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Role of Pituitary Gland in the Aspect of Stem Cell and Hormone Production: A Narrative Review

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Abstract:
In the last two decades, scientists have gained a better understanding of several aspects of pituitary development. The signalling mechanisms that control pituitary development and shape have been discovered, and the balancing interactions between them are now understood. Markers for multipotent progenitor cells are being discovered, and hallmark transcription factors for most hormone-producing cell types have been revealed. Pulsatile hormone secretion now requires a three-dimensional integration of cellular networks. Because of their critical involvement in pituitary development, over a dozen genes are known to induce pituitary hypoplasia when they are altered. Similarly, a few genes that predispose to familial endocrine neoplasia have been identified, as have numerous genes altered in sporadic pituitary adenomas. We expect to learn more about these processes at the molecular level over the next decade, as well as gain insight into the development of the hypophyseal portal blood system and the development of better therapeutics for congenital and acquired hormone deficiencies, as well as common craniopharyngiomas and pituitary adenomas.

Keywords: Adenohypophysis, anterior pituitary, Rathke's pouch, stem cell, neural ectoderm, organizing center

1. INTRODUCTION

The pituitary gland is referred regarded as the body's "master gland" since it regulates growth, reproduction, metabolism, and stress response. Unique cell types in the anterior pituitary gland, such as lactotrophs, somatotrophs, thyrotrophs, corticotrophs, and gonadotrophs, secrete polypeptide hormones such as prolactin (PRL), growth hormone (GH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and gonadotropins such as luteinizing (LH) and follicle stimulating Hormones (FSH). Many species' anatomical stages of pituitary development have been characterised since at least a century ago. [1,2] Lessons acquired in birds (chick-quail), amphibians (bullfrogs), fish (zebrafish), and mammals (mouse and rat) have all contributed to our present understanding of pituitary development and pathology. The basis for understanding the signalling that regulates pituitary hormone production was created by transplant studies [3-6]. The ability to distinguish hormone-producing cell types based on their size, shape, and secretory granules was introduced by electron microscopy, which was later superseded by the availability of antibodies specific to individual hormones, allowing the emergence of differentiating cells to be tracked during embryogenesis [7-9]. The molecular biology period saw the identification of signature transcription factors necessary for cell selection and lineage determination, as well as signalling molecules indicated in early transplant studies [10-12].

Understanding the biology of pituitary progenitors, including cells with stem-like features throughout embryogenesis and in the adult organ, is a recent field of active research [13,14]. There is still a lot to understand about progenitor recruitment, differentiated cell hypertrophy and hyperplasia during puberty, pregnancy, wound healing, and exceptional physiological demands. To get a better knowledge of pituitary development, we must first understand how the hypophyseal portal system develops, which is required for hypothalamic releasing hormones to reach the pituitary gland and hormone delivery to target tissues [15]. The processes that control the development of pituitary cell networks, as well as their function in hormone production, are being studied [16]. Many of the uncommon familial pituitary adenomas and congenital pituitary hormone deficiency syndromes may now be diagnosed using genetic techniques thanks to research into pituitary development. This is critical for determining risk, illness progression, and therapy effectiveness. Despite this advancement, at least half of congenital diseases remain undiagnosed, and the majority of common pituitary adenomas remain unexplained and difficult to treat [17-19]. In this review, we'll concentrate on the areas where more research is needed and refer to recent studies that address well-understood elements of pituitary development and pathology. Future fundamental scientific investigations, we believe, will pave the path for better detection, treatment, and prevention.

Regulating the pituitary organizer and the growth and shape of Rathke's pouch

The neural ectoderm, which gives rise to the posterior lobe, and the surface ectoderm, which gives rise to Rathke's pouch, the predecessor to the anterior and intermediate lobes, are the two ectodermal components that make up the pituitary gland (adenohypophysis or pars distalis and pars intermedia, respectively). The neurohypophysis, or posterior lobe, develops from the ventral diencephalon, and its genesis and patterning are discussed in another article in this book. The ventral diencephalon's patterning is important not only for forming the pituitary posterior lobe, but also for forming an organising centre that determines the size and shape of Rathke's pouch. The use of genetically engineered mice to study the functions of multiple signalling pathways in pituitary development has substantially expanded our knowledge. In the ventral diencephalon, the organising centre is made up of an overlapping expression region of bone morphogenetic protein and fibroblast growth factors (BMP4, FGF8, and FGF10), which evaginates to produce an infundibulum [20, 21]. A domain of sonic hedgehog (SHH) expression is found rostral to the organising centre and the infundibulum [21]. Because Bmp4-/- mice do not produce the pituitary placode or Rathke's pouch at e9.5, BMP4 is a necessary inductive signal for Rathke's pouch formation [5]. FGF signalling is required for cell proliferation in Rathke's pouch after placode development and pouch induction. Fgf10-/- and Fgfr2IIIb-/- are ligand and receptor mutants that generate Rathke's pouch, but it does not enlarge and is eliminated by apoptosis [22, 23]. The ventral diencephalon of Nkx2.1-/- mice does not express Fgf8, and Rathke's pouch is hypoplastic, phenocopying the Fgf10-/- pituitary [5]. The enlargement of the pituitary anterior lobe (adenohypophysis), deletion of the pituitary posterior lobe, and neural ectoderm midline abnormalities, including holoprosencephaly, are all phenotypes of mice with a hypomorphic mutation in Fgf8 [24]. As a result, both BMP and FGF are important during the early phases of pouch formation and expansion, and dose sensitivity has been demonstrated. Many of the genes in the FGF family are expressed in the pituitary gland. The precise functions of FGF8 and FGF10 in the pituitary organising centre remain unknown. FGF8 is required for the establishment of the neuroectoderm midline, whereas FGF10-/- animals show no midline abnormalities [23-25]. FGF8 may be more extensively necessary for patterning the neuroectoderm-derived pituitary organising centre, according to our findings. FGF8 and 10 may cooperate in the development of the mouse infundibulum in a similar way as FGF3 and FGF10 cooperate in the development of the chick infundibulum. To see if there are compensatory changes in expression, researchers should look at Fgf10 expression in Nkx2.1-/- and Fgf8 hypomorphic mutants, as well as Fgf8 expression in Fgf10-/- animals. FGFs 13, 14, and 17 are found in the embryonic pituitary transcriptome [28], while FGF18 is expressed in the organising centre [26, 27]. As a result, the FGF family has a lot of potential for

