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—Original Article—

Localization of SOX2-positive stem/progenitor cells in the anterior lobe of the common marmoset (*Callithrix jacchus*) pituitary

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Abstract. Studies on mouse and rat pituitaries reported that *Sox2*-expressing cells play roles as stem/progenitor cells in the adult pituitary gland. The presence of cells with stem cell-like properties in the pituitary adenoma and SOX2-positive cells has been demonstrated in the human pituitary. However, considering the difficulty in fully examining the stem/progenitor cell properties in the human pituitary, in the present study, we analyzed the SOX2-positive cells in the pituitary of the adult common marmoset (*Callithrix jacchus*), which is used as a non-human primate model. Immunohistochemistry demonstrated that localization pattern of SOX2-positive cells in the common marmoset pituitary was similar to that observed in the rodent pituitary, *i.e.*, in the two types of niches (marginal cell layer and parenchymal-niche) and as scattered single cells in the parenchyma of the anterior lobe. Furthermore, most of the SOX2-positive cells express *S100* and were located in the center or interior of LAMININ-positive micro-lobular structures. Collectively, the present study reveals properties of SOX2-positive cells in the common marmoset pituitary and suggests that the common marmoset proves to be a useful tool for analyzing pituitary stem/progenitor cells in a non-human primate model.

Key words: Common marmoset pituitary, Micro-lobular structure, Stem/progenitor cells, S100

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The pituitary gland is a master endocrine tissue composed of the anterior, intermediate, and posterior lobes. Among them, the anterior lobe has five endocrine cell-types: somatotropes, which produce growth hormone (GH); lactotropes, which produce prolactin (PRL); thyrotropes, which produce thyroid-stimulating hormone (TSH); gonadotropes, which produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH); and corticotropes, which produce adrenocorticotropic hormone (ACTH) [1, 2].

Accumulating evidence from studies on mouse and rat pituitaries demonstrated that *Sex-determining region Y-box 2* (*Sox2*)-expressing cells play roles as stem/progenitor cells in the adult pituitary gland [3, 4]. These SOX2-positive cells form two types of niches (stem/progenitor cell microenvironment); the marginal cell layer (MCL)-niche facing the residual lumen of Rathke's pouch (Rathke's cleft) and the dense SOX2-positive cell clusters scattered in the parenchyma of the adult rodent anterior lobe (parenchymal-niche), in addition to being singly scattered in the parenchyma [2, 5, 6]. Moreover, SOX2-positive stem/progenitor cells in the adult rodent anterior pituitary are composed of sub-populations based on the expression of a calcium-binding protein, *S100β*; approximately 82% of SOX2-positive cells in the adult rat anterior lobe [7] and 60% in the mouse anterior lobe [3] express *S100β*.

Several studies addressing the human pituitary stem/progenitor cells have been reported, including the demonstration of their stem cell-like properties in the human pituitary adenoma [8, 9]. Immunohistochemical analysis also demonstrated that SOX2-positive cells exist in the human pituitary gland [10]. However, considering the limitations in conducting sufficient examination of the property

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Table 1. List of primary antibodies

Antigen-retrieval	Antibody description	Vendor	Dilution
–	Goat IgG against human SOX2	Neuromics, Edina, Minn., USA	1 : 500
	Guinea pig antiserum against rat αGSU	kindly provided by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) through the courtesy of Dr. A.F. Parlow	1 : 10,000
	Guinea pig antiserum against rat FSHβ		1 : 5,000
	Guinea pig antiserum against rat LHβ		1 : 5,000
	Guinea pig antiserum against rat TSHβ		1 : 30,000
	Guinea pig antiserum against human ACTH		1 : 10,000
	Guinea pig antiserum against human GH	kindly provided by Dr. S. Tanaka at Shizuoka University, Shizuoka, Japan	1 : 6,000
	Rabbit IgG against human PRL	Dako, Troy, MI., USA	1 : 800
	Rabbit IgG against rat pan-Laminin *		1 : 700
+	Rabbit IgG against cow S100		1 : 1,000

+ and – indicate with or without antigen-retrieval using ImmunoSaver (0.05% ciraconic anhydride solution, pH 7.4), respectively.
* Pan-Laminin isolated from a rat yolk sac tumor cell line.

of stem/progenitor cells in the human pituitary, studies using a non-human primate model would be preferable.

