INTRODUCTION

Increasingly, neuroendocrine research focuses on its potential for an impact of novel findings on highly-prevalent human health problems, in particular those where the underlying physiology and its dysfunction is poorly understood. Research on the pituitary, the master gland relaying hormonal information between the brain and many peripheral tissues, cannot escape this trend, as exemplified by the growing hope of regenerative medicine with the recent discovery of adult stem cells in the pituitary parenchyma. One exciting aspect of stem cell therapy is its potential to correct a number of pituitary disorders with aetiologies that are poorly understood. This focus on stem cells and their potential may explain how a subpopulation of pituitary cells, devoid of secretory granules, has changed from being described as folliculostellate (FS) cells (coined by Evelyne Vila-Porcile in 1972) to adult Sox2+ve stem cells. Recent studies have highlighted an important aspect of these stem cells, in that they are the

Abstract

Anterior pituitary folliculostellate (FS) cells, first described almost 50 years ago, have a wide range of functions with respect to supporting and coordinating endocrine cell function, in particular through paracrine and gap junction-mediated signalling. Our previous studies identified the morphological organisation of FS cells, which mediates coordinated calcium activity throughout the homotypic FS network and allows signalling across the whole pituitary gland. It is also clear that FS cells can modify endocrine output and feedback on pituitary axes over a range of timescales. Recently, several studies have defined FS cells as a source of anterior pituitary endocrine cell renewal, which has resulted in a renaming of FS cells as “Sox2+ve stem cells”. Here, we highlight the broader potential of the FS cell population in fine-tuning and coordinating pituitary axes function. In addition, we identify a need for: the definition of the possible subtypes of FS cell and their relationship with the stem cell population; the potential role of FS cells in pulsatile hormone secretion and coordination of heterotypic cell networks; and the roles that FS cells may play in both early-life programming of pituitary axes and in memory, or anticipation, of demand. Further studies of FS cells may demonstrate the fundamental importance of this cell type and its potential as a therapeutic target to correct pituitary gland dysfunction, one of which is stem cell therapy. Clearly, a thorough understanding of all of these interactions and relationships of FS and endocrine cells is required whatever therapeutic use is suggested by their various roles.

KEYWORDS

anterior pituitary, cell networks, folliculostellate cells, pulse generation
source of secreted factors regulating not only their own function, but also those of other pituitary cells. This aspect of the biology of pituitary stem cells resonates with roles described in previous studies of FS cells and has prompted us to reassess the biology of this enigmatic cell type and its importance for pituitary gland physiology. Because the stem cell potential of FS cells has been extensively reviewed recently, we focus here on other important aspects of FS cell biology in the regulation of anterior pituitary gland function.

2 | FS CELLS AND THEIR CELL IDENTITY

FS cells were first described in the pioneering electron microscopy studies of the pituitary gland by Farquhar and Rinehart as small agranular cells with long, slender processes (Figure 1A). Although early work identified two types of cell, these were unified as a single cell type by Vila-Porcile, who also described their organisation into a network in the rat. Subsequently, they have been described in the anterior pituitaries in a range of mammalian and non-mammalian species, as well as in anterior pituitaries with morphologically distinct organisation, such as teleosts. Classically, they have been studied in animals such as the rat, where their expression of S100, a family of Ca²⁺-binding proteins transducing Ca²⁺ signals, enables identification based on gene expression as well as morphology. This expression of S100 has subsequently been exploited in the generation of green fluorescent protein (GFP) transgenic rats, allowing the isolation and ready identification of these cells. FS cells can also be identified in ex vivo culture by their uptake of an alanine-lysine dipeptide conjugated to aminomethylcoumarin acetate (AMCA) fluorophore, which is dependent on FS cell expression of a protein peptide symporter. Intriguingly, this uptake of dipeptide-conjugated AMCA was shown to be a feature of posterior pituitary pituicyctes, which also express some of the key proteins related to FS cell function, suggesting that the distinct cell types of the two pituitary lobes may share common features and roles. More recently, specific pituitary expression of aldolase C in FS cells has been described in mice, which may allow increased genetic manipulation in this model species.

Dispersed FS cells in culture readily self-organise into aggregates of cells that resemble those of the intact pituitary and, in mixed cultures with other pituitary cell types, form clusters with hormone producing cells. A role for the chemoattractant molecule CXCL12 and its receptor CXCR4, both expressed by FS cells, has been described in this in vitro recapitulation of cell organisation. Homotypic FS cell interaction are then likely maintained by expression of adherence proteins such as E-cadherin and a differential expression of other adherence molecules likely mediates specific FS cell–heterotypic cell morphological relationships. This suggests a role for FS cells in the organisation of the homotypic networks of all pituitary hormonal cell types studied to date, with important functional consequences. An important interaction of FS cells with the extracellular matrix (ECM) has also been described, with matrix metalloprotease 9 mediating cell organisation, integrin ß1 signalling regulating FS cell proliferation and FS cell production of tissue inhibitors of metalloproteinases in turn regulating the ECM.

