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The Structure and Function of Folliculo-Stellate Cells in the Anterior Pituitary Gland

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Summary. **The folliculo-stellate cells (FS cells) in the anterior pituitary gland are characterized by their star-like appearance and their ability to form follicles. Although FS cells do not produce any pituitary hormones, their special tendency to surrounding endocrine cells with their long cytoplasmic processes suggests that they regulate endocrine cells by intercellular communication. In spite of many morphological and cytophysiological studies recently performed, a precise understanding of the major functions of FS cells in the pituitary gland remains obscure. We review here the morphological characteristics of FS cells and their suspected functions in the anterior pituitary gland. It is well established that the FS cell produces many kinds of growth factors, i. e., fibroblast growth factor, vascular endothelial cell growth factor and interleukin 6. The biological significances of these growth factors in the anterior pituitary gland are also discussed in this paper. The origin and differentiation of FS cells, especially the possibility that the FS cell is a kind of stem cell which has the potential to differentiate into endocrine cells, is also presented.**

The anterior pituitary gland is composed of both granular and agranular cells. The granular cells contain secretory granules in their cytoplasm and produce pituitary hormones which are known to affect processes such as reproduction, growth, metabolism and the immune system. This has led to, a vast number of studies on these granular cells. The discovery of the regulatory system controlling the synthesis and release of these pituitary hormones through hypophysiotropic hormones secreted from the hypothalamus was one of the most important events in endocrinology during the 20 th century. However, we now know that the accumulated information pertaining to these hypothalamic factors alone can not fully explain the regulation of the anterior pituitary gland's functions. In addition to these hypothalamic factors, local regulatory systems within the anterior pituitary gland have been discovered.

Evidence has accumulated supporting the contention that it is the folliculo-stellate cells (FS cells), a major group of agranular cells located in the parenchymal tissue of the anterior pituitary gland, which provide this additional control. These FS cells are characterized by their star-like appearance (RINEHART and FARQUHAR, 1953) and their ability to form follicles (KAGAYAMA, 1965). Their long cytoplasmic processes which surround neighboring glandular cells suggest that these cells might communicate with the glandular cells of the pituitary and contribute to the control of their microenvironment. However, the mechanism of FS cells for regulating neighboring endocrine cells remains to be elucidated. A number of investigations have been made exploring the functions of these FS cells, and recently a number of proposals have appeared which suggest how they might influence the control of secretion of the glandular cells of the anterior pituitary. We will review here the morphological characteristics of FS cells and discuss their suspected functions. We will also comment on the present and future researches on these cells.

General structure of FS cells

Light microscopy

Because FS cells do not produce any type of pituitary hormone, immunocytochemistry using antibodies against such hormones could not be used to detect them. This fact hampered the study of FS cells and delayed their investigation compared with the rapid progress made with hormone-producing pituitary

cells. The finding that S-100 protein (NAKAJIMA et al., 1980; COCCHIA and MIANI, 1980) could be used to specifically demonstrate the FS cells opened up an important avenue for their study. In fact, immunocytochemistry using S-100 protein has become a powerful method which allows the visualization of FS cells with the light microscope.

After the development of the technique using the S-100 protein antibody, some additional substances characteristic of FS cells have been reported. These include the glial fibrillary acidic protein (GFAP) (VELASCO et al., 1982), fibronectin (LIU et. al. 1989), vimentin (MARIN et al. 1989), and cytokeratin (HALLIDAY et al., 1990). However, the immunoreaction for S-100 protein is still in use and is considered to be the most reliable staining method for FS cells.

Interestingly, the antibody for S-100 protein stains not only the FS cells located in the pituitary parenchymal tissue, but also the supramarginal cells in Rathke's pouch (CORRER amd MOTTA, 1985). These cells share characteristics with FS cells such as phagocytotic activity (YOSHIMURA et al., 1977a; CORRER and MOTTA, 1985). Thus a similarity between these cells has been suggested.

