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The Chinese Tree Shrew (*Tupaia belangeri chinensis*) may be a Potential Animal Model for the Posterior Lingual Glands-Related Diseases

La Musaraña Arbórea China (*Tupaia belangeri chinensis*) Podría ser un Posible Modelo Animal para las Enfermedades Relacionadas con las Glándulas Linguales Posteriores

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SUMMARY: The objective of the study was to compare the anatomical and histological features of posterior lingual glands among Chinese tree shrews, mice, and humans, providing morphological evidence for evaluating the tree shrew as a biomedical model. Paraffin sections of lingual tissues from Chinese tree shrews (n=5), mice (n=5), and humans (n=3) were analyzed using hematoxylin-eosin (HE) and alcian blue staining. Morphological structures, including vallate papillae, Von Ebner's glands (deep portion of the posterior lingual glands/gustatory glands), and Weber's glands (superficial portion of the posterior lingual glands/glands of root of tongue), were systematically examined. Chinese tree shrews exhibited V-shaped vallate papillae arrangement, resembling humans but differing from mice. The deep portion of the posterior lingual glands in all three species were pure serous glands (alcian blue-negative), though mice lacked striated ducts. The deep portion of the posterior lingual glands in tree shrews and humans were pure mucous glands (alcian blue-positive), draining via short ducts into mucosal surfaces, while murine the superficial portion of the posterior glands were mixed type and opened into tongue crypts. The anatomical and histological similarities between Chinese tree shrews and humans in posterior lingual gland structures, combined with its utility in studying human-specific diseases, support the tree shrew as a valuable model for investigating pathogenesis of lingual gland-related disorders.

KEY WORDS: Chinese tree shrew (*Tupaia belangeri chinensis*); Posterior lingual glands; Deep portion of the posterior lingual glands; Gustatory glands; Von Ebner's glands; Superficial portion of the posterior lingual glands; Glands of the root of the tongue; Weber's glands; Animal model.

INTRODUCTION

Saliva has a complex composition and its main functions include digestion, lubrication and dissolution of food, moistening and protection of the oral mucosa, dilution and buffering of adverse stimuli, cleansing of the oral cavity, antimicrobial as well as immunological effects (Dawes & Wong, 2019; Roblegg *et al*., 2019). In mammalians, there are three major paired salivary glands named the parotid, submandibular and sublingual glands, which secrete saliva that is discharged into the oral cavity through their respective ductal systems (Proctor, 2016; Khoury & Sultan, 2023). In addition to these three major salivary glands, a large number of minor salivary glands also develop and exist in the oral cavity, and these minor salivary glands primarily secrete saliva into the oral cavity through the oral mucosa (Tucker, 2007).

The posterior area of mammalian tongues includes two sets of minor salivary glands: the posterior deep and superficial lingual glands, which were identified by Von Ebner and Weber respectively, are of significance in digestion, taste and protection of taste buds (Triantafyllou & Fletcher, 2017). Deep portion of the posterior lingual glands (gustatory glands, Von Ebner's glands), a group of tubulo-acinar serous glands located beneath the vallate and

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foliate papillae of the tongue in humans, contribute to renew and maintain taste receptor function by secreting fluids from the opening of its ducts located at the bottom of the sulcus of papillae to wash out the taste pits of taste buds in the papillary sulcus epithelium. And, in rodents lacking foliate papillae, deep portion of the posterior lingual gland only open at the circumvallate papillae (Chen *et al*., 2024). Superficial portion of the posterior glands (glands of root of tongue, Weber's glands), which open onto the crypts of lingual tonsils in human, are located on the lateral margin at the level of the foliate papillae and in the base of the tongue behind the vallate papillae (Chen *et al*., 2022). Whereas in rodents, superficial portion of the posterior gland lingual gland directly open onto the dorsal epithelium at the base of the tongue. Mucus supplied by superficial portion of the posterior gland lingual gland may help to cleanse the crypts and aid food intake (Harada *et al*., 2023; Adrian Florin *et al*., 2024).

Recently, deep portion of the posterior lingual glands and superficial portion of the posterior lingual glands have garnered widespread attention as significant origins of tongue base carcinomas, aside from the tonsillar reticular epithelium (Chen *et al*., 2022). Mice lack the pharyngeal lymphoid ring (Waldeyer's ring) which consists of tonsils and other lymphoid tissues in their oropharynx (Davis, 2001), which eliminates potential interference from the reticular epithelium of the lingual tonsils. Additionally, their small size, strong reproductive capacity, and clear genetic background make them the preferred animal model for studying carcinomas originating from these two glands. Currently, the rising incidence of tongue base cancer is closely associated with the increasing infection rate of HPV, especially in the United States, where the tongue base has surpassed the cervix as the most common site for HPV-related cancers (Van Dyne *et al*., 2018). However, human papillomavirus (HPV), a significant etiological factor for squamous cell carcinoma in the base of the tongue, exhibits strict species specificity, limiting its ability to infect organisms beyond its natural host range (Campo, 2002). This poses a limitation on studying HPV-associated tongue base carcinoma, rendering current models inadequate for accurately simulating its complex biological processes and disease characteristics. Currently, the HPV infection process can only be approximated by the nude mouse model infected with mouse papilloma virus (MmuPV1), a transgenic mouse model carrying the entire HPV16 early genomic region under the control of the Keratin-14 promoter and a spontaneous HPV16 E6/E7-expressing head and neck squamous cell carcinoma model in HLA-A2 transgenic mice (Cladel *et al*., 2016; de Oliveira Neto *et al*., 2021; Peng *et al*., 2022). This undoubtedly poses certain limitations and challenges for studying HPV-related squamous cell carcinoma of the posterior lingual glands.

