Mind the (Gender) Gap: Does Prolactin Exert Gender and/or Site-Specific Effects on the Human Hair Follicle?

Journal of Investigative Dermatology (2010) **130,** 886–891; doi:10.1038/jid.2009.340; published online 5 November 2009

TO THE EDITOR

The pleiotropic, cytokine-like polypeptide neurohormone prolactin (PRL), primarily produced by the pituitary gland, is most widely appreciated for its central role in the regulation of lactation and reproduction. However, PRL is important in a bewildering array of biological processes spanning growth and development, immunoregulation, osmoregulation, metabolism, and the stress response (Ben-Jonathan *et al.*, 1996, 2008; Bole-Feysot *et al.*, 1998; Freeman *et al.*, 2000; Grattan and Kokay, 2008). The importance of PRL in cutaneous biology and pathology was first postulated almost two decades ago (Paus, 1991), and interest in its role in skin biology has recently been revived (Foitzik *et al.*, 2009).

Prolactin has been implicated in the pathogenesis of several inflammatory dermatoses, including psoriasis (Giasuddin *et al.*, 1998) and acne vulgaris (Davidovici *et al.*, 2008), and systemic diseases with cutaneous manifestations, including rheumatoid arthritis (Velkeniers *et al.*, 1998), systemic lupus erythematosus (De Bellis *et al.*, 2005), systemic sclerosis (Shahin *et al.*, 2002), and Behcet's disease (Proença *et al.*, 2007). Moreover, both mouse and human skin have been identified as nonclassical, extrapituitary sites of PRL expression, which also respond to PRL receptor (PRLR)-mediated signaling, for example, with changes in hair growth and hair keratinocyte proliferation *in situ* (Craven *et al.*, 2001; Foitzik *et al.*, 2003, 2006, 2009). This is not surprising given that the regulatory effects of PRL on hair growth, in several species, have been documented for over 20 years (see Foitzik *et al.*, 2009 for review).

However, more detailed analysis of the regulatory effects of PRL on hair growth reveals surprising and at times seemingly contradictory, inter- and intraspecies variations in the hair follicle (HF) response to PRL (Table 1). Murine skin and human scalp HFs express both PRL and functional PRLR at the gene and protein levels, and PRL operates as a potent modulator of HF cycling (Craven *et al.*, 2001, 2006; Foitzik *et al.*, 2003, 2006). In mice, PRL appears to operate primarily as a potent hair growth inhibitor; it induces premature catagen development and hair matrix keratinocyte apoptosis, and inhibits hair matrix keratinocyte proliferation in skin organ culture of back skin pelage follicles, whereas PRLR knockout mice have longer and coarser hair than wild-type controls (Craven *et al.*, 2001, 2006; Foitzik *et al.*, 2003).

HAIR GROWTH MODULATION BY PRL: A CONFUSING PICTURE

Interestingly, administration of bromocriptine, a dopaminergic inhibitor of pituitary PRL secretion, induces telogen effluvium in women (Fabre *et al.*, 1993), but not in men. This is likely to be due to premature catagen induction. This raises the possibility that, in women, PRL may actually be a hair-growth-promoting/anagen-maintaining factor.

The predominantly hair-growth-inhibitory effect seen in (female) mice is recapitulated in the serum-free organ culture of human HFs (Lu *et al.*, 2007; Philpott *et al.*, 1990): high-dose PRL (400 ng ml^{-1}, a level that can be found in patients with macroprolactinoma) stimulated premature catagen development and inhibited hair shaft production and hair matrix keratinocyte proliferation in microdissected HFs from male occipital scalp skin (Foitzik *et al.*, 2006).

Thus, we were surprised to find that, in a repeat HF organ culture experiment, using a small number of HFs derived from female frontotemporal scalp skin, the same dose of PRL (400 ng ml^{-1}) resulted in significant HF shaft elongation. Therefore, we repeated these experiments with a larger number of female HFs, derived from frontotemporal scalp skin specimens from additional donors, used a well-characterized specific PRLR antagonist (Goffin *et al.*, 2005), assessed PRLR expression immunohistologically, and used microarray technology to examine the modulation of intrafollicularly expressed genes.

