Differential antigen expression between human apocrine sweat glands and eccrine sweat glands

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ABSTRACT

Bromhidrosis has a great negative impact on personal occupation and social psychology. It is not yet clear whether bromhidrosis is caused by apocrine sweat glands or the co-action of apocrine sweat glands and eccrine sweat glands. To distinguish between apocrine sweat glands and eccrine sweat glands, specific antigen markers for apocrine sweat glands and eccrine sweat glands must be found first. In the study, we detected the expression of keratin (K) 7, K18, K19, Na^+-K^+-$2Cl^-$ cotransporter 1 (NKCC1), carbonic anhydrase II (CAII), Forkhead transcription factor a1 (Foxa1), homeobox transcription factor engrailed homeobox1 (En1), gross cystic disease fluid protein-15 (GCDFP-15), mucin-1 (MUC-1), cluster of differentiation 15 (CD15) and apolipoprotein (APOD) in eccrine sweat glands and apocrine sweat glands by immunofluorescence staining. The results showed that K7, K18, K19, Foxa1, GCDFP-15 and MUC-1 were expressed in both apocrine and eccrine sweat glands, CD15 and APOD were only expressed in apocrine sweat glands, and CAII, NKCC1 and En1 were only expressed in eccrine sweat glands. We conclude that CD15 and APOD can serve as specific markers for apocrine sweat glands, while CAII, NKCC1 and En1 can serve as specific markers for eccrine sweat glands to differentiate the two sweat glands.

Key words: Apocrine sweat glands; eccrine sweat glands; human; differential markers; immunofluorescence.

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Introduction

Apocrine and eccrine sweat glands are two types of sweat glands distributed close to each other in the region of axillary area.[1] Bromhidrosis has a significant impact on personal occupation and social psychology.[2] So far, it is not clear whether bromhidrosis is caused by apocrine sweat glands or the co-action of apocrine sweat glands and eccrine sweat glands. Some studies showed that the characteristic odor of bromhidrosis was caused only by the apocrine glands, as the number of apocrine glands was increased compared to normal people, while the eccrine glands were unchanged.[1,3,4] However, some studies considered that the special odor was the result of the co-action of apocrine sweat glands and eccrine sweat glands for that the bromhidrosis had a higher density of eccrine and apocrine sweat glands.[5,6] Therefore, to clarify the issue, we must first find reliable markers to distinguish between apocrine sweat glands and eccrine sweat glands.

Apocrine sweat glands and eccrine sweat glands are different in the distribution, structure and function.[7-10] In humans, apocrine sweat glands are mainly distributed in the axillae, ear canal, breast, eyelid, inguinal and perineal, and are associated with hair follicles.[5,7,11] Apocrine sweat glands are present at birth and do not become active until puberty, but little is known about their function in humans.[5,7,11] In contrast, the eccrine sweat glands are distributed almost all over the body, independence of hair follicles, and are active from birth.[7,8,10] The main function of eccrine sweat glands is to regulate body temperature in hot environments or during physical exercise.[7,8,10]

Morphologically, the ducts of the two glands are roughly similar and difficult to distinguish, while the secretory coils of the apocrine sweat glands and the eccrine sweat glands are different.[6,9,12] Generally, the lumens of the apocrine secretory coils are larger, while the lumens of the eccrine secretory coils are smaller.[7,8,10] Apocrine secretory coils have variable appearances in tissue sections, making it sometimes difficult to distinguish apocrine and eccrine sweat glands. In this study, we detected the reported apocrine and eccrine sweat gland markers keratin (K) 7, K18, K19, Na+-K+-2Cl- cotransporter 1 (NKCC1), carbonic anhydrase II (CAII), Forkhead transcription factor a1 (Foxa1), homeobox transcription factor engrailed homeobox1 (En1), gross cystic disease fluid protein-15 (GCDFP-15), mucin-1 (MUC-1), cluster of differentiation 15 (CD15) and apolipoprotein (APOD) by immunofluorescence to find specific markers to differentiate apocrine sweat glands from eccrine sweat glands.

