

Pituitary Stem/Progenitor Cells: Their Enigmatic Roles in Embryogenesis and Pituitary Neoplasia - A Review Article

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Abstract

Although the hypothalamus is the master regulator, it is appropriate terming the pituitary gland as the conductor of endocrine orchestra of the human body. The existence of pituitary stem cells in the adult pituitary gland is supported by such findings as postnatal proliferation, differentiation based on environmental alterations, and development of hormone-producing cells after specific lesions in the pituitary. Stem cell characteristics, including renewal, proliferation abilities, and the presence of stem cells markers, have been demonstrated in adult pituitary cells from mammals. Research into the capacity of "pituitary stem cells" to differentiate *in vitro* and *in vivo* will clarify the regulatory mechanisms of these cells. The characteristics of stem cells include self-renewal capacity, lack of specialization, and pluripotency with the ability to differentiate into different cell phenotypes. Adult pituitary cell lineages might have a pituitary stem cell role and the potential participation of these cells in pituitary tumorigenesis. Inevitably numerous questions remain to be resolved, and future challenges are enormous. Therefore, this review provides a comprehensive overview of the motivating recent developments in the pituitary stem cell exploration. The latest expansion in pituitary stem cell research may commence a stimulating period in the pituitary embryology and pathology.

Keywords: Adenohypophysis; Adenoma; β -catenin; β -catnc; Biomarker; Bmi-1; CD133; CDKN1C; Corticotropes; E-cadherin (Cdh1); EMA; Galectin-3; GFRa2 protein; Gonadotrophs; GPS cells (GFRa2/Prop1/stem cells); Kip2; Klf4; Jag1; Jag2; Lactotrophs Nanog; Nestin; Notch 2; Notch3; Oct-4; P57; Pax6; Pit1; Pituisphere; Pituitary; Pituitary stem/progenitor cells; Prop1; Psoriasis; S100; Sca-1; side population (SC-SP); Somatotropes; Sox2; Sox2+/E-cadherin+ stem cells; Sox-9; Stem cell; TCF3; Thyrotrophs; Tumour

Abbreviations: AP: Anterior Pituitary; Cscs: Cancer Stem Cells; ACTH: Adreno Corticotropic Hormone; ESCs: Embryonic Stem Cells; EGF: Epidermal Growth Factor; EMT: Epithelial-Mesenchymal Transition; FSC: Folliculostellate Cell; GDNF: Glial Cell Line-Derived Neurotrophic Factor; FSH/LH: Follicle-Stimulating Hormone/Luteinizing Hormone; PRL: Prolactin; MSH: Melanocyte Stimulating Hormone; Nscs: Neural Stem Cells; NTN: Neurturin; RP: Rathke's Pouch; GH: Growth Hormone; TSH: Thyroid Stimulating Hormone

Introduction

In this article recent advance on pre and postnatal stem cells, stem cells in adult life, transdifferentiation of anterior pituitary (AP) cells, folliculostellate cells (FSCs) and stemness markers and biomarkers of pituitary cytogenesis were reviewed. In each subtitle impact of the specific markers and cellular reactions of stem cells were addressed in the light of recent cellular and molecular researches.

Pre and postnatal stem cells

Pituitary gland plays an important role in such vital physiological processes as growth, reproduction, metabolism, and immune response. The adenohypophysis, the secretory anterior lobe of the gland, contains 5 different types of hormone-secreting cells: Lactotrophs (prolactin secreting cells), Somatotrophs (growth hormone secreting cells), Corticotrophs (adrenocorticotrophic hormone secreting cells), Gonadotrophs (follicle-stimulating hormone/luteinizing hormone secreting cells), and Thyrotrophs (thyroid stimulating hormone secreting cells) [1]. Pituitary gland of newborns already presents a full set of terminally differentiated hormone-producing cells [1,2]. Surprisingly, how these hormonal cells are formed or renewed during postnatal life remains largely unsolved [3]. However, postnatal gland

undergoes extensive remodeling during one's lifetime. Soon after birth, adenohypophysis enters a phase of growth that results in a dramatic increase in the size of the gland [4]. Adult pituitary gland has the ability to adapt its cellular composition in response to changing physiological conditions, and this ability is thought to be mediated via the hypothalamus. For instance, the total number of GH-secreting cells doubles during puberty, where as the number of PRL-secreting cells expands and contracts several-fold during pregnancy, lactation, and weaning [4]. The pituitary gland also appears to repopulate cells after tissue loss [5,6]. Proposed mechanisms include mitoses of differentiated cells, transdifferentiation between phenotypes, and the differentiation of pituitary stem cells [7]. However, there is no conclusive *in vivo* evidence that any of these processes actually occur. The existence of pituitary stem cells in the adult pituitary gland is supported by such findings as postnatal proliferation, differentiation based on environmental alterations, and development of hormone-producing cells after specific lesions in the pituitary [5,6]. Stem cell characteristics, including renewal, proliferation abilities, and the presence of stem cells markers, have been demonstrated in adult pituitary cells of mammals [6]. However, the proliferation ability observed so far is limited, and the potential of differentiation into hormone-secreting cells remains to be conclusively proven [6,8] (Figure 1).

