Utilizing the hair follicle to dissect the regulation and autocrine/paracrine activities of prolactin in humans

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TO THE EDITOR: Ferraris et al. (4) have recently reported an increase in anterior pituitary cell proliferation in Δ1-9-G129R-hPRL (competitive prolactin receptor antagonist) -expressing transgenic mice compared to wild-type controls. In addition, they reported increased proliferation/decreased apoptosis in primary rat anterior pituitary cell cultures and somatolactotroph GH3 cells treated with Δ1-9-G129R-hPRL, concluding that prolactin (PRL) is an “autocrine/paracrine antiproliferative/proapoptotic factor in the anterior pituitary”.

As Ferraris et al. acknowledge, their findings contrast with the well-documented proliferoprotective effects of PRL that have previously been reported in several tissue sites and cell populations, including keratinocytes (9), thymic epithelial cells (3), lymphoid cells (19), and prostate (18) and mammary gland epithelial cells (10). However, most of the cited studies varied considerably in the methodology they employed, including PRL dose (physiological vs. pharmacological), species (1, 6), tissue site (5, 18), and sex (14) investigated. Moreover, the lack of a human pituitary cell line (1), the absence of functional dopamine-2 receptors on GH3 cells (1), and the inherent difficulties in extrapolating results from rodent studies to humans (1) complicate attempts to understand the autocrine/paracrine actions of PRL. Therefore, the question of whether PRL promotes growth and suppresses apoptosis in well-defined primary human cell populations in situ remains essentially unresolved.

However, the discovery that PRL is produced in several extrapituitary sites in humans has provided new opportunities for studying the local autocrine/paracrine actions of PRL. Indeed, the concept that PRL receptor (PRLR) stimulation exerts antiproliferative and proapoptotic effects (4) in humans is supported by evidence that PRL inhibits the growth of organ-cultured male human scalp hair follicles (HFs) and exerts proapoptotic/antiproliferative effects on male human hair matrix keratinocytes in situ (5).

Traditionally, it is accepted that the regulation of pituitary and extrapituitary PRL production differs. This was based on the existence of the human superdistal extrapituitary PRL promoter (8), 5.8 kb upstream of the pituitary promoter, and the lack of dopaminergic inhibition of PRL production in extrapituitary sites (11). Yet, recent evidence challenges this assumption, since human adipocytes express functional dopamine receptors, whose stimulation inhibits PRL gene expression and PRL release by adipocytes (2). Moreover, both estrogen and thyrotropin-releasing hormone stimulate PRL mRNA and protein expression in situ in organ-cultured human scalp skin and/or HFs (15, 16), mimicking their regulation of pituitary PRL expression. Therefore, the regulation of PRL synthesis and release in the pituitary and in extrapituitary sites may share at least some regulatory principles and mechanisms, just as Ferraris et al. demonstrate functional similarities in the proliferation/apoptosis response of pituitary cells (4) vs. HF keratinocytes in situ (5).

Accepting that the regulation of extrapituitary PRL expression can be established only in appropriate human models (1), we would like to draw attention to the fact that the serum-free organ culture of readily available, microdissected human HFs (12) provides an informative model in which to delineate both the regulation of PRL expression and the cytokine-like, growth-modulatory actions of PRL in the human system and in situ. Not only are human scalp HFs now appreciated to be both a target and a source of extrapituitary PRL expression (5, 15), but PRL is also a potent neuroendocrine regulator of 1) human HF growth (5), potentially in a sex- and site-specific manner (14); 2) selected keratin expression (17); and 3) adult human epithelial progenitor cells (17). Indeed, several of these effects can be reversed by the Δ1-9-G129R-hPRL (14, 17). Therefore, this model could also help address Ferraris et al.’s concern that endogenous PRL may “hamper” the determination of the actions of exogenously added PRL (4). In addition, since gene silencing is possible in intact, cultured human HFs (21), PRL and PRLR knockdown may be employed to further dissect the contribution of a endogenous PRL.

One remaining uncertainty in terms of the human HF is the presence or absence of dopamine receptors and the effect of dopamine on follicular PRL synthesis and release. Dopamine receptors 2 (D2R) and 4 have been identified in murine skin (7), where they play an important role in epidermal barrier homeostasis, whereas D2R antagonists improve cutaneous wound healing by inducing angiogenesis (20). This provides sufficient encouragement to study dopamine receptor expression in human skin and HFs and to dissect whether they regulate human intracutaneous/intrafollicular PRL synthesis and/or secretion.

In summary, female human HFs share at least some of the controls of pituitary PRL and PRLR expression (13, 15), and the antiproliferative/proapoptotic effect of PRL in pituitary cells is recapitulated in male HFs (4, 5). Therefore, human HF organ culture may, if interpreted with caution, serve as an instructive, physiologically and clinically relevant surrogate model in which the regulation and autocrine/paracrine activi-
ties of PRL in the human pituitary gland can be dissected in situ.

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AUTHOR CONTRIBUTIONS

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