In these repeat analyses, PRL treatment (400 ng ml^{-1}) of female frontotemporal scalp HFs again significantly promoted hair shaft elongation in serum-free HF organ culture. This effect was reduced in the presence of a pure PRLR antagonist (del1-9-G129R-hPRL, 4 μg ml^{-1}) (Bernichtein *et al.*, 2003; Figure 1a). In contrast to the prominent catagen-inducing effects seen in male occipital scalp HFs (Foitzik *et al.*, 2006), PRL did not have such an effect in female frontotemporal HFs. Moreover, treatment with PRLR antagonist alone significantly inhibited both HF hair shaft production (Figure 1b) and spontaneous catagen development (Figure 1c). This catagen-promoting effect

Abbreviations: HF, hair follicle; PRL, prolactin; PRLR, PRL receptor

Table 1. Published contradictory effects of PRL on hair growth in various species, with specific reference to site and gender

Species	Gender	Site	Effects of PRL	References
Human	Male	Occipital scalp	Catagen-inducing effect, inhibition of hair growth *in vitro* Decreased proliferation and upregulated apoptosis of HF keratinocytes *in vitro*	Foitzik *et al.* (2006)
Mice	Female Balb/c and PRLR knockout mice, both genders	Dorsal skin	Delayed hair regrowth Differences in dorsoventral HF response to PRL corresponded to site difference in timing of hair growth wave *in vivo.* Sex differences observed in HF behavior in PRLR knockout mice	Craven *et al.* (2006)
Mice	Female (including pregnant females)	Dorsal skin	Induction of premature catagen *in vitro* Decreased proliferation of keratinocytes *in vitro*	Foitzik *et al.* (2003)
Mice	Male and female	Dorsal skin	Advancement in hair replacement in PRLR-deficient mice, more pronounced in female mice, *in vivo.* PRLR-deficient mice had longer and coarser hair with normal sexual dimorphism eliminated	Craven *et al.* (2001)
Sheep	Rams and ewes	Mid-side skin	High circulating PRL and peak PRLR expression correlated with the initiation of HF growth. PRL mRNA downregulation preceded catagen *in vivo.* Specific gender differences not examined	Nixon *et al.* (2002)
Sheep	Ewes	Left mid-side skin	Entry of anagen wool follicles into catagen *in vivo*	Pearson *et al.* (1996)
Cashmere goat	Male and female goats		PRL shown to have a stimulating effect on hair shaft elongation of secondary HFs *in vitro.* In addition, increasing PRL levels reactivate telogen HFs and induce anagen. Keeping Cashmere goats in continuous light (elevating concentrations of blood PRL) increased mean fiber length	Ryder and Stephenson, 1968; Dicks *et al.*, 1994; Ibraheem *et al.*, 1994
Djungarian hamster			Endogenous PRL found to be necessary for the development and maintenance of summer pelage *in vivo*	Duncan and Goldman (1984)
Red deer			Prolactin stimulated hair growth in cultured follicles of red deer summer coat *in vivo.*	Thomas *et al.* (1993)

Abbreviations: HF, hair follicle; PRL, prolactin; PRLR, prolactin receptor.

of the used PRLR antagonist suggests that endogenous, intrafollicular PRL production actually maintains human female frontotemporal scalp HFs in anagen VI. These data were independently confirmed by calculation of the hair cycle score (Figure 1d), and by the microarray-based demonstration that PRL downregulated the steady-state transcript levels for a number of catagen-associated genes (Table 2).

In line with a hair-growth-promoting effect of PRL in female frontotemporal scalp HFs, quantitative immunohistomorphometry revealed increased hair matrix keratinocyte proliferation *in situ.* This was reversed by treatment with a PRLR antagonist (Figure 1e). In fact, a stimulatory effect of PRL on the proliferation of human (epidermal) keratinocytes *in vitro* had been previously published in this journal (Girolomoni *et al.,* 1993).

HAIR GROWTH EFFECTS BY PRL: REVISITING THE LITERATURE

These unexpected findings run contrary to the well-documented hair-growth-inhibitory effects of PRL in mice and humans (Craven *et al.*, 2001, 2006; Foitzik *et al.*, 2003, 2006). They refocus our attention on hair-growth-modulatory effects of PRL that had been reported in the older literature and that cannot be easily reconciled with the notion that PRL is an across-the-board hair-growth inhibitor (see Table 1). Taken together with the increasing awareness of sexual dimorphism in the mammalian response to defined neuroendocrine stimuli (e.g., Aoki *et al.*, 2001; Pi and Voogt, 2002; Rocha *et al.*, 2002; Amador-Noguez *et al.*, 2005; Senovilla *et al.*, 2008), the gender-dependent differences in the response of human scalp HFs to estrogens (Conrad *et al.*, 2005; Ohnemus *et al.*, 2006), and the well-known paradoxical, strictly site-dependent effects of androgens (Randall, 2008), our new findings (Figure 1) beg the question of whether the response of human HFs to PRL stimulation may actually be highly gender and/or location dependent.

