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Identification and clinical significance of folliculo-stellate cells in normal hypophysis and adenomas

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Abstract

Background: Folliculo-stellate cells were first identified with electron microscopy as a non-hormone secreting accessory cells, star-shaped and follicle-forming cells. They represent about 4-20% of pituitary cells from the anterior pituitary lobe. The folliculo-stellate cells control several anterior pituitary activities. However, they do not produce hormones, but they produce growth factors, cytokines, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), leukemia inhibitory factor (LIF), IL-6, and macrophage migration inhibitory factor (MIF), IL-1β and TNF-α. Regardless of a long period of pituitary research and many morphological, cytophysiological studies, it has been reported that a precise understanding of the major functions of folliculo-stellate in the pituitary gland remains unknown. Consequently, there are still many unsolved issues.

Conclusions: This article intends to review the characteristics of folliculo-stellate cells and their uncertain functions in the adenohypophysis, such as their importance as stem cells, in the process of maturation and aging. New researches about the origin and differentiation of folliculo-stellate cells may provide many relevant answers about physiopathology of the pituitary gland and the pathogenesis of pituitary tumors, as well as their influence on the quality of life. Immunohistochemical profile studies of folliculo-stellate cells in pituitary gland, can be useful in elucidation of morphological features and may have a predictive role for the early identification of pituitary microadenomas, prognosis of pituitary tumors and treatment.

Key words: folliculo-stellate cells, S-100 protein, hypophysis, pituitary tumor.

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Introduction

The pituitary gland is a small endocrine regulator complex, essential organ to the human body. It represents an intermediary body between the signal exchanges among the hypothalamus and peripheral organs. It also contains substantial functions in a lot of processes such as growth, reproduction, metabolism and immune response. The anterior pituitary gland includes granular hormone-producing cells, which act by controlling the growth (growth hormone GH), lactation (prolactin PRL), thyroid function (triiodothyronineT3 and thyroxineT4), adrenal function (adrenocorti-cotropic hormone-ACTH-), gonadal function (follicle-stimulating hormone-FSH- and luteinizing hormone-LH-) [1, 2]. The posterior pituitary secretes vasopressin (antidiuretic hormone-ADH-), which is the hormone responsible for maintaining water balance, and oxytocin, that plays a role in uterine contraction and lactation [3, 4].

Along with the discovery of folliculo-stellate cells, a multitude of their important functions have been identified. This literary review focuses on presenting the characteristics of folliculo-stellate cells and their importance as stem cells, in the process of maturation, aging, and in the pathogenesis of pituitary tumors.

This research is a meta-analysis of contemporary scientific literature reported in PubMed and Springer Link database, with reference to folliculo-stellate cells, by the following key words: "folliculo-stellate cells", "S-100 protein", "hypophysis", "pituitary tumor" and selected articles published in the 2000-2019, as well as several earlier articles and books, available in English. During the first stage, we have identified all the articles corresponding to the subject under investigation. After collecting the articles, we proceeded to selecting the valid information from them and extracting relevant data. Finally, we analyzed all the data and drew up the conclusions.

Results and discussion

Folliculo-stellate (FS) cells of the adenohypophysis represent a population of nongranulated cells described in a large number of species [1]. They show typical morphological features including a star shape, with thin cytoplasmic projections extending between granulated cells and well-developed junctional complexes [5]. Joining together, FS cells surround irregular microcavities and project microvilli into the lumina. The immunocytochemical localization of S-100 protein, glial fibrillary acidic protein, and vimentin constitutes an easy method for investigating their presence and distribution in the normal pituitary gland and in pituitary adenomas. FS cells have immunohistoche-mical specificity and express positivity for the S-100 protein [6]. Also it has been reported, that they tend to be immunoreactive to

other markers such as glial fibrillary acidic protein (GFAP), major histocompatibility (MHC) class II surface antigens, cytokeratins, and vimentin [6]. Due to the variable expression levels of these markers, FS cells are currently considered to be phenotypically and functionally heterogeneous, with three main subtypes being proposed: astrocyte-like (also expressing GFAP), dendritic cell-like (also expressing MHC class II), and epithelial cell-like (also expressing cytokeratins) [7].

Although the expression of glial cell markers raised the hypothesis of a neuroectodermal origin of FS cells, most evidence supports that they derive from the epithelium of the Rathke's pouch, as granulated adenohypophyseal cells do [4].

Besides the roles FS cells have in the normal anterior pituitary, their identification in pituitary tumors suggests FS cells may also have major implications in these tumors. However, the available knowledge concerning FS cells in human pituitary tumors comes mainly from IHC studies assuming their presence by means of S-100 immunoreactivity. Their role in the initiation, maintenance, and progression of pituitary tumors or in the functioning phenotype of these tumors remains largely undetermined [3, 8].

