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Review Article

Pituitary Stem Cells: What We Know So Far (Part 2)

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Abstract

The hypophysis is a pea-sized gland located in the sella turcica. The gland's primary function is to regulate the hormonal activity, which is controlled by the outputs received from the hypothalamus. These highly capable cells are derived from pituitary stem cells (PSCs) during the embryogenesis. The previous articles prove that the stem cells are a potential treatment option for a wide spectrum of pathologies. However, it is also undeniable that more research must be done to improve our knowledge of PSCs and to integrate PSCs into our treatment strategies. Our article summarizes and presents the latest findings regarding the biological properties of PSCs. The following review letter focuses on the stemness markers in the pituitary, the differences between the neonatal and adult hypophysis, biologic properties of pituitary diseases, latest approaches, and future aspects of PSCs. The discussed stem cell markers are SOX2, Nestin, Sca-1, E-cadherin, S100, Prop1, Oct4, Bmi1, CD133, Beta-catenin, Pax6, Notch2, Notch3, Pit1, p57, TpiT, and AIP. Beside the roles of stemness markers, the latest advancements concerning the PSCs such as CRISPR/Cas9 technique and organoid formation are reviewed.

Keywords: Pituitary Stem Cells; Hypothalamus; CRISPR/Cas9; Anterior Pituitary

Introduction

The pituitary gland (also known as hypophysis) is a pea-sized structure located in the sella turcica. The main function of the gland is the adjustment of hormonal activity which is regulated by the outputs from the hypothalamus. Two main structures, the anterior pituitary (adenohypophysis, pars anterior) and posterior pituitary (neurohypophysis, pars posterior), of the hypophysis, are responsible for the secretion of different hormones. Diseases concerning the pituitary gland cause a significant impact on the human body.

The existing management strategy of pituitary-related disease is a multi-modality approach concerning medical and surgical treating. Integrating stem cells into our treatment approaches demonstrate promising results in a vast spectrum. But it is also an obvious fact that a lot of investigation is required to improve our knowledge of pituitary stem cells. The main goal of our article is to summarize and present the latest findings concerning pituitary stem cell markers of pituitary gland from the neonatal period to adulthood, biological properties of pituitary diseases, the latest approaches, and future aspects of pituitary stem cells (PSCs).

Stemness markers in the pituitary

Stemness markers are crucial in understanding the mechanism behind PSCs and how they differentiate during different times in our life. The first discovery made in this field was in 2005. Detection of nestin (neuroepithelial stem cell protein) in the pituitary gland of rats was the initial step of many stem cell markers [1]. Consequently, much research has been done on this topic, and there are many ongoing projects as well. It is established that the markers and embryogenic factors are primarily located at the lumen of the adenohypophyseal primordium Rathke's pouch. The other clusters of markers were found to be at the parenchyma of the anterior pituitary, which is suggestive of multiple niches. The equilibrium between differentiation and self-renewal depends on the niche. Different expressions of markers gave us clues about the mecha-

nisms behind the diseases and some similarities between different pathologies. Scientists are targeting to use this information to find solutions to diseases.

All stemness markers have different roles in the developmental processes of the human pituitary. The stemness markers included in our review are Sex-determining region Y (SRY) box 2 (SOX2), Nestin, stem cell antigen 1(Sca-1), E-cadherin, S100, Proposition One (Prop1), Octamer-binding transcription factor 4 (Oct4), Bmi1, CD133, Beta-catenin, Paired Box Protein 6 (Pax6), Notch2, Notch3, POU domain, class 1, transcription factor 1 (Pit1), p57, T box transcription factor (TpiT), and Aryl Hydrocarbon Receptor Interacting Protein (AIP) [2,3].

SOX2 is a member of the SRY-related high-mobility group (HMG) box B1 (SOXB1) subfamily of transcription factors. SOX2+ cells can differentiate into endocrine cells at the anterior pituitary and maintain the self-renewal function of the cell. During this process, they form "pituispheres," which contain more than one endocrine cell type. It explains "spheres" multipotency. Due to the abilities of SOX2+ cells, SOX2 marks the rate and capacity of cell differentiation. It is expressed during embryonal development at the entire epithelium of the brain and posterior neural tube, including the cortex, hippocampus, cerebellum, and spinal cord, developing the eye (esp. lens, neural retina, and optic nerve) via organs derived from endoderm (trachea, esophagus, stomach, and posterior gut) and at embryogenesis of hypothalamus and Rathke's Pouch (not expressed in the infundibulum and posterior pituitary). On the other hand, only a small group of cells express SOX2 in the adult pituitary [2,4-8].