Materials and Methods

Skin samples

Eight finger skin samples and eight axillary skin samples were used. Finger skin samples were obtained from 3- to 26-year-old individuals undergoing polydactylectomy, and axillary skin samples were obtained from 3- to 30-year-old individuals undergoing axillary surgery unrelated to axillary apocrine glands in Department of Wound Repair and Dermatologic Surgery, Taihe Hospital, Hubei University of Medicine. Ethical permission was granted by the Ethics Committee of Hubei University of Medicine, and informed consents were obtained from patients or their guardians. The samples were fixed in 4% paraformaldehyde, paraffin-embedded and cut into 5 μm-thick sections.

Hematoxylin and eosin (H&E) staining

The sections were dewaxed in xylene, rehydrated through grades of alcohol (100%, 95%, 85% and 75%) to double distilled water, stained in H&E and mounted in resin.

Immunofluorescence staining

The sections were routinely deparaffinized and hydrated, and then the sections were heated to 95°C in Tris-EDTA buffer (pH 9.0) for 15 min for antigen retrieval. Subsequently, the sections were incubated with 1% bovine serum albumin (BSA) in phosphate-buffered saline (PBS) for 30 min at 37°C to block nonspecific sites. Third, the sections were incubated respectively with different primary antibodies (data on the primary antibodies are described in Table 1) at 4°C overnight, followed by incubation with Cy3-labeled goat anti-rabbit IgG (H + L) (A0516, Beyotime, Jiangsu, China) for rabbit-derived primary antibodies, Cy3-labeled goat anti-mouse IgG (H+L) (A0521, Beyotime) for mouse-derived primary antibodies, or Cy3-labeled donkey anti-goat IgG (H+L) (A0502, Beyotime) for goat-derived primary antibody, at room temperature in the dark at 1:500 dilution for 1 h. Finally, the sections were counterstained with 4′, 6-diamidino-2-phenylindole (DAPI; Beyotime) for 2 min at room temperature in the dark and mounted with anti-fade mounting medium (P0128, Beyotime). PBS was used for rinsing between steps. Sections omitting the primary antibodies or using normal serum of the same species as the primary antibodies were used as negative controls.

Results

Typical eccrine sweat glands could be easily differentiated from apocrine sweat glands morphologically

In axillary skin, apocrine sweat glands and eccrine sweat glands were both located in the dermis of the axillary skin (Figure 1A). The lumens of apocrine secretory coils (Figure 1A,A1) were obviously larger than those of eccrine secretory coils (Figure 1A, A2). In fingers, there were only eccrine sweat glands, and most of the eccrine sweat glands were located in the deep part of the dermis and the upper part of the subcutaneous tissue (Figure 1B). The morphology of the eccrine sweat glands in the finger skin was similar to that in the axillary skin, with a small lumen (Figure 1 A,B).

Table 1. Primary antibodies used.

Primary antibodies	Source	Dilution
Mouse anti- CD15 (ab241552)	Abcam, UK	1:200
Rabbit anti- APOD (Ab108191)	Abcam, UK	1:200
Mouse anti- CAII (sc-133111)	Santa Cruz, USA	1:50
Goat anti- NKCC1 (sc-21545)	Santa Cruz, USA	1:200
Rabbit anti- En1 (HPA073141)	Atlas, Sweden	1:50
Rabbit anti- MUC-1 (ab109185)	Abcam, UK	1:250
Rabbit anti- GCDFP-15 (ab133290)	Abcam, UK	1:200
Rabbit anti- K7 (ab181598)	Abcam, UK	1:1000
Rabbit anti- K18 (ab181597)	Abcam, UK	1:500
Rabbit anti- K19 (Ab52625)	Abcam, UK	1:500
Rabbit anti- Foxa1 (ab170933)	Abcam, UK	1:1000

APOD, apolipoprotein D; CAII, carbonic anhydrase II; NKCC1, Na^+-K^+-$2Cl^-$ cotransporter 1, EN1, Homeobox transcriptional factor engrailed homeobox1; GCDFP-15, gross cystic disease fluid protein-15; Foxa1, Forkhead transcription factor A1.

CD15 and APOD were specific markers of apocrine sweat glands

The expression and localization of all detected antigens were consistent in all skin samples. Negative controls did not show non-specific binding and false positive results (Figure 2C1-3). CD15 was positive in the apocrine sweat glands (Figure 2A1; Table 2), while was negative in the eccrine sweat glands (Figure 2A2,A3; Table 2). APOD showed a strong reaction in the apocrine sweat glands (Figure 2B1; Table 2), but showed an absence of staining in the eccrine sweat glands (Figure 2B2,B3; Table 2).

