The Pituitary

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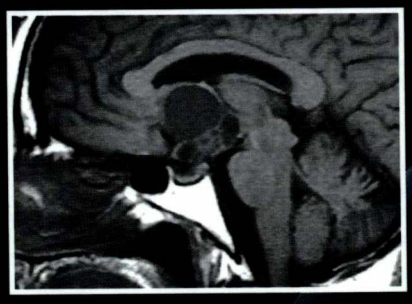

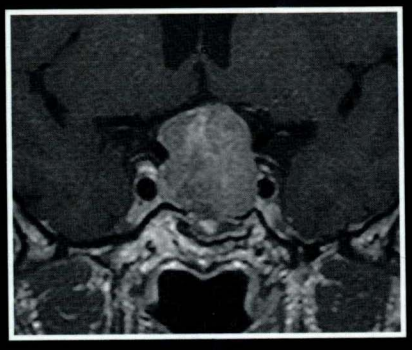

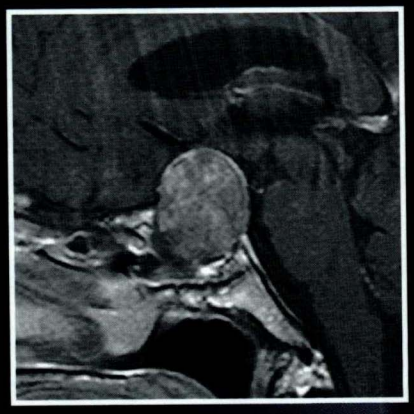

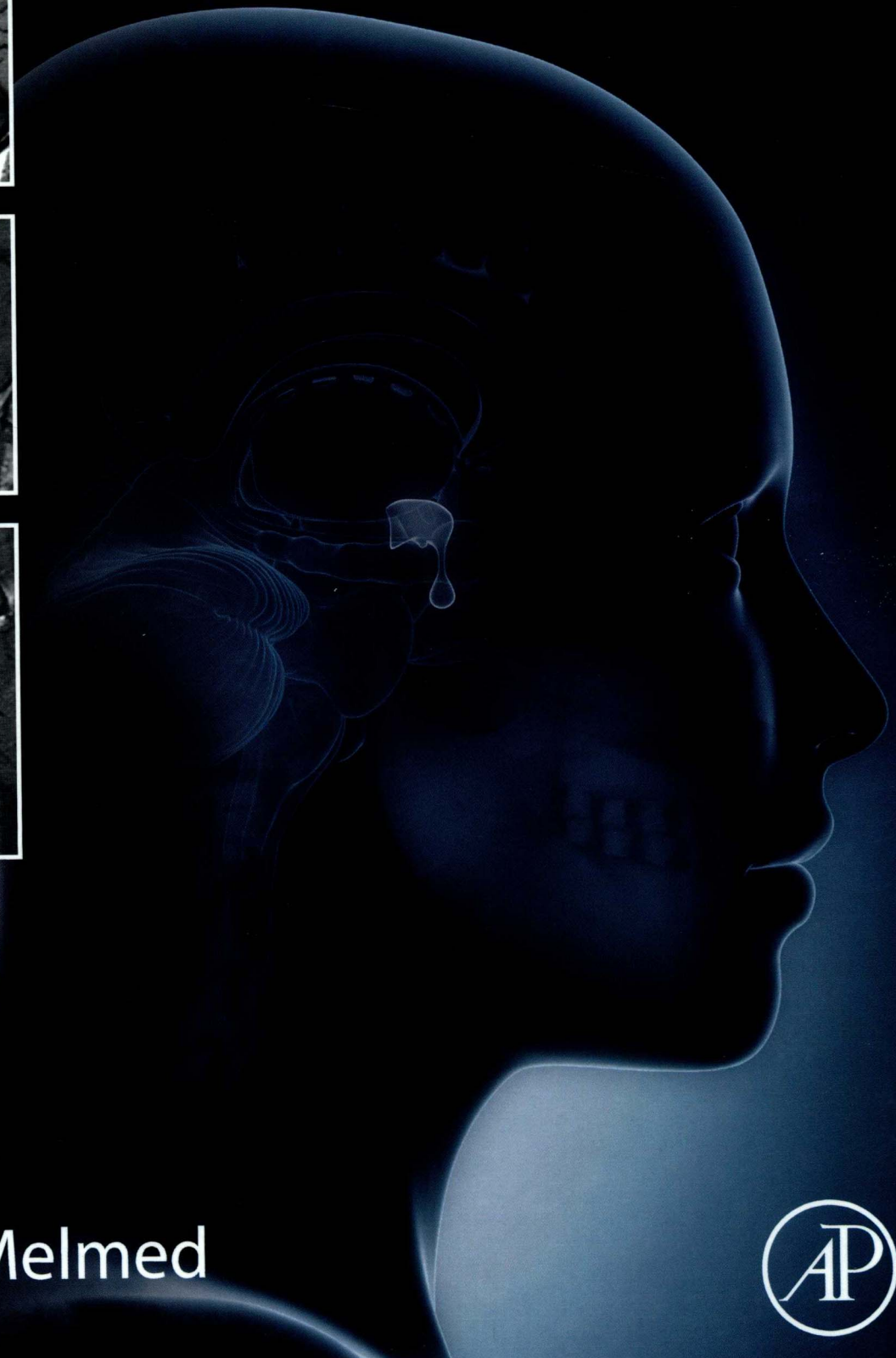

Shlomo Melmed

THE PITUITARY

FOURTH EDITION

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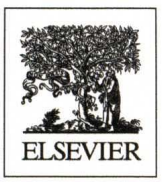

ACADEMIC PRESS

An imprint of Elsevier

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Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-804169-7

Publisher: Mica Haley
Acquisition Editor: Tari Broderick
Editorial Project Manager: Joslyn Chaiprasert-Paguio
Production Project Manager: Julia Haynes
Designer: Matt Limbert

Typeset by MPS Limited, Chennai, India

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Dedication

Dedicated to my wife Ilana, children, and grandchildren, in appreciation of their devoted support and continued inspiration.

In appreciation of the superb expertise and professionalism of my scholarly colleagues who contributed to this text.

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Preface

The fourth edition of *The Pituitary* follows three widely read prior volumes published in 1995, 2002, and 2011. This textbook continues the tradition of a cogent blend of basic science and clinical medicine which was the successful hallmark of prior editions. The comprehensive text written by expert pituitary scholars is devoted to the pathogenesis, diagnosis, and treatment of pituitary disorders. The new fourth edition is extensively revised to reflect new knowledge derived from advances in genomics, molecular and cell biology, biochemistry, diagnostics, and therapeutics as they apply to the pituitary gland. Notably, new chapters devoted to genetics of pituitary tumor syndromes, atypical adenomas, and psychiatric dysfunction related to pituitary disease have been added to complement a comprehensive updated description of pituitary physiology, as well as management options for patients harboring pituitary tumors or exhibiting features of pituitary failure.

The wide spectrum of clinical disorders emanating from dysfunction of the "master gland" is described in detail, as is the fundamental science underlying pituitary dysfunction. Descriptions of mechanisms for disease pathogenesis provide the reader with an in-depth understanding of both subcellular and extrinsic mechanisms subserving normal and disordered pituitary hormone secretion and action.