The Chinese tree shrew (*Tupaia belangeri chinensis*), a small rat-sized (100-150 g) mammalian species similar in appearance to squirrels with a moderate life span (6-8 years), possesses unique advantages in biomedical research (Fan *et al*., 2019). Due to its closer phylogenetic relationship to primates compared to rodents, dogs, and other animals, the Chinese tree shrew can more accurately simulate human physiological and pathological conditions. This characteristic makes it a highly potential novel animal model. Over the past few decades, the Chinese tree shrew has been widely applied in various biomedical research fields, including viral infection studies, cancer research, myopia research, visual cortex function, and neuroscience (Xiao *et al*., 2017). In the study of nasopharyngeal carcinoma, a successful establishment of a tree shrew infection model for Epstein-Barr virus (EBV), which shares the same species specificity with HPV, has been achieved (Xia *et al*., 2021). This prompts us to consider whether the Chinese tree shrews are suitable to be developed into an HPV-related oropharyngeal carcinoma model.

This study carried out an in-depth examination of three intact adult carcasses of the Chinese tree shrew, revealing the morphological features of the posterior lingual glands of this small mammal in Southeast Asia. Furthermore, a comparative observation was performed with the posterior lingual glands of humans and mice, aiming to delve into their histological features and lay a solid foundation for future establishment of disease models related to the posterior lingual glands of the Chinese tree shrew.

MATERIAL AND METHOD

Ethics approval. All procedures were conducted according to the guidelines assigned by the First Affiliated Hospital of Guangxi Medical University ethical review committee, China (Approval No. 2024-E340-01).

Sample collection. Samples of the posterior lingual glands were obtained after the euthanasia of the three Chinese tree shrews (*Tupaia belangeri chinensis*) and mice (*Mus musculus*) that had been used in other studies. Photographs of fresh tongue tissues were taken using a digital camera (Canon EOS 300D, Diegem, Belgium). These samples were fixed in 4 % buffered paraformaldehyde at room temperature for 24 hours, dehydrated in a tissue processor (Microm STP420D, Prosan, Merelbeke, Belgium), and embedded in paraffin using an embedding station (Microm EC350-1 and 350-2, Prosan, Merelbeke, Belgium).

Paraffin samples of 3 cases of tongue squamous cell carcinomas that had been excised in surgery and diagnosed by pathology between September 2023 and March 2024 from

the Affiliated Stomatological Hospital of Guangxi Medical University were selected, and the vallate papillae of normal tissues around the carcinomas were resected for further experimental study.

All the specimens were routine serial sections with a thickness of 4mm, and 6 sections were obtained from each sample.

Hematoxylin and Eosin (HE) Staining. The paraffin was removed from the samples using four changes of xylene for 7 minutes each. The slides were hydrated in gradient ethanol and rinsed three times in tap water. The samples were stained for 7 min in hematoxylin solution, and the slides were rinsed three times in tap water. Then the samples were stained in eosin solution for 2 min, the slides were rinsed three times in tap water, conventionally dehydrated in alcohol, and cleared in three changes of xylene for 2 min each. Finally, each slide was sealed with neutral balsam.

Alcian blue staining. The paraffin was removed from the samples for alcian blue staining in four changes of xylene for 6 min each. The slides were hydrated in gradient ethanol, rinsed the slides three times in tap water. Then the slides were equilibrated in 5 % acetic acid for 3 min, stained in alcian blue solution (pH=2.5) for 30 min, and rinsed in running tap water for at least 5 min. The slides were then counterstained for 10 min with nuclear fast red staining solution before being rinsed for at least 1 minute in running tap water. Finally, the slides were conventionally dehydrated in alcohol, cleared in xylene, and sealed with neutral balsam.

Microscopic observation. The histological features of the posterior lingual glands in the Chinese tree shrew were observed with HE and Alcian blue staining, and all slides were examined by light microscopy (Eclipse Ni-U, Nikon, Tokyo, Japan).

RESULTS

Macroscopic overview. Macroscopically, the tongue of the Chinese tree shrew 130 g, female, two months of age) was elongated and terminated in a rounded apex, and the size of it was 32 (length)×10 (width)×6 (thickness) mm (The size of width and thickness was that of the base of the tongue) (Fig. 1). On the dorsal surface of the posterior tongue, three vallate papillae were observed. They were positioned posterior to a structure resembling the sulcus terminalis in humans. Each papilla was surrounded by a deep wide vallate papilla furrow, and the lingual mucosa outside the vallate papilla furrow was slightly elevated, forming the papilla vallate's boundary. And there were parallel ridges of the foliate papillae present at the lateral margin of the posterior tongue near the vallate papillae which is different from mice.