In recent decades, the common marmoset (*Callithrix jacchus*), or New World monkey, has been increasingly employed as a non-human primate model. The common marmosets have an early onset of puberty (at 1.5 years of age), a relatively short gestation period (145–148 days), high reproductive efficiency (an approximately 28-day ovarian cycle, similar to humans), and a relatively high frequency of deliveries (twice a year), along with its small size [11]. Therefore, the common marmoset is an important primate model in various areas of biomedical research, such as neuroscience, toxicology, reproductive biology, and regenerative medicine, to bridge the gap between rodent studies and clinical applications [12].

In the present study, we analyzed the stem/progenitor cells in the adult common marmoset pituitary, focusing on SOX2-positive cells. Taken together, we identified the localization of SOX2-positive cells and their niches, and observed that most of the SOX2-positive cells express *S100* in the adult common marmoset pituitary.

Materials and Methods

Animals

Five-year-old common marmosets (*Callithrix jacchus*), both female and male, were obtained from CLEA Japan (Tokyo, Japan). The animals were housed in pairs, in stainless steel cages, in a conditioned animal room maintained at 26–28°C and 40–60% humidity with a 12:12 h light/dark cycle. The animals were fed a commercial New World primate diet (CMS-1M, CLEA Japan) with added vitamins, and tap water was available *ad libitum*; the food was moistened with hot water to vary the texture. The marmosets were also fed supplemental food, such as sponge cake, apple jelly, or biscuits. The animals were exsanguinated under anesthesia with intramuscular injection of 50 mg/kg of ketamine (Fujita Pharmaceutical, Tokyo, Japan) and 4 mg/kg xylazine (Bayer, Leverkusen, Germany), and inhalation of isoflurane (Pfizer Japan, Tokyo, Japan). The animal experimental protocol was approved by the CIEA Institutional Animal Care and Use Committee (approval no. 17029A).

Wistar-Imamichi rats (10-week-old males) were housed individually in a temperature-controlled room under a 12:12 h light/dark cycle. Rats were sacrificed by cervical dislocation under anesthesia.

Immunohistochemistry

The pituitary glands of the female and male common marmosets (part of the intermediate lobes were missing upon removal) and those of the male rats were fixed with 4% paraformaldehyde in 20 mM phosphate buffer (pH 7.5) overnight at 4°C, followed by immersion in 30% trehalose in 20 mM HEPES to cryoprotect the tissues. They were embedded in Tissue-Tek O.C.T. Compound (Sakura Finetek Japan, Tokyo, Japan) and frozen immediately. Frozen sections (6-μm thick) were prepared from the coronal planes of the pituitaries. Depending on the antibody, the sections were subjected to antigen retrieval by an ImmunoSaver (0.05% citraconic anhydride solution, pH 7.4; Nisshin EM, Tokyo, Japan) (Table 1) for 60 min at 80°C. The sections were incubated with 10% (v/v) fetal bovine serum and 0.4% (v/v) Triton X-100 in HEPES buffer (blocking buffer) for 60 min at room temperature. After washing, the sections were incubated with primary antibodies (Table 1) in blocking buffer at 4°C overnight. After the immunoreaction, the sections were incubated with secondary antibodies using Cy3-, Cy5-, or FITC-conjugated AffiniPure donkey anti-goat, guinea pig, and rabbit IgG (1:500; Jackson ImmunoResearch, West Grove, PA, USA). The sections were washed and incubated in VECTASHIELD Mounting Medium (Vector Laboratories, Burlingame, CA, USA) with 4,6′-diamidino-2-phenylindole dihydrochloride (DAPI). Immunofluorescence was observed under a BZ-8000 fluorescence microscope (KEYENCE, Osaka, Japan). For multi-staining of rabbit IgG against rat LAMININ and rabbit IgG against human PRL, we labeled rabbit IgG against rat LAMININ by Zenon Alexa Fluor 488 Rabbit IgG Labeling Kit (Thermo Fisher Scientific, Waltham, MA, USA). The proportion of SOX2-positive cells and S100-positive cells in the SOX2-positive population in the parenchyma of anterior lobe was measured by counting three areas (1,001–1,178 cells counted in each area of 0.16 mm^2) in the independent sections prepared from each of the single female and male common marmosets. The data are presented as means ± SE for three sections.