A cytoskeletal intermediate filament called nestin is expressed in various stem (Sox2+) cells in situ (marginal zone) and in culture (pituispheres). It is characteristically found in neural stem cells. Other structures expressing nestin are pancreatic islets, skeletal muscle satellite cells, developing myotomes, testis, hair follicle, heart, and the non-hematopoietic fraction of the bone marrow. It is also described that these stem cells have a role in different malignancies, such as osteosarcoma, neuroblastoma, glioma, melanoma, and pancreatic and prostate cancers. In addition to that, nestin is a valuable marker of glioblastoma infiltration. Besides these characteristic properties of nestin, it has a role in the differentiation and migration of stem cells as well [4,8,9].

Sca1 is a transient putative marker expressed in SOX-positive cells. The marker is expressed in Stem Cell-enriching Side Population (SC-SP), pituispheres, and some colony-forming cells. The side population comprises a high-SCA expressing part and a non-high SCA expressing side. According to Vankelecom., *et al*., 2009 the non-high SCA expressing part has a higher capacity for renewal and differentiation to different hormone-producing cells [2-4].

Tumor-suppressing gene (TSG) E-cadherin is a member of the cadherin superfamily, expressed in Rathke's cleft and S100+ cells within the AP lobe, and encodes the calcium-dependent adhesion molecule (type 1 transmembrane protein) and, has a role in regulating signaling pathways of proliferation and motility. According to Castinetti., *et al*., it functions in the transition from proliferation to differentiation [2,3,10].

The S100 protein is involved in Ca+2 homeostasis, protein phosphorylation, the dynamics of cytoskeleton constituents, cell growth and differentiation, transcription factors, inflammatory response, and enzyme activities. Folliculostellate cells of the pituitary express S100, which are believed to be analogs of the brain glial cells [2,3].

PROP1 protein is encoded by the PROP1 gene and is also a homeobox protein prophet of PIT-1. The primary functions of this protein are the ability to activate transcription and DNA binding. In addition, it governs the movement of embryonic stem and progenitor cells from the marginal zone (MZ) to the anterior pituitary (AP). Consequently, it significantly affects the ontogenesis of pituitary gonadotrophs, as well as somatotrophs, lactotrophs, and caudomedial thyrotrophs. The deficiency of this protein causes dysmorphic fetal pituitary due to the retained fetal cells in the periluminal area, which fail to differentiate. Dysmorphic pituitary also lacks proliferation and enhances apoptosis after birth. The reason is that the progenitors are not seeded at the mutant anterior lobe [2,11].

Oct-4 is a homeodomain transcription factor of the POU family, and it has the function of dedifferentiating the somatic cells into multipotent cells [2,3].

Bmi1 is a polycomb repressive complex 1 (PRC1) member responsible for gene repression by regulating cell cycle inhibitors during embryologic development. The overexpression is observed in more than half of pituitary adenomas that are interpreted to be an important marker in tumorigenesis [2,3].

CD133 is also called Prominin-1 (PROM1), a member of pentaspan transmembrane glycoproteins (5-transmembrane, 5-TM).

It is expressed in neural and hematopoietic stem cells, marginal zone cells in the pituitary, and some pituitary adenomas [7]. According to Yunoue., *et al*., the expression ratio is 25,7% in pituitary adenomas, and it is suggested that the marker might represent the immature endothelial progenitor cells responsible for neovascularization in pituitary adenomas [2,12,13].

The protein, beta-catenin, has a role in the regulation of cell-cell adhesion coordination and gene transcription. Acts as a critical effector in Wnt-signaling in the nucleus. It is defined within somatotrophs and the marginal cell layer of the anterior pituitary. An imbalance in the expression of this protein may result in cancer or metastasis [2,14].