3 | FS CELL NETWORK COMMUNICATION AND REGULATION OF ANTERIOR PITUITARY ENDOCRINE OUTPUT

3.1 | FS cell network communication

The extensive FS organisation across the pituitary gland recognised by Vila-Porcile, as well as the relationship with other

![Figure 1](image-url)
pituitary hormonal cell types, led to a recognition that FS cells may mediate pituitary scale regulation and the coordination of endocrine output. We have investigated this using the uptake of dipeptide-conjugated AMCA dye in ex vivo pituitary slices, allowing us to identify FS cells and, with the use of high-resolution 3D microscopy that allows large-scale reconstruction of cell organisation, we have shown that a network of connected FS cells wires the whole pituitary gland26 (Figure 1B). Furthermore, because the AMCA dye can be imaged in live cells, we were able to record calcium activity in FS cells, revealing spontaneous changes in cytosolic calcium, with a large proportion of cells firing monophasic calcium spikes. Communication across the gland is apparent as a wave of calcium activity that travels through the FS cell network from one wing of the pituitary to the other. Moreover, more localised cell–cell communication was evident within subsets of FS cells, suggesting specialised communication modes with endocrine cell neighbours.27 This calcium wave propagation is mediated by gap junctions between FS cells, which may also allow other small molecules (such as cAMP, inositol trisphosphate) to act as signals that can be transferred through the network.28 The role of this communication for FS cell function is currently unclear; however, pituitary cell organisation has been shown to have coordinating roles in a range of cell activities, including secretion and the regulation of gene expression.28

3.2 Communication with other pituitary cell types

An attractive hypothesis for a role of the FS cell network is in coordinating anterior pituitary hormone cell function, which is suggested by the morphological interdigitation of FS cells with network motifs of endocrine cells (Figure 1C). The importance of FS cells for normal pituitary function is exemplified by a recent study showing that FS cell dysregulation through the loss of Patched expression results in multiple alterations of anterior pituitary endocrine axes in adulthood.29 Gap junction-mediated communication has been principally described as occurring within the homotypic FS cell network;29; however, this does not preclude some communication by this mechanism with other cell types. Indeed, functional gap junctions between FS and pituitary hormonal cells have been reported.31,32 Because gap junctions allow endocrine cell network propagation of calcium signals (similar to that shown for FS cells), only a low level of FS cell–endocrine cell communication may be required for a propagation through endocrine homotypic networks, resulting in the coordination of FS cell regulation on a much larger scale.

There has been much more extensive characterisation of paracrine communication between FS and endocrine cells. FS cells have been shown to produce a range of growth factors and cytokines, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, annexin 1 (ANXA1) and interleukin-6, as well as nitric oxide (NO), all of which have clear roles in the regulation of specific endocrine pituitary cell types. For example, in the embryo, NO has been shown to increase both growth hormone gene expression and the number of somatotrophs,33 whereas FS cell (intriguingly those near blood vessels) NO synthase expression has been shown to be increased by dopamine, potentially mediating some of the inhibitory actions of this small transmitter on prolactin release.34 To this list, we can now add the Wnt ligands because these have been shown to be secreted from Sox2-positive stem cells.2 The alteration of many of these ligands in differing physiological states (see below) suggests an important role in the communication of FS with endocrine cells. It also raises the question of whether FS cells are either a single unique population (as proposed by Vila-Porcile3) or a modular ensemble of FS cell subsets that adapt their range of paracrine communication in response to demands.

4 ROLE AS A RELAYER OF PERIPHERAL FEEDBACK SIGNALS?

Perhaps the most intriguing potential roles for FS cells, in terms of potential coordinators of endocrine function as well as stem cells, is their response to pituitary target organ feedback and mediators. This would place them as key modifiers of pituitary function that fine-tune and adapt the various endocrine systems to ensure an optimal response to physiology, rather than as supportive cells as has been suggested previously.35 For example, in the prolactin axis, FS cells have been shown to mediate lactotroph proliferation in response to estradiol,36 an effect that is blocked by progesterone37; to have distinct morphological relationships with lactotrophs in seasonal breeding animals, with long FS cell processes wrapping around lactotrophs in the breeding season38; and to be increased in number in lactotroph-tumour susceptible Fischer 344 rats compared to non-susceptible strains.36 These effects are most likely primarily through paracrine interactions, especially because interleukin-6 has a regulatory role on lactotrophs.39 However, the expression of enzymes and transporters in FS cells will alter the exposure of surrounding endocrine cells to feedback, such as type II iodothyronine deiodinase-2 (Dio2) and monocarboxylate transporter 8 (MCT8), modifying triiodothyronine exposure40,41 and 11β-hydroxysteroid dehydrogenase type 1, activating cortisone and increasing glucocorticoid feedback in the pituitary.42