Re-analysis of the older literature reveals an awareness of the existence of gender differences in the response of the HF to PRL and hyperprolactinemia. For example, although hirsutism can be

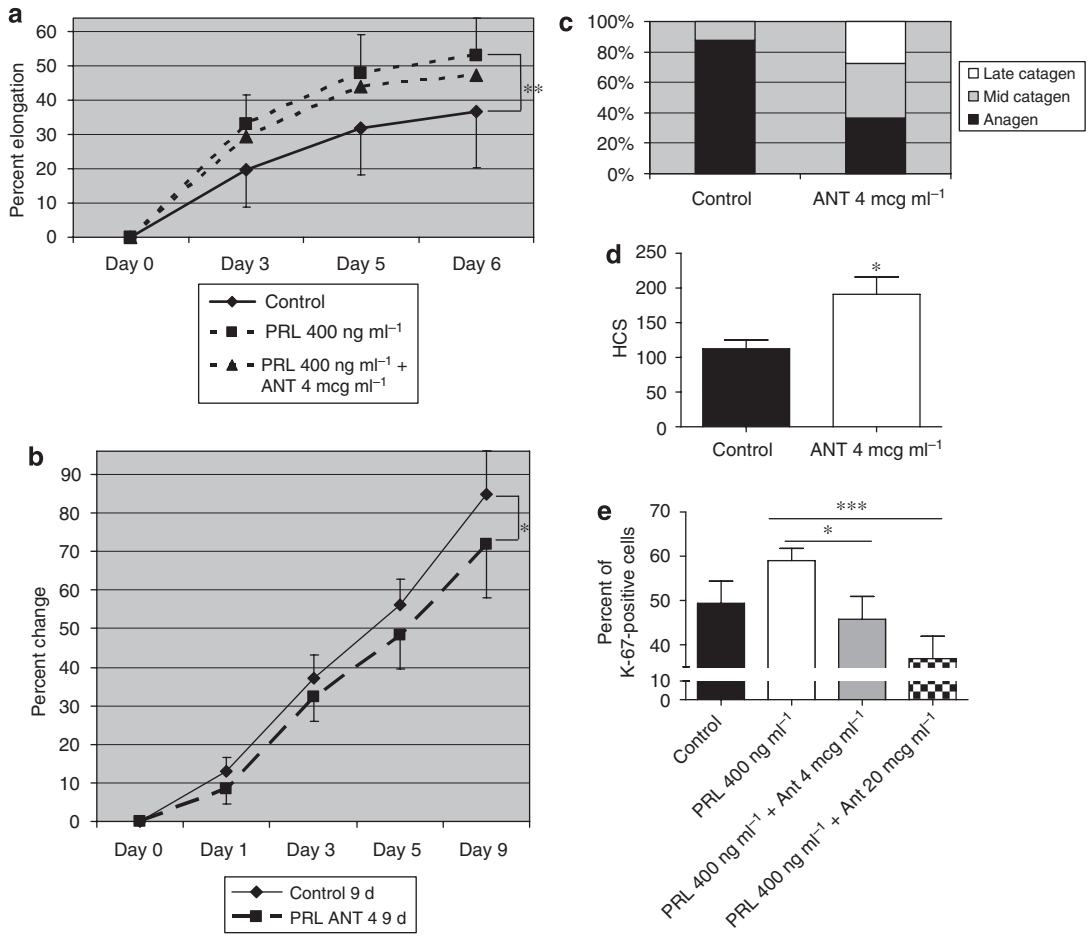

Figure 1. Effects of prolactin (PRL; 400 ng ml^{-1}) on female frontotemporal hair follicles (HFs). (**a**) Elongation data showing PRL-mediated increase in hair shaft elongation, partially reversed by PRL receptor (PRLR) antagonist treatment, in human female frontotemporal scalp HFs. (**b**) PRLR antagonist alone caused significant inhibition of elongation after 9 culture days. (**c**, **d**) Catagen-like inducing effects of the PRLR antagonist. (**c**) Percentage of HFs at different hair cycle stages after 9 days in culture. (**d**) Calculation of the hair cycle score. Each stage of the hair cycle was scored as follows: anagen VI = 100, early catagen = 200, mid catagen = 300. HCS, hair cycle score. (**e**) PRL treatment increased hair bulb expression of the proliferation marker Ki67 in anagen VI HFs; this was reversed by addition of PRLR antagonist. *P<0.05; **P<0.01; ***P<0.001.