functional redundancy. The signalling channels in the ventral diencephalon are intricately intertwined. Single gene disruptions in one signalling pathway alter gene expression in another signalling pathway. BMP4 activity is inhibited by Noggin, which is expressed in the pituitary organiser. BMP4 has an enlarged domain in Nog-/- mice, while FGF10 expression is reduced, indicating that both signalling pathways interact [29]. The pituitaries show extremely varied dysmorphologies, and a wider region of surface ectoderm is induced to develop Rathke's pouch. BMP and FGF expression are also influenced by the Wnt signalling pathway. Wnt5a-/- mice and Tcf7l2-/- (TCF4) mice had enlarged glands and increased BMP4 and FGF10 expression domains. Wnt5a mutants have a little dysmorphology that goes away after birth, whereas Tcf7l2 mutants have a substantially enlarged pituitary gland that protrudes through the cartilage plate [30-33]. WNT5A is most likely acting via a non-canonical Wnt signalling route, as there is little or no stable beta catenin in the nucleus at that point. As a result, Tcf7l2 mutants' overgrowth is most likely owing to a lack of transcriptional regulation. Many members of the WNT gene family are expressed in the developing pituitary and its surrounding tissues. Wnt11 and Wnt16 are non-canonical and canonical WNTs, respectively, that are expressed in the ventral diencephalon [33]. Wnt16 is therefore one option for controlling the pituitary organiser via TCF7L2. ROR1 and ROR2 receptors have recently been discovered to mediate non-canonical WNT5A signalling. The limb truncation phenotype of Ror1-/-; Ror2-/- mice phenocopies several characteristics of the Wnt5a-/- animals, while the pituitary phenotype was not documented [34]. More research is needed to identify the key actors and understand the functions of canonical and non-canonical WNT signalling in pituitary organiser formation.

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SHH expression and activity are regulated by transcription factors from the SOX, T-box, and GLI families, which are involved in pituitary growth regulation. Both the oral ectoderm and the pituitary organiser in the ventral diencephalon express Sonic hedgehog. The pituitary placode emerges from a region of oral ectoderm that is SHH negative, similar to how the pancreatic bud emerges from the gut tube in a SHH negative zone. SHH expression in the ventral diencephalon is required to limit pituitary gland development. The ventral diencephalon's conditional loss of Shh function is linked to the organising center's growth and pituitary hypertrophy. [35] SOX2 and SOX3, which bind the Shh enhancer, SBE2, and promote expression, control Shh transcription in the ventral diencephalon. Reduced Shh expression in the ventral diencephalon and an expansion of the pituitary organiser. [35] result from a dose-dependent decrease in Sox2 and Sox3. The T-box transcription factors TBX2 and TBX3 prevent SOX2 and SOX3 from acting. They bind SOX2 and SOX3, inhibiting Shh expression through the SBE2 enhancer from being activated. Tbx3-/- animals had more SHH expression and less BMP4 and FGF10 expression, resulting in a hypomorphic pituitary [36]. The Gli transcription factors Gli2 and Gli3 are involved in the transmission of SHH signals. GLI2 largely activates SHH transcriptional targets, whereas GLI3 primarily represses them [37]. Gli2-/- embryos show lower levels of Bmp4 and Fgf8 expression in the pituitary organiser and hypomorphic pituitaries, whereas Gli2-/- and Gli3-/- embryos have no pituitary at all [38]. Given the active and repressive roles of GLI proteins, it's difficult to say whether early, active SHH signalling is required to induce Bmp4 and Fgf8 expression in the pituitary organiser, or if the repressive activity of GLI2 and GLI3 is required to ensure Bmp4 and Fgf8 expression in the pituitary organiser. The pituitary-organizing centre is regulated by the homeobox transcription factors LHX2 and RX, which include LIM and paired type homeodomains, respectively. Both Lhx2-/- and Rx-/- embryos show larger

pituitaries, which are characteristic of genetic mutants with increased BMP4 and FGF8 expression in the ventral diencephalon but decreased SHH expression. FGF8 expression was increased in Lhx2 mutants, although BMP4 expression remained unaltered [39]. FGF10 expression is decreased in Rx-/- animals, and while BMP4 and FGF8 levels were not studied, we expect their expression regions to be extended [40]. Additional characterization of these mice models might show more transcriptional modulation of the pituitary organiser and, as a result, the induction of Rathke's pouch.

Activities of signaling pathways intrinsic to Rathke's pouch

BMPs and FGFs are found in and around Rathke's pouch, and their functions in cell specification in the anterior lobe are debatable. Excess signalling can influence cell specification and/or affect the size of specific cell populations, according to gain of function models. Loss of function models support the role of these signalling molecules in growth and shape but not cell specification, whereas gain of function models suggest that excess signalling can influence cell specification and/or affect the size of specific cell populations. FGF8 and FGF10 are expressed in the infundibulum, dorsal to Rathke's pouch, at e10.5 of mouse development, while BMP is expressed on the ventral side and surrounding mesoderm [20, 21]. Depending on where the progenitor cells are positioned relative to the gradient, countering gradients of FGF and BMP signalling has been proposed to govern determination of anterior lobe cell types. [20,21] Somatotropes are initially positioned more dorsally than gonadotropes on the ventral side of the developing anterior lobe, which might suggest that progenitor cells closer to the source of BMP2 become gonadotropes, while progenitor cells closer to the source of FGF become somatotropes. There have been no trials to follow progenitor cells and their progeny from a precise beginning site near the lumen of Rathke's pouch to a specified ultimate location and cell type in the anterior lobe, such as diI or genetic tagging. The identification of cell type specific networks inside the anterior lobe, as well as the migration of hormone secreting cells to create those networks, suggests that the ultimate position of cells in the anterior lobe is not directly tied to their beginning position in Rathke's pouch [41]. In fact, a birth date investigation discovered that progenitor cells exiting the cell cycle at the same time are dispersed across the front lobe, signifying active cell migration [42]. As a result, we don't know if all progenitor cells near the lumen are the same or if progenitor cells are designed differently depending on where they are in Rathke's pouch before cell cycle departure. Between e11.5 and e13.5, anterior lobe cell types begin to end the cell cycle and begin to differentiate [42, 43]. When progenitor cells leave the cell cycle, they transition to a non-cycling, undifferentiated state marked by the expression of p57Kip2 (Cdkn1c) [44]. As they leave the lumenal epithelia and reach the anterior lobe, these cells may be seen on the ventral side of the lumen. Cell cycle departure begins at e11.5, which coincides with a phase when Rathke's pouch explants become resistant to exogenous signals like FGF and BMP [20, 21], suggesting that Rathke's pouch signals are likely to drive cell specification. Changing BMP and FGF expression in the pituitary organiser has no effect on anterior lobe cell specification [29,31, 33, 39]. Extrinsic FGF may impact anterior lobe cell specification and/or population size at birth, as evidenced by the fact that embryos homozygous for a FGF8 hypomorphic mutation have fewer gonadotrope cells [24, 39].