Of the paracrine FS cell actions, perhaps the best characterised example is the modification of corticotroph function in response to glucocorticoid feedback through ANXA1. In the pituitary gland, ANXA1 is primarily produced by FS cells and is concentrated at points of FS–endocrine cell interaction.43,44 Glucocorticoids increase FS cell ANXA1 expression resulting in translocation of the protein to the external surface of the plasma membrane.45 The externalised ANXA then binds to high affinity binding sites on corticotrophs,46 resulting in a reduction of adrenocorticotropic hormone (ACTH) secretion in response to corticotrophin-releasing hormone.47,48 The regulation of ANXA1 activity may suggest one role for spatially localised calcium waves that we have described propagating through subsets of the FS cell network;26,27: the structure of ANXA1 has been shown to be calcium sensitive, with increased biological activity in
the presence of Ca\textsuperscript{2+}.\textsuperscript{49} The importance of ANXA1 in corticotroph regulation is also highlighted by a four-fold increase in corticotroph cell number in male ANXA1-knockout mice compared to wild-type controls, although, interestingly, this effect is much less pronounced or even absent in females.\textsuperscript{50} Finally, FS cells may be programmed by early-life exposure to glucocorticoids because ANXA-1 expression is reduced in adult mice following prenatal dexamethasone exposure.\textsuperscript{51}

5 | PERSPECTIVES

If we combine the biology described above with their more recent description as pituitary stem cells, it is clear that FS cells have a central role in anterior pituitary biology and that these different facets of their activity should not be considered in isolation. As a non-hormonal cell type that allows communication across the entire gland and has modifying functions on all endocrine cell types, FS cells are ideally placed to coordinate the various pituitary axes. In the remainder of this review, we highlight two aspects of FS cell biology that we consider important in elucidating their role in regulating pituitary hormone output: heterogeneity and pulse generation. We then speculate on the fundamental role that FS cells may have in fine-tuning physiology ranging from reproduction to metabolism and stress. Each of these may be defined through dual recording of specific molecules and pathways and determining in vivo consequences. This will require cell-type specific markers and targets, although the increasing availability of transcriptome data that includes FS cells suggests that these may be identified in the near future.

5.1 | Heterogeneity

FS cells were originally identified as two distinct cell types, each agranular and characterised by long cytoplasmic projections, but with distinct morphological arrangements based on whether they surround cavities filled with colloidal milieu.\textsuperscript{9,10} The morphological heterogeneity is further emphasised by differential protein expression and this has led many to question whether FS cells are a single cell type, both in developmental origin and in function.\textsuperscript{4} An excellent example of this and its importance is the pars tuberalis VEGF-secreting FS cell population\textsuperscript{52}; because VEGF is a target for treatment of cancer and other diseases,\textsuperscript{53} an understanding of the relationship of this cell population with other FS cells is required to recognise the potential side-effects of VEGF therapy on pituitary function. Recent reports analysing single cells RNA sequencing (scRNAseq) of rodent anterior pituitary cells utilising unbiased clustering methods have variably described FS and Sox2-ve cells as single or multiple cell types.\textsuperscript{54-57} It is important to note that differences in pituitary dissection, with the inclusion of the intermediate and posterior pituitary that contains cell types such as pituicytes and epithelial-like cells expressing markers associated with FS cells,\textsuperscript{58} may affect the identification of potential subpopulations. Indeed, this recent description of the expression in pituicytes and epithelial-like cells of markers used in previous analyses of FS cell function may require the reinterpretation of some older studies, in particular those using dispersed pituitary cells. However, there is a clear potential for FS cell subpopulations and this requires further analysis.

The heterogeneity of FS cells calls into question their common identity with stem cells: are they identical cell populations or is one a subtype of the other? Whether differential protein expression represents a distinct cell trajectory or simply transient differences in gene expression dependent on cell location and physiological status is currently unclear.\textsuperscript{59} If there is substantial overlap between FS and stem cell populations, then it is difficult to understand how they can have so many functions at the same time as maintaining a specialised stem cell role, especially because the stem cell population is depleted with age or following injury.\textsuperscript{59} In addition, if we are to understand the dynamic functional relationship between FS and other pituitary cell types, then elucidating the possible plasticity in FS cell roles becomes essential. For example, modelling and understanding thyrotroph function and how this relates to altered thyroid status requires a clear understanding of the role of the subset of FS cells found to express MCT8 and Dio2 in humans.\textsuperscript{40} The terminal differentiation of FS cells into distinct functional types also has important implications for their potential role in programming and memory (see below). Functional heterogeneity, whether permanent or transient, is increasingly becoming recognised in various pituitary cell types\textsuperscript{50}; the importance in FS cell function may become apparent with further analysis of scRNAseq profiling of the transcriptome of the anterior pituitary, which may define subtypes of cells and possible specific ligand-receptor co-expression between certain FS cells and specific endocrine cells (or subsets).