CAII, NKCC1 and En1 were specific markers of eccrine sweat glands

CAII (Figure 3A1-3) and NKCC1 (Figure 3B1-3) stained the cell membrane and cytoplasm, and En1 (Figure 3C1-3) stained the nucleus. CAII was strongly expressed in the eccrine sweat glands (Figure 3A2, 3A3; Table 2), but was not expressed in the apocrine sweat glands (Figure 3A1; Table 2). NKCC1 showed almost no staining in the apocrine sweat glands (Figure 3B1; Table 2), while showed positive staining in the eccrine sweat glands (Figure 3B2,B3; Table 2). En1 immunoreactivity (Figure 3C1-3; Table 2) was found in the eccrine sweat glands (Figure 3C2,C3; Table 2), but not in the apocrine sweat glands (Figure 3C1; Table 2).

MUC-1, GCDFP-15, K7, K18, K19 and Foxa1 were the common antigens of apocrine and eccrine sweat glands

MUC-1 (Figure 4A1-3) was expressed in cell membrane, GCDFP-15 (Figure 4B1-3), K7 (Figure 4C1-3), K18 (Figure 4D1-3) and K19 (Figure 4E1-3) were expressed in cytoplasm, and Foxa1 (Figure 4F1-3) were expressed in nucleus. Both apocrine sweat glands (Figure 4A1-F1) and eccrine sweat glands (Figure 4A2-F2, A3-F3) were labelled by MUC-1 (Figure 4A1-3; Table 2), GCDFP-15 (Figure 4B1-3; Table 2), K7 (Figure 4C1-3; Table 2), K18 (Figure 4D1-3; Table 2), K19 (Figure 4E1-3; Table 2) and Foxa1 (Figure 2F1-3; Table 2).

Table 2. Localization of antigens in human apocrine sweat glands and eccrine sweat glands.

Antigen	Apocrine sweat glands	Eccrine sweat glands
CD15	+	–
APOD	+	–
CAII	–	+
NKCC1	–	+
En1	–	+
MUC-1	+	+
GCDFP-15	+	+
K7	+	+
K18	+	+
K19	+	+
Foxa1	+	+

+, expressed; –, not expressed;