The size of the BALB/c mouse's tongue (20 g, female, six months of age) was 13 (length)×4(width)×3 (thickness) mm (The size of width and thickness was that of the base of the tongue). The anatomical structure of the mouse tongue revealed a prominent feature known as the inter molar eminence, located at the junction where the anterior two-thirds met the posterior one-third of the tongue dorsum. This eminence was an integral part of the tongue's anatomy. The posterior margin of the inter molar eminence resembled the human's sulcus terminalis. Immediately anterior to this eminence, one could find a solitary, Ω-shaped circumvallate papilla (Fig. 1). And there was no parallel ridge of foliate papillae present on the lateral margins of the posterior tongue in mice.

Fig. 1. Photograph (from above) of the dorsal surface of the tongue of the Chinese tree shrew (*Tupaia belangeri chinensis*) and the BALB/c mouse (*Mus musculus*). Three fungiform vallate papillae are present on the posterior tongue, which are arranged in a V-shape behind a structure resembling the human sulcus terminalis. parallel ridges of the foliate papillae can be observed at the lateral margin of the posterior tongue near the vallate papillae (V, Vallate papillae; F, Foliate papillae); There is only one circumvallate papillae at the base of the tongue of mice, lacking foliate papillae (C, circumvallate papillae).

Microscopic findings

Posterior lingual glands consisted of two sets of the minor salivary glands.

One of the posterior lingual glands was named Von Ebner's glands. The deep portion of the posterior lingual glands of the Chinese tree shrews were located beneath the lamina propria around the vallate papillae, mingled with lingual muscular bundles, and they were typical serous glands. Serous acini of the deep portion of the posterior lingual glands consisted of several cells with typical spherical nuclei, basophilic cytoplasm, numerous apically-

located secretory granules and different shapes such as oval, spherical and pyramidal. These characteristics were essentially identical to the acinar cells of the human deep portion of the posterior lingual glands. The reaction of serous acini of the deep portion of the posterior lingual glands to the alcian blue staining was negative. Striated, intercalated and stratified columnar ducts could be seen in deep portion of the posterior lingual glands, which ultimately opened at the furrow of vallate papillae. Vallate papilla of the Chinese tree shrew was encircled by a deep furrow and the dorsal epithelium was covered with a thin keratinized layer. There were a large number of taste buds on the middle and inferior portion of its side wall connected with the deep furrow. In both humans and mice, deep portion of the posterior lingual