I am especially indebted to my erudite expert colleagues for their creative scholarly contributions and dedicated efforts in compiling this extensive body of knowledge for students, trainees, physicians, and scientists geared to understanding pituitary function and caring for patients with pituitary disorders. Our desire is to continue to provide medical and doctoral students, clinical and basic endocrinology trainees, endocrinologists, internists, pediatricians, gynecologists, and neurosurgeons with a comprehensive yet integrated text devoted to the science and art of pituitary medicine.

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Jacques Drouin

INTRODUCTION

The pituitary gland has a relatively simple organization despite its central role as *chef d'orchestre* of the endocrine system. Indeed, the glandular portion of the pituitary, comprised of the anterior and intermediate lobes, contains six secretory cell types, each dedicated to the production of a different hormone. Long thought to be a random patchwork of cells, we are just now discovering that pituitary cells are organized in three-dimensional structures and that the tissue develops following a precise stepwise plan. As for most tissues and organs, numerous signaling pathways are involved in pituitary organogenesis but it is mostly the discovery of regulatory transcription factors that has provided insight into mechanisms of pituitary development. Genetic analyses of the genes encoding these transcription factors have defined mechanisms for the formation of Rathke's pouch, the pituitary anlage, and for expansion and differentiation of this simple epithelium into a complex network of endocrine cells that produce hormones while integrating complex inputs from the hypothalamus and bloodstream. The understanding of normal developmental processes provides a novel insight into mechanisms of pathogenesis: e.g., critical regulators of pituitary cell differentiation become the cause of hormone deficiencies when their genes carry mutations. This chapter surveys current notions of pituitary development highlighting the impact of this knowledge on understanding pituitary pathologies as well as identifying the challenges and gaps for the future.