Pax6 is a member of transcriptional regulators and signaling factors. It is mainly expressed in the non-Sca high side population. It has a critical role in the embryogenesis of the eye and pituitary. In addition, it also affects the development of the olfactory, pancreas, and other parts of the CNS [2,15].

Notch2 is a member of the notch signaling pathway family; it is observed in the embryonic periluminal progenitor zone and implicated in the differentiation of cell lineages. Functions as one of the regulators of cell differentiation. The influence is little on early embryonic proliferation, but it has a crucial effect on postnatal progenitor maintenance and proliferation. On the other hand, Prop1, which might have a direct or indirect influence, is an essential protein in the expression of Notch2 [2,16,17].

Notch3 is a transgenically activated gene that encodes notch pilots to amplify Sox2 immunoreactivity in the embryonic pituitary. That is why it has the role of protecting stem cell renewal and proliferation. In addition, Miao., *et al.* Notch3 is an effective substance in the progression of non-functioning adenomas, and they suggest that over-expression influences tumor growth [2,18].

Pit-1 is a member of the POU family of transcription factors. It is composed of 2 protein domains, POU specific, and POU-homeo; both have a role in DNA binding on genes, which encode GH and PRL. It is involved in the process of somatolactotroph and thyrotroph lineage differentiation. In addition, Palmieri., *et al.* represented that Pit1 upregulation by HMGA proteins has a role in tumorigenesis of the pituitary [2,3,19-21].

P57 is a cyclin-dependent kinase inhibitor 1C (p57, Kip2, CDKN1C) encoded by the CDKN1C imprinted gene in humans. Cyclin dependent kinase inhibitor 1C (CDKN1C) is the gene silenced in Beckwith-Wiedemann syndrome (BWS), a syndrome associated with malignant neoplasms during infancy. P57 is the only CDK inhibitor required for embryonic development. It is a tight-binding inhibitor of several G1 cyclin/Cdk complexes and a negative regulator of cell proliferation [2,22].

Tpit promotes corticotroph differentiation by having a role in cell-specific transcription of the proopiomelanocortin (POMC) gene [3].

Aryl hydrocarbon receptor-interacting protein (AIP) is thought to be involved in familial pituitary adenomas [3].

Pituitary Gland from Neonatal Period to Adulthood

The hormonal requirements of the body change during life. The plasticity of the pituitary gland has a crucial role in the adaptation process. Herein we should emphasize the changes occurring in the pituitary gland and different abilities during a lifetime.

PSCs and cell types have different roles in the differentiation process. The body arranges hormonal responses according to the needs at a particular time (neonatal period, puberty, adulthood, and other physiological processes like lactation or stress). Hypothalamo-pituitary axis plays a significant role in this response [23]. Major differences are recorded in 3 different periods during life, i.e., neonatal period, puberty, and adulthood. During the neonatal period, the most critical responses are growth and maturation. To answer that demand, PSCs and pituitary cells have different functions than other time intervals. Pit1 lineage has a role in the development of somatotrophs, lactotrophs, and thyrotrophs. Gonadotroph development is regulated via steroidogenic factor-1/GATA-binding protein 2 (SF1/GATA2) lineage. The development of corticotrophs is sustained by T-box transcription factor 19 (TBX19). Another important aspect of this phase is the migration of PSCs from the MZ to AP, provided by PROP1. The last important change is the decline of nestin+ cells after birth [23-26].

During puberty, developmental processes occur. Pit1 protein encoded by Pou1f1 is responsible for the somatotroph peak at the pubertal phase. Another significant difference in medaka fish is hypertrophy and proliferation of FSH and LH-producing cells [23-27].

A decrease in homeostatic turnover and reparative capacity is reported in adulthood and aging. Thyrotroph, gonadotroph, and

GH+ cells decrease in number and size. A decline in ghrelin and GnRH is observed. Somatostatin appeared to be increased in adulthood. FS cells (encompass SCs) decreased in number in rats but increased in humans [23,27-32].

On the other hand, changes in PSCs and pituitary cells also have a massive impact on the processes such as proliferation, regeneration, and differentiation. Moreover, this function of cells causes different responses throughout life [28].

The stem cells in the maturing gland have a higher potential to differentiate into endocrine cells. However, the adult pituitary gland cells are more stable and do not have a high differentiation potential [33]. Differentiation to hormone-producing cells has a role in doubling the pituitary gland in size as the hormone-containing secretory granules accumulate in the first week of life in rats [23,34,35].