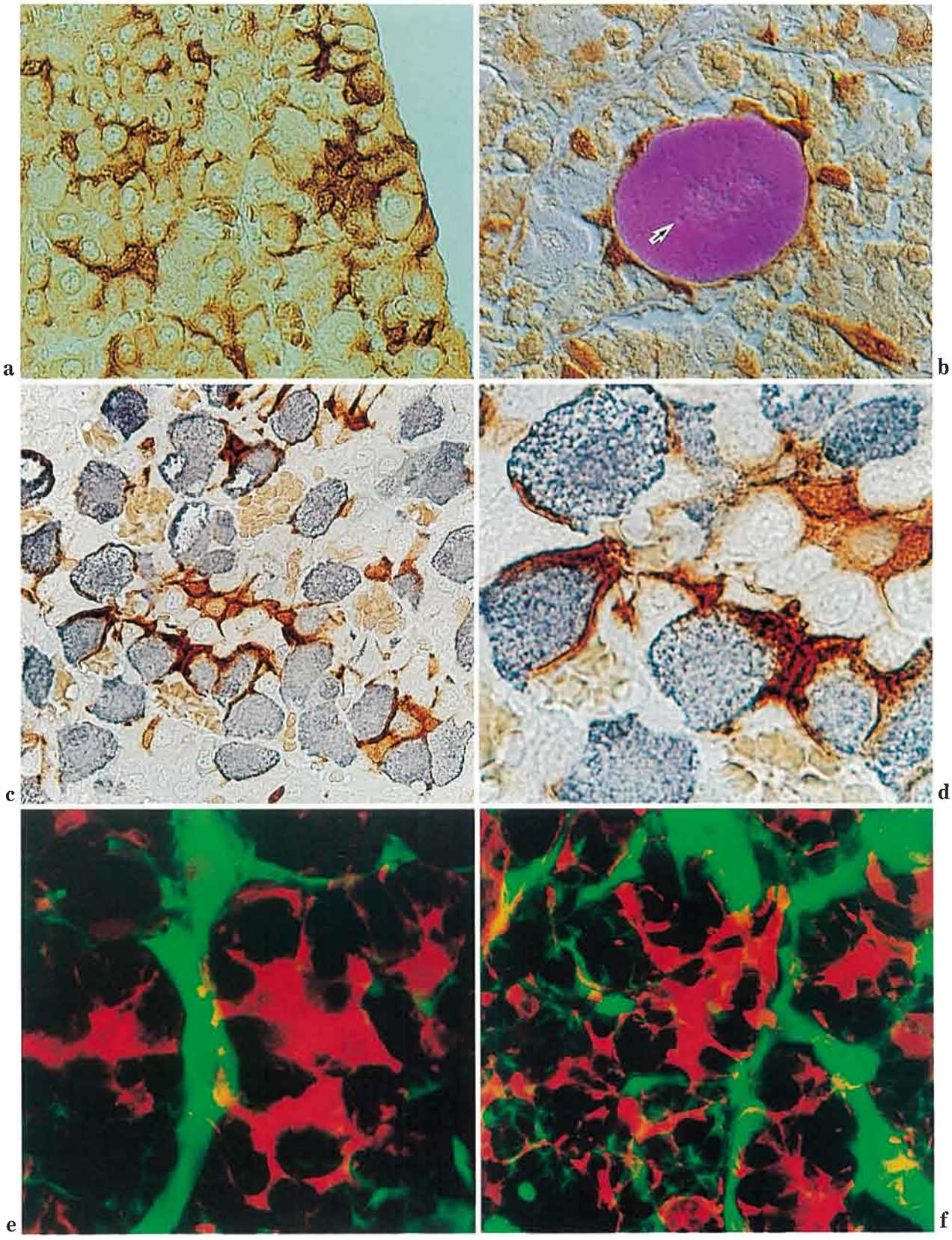
As shown in Figure la, the immunocytochemistry targeted to S-100 protein discloses a rather large number of FS cells in the rat anterior pituitary gland. The FS cells usually aggregate to form cell clusters, but some of the S-100 protein positive stellate cells are solitary. The most peculiar characteristic of FS cells is their extremely long cytoplasmic processes which extend onto neighboring endocrine cells (Fig. 1). This characteristic of FS cells can be demonstrated by confocal microscopy combined with computer imaging as shown in Figures 1e and f.

Electron microscopy

FS cells were first identified by electron microscopy (RINEHART and FARQUHAR, 1953) and named after characteristics seen with the electron microscope, i. e., their star-like appearance and follicle formation (VILA-PORCILE, 1972). Many morphological studies have been conducted using the electron microscope. Typical FS cells in the rat pituitary are easily recognized by electron microscopy by their lack of cytoplasmic granules and by the presence of tiny follicles they produce (Figs. 4, 5). The FS cells also have many microvilli on their apical portion facing the follicular lumen (Figs. 2b, 3, 5b). Fibrous structures in their cytoplasmic processes are also numerous (Fig. 4a insert). Primary cilia (central cilia) which face the follicular lumen have also been observed (HARRISSON, 1989). The follicles they form are surrounded by tight junctions, but these junctions are not complete and are permeable to some substances (VILA-PORCILE, 1972; ALLAERTS et al., 1990). For this reason the follicles have also been called pseudo-follicles (BENJAMIN, 1981). The follicular lumens are mostly empty in normal rats, but occasionally electron dense material can be seen within the follicular colloid (Fig. 2b). Also present in the colloid are many electron dense particles about 22 nm in diameter, which have yet to be identified chemically. Another characteristic of FS cells is the existence lysosomes which may reflect phagocytotic activity in these cells (SHIOTANI, 1980; STOKREEF et al., 1986; REIFEL et at., 1989).

The presence of gap junctions has been reported in the anterior pituitary gland (FLETCHER et al., 1975), and these junctions are also present between FS cells (See review: PERRYMAN, 1989). Their presence has been confirmed by SOJI and HERBERT (1989) who showed that the gap junctions between FS cells change after castration, after GnRH treatment (SOJI and HERBERT, 1990), by postnatal development, and during the estrus cycle (SOJI et al., 1991). The formation of gap junctions between FS cells has also been confirmed by immunocytochemistry through the localization of connexin 43, a known gap junctional protein (YAMAMOTO et al., 1993). Most of the gap junctions occur between FS cells themselves, but heterologous junctions between FS cells and prolactin cells have been reported (MORAND et al.,

Fig. 1. Light microscopic appearance of folliculo-stellate cells (FS-cells) in the pituitary gland. **a.** FS-cells in the normal rat anterior pituitary gland. The FS-cells were stained by immunocytochemistry using an antibody against S-100 protein. **b.** PAS positive colloid in the senescent porcine pituitary gland. Note how colloid is completely surrounded by S-100 protein positive FS cells. Debris exist in the colloid (*arrow*). **c.** Double immunocytochemical preparation of FS-cells (brown) and gonadotrophs (blue) in the anterior pituitary of a castrated rat. **d.** High magnification of **c**. Note that the LH immunopositive gonadotrophs (blue) are surrounded by S-100 immunopositive FS-cells (brown). Confocal images of FS-cells (red) in normal (**e**) and castrated rats (**f**). The blood vessels (green) were stained by perfusion with FITC-labeled gelatin through the left ventricle. Note how close contact site (yellow) between the FS-cell processes and the blood vessels increase in the castrated rat pituitary gland (**f**). The extremely narrow processes of the FS-cell in the castrated rat are also well demonstrated (**f**). a: ×390, b: ×310, c: ×390, d: ×970, e: ×970, f:×680