THE PITUITARY GLAND

The pituitary gland was ascribed various roles by anatomists over the centuries, including the source of phlegm that drained from the brain to the nose or the seat of the soul. It was at the beginning of the 20th century that its endocrine functions became recognized [1] and thereafter the various hormones produced by the pituitary were characterized, isolated and their structure determined. The major role of the hypothalamus in the control of pituitary function was recognized by Harris in the mid-20th century and that marked the beginning of the new discipline of neuroendocrinology [2]. The adult pituitary is linked to the hypothalamus through the pituitary stalk that harbors a specialized portal system through which hypophysiotrophic hypothalamic hormones directly reach their pituitary cell targets [3,4]. The adult pituitary is composed of three lobes, the anterior and intermediate lobes that have a common developmental origin from the ectoderm, and the posterior lobe that is an extension of the ventral diencephalon or hypothalamus. Whereas the intermediate pituitary is a relatively homogeneous tissue containing only melanotroph cells that produce α-melanotrophin (αMSH), the anterior lobe contains five different hormone-secreting lineages, including the corticotrophs that produce adrenocorticotrophin (ACTH), the gonadotrophs that produce the gonadotrophins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), the somatotrophs that produce growth hormone (GH), the lactotrophs that produce prolactin (PRL) and, finally, the thyrotrophs that produce thyroid-stimulating hormone (TSH). In addition, these tissues contain support cells, known as pituicytes or folliculostellate cells. The neural or posterior lobe of the pituitary is largely constituted of axonal projections from the hypothalamus that secrete arginine vasopressin and oxytocin (OT) as well as support cells. The intermediate lobe is present in many species, in particular in rodents, mice and rats, that have been used extensively to study pituitary development and function, but it regresses in humans at about the 15th week of gestation: it is thus

The Pituitary. DOI: http://dx.doi.org/10.1016/B978-0-12-804169-7.00001-5

absent from the adult human pituitary gland. In view of the critical importance of the intermediate lobe in embryonic development, it is possible that the tissue is maintained in the developing human embryo for this very reason. Most of our recent insight into the mechanisms of pituitary development has come from studies in mice: the review of our current knowledge presented in this chapter will therefore primarily focus on mouse development with references to other species (including humans) when significant differences are known or in cases of direct clinical relevance.

FORMATION OF RATHKE'S POUCH

The glandular or endocrine part of the pituitary gland derives from the most anterior segment of the surface ectoderm. It ultimately comprises the anterior and intermediate lobes of the pituitary. This was shown using chick-quail chimeras [5,6]. It is thus the most anterior portion of the midline surface ectoderm, the anterior neural ridge, which harbors the presumptive pituitary. Interestingly, fate-mapping studies also indicated that the adjoining neural territory will form the ventral diencephalon and hypothalamus. As head development is initiated and the neuroepithelium expands to form the brain, the anterior neural ridge is displaced ventrally and eventually occupies the lower facial and oral area. It is thus the midline portion of the oral ectoderm that invaginates to become the pituitary anlage, Rathke's pouch. This invagination does not form through an active process but it rather appears to result from sustained contact between neuroepithelium and oral ectoderm at the time when derivatives of prechordal mesoderm and neural crest invade the space between neuroepithelium and surface ectoderm and thus separate these tissue layers everywhere except in the midline at the pouch level. Rathke's pouch is thus a simple epithelium that is a few cells thick extending at the back of the oral cavity towards the developing diencephalon, with which it maintains intimate contact. This contact is essential for proper pouch and pituitary development since its rupture either physically [7–10] or through genetic manipulations [11,12] leads to aborted pituitary development. Indeed, a number of transcription factors expressed in diencephalon and infundibulum, but not in the pituitary itself, such as Nkx2.1 [11,13], Sox3 [14], and Lhx2 [12], are required for proper diencephalon development and secondarily affect pituitary formation. In humans, *SOX3* mutations have been associated with hypopituitarism [14]. Collectively, these data have supported the importance of signal exchange between diencephalon and forming pituitary [15] for proper development of both tissues.