Table 2. Genes related to catagen induction that appear to be downregulated by PRL treatment of female scalp HFs

Gene	Fold change	*P*-value	References
TGFBR1	**−1.55**	**0.017**	Foitzik *et al.*, (2000); Sowden *et al.*, (2007)
TGFBR2	**−1.81**	**0.0005**	Foitzik *et al.*, (2000); Sowden *et al.*, (2007)
TGFBR3	**−2.37**	**0.001**	Foitzik *et al.* (2000); Sowden *et al.* (2007)
TAIP-2	**−6.06**	**1,75E-11**	Foitzik *et al.* (2000); Sowden *et al.* (2007)
BMP2	**−1.83**	**0.00007**	Blessing *et al.* (1993); Paus and Foitzik (2004)
BMP4	**−1.44**	**0.01**	Blessing *et al.* (1993); Paus and Foitzik (2004)
IGFBP3	**−1.5**	**0.006**	Schlake *et al.* (2004); Buckbinder *et al.* (1995)

Abbreviations: BMP, bone morphogenetic protein; IGFBP, insulin-like growth factor binding protein; TAIP, TGF-β-induced apoptosis protein; TGFBR, transforming growth factor-β receptor.
Gene expression analysis of freshly isolated human scalp HFs (25 per group) treated with vehicle/PRL (400 ng ml^{-1}) for 48 h. The analysis was performed using Human Whole Genome Oligo Microarray (44K) by Miltenyi Biotech GmbH (Bergisch-Gladbach, Germany).

a feature of hyperprolactinemia in females (Tekin *et al.*, 2004), males with hyperprolactinemia usually suffer from reduced growth of facial and/or body hair (Buvat *et al.*, 1985; Walsh *et al.*, 1994). In addition, dopaminergic agonists, which inhibit pituitary PRL secretion and are used to treat PRL-secreting prolactinoma, reportedly cause hair loss. Strikingly, out of the 14 dopamine agonist-induced hair loss cases reported in the literature, only 1 patient was man (Grauer and Sieb, 2002; Miwa and Kondo, 2003; Katz *et al.*, 2006). Even in that patient, alopecia was reported in the beard area, and not in the scalp (Grauer and Sieb, 2002).

Gender differences in the hair response to PRL have also been reported earlier in mice (Craven *et al.*, 2001). In PRLR knockout mice, female pelage replacement was advanced by 4 weeks, compared to an advancement of only 4 days in males. This led to the elimination of the normal sexual dimorphism in murine pelage replacement (Craven *et al.*, 2001).

In addition, site-dependent differences in HF sensitivity to PRL, as well as to bromocriptine treatment, were also observed when dorsal was compared with axillary mouse skin. For example, bromocriptine treatment resulted in new hair growth, in both axillae and dorsal skin, at a younger age than in control mice. PRL treatment abrogated this premature hair growth (Craven *et al.*, 2006). Although these differential effects were attributed to distinct hair cycle stages, they may well have also represented site-specific differences in the HF response. Interestingly, human skin appears to show related site-specific differences; such as, PRL and PRLR are expressed at the gene and protein levels in human scalp skin (Foitzik *et al.*, 2006), whereas no evidence for PRL gene transcription was found in corporal skin (Slominski *et al.*, 2001).

HYPOTHESIS: PRL EFFECTS ON HAIR GROWTH ARE GENDER AND/OR SITE DEPENDENT

On this basis, we propose the unreported hypothesis that intracutaneous PRL effects are highly gender and/or site dependent. Conversely, this may be related to gender- and/or location-dependent differences in the distribution of PRLR. This differential response may depend on the post-receptor signal transduction pathways that are predominantly used by the same cell populations in different genders/skin locations, and/or on gender- and/or site-specific differences in the key target genes, whose expression is up- or downregulated after PRLR stimulation (Figure 2). We speculate that this can account for diametrically opposed functional effects of PRL and PRLR antagonists on identical peripheral target organs, such as the skin and its appendages. Thus, we propose that the distinct hair-growth-modulatory effects of PRL in female frontotemporal (Figure 1) versus male occipital scalp HFs (Foitzik *et al.*, 2006) are the manifestation of gender- and/or location-dependent differential responses to PRL.