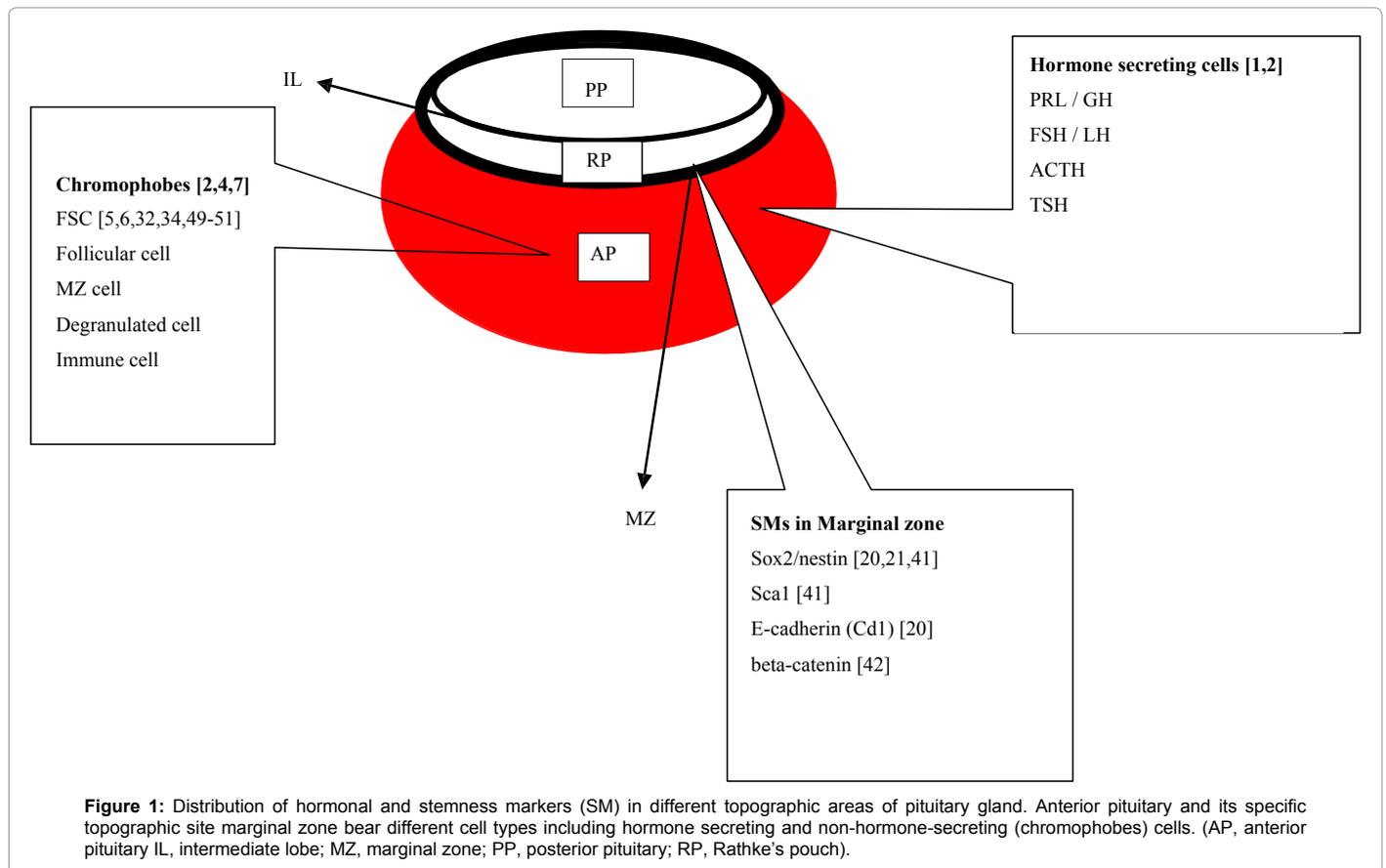
Pituitary stem cells only come into play under more extreme conditions such as injury (so-called facultative stem cells). From the currently available data, embryonic developmental programs seem to be

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re-used during postnatal stem cell differentiation [3]. Stem cell markers have also been detected in animal models of pituitary tumorigenesis [8]. However a direct connection has not been demonstrated so far. Upcoming research about the capacity of “pituitary stem cells” to differentiate *in vitro* and *in vivo* will clarify the mechanisms for regulation of these cells. Recent stem cell researches shed light on molecular and physiologic mechanisms which most likely to be used in management of pituitary adenomas and the implantation of pituitary stem cells for hormonal deficiencies [9]. Alternatively stem cells may offer life-long cures for genetically, environmentally and/or surgically induced pituitary deficiencies [3].

