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Review Article

Pituitary Stem Cells: What We Know So Far (Part 1)

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Abstract

The pituitary gland is a pea-sized gland located at the sella turcica and has major impacts on the hormonal balance of human body which is regulated by the inputs received from hypothalamus. Hypophysis is composed of two main structures, which are responsible for the secretion of different hormones. These cells with different functions are derived from special pituitary stem cells (PSCs) during the embryogenesis. It is a well-established fact that the stem cells are a potential treatment option for the treatment of a wide spectrum of pathologies. Integration of PSCs to the treatment approaches requires a lot of investigation related to the biological properties of these highly capable cells. Therefore, the goal of our review article is to summarize and present the latest findings concerning PSCs. The following article focuses on the anatomy and the cells of the pituitary, and the possible stem cells of the gland. The stem cell candidates discussed in detail are Folliculostellate cells, Follicular cells, Marginal cells, Side population cells, Pituitary colony-forming cells, SOX2+ cell population and GFRa2/Prop1/Stem cells. We strongly believe that our review concerning the aforementioned topics provides detailed information for the researchers and physicians working on pituitary pathologies and PSCs.

Keywords: Pituitary Stem Cells; Folliculostellate Cells; Marginal Cells; SOX2+ Cell

Introduction

The pituitary gland (also known as hypophysis) has a significant role in regulating hormonal activity. The gland releases hormones according to the outputs delivered from the hypothalamus. Besides the role of pituitary control, the hypothalamus also releases conventional neurotransmitters, neuropeptides, and hormones, which control some essential physiologic functions of the human body; such as the sleep-wake cycle, thermoregulation, and sexual behavior [1]. The activity of the hypothalamus depends on the input it receives from all over the body. The input that regulates hypothalamic activity includes hormonal feedback mechanisms, autonomic function, cortical signals, and environmental signs such as temperature and light.

The pituitary gland is a pea-sized gland located at the sella turcica, just below the hypothalamus. The hypophysis consists of two main structures, the anterior pituitary (adenohypophysis, pars anterior) and the posterior pituitary (neurohypophysis, pars posterior). The lobes are responsible for the secretion of different hormones. The hormones released by the anterior pituitary are Adrenocorticotropic hormone (ACTH or corticotrophin), Follicle-stimulating hormone (FSH), Growth hormone (GH), Luteinizing hormone (LH), Prolactin and Thyroid-stimulating hormone (TSH). These hormones are produced and secreted by the anterior pituitary. On the other hand, the hormones released by the posterior pituitary are produced by the hypothalamus and stored in the posterior pituitary. These hormones are: Antidiuretic hormone (ADH, or vasopressin) and Oxytocin [2]. Therefore, it would seem evident that diseases of the pituitary gland would cause significant harm to the human body and health. Thus, there is a lot of ongoing research with the hope of treating and/or preventing these diseases and gaining more insight into how different cell types act.

Treatments, including stem cells, are relatively new in medicine but show many promising results in a vast spectrum. The stem cell research involving pituitary stem cells (PSCs) is also new, but the improvements in this field is fascinating. Researchers hope to find better management options for patients suffering from pituitary-related diseases.

The main goal of our article is to summarize and present the latest findings concerning pituitary stem cells. Therefore, the main topics of our review article will be the anatomy and the cells of the pituitary, and the possible stem cells of the gland.

Pituitary Anatomy

The pituitary gland plays a crucial role in maintaining homeostasis in the body. It is also an important part of the hypothalamic–pituitary–adrenal (HPA) axis.

Its size is approximately 1 cm in length, 1-1.5 cm in width, and 0.5 cm in height [3]. On average, the gland weighs 500-600 mg [3]. Generally, the female pituitary gland is heavier than the male pituitary gland. This stems from the differences in the size of pars distalis [3]. During pregnancy, the weight of the pea-sized gland increases by 12% to 100% due to the hypertrophy of lactotroph cells [3,4]. The progressive increase in estrogen levels is responsible for this hypertrophy and, therefore, the increased size of the gland during pregnancy [4].

The pituitary gland is located in sella turcica [5]. This Latin name translates into "Turkish saddle". Sella turcica is the superior depression of the sphenoid bone [6]. The pituitary gland's lateral and superior neighbors are cavernous sinuses and diaphragm sellae, respectively [7]. The gland is connected to the hypothalamus via the infundibular stalk anatomically and functionally [5].