Another difference is the highly Epithelial/Mesenchymal (E/M) phenotype (expressing both epithelial and mesenchymal markers) SCs. This phenotype, which fades into adulthood, has a role in the intense maturation of the pituitary gland, as in the embryogenesis of the human pituitary [36]. In addition, it is described in research done on rats that the E/M phenotype has a role in the migration of SCs from the marginal zone (MZ) to AP (anterior pituitary) [28,37,38].

One of the most stunning differences is the higher capacity of the neonatal pituitary gland to proliferate and regenerate after local damage. After somatotroph ablation, there has been 50-60% regeneration in 5-6 months of adult pituitary. On the other hand, following a three-day diphtheria toxin (DT) injection to pups, 50-60% of GH-positive cell ablation is observed in the neonatal pituitary. Although there was no reaction in the SC compartment, the pituitary gland of the neonates fully regenerated in 2 months. The most probable explanation for that kind of response is the already active SCs in the pituitary, which does not require any stimulation to proliferate. There has not been any IL-6 increase or WNT expression immediately or after two weeks. WNT expression is assessed by Lgr-5 and Axin2 target genes in that research [39].

IL-6 increases following injury to the adult pituitary gland [40]. Although there is a higher regeneration capacity of the neonatal pituitary, there has not been any increase in IL-6 observed. There are several elucidations to this interesting fact. Initially, the amount of SC population is more in the adult gland than in the neonatal gland, as showed by staining SOX2+ cells with in situ immunofluorescence analysis and revealed by scRNA-seq as proliferative cell clusters [28]. It is also declared that local SCs (SOX2+) are predominant in the neonatal pituitary compared to adults [41]. Another potential explanation for low IL-6 expression is the high expression of IL-6 family cytokines, e.g., IL-11 or leukemia inhibitory factor (LIF) [28,42]. These cytokines might have a role in the activation of SCs.

The WNT signaling pathway also has a crucial impact on the proliferation capacity of SCs. Differential Expressed Genes (DEG) analysis reported increased expression of WNT-associated genes (e.g., Frizzled (Fzd) 2, Fzd3, Gsk3b, Ctnnb1, and Tnks) in the SC of neonatal pituitary gland. In addition, WNT transcription factors (Tcf7l1 and Tcf7l2) are found to be more in neonates than in adults, and the number of ligands and receptors effective in WNT signaling is also more in neonates [28].

In an experiment, which targets to prove the influence of the WNT signaling pathway in organoid formation, WNT-inhibitor XAV-939 is applied to a Mouse. A complete stop in organoid formation is observed. Furthermore, the genes effective in this result are correlated with the human body being similar to humans [28].

Pou1f1 (Pit1) is a transcriptional regulator of hormone expression in somatotrophs, lactotrophs, and thyrotrophs [33]. Progenitors of this lineage were observed in the neonatal pituitary gland [28], which did not appear in the adult pituitary [39].

A last exciting part about this topic is that DEG and Gene Ontology (GO) analysis revealed higher Notch values in the normal anterior pituitary compared to the damaged anterior pituitary. In regeneration, Notch inhibition is required for cell differentiation, as in embryogenesis [43].

Biologic Properties of Pituitary Diseases, Latest Approaches, and Future Aspects of PSCs

It is a well-known fact that research on stem cells promises many crucial opportunities in medicine, regardless of the topic. However, we are still far from our target, which is finding new and better solutions for pathologies. This section explains the latest approaches, pituitary diseases' biological properties, and PSCs' future aspects.

There is a long list of diseases related to the pituitary. Therefore, it would be appropriate to divide pituitary disorders into two main groups; Pituitary tumors and pituitary disorders related to hormonal imbalances. A tremendous amount of factors has been determined regarding genetic hypopituitarism. The established factors are homeobox expressed in ES cells 1 (HESX1), bicoid homeodomain factors (PITX1 and PITX2), LIM homeobox 3 (LHX3), LIM homeobox 4 (LHX4), SOX2 (transgenic deletion resulted in decreased proliferation) and Pit1 mutation [44].