Results

Localization of SOX2-positive cells in the anterior pituitary of adult common marmosets

We first analyzed the localization of SOX2-positive cells in the adult common marmoset pituitary. Immunohistochemistry for SOX2 clearly demonstrated that SOX2-positive cells exist in the MCL of both anterior and intermediate lobes (Fig. 1, dotted lines). In the parenchyma of the anterior lobe, although most of the SOX2-positive cells were singly scattered, dense SOX2-positive cell clusters were also detected (Fig. 1, arrowhead). The proportion of SOX2-positive cells in the parenchyma of the anterior lobe was approximately 14.9 ± 0.9% and 15.4 ± 0.3% in the female and male animals, respectively. In the mouse pituitary, but not that of the rat, immuno-positive signals for SOX2 in the cytoplasm (cytoplasmic-SOX2) were also observed [13]. However, in the adult common marmoset pituitaries, these cytoplasmic-SOX2 were not observed (Fig. 1).

Co-localization of SOX2 and S100 in the anterior lobe of adult common marmosets

We performed double-immunohistochemistry for SOX2 and S100 in the adult common marmoset pituitary. Double-immunohistochemistry demonstrated that most of the SOX2-positive cells were positive for S100 in the MCL (Fig. 2A). In the parenchyma of the anterior lobe, SOX2 mostly co-localized with S100 at a high frequency, while SOX2-positive/S100-negative cells (Fig. 2A and 2B, closed-arrowheads) and SOX2-negative/S100-positive cells (Fig. 2C, open-arrowheads) were also detected. The proportion of S100-positive in SOX2-positive cells in the anterior lobe was approximately 88.7 ± 1.2% and 89.2 ± 2.1% in female and male animals, respectively.

Localization of SOX2-positive cells in the micro-lobular structure of the anterior lobe of the adult common marmoset pituitary

In the anterior lobe of adult common marmoset pituitary, to analyze the localization of SOX2-positive cells within the micro-lobular structure composed of basement membranes [14], we performed immunohistochemistry using an antibody against SOX2 and pan-LAMININ, which is a major component of basement membranes. Immunohistostaining demonstrated that LAMININ-positive micro-lobular structures, including blood vessels, exist as round or elliptical structures in the pituitary section (Fig. 3). In the parenchyma, the immunohistochemical staining for LAMININ and SOX2 demonstrated that most of the SOX2-positive cells were located either in the center or interior of the LAMININ-positive micro-lobular structures, and very few SOX2-positive cells were attached to the LAMININ-positive basement membranes (Fig. 3A). In addition, although most of the LAMININ-positive micro-lobular structures in the parenchyma of the pituitary sections include SOX2-positive cells, a few micro-lobular structures without SOX2-positive cells were also detected in the sections (Fig. 3A, asterisks). On the contrary, in the MCL-niche, the LAMININ-positive micro-lobular structures were not observed, and SOX2-positive cells were hardly attached to the LAMININ-positive cells (Fig. 3B).

Localization of hormone-positive cells and SOX2-positive cells in the micro-lobular structure of the anterior lobe of the adult common marmoset pituitary

Finally, we performed immunohistochemistry for each pituitary hormone, SOX2, and LAMININ. Immunostaining demonstrated that SOX2-positive cells exist as non-hormone-producing cells in the common marmoset pituitary as well as rodent ones (Fig. 4 and Supplementary Fig. 1: online only). Furthermore, most of the hormone-positive cells were attached to the LAMININ-positive basement membranes in the common marmoset pituitary of both female (Fig. 4) and male animals (Supplementary Fig. 1). In addition, a few hormone-positive cells were located in the center of the LAMININ-positive micro-lobular structure (Fig. 4 and Supplementary Fig. 1). Especially, GH-positive cells, but not PRL-positive cells, tended to remain attached to LAMININ-positive basement membranes (Fig. 4 and Supplementary Fig. 1).