The dual-origin gland has two distinct lobes: The anterior pituitary (adenohypophysis) has an epithelial origin and is derived from the oral ectoderm, and the posterior pituitary (neurohypophysis) is derived from the neural ectoderm [7]. The adenohypophysis encompasses six different cell lines, five of which are hormone-producing. These hormone-producing cells are called: Somatotrophs, Lactotrophs, Corticotrophs, Gonadotrophs, and Thyrotrophs. The sixth cell type, which does not produce any hormone, is called the folliculostellate cells, also called adult SOX2+ stem cells, because they are considered the stem cells of the pituitary gland [8,9]. The adenohypophysis consists of 3 anatomical parts: 1) The pars tuberalis (pars infundibularis) encapsulates the region consisting of unmyelinated axons from the hypothalamic nuclei called the infundibular stem. Temporary hormone storages, Herring bodies, are found here, which are the swellings made up of the aggregates of the hormones oxytocin and vasopressin in these axons [9]. 2) The pars intermedia is rudimentary in adult humans and consists of remnants of the Rathke's pouch [7,9]. 3) The pars distalis also called the anterior lobe is where most hormones are secreted [9]. The neurohypophysis, made up of 2 parts called the pars nervosa and the infundibular stalk, does not contain hormone-producing cells; thus, it does not produce any hormones [7,9]. The posterior pituitary consists of axons surrounded by specialized glial cells called pituicytes, arising from the supraoptic and paraventricular nuclei. The hypothalamo-hypophyseal tract is formed by these axons coming together. Besides, the sinusoids of the posterior lobe are the terminals of the end of the axons. The hormones oxytocin and vasopressin are produced in the hypothalamus and travel to the posterior pituitary via the hypothamalo-hypophyseal tract. These hormones are then released into the circulation by the posterior pituitary [3,9].

Cells of the pituitary

The cells in the anterior pituitary differentiate into various cell types under the influence of specific pituitary transcription factors [10]. There are six different cell types in the adenohypophysis, five of which are hormone-producing.

The cells in pars distalis are separated into two categories based on their ability to stain with periodic acid-Schiff dye: chromophils and chromophobes. Chromophils are further divided into two categories: basophilic cells stain intense with basic dyes whereas acidophilic cells stain well with acidic dyes [11]. There are three types of basophilic cells in the pars distalis. Corticotroph cells produce and secrete ACTH (corticotropin), which stimulates the adrenal cortex. Gonadotroph cells produce and secrete FSH and LH, both of which affect the gonads. Thyrotroph cells produce and secrete TSH (thyrotropin), which regulates the functions of the thyroid gland [11]. Acidophilic cells in the pars distalis are somatotrophs and lactotrophs, which produce growth hormone (GH) and prolactin, respectively [10,11]. Chromophobic cells, a heterogeneous group of cells that are thought to encompass the pituitary stem cells, include follicular cells, folliculostellate cells, marginal zone cells, supportive mesenchymal cells, and immune cells such as macrophages and

dendritic cells [12]. The folliculostellate cells are composed of several different subgroups of cells. FS cells are thought to have a variety of functions [8,13]. They likely play a role in the pituitary cell organization and network [8]. In a study, communication across the gland and a more localized cell-cell communication were seen by observing calcium activity in folliculostellate cells using AMCA dye [8]. This pituitary cell organization seems to have roles in various cell activities like regulating gene expression and secretion of hormones [8]. FS cells communicate with pituitary endocrine cells via gap junctions and paracrine communication [8]. The cytokines and growth factors they produce influence and regulate a specific pituitary endocrine cell type [8]. Most importantly, folliculostellate cells are proposed to have stem cell properties since they show reactions and changes under different physiological and pathological conditions, which have earned them the name "adult Sox2+ve stem cells" [8,13]. Marginal zone cells are found along the lining of the cleft, lumen between the anterior pituitary and the intermediate lobe [13]. During the embryonic period, marginal zone cells proliferate and migrate to the anterior lobe, where they differentiate into various hormonal cell lineages [13,14]. In addition to the embryonic development period, these cells are proposed to be stem/progenitor cells of the pituitary in the postnatal period [13]. Follicular cells are small cells with irregular shapes found throughout the anterior pituitary [13,14]. They have islet-like clusters around a pseudolumina, and "ambiguous" cells have been seen at the circumference of the clusters [13,14]. This suggests that after mitosis, follicular cells migrate to the periphery of the clusters and ultimately differentiate into acidophil and basophil cells [13,14]. Finally, side population (SP) cells, cells that deploy different markers in the flow cytometry than the main cell population and have different cell characteristics (such as having stem cell properties), have been identified in the anterior postnatal pituitary of mouse, rat, and chicken [14]. Side population cells are small cells with low cytoplasmic complexity and are therefore thought of as agranular (chromophobe) cells [14]. SP cells *in vitro* can clonally expand to floating spheres, a characteristic of stem cells of some tissues. However, more extensive research is necessary for this study area [14]. The majority of the cells that make up pars tuberalis are gonadotroph cells, while pars intermedia contain corticotroph cells and some chromophobic cells [11].