More research is needed to fully understand the functions of BMP and WNT within Rathke's pouch. The pouch expresses BMP2, WNT4, WNT6, WNT11, and WNT16, which may have a function [21, 29, 33]. The expression of a dominant negative Bmpr2 receptor in Rathke's pouch significantly inhibits BMP signalling, resulting in the loss of the POU1F1 (Pit1) lineage, which includes thyrotropes, somatotropes, and lactotropes, as well as corticotrope growth [21]. Stimulating BMP signalling in Rathke's pouch by driving BMP4 expression increases intermediate cell differentiation, notably in cells that express Gata2 and Isl1, but it hinders the terminal development of all hormone cell types except corticotropes [21]. It's difficult to say if the results of non-physiological gain of function tests accurately represent the inherent functionalities of signalling pathways. Rathke's pouch's expression of several WNTs suggests functional redundancy and the usage of both canonical and non-canonical pathways. Somatotropes and thyrotropes are reduced in Wnt4 insufficiency, but

Wnt6 loss has no effect on pituitary cell specification [21,33]. Because conditional silencing of β-catenin in the early pouch results in the loss or decrease of all cell types except corticotropes, canonical Wnt signalling appears to be crucial for cell specification [45]. Depending on the cre driver utilised to activate -catenin, expression of an activated version of the protein in the early Rathke's pouch results in a variety of phenotypes. The pituitary is halted early in organogenesis when Pitx1-cre is used [45]. Hesx1-cre causes a rise in pituitary stem cells, resulting in craniopharyngiomas, and changes cell specification, lowering all cell types except corticotropes [46]. Despite the existence of a gene producing a degradation-resistant version of -catenin in all anterior lobe cells, nucleus localised -catenin is not found in cells that have begun to differentiate outside of the stem cell niche. The anterior pituitary appears to have systems in place to prevent β-catenin activation. Pitx1 and Hesx1 are both expressed extremely early in the development of Rathke's pouch, although they are also expressed in other anterior tissues prior to pouch formation [6]. The differential phenotypes observed are likely due to spatial and temporal variations in expression of these two cre drivers. Furthermore, dosage sensitivity for HESX1 and other pituitary transcription factors [47-49] might be a role in situations where cre expression is achieved at the expense of an endogenous allele. Gain and loss of function investigations in mice imply that SHH signalling has a role within the pouch. Shh is originally expressed throughout the oral ectoderm, although it is not found in Rathke's pouch placode. Despite this, Rathke's pouch cells appear to be receiving SHH signals due to the expression of the downstream target gene patched (Ptc1) [50]. Because inhibiting SHH signalling by promoting expression of the Shh inhibitor, Hip, in the pouch lowers progenitor cell proliferation, Bmp2 and Lhx3 are not expressed, and the pituitary is hypoplastic, receiving these signals must be significant [50]. In Rathke's pouch, overexpression of Shh promotes a rise in Bmp2 expression as well as thyrotropes and gonadotropes [50]. Embryos with conditional Gli2 inactivation in the pituitary, on the other hand, show a reduction in progenitor proliferation, but the pituitary is properly formed, and the hormone-producing cells are unharmed other than a reduction in corticotropes [38]. In loss of function mutants, compensatory alterations in gene expression may give a partial rescue, but gain of function may outstrip the ability to make adaptations. Shh signalling in the pituitary is activated by ectopic production of SmoM2, which enhances proliferation without changing cell specification [38]. The differences between the HIP transgenic and conditional Gli2 loss of function studies could indicate a broader range of action for the secreted inhibitor, HIP, such as inhibiting SHH signalling in the ventral diencephalon as well as Rathke's pouch, or non-canonical SHH signalling in the pituitary, such as non-Gli-dependent activation of RAC1 or RHO [51]. Because Ptc1 possesses Smo and Gli independent roles, the different outcomes for ectopic activation of the SHH pathway in Rathke's pouch might be explained by non-canonical SHH signalling [51]. The Notch signalling system has been shown to have a role in anterior lobe cell specification. Hes1 is a Notch-responsive transcription factor that causes a cell fate flip from melanotropes to somatotropes in Hes1-/- embryos [52]. The conditional deletion of Rbpjk, an intracellular Notch signalling mediator, in Rathke's pouch promotes corticotrope differentiation and the loss of the POU1F1 lineage [53]. Notch signalling stimulation suppresses differentiation in the corticotropes and melanotropes [54], whereas ectopic Notch signalling in the POU1F1 lineage hinders terminal differentiation [53]. Corticotropes express the Notch ligand Dll3, however it is not needed for corticotrope development [55]. The Dlk1 Notch ligand is expressed in all hormonal cell types, and deletion of Dlk1 causes a reduction in all cell types, with somatotropes seeing the greatest drop [56, 57]. To further understand the role of notch family receptors, ligands, and target genes in controlling pituitary progenitor development and cell specification, more research is needed. In conclusion, BMP, FGF, WNT, and Notch all play vital functions in the pituitary gland and its surroundings. The many ligands and receptors, as well as interactions between pathways, provide a level of complexity that is difficult to fully comprehend. Future study is needed to better understand the functions of distinct signalling pathways in cell specification, as well as the compensatory modifications that may be made to guarantee correct cell type distribution within the pituitary anterior lobe.