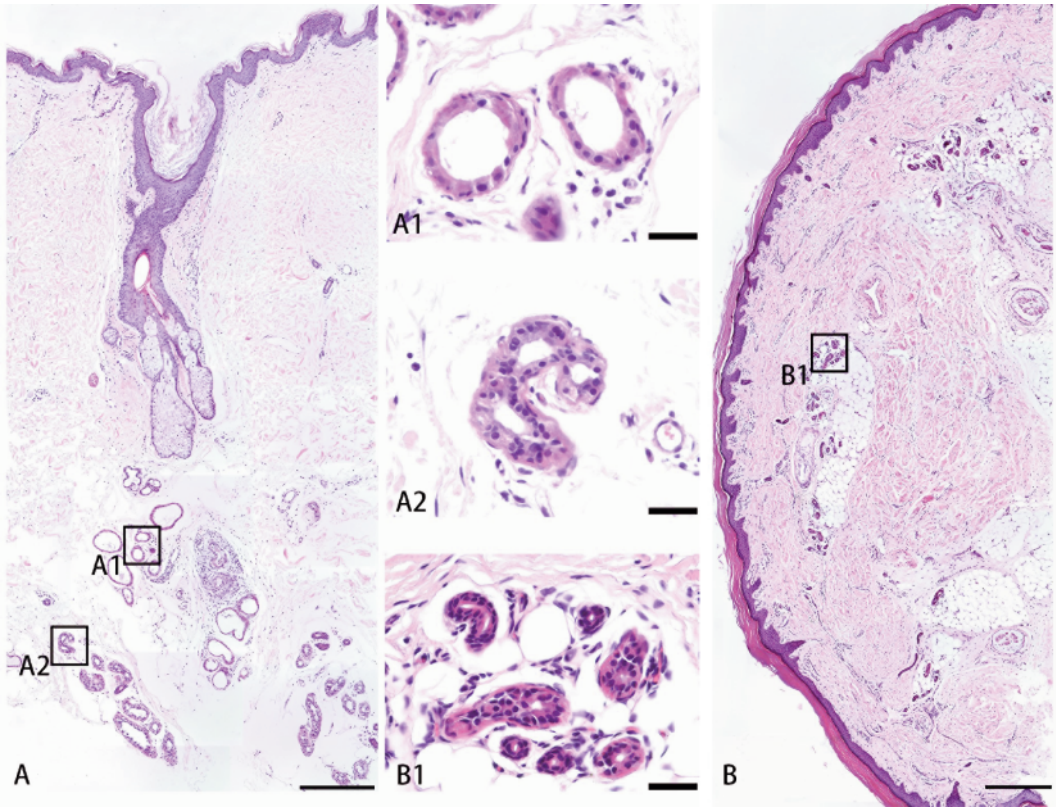

Figure 1. The morphology and distribution of eccrine sweat glands and apocrine sweat glands in axillary skin and finger skin. Eccrine sweat glands and apocrine sweat glands in the axillary skin after H&E staining (A, A1, A2). A higher magnification of apocrine sweat glands (A1) and eccrine sweat glands (A2) in the boxed areas in A. Eccrine sweat glands in the finger skin after H&E staining (B,B1). A higher magnification of eccrine sweat glands in the boxed areas in B (B1). Scale bars: 50 μm.

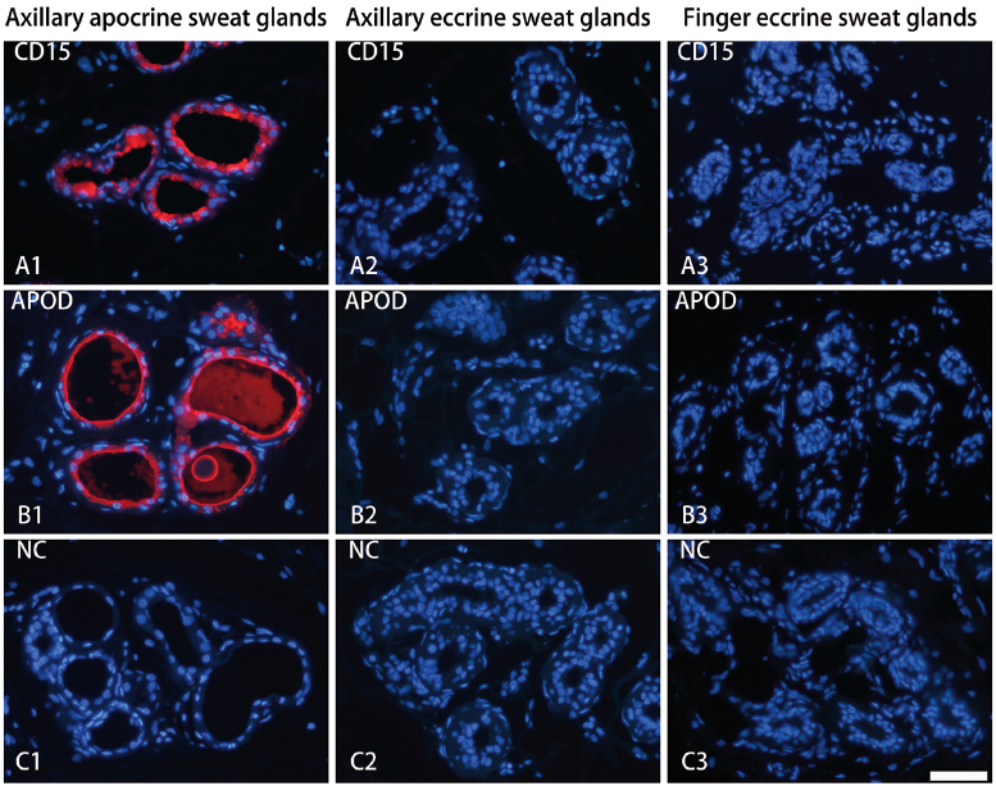

Figure 2. Specific markers for apocrine sweat glands. Immunofluorescence staining for CD15 (A1-3), APOD (B1-3) and Negative control (C1-3) in axillary apocrine sweat glands (A1-C1), axillary eccrine sweat glands (A2-C2), and finger eccrine sweat glands (A3-C3). APOD, apolipoprotein D; NC, negative control. Scale bar: 50 μm.