Stem cells in adult life

Recent data supports the role of stem cells in the repair and plasticity of different organs in the human body such as the heart and brain [10,11,12]. These specific cells in these organ systems have displayed the fundamental characteristics of a stem cell. Among the characteristics include self-renewal capacity, lack of specialization, and pluripotency with the ability to differentiate into different cell phenotypes [3,6,11]. Stem cells possess multipotent differentiation capacity to generate the desired tissue cell types [11,13]. Initially stem cells give rise to daughter (progenitor) cells that proliferate to expand as a pool of transit-amplifying cells, which further perpetrate to precursor cells those of which differentiate and specialize to compensate pituitary cells [14,15]. Besides these cells characteristically form into sphere like structures and, in the example of neural stem cells (NSCs), are called neurospheres. In culture, the stem cells form colonies of undifferentiated, pluripotent cells that contain unique stem cell surface, cytoplasmic, and nuclear markers. Similar to these other organ systems, the plasticity of the

pituitary gland and its alterations during adult life may be secondary to the activity of adult stem cells present in the gland [5,16-22]. Stem cell markers such as Sox-2 [20], nestin [21], Sca-1 [21], and CD133 [23] have been identified in subpopulations of cells in the adult pituitary gland of animal models [23,24]. In addition, “pituispheres” have been generated *in vitro* in these models [17,19]. These findings support a potential role for pituitary stem cells in adult pituitary plasticity. It is clear that the proposed models are still hypothetical on many points, and will need further thorough investigation and experimental support. So far the distinctive problem is the topographic network of newborn cells in addition to their functional incorporation into the presented homo- and/or heterotypic cell networks [3]. Pituitary stem cells express several stemness markers (such as Sox2) and pituitary-embryonic factors (such as Prop1), and that they prominently occupy the marginal zone around the cleft, the residual lumen of the adenohipophysial primordium Rathke’s pouch (RP) [25]. Concisely pituitary stem cells, studies are only now beginning to address their role and participation, particularly in processes of postnatal pituitary maturation, repair and pathology [3] (Table 1).

Apart from hormone producing cells of adenohipophysis, there is a substantial cohort of cells that lack hormonal markers [2,4,7,23]. This group of cells with non-hormone-secreting properties are referred as chromophobes. They are non reactive with periodic acid-Schiff stain since they are devoid of secretory hormone containing granules. In the late sixties the pioneer experimental studies by Yoshimura et al. showed the chromophobes acting as pituitary stem cells [7,23]. In this study, chromophobes were purified from 1-year-old mice and transplanted in the hypophysiotrophic area of the hypothalamus after surgical resection of the animal’s own pituitary gland. The authors reported that

SMs in Embryonic Phase	
Marker	References
Oct-4	5,6,50,51
Sox2	5,6,50,51
Nanog	5,6,50,51
Wnt/ b-beta-catenin	69
Pax6	70-75
Lhx4	70-75
Prop1	25,70-75
Otx2	55,70-75
Notch2	70-75
Notch3	70-75,78
Non Sca1 high	70-75

SMs in Adult Pituitary	
Marker	References
CD133	22
Oct-4	22
Nanog	22
Nestin	22
Bmi-1	22
Jag1	25,41,76
Notch2/3	79
Hes1	25,41,76
Hey1	25,41,76
Pit-1	3,54,83
Prop1	54
P57	25
P27	25

Table 1: Distribution of stemness markers in embryonic and adult phases of pituitary gland. Various stemness markers in different phases of pituitary gland are depicted in pertinent references within the manuscript.

pituitary like structures formed via proliferation and differentiation of chromophobes into acidophils and basophils [7,23].

In a follow-up study by Otsuka et al., [26] chromophobes differentiated *in vitro* into mature acidophils and basophils after the addition of hypothalamic hormones. However, the authors were unable to demonstrate one of the fundamental characteristics of a stem cell: the capacity of one single cell to originate more than one lineage of cells. The failure to demonstrate pluripotency may be partially explained by the heterogeneity of the cell group classified as chromophobes. This group includes agranular cells such as folliculostellate cells [FSC], follicular cells, marginal zone cells, degranulated hormonal cells, and mesenchymal and immune cells [5] (Figure 1).