Rathke's pouch rapidly forms a closed gland through disruption of its link with the oral ectoderm. This occurs through apoptosis of the intermediate epithelial tissue [16]. The oral ectoderm and Rathke's pouch are marked by expression of transcription factors that are essential for early pouch development (Fig. 1.1). The earliest factors are the pituitary homeobox (Pitx, Ptx) factors, Pitx1 and Pitx2 [17,18]. Indeed, these two related transcription factors are coexpressed throughout the oral ectoderm and their combined inactivation results in blockade of development at the early pouch stage [16]. The double mouse mutant $Pitx1^{-/-}Pitx2^{-/-}$ exhibits delayed and incomplete disruption of tissues between developing pituitary and oral ectoderm, and pituitary development does not appear to be able to progress beyond this stage. The single $Pitx2^{-/-}$ mutant is somewhat less affected, reaching the late pouch stage [19–21]. The $Pitx1^{-/-}$ mutant has relatively normal pituitary organogenesis, except for underrepresentation of the gonadotroph and thyrotroph lineages [22] that express higher levels of Pitx1 protein in the adult [23]. The two Pitx factors thus have partly redundant roles in early pituitary development with Pitx2 having predominant and unique functions in organogenesis.

Another pair of homeodomain transcription factors, the Lim-homeo factors Lhx3 and Lhx4, are also expressed in Rathke's pouch after Pitx1 and Pitx2. The expression of Lhx3 and Lhx4 is in fact dependent on Pitx factors, and thus, the Pitx pair of factors may be considered to be at the top of a regulatory cascade for pituitary development. Interestingly, the double $Lhx3^{-/-}Lhx4^{-/-}$ mutant mice pituitary exhibits blocked development at the early pouch stage; it is thus a phenocopy of the double *Pitx1/2* mutant [24]. The single *Lhx3* and *Lhx4* mutants have less-pronounced phenotypes, indicating that the actions of the two Lhx factors are also partly redundant with each other [25]. The phenocopy of the $Pitx1^{-/-}Pitx2^{-/-}$, and $Lhx3^{-/-}/Lhx4^{-/-}$ pituitary phenotypes clearly suggests that many of the actions of the Pitx factors are mediated through the Lhx3/4 factors. Consistent with these mouse studies, mutations in the *LHX3* and *LHX4* genes have been associated with combined pituitary hormone deficiency (CPHD), together with neck and/or skull malformations [26].

Rathke's pouch is also marked by expression of the paired-like homeodomain factor Hesx1 (also known as Rpx). This factor has a complex pattern of expression in the early prechordal area, but its expression becomes restricted to the ventral diencephalon and Rathke's pouch by e9.5 [27,28]. It thus marks the two sides of the developing neuroendocrine hypothalamo-pituitary system [28,29]. Pituitary *Hesx1* expression is transient and is extinguished by about