Understanding tumorigenesis is a critical point. Having better knowledge adds to the present armamentarium. In looking for solutions to pituitary tumors, the process of SC activation might play an essential role in tumor growth and proliferation. Although the relationship between 'Tumor Stem Cells' (TSCs) and SCs has not proven yet, there is a common belief that they are connected [44]. The proliferation of cells is mainly regulated by SOX2-positive cells, and this process is forced by WNT signaling [5,44]. During tumor maturation, SOX2-positive cells are activated. However, it is still an unproven fact whether SCs give rise to tumors or it is a reaction against tumorigenesis [44]. According to recent articles, one of the factors involved in tumor development is the entrance of mutant cells into senescence and afterward activation of the senescence-associated pathway (SASP), which leads to the release of mitogens, cytokines, and chemokines [44]. Research that supports the influence of SASP activation is done on mouse models. In mice with low SASP response, the development of tumors has not been observed [44]. The Hippo signaling pathway appears as another vital player in tumorigenesis. It was first described in Drosophila and mammals. This kinase cascade has a negative effect on YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif). These key effectors promote proliferation and prevent apoptosis [44]. Therefore, it is expected that the Hippo signaling pathway promotes tumor development [45]. It has been described that poorly differentiated pituitary tumors (i.e., null-cell adenomas, adamantinomatous craniopharyngiomas (ACPs), and papillary craniopharyngiomas [PCPs], show an increased expression of YAP/TAZ. In contrast, these effectors are expressed at low levels or have not been expressed in various adenomas. So, the usage of this pathway as a target of anti-cancer treatment promises a lot [44]. As noted above, kinases play a pivotal role in the formation of diseases. Another important example of the role of kinases is described in research, where one of the core kinases, LATS1, is deleted, and pituitary disorders, such as pituitary hyperplasia and hormone deficiency, were observed [44].

The two most important technologies for deciphering PSC biology are organoid formation and the CRISPR/Cas9 genome editing technique. As stated in the first paragraph of this chapter, SCs offer us many opportunities, such as the treatment of primary hypogonadism, which showed satisfactory results [46]. Nevertheless, collecting them raises ethical questions in our minds because they are primarily maintained from embryonic tissues. Moreover, the lack of human samples is not the only issue, maintenance of cells and stabilization are also obstacles [44]. In the first trials, SCs were obtained from dermal fibroblasts, but these experiments did not result as expected [47]. Therefore, this approach was followed by trials, which target the development of particular cells, such as corticotrophs and somatotrophs [44].

Subsequently, there were multiple trials done to improve approaches. Among these, the most critical technology is organoid formation. Organoids are 3D structures that develop from a tissue's SC under certain conditions. They appeared to have a crucial role in this process [48,49]. Although this fascinating technique provides a lot of development, the main problem regarding organoids appeared to be their lack of ability to produce specific hormones [44]. Based upon the usage of human-induced pluripotent cells, functioning hypothalamus-pituitary axis was established, apparently to be very similar to the real one [50]. Even though the current best method looks like CRISPR/Cas9 genome editing technique, this method provides us with a huge chance to find the responsible genes for diseases that may end up discovering new drugs. Despite the presence of significant barriers due to the lack of human samples, it has been showed that after some regulations on the OTX2 gene with CRISPR/Cas9 technique, improvements in some hormone deficiencies were observed [44].

Conclusion

Stem cells of the pituitary gland are of significant importance since they can shed light on new treatment modalities in patients with pituitary pathology. There is inevitably progressive improvement in molecular pathology for the understanding of diverse mechanisms of pituitary tumorigenesis, and pituitary hormone deficiencies. However, the impact of pituitary stem cells underlying these mechanisms much research is needed. It is to emphasize that with the upcoming improvements and knowledge of pituitary stem cells, it might be possible in the future to transplant SCs and find treatment modalities for several pituitary pathologies. In conclusion, we summarized potential stem cell candidates, i.e., folliculostellate cells, follicular cells, marginal cells, side population cells,

pituitary colony-forming cells, SOX2+ cells, and GFRa2/Prop1/ Stem cells, as the candidates. More work has to be done on any one or all of these pituitary stem cells which will be beneficial for patients suffering from primary pituitary pathologies.

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