Agranular cells have the ability to differentiate into acidophils and basophils [7,23,26] supports the hypothesis that chromophobes might display stem cell characteristics [5]. However, only a small subpopulation of chromophobes actually displays these characteristics [5,6,7,23]. Therefore, the individual study of such cells as FS cells, follicular cells, or marginal cells represents the current trend in pituitary stem cell research in an attempt to identify this subpopulation [5,23].

The presence of minimal mitotic activity in occurrence of plurihormonal and null cell-type adenomas and in the hyperplastic pituitary gland support the hypothesis that pituitary stem cells are potential cellular source for pituitary adenomas [27]. Alterations in

the hormonal environment might be associated with changes in the normal pattern of growth/differentiation of these cells and therefore promote pituitary tumorigenesis.

The majority of the pituitary pathophysiology data have been obtained in animal models. The study of human pituitary tissue still presents several limitations, including lack of functional human cell lines in culture, the anatomic inaccessibility of the pituitary gland, unique murine tumor growth characteristics and paucity of reliable animal models, and [23,27]. For instance, the higher mitotic activity and expansion of murine pituitary tissue must be considered before the results are analyzed and extrapolated as a representation of the human pituitary gland [23,28]. However, animal studies have provided important information about pituitary physiology and the mechanisms of pituitary tumorigenesis. It is discussed which adult pituitary cell lineages might have a pituitary stem cell role and the potential participation of these cells in pituitary tumorigenesis. In addition, some researchers propose possible future clinical applications like the development of new treatment strategies for pituitary adenomas and hormone deficiencies [23,27].

Transdifferentiation of anterior pituitary (AP) cells

The majority of anterior pituitary is formed by chromophobes those of which have differentiation capacity into mature acidophils and basophils after the addition of hypothalamic hormones. This group includes agranular cells such as folliculostellate cells, follicular cells, marginal zone cells, degranulated hormonal cells, and mesenchymal and immune cells [6]. The heterogeneous ability of agranular cells to differentiate into acidophils and basophils [7,26] supports the hypothesis that chromophobes might display stem cell characteristics [6]. However only a small subpopulation of chromophobes actually display these characteristics [5,6,7]. Therefore, the individual studies of these cells such as folliculostellate cells, follicular cells, or marginal cells represent the current trend in pituitary stem cell research in an attempt to identify these subpopulations [29].

Folliculostellate cells (FSCs)

Ultrastructural features of follicular structures reveal elongate or stellate cells (folliculo-stellate cells) attached to each other via terminal bars at their apical surface and by desmosomes at their lateral cell membranes that form major parts of the adenohypophyseal parenchyma [30,31]. FSCs occupy an approximately central position within every acinus in the adult human gland. Electron microscopically, these specific cells are furnished with a small nucleus and inconspicuous nucleolus, numerous free cytoplasmic polyribosomes but scant rough endoplasmic reticulum (RER), small Golgi apparatus. Additionally there might be a few intermediate filaments, and/or glycogen particles. Immunohistochemically, they are immunoreactive for S-100 and for GFAP [32-34]. Unfortunately, these immunoreactivity patterns are not coexisting and are only temporary as related to phases of the FSC life cycle. Lately, it was found that these cells are also immunoreactive with EMA and galectin-3 [35,36].

Due to a wide variety of perplexing capacities of stem cells from hormone production to immune roles, coupled with morphologic variations some investigators supposed dual derivation of FSC: pituitary and hemopoetic (dendritic cells) [23,37]. In a detailed study in which electron microscopic and ultrastructural immunocytochemical analyses were used, it was well documented formation of follicles within the pituitary primordium with stubby villi filling most of small lumina were noticeable as early as 6 weeks of gestation [38]. Later (8-10 weeks

of gestation), the morphology of the follicles is not much different from that of what is seen in the adult gland. In the fetal gland the follicles may contain FSC possessing a few small secretory granules, fulfilling the criteria of endocrine differentiation, but not more differentiated forms [23,38].

Structural evolution of pituitary acinus is incessantly ongoing in distinctive developmental phases of antenatal and postnatal life [23,30]. The newborn adenohypophysis contains no cells immunoreactive for S-100 or GFAP. Soon after a number of GFAP-positive cells appear in the cleft area, within the small embryonic remnants of the Rathke's pouch. The late appearance of S-100 and GFAP immunoreactivities most likely results from the previously described mechanism [30]. Follicles are not static structures: new FSC are formed by glandular cells around single-cell necroses by forming terminal bars and desmosomes, in this manner isolating the debris [30]. Subsequently, they dismantle their endocrine machinery, taking up the non-endocrine phenotype of FSC. This process was interpreted to be ubiquitous as well as reversible [39]. This particular reversibility most probably may be explained as both becoming a progenitor null cell followed by differentiation to participate in tissue repair or in hyperplastic processes, and tumorigenesis [23,39].