The role of signature transcription factors in cell specification

Many transcription factors that play key roles in the specification and/or growth of pituitary hormone-producing cells have been discovered, and many of them are crucial in human illness. POU1F1, for example, was discovered because of its function in trans-activating the growth hormone and prolactin genes [58-61]. Recessive hypopituitarism is defined by a congenital absence of GH, PRL, and TSH in mice and people with inactivating mutations in this gene. POU1F1 is the somatotrope, lactotrope, and thyrotrope lineage's hallmark transcription factor [62]. POU1F1 mutants are unable to form these cells. Other essential transcription factors such as PITX1, the orphan nuclear hormone receptor, NR5A1 or Steroidogenic Factor 1, the helix-loop-helix factor NeuroD1, and the T-box factor TPIT were discovered using similar methods [63-67]. In other circumstances, a lack of transcription factors does not result in the entire absence of the cell type, but just partial differentiation. NR5A1-deficient animals, for example, do not generate gonadotropins, but hyperstimulation with GnRH is an efficient inducer, suggesting that NR5A1 is not required for gonadotrope differentiation [68]. Similarly, neither NeuroD1 nor TPIT are required for corticotrope formation, but their absence causes POMC expression to be delayed or diminished [65, 66]. Failure to encourage divergence down one route might open the door to other possibilities. Intermediate lobe cell types develop into gonadotropes and POU1F1 independent thyrotropes in the absence of TPIT, showing that TPIT plays a crucial role in regulating anterior lobe cell fates, in part via antagonising NR5A1 [69, 70]. Ectopic differentiation in the intermediate lobe can also be caused by HES1 deficiency: instead of melanotropes, the hypoplastic intermediate lobe includes POU1F1 dependent somatotropes. The underlying permissive element appears to be premature cell cycle exit [71]. It's an oversimplification to believe that single signature transcription factors control cell specification. To develop the distinctive characteristics of specialised hormone-producing cell types, a large number of transcription factors are necessary. Additional variables, both positive and negative, have been implicated in moving POU1F1 expressing cells toward specialisation in GH, PRL, or TSH synthesis [72]. Factors that encourage specialisation include glucocorticoid and oestrogen receptors, as well as ETS factors [73-75]. Furthermore, elements of the combinatorial code of factors can vary during development in order to reach or maintain the completely differentiated hormone-producing cell [76].

The current state of the art necessitates an understanding of the epigenetic control that allows transcription factors to bind to chromatin, as well as the processes that cause this condition to occur. The use of genome-wide analyses of DNase-sensitive open chromatin and transcription factor binding sites to deconstruct the differentiation processes of hormone-producing cells is a potent technique. PAX7, a pioneer transcription factor that binds enhancers from several genes, either opening the chromatin to allow TPIT binding or inhibiting binding, is a recent example [77].

Intermediate lobe cells that lack the PAX7 selector develop into corticotropes rather than melanotropes. Understanding similar starting, selective processes for different hormone-producing cell types is a significant future endeavour. Because embryonic pituitary tissue is scarce, these tests are particularly difficult unless cell culture techniques that can mimic the differentiation process are available.

Early acting transcription factors

PROP1 is the first transcription factor expressed in the pituitary during development. This paired homeodomain protein is essential for the activation and silencing of numerous genes, each of which plays a key function in organogenesis. It is required for the initial activation of POU1F1 and NOTCH2, as well as the timely silencing of HESX1 and OTX2 [55,78-81]. Beta-catenin may regulate PROP1's transition from repressor to activator, although other data shows that beta-catenin must be substantially inhibited for proper development [31,45,46]. PROP1 deficiency affects all hormone-producing cell types in the anterior lobe in humans [82], and it causes congenital GH, TSH, PRL, and gonadotropin deficit in mice [83, 84]. Proliferating cells along Rathke's cleft fail to delaminate in the

absence of PROP1, simulating a failed epithelial to mesenchymal transition [85, 86]. In mice, this results in a highly dysmorphic and hypoplastic organ, whereas in humans, it results in a diversity of organ sizes [76, 85]. Many transcription factors that work early in pituitary development have many pituitary cell types as targets. Unlike PROP1, most of these genes are not pituitary specific, and when they are altered, they impact numerous developmental tissues, leading in syndromic hypopituitarism [76]. Because of their pleiotropic consequences, loss of function mutations in several genes are likely deadly in humans. PITX1, PITX2; LHX2, LHX3, LHX4; and OTX1, OTX2 have very varied craniofacial and pituitary characteristics, probably due to functional overlap amongst members of the same gene family. Many of these genes have mutations that cause decreased proliferation and increased apoptosis [49, 87-89].

In the developing mouse embryo's skull, OTX1, OTX2, EMX1 and EMX2 show overlapping expression patterns [90]. Gene targeting tests indicated that each of these transcription factors plays an important function in embryogenesis and that members of the gene family compensate for each other. Otx2-/- mice have no head structures anterior to rhombomere 3, whereas Otx2+/- heterozygotes show a wide variety of craniofacial abnormalities, ranging from pituitary aplasia to severe pituitary dysmorphology and hypoplasia [91]. Otx1-/- mutants display a milder phenotype, with a temporary delay in growth and puberty [92], indicating that both Otx1 and Otx2 play a role in pituitary development, with Otx2 being the most important for normal organ form and function. The neural ectoderm, which generates FGF and drives the formation of Rathke's pouch, has a high level of Otx2 expression [79]. When Pou1f1 transcription begins, Otx2 expression in Rathke's pouch is very low and transitory, with little or no expression visible. This shows that OTX2 mutations in people and mice induce hypopituitarism because OTX2 is essential for the development of the posterior lobe and pituitary stalk. The neural ectoderm defect, which results in diminished inductive impulses that typically originate from the organising centre, is thought to be the cause of the anterior lobe hypoplasia. Members of the same gene family are not the only ones who benefit from compensation and functional overlap. In addition to the EMX and OTX genes, other genes that increase or inhibit the Otx2 mutant phenotype exist, and they differ amongst inbred strains [91]. The C57BL/6 background increases Otx2 heterozygotes' vulnerability to severe craniofacial abnormalities, but CBA protects them [93, 94]. Otx2 heterozygotes range in appearance from normal to severe acephalic late in gestation, on a mixed background of B6 and CBA. Although the particular genes are unknown, traditional genetic mapping of the modifier genes identified relevant locations on numerous chromosomes. These kinds of mice investigations might lead to the discovery of genes that determine the degree of craniofacial deformities in human OTX2 mutant carriers. The heterozygous mutations are not totally penetrant in situations where the transmission of OTX2 variations has been examined in pedigrees [95]. Sequencing the genomic DNA of these human patients may reveal genes with harmful mutations that contribute to the OTX2 mutant phenotype's penetrance. This method has been used to successfully discover genes that contribute to hypogonadotropic hypogonadism, as well as a variety of digenic and oligogenic disorders [96, 97].