Discussion

Accumulating evidences from rodent models show that SOX2-positive cells exist as stem/progenitor cells in the anterior lobe of the adult pituitary. In the present study, we performed immunohistochemical analysis of SOX2-positive cells in the pituitary of the common marmosets, a non-human primate model.

In the adult rodent pituitary, SOX2-positive stem/progenitor cells showed three localization patterns: lining the MCL (MCL-niche, also known as a primary niche), clustering in the parenchyma (parenchymal-niche, also known as secondary niches), and singly scattered in the parenchyma [2, 5, 6]. In the human pituitary, although the immunohistochemistry demonstrated that SOX2-positive cells exist in the MCL around the Rathke's cleft and parenchyma of the anterior lobe, the existence of parenchymal-niches has not been shown yet. The present study demonstrated that the localization pattern of SOX2-positive cells in the common marmoset pituitary was similar to that in rodents. In relation to the niches of the rodent pituitary, the formation of the parenchymal-niche occurs during the neonatal period by migration of SOX2-positive cells from the MCL-niche, which is formed during the early embryonic period [5]. These data suggest that the parenchymal-niche might have important roles in pituitary function, especially in postnatal pituitary across species. While there are some conserved points of pituitary SOX2-positive cells between rodents and the common marmoset, the present study also showed distinct cellular localization patterns of SOX2, unlike that in the mouse pituitary, cytoplasmic-SOX2 was not observed in the adult common marmoset pituitaries as that in rats [7, 13]. Vankelecom and colleagues reported that cytoplasmic-SOX2 in the mouse pituitary tend to be co-localized with hormones, and hypothesized that the cytoplasmic localization by post-translational regulation promoted the initiation of differentiation [2, 13]. Although SOX2 must be a common factor showing undifferentiated cells in the anterior lobe of the pituitary of common marmoset as well as rodents, further post-translational regulation and functional analysis of SOX2 are needed.

Several studies using rodent pituitary demonstrated that SOX2-positive stem/progenitor cells are composed of sub-populations based on the expression of several genes [2]. Among them, S100

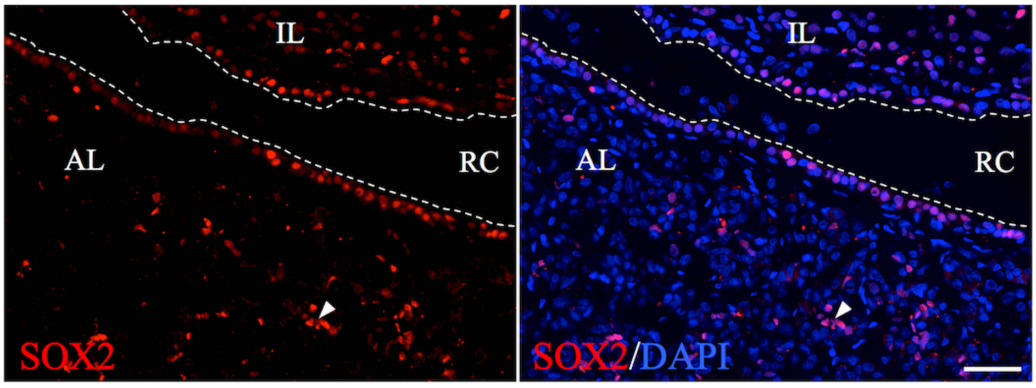

Fig. 1. Immunohistochemistry for SOX2 in the anterior lobe of the adult female common marmoset pituitary. Immunohistochemistry for SOX2 was performed using 4% paraformaldehyde-fixed frozen sections of the anterior lobe of an adult female common marmoset. SOX2 was visualized with Cy3 (red), and the nucleus was stained with DAPI (blue). AL, anterior lobe; IL, intermediate lobe; RC, Rathke's cleft. Dotted lines indicate the marginal cell layer (MCL). Closed-arrowheads indicate dense SOX2-positive cell clusters (parenchymal-niche). Bar indicates 50 μm.

