV, Yemelyanov AY, Lavker RM, Budunova IV. Epithelial cells in the hair follicle bulge do not contribute to epidermal regeneration after glucocorticoid-induced cutaneous atrophy. *The Journal of Investigative Dermatology*. 2007;**127**(12):2749-2758

- [117] van Steensel M, Vreeburg M, Urbina MT, Lopez P, Morice-Picard F, van Geel M. Novel KRT83 and KRT86 mutations associated with monilethrix. *Experimental Dermatology*. 2015;**24**(3):222-224
- [118] Naeem M, Wajid M, Lee K, Leal SM, Ahmad W. A mutation in the hair matrix and cuticle keratin KRT5B5 gene causes ectodermal dysplasia of hair and nail type. *Journal of Medical Genetics*. 2006;**43**(3):274-279
- [119] Horev L, Babay S, Ramot Y, Saad-Edin B, Moorad S, Ingber A, et al. Mutations in two genes on chromosome 13 resulting in a complex hair and skin phenotype due to two rare genodermatoses: KLICK and autosomal recessive woolly hair/hypotrichosis simplex. *The British Journal of Dermatology*. 2011;**164**(5):1113-1116
- [120] Molho-Pessach V, Sheffer S, Siam R, Tams S, Siam I, Awwad R, et al. Two novel homozygous desmoplakin mutations in carvajal syndrome. *Pediatric Dermatology*. 2015;**32**(5):641-646
- [121] Ramot Y, Molho-Pessach V, Meir T, Alper-Pinus R, Siam I, Tams S, et al. Mutation in KANK2, encoding a sequestering protein for steroid receptor coactivators, causes keratoderma and woolly hair. *Journal of Medical Genetics*. 2014;**51**(6):388-394
- [122] Foitzik K, Langan EA, Paus R. Prolactin and the skin: A dermatological perspective on an ancient pleiotropic peptide hormone. *The Journal of Investigative Dermatology*. 2009;**129**(5):1071-1087
- [123] Langan EA, Foitzik-Lau K, Goffin V, Ramot Y, Paus R. Prolactin: An emerging force along the cutaneous-endocrine axis. *Trends in Endocrinology and Metabolism*. 2010;**21**(9):569-577
- [124] Langan EA, Griffiths CE, Paus R. Utilizing the hair follicle to dissect the regulation and autocrine/paracrine activities of prolactin in humans. *American Journal of Physiology. Endocrinology and Metabolism*. 2012;**302**(10):E1311-E1312
- [125] Langan EA, Ramot Y, Goffin V, Griffiths CE, Foitzik K, Paus R. Mind the (gender) gap: Does prolactin exert gender and/or site-specific effects on the human hair follicle? *The Journal of Investigative Dermatology*. 2010;**130**(3):886-891
- [126] Paus R. Exploring the "brain-skin connection": Leads and lessons from the hair follicle. *Current Research in Translational Medicine*. 2016;**64**(4):207-214
- [127] Marshall RC, Orwin DF, Gillespie JM. Structure and biochemistry of mammalian hard keratin. *Electron Microscopy Reviews*. 1991;**4**(1):47-83
- [128] Gong H, Zhou H, McKenzie GW, Yu Z, Clerens S, Dyer JM, et al. An updated nomenclature for keratin-associated proteins (KAPs). *International Journal of Biological Sciences*. 2012;**8**(2):258-264
- [129] Samuelov L, Sprecher E, Tsuruta D, Biro T, Kloepper JE, Paus R. P-cadherin regulates human hair growth and cycling via canonical Wnt signaling and transforming growth factor-beta2. *The Journal of Investigative Dermatology*. 2012;**132**(10):2332-2341