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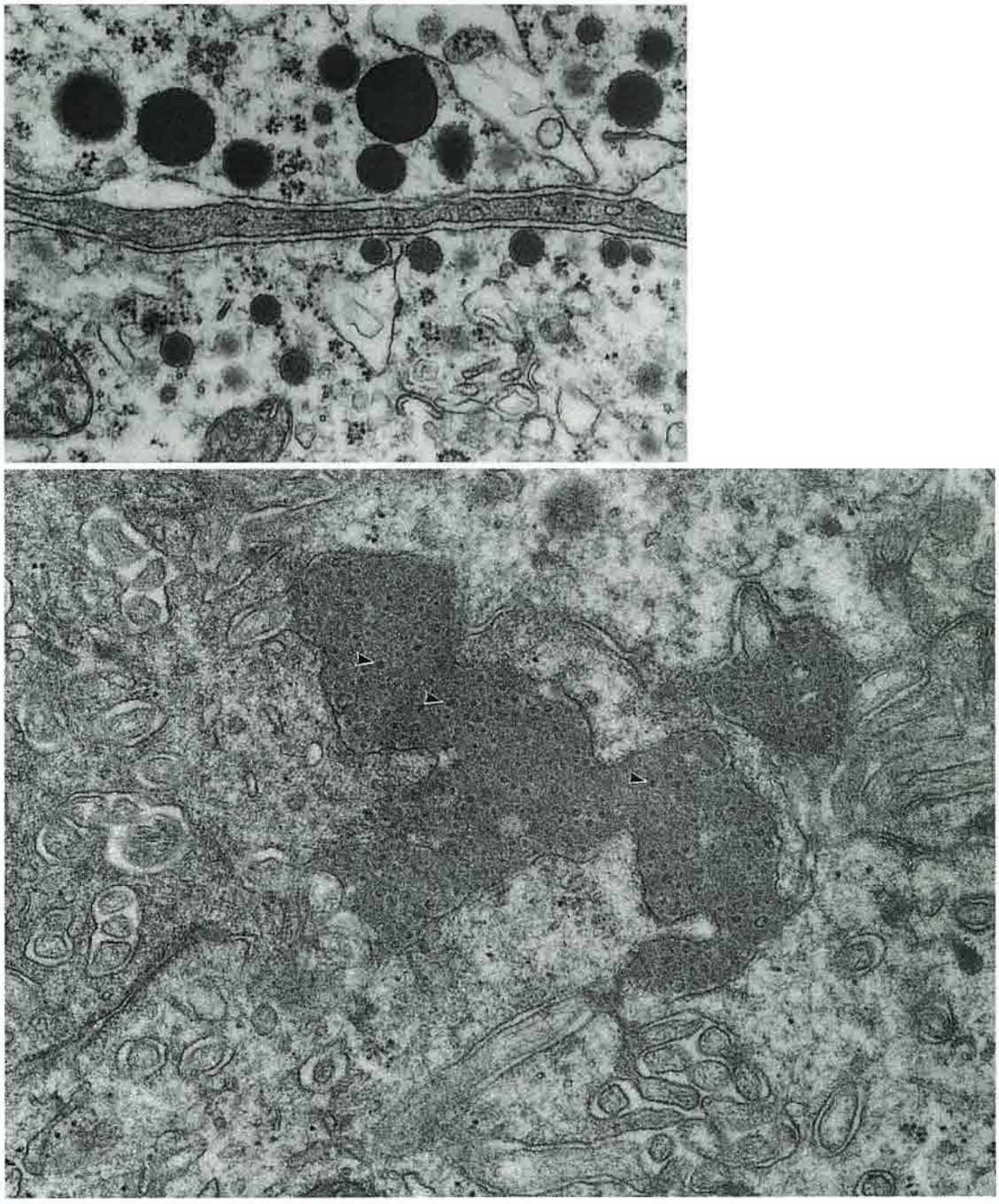


Fig. 2. Electron microscopic view of the cytoplasmic process of a FS-cell (**a**) and colloid substances formed by FS-cells in the normal rat pituitary gland (**b**). Note the electron dense particles (*arrowheads*) that exist in the colloid (**b**). a: ×35,000, b: ×47,000