Emerging roles for additional transcription factor families: the forkheads

Many distinct transcription factor genes with unclear roles are found in the pituitary gland, according to transcriptome research [28]. The SIX gene family has been linked to pituitary development [98, 99], and the family's shared effects on eye and pituitary development support the hypothesis that organs growing from placodes share regulatory circuits ref. Review of Bonner-Fraser. Many homeobox, HMG box, helix-loop-helix, and orphan nuclear receptors are yet to be studied, according to the Brinkmeier and Davis articles. The first step in understanding the function of these new genes is to look at their expression during development. The significance of forkhead genes in pituitary development is starting to emerge, and it offers as an example of the intricacy that may define other gene families that have yet to be investigated. Forkhead transcription factors have a conserved, winged helix DNA binding domain and are called for the phenotype of the Drosophila mutant that

gave rise to the group. Many physiological processes, including development, metabolism, cell cycle progression, and chromatin modification, have been linked to forkheads [100, 101]. In humans, 50 forkhead factors have been discovered, and 44 in mice. Forkhead factors have been given a consistent nomenclature. FOX (for forkhead box) is a letter that designates the subfamily to which the factor belongs, as well as a number that identifies each subfamily member [102, 103]. In humans, mutations in forkhead genes frequently cause autosomal dominant diseases with haploinsufficiency.

FOXL2, also known as Pfrk, was the first pituitary forkhead to be discovered [21]. FOXL2 has a role in ovarian development and function [104, 105], as well as female sex determination [100, 106, 107]. Blepharophimosis, ptosis, and epicanthus inversus syndrome (BEPS), caused by mutations in the human FOXL2 gene, is an autosomal dominant loss of function illness that causes eyelid deformities and early ovarian failure [108]. Humans with BPES do not have pituitary problems, but homozygous mutant mice show that FOXL2 plays a role in pituitary function, implying that both Foxl2 alleles must be lost to affect pituitary function [109-112]. FOXL2 expression has been found in mouse and human gonadotropes and thyrotropes [113,114]. FOXL2 is expressed in the majority of null cell and gonadotropin-subunit-producing adenomas, indicating that it plays a role in gonadotrope differentiation and proliferation [115]. FOXL2 cooperates with clusterin to control gonadotroph adenoma development. In T3-1 cells, FOXL2 controls follistatin (Fst) activin responsiveness in collaboration with SMAD3 [116], and it activates the activin responsive region of the Gnrhr gene promoter [117]. However, FOXL2 is not required for Gnrhr expression, indicating that there may be genetic overlap and/or compensation [109]. In transgenic mice, ectopic FOXL2 expression is sufficient to promote ectopic expression of the Cga gene, which encodes the glycoprotein hormone -subunit (GSU) [113]. Because Cga expression is decreased in Foxl2 knockout mice but transcripts are normal in a pituitary-specific deletion of Foxl2 [109, 118], the need of FOXL2 for Cga expression is unclear. This apparent disparity might be attributable to FOXL2's hypothalamic contributions to Cga expression regulation, or the timing or efficiency of Foxl2 deletion in conditional knockout animals. The most well-studied FOXL2 target gene is the follicle-stimulating hormone (Fshb) gene [119-121]. Both systemic and pituitary-specific Foxl2 deletions cause gonadotrope cell specification, although both men and females have drastically reduced basal and activin-stimulated FSH levels. Male Foxl2 knockout mice have smaller testicles and spermatogenesis, whereas female Foxl2 knockout mice have smaller ovarian weight and oogenesis. [109]. Activin does not induce FSH production from primary pituitary cells from Foxl2 mutant animals, which is consistent with recent observations [118]. Several studies have provided mechanistic insight into how FOXL2 regulates Fshb expression. FOXL2 collaborates with SMADs to mediate activin activation of the Fshb genes in mice and pigs [122-124]. FOXL2 is also engaged in the Fshb promoter synergy between activin and progestins [125]. Other forkhead transcription factors' involvement in pituitary development are less well understood. FOXO1 may be found in a variety of organs, including the pancreas, liver, brain, adipose tissue, and the ovary [103,126]. FOXO1 is found in quiescent cells of the developing pituitary, indicating that it plays a function in cell cycle arrest [127]. In the pituitary, the cell specificity of FOXO1 expression is unknown. In one research [127], FOXO1 was found in half of somatotrope cells and one-tenth of gonadotropes, whereas in another, it was found exclusively in gonadotropes with functional inhibition of Lhb expression [128]. More research is needed to determine the role of FOXO1 in pituitary development. FOXE1 is required for thyroid organogenesis and is expressed transiently in the oral ectoderm that forms Rathke's pouch between the ages of 9.5 and 10.5 [129,130]. Foxe1 null animals, on the other hand, showed no pituitary abnormalities, suggesting that this gene isn't essential for proper pituitary development [129].

Autoimmune hypophysitis is an uncommon condition in which the pituitary gland becomes inflamed and produces less hormone. The immune system and pituitary hormone synthesis are influenced by several forkhead genes, although the mechanisms are unknown. FOXP3 and FOXD1, for example, are not expressed in the developing pituitary gland but have an impact on pituitary hormone synthesis [131,132]. FOXP3 is required for regulatory T-cell growth and function, and FOXP3 loss results in

severe autoimmune illness [133, 134]. The expression of the gonadotropins Lhb, Fshb, and Cga is decreased in mice with an inactivating Foxp3 mutant (scurfy mice), showing that FOXP3 is indirectly crucial for gonadotrope function [132]. At e10.5, Foxd1 is expressed in the kidney and the mesenchyme surrounding the developing pituitary, in addition to renal expression. Foxd1-deficient mice die within 24 hours of birth owing to renal insufficiency [135,136], with a considerable drop in Lhb expression in particular. The sella turcica in these mice also fails to develop adequately [131]. As a result, both FOXB3 and FOXD1 have an impact on pituitary function. Forkhead variables appear to have an essential role in pituitary growth and function, according to these research. We still have a long way to go before we fully comprehend the role of this family of variables in pituitary organogenesis and hormone production. The members of the forkhead family, like many other transcription factor families, may have functional overlap.