To identify, characterize, and mechanistically dissect gender- and/or site-specific differences in the response of peripheral tissues to PRLR ligands is of evident biological and clinical importance. Not only is this needed to adequately and more efficiently tailor PRL-related therapeutic strategies to each gender and/or to PRL target organs in defined anatomical locations, but also because the increasingly appreciated adverse effects of PRL and its antagonists in rodents and humans (Buvat *et al.*, 1985; Katz *et al.*, 2006; Harvey *et al.*, 2008) may differ between the genders and/or distinct tissue locations.

Furthermore, we propose that the serum-free organ culture of human HFs from female versus male scalp skin, and from defined scalp skin locations (frontotemporal vs occipital), offers a very sensitive and instructive, physiologically and clinically highly relevant research tool to further dissect the proposed gender and/or location dependence of PRL effects on nonclassical, peripheral PRL target tissues in the human system.

POSSIBLE MECHANISMS

Drawing from the example of sexual dimorphism in the human HF response to estrogens (Conrad *et al.*, 2005; Ohnemus *et al.*, 2006), and the recognized gender differences in PRLR expression, for example, in rat brains (Pi and Voogt, 2002), one reasonable explanation for gender- and/or location-dependent differences in the response to PRL and PRL antagonists could arise from differences in PRLR distribution and expression level. In fact, we had previously observed striking differences in estrogen receptor expression between male and female scalp skin HFs (Conrad *et al.*, 2005). In addition, various isoforms of the PRLR exist, whose stimulation exerts different biological effects (Gadd and Clevenger, 2006). Thus, gender- and/or location-dependent differences in the predominant PRLR isoform need to be considered (Figure 2). The constitutive gender difference in human daytime serum PRL levels may ''prime'' gender-dependent differences in PRLR expression and/or sensitivity to PRL stimulation. Furthermore, gender- and/or location-dependent differences in post-receptor signaling and PRL target genes need to be considered (Figure 2). The previously noted major differences in the gene expression profile induced by 17-β-estradiol in male versus female

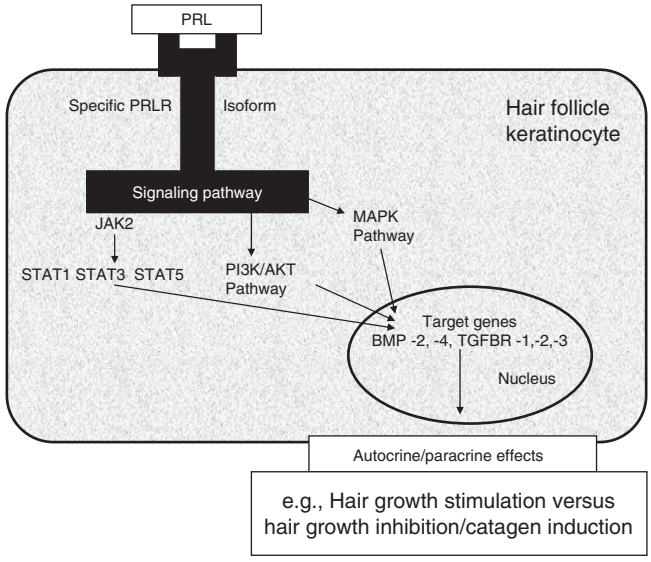

Figure 2. Possible pathways for gender- and/or site-specific responses to prolactin receptor (PRLR)-mediated signaling. Modified after Goffin *et al.*, 2006 and Foitzik *et al.*, 2009.

Table 3. PRL-mediated site and gender-specific gene regulation in human scalp HFs

	Male occipital[1]			
Gene name	**Patient 1**	**Patient 2**	**Female temporal[2]**	**Female occipital[2]**
Genes downregulated in male occipital scalp HFs (>2.1-fold change in at least 1 patient)				
RBP4	−1.54	−2.86	−1.65	1.07
Ubiquitin	2.25	1.52	−1.28	−1.14
CYP1B1	2.12	1.53	−1	−1.15
SERPINA1	2.04	2.23	1.64	1.08
LCN2	1.81	2.41	1.2	1.3
Genes regulated in female frontotemporal scalp HFs (>2.1-fold change)				
GJA1	1.25	1.28	−2.44	1.44
Cornifin B	1.3	1.69	−2.42	1.05
BAX	1.07	1.05	−2.39	−1.33
COL3A1	−1.12	−1.2	−2.27	1.12
ABME	1.07	1.12	2.26	−1.1
HMOX1	−1.32	−1.08	−2.16	1.08
COL6A1	1.08	−1.1	−2.13	1.27
Genes regulated in female occipital scalp HFs (>2.1-fold change)				
CDC2L1	−1.23	1.02	−2.05	−2.19
NKTR	1.1	0.96	1.06	−2.18