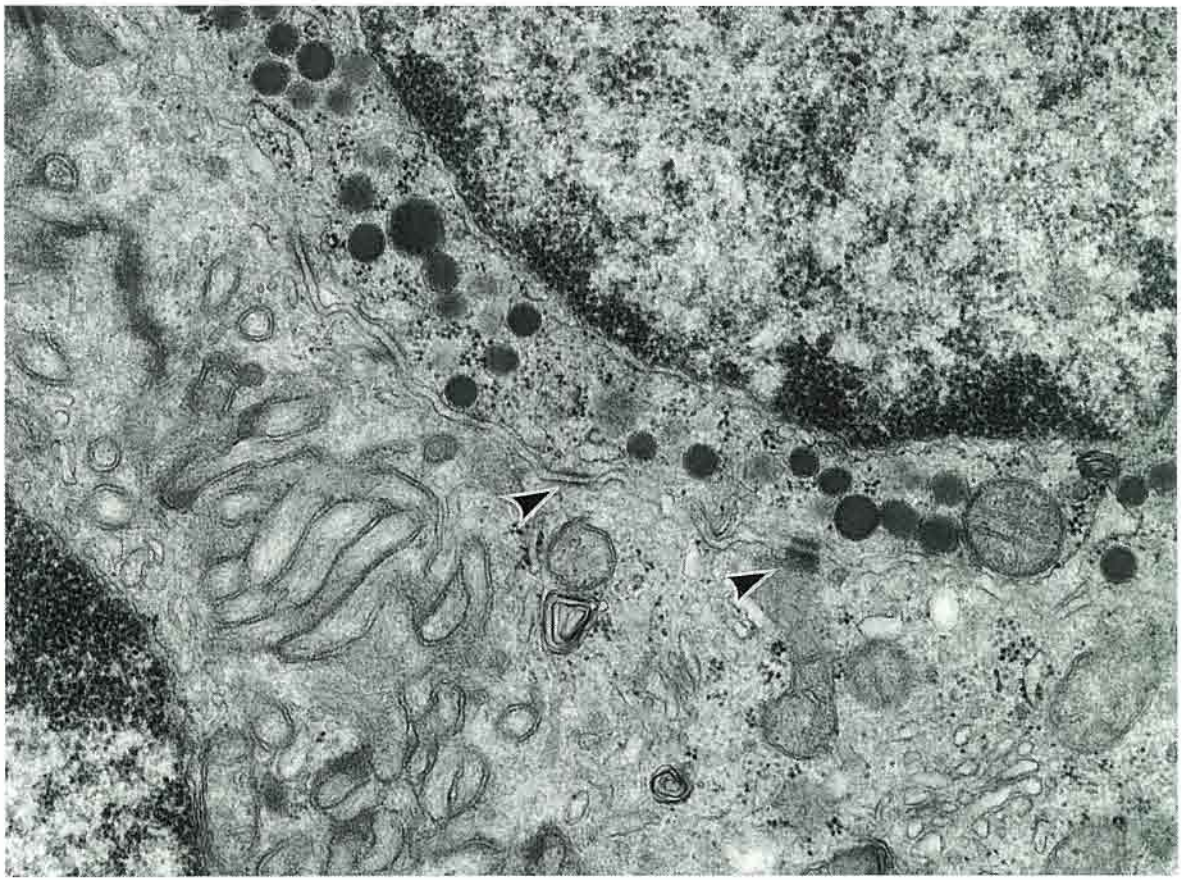


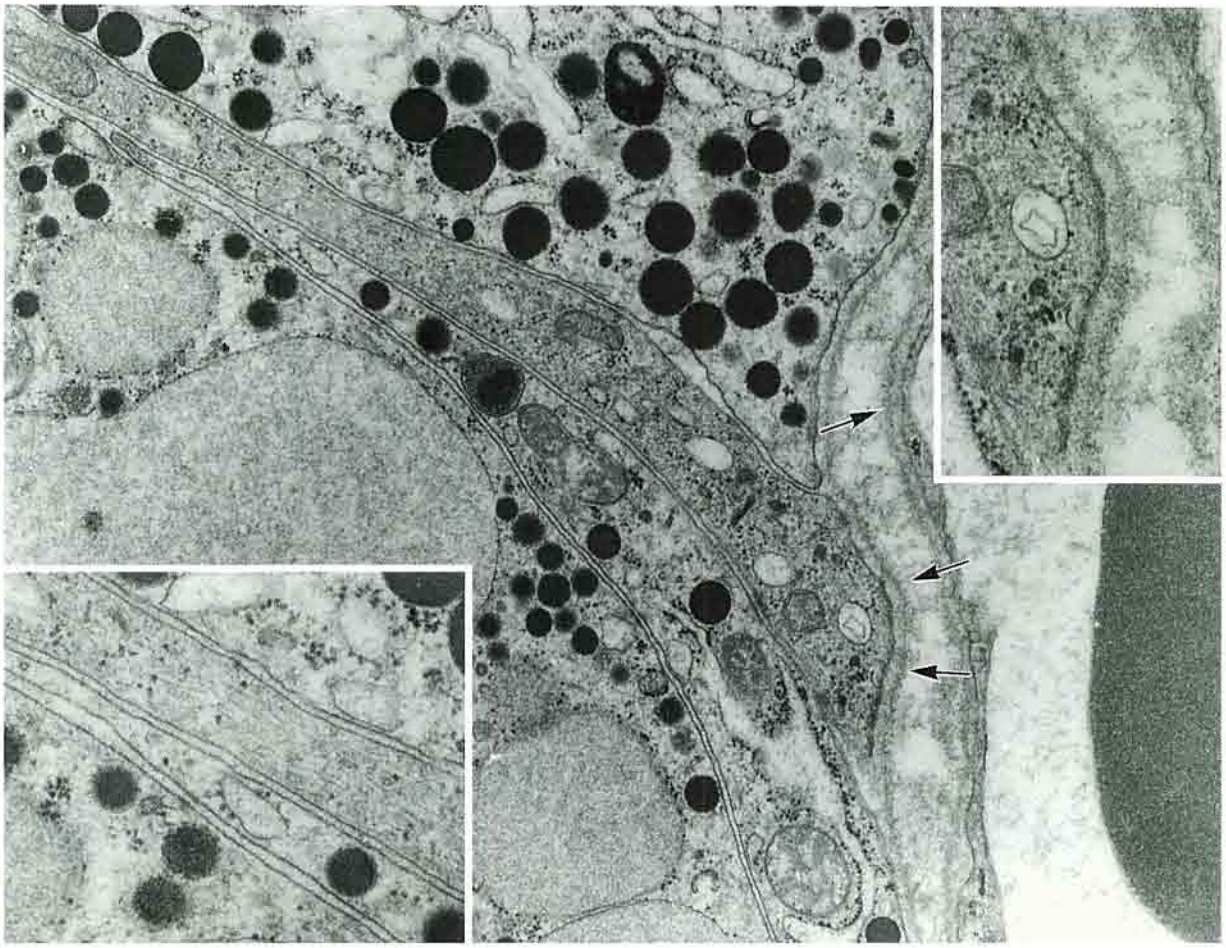
Fig. 3. Close association of folliculo-stellate cells and glandular cells. Note that desmosomes exist between the endocrine cell and the FS cells (*arrowheads*). Many microvilli are present. ×34,000

1996). The presence of gap junctions in the FS cells indicates that the FS cells forming electrical syncytia and are responding synchronously through these gap junctions. Transport of nutrients and regulatory molecules from FS cells to endocrine cells through gap junctions is also suspected. Desmosomes can occasionally be seen between FS cells and neighboring endocrine cells as seen in Figure 3. The FS cells and the endocrine cells are both surrounded by a common basal lamella (Fig. 4a), and the presence of desmosomes may be an indication that the FS cells have epithelial characteristics, and that both are derived from the same ancestral cell.