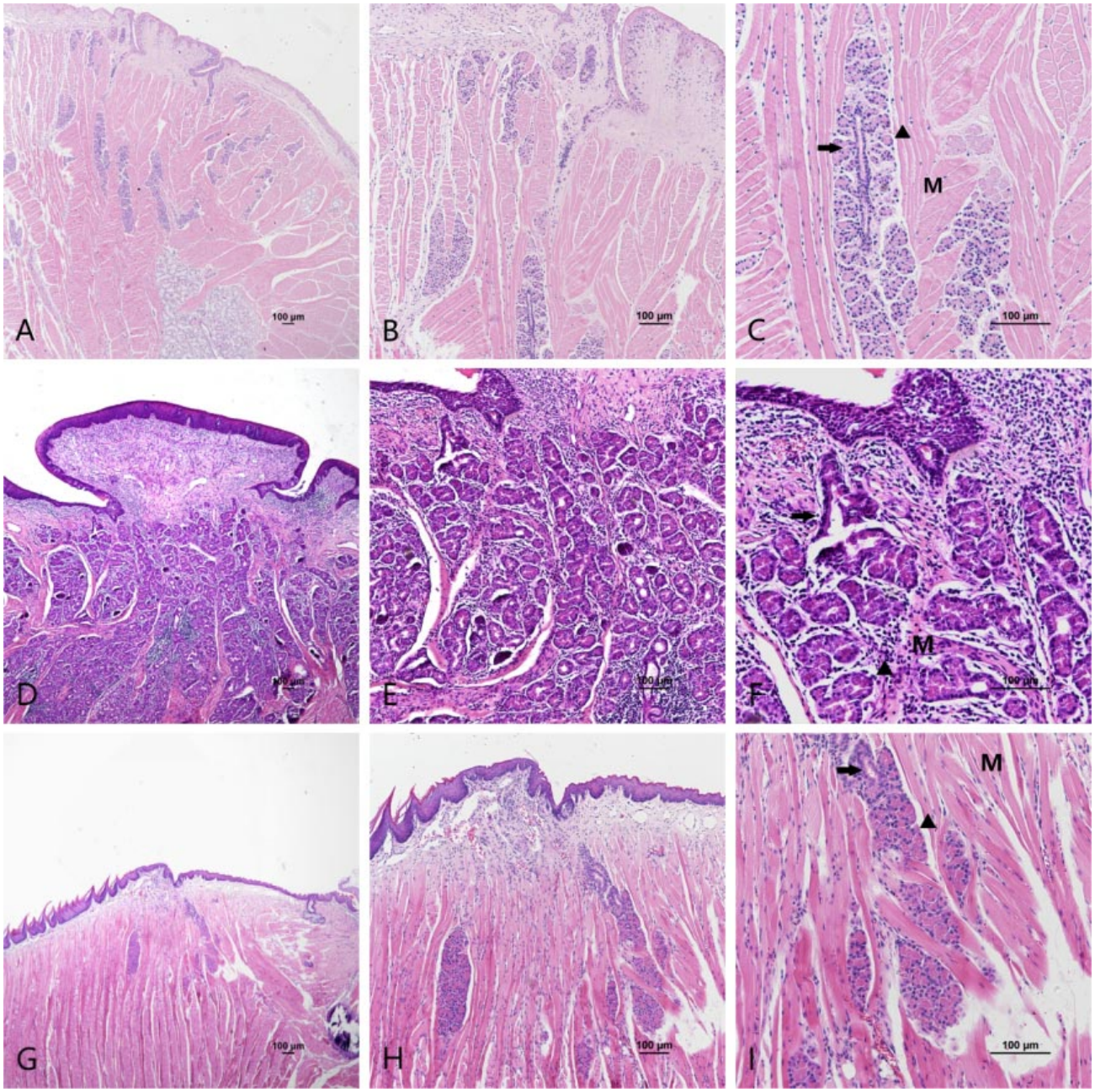

Fig. 2. HE staining of deep portion of the posterior lingual glands in Chinese tree shrew, human and mouse. (A.B.C. In Chinese tree shrew; D.E.F. In human; G.H.I. In mouse.) The deep portion of the posterior lingual glands of Chinese tree shrew, human and mouse are typical serous glands, located beneath the lamina propria around the vallate papillae. Collections of acini consisted of serous cells (arrowhead), surround ducts (arrow) and are between skeletal muscle fibers (M). However, it was notable that mice were devoid of striated ducts. (A.D.G.×40; B.E.H.×100; C.F.I.×200).