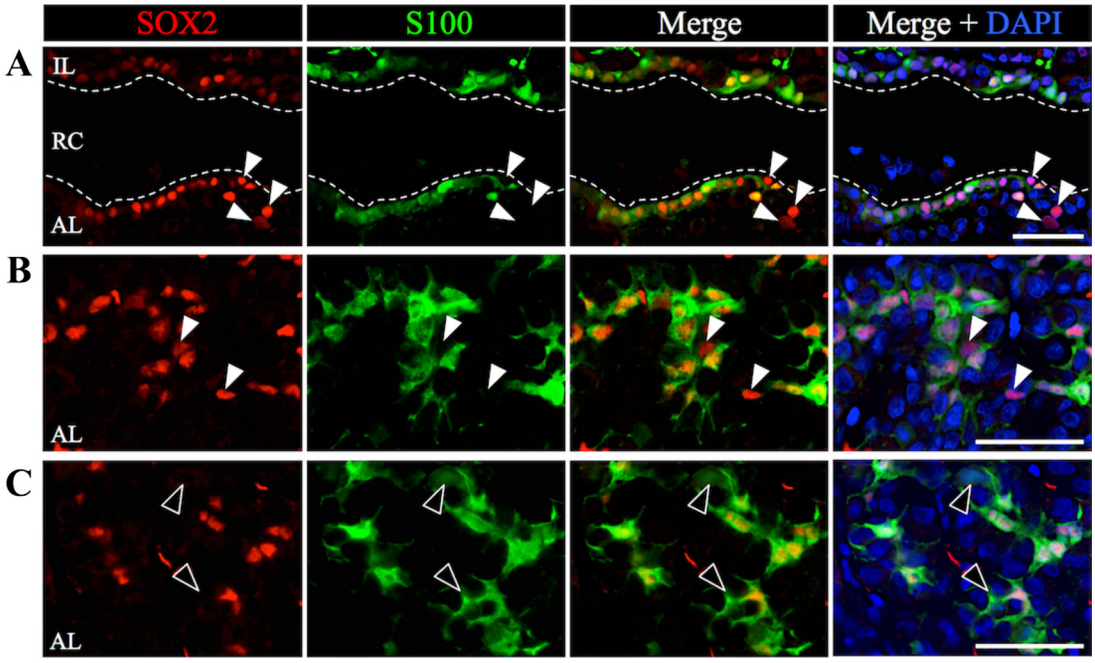

Fig. 2. Immunohistochemistry for SOX2 and S100 in the anterior lobe of the adult female common marmoset pituitary. Immunohistochemistry for SOX2 and S100 was performed using 4% paraformaldehyde-fixed frozen sections of the anterior lobe of an adult female common marmoset. SOX2 was visualized with Cy3 (red) and S100 was visualized with Cy5 (green); merged image showing both SOX2 and S100 with nuclear DAPI staining (blue) are shown in the MCL (A) and parenchyma of anterior lobe (B and C). AL, anterior lobe; IL, intermediate lobe; RC, Rathke's cleft. Dotted lines indicate the MCL. Closed-arrowheads and open-arrowheads indicate SOX2-positive/S100-negative cells and S100-positive/SOX2-negative cells, respectively. Bars indicate 50 μm.

is known to partially exist in the SOX2-positive cells of remnants of Rathke's cleft cysts in the human pituitary [10]. In the common marmoset pituitary, characterization with S100 clearly showed that SOX2-positive cells were positive for S100 in the MCL-niche and parenchyma of the anterior lobe. Notably, the main population of SOX2 exists as S100-positive cells, while each SOX2-positive/S100-negative and S100-positive/SOX2-negative cells exists similar to that in the rat pituitary [7]. Recently, we reported that SOX2-positive cells isolated from the parenchymal-niches of the rat pituitary show different properties based on the difference in *S100β* expression, where *S100β*-expressing SOX2-positive cells exhibit high proliferation and differentiation activities than non-*S100β*-expressing cells [15]. Although we analyzed an insufficient number of common marmoset pituitaries (one female and one male) by only immunohistochemical