The extension of cell processes into blood capillaries is an interesting feature of the FS cell. As shown in Figure 4a, the terminal ends or end feet (CARDELL, 1969) of the processes are swollen at the site of the blood capillary and have a rigid plasma membrane in this area. The FS cells, however, never make direct contact with the endothelial cells. Their two basal laminae are separated from each other (Fig. 4a). The close relationship between FS cells and blood capillaries becomes more prominent in the castrated animal, as will be discussed in the following section.

Origin and differentiation of FS cells

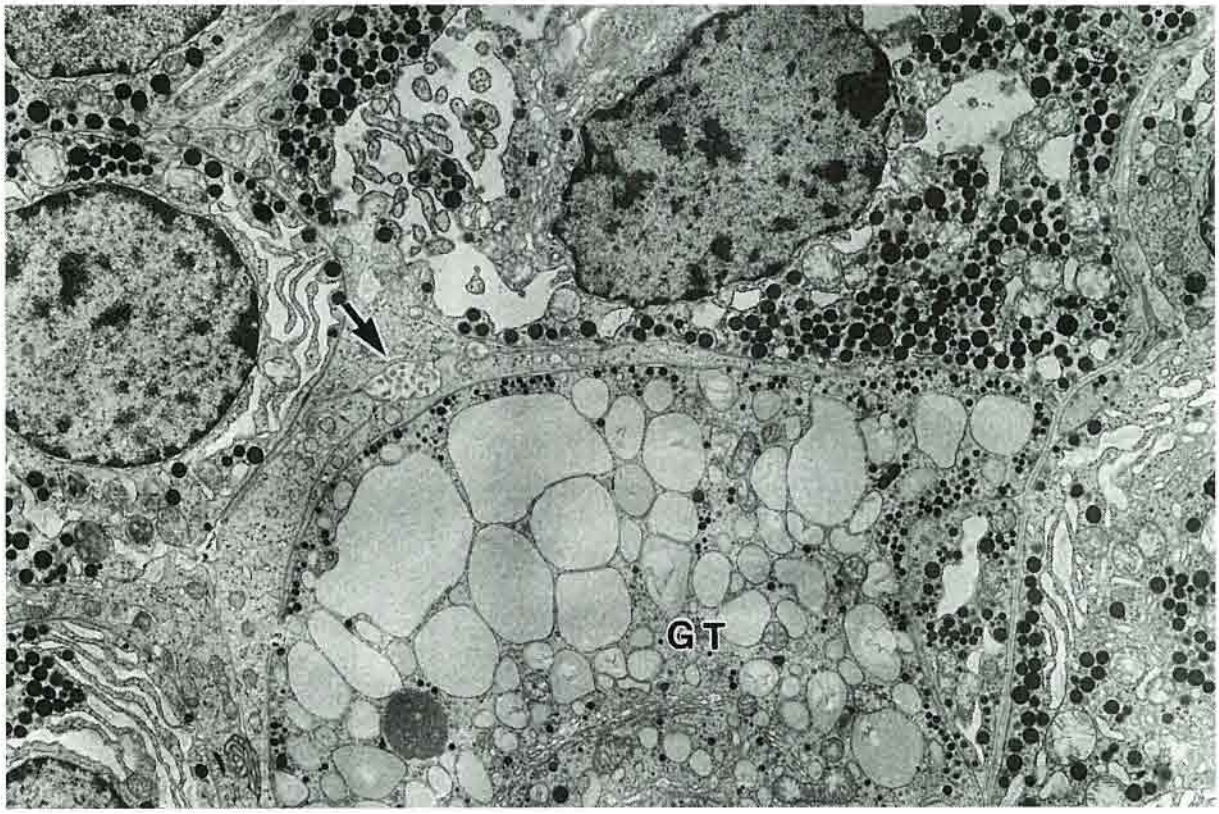
The origin of FS cells poses an interesting question. In general it has long been the view that the adenohypophysis originates from Rathke's pouch, a structure derived from the oral cavity, which is considered to be of ectodermal origin. However, it has also been proposed that some cells in the pituitary gland are derived from the APUD (amine precursor uptake and decarboxylation) system (TAKOR and PEARSE, 1975) or from paraneurons (FUJITA, 1980). The later theories have gained support in work by COULY and LE DOUARIN (1985, 1987) in experiments showing a close relationship between the adenohypophysis and the



4a

neuroectoderm. They performed heterologous transplantations of the neural cleft from quails and chickens and concluded that the adenohypophysis may be derived from the neuroectoderm instead of the ectoderm. Their findings were further analyzed by KAWAMURA and KIKUYAMA (1992), who performed an homologous transplantation of the anterior neural ridge or neural plate from normal and albino frog embryos. They also concluded that essentially all of the epithelial elements that compose the anterior pituitary gland are derived from the anterior neural ridge and not from the neural plate. These data suggest that the FS cell, which is an epithelial element of the anterior pituitary gland, is also derived from the neuroectoderm. Moreover, these findings suggest that FS cells and endocrine cells must be of the same cell lineage and that both originate from the neuroectoderm. Indeed, the production of S-100 protein and GFAP, which are known to be specific proteins of neuroglial cells, supports the contention that FS cells share similar characteristics with neuroglial cells.