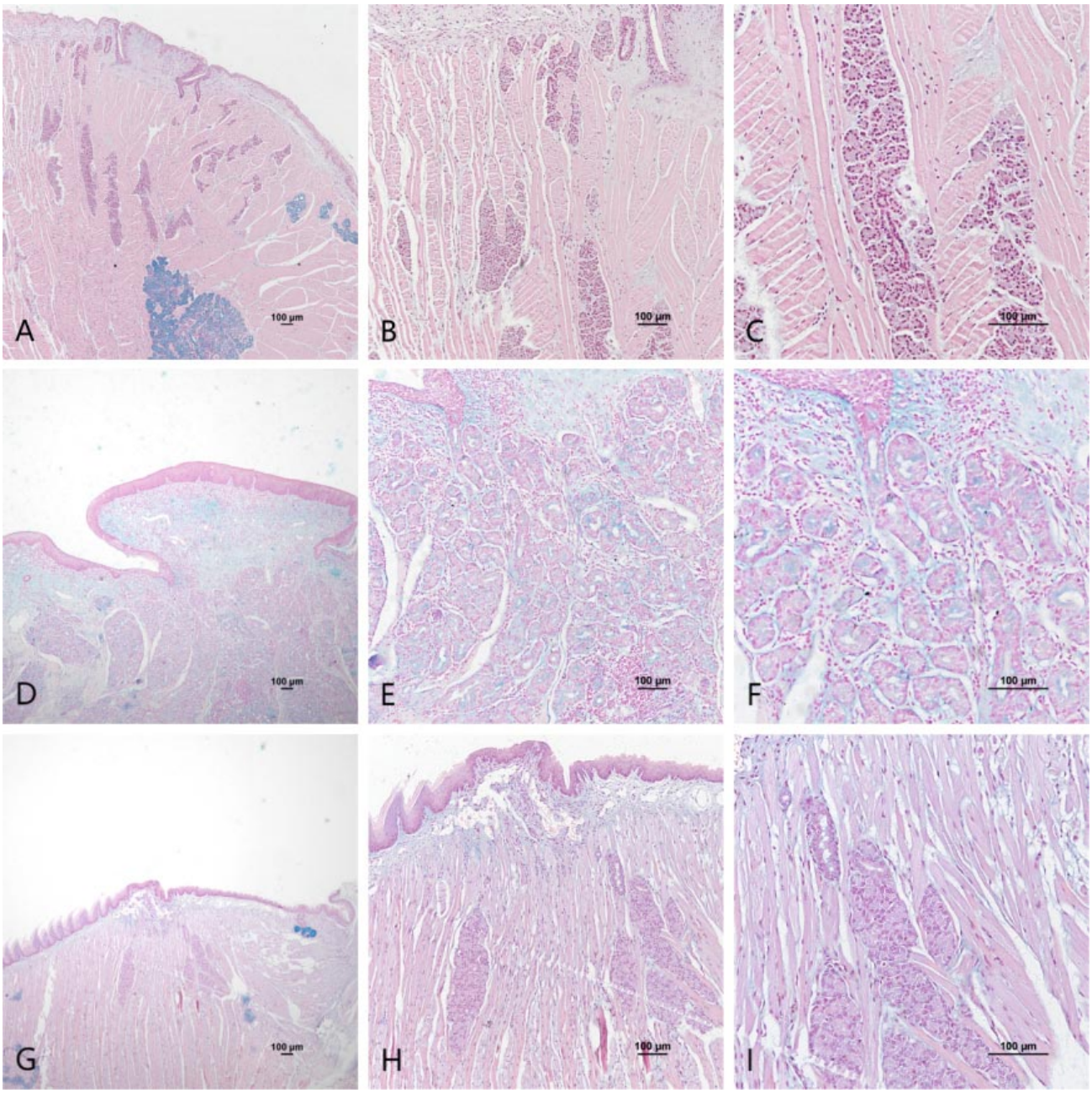

Fig. 3. Alcian blue staining of deep portion of the posterior lingual glands in Chinese tree shrew, human and mouse. (A.B.C. In Chinese tree shrew; D.E.F. In human; G.H.I. In mouse.) Image showed negative reaction of deep portion of the posterior lingual glands acini to alcian blue (pH = 2.5) staining. (A.D.G.×40; B.E.H.×100; C.F.I.×200).

glands were likewise pure serous glands, which exhibited a negative reaction to alcian blue staining, located amidst the lingual muscular bundles beneath the vallate papillae. These serous acini consisted of spherical or elliptical cells accompanied by intercalated ducts. However, it was notable that mice were devoid of striated ducts, whereas they can be observed in the deep portion of the posterior lingual glands of humans and tree shrews (Figs. 2 and 3).

Another of the posterior lingual glands was known as Weber's glands. The superficial portion of the posterior lingual glands of the Chinese tree shrews were primarily located beneath the lamina propria on the lateral and posterior to deep portion of the posterior lingual glands and were typical mucous glands. The glandular parenchyma exhibited the lobule-like structures, with a collection of secretory end pieces. The acini were invested by

myoepithelium, and neither striated nor intercalated ducts were observed. The tubulo-acini drained abruptly into short terminal ducts composed of stratified squamous epithelium, with these ducts opening directly onto the mucosal surface. The secretory cells of superficial portion of the posterior lingual glands were huge, with flattened nuclei against the basal surface and apical cytoplasm tilled with large pale granules that display little affinity for routine histological stains. However, the mucous acini of superficial portion of the posterior lingual glands react positively to alcian blue staining. In human, the superficial portion of the posterior lingual glands, which open onto the crypts of lingual tonsils,