The posterior pituitary does not contain the cells synthesizing the two hormones it secretes. There are no hormone-producing cells in the neurohypophysis. Instead, the posterior pituitary consists of unmyelinated axons arising from the supraoptic and paraventricular nuclei, and pituicytes, the most abundant cell type in the neurohypophysis, wrapping these axons [3,11]. Pituicytes are thought to maintain the extracellular fluid compartment's ionic composition and have a supportive function [15].

Stem cell candidates in the pituitary gland

Folliculostellate cells

Rinehart and Farquhar first identified Folliculostellate cells (FS) as small agranular cells via electron microscopy, although the name "folliculostellate cells" has not been suggested yet [16,17]. These cells were stellate-shaped and had follicle-forming properties, and the name "folliculostellate cells" was suggested by Vila-Porcile in 1972 [17,18]. However, immunochemical detection with an antibody against a specific hormone cannot be used since these cells are not endocrine cells and many aspects were unknown until the S100 protein, a family of Ca^{+2}-binding proteins transducing Ca^{+2} signals, was discovered as a cell marker for FS cells [8,17]. Glial fibrillary acidic protein (GFAP), which is a monomer protein subunit of glial intermediate filaments (IFs) in differentiated astrocytes and belongs to the class III of IF proteins, is also another cytochemical marker for FS cells and is promising in exploring the FS cell line [17,19,20].

FS cells are considered a heterogeneous group of cells due to the differences in some protein expressions. However, it is currently unclear whether these differences are due to different FS cell subtypes or transient differences in gene expression depending on the cell location and physiologic status [8]. More research is needed to elucidate if FS cells are a single unique population or a heterogeneous group of FS cell subtypes that adapt in response to demands [8].

Folliculostellate cells are thought to have several functions. First, it was demonstrated that FS cells are 'excitable cells,' as shown through the calcium activity in FS cells [8,21]. Communication across the gland and a more localized cell-cell communication were observed via calcium waves between FS cells [8]. Third, functional gap junctions were demonstrated between FS cells and pituitary endocrine cells, suggesting FS cell coordination on a larger scale [22]. Paracrine communication between FS cells and pituitary hormonal cells has been studied much more extensively. FS cells have been shown to produce a range of growth factors, peptides, and cytokines such as basic fibroblast growth factor (bFGF),

vascular endothelial growth factor (VEGF), follistatin, annexin 1 (ANXA1), leukemia inhibitory factor (LIF), interleukin-6 (IL-6), and macrophage migration inhibitory factor (MIF) as well as nitric oxide (NO) [8,23,24]. In different physiological states, these ligands seem to be altered, suggesting an essential paracrine communication between the FS and endocrine cells in the pituitary [23]. Another interesting potential role for FS cells is their response to pituitary target organ feedback and mediators. An example would be an alteration in corticotroph function in response to glucocorticoid feedback through ANXA1 [25]. Glucocorticoids increase the expression of ANXA1, which results in the translocation of ANXA1 to the external surface of the plasma membrane [26,27]. The externalized ANXA1 then binds to the hu-r-LC1 binding sites on corticotrophs [26]. This results in the decline of adrenocorticotrophic hormone (ACTH) secretion in response to corticotrophin-releasing hormone (CRH) [8,26,27]. While there is much more research to be done, what we know so far gives us an insight into the potential role of folliculostellate cells as large-scale communicators and regulators in the adenohypophysis [8,14].