5.2 | Pulse generation

Perfusion studies of isolated pituitaries have shown that hormone output is spontaneously pulsatile in the absence of hypothalamic input.\textsuperscript{51,62} Our descriptions of pituitary hormone networks\textsuperscript{28} have provided, in part, a mechanism where these spontaneous pulses could occur. However, it was the FS cell network that pioneered the description of the endocrine networks: the finding of spontaneous pulsatile activity in these cells, and in particular the identification of a proportion that apparently acts as a pacemaker,\textsuperscript{26} suggests that they may have a role. Indeed, the paracrine and gap junction-mediated communication between FS and endocrine cells would provide a mechanism allowing the coordination of pulsatile release over different timescales. The interaction between endocrine and FS cells is, however, bidirectional, especially if peripheral feedback is considered, and the identification of which cell type is acting as a pulse generator is therefore complex. An example of this is FS cell modulation of gonadotrophin-releasing hormone (GnRH) priming of luteinising hormone secretion from gonadotrophs\textsuperscript{63} which could not only be driven by long-term paracrine or gap junction-mediated signalling from FS cells, but also be a result of altered FS cell function in response to GnRH stimulation of
FS cell role in pituitary plasticity, memory and fine-tuning function

Functional plasticity is an important feature of pituitary gland biology because the appropriate output of each pituitary hormone does not simply maintain homeostasis but is required to change dramatically in response to, as well as in anticipation of, physiological status. Modification of the number, size and morphological relationship of FS and endocrine cells in different physiological states, as well as with age, has been described, suggesting an altered function, although it is possible that FS cells play a more fundamental role. Obviously, stem cell function allows FS cells to alter the number of endocrine cells and this is likely an important feature in the expansion of specific cell types in response to challenge, such as the expansion of the lactotroph population in pregnancy and lactation in humans or the thyrotroph population in response to hypothyroidism. An altered relationship of FS and endocrine cells, as occurs in seasonal breeding animals, will clearly change paracrine signalling relationships, although ECM-remodelling and maintenance roles for FS cells may also have important implications for endocrine cell network organisation, signalling and hormone output. Altered gap junction-mediated signalling does not require a morphological rearrangement or change in cell number and we have observed changes in gap junction distribution in the lactotrophs of lactating dams. Thus, each of the aspects of FS cell biology described here are likely to impact on the plasticity of gland function and further studies are likely to be inspired by scRNAseq experiments that characterise the altered gene expression of all cell types in response to physiological and pathological challenge.

The memory of previous physiological status is another key aspect of anterior pituitary gland biology. Excellent examples of this are the programming of the hypothalamic pituitary adrenal axis by prenatal and perinatal stress and memory in the prolactin axis of lactational demand. Previous studies of the response of FS cells to early-life exposure to dexamethasone, showing alterations that persist until adulthood, suggest that fetal and early-life programming of pituitary axes may be mediated by changes in FS cell function. This may also be possible in adult programming, or memory of demand, and the extent by which changes in FS-endocrine cell relationships, including gap junction remodelling, may be permanently changed is unclear and warrants further study.

Finally, we would suggest that, in addition to roles in maintenance of homeostasis, plasticity and memory, FS cells are uniquely placed to fine-tune functional output and coordinate the function of pituitary axes. Key to this may be the FS cell response and modification of target organ feedback through altered paracrine and gap junction-mediated signalling, as well as modification of feedback signals such as glucocorticoids or thyroid hormone. In addition, the role of stem cells allows adjustment of the proportion of the different pituitary cell types, which may allow prioritisation of various axes with age; for example, increased growth hormone output at puberty which then declines with age. Two additional features of FS cell biology may be permissive to this fine-tuning: the lack of expression of several receptors for hypothalamic secretagogues and the ability to signal throughout the pituitary independent of blood flow. Both of these may allow temporal coordination that otherwise would occur as a dorsal–ventral wave, as well as a degree of regulation that is independent of direct hypothalamic input. Again, pars tuberalis FS cell secretion of VEGF, mediating seasonal alterations of angiogenesis and lactotroph function, may be another example of this, in addition to highlighting the diversity of FS cells in the pituitary.