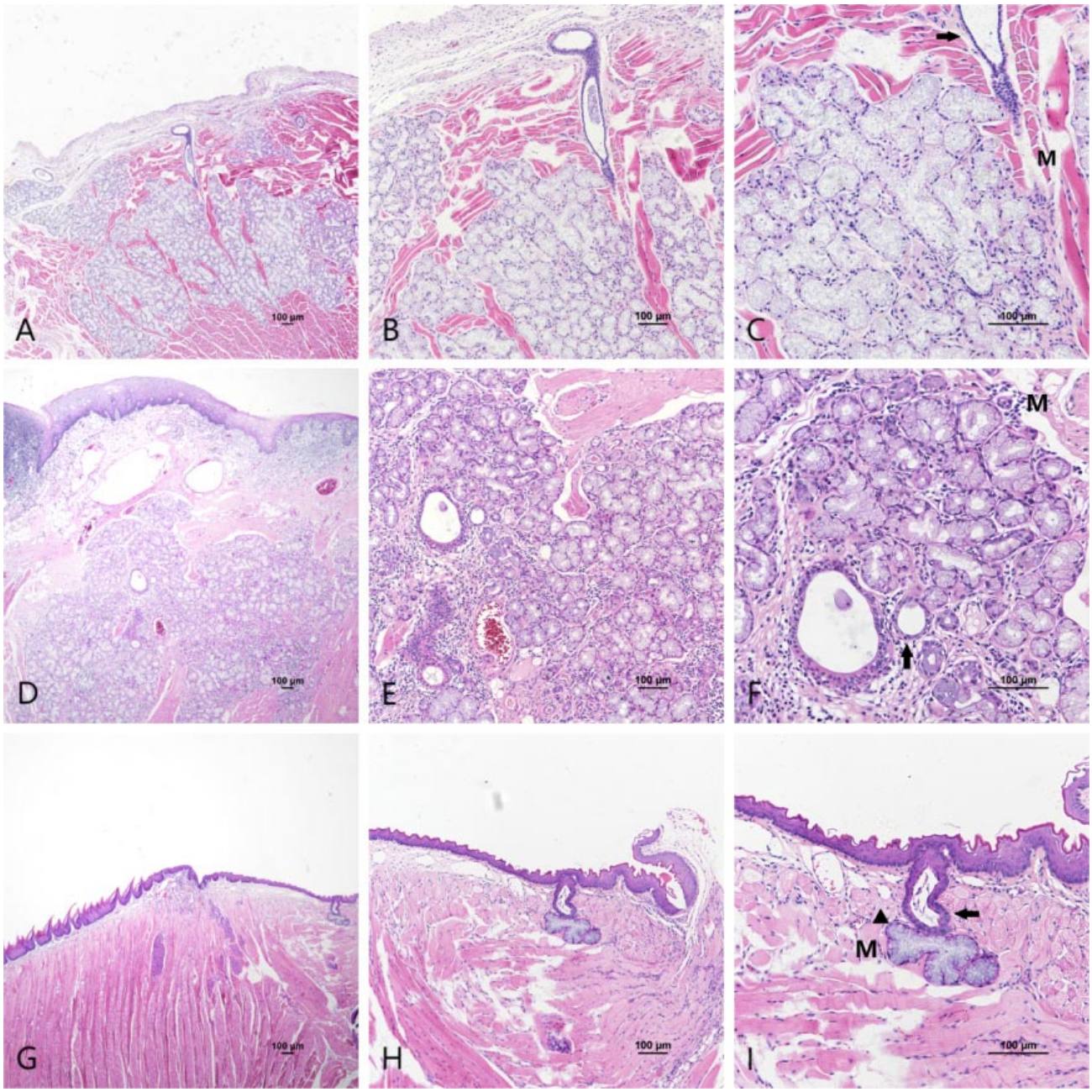

Fig. 4. HE staining of superficial portion of the posterior lingual glands in Chinese tree shrew, human and mouse. (A.B.C. In Chinese tree shrew; D.E.F. In human; G.H.I. In mouse.) The superficial portion of the posterior lingual glands of Chinese tree shrew and human are typical mucous glands, with their acini only consisting of mucous cells. However, in mouse, superficial portion of the posterior lingual glands were mixed glands wherein the serous cells (arrowhead) form a crescent-shaped structure. The tubulo-acini drained abruptly into short terminal ducts (arrow) composed of stratified squamous epithelium and are between skeletal muscle fibers (M). (A.D.G.×40; B.E.H.×100; C.F.I.×200).