Abbreviations: ABME, apolipoprotein B mRNA-editing enzyme; BAX, BCL2-associated X protein; CDC2L1, PITSLRE protein kinase; COL3AI, collagen type III, α1; COL6A1, collagen type VI, α1; CYP1B1, cytochrome P450 1B1; GJA1, gap junction α1 protein (connexin 43); HMOX1, heme oxygenase 1; LCN2, lipocalin 2; NKTR, NK-tumor recognition protein; RBP4, retinal-binding protein 4. Gene expression analysis of HFs from male occipital and female temporal and occipital scalp HFs treated with 400 ng ml^{-1} PRL. Several genes are differentially regulated in a site, and gender-specific manner. For example, *ubiquitin* is significantly upregulated in male occipital skin HF, but downregulated in female temporal and occipital HFs treated with prolactin. *ABME* is only upregulated in PRL-treated female temporal HFs, and NKTR only downregulated in PRL-treated female occipital scalp HFs. The analysis was performed using Human Whole Genome Oligo Microarray (44K) by Miltenyi Biotech GmbH.
[1]Microarray 1.
[2]Microarray 2.

organ-cultured human HFs (Conrad *et al.*, 2005) further suggests that male and female HFs can show distinct gene regulation in response to the same hormonal stimulus.

Using microarray technology, we carried out a tentative attempt to explore gender- and/or location-dependent differences in the response of HFs to PRL. The limited available results suggest that these do indeed exist (Table 3). This underscores that human scalp HFs are indeed well suited as a biologically and clinically highly relevant, PRL-sensitive test system for picking up differentially expressed genes, whose transcription appears to differ between the genders and skin locations tested, and supports our hypothesis of gender- and/or site-dependent differences in the HF response to PRL stimulation (Table 3). Although these data evidently require quantitative confirmation on the mRNA and protein levels, and reproduction in additional human donors, they lend further support to our hypothesis of gender- and/or site-specific differences in the effect of PRL on an exemplary, nonclassical peripheral human target tissue: the scalp HF.

The effects of PRL on hair growth have been studied in many species, including mammals with both seasonally dependent and independent hair pelage replacement cycles. The seemingly conflicting effects reported in the literature (Table 1) may well be reconciled if one interprets them as representations of site- and/or gender-dependent HF responses to PRL. If confirmed, these differences will add a fascinating new dimension to our understanding of sexual dimorphism in HF responses to hormonal stimulation, and highlight the need for a systematic exploration of gender- and/or location-specific PRL-mediated signaling in the physiology and pathology of peripheral PRL target tissues in the human system.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

CEMG and RP received funding from the Manchester Biomedical Research Centre, National Institute for Health Research.

Ewan A. Langan[1,6], Yuval Ramot[2,3,6], Vincent Goffin[4], Christopher E.M. Griffiths[1], Kerstin Foitzik[5] and Ralf Paus[1,2]

[1]Dermatological Sciences, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK; [2]Department of Dermatology, University of Luebeck, Luebeck, Germany; [3]Department of Dermatology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [4]INSERM, U845, Research Center Growth and Signaling, Faculté de Médecine, Université de Paris Descartes, Paris, France and [5]Department of Paediatric Dermatology, Children's Hospital Wilhelmstift, Hamburg, Germany
E-mail: ralf.paus@uk-sh.de
[6]These authors contributed equally to this work.

REFERENCES

Amador-Noguez D, Zimmerman J, Venable S, Darlington G (2005) Gender-specific alterations in gene expression and loss of liver sexual dimorphism in the long-lived Ames dwarf mice. *Biochem Biophys Res Commun* 332:1086–100

Aoki MP, Aoki A, Maldonado CA (2001) Sexual dimorphism of apoptosis in lactotrophs induced by bromocryptine. *Histochem Cell Biol* 116:215–22

Ben-Jonathan N, LaPensee CR, LaPensee EW (2008) What can we learn from rodents about prolactin in humans? *Endocr Rev* 29:1–41

Ben-Jonathan N, Mershon JL, Allen DL, Steinmetz RW (1996) Extrapituitary prolactin: distribu-

tion, regulation, functions, and clinical aspects. *Endocr Rev* 17:639–69

Bernichtein S, Kayser C, Dillner K *et al.* (2003) Development of pure prolactin receptor antagonists. *J Biol Chem* 278:35988–9