As for extensive use of immunohistochemistry, EM, and immunoelectron microscopy enlightened the concept of inflexible one cell-one hormone, thus 5-cell-type model. Therefore, using of modern techniques and new horizons in understanding of new adenoma types and previously undisclosed cell types belonging to or resident in the human adenohypophysis [23,40]. So far, not only morphologic, *in vitro* biochemical, and genetic data but neoplastic potential make the small FSC more than just an equal member of the pituitary cell population: it emerges into a pluripotent pituitary-specific adult stem cell [23,39].

Stemness markers and biomarkers of pituitary cytogenesis

Numerous biomarkers of having different effects either in pituitary embryogenesis and tumor development are designated as stemness markers. This perplexing group consists of several constituents, i.e. nestin, Sca1, Sox2+/E-cadherin, S100 proteins, Prop-1, GFRA2, Oct-4, Bmi-1, CD133, beta-catenin, SOX2, Pax6, Notch2, Notch3, Pit1, p57 and cancer stem cells.

Nestin has been found expressed in some stem (Sox2+) cells *in situ* (marginal zone) and in culture (pituospheres) by a number of investigators [20,21,41] but not by others [42]. Certainly, nestin is not restricted to the pituitary stem cells but shows a heterogeneous expression pattern in the pituitary's non-hormonal cell population, including in some pericytes [5,6,43].

Sca1-(Stem Cell Antigen 1) another marker that seems contentious is Sca1, not or only modestly expressed in the stem cell-enriching side population (SC-SP) fraction [41] but immunodetected in pituospheres [20] and in a subpopulation of colony-forming cells [44]. However, the role of Sca1 expressivity in the pituitary and its tumors remains to be shown.

Sox2+/E-cadherin+ stem cells start to express Sox9, nestin and/or S100 as well as Prop1 during their transition to the progenitor phase, and subsequently loose expression of these markers before or during terminal differentiation to the hormonal cells. E-cadherin is a tumor suppressor gene [45,46] and a classical member of the cadherin superfamily. Cadherins act so structural cell glue, regulate signaling pathways that organize cell proliferation and motility which is fundamentally driven by the process of epithelial-mesenchymal

transition (EMT) [3]. Loss of E-cadherin function or expression has been implicated in cancer progression and metastasis [47]. Marginal cells facing the Rathke's cleft and hormone negative but S100+ cells within AP lobe strongly express E-cadherin (Cdh1)[20]. E-Cadherins promote coordinated actions to changing endocrine needs and conditions [48].

S100 proteins have been implicated in a variety of intracellular and extracellular functions [49]. S100 proteins are involved in regulation of transcription factors, Ca⁺⁺ homeostasis, protein phosphorylation, the dynamics of cytoskeleton constituents, cell growth and differentiation, enzyme activities, and the inflammatory response. S100A7 (psoriasin) and S100A15 have been found to act as cytokines in inflammation, particularly in autoimmune skin conditions such as psoriasis [49]. Follicle-stellate cells of pituitary display diverse nuclear and cytoplasmic S100 reactivity FSCs are presumed to be the analogs of brain glial cell lineage [5,6,50,51].

Prop1: Homeobox protein prophet of PIT-1 is a protein that in humans is encoded by the PROP1 gene [52]. PROP1 has both DNA-binding and transcriptional activation ability. Its expression leads to ontogenesis of pituitary gonadotropes, as well as somatotropes, lactotropes, and caudomedial thyrotropes. Inactivating mutations in PROP1 result in deficiencies of luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), prolactin (PRL), and thyroid-stimulating hormone (TSH) [52]. In pituitary genetic inactivation of Prop1 results in failure of embryonic progenitors to leave the dorsal proliferative region of RP for further differentiation and colonization of the developing AP [53]. One of the optional functions of Prop1 is playing a pivotal role for cells differentiating from the stem cell cohort into the differentiating zone of the gland. It is a compulsive marker for transition of stem cells from the in-gland Sox2+ cell clusters to the neighboring pituitary parenchyma [54].

GFRA2 protein is a glycosylphosphatidylinositol (GPI)-linked cell surface receptor. It is a part of the GDNF receptor family. Glial cell line-derived neurotrophic factor (GDNF) and neurturin (NTN) are two structurally related, potent neurotrophic factors that play key roles in the control of neuron survival and differentiation. They both bind the GFRA2 receptor [55].