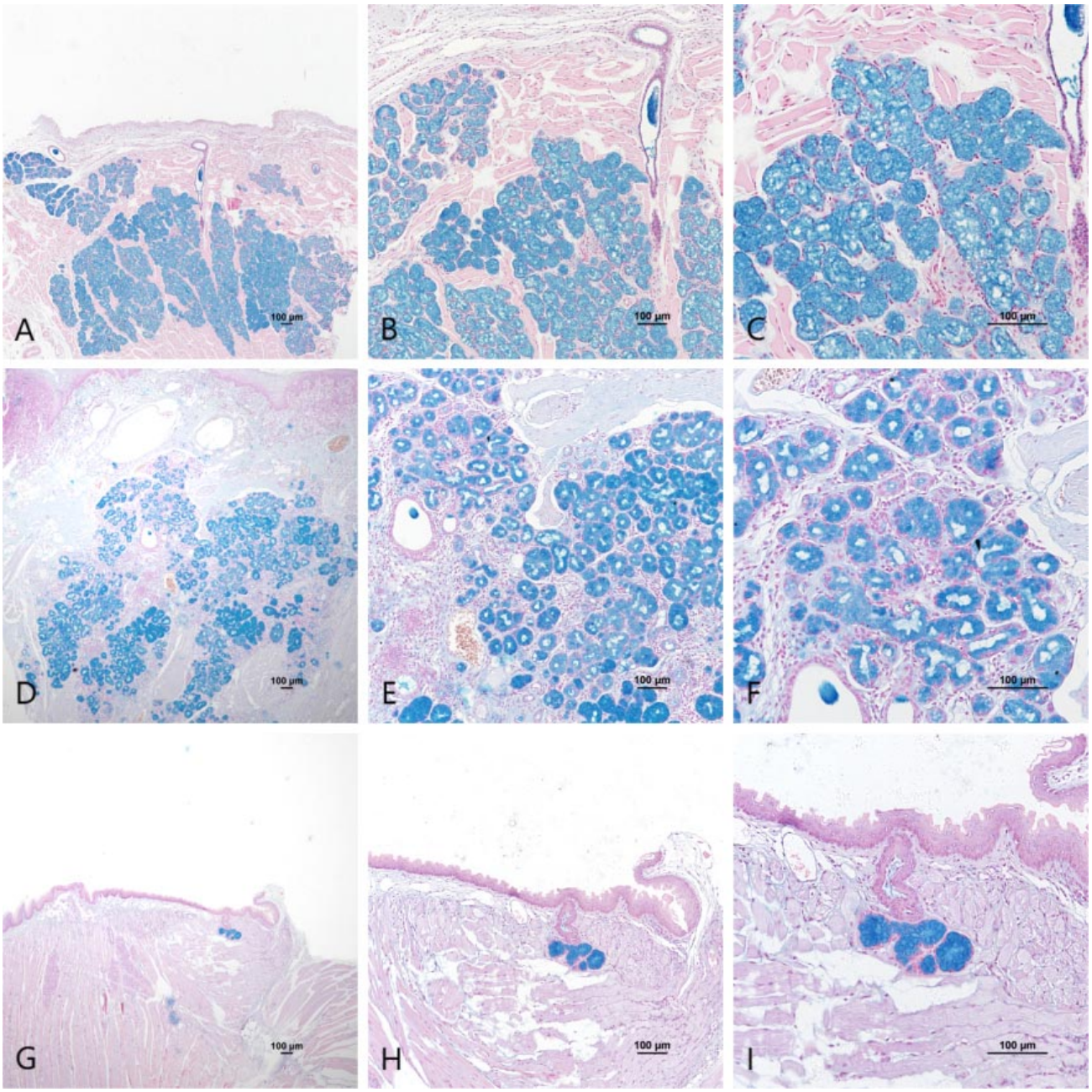

Fig. 5. Alcian blue staining of superficial portion of the posterior glands in Chinese tree shrew, human and mouse. (A.B.C. In Chinese tree shrew; D.E.F. In human; G.H.I. In mouse.) Image showed positive reaction of superficial portion of the posterior lingual glands mucous acini to alcian blue (pH = 2.5) staining. (A.D.G.×40; B.E.H.×100; C.F.I.×200).

were also typical mucous glands. The acini were invested by myoepithelium, and neither striated nor intercalated ducts were observed. And the mucous acini of superficial portion of the posterior lingual glands exhibited a positive reaction to alcian blue staining. In mice, superficial portion of the posterior lingual gland were mixed glands wherein the serous cells form a crescent-shaped structure, known as the demilune, which covers the blind-ended surface of the mucous cells. The tubulo-acini abruptly drained into short terminal ducts composed of stratified squamous epithelium, which opened directly onto the dorsal epithelium at the base of the tongue, similar to the anatomy observed in tree shrews. And the mucous cells within their acini exhibited a positive reaction to alcian blue staining (Figs. 4 and 5). These findings suggested that the structure of superficial portion of the posterior lingual glands in Chinese tree shrews are more similar to human beings than mice.

DISCUSSION

The Chinese tree shrew, a squirrel-like rat sized mammal, exhibits a close relationship to primates, including humans (Fan *et al*., 2019). Macro anatomically, the tongue morphology of the Chinese tree shrew aligns more closely with that of humans compared to the tongues of mice, which lack foliate papillae and possess only a single Ω-shaped circumvallate papilla lied directly anterior to the posterior margin of the inter molar eminence (Chen *et al*., 2024). Three fungiform vallate papillae are present on the posterior tongue of the Chinese tree shrew, which are arranged in a V-shape behind a structure resembling the human sulcus terminalis. Furthermore, parallel ridges of the foliate papillae can be observed at the lateral margin of the posterior tongue near the vallate papillae.

Histologically, the deep portion of the posterior lingual glands of the Chinese tree shrews, humans and mice are all pure serous glands. The acini of these glands are primarily composed of pyramidal serous cells, characterized by basophilic cytoplasm and round nuclei located at approximately one-third of the basal part of the cell. However, compared to mice, the deep portion of the posterior lingual glands of the Chinese tree shrews and humans are structurally more complex, featuring both striated and intercalated ducts. Whereas in mice, the duct system lacks striated ducts and exhibits solely the traits of intercalated ducts containing small secretory granules. Furthermore, in mice, the taste buds are not only distributed in the lateral wall of the vallate papilla furrow, as seen in humans and Chinese tree shrews, but also extend to the base of furrow, with deep portion of the posterior lingual glandular ducts opening below the taste buds at the base of the vallate papilla furro (Redman, 2012; Dzioba *et al*., 2017; Chen *et al*., 2024). In humans, the ducts of superficial portion of the posterior glands primarily open into the lingual tonsillar follicles and the interfollicular clefts at the base of the tongue (Riva *et al*., 1999). Interestingly, Chinese tree shrews, unlike humans, lack lingual tonsils at the base of their tongue. Instead, their superficial portion of the posterior glands exhibit a duct opening pattern akin to that of mice, where the tubulo-acini abruptly drain into short terminal ducts composed of stratified squamous epithelium, directly opening onto the dorsal epithelium at the base of the tongue. Notably, the deep portion of the posterior lingual glands of Chinese tree shrews are pure mucous gland, with their acini only consisting of mucous cells. These cells are predominantly triangular or pyramidal in shape, with flat nuclei located at the base of the cell and a deeper staining pattern. The cytoplasm exhibits a transparent reticular structure. Compared to the superficial portion of the posterior glands of mice, which are mixed glands, the acinar structure of superficial portion of the posterior gland lingual gland of Chinese tree shrews is more histologically similar to that of humans.