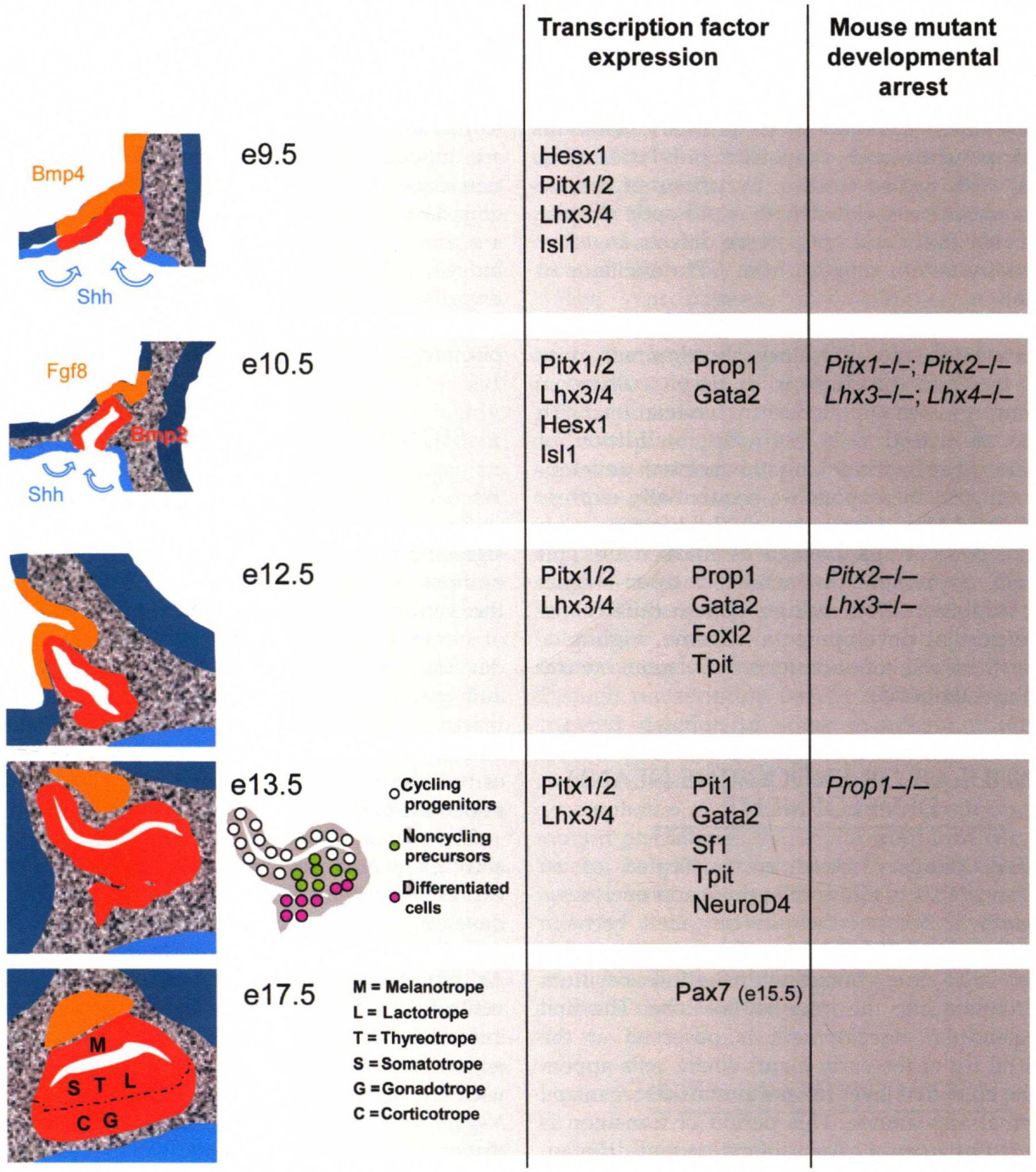

FIGURE 1.1 Development of the pituitary gland in mouse. Critical steps, signaling molecules, and transcription factors for pituitary development are highlighted on drawings representing the developing pituitary or Rathke's pouch (red) from e9.5 to e17.5 of mouse embryonic development. At e9.5 and e10.5, the ventral diencephalon sequentially expresses Bmp4 and Fgf8 that are critical for Rathke's pouch development; also, sonic hedgehog (Shh) expressed throughout the oral ectoderm, but excluded from Rathke's pouch, is important for pituitary formation. The expression of critical transcription factors for either pituitary organogenesis or cell differentiation is listed in the middle column whereas the consequence of their gene inactivation is listed on the left. The position of the various mouse genotypes along the developmental time sequence indicates the stage at which pituitary development is interrupted by these mutations.

e12.5 following a pattern that is complementary to the appearance of Prop1 which antagonizes Hesx1 [15,30,31]. Inactivation of the mouse *Hesx1* gene results in complex brain, optic and olfactory developmental defects; pituitary development is also perturbed, ranging from complete absence to multiple invaginations and nascent glands [32]. *Hesx1* thus appears to be involved in restriction of the neuroepithelium–ectoderm contact at the midline where Rathke's pouch is normally induced. This restriction/induction may be mediated through FGF10 since its expression is extended rostrally in *Hesx1*$^{-/-}$ mutants [31].

Hesx1 is a transcriptional repressor that recruits the Groucho-related corepressor Tle1 [31]. Other Tle-related proteins are expressed during pituitary development and interestingly, inactivation of *Aes* that is transiently expressed in the pituitary results in bifurcated pouches and dysplastic pituitaries [33]. Consistent with mouse studies, mutations of human *HESX1* have been associated with septo-optic dysplasias that cause brain and optic nerve defects, together with hypopituitarism ranging from GH deficiency to CPHD [26].

A striking demonstration of the importance of tissue interactions for pituitary development was provided by the reproduction in tissue culture of self-forming pituitary pouches in association with aggregates of neural cells [34]. Upon addition of appropriate signals mimicking the normal developmental sequence, these pouches sequentially express Pitx1 followed by Lhx3; terminal differentiation toward the corticotroph lineage as marked by Tpit and ACTH expression, is achieved upon Notch signaling inhibition. This culture system thus reproduces the normal developmental scheme, highlighting the critical role of interactions between neural and surface ectoderms.