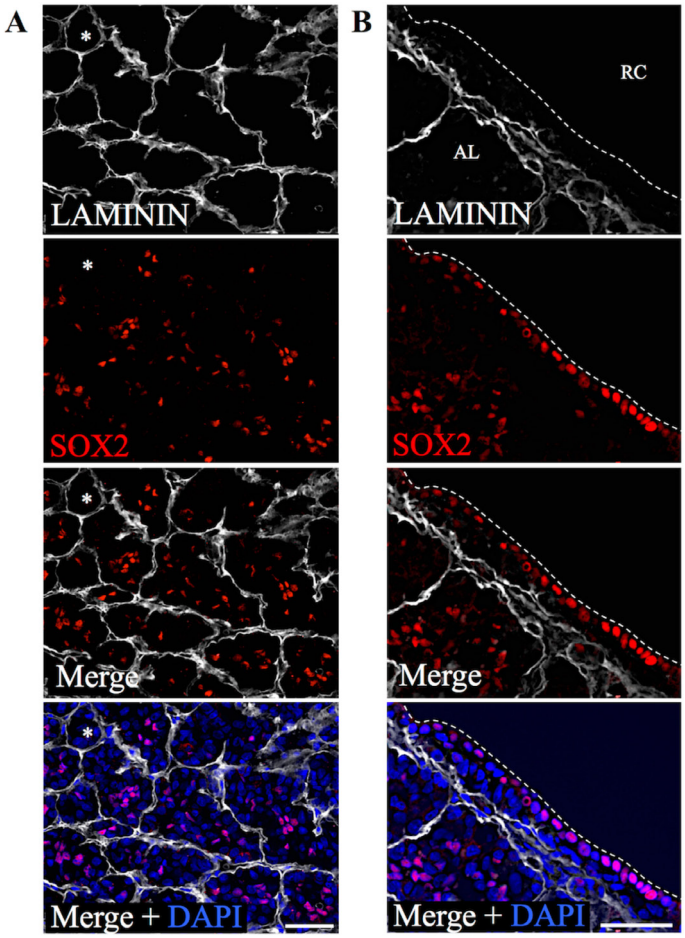

Fig. 3. Immunohistochemistry for SOX2 and LAMININ in the anterior lobe of the adult female common marmoset pituitary. Immunohistochemistry for SOX2 and LAMININ in the parenchyma (A) and the MCL of the anterior lobe (B) was performed using 4% paraformaldehyde-fixed frozen sections of the anterior lobe of an adult female common marmoset. SOX2 visualized with Cy3 (red), LAMININ visualized with Cy5 (white), merged image showing both SOX2 and LAMININ, and those with nuclear DAPI staining (blue) are shown. AL, anterior lobe; RC, Rathke's cleft. Asterisks in (A) indicate LAMININ-positive micro-lobular structures without SOX2-positive cells in the pituitary section. A dotted line in (B) indicates the MCL. Bar indicates 50 μm.