Oct-4 (Octamer-binding transcription factor 4) is a homeodomain transcription factor of the POU family [56]. This protein is critically involved in the self-renewal of undifferentiated embryonic stem cells (ESC). It has often been used as a marker of stemness, as differentiated cells show reduced expression of this marker. Several studies suggest a role for Oct-4 in sustaining self-renewal capacity of adult somatic stem cells (i.e. stem cells from epithelium, bone marrow, liver, pituitary, etc.) [57]. Oct-4 has also been implicated as a marker of cancer stem cells (CSCs). Oct-4, Sox2, and Nanog, and Klf4 constitutes the pluripotency transcription-factor core of embryonic stem (ES) cells [5,6,50,51].

Bmi-1: The Polycomb group transcriptional repressor Bmi-1 was discovered as a common oncogene activated in lymphoma [58], specifically regulate HSCs [59] and neural stem cells [60]. Human pituitary adenomas also show Bmi-1 overexpression in about half of the cases so the stem cell marker Bmi-1 could be included in pituitary neoplasia [61].

CD133 originally known as AC133 [62]. CD133 is a glycoprotein also known in humans and rodents as Prominent 1 (PROM1) [63]. It is a member of pentaspan transmembrane glycoproteins (5-transmembrane, 5-TM), which specifically localize to cellular protrusions. CD133 is expressed in hematopoietic stem cells [64],

endothelial progenitor cells [65], glioblastoma, neuronal and glial stem cells [66], various pediatric brain tumors [66] as well as adult kidney, mammary glands, trachea, salivary glands, placenta, digestive tract, testes, and some other cell types [67]. After analyzing isolated stem/progenitor-like cells from pituitary adenoma by the sphere method, the presence of expression of neuronal progenitor markers including CD133 supported CD133+ cells existence in pituitary adenomas [68].

Beta-catenin (or β -catenin) is a dual function protein, regulating the coordination of cell-cell adhesion and gene transcription. Its role in stem cell renewal is being one of the most important results of Wnt signaling and the elevated level of beta-catenin in certain cell types is the maintenance of pluripotency [69]. In other cell types and developmental stages, β -catenin may promote differentiation, especially towards mesodermal cell lineages. β -catenin constitutes an integral constituent of the classic cadherin complexes. Widespread membranous β -catenin is dispersed in AP extensively. It is intensely expressed in somatotropes as well as marginal zone [42]. β -catenin is not only accumulated in the nucleus and cytosol (nucleocytoplasmic beta-catenin or β -catnc) only in small clusters of cells during the pre-tumoral stage of late-embryonic and early-postnatal life, but in the subsequent phases virtually all tumor cells exhibits accumulation of β -catenin in the nucleus, cytoplasm or both [3].

Sox2: SRY (sex determining region Y)-box 2, also known as Sox2, is a transcription factor that is essential for maintaining self-renewal, or pluripotency, of undifferentiated embryonic stem cells. Co-expression of nestin and Sox2+ in some stem cells (marginal zone) and in culture (pituispheres) was documented [20,21,41]. Prop1 is probably downregulated before stem cell differentiation enhances [3]. Sox2 expression and side population (SP) phenotype assessed stem cell population is more profuse throughout the postnatal first week than in the next phases. Thereby higher proliferation rate and quicker differentiation capacity show an activated status as obtained from pituisphere cultures [48].

Pax6 serves as a regulator in the coordination and pattern formation required for differentiation and proliferation to successfully take place, ensuring that the processes of neurogenesis and oculogenesis are carried out successfully. As a transcription factor, Pax6 acts at the molecular level in the signaling and formation of the central nervous system. Pax6 as being a member of transcriptional regulators and signaling factors those have critical roles in early embryogenesis of the pituitary, (viz. Hesx1, Lhx4, Prop1, Pax6, Otx2, and specific Notch pathway components). Pax6 is also climaxes its expressivity in the non-Scalhigh SP [70-75].

Notch 2 a member of the notch family. Notch family members play a role in a variety of developmental processes by controlling cell fate decisions. Notch signaling pathway has been identified in the embryonic periluminal progenitor zone [73,75] as well as in the adult pituitary SC-SP (in particular Jag1, Notch2, Notch3, Hes1 and Hey1) [25,41,76]. Adult pituitary cells present prominent expression of several transcriptional, signaling and growth-regulatory factors previously thought to be restricted to the pituitary embryonic phase (such as Hesx1, Lhx4, Pax6, Prop1, Otx2, Notch2, Notch3 [25,41]. Notch receptors Notch1 and Notch2, and ligands Jag1 and Jag2 are not co localized with hormones but with S100 (except for Jag2) in about half of the (S100+) marginal cells [77].