Pituitary progenitors: stem cells and the niche

In rats, differentiated hormone-producing cell types may be detected at birth [137]. After birth, each population expands as the gland grows, fueled by hypothalamic releasing hormones and physiological needs [138 -143]. Some hormone-producing cells re-enter the cell cycle during postnatal organ expansion [144 -146]. After tissue damage, the adult pituitary gland has some potential to regenerate [147-149]. Growth hormone synthesis regenerates slowly after ablation, while prolactin cells regenerate slowly or not at all [150]. As a result, the extent to which regeneration is feasible and the processes that underpin it are not completely understood. Proliferation of terminally differentiated cells, trans-differentiation of differentiated cells, such as conversion of somatotrophs to lactotrophs, and/or differentiation of progenitors/stem cells have all been proven to occur in the pituitary in response to physiological demand. Adult organs with strong regeneration ability and/or turnover, such as skin, liver, gut, and bone marrow, were the first to be discovered to contain stem cells [151]. Furthermore, stem cells have been discovered in organs where the majority of the cells are post-mitotic, such as the brain [152] and heart [153]. Stem cells have three basic properties in all of these organs: the ability to proliferate and self-renew, differentiation potential, and the ability to rebuild tissue following cell loss. The pituitary gland has a low cell turnover rate [150], and while differentiated cells can re-enter the cell cycle, the majority of hormone-producing cells do not divide [42]. In the last several years, a lot has been discovered about anterior pituitary stem cells [154]. The niche, which appears to be connected with Rathke's cleft in humans and mice [155], is being identified. Other important research areas include the cellular connections required to keep stem cells in the niche and drive differentiation. The phases in the control of multipotent progenitors, as well as the mechanisms for guidance to specific cell fates, will be a future challenge.

We explore some of the cornerstone research to have a better understanding of the present state of the art. Pituitary stem cells were first characterised in 1969 as a type of hormone-negative cells known as chromophobes [156]. Proliferation and differentiation of chromophobes transplanted into the hypothalamus of hypophysectomized rats resulted in mature basophils (thyrotrophs, gonadotrophs, and corticotrophs) and acidophils (somatotrophs and lactotrophs). A methodology for separating chromophobes into basophils and acidophils in vitro was devised shortly after [157]. According to recent research, chromophobes are pituitary progenitors or stem cells that react to hypothalamic signalling hormones [158]. The presence of cells in the pituitary with progenitor or stem cell capabilities such as self-renewal and differentiation into several cell types has been established by various researchers using various methodologies. More research is needed to describe pituitary stem cells, progenitors, and transit amplifying cells, as well as to understand how advancement through these processes is regulated. The many ways of identifying pituitary stem cells are discussed in this review. Non-granular cells with lengthy cytoplasmic projections that give them a star-like appearance are known as foliculo-stellate cells. They are found in the anterior pituitary gland's parenchymal tissue. Folliculo-stellate cells are S100 and glial fibrillary acidic protein immunopositive cells that make up 5–10% of the pituitary cells in the adult gland. They form a functional network with

endocrine cells, which they control through the production of growth factors and cytokines in a paracrine way. Intercellular communication is facilitated by their lengthy cytoplasmic processes and gap junctions. They also have phagocytic activity and operate as scavenger cells [159]. A subset of folliculo-stellate cells might be a source of pituitary stem cells, whereas another group could be engaged in niche creation or nurturing. To clarify the distinct populations of folliculo-stellate cells and examine their function more directly, new markers are required. The ability to form colonies in vitro is one of the characteristics of progenitors and stem cells. This was demonstrated for the pituitary for the first time by Thomas's group [160]. Based on the expression of S100 and GFAP, as well as their ability to take up the fluorescent dipeptide -Ala-Lys-Ne-AMCA [160], the murine colony-forming cells (CFC) make up 0.2 percent of the anterior pituitary cells and may constitute a subpopulation of folliculo-stellate cells. Only AMCA-positive cells, which make up 3.7 percent of pituitary cells, were able to generate CFC, but only 12.3 percent of them did, indicating the folliculo-stellate cell population's apparent heterogeneity [160]. In the adult pituitary, angiotensin-converting enzyme is expressed in cells lining the remainder of Rathke's cleft and the subluminal zone, which are thought to be the niche and a source of precursor cells [161]. The AMCA positive population in CFC was enriched by cells selected for angiotensin converting enzyme but not SCA1 [161]. Furthermore, 3.3 percent of AMCA-positive, GH-negative cells may develop in vivo and express GH 6 weeks after implantation [162]. Based on their ability to form colonies in vitro and differentiate in vivo, these investigations have established the progenitor potential of a subset of folliculo-stellate cells. To infer that CFC bearing these markers are genuinely pituitary stem cells, evidence of self-renewal and differentiation into other pituitary lineages is required. Vankelecom and colleagues discovered adult pituitary cells with progenitor or stem cell features using several methods [158]. One strategy is based on the idea that stem cells filter out hazardous components like Hoechst dye efflux, while the other depends on clonal sphere creation. Cell sorting of Hoescht 33342-treated bone marrow cells revealed a pool of cells with fast efflux that includes multipotential hematopoietic stem cell markers [163]. This method has been used to find stem cells in a variety of organs, including the pituitary gland [158, 164]. This side population in the pituitary is made up of cells that express high and low amounts of the stem cell marker SCA1, accounting for 60% and 40% of the population, respectively. Pituitary progenitor cells are thought to be in the non-high SCA1 fraction, according to two pieces of evidence. This latter set of cells also expresses transcription factors including Hesx1, Prop1, Pax6, and Lhx4 that are seen in Rathke's pouch progenitors. More crucially, only non-high SCA1 cells can form spheres, which can give birth to all of the anterior pituitary's endocrine cell types [165]. This is consistent with the finding that progenitors are restricted to the SCA1 negative, angiotensin-converting enzyme positive fraction [161]. To establish their ability for pluripotency and self-renewal, as well as to discover markers that separate them from the heterogeneous side population, further characterisation of the non-high SCA1 cells is required. Yamanaka and colleagues demonstrated that inducing the expression of a set of transcription factors found in stem cells reprograms developed cells to become pluripotent stem cells in a Nobel Prize-winning series of research [166]. In the quest for pituitary tissue stem cells, the expression of two of these pluripotency factors, SOX2 and OCT4, has been investigated [155,167]. SOX2, SOX9, and OCT4 have been identified as markers of pituitary progenitors that share many features with stem cells [168]. SOX2, an HMG box transcription factor belonging to the SOXB1 subfamily, is necessary for the maintenance of numerous stem cell populations in humans and rats, including the central nervous system [169]. SOX2 is expressed during development in Rathke's pouch and in around 3% of adult pituitary cells, where it was identified lining the cleft and dispersed throughout the parenchyma. SOX9 is a member of the SOXE family and a stem cell marker in the pancreas, retina, and central nervous system [170-173]. SOXE family members influence SOXB1 family members' activity in various organs by encouraging differentiation along particular routes [174, 175]. SOX9 is expressed in the mature rodent pituitary gland in a similar way to SOX2, although its expression in the embryo appears to be later than SOX2. A tiny population of SOX2-positive, SOX9-negative, hormone-negative progenitors in the adult pituitary gland may