GLANDULAR OR ENDOCRINE GLAND DEVELOPMENT

The early pituitary gland is constituted of an epithelial layer that is a few cells thick and encloses a lumen that will become the pituitary cleft between intermediate and anterior lobes. The portion of this pouch that is in close contact with the infundibulum will differentiate into the intermediate lobe. The first sign of glandular development is observed at the ventrorostral tip of the early gland where cells appear to leave the epithelial layer to take a more disorganized mesenchymal appearance. This period of transition is accompanied by intense cell proliferation and differentiated cells appear at the same time, as discussed below. This process is similar to epithelium–mesenchyme transition (EMT) and it appears to be dependent on the homeodomain transcription factor, Prophet-of-Pit (Prop1). Prop1 is transiently expressed in the e10.5–e14.5 developing pituitary [35] and all adult pituitary cells derive from cells that have expressed Prop1 [36]. The *Prop1* mutation prevents EMT and exhibits extensive expansion of the epithelial pituitary that becomes convoluted with an extended lumen [37,38]. At early stages, this mutant gland appears to be larger than normal but it then decreases in size through cell loss by apoptosis [38,39]. The *Prop1*$^{-/-}$ mutant is not entirely deficient in EMT and anterior lobe development eventually proceeds. However, Prop1 is also required for activation of the *Pit1* transcription factor gene, as indicated by its name [35,40], which is itself required for differentiation of the somatotroph, lactotroph, and thyrotroph lineages. Hence, *Prop1* mutants are deficient in these lineages [35,40,41] but the mutation does not prevent corticotroph, melanotroph, or gonadotroph differentiation. The *Prop1* mutant mice are thus dwarfed because of their deficit in GH and, indeed, *PROP1* mutations have been associated with dwarfism and CPHD in humans [42]. With age, patients with PROP1 mutations often develop more extensive pituitary hormone deficiencies [43,44].

SIGNALS CONTROLLING PITUITARY DEVELOPMENT

One of the early evidences for asymmetry and signaling at the onset of pituitary-hypothalamic development is the expression of BMP4 in the region of the ventral diencephalon that is overlying the area of stomodeal oral ectoderm where Rathke's pouch will develop (Fig. 1.1). This expression is present at e8.5, and by around e10.5 it is replaced by Fgf8. Although inactivation of the BMP4 gene is early-lethal, analysis of a few surviving embryos at e9.5 suggested a failure of ectoderm thickening and initiation of Rathke's pouch development [13].

The early phases of pituitary development are accompanied by complex and dynamic patterns of expression for many signaling molecules involved in development and organogenesis [45,46]. The BMPs are actually a good illustration of this complex interplay. As noted above, early expression of BMP4 in the ventral diencephalon appears to be important for induction of the ectodermal pituitary anlage and experiments designed to further test this role have used transgenic overexpression of the BMP antagonist *Noggin* in the oral ectoderm, including Rathke's pouch, driven by the *Pitx1* promoter [45]. This blockade of BMP signaling led to arrested pituitary development at the pouch stage, without much cell differentiation except for a few corticotrophs. This phenotype is similar to that of *Pitx2*−/− and *Lhx3*−/− mice [25]. BMP4 signaling may thus regulate *Lhx3* expression or even the upstream Pitx factors, but this experiment tested the importance of continued BMP signaling more than its initial action as assessed in *BMP4*$^{-/-}$ embryos. Inactivation of the *Noggin* gene itself supported the critical role of BMPs in pituitary induction [47]. The early expression of BMP4 in ventral diencephalon is thus on the dorsal side of the developing pouch; in parallel with its extinction, the related BMP2 is expressed on the ventral side of

the developing pituitary and in the surrounding mesenchyme (around e10.5). It has been proposed that ventral BMP2 may promote differentiation of so-called "ventral" lineages such as corticotrophs and this has been supported through transgenic gain-of-function experiments [45]. However, the use of organ culture systems to test the role of BMP2/4 in differentiation rather led to the conclusion that BMP signaling is repressing the corticotroph fate [46]. This latter finding is actually in agreement with a repressor effect of BMP signaling on proopiomelanocortin (POMC) gene transcription [48].

Whereas the highly dynamic pattern of expression of these two related BMPs, BMP4, and BMP2, and the consequences of their manipulation are highly suggestive of important roles in pituitary development and cell differentiation, the same rapid changes in expression and seemingly contradictory experimental results also hint that BMPs have multiple effects depending on the timing of action and target cells. We are thus still lacking a coherent and complete picture for the multiple actions of these signaling molecules.