FS cells have been proposed numerous times as potential stem/progenitor cells in the postnatal pituitary [28]. Some studies demonstrate the reactive changes in FS cells under different physiological and pathological conditions [13,29,30]. In an experiment, the anterior pituitary glands of male rats were auto transplanted under their renal capsules. Firstly, the FS cells formed cyst-like structures with neighboring FS cells and surrounded the small number of granular cells. On the fifth day after the transplant, both FS cells and granular cells showed an increase in their number. These observations suggest that FS cells may have a potential role in the regeneration of the pituitary gland and thus may be a candidate for stem cells of the pituitary [31]. In another study, FS cells of castrated rats were immunostained with S100 protein antiserum, and the reactive changes in FS cells were observed. In castrated rats, the number of immunostained FS cells increased, and they had cytoplasmic processes encircling the gonadotrophs. These findings may be attributed to the potential stem cell properties of FS cells, but they are not conclusive [32]. FS cells have been shown to be in close connection with immature endocrine cells, sometimes surrounding them. These findings may suggest that FS cells have the ability to differentiate into endocrine cells or are at least involved in the differentiation [13,28,33]. Furthermore, it was proven that FS cells have the ability to transform into striated muscle cells [34,35]. When the pituitary glands of rats were transplanted beneath their kidney capsules, myoglobulin-positive striated muscle cells appeared in the center of the pituitary graft. These findings were interesting because FS cells are most likely of ectodermal origin and muscle cells are of mesodermal origin, which makes this a transgerminal differentiation [34,35]. The hypothesis that organ-specific stem cells, such as neuronal stem cells, are multipotent and that transgerminal differentiation is one of the characteristics of organ-specific stem cells; supports the candidacy of FS cells as stem cells of the pituitary [34,36]. Although this hypothesis is still highly controversial, and if FS cells are stem cells remains inconclusive [13].

Follicular cells

Follicular cells are non-hormonal small cells with irregular shapes that form islet-like clusters around small lumina [13]. Between the embryonic and postnatal periods, the number of follicular cells declines [37]. This was theorized to be due to progressive cell differentiation, giving rise to the hormonal cells of the pituitary [37]. However, their number remained the same after sexual maturation [37]. It has been suggested numerously that follicular cells may overlap with FS cells or may even be a subset of the heterogeneous FS cell group [38]. In a recent study, this hypothesis was shown to be incorrect, and follicular cells are a distinct group of cells [39]. Follicular cells have shown immunoexpression of CAM5.2, CK17 (cytokeratin 17), CK18, CK19, AE1/AE3, and epithelial membrane antigen (EMA) [38,39]. Based on what we know so far; it seems possible that follicular cells were derived from hormone-producing cells [38-40].

Mitotic figures are primarily detected in follicular cells in the anterior pituitary, except marginal cells [8,41]. Follicular cells sustain their structural immaturity and mitotic capacity throughout life [8,37,41]. At the periphery of the clusters, 'ambiguous cells' with a few number granules have been observed [37]. Therefore, it was suggested that after mitosis, follicular cells migrate to the periphery of the clusters to granulate through an intermediary stage and finally transform into acidophils or basophils [37]. When follicular cells were auto-transplanted under the kidney capsule, granulation and an increase in cell number were both observed [13,37]. Based on these findings, follicular cells are suggested to be stem cells of the pituitary [8,13,37]. While the research done is promising, but not conclusive.

Marginal cells

Marginal cells are part of the heterogeneous group of cells in the anterior pituitary. These cells are found along the lining of the cleft, the lumen between the anterior pituitary and the intermedi-

ate lobe [13]. Marginal cells have been suggested numerously as the stem/progenitor cells of the pituitary gland [13].