Notch 3 gene encodes the third discovered human homologue of the *Drosophila melanogaster* type I membrane protein notch. Transgenically activated Notch pilots to amplify Sox2 immunoreactivity

in the embryonic pituitary [78]. Suppression of Notch signaling results in a drop off in Sox2 expression and an increase in differentiated cells in other developing systems [79]. Notch signaling system in adult pituitary stem cells intensifies Prop1 and Sox2 expression. It sustains self-renewal/proliferation of stem cells likewise in other adult tissues [80,81].

Pit-1 is a pituitary-specific transcription factor responsible for pituitary development and hormone expression in mammals and is a member of the POU family of transcription factors that regulate mammalian development. The POU family is so named because the first 3 members identified were Pit-1 and Oct1 (MIM 164175) of mammals, and Unc-86 of *C. elegans*. Pit1 contains 2 protein domains, termed POU-specific and POU-homeo, which are both necessary for high affinity DNA binding on genes encoding growth hormone (GH) and prolactin (PRL). Pit1 is also important for regulation of the genes encoding prolactin and thyroid-stimulating hormone beta subunit (TSHB) by thyrotropin-releasing hormone (TRH) and cyclic AMP [82,83]. In embryonic rat pituitary Pit-1 and Prop1 are co-localized in pituitary in as small percentage of cells (1-10%) but in postnatal life Pit-1+ cells decline in number whereas no Prop1 cells are present in adult pituitary [54]. Prop1 is probably downregulated before stem cell differentiation enhances [3].

P57 is a cyclin-dependent kinase inhibitor 1C (p57,Kip2), also known as CDKN1C, is protein which in humans is encoded by the CDKN1C imprinted gene. This cyclin-dependent kinase inhibitor 1C is a tight-binding inhibitor of several G1 cyclin/Cdk complexes and a negative regulator of cell proliferation. Mutations of CDKN1C are implicated in sporadic cancers and Beckwith-Wiedemann syndrome suggesting that it is a tumor suppressor candidate. CDKN1C is a tumor suppressor human gene on chromosome 11 (11p15) and belongs to the *cip/kip* gene family. It encodes a cell cycle inhibitor that binds to G1 cyclin-CDK complexes [84]. Thus p57KIP2 causes arrest of the cell cycle in G1 phase. P57 expression causes cell arrest of progenitor cells and the switch to another cyclin-dependent kinase inhibitor, p27, to some extent heralding the manifestation of differentiation markers to preclude re-entry of differentiated cells into the cell cycle [85]. High levels of p57 (CDKN1C) mRNA has also been found in the adult SC-SP which may point to a similar role for p57 in the stem cell compartment of the adult pituitary gland [25].

Cancer stem cells (CSCs) are cancer cells (found within tumors or hematological cancers) that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. Therefore CSCs are tumorigenic (tumor-forming), conceivably in contrast to other non-tumorigenic cancer cells. CSCs may produce tumors through the stem cell processes of self-renewal and differentiation into multiple cell types. Such cells are proposed to persist in tumors as a distinct population and cause relapse and metastasis by giving rise to new tumors. Therefore, development of specific therapies targeted at CSCs holds hope for improvement of survival and quality of life of cancer patients, especially for sufferers of metastatic disease. As CSCs would form a very small proportion of the tumor, this may not necessarily select for drugs that act specifically on the stem cells. The theory suggests that conventional chemotherapies kill differentiated or differentiating cells, which form the bulk of the tumor but are unable to generate new cells. A population of CSCs, which gave rise to it, could remain untouched and cause a relapse of the disease. In experimental pituitary models mice bearing mutations affecting-catenin proteolysis in the pituitary and leading to constitutive activation of the WNT/ β -

catenin pathway (obtained by crossing a Hesx1-cre knock-in strain to a β -catenin strain that produces degradation-resistant β -catenin mutant, upon recombination), developed tumors resembling, as far as histological appearance and marker expression are concerned, human adamantinomatous craniopharyngiomas [86]. Based upon this data, it could be hypothesized that beta-catenin, which controls the balance between self-renewal and differentiation, is inactivated in normal pituitary through altered epigenetic mechanisms may cause sustained progenitor proliferation and eventually tumor development [87]. Importantly, these data strongly support the hypothesis that genetic alterations in pituitary stem/progenitor cells may result in pituitary tumors [88].