In previous research, due to the relatively concealed anatomical location of the posterior lingual glands and their close proximity to the lingual tonsils (Chen *et al*., 2022), coupled with the focus on the lingual tonsils as a key research subject for diseases of the tongue base (Ramqvist *et al*., 2015), diseases in this region were often attributed to the lingual tonsils, thereby overlooking the posterior lingual glands. These biases have led to a significant lack of research on diseases related to the posterior lingual glands. However, with the gradual deepening of scientific research, we have observed that various diseases occurring in this region exhibit significant differences in their pathophysiological mechanisms compared to tonsil-related diseases (Biesaga *et al*., 2023). Based on these new findings, the importance of the posterior lingual glands in tongue base diseases is gradually gaining attention in the academic community. Currently, the primary focus of research in the base of the tongue, where the posterior lingual glands are situated, revolves around tongue base carcinomas. Human papillomavirus (HPV), a key etiological factor, has been implicated in the rising incidence of these carcinomas in recent years, mirroring the escalation in HPV infection rates (Ferris Westra, 2023). Despite this, the posterior lingual glands have historically received less attention compared to the lingual tonsils, which have been the primary focus due to their susceptibility to HPV infection and subsequent malignant transformation (Johnson *et al*., 2020).

However, recent advancements have highlighted the significant role of the posterior lingual glands in the pathogenesis of tongue base carcinomas (Cladel *et al*., 2016; de Oliveira Neto *et al*., 2021; Peng *et al*., 2022). In this context, the Chinese tree shrew (*Tupaia belangeri chinensis*) emerges as a promising animal model due to its anatomical and histological similarities to humans (Fan *et al*., 2019). Our study has demonstrated that the deep portion of the posterior lingual glands and superficial portion of the posterior lingual glands in Chinese tree shrews share numerous features with their human counterparts, including their location, duct system, and glandular composition. In particular, the superficial portion of the posterior lingual glands of Chinese tree shrews are pure mucous glands, similar to those in humans, unlike the mixed glands observed in mice. This histological similarity, combined with the Chinese tree shrew's unique advantages in simulating human physiological and pathological conditions, particularly in viral infections, underscores its potential as a model for studying HPV-related diseases (Xiao *et al*., 2017; Xia *et al*., 2021). Although the establishment of HPV infection models remains challenging due to the virus's strict species specificity (Campo, 2002),

the Chinese tree shrew's capability to replicate human-specific viral infections, as evidenced by previous studies on Epstein-Barr virus (EBV), provides a solid foundation for future exploration in this area. Given the anatomical and histological similarities between Chinese tree shrews and humans in the posterior lingual glands, this species could potentially serve as a valuable model for elucidating the mechanisms of posterior lingual gland-related diseases, particularly HPV-associated tongue base carcinomas, thereby enhancing our understanding of these complex diseases.

CONCLUSION

The histological structures of the tongue and posterior lingual glands in the Chinese tree shrew closely resemble those of humans, providing a solid foundation for in-depth research into human posterior lingual glands-related diseases. Furthermore, the immunological similarities between the Chinese tree shrews and humans offer the potential for constructing an HPV-associated tongue base carcinoma infection model, which is expected to facilitate further research in this field.

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CHEN, X.; JIANG, Q.; LIN, L.; YU, D. & TAO, R. La musaraña arbórea china (*Tupaia belangeri chinensis*) podría ser un posible modelo animal para las enfermedades relacionadas con las glándulas linguales posteriores. *Int. J. Morphol., 43(6)*:2104-2113, 2025.

RESUMEN: El objetivo del estudio fue comparar las características anatómicas e histológicas de las glándulas linguales posteriores entre musarañas arbóreas chinas, ratones y humanos, proporcionando evidencia morfológica para evaluar a la musaraña arbórea como modelo biomédico. Se analizaron secciones de parafina de tejidos linguales de musarañas arbóreas chinas (n=5), ratones (n=5) y humanos (n=3) mediante tinción con hematoxilina-eosina (HE) y azul alcián. Se examinaron sistemáticamente las estructuras morfológicas, incluyendo las papilas valladas, las glándulas de Von Ebner (parte profunda de las glándulas linguales posteriores/ glándulas gustatorias) y las glándulas de Weber (parte superficial de lsa glándulas linguales posteriores /glándulas de la raíz de la lengua). Las musarañas arbóreas chinas exhibieron papilas valladas en forma de V, similares a las de los humanos, pero diferentes a las de los ratones. La parte profunda de las glándulas linguales posteriores en las tres especies eran glándulas serosas puras (azul alcián negativo), aunque los ratones carecían de conductos estriados. La parte superficial de las glándulas linguales posteriores en las musarañas arbóreas y en los humanos eran glándulas mucosas puras (azul alcián positivo), que drenaban a través de conductos cortos hacia las superficies mucosas, mientras que la parte superficial de las glándulas linguales posteriores murinas eran de tipo mixto y se abrían hacia las criptas linguales. Las similitudes anatómicas e histológicas entre las musarañas arbóreas chinas y los humanos en las estructuras de las glándulas linguales posteriores, junto con su utilidad en el estudio de enfermedades específicas de los humanos, respaldan a la musaraña arbórea como un modelo valioso para la investigación de la patogénesis de los trastornos relacionados con las glándulas linguales.

PALABRAS CLAVE: Musaraña arbórea china (*Tupaia belangeri chinensis*); Glándulas linguales posteriores; Parte profunda de las glándulas linguales posteriores; Glándulas gustatorias; Glándulas de Von Ebner; Parte superficial de la glándulas linguales posteriores; Glándulas de la raíz de la lengua. Glándulas de Weber; Modelo animal.

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