Another important signaling molecule for pituitary development is Sonic Hedgehog (Shh). Indeed, Shh is expressed in the ventral diencephalon and fairly widely in the oral ectoderm, but it is specifically excluded from the region of the oral ectoderm that becomes Rathke's pouch [49]. In contrast, Shh target genes such as *Patched1* are expressed in the developing pituitary, indicating that it is responsive to Shh signaling. These patterns are thus suggestive of an important role for the Shh pathway in pituitary induction. However, the *Shh*−/− mutant mouse was not extremely informative in precisely defining this role since Shh is critical for formation of midline structures and the bulk of these structures are affected in the *Shh* mutants [50]. Nonetheless, the importance of Shh signaling for early pituitary development is also supported by mouse mutants for the Gli zinc finger transcription factors that mediate the effects of the Shh pathway. Indeed, the double mouse mutant *Gli1*−/−; *Gli2*−/− fails to develop the pituitary whereas the single *Gli2*−/− mutant exhibits variable defects in pituitary formation [51]. Furthermore, overexpression of the Shh antagonist HIP blocked Rathke's pouch development [49].

As indicated above, the early expression of BMP4 in the ventral diencephalon is replaced from about e10.5 by FGF8 and FGF10 and the expression of these growth factors is maintained throughout the active phase of pituitary expansion (e11.5–e14.5). The FGFs appear to be important for survival of early pituitary cells since mutant mice for FGF10 or for its receptor FGFR2IIIb initially form Rathke's pouch and then it regresses because of widespread apoptosis [52,53]. In agreement with this, transgenic overexpression of FGF8 led to pituitary hyperplasia [45]; further, these experiments suggested that FGF8 stimulates *Lhx3* expression. This idea was also supported by analyses of the *Nkx2.1* mutant mice that fail to express FGF8 in diencephalon and pituitary Lhx3 [13]. It is thus possible that the FGF effect on proliferation and/or maintenance of early pituitary cells is mediated through induction of *Lhx3*.

The Wnt pathway also appears important for proliferation and/or survival of pituitary cells, but again the large number of Wnt molecules and their receptors expressed in and around the developing pituitary make it difficult to develop a coherent and complete picture of their role. Canonical Wnt signaling involves beta-catenin and targeted deletion of this gene using a *Pitx1-Cre* transgene resulted in a small pituitary, together with deficient *Pit1* expression and Pit1-dependent lineages [30]. It was suggested that beta-catenin is acting directly on the *Pit1* gene to regulate its expression through interaction with the upstream factor Prop1. Further, the canonical Wnt/beta-catenin pathway is acting through transcription factors related to Lef/TCF and targeted deletion of some members of this family altered pituitary development [30,32]. The involvement of these factors, such as TCF4, in both ventral diencephalon and Rathke's pouch produces complex mutant phenotypes that result from intrinsic pituitary defects as well as from defective pituitary induction by overlying diencephalon [54]. Finally, the Notch pathway is also active in early pituitary development and recent work has suggested that its major involvement may be in pituitary progenitor cells; hence, this aspect is discussed below.

CELL DIFFERENTIATION

Cell differentiation starts early during pituitary development, as assessed by expression of the hormone genes characteristic of each lineage [55]. The hormone-coding genes have also served as a starting point to identify cell-autonomous transcription factors that are involved in their own expression but also in lineage-restricted functions and differentiation. Hence, most of what we know about pituitary cell differentiation relates to the terminal stages of differentiation for each lineage and involves cell-restricted transcription factors that are responsible for terminal differentiation. The transcription factors that mark terminal differentiation are usually expressed 12–24 hours before the hormone gene itself and they have so far not been useful in directly identifying or studying multivalent progenitors of the

developing or adult pituitary. However, the analysis of their loss-of-function mutations has provided considerable insight into the relationships between different lineages. Investigation of the *Jackson* and *Snell* dwarf mice that carry *Pit1* mutations thus revealed the requirement for this Pou-homeo transcription factor for differentiation of three lineages, the somatotrophs, lactotrophs, and thyrotrophs [56,57]. Analyses of *Pit1* mutants in both mice and humans thus supported the model of a common precursor for these three lineages [58].