Blessing M, Nanney LB, King LE, Jones CM, Hogan BL (1993) Transgenic mice as a model to study the role of TGF-beta related molecules in hair follicles. *Genes Dev* 7: 204–15

Bole-Feysot C, Goffin V, Edery M, Binart N, Kelly PA (1998) Prolactin (PRL) and its receptor: actions, signal transduction pathways, and phenotypes observed in PRL receptor knockout mice. *Endocr Rev* 19:225–68

Buckbinder L, Talbott R, Velasco-Miguel S *et al.* (1995) Induction of the growth inhibitor IGF-binding protein 3 by p53. *Nature* 377:646–9

Buvat J, Lemaire A, Buvat-Herbaut M, Fourlinnie JC, Racadot A, Fossati P (1985) Hyperprolactinemia and sexual function in men. *Horm Res* 22:196–203

Conrad F, Ohnemus U, Bodo E *et al.* (2005) Substantial sex-dependent differences in the response of human scalp hair follicles to estrogen stimulation *in vitro* advocate gender-tailored management of female versus male pattern balding. *J Investig Dermatol Symp Proc* 10:243–6

Craven A, Ormandy C, Robertson F, Kelly P, Nixon A, Pearson A (2001) Prolactin signaling influences the timing mechanism of the hair follicle: analysis of hair growth cycles in prolactin receptor knockout mice. *Endocrinology* 142:2533–9

Craven AJ, Nixon AJ, Ashby MG *et al.* (2006) Prolactin delays hair regrowth in mice. *J Endocrinol* 191:415–25

Davidovici BB, Orion E, Wolf R (2008) Cutaneous manifestations of pituitary gland diseases. *Clinics Dermatol* 26:288–95

De Bellis A, Bizzarro A, Pivonello R, Lombardi G, Bellastella A (2005) Prolactin and autoimmunity. *Pituitary* 8:25–30

Dicks P, Russel AJ, Lincoln GA (1994) The role of prolactin in the reactivation of hair follicles in relation to moulting in Cashmere goats. *J Endocrinol* 143:441–8

Duncan MJ, Goldman BD (1984) Hormonal regulation of the annual pelage color cycle in the Djungarian hamster, *Phodopus sungorus*. II. Role of prolactin. *J Exp Zool* 230:97–103

Fabre N, Montastruc JL, Rascol O (1993) Alopecia: an adverse effect of bromocriptine. *Clin Neuropharmacol* 16:266–8

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

Foitzik K, Krause K, Nixon AJ *et al.* (2003) Prolactin and its receptor are expressed in murine hair follicle epithelium, show hair cycle-dependent expression, and induce catagen. *Am J Pathol* 162:1611–21

Foitzik K, Langan EA, Paus R (2009) Prolactin and the skin: a dermatological perspective on an ancient pleiotropic peptide hormone. *J Invest Dermatol* 129:1071–87

Foitzik K, Lindner G, Mueller-Roever S *et al.* (2000) Control of murine hair follicle regression (catagen) by TGF-beta1 *in vivo*. *FASEB J* 14:752–60

Freeman ME, Kanyicska B, Lerant A, Nagy G (2000) Prolactin: structure, function and regulation of secretion. *Physiol Rev* 80:1523–89

Gadd SL, Clevenger CV (2006) Ligand-independent dimerization of the human prolactin receptor isoforms: functional implications. *Mol Endocrinol* 20:2734–46

Giasuddin AS, El-Sherif AI, El-Ojali SI (1998) Prolactin: does it have a role in the pathogenesis of psoriasis? *Dermatology* 197: 119–22

Girolomoni G, Phillips JT, Bergstresser PR (1993) Prolactin stimulates proliferation of cultured human keratinocytes. *J Invest Dermatol* 101:275–9

Goffin V, Bernichtein S, Touraine P, Kelly PA (2005) Development of potential clinical uses of human prolactin receptor antagonists. *Endocr Rev* 26:400–22

Goffin V, Touraine P, Culler MD *et al.* (2006) Drug insight: prolactin-receptor antagonists, a novel approach to treatment of unresolved systemic and local hyperprolactinermia?. *Nat Clin Pract Endocrinol Metab* 2:571–81

Grattan DR, Kokay IC (2008) Prolactin: a pleiotropic neuroendocrine hormone. *J Neuroendocrinol* 20:752–63

Grauer MT, Sieb JP (2002) Alopecia induced by dopamine agonists. *Neurology* 59:2012