Another fact regarding the pituitary development became evident after we implanted an adult rat pituitary gland beneath the kidney capsule. We found that the graft underwent ectopic differentiation into cells containing striated muscle fibers (INOUE et al., 1987). The appearance of striated muscle in primary cultured cells of the anterior pituitary has also been reported by BRUNNER and TSCHANK (1982). This work by BRUNNER and TSCHANK (1982) therefore supports the hypothesis that the muscle cells we saw in the graft were derived from the anterior pituitary itself and not from extra pituitary tissue. We have performed immunocytochemical and electron microscopic studies to further examine the nature of these ectopic muscle cells derived from pituitary cells. These studies of ours support the idea that the cells from the pituitary that contained muscle fibers are derived from FS cells (INOUE et al., 1987). Our find-



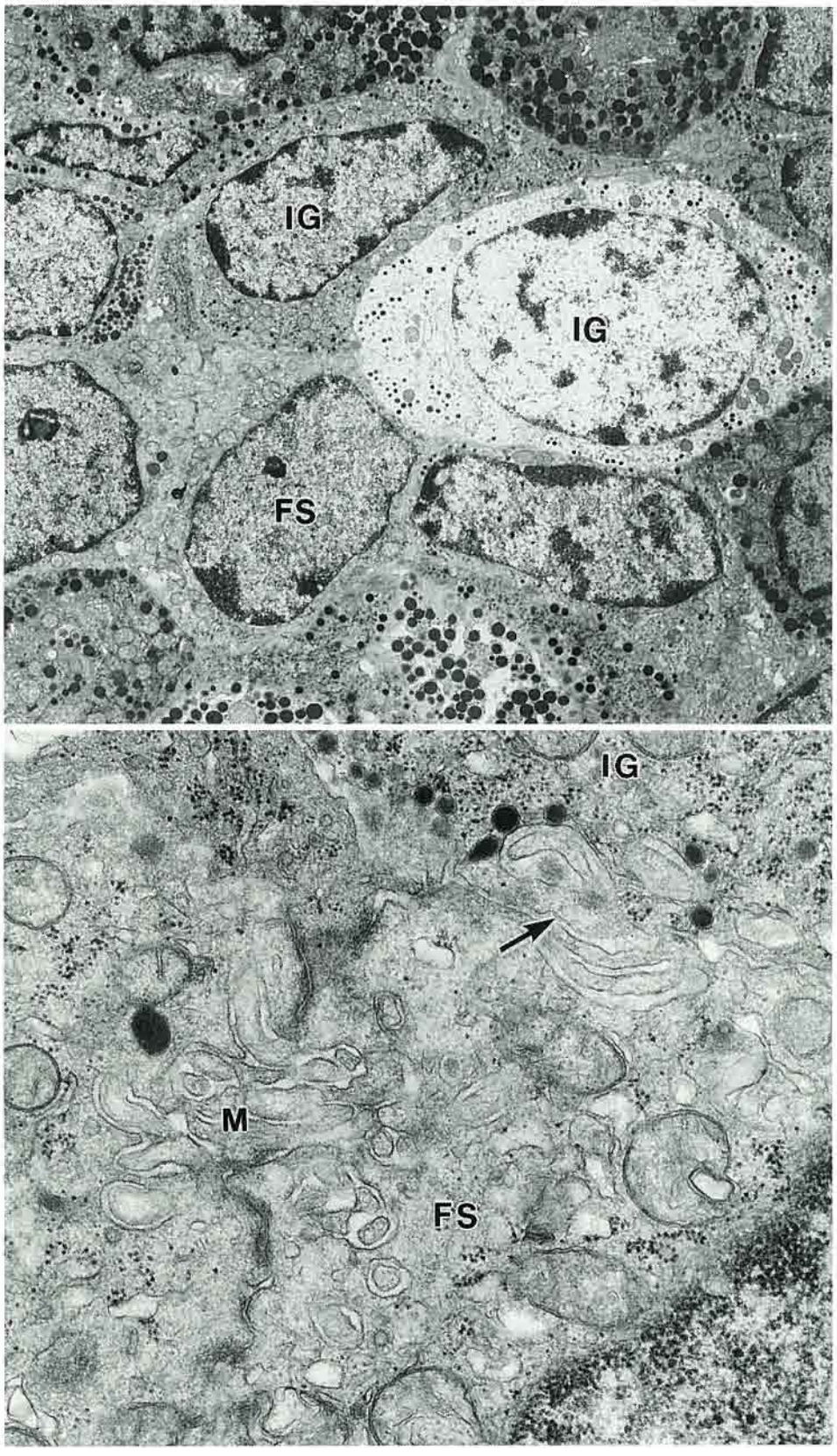
4b

Fig. 4. a and **b.** Electron microscopic appearance of folliculo stellate cells in the castrated rat. **a.** Demonstration of long cytoplasmic process of a FS-cell. The processes elongates to the blood vessel. Two basement membranes separate the endothelial cells and FS-cell (*arrows*). The rigid membrane is shown in the **upper right insert**. Numerous filaments present in the cytoplasrme process are shown in the high magnification (**lower left insert**). At low magnification (**b**), FS-cells are seen in close contact with a hypertrophied gonadatroph (*GT*). A tiny follicular lumen can be seen (*arrow*). a: ×26,000, b: ×3,500, inserts: ×46,000

ings were subsequently confirmed by studies carried out by HOSOYA and WATANABE (1997), who found that striated muscle fibers appear in cultures rich in FS cells. As mentioned previously, if FS cells are indeed derived from the neuroectoderm, the above findings correlate well with reports that neuroglial cells (DIEHL, 1978; NAKAMURA et al., 1984) and pineal cells (WATANABE et al., 1988) have the potential to differentiate into striated muscle under pathological or *in vitro* conditions.

It is also noteworthy that FS cells are frequently found surrounding immature glandular cells as shown in Figure 5. Similar associations with immature glandular cells are also observed in cells surrounding the marginal cells of the Rathke's residual pouch. It is also significant that many GH immunopositive cells are distributed just beneath the marginal epithelium of the Rathke's residual pouch in the normal male rat. However, they disappear after castration and are replaced by a few LH (luteinizing hormone) immunopositive cells. These observations indicate that FS cells or marginal epithelial cells are involved in endocrine cell differentiation.