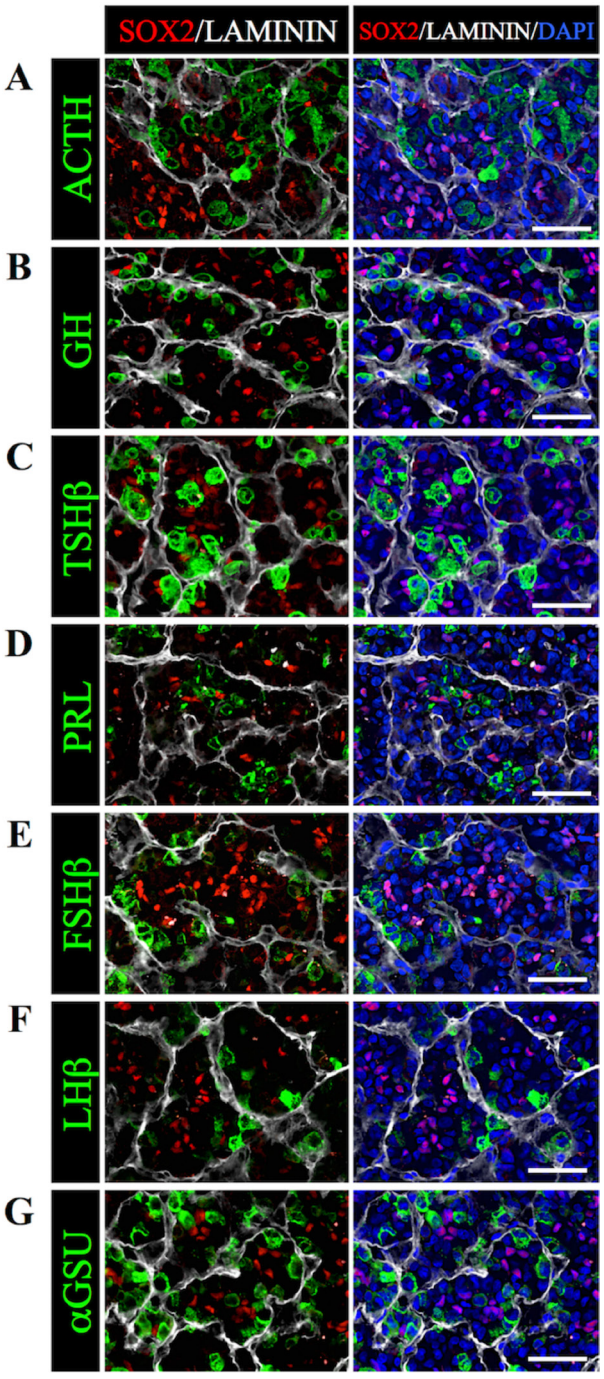

Fig. 4. Immunohistochemistry for SOX2, LAMININ, and each pituitary hormone in the anterior lobe of the adult female common marmoset pituitary. Immunohistochemistry for SOX2, LAMININ, and each pituitary hormone (A, adrenocorticotropic hormone [ACTH]; B, growth hormone [GH]; C, thyroid-stimulating hormone β [TSHβ]; D, prolactin [PRL]; E, follicle-stimulating hormone β [FSHβ]; F, luteinizing hormone β [LHβ]; and G, glycoprotein α-subunit [αGSU]) using 4% paraformaldehyde-fixed frozen sections of the anterior lobe of an adult female common marmoset. Merged images with SOX2 visualized with Cy3 (red), LAMININ with Cy5 (white), and each pituitary hormone with FITC (green), and merged images with nuclear staining by DAPI (blue) are shown. Bars indicate 50 μm.

analysis, the present study suggests that a sub-population of SOX2-positive cells and their properties may be conserved across rodent and common marmoset pituitaries.

In the rat pituitary, scanning electron microscopy images demonstrated that micro-lobular-like structures, but not really micro-lobular, composed of basement membranes, exist in the anterior lobe [14]. Indeed, it is difficult to identify the micro-lobular-like structure by immunohistochemistry for LAMININ using rat pituitary sections (Supplementary Fig. 2: online only). In the present study using the common marmoset pituitary sections, LAMININ-positive cells outlined the micro-lobular structure more clearly than in rat sections. Notably, most of the SOX2-positive cells were located in the center or interior of the LAMININ-positive basement membranes,

whereas most of hormone-positive cells were located attached to the LAMININ-positive basement membranes. Since a few LAMININ-positive micro-lobular structures, having no SOX2-positive cells, exist in the section, the present study, lacking a three-dimensional analysis, could not conclude whether SOX2-positive cells exist in all micro-lobular structures. However, considering that most of the LAMININ-positive micro-lobular structures include SOX2-positive cells in the pituitary sections, these data suggest that SOX2/S100-double positive cells might generally exist in the micro-lobular structure of the anterior lobe. Moreover, the central localization of SOX2/S100-double positive cells might suggest the migration of some of the SOX2-positive cells to the outside for differentiation into hormone-producing cells.

In summary, immunohistochemistry of the common marmoset pituitary demonstrated that localization of SOX2-positive stem/progenitor cells in the common marmoset pituitary is similar to that in rodent pituitary, and has some commonalities with the human pituitary as well. Therefore, the common marmoset might prove to be a useful experimental animal to analyze pituitary stem/progenitor cells and their functions in non-human primate models.

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