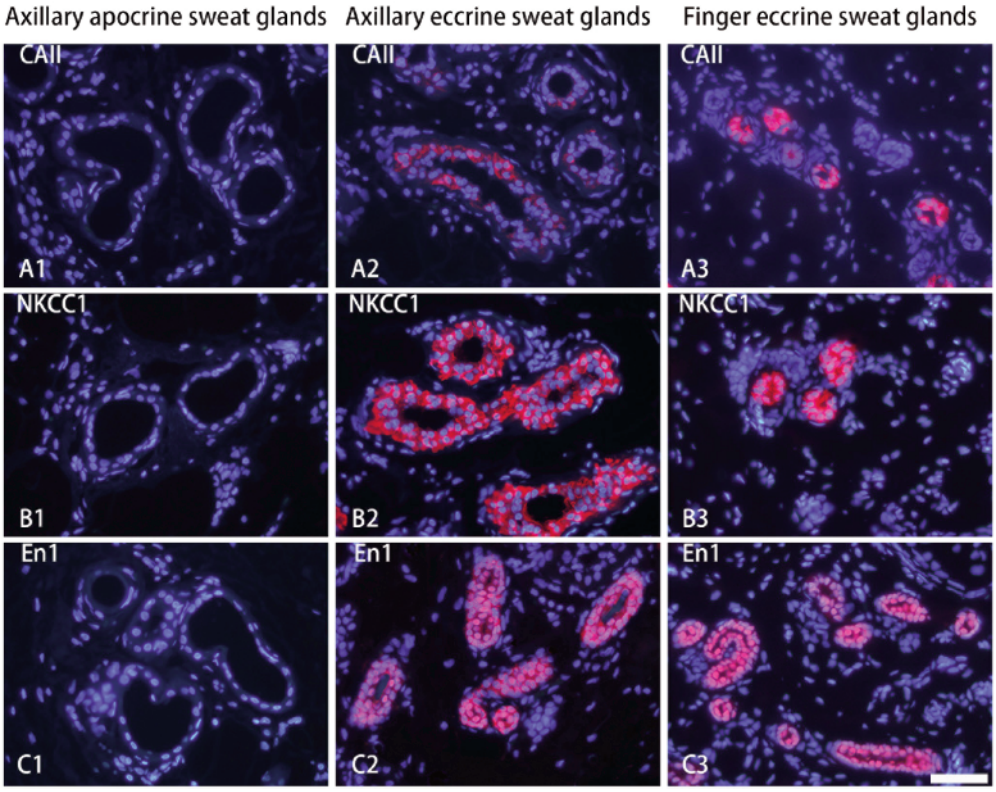

Figure 3. Specific markers for eccrine sweat glands. Immunofluorescence staining for CAII (A1-3), NKCC1 (B1-3) and En1 (C1-3) in axillary apocrine sweat glands (A1-C1), axillary eccrine sweat glands (A2-C2), and finger eccrine sweat glands (A3-C3). CAII, carbonic anhydrase II; NKCC1, Na+-K+-2Cl- cotransporter 1; En1, engrailed 1. Scale bar: 50 μm.

Discussion

Some previous studies have reported the differential antigens between eccrine sweat glands and apocrine sweat glands, but most of these antigens are not true differential antigens, so they cannot be used to distinguish between eccrine sweat glands and apocrine sweat glands. In this study, the expression of a series of antigens in finger skin and axillary skin were detect by immunofluorescence staining to find specific markers that can differentiate eccrine sweat glands from apocrine sweat glands.

