

# Frontiers in the (Neuro-)endocrine Controls of Hair Growth

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The human hair follicle is a unique mini-organ, capable of life-long cycles of massive growth (anagen), regression (catagen), and resting (telogen). Recent work has identified complex, stringently localized signaling mechanisms between skin neuro-ectoderm and mesoderm that drive these cyclic organ transformations (hair cycle). Pilosebaceous units have recently surfaced as both prominent targets and sources of prototypic stress mediators. This presentation discusses these recent findings and their possible role in the control of the hair cycle and melanogenesis.

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## INTRODUCTION

The human hair follicle (HF) is a unique miniorgan, capable of life-long cycles of massive growth (anagen), which are followed by rapid, apoptosis-driven organ involution (catagen) and periods of relative quiescence (telogen), and interspersed with a phase of active hair shaft shedding (exogen). Recent work has identified complex, stringently localized signaling mechanisms between skin neuro-ectoderm and mesoderm that drive these cyclic organ transformations (hair cycle). An elusive intrafollicular biological clock mechanism (hair cycle clock) regulates this process, which may be located in the specialized inductive fibroblasts of the dermal papilla, and results in defined switches of the intra- and perifollicular signaling milieu of important growth factors such as transforming growth factor- $\beta$ , IGF-1, nerve growth factor, and vascular endothelial growth factor, as well as of a multitude of locally generated (neuro-)hormones, neuropeptides and other mediators. The basic autonomy of the hair cycle clock is evident, for example, from the fact that even single isolated human hair bulbs spontaneously undergo an anagen-catagen transformation *in vitro*.

## “STRESS” AND THE HF

Like few other organs, the skin and its appendages are continuously exposed to numerous exogenous, endogenous, and psychological stressors, which affect its physiology and pathology. Intriguingly, skin and its pilosebaceous units have recently surfaced as both prominent targets of prototypic stress mediators (such as corticotropin-releasing hormone, ACTH, cortisol, catecholamines, prolactin (PRL), substance P, and nerve growth factor) and as potent sources of these key mediators of systemic stress responses. In fact, it has become clear that the skin – and, again most prominently, the HF (including human

scalp HFs!) – has established primitive, but fully functional peripheral equivalents of the hypothalamic-pituitary-adrenal axis as independent, local stress response systems.

To cope with the key biochemical and biophysical stressor, oxidative damage, HFs also express a number of highly effective free-radical scavenging and DNA-repair enzyme systems. This is complemented by the intrafollicular synthesis of melatonin, the key hormone of the pineal gland and probably the most potent antioxidant among all the neurohormones produced by the mammalian body. Disturbances in the slowly unfolding “brain-skin connection”, into which the HF is fully integrated on multiple levels, may underlie inflammatory skin diseases that are triggered or aggravated by stress.

The HF ranks among the most exciting current research frontiers in skin, hair, and stress biology as well as in cutaneous neuroimmunology. The drive is to determine how central stress response axes are linked and interact with local, intrafollicular stress response systems. To study exemplarily in the HFs of mice and men, the cross talk between peripheral and systemic responses to psychological and oxidative stress has already helped greatly to identify promising molecular targets for therapeutic stress intervention. This may revolutionize our approach to the treatment of skin diseases by the targeted pharmacological or biophysical manipulation of intracutaneous neuroendocrine regulatory loops.

## Recommended reading

Alonso L, Fuchs E (2006) The hair cycle. *J Cell Sci* 119 (Part 3):391–3

Arck PC, Slominski A, Theoharides TC, Peters EM, Paus R (2006) Neuroimmunology of stress: skin takes center stage. *J Invest Dermatol* 126:1697–704

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Abbreviations: HF, hair follicle; MC, melanocortin; PRL, prolactin

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Slominski A, Wortsman J, Tuckey RC, Paus R (2007) Differential expression of HPA axis homolog in the skin. *Mol Cell Endocrinol* 265–66:143–9

### MELANOCORTINS

The melanocortin (MC) system is probably the best-characterized neuropeptide network of the skin. Many cutaneous cell types not only express MC receptors but also synthesize MCs, such as  $\alpha$ -melanocyte-stimulating hormone or ACTH that act in an autocrine and paracrine manner. In human skin cells, activation of adenylate cyclase by MCs occurs at  $10^{-6}$  h. Besides the long-recognized pigmentary action of MCs on epidermal melanocytes, multiple additional regulatory functions of MCs in skin biology (including e.g., immunomodulation, local stress responses, lipogenesis, connective tissue turnover, cytoprotection etc.) have recently become appreciated.

Given that the HF is a potent source and major target for MC bioregulation, one key frontier in neuroendocrine hair research is to characterize the specific, non-pigmentary functions of intrafollicularly generated MCs in pilosebaceous biology and pathology (e.g. maintenance and restoration of HF immune privilege, regulation of sebum production, stimulation of local glucocorticoid synthesis, cytoprotection against UVB-induced apoptosis and DNA damage). Better definition of these – as yet, largely obscure – functions and their regulation by key-upstream regulators of MC production (i.e., corticotropin-releasing hormone, which is not only the chief hypothalamic “stress hormone” but also produced, e.g., by human scalp HFs!) should improve our understanding of skin physiology and pathophysiology and is likely to invite novel strategies for the management of hair growth disorders that target intrafollicular MC production and MC receptor expression.