Pituitary Stem Cells and Pituitary Neoplasia

The identification of a classic pituitary stem cell could have major contributions to basic and clinical science. It is hypothesized aberrant proliferation of pituitary stem cells occurs after an abrupt change in the pituitary environment directing to the formation of pituitary adenomas [12,27]. Hitherto only one animal study has explored the role of potential stem cells in pituitary tumorigenesis by using genetic techniques to examine the role that nestin+ cells in tumorigenesis. Mice having one functional retinoblastoma allele (Rb+/-) were crossed with nestin and GFP-positive (Green Protein Fluorescent) mice [21]. The offspring of the cross mice with predominantly produces and releases melanocyte stimulating hormone (MSH) tumors. Unexpectedly none of the tumor cells reacted with nestin; however, nestin+ cells that expressed Lhx3 and SOX-2 in encapsulated the tumors. Based on anatomical propinquity, the authors concluded that nestin+ cells contribute to the initiation of MSH-positive adenomas [21]. In regard to this compelling hypothesis of pituitary tumorigenesis if it would be correct so the suggestions for pituitary adenoma treatment would have been substantial. The other suggestion is if aberrant pituitary stem cells are removed then an indefinite risk subsists for tumor recurrence even though near total resection of adenoma is surgically accomplished. Moreover, if only a unique cell surface marker of aberrant stem cell is identified, then it would be possible to identify the cells with a specific antibody by using immunohistochemical analysis to make certain that the stem cell cohort is removed [89] (Table 2).

Concisely the pituitary is a dynamic organ which undergoes a number of changes in response to physiological stimuli and pituitary microenvironment changes. These subtle changes are thought to be mediated by differentiation of pituitary stem cells. Unlike neural stem cells, pituitary stem cells have not been clearly delineated to a certain cell type, therefore many potential candidates exist. Among this great

SM in Pituitary Tumorigenesis	
Marker	Ref#
E-cadherin(Cdh1)	3, 47
CSC – OCT-4	60, 61
Bmi-1	66
CD133	76
beta-catenin	82, 111-113
Sox2/Sox9	113
Lhx3	21
Sox2	21
nestin	21

Table 2: List of various stemness markers in pituitary tumorigenesis.

deal candidates include the chromophobes, folliculostellate cells and marginal cells, the side population cells, SOX2+/SOX9- cells, and GPS cells (GFRA2/Prop1/stem cells). Some authors suppose the current evidence implies that FSCs are the apparently cell type to represent pituitary stem cells. Contribution of pituitary stem cells to pituitary tumorigenesis remains to be further clarified. Due to a large scale of proliferative biomarkers and growth factors involved in proliferation, survival, cell migration and tumorigenesis, cells harboring prominent intracellular signal transducing systems may proceed as paracrine signaling alliance [90]. Hitherto numerous studies confirm the existence of multipotent stem/progenitor cells in the adult pituitary. Even though there is no consensus some characteristics, i.e., Sox2/SOX-9 expression, SC-SP appear to illustrate identifiable phenotype of these cells. So the upcoming step ahead ought to be corroborating these items in human pituitary pathologies [88]. Unfortunately there is scant support to emphasize that a specific cell type is definitive of a true pituitary stem cell. There has been a considerable amount of studies investigating the potential of folliculostellate cells to act as pituitary stem cells. Nonetheless, forthcoming studies need to undoubtedly clarify the pluripotent capacity of FSCs. Moreover, emerging evidence about the contention of GPS cells and SOX2+/SOX9- cells needs to be investigated further. The implications of the discovery of pituitary stem cells are considerable, and could possibly help improve not only basic information but clinical diagnosis and medical management of pituitary adenomas.

Conclusion

Discovery of pituitary stem/progenitor cells indisputably expand our understanding of organ specific physiology and pathology. The stem cell data in relation with pituitary neoplasia, cell replacement due to damaging of non-neoplastic conditions and aging of pituitary tissue will undeniably be used in the specific treatment modalities. Currently it is formidable that by using different approaches to stratify and extract intersecting putative stem cells will allow us to manage brand new treatment modalities of diverse pituitary physiologic and pathologic circumstances. Consequently as this miniature magic gland plays a pivotal role in a wide variety of key physiological processes, continuously expanding and fundamental stem cell studies will lead to specific substitution of pituitary stem cells as an incentive step in the regenerative medicine.

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SM in Pituitary Tumorigenesis	
Marker	References
E-cadherin(Cdh1)	3,47
CSC–OCT-4	50,51,56,57
Bmi-1	61
CD133	68
beta-catenin	86,87,88
Sox2/Sox9	88
Lhx3	21
Sox2	21
nestin	21

Table 2: List of various stemness markers in pituitary tumorigenesis.

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