In one of the biggest studies, Voit et al., studied FS cells. 286 cases of pituitary tumors have been researched in patients presenting acromegaly [9]. The authors reported that FS cells were found to be either isolated or grouped, forming network-like structures. These structures were frequently in close relationship with the tumor cells. Their results showed that 198 out of 286 tumors (69%) contained FS cells. The number and distribution of FS cells were varying: 35% of the tumors (100 cases) presented few widely sparse FS cells, 15% of the tumors (43 cases) presented FS cells scattered throughout the tumor, and 19% of the tumors (55 cases) showed abundant FS cells. When they examined clinical correlations, the researchers noticed the existence of a negative correlation between the density of FS cells and the preoperative mean prolactin levels. It is an observation rather contradictory to what was published *in vitro* work that generally showed that the interaction between prolactin-secreting cells and FS cells, and/or their secreted molecules, results in an increased prolactin level. The same researchers found that preoperative mean growth hormone levels were higher in patients with tumors containing few widely sparse (64.5-8.1 g/L) or scattered FS cells (83.1-17.1 g/L) than in those patients with tumors lacking FS cells (44.9-4.1 g/L). This observation supports the possibility that part of the role of FS cells in pituitary tumors may be similar to the function of FS cells in the normal pituitary, where one of their roles is to regulate the secretory capacity of normal endocrine pituitary cells [3]. However, it is interesting that the difference observed with the widely sparse or scattered FS cells was not noticed in the case of abundant FS cells. Indeed, the preoperative mean growth hormone level was lower in patients with tumors containing abundant FS cells (41.0-5.7 g/L) than in patients with tumors without FS cells (44.9-4.1 g/L). This may suggest that during tumor microenvironment remodeling, the function of these cells is modified or there are different types of FS cells [9, 10].

Another study, Vajtai et al. started by analyzing three cases of pituitary tumors, two prolactinomas, and one gonadotroph tumor. These tumors presented with an inflammatory reaction mediated by T lymphocytes that selectively involved the tumoral tissue [9]. The authors observed that perivascular T lymphocytes (predominantly CD4+) tended to mix with cells immunopositive for the S-100 protein. In order to differentiate the FS cells from inflammatory foci presented monocytic/dendritic properties, researchers performed double immunohistochemical staining for S-100 protein and the MHC class II antigen HLA-DR and they found that in these 3 cases, many of the FS cells co-expressed both epitopes. These cells that could not be morphologically distinguished from the FS cells negative for the MHC class II antigen HLA-DR were distributed both between tumoral acini and alongside intratumoral vessels, mingling with the T lymphocytes [9]. CD1a (as a marker for Langerhans' cells) and CD21 (as a marker for follicular dendritic cells of lymphoid type), as well as cytokeratins, tested negative. Moreover, no FS cell co-expressing S-100 protein and HLA-DR in the peritumoral tissue in these 3 cases, neither in the tumoral tissue of other 48 cases of pituitary tumors lacking an inflammatory reaction. The scientists postulated that an appropriate inflammatory TME may induce an FS cell subset to adopt a dendritic cell-like phenotype and that these cells may have an antigen presentation function in pituitary tumors [11].

To understand the mutual interactions between the tumor and the peritumoral tissue during tumor progression, Farnoud et al. looked at the boundary between the tumor and the adjacent normal anterior pituitary tissue in a series of 18 pituitary tumors [12]. Researchers reported the presence of a transition zone between the tumor and the peritumoral tissue, with a modified architecture. Intriguing, they observed that density of the FS cells tends to be higher in the transition zone and its vicinity compared to the density observed in the tumor center or in the normal pituitary tissue distant from the tumor. In addition, alterations of the basement membrane were observed in the peritumoral tissue adjacent to this transition zone [13].

In 2000, the first FS cell line derived from a human gonadotroph pituitary tumor was established and named PDFS, for pituitary-derived FS cells. PDFS were demonstrated to show an epithelial-like morphology and to express S-100 protein and vimentin. The presence of FS cells in the TME of pituitary tumors and their association with clinical traits support their potential role in tumor genesis related processes, but a better understanding of their heterogeneity and their functions in tumors is still needed before we can assess their potential use as a therapeutic target [9].

Another study is focusing on the development of the folliculo-stellate cells in human fetal pituitaries [5]. They also have been investigated by immunohistochemical methods for S-100 protein and glial fibrillary acid protein. S-100 positivity was first observed in pars intermedia cells in a 13-

week fetus. Staining with this antiserum is seen in cells of the pars distalis after 15 weeks. Glial fibrillary acid protein was not apparent until 18 weeks, when only cells in the pars intermedia were stained. These cells were not seen in the pars distalis before 28 weeks' gestation, but were present in a 39-week specimen and in a 5-day old baby. In most pituitaries examined, cells staining for S-100 and glial fibrillary acid protein were more concentrated in the pars intermedia than the pars distalis. These results suggest that folliculo-stellate cells in the human pituitary originate in the neurally associated facet of the pars intermedia and pass through this lobe to reach the pars distalis. Since these cells stain for glial related antigens, they may be a modified form of glial cells and arise in the neuroectoderm. Evidence for this hypothesis is given by a lack of both S-100 and glial fibrillary acid protein in the pituitaries of 3 anencephalic pituitaries. Differences in the timing of S-100 and glial fibrillary acid protein immunoreactivity may be related to developmental aspects of the folliculo-stellate cell, or to the presence of two distinct cell types [14].

Conclusions

New studies about the origin and diferentiation of FSCs will provide answers about physiopathology of the pituitary gland. The immunohistochemical localization of S-100 protein, glial fibrillary acidic protein, and vimentin constitutes represent an easy method for investigating follicular-stelated cells presence and distribution in the normal pituitary gland and in pituitary adenomas. Expression of glial cell markers supports the hypothesis of a neuroectodermal origin of FS cells, still, most evidence supports the idea that they derive from the epithelium of the Rathke's pouch. The elucidation of morphological features of folliculo-stellate cells will have a predictive role for the early identification of pituitary microadenomas. Further research using immunohistochemical markers may clarify the origin and the role of this mysterious cell type in the normal and pathological pituitary glands.

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Author's contributions
EP designed the trial and drafted the first manuscript, interpreted the data and revised the manuscript critically. The author revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
No approval was required for this review study.

Conflict of Interests
No competing interests were disclosed.