The possibility that the FS cell is a type of stem cell with the potential to differentiate into endocrine cells has been suggested (RENNELS, 1964; YOSHIMURA et al., 1977b). The observation that immature endocrine cells are frequently associated with FS cells and cluster with them to form incomplete follicles (Fig. 5 a, b) suggests that the FS cells have the potential to differentiate into endocrine cells, or at least are involved in their differentiation. This is further supported by the finding that Ptx 1, which is known to be expressed in the common ancestral cells of the hormone producing pituitary cells, is also expressed in FS cells (KUROTANI et at., 1999). This suggests a close relationship between FS cells and endocrine cells. Supposedly, both are derived from a common



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precursor cell in the adenohypophysis. This idea has lead to the assumption that the FS cell may be derived from a single cell lineage; however, it has been reported that FS cell are not a homogeneous cell type, but instead are heterogeneous (ALLAERTS et al., 1997). Thus we can not discount the possibility that FS cells constitute a group of cells that are both functionally and ontogenically heterogeneous..

FS cells in castrated rats

If FS cells regulate neighboring endocrine cells by controlling their microenvironment, FS cells should respond to endocrine cell manipulations. Pursuing this idea, SHIRASAWA et al. (1983) made morphological observations of FS cells after altering their endocrine environment by gonadectomy, thyroidectomy and adrenalectomy. They found changes in the FS cells after castration, but not after removal of the thyroid or adrenal glands. We have confirmed their results and demonstrated that FS cells surround hypertrophied gonadotrophs with their long cytoplasmic processes (Fig. lc, d). Furthermore, we found that the FS cells increased in cell size and number after castration (unpublished results). In castrated animals, the blood vessels were well developed in the anterior pituitary gland, and long cytoplasmic processes from FS cells occasionally made contact with these (Figs. le, f, 4a). These morphological changes in the FS cells and blood vessels in the castrated animals suggest that the FS cells interact with hypertrophied gonadotrophs and blood vessels, possibly by producing a certain substance which might support the metabolism of the hypertrophied gonadotrophs in castrated animals.

FS cells and colloid accumulation in the senescent animal

As previously stated, one typical characteristic of FS cells is their ability to form follicles. As shown in Figures 2b and 4b, the follicles formed by FS cells are generally small and contain an electron lucent substance which sometimes includes a small amount of an electron dense substance. With age these follicles become highly developed in humans (CIOCCA et al., 1984), in guinea pigs (KAMEDA, 1990, 1991) and in pigs (KUBO et at., 1992). The colloids in the follicles can also change during hibernation in the bat (NUNEZ and GERSHON, 1982). This indicates that the contents of the colloid responds to physiological changes. Interestingly, a paracrystalline material also forms in the follicular colloid in the bat (ANTHONY and GUSTFSON 1982; NUNEZ and GERSHON, 1982). Electron microscopy has shown that these colloids are completely surrounded by FS cells (KAMEDA, 1991). We also have confirmed these results and have extensively analyzed the follicles by cytochemistry. We found that Asn-linked sialoglycoproteins are localized in the colloid of senescent porcine pituitary glands (OGAWA et al., 1997). This colloid has been further purified and analysed by OGAWA et al. (1996). Two major components of the colloid —clusterin and glycosilated albunin— were found and sequenced. Clusterin proved to be the major component of the colloid.

Immunocytochemistry of clusterin revealed, however, that it was not present in the cytoplasm of FS cells. Instead it was present in some of the endocrine cells (unpublished data). Clusterin has recently been shown to have a relationship with apoptosis, i. e., clusterin appears before apoptosis in an apparent attempt by the cell to protect itself from death (VIARD et al., 1999). Taking into consideration the scavenger function of FS cells after experimentally inducing apoptotic cells (DREWETT et al., 1993), the following hypothesis is proposed. Some endocrine cells produce clusterin before cell death, but ultimately these cells undergo apoptosis. Following this, the apoptotic cells containing clusterin are phagocytosed by FS cells and are digested by their lysosomes. Clusterin, however, may be protected from lysosomal enzyme degradation by its highly glycosilated form, and consequently becomes stored in the colloid as a residual body. Credence may be lent to this hypothesis by the observation that some phagocytosed cell debris has been observed in the colloid (HARRISSON et al., 1982, KAMEDA, 1991).

Production of growth factors, cytokine and NO

The morphological characteristic of FS cells to surround neighboring endocrine cells suggests that they may be contributing to the regulation of these cells by the secretion of paracrine factors. Basic fibroblast

Fig. 5. Association of immature glandular cells with folliculo-stellate cells. **a.** Present is an immature glandular cell (*IG*) characterized by small secretory granules which are associated with FS-cells (*FS*). High magnification (**b**) shows immature endocrine cells (*IG*) forming a common follicular lumen with FS cells (*arrow*). *M* microvilli. a: ×5,500, b: ×30,000

growth factor (bFGF) is one of the most important paracrine factors, and the anterior pituitary gland is known to produce much more bFGF than any other tissue. In fact, bFGF was first purified from the bovine anterior pituitary gland (GOSPODAROWICZ, 1975), and the FS cell is considered to be the site of this bFGF production (FERRARA et al. 1987). Some effects of bFGF on the pituitary endocrine cells have been reported (HAYASHI et at., 1978; BAIRD et al., 1985; INOUE et al., 1991), but the discovery of a more explicit role for bFGF in the anterior pituitary gland is anticipated. One possible role involves the well known angiogenic function of bFGF. The anterior pituitary gland is highly vascular, and the bFGF present in it may be the factor promoting this extensive angiogenesis (SCHECHTER et al., 1993). In addition to bFGF, vascular endothelial growth factor (VEGF) has been found and purified from a primary culture of FS cells (GOSPODAROWICZ and LAU, 1989). VEGF is also known to be a potent stimulator of angiogenesis and the permeability of blood vessels (ROBERTS and PALADE, 1995). It may contribute to capillary fenestration formation in the pituitary gland, a gland known to be densely endowed with fenestrated capillaries.