Keratins are the major structural proteins of the epidermis and provide specific markers to differentiate different epithelial cell types.[13,14] K7, K18, and K19 are reported to be specific markers for eccrine sweat glands, so we examined their expression in apocrine and eccrine sweat glands.[15-19] The results showed that K7, K18 and K19 were positively expressed in eccrine sweat glands and apoc-

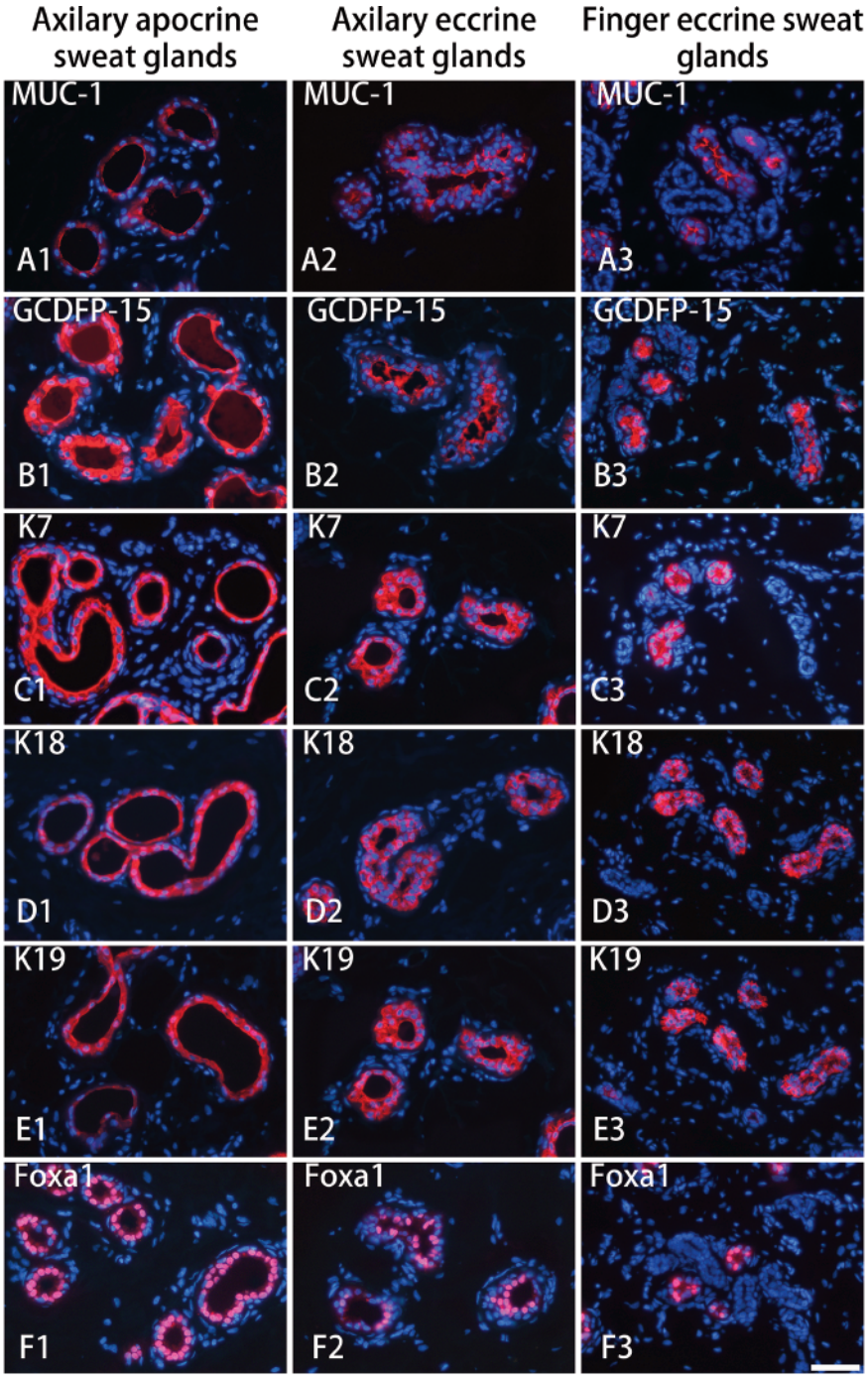

Figure 4. Common markers of apocrine sweat glands and eccrine sweat glands. Immunofluorescence staining for MUC-1 (A1-3), GCDFP-15 (B1-3), K7 (C1-3), K18 (D1-3), K19 (E1-3) and Foxa1 (F1-3) in axillary apocrine sweat glands (A1-F1), axillary eccrine sweat glands (A2-F2), and finger eccrine sweat glands (A3-F3). GCDFP-15, gross cystic disease fluid protein-15; Foxa1, Forkhead transcription factor a1. Scale bar: 50 μm.