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Böhm M, Luger TA, Tobin DJ, Garcia-Borrón JC (2006) Melanocortin receptor ligands: New horizons for skin biology and clinical dermatology. *J Invest Dermatol* 126:1966–75

Ito N, Ito T, Kroneminger A *et al.* (2005) Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesis of cortisol. *FASEB J* 19:1332–4

Slominski A, Wortsman J, Tuckey RC, Paus R (2007) Differential expression of HPA axis homolog in the skin. *Mol Cell Endocrinol* 265–66:143–9

### PROLACTIN

PRL is another key pituitary hormone PRL, which – like ACTH – is prominently upregulated during stress responses. PRL exerts a wide variety of non-mammotropic bioregulatory effects in mammals and is also found in extrapituitary sites. As shown by reverse transcriptase-PCR and immunohistology, human skin and normal human scalp HFs, in particular, express both PRL and PRL receptors at the mRNA and protein level. During the anagen-catagen transformation, PRL and PRL receptors immunoreactivity appears upregulated in human scalp HFs. Treatment of organ-cultured human scalp HFs with high-dose PRL results in a significant inhibition of hair shaft elongation and in premature catagen development, along with reduced proliferation and increased apoptosis of hair bulb keratinocytes. This shows that human skin and human scalp HFs are both direct targets and sources of PRL and suggests that PRL acts as an autocrine hair growth modulator with catagen-promoting functions. These new findings may help to understand the as yet ill-explained hair loss in patients with hyperprolactinemia, and may be exploited for treating, for example, unwanted hair growth.

### Recommended reading

Foitzik K, Krause K, Conrad F, Nakamura M, Funk W, Paus R (2006) 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. *Am J Pathol* 168:748–56

### SEX STEROIDS: BEYOND THE ANDROGEN HORIZON

Last but not least, another frontier in (neuro-)endocrine hair growth controls is that our concepts on the relevant classical endocrine controls of hair growth are becoming much more comprehensive by the steadily increasing recognition that other sex steroids besides androgens deserve very careful scrutiny. Evidently, androgens have long dominated endocrine research in hair growth control, and dihydrotestosterone synthesis and the androgen receptor are key targets for systemic, pharmacological hair growth control in clinical medicine. However, it has equally long been known that estrogens can alter HF growth and cycling profoundly by binding to locally expressed high-affinity estrogen receptors (ERs).

The recent renaissance of estrogen research in hair research reflects the (re-)discovery that the HF offers an ideal, clinically relevant test system for studying the role of sex steroids, their receptors, and interactions in neuroectodermal-mesodermal interaction systems in general. In addition, it can be exploited to identify novel functions and signaling cross talks of ER-mediated signaling. Besides altering the transcription of genes with estrogen-responsive elements,  $17\beta$ -estradiol also modifies androgen metabolism within distinct subunits of the pilosebaceous unit (i.e., HF

and sebaceous gland). The latter displays prominent aromatase activity, the key enzyme for androgen conversion to  $17\beta$ -estradiol, and is, thus, both an estrogen source and target.

However, the – often underestimated – complexity of ER-dependent and ER-independent signaling events as well as the species-, gender-, and site-dependency of  $17\beta$ -estradiol-induced effects on the HF make it a truly formidable task to dissect the most promising targets for clinically relevant pharmacological intervention to manipulate HF cycling by targeting ER and associated signaling systems, ranging from androgenetic alopecia and hirsutism via telogen effluvium to chemotherapy-induced alopecia.

This complexity has further increased by recent evidence that points towards glucocorticoid-dependent mechanisms, which may operate in the “mesenchymal command center” of HFs, the dermal papilla, whereby the selective action of one ER ( $ER\beta$ ) can be differentially promoted, along with upregulation of (estrogen-generating) aromatase activity. On the one hand, this adds to the complexity of androgen-independent endocrine controls of hair growth. On the other hand, this amply documents that the time has come to look well beyond the “androgen horizon” when investigating the endocrine controls of hair growth by sex steroids – and when exploring how these may be exploited in future, innovative “hormonal” therapy of common hair growth disorders.

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Thornton MJ, Nelson LD, Taylor AH, Birch MP, Laing I, Messenger AG (2006) The modulation of aromatase and estrogen receptor alpha in cultured human dermal papilla cells by dexamethasone: a novel mechanism for selective action of estrogen via estrogen receptor beta? *J Invest Dermatol* 126:2010–8

#### CONCLUSION

The HF ranks among the most exciting current research frontiers in skin, hair, and stress biology and, in cutaneous neuroimmunology and neuroendocrinology. The elusive intrafollicular biological clock mechanism that regulates hair follicle cycling may well be influenced by local neuroendocrine, stress-modulated events that ultimately result in defined switches of the intra- and perifollicular-signaling milieu of important growth factors.

#### CONFLICT OF INTEREST

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