Similarly, the *Tpit*−/− mutant mice revealed an antagonistic relationship between corticotrophs/melanotrophs and gonadotrophs, suggesting that these lineages share a common precursor [59]. Taken collectively, the data on these mutants have suggested a binary model of pituitary cell differentiation (Fig. 1.2). Although consistent with current data, this model has not been ascertained more directly, e.g., through characterization of the putative common progenitors. Nonetheless, it provides a useful framework for ongoing

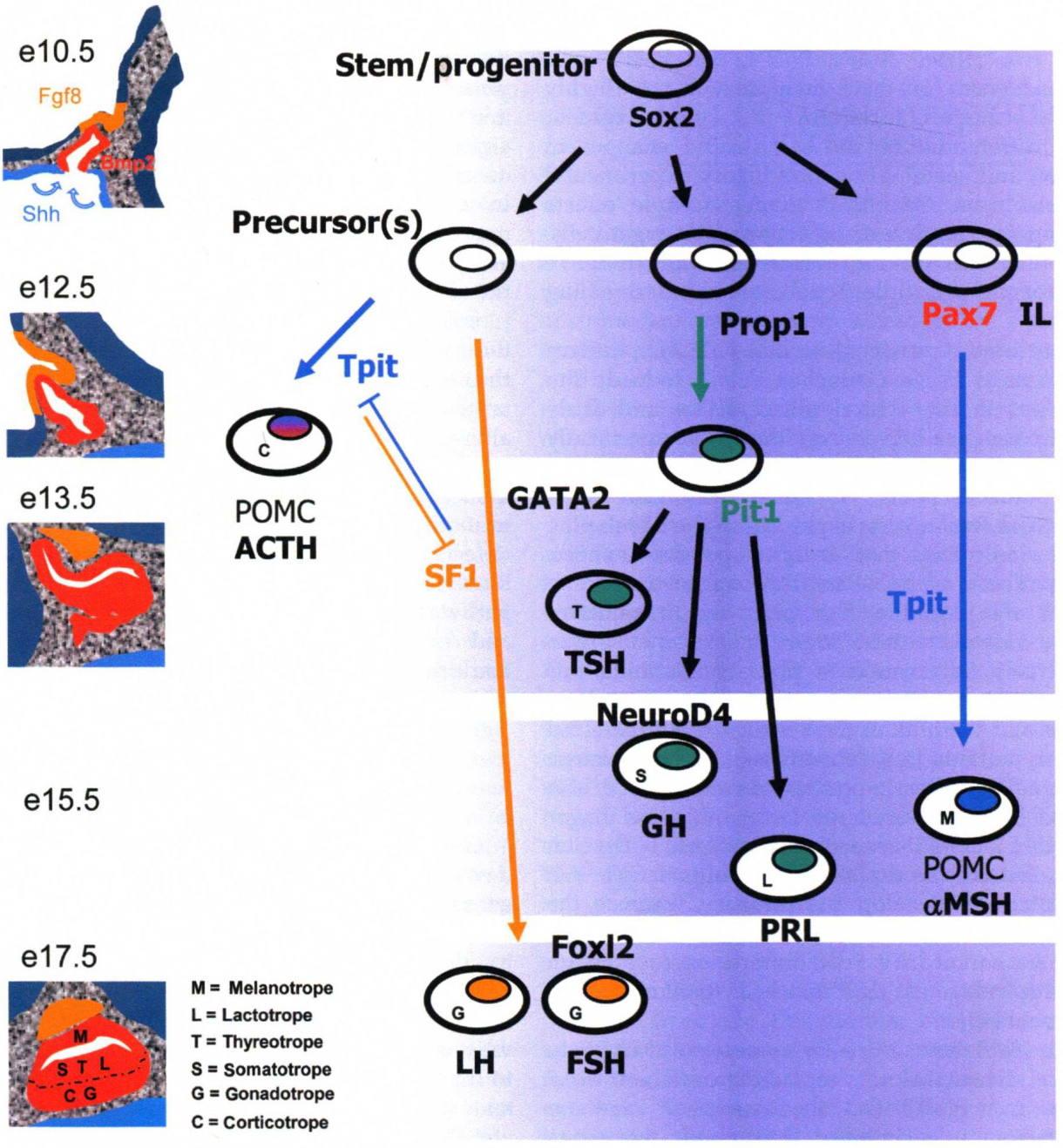

FIGURE 1.2 Differentiation of pituitary cells. A scheme for sequential differentiation of cells in the developing pituitary was derived from studies of mutants for the critical cell-restricted regulators of differentiation. Putative pituitary stem and progenitor cells are marked by expression of Sox2. While critical regulators of terminal differentiation such as Tpit, SF1, Pit1, and Pax7 have been well characterized, regulators for the early commitment of putative precursors are still elusive. IL, intermediate lobe.