CONCLUSIONS

The increasing interest in pituitary stem cells has highlighted the important roles that FS cells play in ensuring an appropriate output of hormone for regulation of a range of physiology. An understanding of each of these roles and how they are related is not only important for our fundamental understanding of physiology and disease, but also essential if these cells are to be targeted for therapeutic correction of pituitary deficiency or tumours. A key aspect of this is the question of whether FS and stem cells are a single population with a myriad of functions; if this is the case, then there may be a far-reaching physiological impact of transplanting a large number of these cells into a pituitary for stem cell therapy.

Despite the lack of fundamental markers, as well as possible subtype and species differences, which has hindered studies of FS cells, there is an impressive body of evidence concerning their importance. However, this also highlights the need for further studies of what may turn out to be the most important aspect of all for pituitary cell types in terms of the coordinated regulation of fundamental processes. As interests in various cellular functions change with time, it is perhaps inevitable that cell types will change names, although it is nevertheless important to consider all of the functions of this cell type, regardless of whether they are called FS or Sox2+ve stem cells.
ACKNOWLEDGEMENTS
This work was supported by ANR-18-CE14-0017 grant (PM) and the Medical Research Council project grant Ref MR/V012290/1 (PLT).

CONFLICT OF INTERESTS
The author declares that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS
Paul Le Tissier: Conceptualisation; Writing – original draft. Patrice Mollard: Conceptualisation; Writing – original draft.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/jne.13053.

DATA AVAILABILITY STATEMENT
Not required.