Previous work in our laboratory established a FS cell-like cell line (TtT/GF) from a thyrotropic pituitary tumor (INOUE et al., 1992). We found that the cotransplantation of the TtT/GF together with a somatotropic pituitary tumor cell line (MtT/S) into nude mice produced large tumors as compared to mice receiving the MtT/S cell line alone or cotransplanted with fibroblasts (KOYAMA et al 1995). One explanation for these results is that the FS cells contributed an angiogenic factor that promoted blood vessel formation and thus subsequent tumor growth. A related work by GLODDEX et al. (1999) has demonstrated that TtT/GF and FS cells produce bFGF and VEGF. Their report also showed that PACAP (pituitary adenylate cyclase-activating peptide) and IL-6, but not VIP, stimulate VEGF production, and that VEGF is inhibited by glucocorticoids. These data indicate that FS cells secrete VEGF through a regulation imposed by PACAP. The contribution of FS cells to pituitary tumorigenesis through angiogenesis has been well reviewed in a previous article (RENNER et al., 1998). We have also noted a cell survival effect provided by TtT/GF cells to MtT/S cells when cultured together in a serum free medium. MtT/S cells normally die in a serum free medium, but they survive when they are cultured in a medium conditioned by TtT/GF cells. We have analyzed the survival factor produced by the TtT/GF cells and have identified it to be a tissue inhibitor of metaroprotase (TIMP) (MATSUMOTO et al., 1993b). TIMP is known to inhibit collagenase and may protect the extracellular matrix of the MtT/S cells in the serum free medium.

It has been reported that nitrogen oxide modulates the pituitary endocrine cell function (KATO, 1992). Some endocrine cells and FS cells are known to express neuronal NO synthasc (nNOS) and to produce NO (CECCATELLI et al., 1993). It is suspected that FS cells control NO production in neighboring endocrine cells in a paracrine fashion. Glutamine synthetase (GS) production by FS cells has been recently reported, and FS cells stain specifically with antibodies for GS (SHIRASAWA and YAMANOUCHI, 1999). GS is known to synthesize glutamine by the ATP-dependent condensation of glutamate and ammonium. Therefore FS cells may control glutamate levels and work as a scavenger of ammonia in the anterior pituitary gland. Activin, together with its binding protein, follistatin, have been localized in the anterior pituitary gland (KAISER et al., 1992, KATAYAMA et al., 1992). Activin and its related protein may contribute to the regulation of FSH secretion. Both of these peptides are known to be produced by the FS cell. Calcium dependent ATPase has been reported in FS cells, being detected in the cytoplasmic space where FS cells and endocrine cells are closely associated. This suggests that the enzyme may contribute to calcium transport in those cells (PEUTE et al., 1990).

The production of cytokines in FS cells is worth noting, especially the production of interleukin 6 (IL-6). This has been extensively studied by VANKELECOM (1989, 1993). Both VIP and PACAP are known to stimulate cAMP accumulation and increase IL-6 production in the anterior pituitary gland (SPANGELO et al., 1990; MATSUMOTO et al., 1993a). It is also reported that FS cells have TNF receptors, and that TNF stimulates IL-6 levels in *in vitro* systems (KOBAYASHI et al., 1997). These reports clearly indicate that IL-6 levels in the anterior pituitary gland are changed by some physiological conditions. Concerning the function of IL-6 in the anterior pituitay gland, it is reported that IL-6 stimulates the growth of pituitary tumor cells (ARZT et al., 1993; SAWADA et al., 1995). A possible paracrine function of this cytokine on endocrine cells has been also thoroughly reviewed by RENNER et al. (1998). However, further work is needed to unravel the precise functions of IL-6 in the anterior pituitary gland.

This cytokine production and the similarity of FS cells to the dendritic cells of the immune system makes one suspect a close relationship between them. However, the biological significance of this similarity

has yet to be explained.

Perspective FS cell studies

As mentioned previously, accumulating evidence shows that FS cells are multifunctional. They are known to act as scavengers, regulate ion transport, and control neighboring endocrine cells through the secretion of NO, cytokines, or other growth factors. Although these functions seem to be just supportive roles for neighboring endocrine cells, they are vital for the control of normal functions in the anterior pituitary gland. Besides these functions, which will probably attract a great deal of attention from researchers in the future, new functions of FS cells are anticipated. FS cells may also prove to be especially useful in the analysis of cell differentiation and cell death. To analyze these and other functions, a specific cell line with well conserved normal FS cell characteristics would be a valuable tool. The TtT/GF cell line is a good model for the FS cells and may prove very useful in this quest, but some of its functions—such as a lack of nNOS production—do differ from normal pituitary FS cells. These differences may be caused by the heterogeneity of FS cells, or the may be related to functional diversity. A culture system or cell line with characteristics closer to authentic FS cells would be most useful in future investigations. In pursuit of an improved cell line, we have recently established a line from temperature sensitive T antigen transgenic mice (in preparation for publication), isolating a cell called Tpit/Fl which has FS cell-like characteristics. Most of the characteristics of this Tpit/Fl cell line are similar to the TtT/GF cell line in that it produces IL-6 and is stimulated by LPS and PACAP. But unlike TtT/GF, the new line contains nNOS. Interestingly, the Tpit/Fl cells also differentiate into muscle cells when stimulated by Azacytidine. We hope to uncover additional functions of FS cells through the analysis of this cell line.

Clues to FS cell function should also be able to be gleaned from the morphological similarities they share with brain astrocytes, dendritic cells in the lymph tissue, Langerhans cells of the skin, sustentacular cells in the adrenal gland and Sertoli cells in the testis. Interestingly, all of these cells are positive for the S-100 protein. We expect that the further analysis of the pituitary FS cells will bring to light functions common to all of these cells.

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