During the postnatal period, these cells have been shown to retain some embryo-typical features such as agranularity and the presence of microvilli and cilia [13,14]. Proliferative activity has been shown to be present from birth until adulthood in marginal cells, which may suggest that these cells proliferate to give rise to new granular cells [13,14]. Hormone-immunoreactive cells have been found at a close distance from marginal cells, which may be hypothesized to be due to the marginal cells giving rise to endocrine cells [13,14,21]. Marginal cells have shown activated status and reactive changes in some experimental studies [13,14,43]. When the hemipituitary glands of rats were auto-transplanted under their renal capsules and two days after the transplant, the central area of the graft showed necrosis, but the marginal cells survived. In the upcoming days, firstly, mitotic activity in marginal cells has been observed, and cyst-like structures formed. On day 20 after the transplantation, granular cells lining the cavity were observed [43]. These findings may suggest, but not prove, that the marginal cells are indeed stem cells. Because the findings are still circumstantial, marginal cells may just be supportive cells or act as regulators of the cell differentiation process [14]. Some stem cell-associated markers have been found in the marginal zone cells, including nestin, Lewis X antigen, a marker of embryonic and neural stem cells, and prominin-1 (CD133), which is found in neural and hematopoietic stem cells [8,13,44,45]. Marginal zone cells have been repeatedly reported as possible stem/progenitor cells of the pituitary; however, all the evidence supporting this hypothesis is still circumstantial [8,13,14,41].

Side population cell

Side population (SP) cells show one of the cardinal characteristics of stem/progenitor cells that set them apart from the other cell groups [46]. SP cells have the ability to exclude hostile and toxic products as means of self-defense [47]. SP cells have a high efflux capacity for Hoechst 33342 dye, and an ATP-binding cassette multidrug transporter, specifically ABCG2, is responsible for this efflux activity [46,47]. It was also demonstrated that SP cells contained no or very few secretory granules and expressed stem cell markers and signaling pathways at a much higher level than the main population cells [8,19]. SP cells express stem cell antigen-1 (Sca1), Oct-4, Bmi1, CD133, Nanog, Nestin [46,48,49]. They also express components of Notch, Wingless-type MMTV integration site family (Wnt), and Sonic hedgehog (Shh) pathways [46,50,51]. SP cells of the pituitary contain cells that *in vitro* can clonally into spheres, known as pituispheres, a hallmark of many tissues stem/progenitor cells [14,46,52]. SP cells were observed based on their Sca1 expression levels, and it was surprising that the non-Sca1^{high} subset was found to cluster the stem/progenitor cells, not the Sca1^{high} subset [53]. The second important feature of stem cells, long-term self-renewal capacity, has not yet been fully shown. Although this may be due to technical obstacles, there is no way of being certain that SP cells are stem/progenitor cells of the pituitary, and more extensive research is needed [46].

Pituitary colony-forming cells

Pituitary colony-forming cells (PCFC) have been identified in the adult and embryogenic pituitaries [8,54]. These cells have *in vitro* clonal expansion capacity, thereby forming adherent colonies [87,54]. Individual cells forming colonies are called colony-forming units (CFU) (109). Colony-forming cells constituted a very small portion of the cells in (0.2%) of the pituitary [8,46]. These cells represent a small subset of the heterogeneous FS cell group since they imported the fluorescent dipeptide β-Ala-Lys-Nε-AMCA, a characteristic of the FS cells [13,54-57]. Further purification was achieved by categorizing the AMCA+ cells for angiotensin-converting enzyme (ACE) and stem cell antigen-1 (Sca1) [8,46]. More AMCA+/ACE+ cells displayed colony-forming behavior than AMCA+ only cells [8,46,47]. This is suggestive of the important role of ACE in elaborating the PCFCs [55]. A few GH-immunoreactive cells were observed two weeks after the seeding, suggesting some limited somatotroph differentiation potential for a small portion of the PCFCs [8,58]. PCFCs have shown the capacity to differentiate into GH+ (growth hormone) cells *in vivo* [46,58]. Cells with a stellate shape and long cytoplasmic processes, similar to the FS cell morphology, were seen in the majority of the PCFC colonies [8,14]. The colonies also contained some small and refractile cells [8,14].

Since colony-forming capability is not identical to self-renewal capacity, pituitary colony-forming cells cannot conclusively be named stem/progenitor cells, and more extensive research is needed [8].