ORCID
Paul R. Le Tissier https://orcid.org/0000-0002-7220-5705

REFERENCES
1. Vila-Porcile E. The network of the folliculo-stellate cells and the follicles of the adenohypophysis in the rat (pars distalis). Z Zellforsch Mikrosk Anat. 1972;129(3):328-369.
2. Russell JP, Lim X, Santambrogio A, et al. Pituitary stem cells produce paracrine WNT signals to control the expansion of their descendant progenitor cells. Elife. 2021;10:e59142.
3. Venneken A, Laporte E, Hermans F, et al. Interleukin-6 is an activator of pituitary stem cells upon local damage, a competence quenched in the aging gland. Proc Natl Acad Sci U S A. 2021;118(25):e2100052118.
4. Allaerts W, Vankelecom H. History and perspectives of pituitary folliculo-stellate cell research. Eur J Endocrinol. 2005;153(1):1-12.
5. Kato Y, Yoshida S, Kato T. New insights into the role and origin of pituitary S100beta-positive cells. Cell Tissue Res. 2021 Sep 22. doi: 10.1007/s00447-021-03523-7. Online ahead of print.
6. Even-Zohar N, Metin Armagan D, Melmed S. Pituitary stem cells. Vitam Horm. 2021;116:1-19.
7. Laporte E, Venneken A, Vankelecom H. Pituitary remodeling throughout life: are resident stem cells involved? Front Endocrinol (Lausanne). 2020;11:604519.
8. Rinehart JF, Farquhar MG. Electron microscopic studies of the anterior pituitary gland. J Histochem Cytochem. 1953;1(2):93-113.
9. Rinehart JF, Farquhar MG. The fine vascular organization of the anterior pituitary gland; an electron microscopic study with histochemical correlations. Anat Rec. 1955;121(2):207-239.
10. Salazar H. The pars distalis of the female rabbit hypothalamus: an electron microscopic study. Anat Rec. 1963;147:469-497.
11. Trudeau VL, Somoza GM. Multimodal hypothalamo-hypophysial communication in the vertebrates. Gen Comp Endocrinol. 2020;293:113475.
12. Golan M, Hollander-Cohen L, Levavi-Sivan B. Stellate cell networks in the teleost pituitary. Sci Rep. 2016;6:24426.
13. Mandinova A, Atar D, Schafer BW, Spiess M, Aebi U, Heizmann CW. Distinct subcellular localization of calcium binding S100 proteins in human smooth muscle cells and their relocation in response to rises in intracellular calcium. J Cell Sci. 1998;111(Pt 14):2043-2054.
14. Nakajima T, Yamaguchi H, Takahashi K. S100 protein in folliculostellate cells of the rat pituitary anterior lobe. Brain Res. 1980;191(2):523-531.
15. Itakura E, Odaika Y, Yokoyama K, Osuna M, Hara T, Inoue K. Generation of transgenic rats expressing green fluorescent protein in S-100beta-producing pituitary folliculo-stellate cells and brain astrocytes. Endocrinology. 2007;148(4):1518-1523.
16. Otto C, tom Dieck S, Bauer K. Dipeptide uptake by adenohypophysial folliculostellate cells. Am J Physiol. 1996;271(1 Pt 1):C210-217.
17. Anbalagan S, Gordon L, Blechman J, et al. Pituicyte cues regulate the development of permeable neuro-vascular interfaces. Dev Cell. 2018;47(6):711-726 e715.
18. Fujisawa K, Tsukada T, Horiguchi K, et al. Aldolase C is a novel molecular marker for folliculo-stellate cells in rodent pituitary. Cell Tissue Res. 2020;381(2):273-284.
19. Horiguchi K, Kikuchi M, Kusumoto K, et al. Living-cell imaging of transgenic rat anterior pituitary cells in primary culture reveals novel characteristics of folliculo-stellate cells. J Endocrinol. 2010;204(2):115-123.
20. Horiguchi K, Ilmiawati C, Fujiwara K, Tsukada T, Kikuchi M, Yashiro T. Expression of chemokine CXCL12 and its receptor CXCR4 in folliculostellate (FS) cells of the rat anterior pituitary gland: the CXCL12/CXCR4 axis induces interconnection of FS cells. Endocrinology. 2012;153(4):1717-1724.
21. Chauvet N, El-Yandouzi T, Mathieu MN, et al. Characterization of adherens junction protein expression and localization in pituitary cell networks. J Endocrinol. 2009;202(3):375-387.
22. Mollard P, Hodson DJ, Lafont C, Rizzotti K, Drouin J. A tridimensional view of pituitary development and function. Trends Endocrinol Metab. 2012;23(6):261-269.
23. Ilmiawati C, Horiguchi K, Fujiwara K, Yashiro T. Matrix metalloproteinase-9 expression in folliculostellate cells of rat anterior pituitary gland. J Endocrinol. 2012;212(3):363-370.
24. Horiguchi K, Fujiwara K, Ilmiawati C, et al. Caveolin 3-mediated integrin beta1 signaling is required for the proliferation of folliculostellate cells in rat anterior pituitary gland under the influence of extracellular matrix. J Endocrinol. 2011;210(1):29-36.
25. Azuma M, Tofrizal A, Maliza R, et al. Maintenance of the extracellular matrix in rat anterior pituitary gland: identification of cells expressing tissue inhibitors of metalloproteinases. Acta Histochem Cyttochem. 2015;48(6):185-192.
26. Faquier T, Guerineau NC, McKinney RA, Bauer K, Mollard P. Folliculostellate cell network: a route for long-distance communication in the anterior pituitary. Proc Natl Acad Sci U S A. 2001;98(15):8891-8896.
27. Faquier T, Lacampagne A, Travo P, Bauer K, Mollard P. Hidden face of the anterior pituitary. Trends Endocrinol Metab. 2002;13(7):304-309.
28. Le Tissier P, Fiordelisio Coll T, Mollard P. The Processes of Anterior Pituitary Hormone Pulse Generation. Endocrinology. 2018;159(10):3524-3535.
29. Ren YA, Monkonen T, Lewis MT, et al. S100a4-Cre-mediated deletion of Patched1 causes hypogonadotropic hypogonadism: role of pituitary hematopoietic cells in endocrine regulation. JCI. Insight. 2019;5.
30. Soji T, Herbert DC. Intercellular communication between rat anterior pituitary cells. Anat Rec. 1989;224(4):523-533.
31. Morand I, Fonlupt P, Guerrier A, et al. Cell-to-cell communication in the anterior pituitary: evidence for gap junction-mediated exchanges between endocrine cells and folliculostellate cells. Endocrinology. 1996;137(8):3356-3367.
32. Hodson DJ, Schaeffer M, Romano N, et al. Existence of long-lasting experience-dependent plasticity in endocrine cell networks. Nat Commun. 2012;3:605.
33. Chen HP, Zhang L, Xu BH, et al. Nitric oxide stimulates embryonic somatotroph differentiation and growth hormone mRNA and protein expression through a cyclic guanosine monophosphate-independent mechanism. Tissue Cell. 2009;41(2):133-140.
34. Carretero J, Weruaga E, Hernandez E, et al. Dopaminergic modulation of nNOS expression in the pituitary gland of male rat. Anat Embryol (Berl). 2003;207(4–5):381-388.

35. Inoue K, Mogi C, Ogawa S, Tomida M, Miyai S. Are folliculo-stellate cells in the anterior pituitary gland supportive cells or organ-specific stem cells? Arch Physiol Biochem. 2002;110(1-2):50-53.

36. Oomizu S, Chaturvedi K, Sarkar DK. Folliculostellate cells determine the susceptibility of lactotropes to estradiol’s mitogenic action. Endocrinology. 2004:145(3):1473-1480.

37. Heinzlmann A, Kovess K. The characteristic change in the distribution of S-100 immunoreactive folliculostellate cells in rat anterior pituitary upon long-term estrogen treatment is prevented by concomitant progesterone treatment. Endocrine. 2008;33(3):342-348.