Harvey PW, Everett DJ, Springall CJ (2008) Adverse effects of prolactin in rodents and humans: breast and prostate cancer. *J Psychopharmacol* 22(2 Suppl):20–7

Katz KA, Cotsarelis G, Gupta R, Seykora JT (2006) Telogen effluvium associated with the dopamine agonist pramipexole in a 55-year-old woman with Parkinson's disease. *J Am Acad Dermatol* 55:S103–4

Ibraheem M, Galbraith H, Scaife J, Ewen S (1994) Growth of secondary hair follicles of the Cashmere goat *in vitro* and their response to prolactin and melatonin. *J Anat* 185: 135–42

Lu Z, Hasse S, Bodo E, Rose C, Funk W, Paus R (2007) Towards the development of a simplified long-term organ culture method for human scalp skin and its appendages under serum-free conditions. *Exp Dermatol* 16:37–44

Miwa H, Kondo T (2003) Hair loss induced by dopamine agonist: case report and review of the literature. *Parkinsonism Relat Disord* 10:51–2

Nixon AJ, Ford CA, Wildermoth JE, Craven AJ, Pearson AJ (2002) Regulation of prolactin receptor expression in ovine skin in relation to circulating prolactin and wool follicle growth status. *J Endocrinol* 172:605–14

Ohnemus U, Uenalan M, Inzunza J, Gustafsson JA, Paus R (2006) The hair follicle as an estrogen target and source. *Endocr Rev* 27:677–706

Paus R (1991) Does prolactin play a role in skin biology and pathology? *Med Hypotheses* 36: 33–42

Paus R, Foitzik K (2004) In search of the ''hair cycle clock'': a guided tour. *Differentiation* 72:489–511

Pearson AJ, Parry AL, Ashby MG, Choy VJ, Wildermoth JE, Craven AJ (1996) Inhibitory effect of increased photoperiod on wool follicle growth. *J Endocrinol* 148: 157–66

Philpott MP, Green MR, Kealey T (1990) Human hair growth *in vitro*. *J Cell Sci* 97:463–71

Pi X, Voogt JL (2002) Sex difference and estrous cycle: expression of prolactin receptor mRNA in rat brain. *Brain Res Mol Brain Res* 103:130–9

Proença H, Ferreira C, Miranda M, Castanheira-Dinis A, Monteiro-Grillo M (2007) Serum prolactin levels and Behcet disease. *Eur J Ophthalmol* 17:404–7

Randall VA (2008) Androgens and hair growth. *Dermatol Ther* 21:314–28

Rocha EM, Hirata AE, Carneiro EM *et al.* (2002) Impact of gender on insulin signaling pathway in lacrimal and salivary glands of rats. *Endocrine* 18:191–9

Ryder M, Stephenson S (1968) *Wool Growth*. London: Academic Press

Schlake T, Beibel M, Weger N, Boehms T (2004) Major shifts in genomic activity accompany progression through different stages of the hair cycle. *Gene Expr Patterns* 4:141–52

Shahin AA, Abdoh S, Abdelrazik M (2002) Prolactin and thyroid hormones in patients with systemic sclerosis: correlations with disease manifestations and activity. *Z Rheumatol* 61:703–9

Senovilla L, Núñez L, Villalobos C, García-Sancho J (2008) Rapid changes in anterior pituitary cell phenotypes in male and female mice after acute cold stress. *Endocrinology* 149: 2159–67

Slominski A, Malarkey WB, Wortsman J, Asa SL, Carlson A (2001) Human skin expresses growth hormone but not the prolactin gene. *J Lab Clin Med* 136:476–81

Sowden HM, Karoo RO, Tobin DJ (2007) Transforming growth factor-beta receptor II is preferentially expressed in the companion layer of the human anagen hair follicle. *Br J Dermatol* 157:161–4

Tekin O, Avci Z, Isik B *et al.* (2004) Hirsutism: common clinical problem or index of serious disease? *Med Gen Med* 6:56

Thomas D, Brinkow B, Randall V (1993) Prolactin and triiodothyronine (T3) stimulate hair growth in cultured follicles of red deer summer coat. *J Endocrinol* 130:50

Velkeniers B, Dogusan Z, Naessens F, Hooghe R, Hooghe-Peters EL (1998) Prolactin, growth hormone and the immune system in humans. *Cell Mol Life Sci* 54:1102–8

Walsh JP, Bhagat CI, Pullan PT, Rampono JG (1994) Drug-induced hyperprolactinaemia. *Med J Aust* 161:443–4