rine sweat glands. Therefore, K7, K18 and K19 cannot be used to as specific markers to distinguish between apocrine and eccrine sweat glands. Likewise, Foxa1 had previously been shown to be expressed in the secretory coils of eccrine sweat glands and involved in eccrine sweat gland development.[20,21] The immunofluoresence staining in our study shows that Foxa1 was negatively expressed in epidermis, hair follicles and sebaceous glands (*data not shown*), and positively expressed in the secretory coils of apocrine and eccrine sweat glands. Therefore, Foxa1 can be used a specific marker for skin sweat glands, but it is not the desired makers for distinguishing eccrine sweat glands and apocrine sweat glands.

GCDFP-15, also known as BRST-2, is considered a marker of apocrine differentiation.[22,23] However, some studies had shown that GCDFP-15 expression was also present in eccrine sweat glands, ceruminous glands and Moll's glands.[24,25] In our study, immunofluorescence staining showed that GCDFP-15 was expressed in both apocrine and eccrine sweat glands. Combined with previous studies, GCDFP-15 may be more suitable as a marker for glandular differentiation, rather than a specific marker for distinguishing apocrine and eccrine sweat glands. MUC1 is constitutively expressed in the epithelial cells.[26] It was previously considered to be an apocrine marker that distinguishes apocrine sweat glands from eccrine sweat glands, because human milk fat globule membranes-1 (HMFG-1), a monoclonal antibody detecting the fully glycosylated MUC1, stained only apocrine sweat glands but not eccrine sweat glands.[26] However, in our study, MUC1 was positively expressed not only in apocrine sweat glands, but also in eccrine sweat glands. Therefore, MUC-1 is not the specific marker that we are looking for to differentiate between apocrine and eccrine sweat glands.

CAII is a cytoplasmic enzyme that catalyzes the reversible conversion of carbon dioxide and water into carbonic acid, protons and bicarbonate ions, and NKCC1 is an ion transport protein that transport Na, K, and Cl ions inside or outside the cells.[27,28] CAII had been used as a specific marker for clear secretory cells of eccrine sweat glands, and NKCC1 had been used as a specific marker for eccrine sweat glands to distinguish eccrine sweat glands from hair follicles.[15,29] In our study, CAII and NKCC1 were expressed in eccrine sweat glands, but not in the apocrine sweat glands, which was consistent with the study by Bovell *et al*.[30] En1, a member of the homeobox transcription factor family, is a marker of eccrine sweat glands and is involved in the development of eccrine sweat glands.[23,31] Ectopic expression of En1 in the hair follicle placodes promoted the differentiation of hair follicle into eccrine sweat glands.[17] En1 heterozygote mutant mice showed less eccrine sweat glands.[31] A previous study by Miura *et al*. showed that En1 was specifically expressed in normal eccrine sweat glands and eccrine differentiated tumors, but not in apocrine sweat glands, sebaceous glands and hair follicles.[23] In our study, the positive nuclear staining for En1 was found in eccrine sweat glands, but negative in apocrine sweat glands, which was consistent with the study by Miura *et al*.[23] Therefore, En1, NKCC1 and CAII can be used as specific markers for eccrine sweat glands to distinguish eccrine sweat glands from apocrine sweat glands.

The glycan determinant CD15, also known as stage specific embryonic antigen 1 (SSEA-1), have originally identified as a monocyte cell marker.[32,33] Previous studies had shown that CD15 is only expressed in apocrine sweat glands but not in the eccrine sweat glands.[12,30,34,35] APOD is an extracellular glycoprotein of the lipocalin family involved in lipid transport, food intake and development.[36] A previous study showed that APOD was expressed in the apocrine sweat glands of patients with bromhidrosis and healthy subjects, but the expression level of APOD in patients with bromhidrosis was twice that of healthy subjects.[37] In our study, CD15 and APOD were only expressed in the apocrine sweat glands. Therefore, CD15 and APOD can be used as specific markers for apocrine sweat glands to distinguish apocrine sweat glands from eccrine sweat glands.

In conclusion, CD15 and APOD can be used as specific markers for apocrine sweat glands, whereas NKCC1, CAII and En1 can be as specific markers for eccrine sweat glands to distinguish between eccrine and apocrine sweat glands.

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