38. Christian HC, Imitziasdis L, Tortoneze D. Ultrastructural changes in lactotrophs and folliculo-stellate cells in the ovine pituitary during the annual reproductive cycle. J Neuroendocrinol. 2015;27(4):277-284.

39. Yamaguchi M, Matsuzaki N, Hirota K, Miyake A, Tanizawa O. Interleukin 6 possibly induced by interleukin 1 beta in the pituitary gland stimulates the release of gonadotropins and prolactin. Acta Endocrinol (Copen). 1990;122(2):201-205.

40. Alkemade A, Friesema EC, Kuiper GG, et al. Novel neuroanatomical pathways for thyroid hormone action in the human anterior pituitary. Eur J Endocrinol. 2006;154(3):491-500.

41. Fliers E, Unmehopa UA, Alkemade A. Functional neuroanatomy of thyroid hormone feedback in the human hypothalamus and pituitary gland. Mol Cell Endocrinol. 2006;251(1-2):1-8.

42. Korbonits M, Bujalska I, Shimojo M, et al. Expression of 11 beta-hydroxysteroid dehydrogenase isoenzymes in the human pituitary: induction of the type 2 enzyme in corticotropicinomas and other pituitary tumors. J Clin Endocrinol Metab. 2001;86(6):2728-2733.

43. Traverso V, Christian HC, Morris JF, Buckingham JC. Lipocortin 1 (annexin 1): a candidate paracrine agent localized in pituitary folliculo-stellate cells. Endocrinology. 1999;140(9):4311-4319.

44. Chapman L, Nishimura A, Buckingham JC, Morris JF, Christian HC. Externalization of annexin I from a folliculo-stellate-like cell line. Endocrinology. 2002;143(11):4330-4338.

45. Buckingham JC. Fifteenth Gaddum memorial lecture December 1994 Stress and the neuroendocrine-immune axis: the pivotal role of glucocorticoids and lipocortin 1. Br J Pharmacol. 1996;118(1):1-19.

46. Christian HC, Taylor AD, Flower RJ, Morris JF, Buckingham JC. Characterization and localization of lipocortin 1-binding sites on rat anterior pituitary cells by fluorescence-activated cell analysis/sorting and electron microscopy. Endocrinology. 1997;138(12):5341-5351.

47. Taylor AD, Cowell AM, Flower J, Buckingham JC. Lipocortin 1 mediates an early inhibitory action of glucocorticoids on the secretion of ACTH by the rat anterior pituitary gland in vitro. Neuroendocrinology. 1993;58(4):430-439.

48. Pompeo A, Luini A, Hirata F, Baldassarre M, Buccione R. Neutrophil extracted lipocortin inhibits corticotropin secretion in the AtT-20 D16:16 clonal mouse pituitary cell line. Lipocortin inhibition of ACTH release in vitro. Regul Pept. 1997;72(2-3):169-177.

49. Rosengarth A, Luecke H. A calcium-driven conformational switch of the N-terminal and core domains of annexin A1. J Mol Biol. 2003;326(5):1317-1325.

50. Morris JF, Omer S, Davies E, et al. Lack of annexin 1 results in an increase in corticotroph number in male but not female mice. J Neuroendocrinol. 2006;18(11):835-846.

51. Theogaraj E, John CD, Christian HC, Morris JF, Smith SF, Buckingham JC. Perinatal glucocorticoid treatment produces molecular, functional, and morphological changes in the anterior pituitary gland of the adult male rat. Endocrinology. 2005;146(11):4804-4813.

52. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science. 1989;246(4935):1306-1309.

53. Ferrara N, Adams AP. Ten years of anti-vascular endothelial growth factor therapy. Nat Rev Drug Discov. 2016;15(6):385-403.

54. Fletcher PA, Smiljanic K, Maso Previde R, et al. Cell type- and sex-dependent transcriptome profiles of rat anterior pituitary cells. Front Endocrinol (Lausanne). 2019;10:623.

55. Ho Y, Hu P, Peel MT, et al. Single-cell transcriptomic analysis of adult mouse pituitary reveals sexual dimorphism and physiologic demand-induced cellular plasticity. Protein Cell. 2020;11(8):565-583.

56. Mayran A, Sochodosky K, Khetchochumian K, et al. Pioneer and non-pioneer factor cooperation drives lineage specific chromatin opening. Nat Commun. 2019;10(1):3807.

57. Cheung LYM, George AS, McGee SR, et al. Single-cell RNA sequencing reveals novel markers of male pituitary stem cells and hormone-producing cell types. Endocrinology. 2018;159(12):3910-3924.