SOX2+ cell population

Sox2 is a transcription factor of the high mobility group (HMG) family [59,60]. It expressed at high levels in the embryos, plays a

paramount role in CNS development, and is also required for the development of the pituitary gland [57,60]. In the murine postnatal pituitary, the SOX2 expression pattern is similar to that of the embryonic gland, which is mainly located in the marginal zone [57,59]. In the adult gland, less than 5% of the anterior lobe cell population expresses Sox2; from this 5%, only 1% is Sox9+ [57]. Pituitary SOX2-expressing cells from embryos and adults have been shown to have the capacity to differentiate into multiple pituitary endocrine cell types in culture and *in vivo*, proposing these cells as stem/progenitor cells of the pituitary gland [61-63]. When Sox2 expression was deleted in mice, severe anterior hypoplasia and severe disruption of somatotroph and thyrotroph differentiation were due to insufficient periluminal progenitors [64]. The pituitary Sox2+ cells after cell-ablation injury were shown to be involved in regeneration [65,66]. When large depletion of the Sox2+ cells was achieved in the adult pituitary, pituisphere formation dramatically decreased and, therefore, the stem cell function [67]. Interestingly, the remainder of the Sox2+ cell population did not restore the stem cell population, and the hormonal cell population proportions stayed the same. No support system, such as higher proliferative activity or differentiation, was observed to make up for the depletion of Sox2+ cells. It may be proposed that there may be an additional stem cell population. Since other known stem cell markers, such as Sox9 and E-cadherin, usually co-localize with Sox2+ cells, they were also reduced and did not repopulate [67]. One hypothesis may be that there should be a sufficient reserve of stem cells for functionality [67].

In BrdU labeling experiments, Sox2+/Sox9+ cells were observed to have significant proliferation rates, while Sox2+/Sox9- cells showed persistence of staining during label-retaining experiments, which is a property seen in adult stem cells suggesting low cell-turnover. It was theorized that Sox2+/Sox9+ cells were transit-amplifying cells and that tranquil multipotent Sox2+/Sox9- cells would turn into Sox2+/Sox9+ cells in response to adaptive requirements [57,61,68]. Nevertheless, in a later study, Sox9+ cells maintained their identity in long-term lineage experiments, and therefore Sox2+/Sox9+ cells were presented as stem/progenitor cells, not transit-amplifying cells [62]. In short-term BrdU incorporation experiments, it was shown that Sox2+/Sox9+ cells, even though at a low rate, proliferate [62]. Very few Sox2+ cells were BrdU positive in the label-retaining assays. These results strongly suggest that the stem cells renew but rarely differentiate in the adult [62]. While there is strong evidence that the Sox2+ cells are the stem/progenitor cells of the pituitary, many different stemness markers co-localize with Sox2. Therefore, more detailed study is needed to pinpoint the exact stem cells.

GFRa2/Prop1/Stem cells (GPS)

According to the expression of GFRa2, the GDNF co-receptor, another possible group of stem cell candidate, was identified [57,69]. GFRa2-expressing cells constituted 0.9% of all pituitary cells [57,69]. GFRa2-expressing cells were found to express β-catenin, E-cadherin, OCT4, and SSEA4 (stage-specific embryonic antigen-4) 90% of them also expressed Sox2 and Sox9, and 50% also expressed S100 [57,70]. Surprisingly, these cells also expressed PROP1, a transcription factor required for differentiation into Pit-1 positive cells [57,71]. This phenotype raised the suggestion that GPS cells are transit-amplifying cells rather than stem/progenitor cells [57,61,70]. GPS cells were mainly identified in the periluminal zone as a single layer of cells lining the cleft [57,70].

In another study, GFRa2+ cells were shown to form spheres in culture, and these spheres had the ability to differentiate into hormone-producing cells [59,69,70]. In addition, GPS cells were shown to display slow proliferation after birth, retain the BrdU label and show long telomeres in their nuclei *in vivo*, which may be suggesting of them as stem/progenitor cells of the pituitary [59,69,70].

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. To better understand the mechanisms of pituitary tumorigenesis, pituitary hormone deficiencies, and how pituitary stem cells take part in those, a lot more research is needed.

In this article, we have summarized potential stem cell candidates of the pituitary gland. Folliculostellate cells, follicular cells, marginal cells, side population cells, pituitary colony-forming cells, SOX2+ cells, and GFRa2/Prop1/Stem cells are thought of as the candidates. There are compelling evidence to all any one of them stem cells of the pituitary gland, much more research is needed to be certain.

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