create pituispheres in vitro, which can self-renew, giving birth to secondary spheres, and develop into all five endocrine cells of the AP, as well as folliculo-stellate cells [167]. While these traits meet the majority of the requirements for being classified as stem cells, the traditional definition calls for at least five passes to clearly indicate self-renewal. It's likely that if they're raised in an environment that more closely resembles the niche and/or inductive elements created by the ventral diencephalon's organising centre, they'll be able to go through several cycles of self-renewal. The choice to maintain stem cells vs. divide to create transit-amplifying cells is likely regulated by cell communication between progenitors and other cells in the niche. Developing regenerative therapeutics requires identifying these pathways and characterising the milieu for stem cell survival. GFRa2, or glial cell line derived neurotrophic factor receptor alpha 2, was identified to be a pituitary stem cell marker by Alvarez's team [155]. GFRa2 is found in 0.9 percent of adult pituitary cleft cells and a few cells distributed throughout the anterior pituitary parenchyma. These cells display multiple stem markers, including SOX2 and OCT4, as well as PROP1, an early-acting, pituitary-specific transcription factor required for the maintenance of all pituitary cell types in humans [176]. Slowly proliferating GFPRa2+ PROP1+ cells may form spheres in vitro, create secondary pituitary spheres, and develop into the five pituitary lineages. To characterise the progenitors and supportive cells, further markers are required. Proliferating cells are abundant near the remains of Rathke's cleft during embryonic development. The marginal zone or niche for prospective pituitary stem cells is defined as a multilayer zone. Marginal cells lack granularity and have a poorly formed endoplasmatic reticulum, as well as a large number of free ribosomes and polysomes [154]. The discovery that nestin is expressed in cells lining the pituitary fissure next to the marginal zone [177] led to the hypothesis that marginal cells are stem cells. An adult pituitary stem cell population that expresses nestin and can produce all of the differentiated anterior pituitary cell types was found using a genomic method [178]. However, the expression of the nestin transgene appears to identify a subgroup of cells in Rathke's pouch that do not express endogenous nestin [179]. Regardless, individual progenitors have been shown in pituisphere cultures to be capable of producing all anterior pituitary cell types [167]. PROP1 might have a role in forming and/or sustaining a pool of pituitary progenitors. PROP1 mutations cause progressive hormone deficits in humans, which are generally first seen as growth insufficiency and decreased synthesis of growth hormone, TSH, and gonadotropins. Pituitary hormone levels fall over time if left untreated, and all anterior pituitary hormones, including ACTH, may finally be eliminated [176]. While this evolution does not appear to be replicated in mice, there is evidence that it plays a role in the shift from proliferation to differentiation [180]. Several stem cell markers, such as SOX2, OCT4, and GFRa2, have PROP1 expression overlap [155,181,182]. During foetal pituitary organogenesis, Prop1 is also expressed in a transitional zone between proliferating and differentiating cells. Expression of cyclin E and Notch2 is also seen in this transitional zone [44, 55]. Prop1 expression is stimulated by Notch signalling, implying a feed forward loop [53, 55]. To assess the capacity of Prop1 expressing cells to generate pituispheres and to track the lineages of cells that arise from Prop1 expressing progenitors, more research is needed. Sasai and colleagues revealed that embryonic stem cells may be manipulated to mimic Rathke's pouch development and create functional, differentiated corticotrophs in an elegant work [183]. Surprisingly, transplanting these generated corticotrophs into hypophysectomized mice's kidney capsule was enough to restore their stress response. The interventions that directed this differentiation were based on the understanding that the neural ectoderm stimulates anterior pituitary growth and is controlled by WNT, Notch, BMP, and FGF signalling. It would be particularly fascinating if methods could be devised to consistently guide the growth of other lineages.

Cell cycle regulation

Normal organ development necessitates the control of the transition from proliferation to differentiation, as well as the preservation of the capacity to attract progenitors to differentiation while avoiding excessive growth and adenoma formation. The cell cycle stages are fundamentally

comparable in eukaryotic cells from yeast to mammals, and a quick summary is useful for understanding normal pituitary development and disease states 184, 185. In the synthetic (S) phase, the genetic material is replicated and then split into two daughter cells in the mitotic (M) phase. As the cell prepares for the next phase, gaps (G1 and G2) separate these two stages. Cell differentiation usually occurs at the same time that the cell cycle exits the G1 phase and enters the G0 phase. In rare situations, stimulation can bring dormant cells back into the cell cycle. During normal tissue homeostasis, physiological stressors, regeneration, and wound healing, such recruitment might occur [186].