58. Chen Q, Leshkowitz D, Blechman J, Levkowitz G. Single-cell molecular and cellular architecture of the mouse neurohypophysis. eNeuro. 2020;7(1):ENEURO.0345-19.201.

59. Willems C, Fu Q, Roose H, et al. Regeneration in the pituitary after luteinizing hormone gonadotropin releasing hormone in rat pituitary cell aggregates. Eur J Endocrinol. 2017;158(6):1849-1858.

60. Stewart JK, Clifton DK, Koerker DJ, Rogol AD, Jaffe T, Goodner CJ. Pulsatile release of growth hormone and prolactin from the primate pituitary in vitro. Endocrinology. 1985;116(1):1-5.

61. Gambacciani M, Liu JH, Swartz WH, Tueros VS, Rasmussen DD, Yen SS. Intrinsic pulsatility of ACTH release from the human pituitary in vivo. Clin Endocrinol (Oxf). 1987;26(5):557-563.

62. Allaerts W, Tijssen AM, Jeucken PH, Drexhage HA, de Koning J. Influence of folliculo-stellate cells on biphasic luteinizing hormone secretion response to gonadotropin-releasing hormone in rat pituitary cell aggregates. Eur J Endocrinol. 1994;130(5):530-539.

63. Lyles D, Tien JH, McCobb DP, Zeeman ML. Pituitary network connectivity as a mechanism for the luteinising hormone surge. J Neuroendocrinol. 2010;22(12):1267-1278.

64. Walker JJ, Spiga F, Waite E, et al. The origin of glucocorticoid hormone oscillations. PLoS Biol. 2012;10(6):e1001341.

65. Samuels MH, Veldhuis J, Ridgway EC. Copulsatile release of thyrotropin and prolactin in normal and hypothyroid subjects. Thyroid. 1995;5(5):369-372.

66. Walker JJ, Terry JR, Lightman SL. Origin of ultradian pulsatility in the hypothalamic-pituitary-adrenal axis. Proc Biol Sci. 2010;277(1688):1627-1633.

67. Prummel MF, Brokken LJ, Meduri G, Misrahi M, Bakker O, Wiersinga WM. Expression of the thyroid-stimulating hormone receptor in the folliculo-stellate cells of the human anterior pituitary. J Clin Endocrinol Metab. 2000;85(11):4347-4353.

68. Soji T, Yashiro T, Herbert DC. Intercellular communication within the rat anterior pituitary gland: IV. Changes in cell-to-cell communications during pregnancy. Anat Rec. 1992;233(1):97-102.

69. Sakuma E, Wada I, Soji T, Wakabayashi K, Otsuka T, Herbert DC. The changes of gap junctions between pituitary folliculo-stellate cells during the postnatal development of Zucker fatty and lean rats. Micros Res Tech. 2014;77(1):31-36.

70. Cukuranovic Kokoris J, Jovanovic I, Pantovic V, et al. Morphometric analysis of the folliculostellate cells and luteinizing hormone gonadotropin cells of the anterior pituitary of the men during the aging process. Tissue Cell. 2017;49(1):78-85.
72. Pavlovic M, Jovanovic I, Ugrenovic S, et al. Morphometric analysis of the human anterior pituitary’s folliculostellate cells during the aging process. *Ann Anat*. 2013;195(3):231-237.

73. Scheithauer BW, Sano T, Kovacs KT, Young WF Jr, Ryan N, Randall RV. The pituitary gland in pregnancy: a clinicopathologic and immunohistochemical study of 69 cases. *Mayo Clin Proc*. 1990;65(4):461-474.

74. Quintanar-Stephano A, Valverde C. Mitogenic effects of thyroxine and TRH on thyrotrophs and somatotrophs of the anterior pituitary gland in thyroidectomized rats. *J Endocrinol*. 1997;154(1):149-153.

75. Sheng JA, Bales NJ, Myers SA, et al. The hypothalamic-pituitary-adrenal axis: development, programming actions of hormones, and maternal-fetal interactions. *Front Behav Neurosci*. 2020;14: 601939.

76. Castle-Miller J, Bates DO, Tortonese DJ. Mechanisms regulating angiogenesis underlie seasonal control of pituitary function. *Proc Natl Acad Sci U S A*. 2017;114(12):E2514-E2523.

77. Perryman EK. Folliculo-stellate Cells of the Pituitary Gland: What role do these star-shaped cells play? *Bioscience*. 1989;39(2):81-88.

How to cite this article: Le Tissier PR, Mollard P. Renewing an old interest: Pituitary folliculostellate cells. *J Neuroendocrinol*. 2021;33:e13053. [https://doi.org/10.1111/jne.13053](https://doi.org/10.1111/jne.13053)