Critical checkpoint surveillance systems control cell cycle progression. These are concerned with mitotic spindle formation and location, as well as DNA integrity, which includes full replication and DNA damage proofreading [187,188]. Cell cycle arrest is caused by checkpoint blockage, although surveillance failure can lead to unregulated growth. The duration of a cell cycle varies greatly. Adult tissue stem cells and differentiated cell types have a longer cycle period than embryonic stem cells [189]. Sorting cells stained with the DNA binding dye propidium iodide revealed that the G1-phase lengthens significantly with time as cells proceed toward differentiation [190-192]. Multiple controller protein heterodimers offer checks and balances in mammalian cells, which have acquired a high degree of molecular regulation of the cell cycle [184]. Different cell cycle stages can be dominated by the presence of cyclins (Ccn) and cyclin-dependent kinases (Cdk). Endogenous checkpoint monitoring and responsiveness to external stimuli are regulated by several signalling pathways [193]. This process includes phosphorylation and dephosphorylation reactions, as well as regulated protein breakdown. Phosphorylation of the tumour suppressor retinoblastoma protein in late G1 phase, which facilitates dissociation from the E2F1 transcription factor and activation of gene expression required for G1 to S phase transition [194], is one example. Until M-phase is finished, retinoblastoma stays phosphorylated and E2F1 is dissociated. At least 30 cyclin and 25 cyclin-dependent kinase and kinase-like genes have been identified in humans and mice (http://www.ncbi.nlm.nih.gov/gene/), demonstrating the complexity and potential for redundancy in cell cycle control. With their phase representative counterparts, cyclin-dependent kinase inhibitors (Cdkns) create inhibitory protein complexes. Ccnd1-3, Ccne1-2, and Cdk2/4/6 are among the Cdkns that impact at least G1 specific Ccns and Cdks [184, 195, 196]. Cdkn1a, Cdkn1b, and Cdkn1c, also known as p21, p27, and p57, are members of the CIP/KIP group. INK4 (CDK4 inhibitor) and Cdkn2a, Cdkn2b, Cdkn2c, and Cdkn2d (p16, p15, p18, and p19, respectively) belong to a separate group [44]. p57Kip2 (Cdkn1c) and cyclin E (Ccne) signal the exit of proliferative progenitors from the cell cycle during pituitary development, resulting in non-cycling, undifferentiated precursors [100]. p57Kip2 and cyclin E expression are lost during differentiation, but p27Kip1 (Cdkn1b) expression is activated. Pituitary overgrowth is caused by p57Kip2 deficiency, which may be due to the fact that it typically controls progenitor expansion, hence regulating the size of the progenitor niche and the organ. As inhibitors of the cyclin E complex, p57Kip2 and p27Kip1 are likely redundant. Understanding how the gateway to differentiation is controlled, and how transcription factor shortages result in misregulation of this process, is difficult due to the redundancy of cell cycle regulators.

A pituitary phenotype is unusual when a single gene of cell cycle regulators is knocked off globally [197]. The intermediate lobe, which includes melanotropes in mice and is rudimentary in humans [77], is the most commonly afflicted. In contrast to other knockouts, p57-/- animals show anterior pituitary hyperplasia early in life, whereas other knockouts show hyperplasia much later. The usual high occurrence of adenomas at advanced ages, a trait that is genetic background dependent [198], can complicate the investigation of pituitary adenomas in mice. Pttg1 and Cdk4 knockouts have hypoplasia of the pituitary gland [199-201]. Due to the overlapping activities of cell cycle regulators, multiple and triple loss of function mutations frequently result in more severe abnormalities [44, 199, 202-205]. Triple knockouts of Cdk2, Cdk4, and Cdk6, for example, die around E14.5, emphasising Cdk1's importance in the cell cycle [206]. Because these pathways are so critical, there is a lot of functional overlap and compensation across cell cycle regulators. Cell cycle regulators, oncogenes,

and tumour suppressors are all being studied in pituitary adenomas [207, 208]. Although certain familial variants of pituitary adenomas exist [18, 209], the majority of pituitary adenomas are benign and random. Mutations in menin (MEN1) or cyclin-dependent kinase inhibitor 1B (p27, MEN4) induce multiple endocrine neoplasia, Carney Complex is caused by mutations in protein kinase A regulatory subunit-1-alpha, PRKAR1A, and aryl hydrocarbon receptor interacting protein is caused by mutations in PRKAR1A. (AIP). The therapeutic potential of medicines that impact cell cycle regulators, such as histone deacylase inhibitors (HDACs) that disrupt the p53, p21 DNA-damage pathway [187, 210], is a hot topic of research.

Vascularization and the hypophyseal portal system

The development of the hypophyseal portal system is required for normal pituitary function. Although the phases in anatomical development have been documented using India ink, fluorescent gelatin, and immunostaining for markers such as platelet endothelial cell adhesion molecule, the molecular processes that control vascular growth are mostly understood [15, 139, 211]. Furthermore, it is unclear whether the invasion of the vasculature has a direct function in pituitary differentiation stimulation. VEGF and FGF are two of the most well-studied angiogenic and anti-angiogenic factors expressed in the normal pituitary gland [212]. VEGFA is produced at the right moment to aid in the vascularization of the pars distalis. At e15.5 in the rat, expression corresponds with portal vessel penetration into the pars distalis and association with the secondary capillary plexus [211]. In the pars distalis, VEGFA expression can be seen in folliculostellate cells and certain hormone-positive cells. The pars distalis is more vascularized than the pars intermedia in most cases. Reduced expression of the differentiation markers MSH and prohormone convertase 2 and enhanced lobe development are caused by ectopic expression of VEGFA in the pars intermedia [213]. Does the pars distalis' vascularization alter its differentiation? In mice prone to multiple endocrine neoplasia, treatment with an anti-VEGFA antibody lowers pituitary growth and serum prolactin levels [214]. Radiologic investigations reveal that in certain infants with hypopituitarism, the development of the hypophyseal arteries and portal system may be aberrant, although it is unclear whether this is the source or the effect [215]. Prop1 mutant pituitaries express VEGFA but have inadequate vascularization, failed differentiation, and increased apoptosis [139], indicating that VEGFA expression is insufficient for normal angiogenesis. More study is needed to figure out the processes that control proper vascularization and how vascularization affects pituitary differentiation.

2. CONCLUSION

We will surely increase our understanding of pituitary development by utilising new technologies and varied model systems. On a genome-wide scale, next-generation sequencing and bioinformatics make it possible to track developmental and cell-specific changes in gene expression and chromatin accessibility. At various embryonic stages, zebrafish allows for the enhancement and suppression of gene expression [216]. Tissue transplantation is possible in the chick and frog throughout development [217-219]. The mouse is a master of genetic engineering, and it has lately made advancements in the manipulation of stem cells to develop into hormone-producing cells [183]. Finally, human patients always recognise the relevant genes.

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