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Hypothesis Letter

Is the eccrine gland an integral, functionally important component of the human scalp pilosebaceous unit?

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Abstract: The pilosebaceous unit (PSU) and the eccrine sweat gland (ESG) are classically described as completely independent skin appendages. However, careful inspection of scalp follicular units reveals that the secretory segment of the ESG spatially approximates the hair follicle in a position below the sebaceous gland and the insertion of the arrector pili muscle. Therefore, we propose here that, contrary to conventional wisdom, the PSU and the ESG should not be viewed in isolation, and may form instead, along with the arrector pili muscle and the apocrine gland (where present),one functional unit. For this, we suggest the more inclusive term of 'Hair Cluster' (HC). If confirmed, e.g. by 3D imaging techniques, the novel concept of a functional HC, whose individual components may communicate via secreted molecules and may share selected progenitor cell populations for HC repair/regeneration, has major physiological and pathological implications, which are briefly discussed.

Key words: eccrine sweat gland – hair follicle

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Background & premises

Conventionally, the pilosebaceous unit (PSU) and the eccrine sweat gland (ESG) are described as independent skin appendages. However, if one systematically follows the whole trajectory of the ESG from the epidermis to the adipose tissue in serial horizontal sections, rather than by routine histology (Text S1), it becomes evident that the eccrine duct (ED) often spatially approximates the hair follicle (HF), at least in human scalp skin (Fig. 1a–c). Moreover, the secretory segment of the ESG rests below the insertion of the arrector pili muscle, close to the hair follicle′s outer root sheath (ORS) (Figs 1b, S1–3), (Text S2). Even in a narrow 1 mm punch of scalp skin this close proximity is visible (Fig. 1c). Thus, in scalp skin, key ESG components are located almost as closely to the HF as the sebaceous gland, raising the important question whether this represents a general principle of human skin architecture. Interestingly, the association of adnexal structures of the skin was already hinted at by Pinkus' 'Haarfeld' (hair field) concept (1) and also in older literature, including non-human primate skin anatomy literature (Text S3).

Hypothesis

On this basis, we propose that, contrary to conventional wisdom, the PSU and the ESG cannot be viewed in isolation and form an interconnected functional unit, important for both skin physiology and pathology, at least in human scalp skin. We hypothesize that, together with the arrector pili muscle and the apocrine gland (where present), the PSU and the ESG form what may be termed a *'hair cluster'* (HC).

How to test the hypothesis

The current hypothesis is eminently testable, since the spatial arrangement of the ESG and ED can be clarified by 3D reconstruction imaging obtained using serial, consecutive sections reconstructed using widely available image processing software (Text S4). This will refute or confirm the proposed HC concept.

It is also possible to test whether these structures communicate by analysis of secreted compounds. For example the human ESG secretory coil may secrete prolactin (2), a major neurohormone generated in human skin and HFs, which significantly modulates both hair growth and sebaceous gland function (3, s1–s4). Moreover, the ESG and/or ED epithelium contain pro-inflammatory antimicrobial peptides, such as cathelicidin (4, s5), chemokines (s6), and cytokines (5), whose local release could well impact on the immediately adjacent HF.

One key experimental strategy to confirm the HC concept is to re-investigate the expression pattern and secretion of molecules produced in the HC as a whole. Next, the expression and secretion of key candidate signals that may regulate inter-appendage communication within the proposed HC could be selectively manipulated in either eccrine or HF epithelium, followed by demonstrating a reciprocal response in the other HC component, or by dissecting the consequences for either appendage when the other one is absent, even though the latter is experimentally very challenging (Text S5).

The ESG is also a main source and site of epithelial-ESG progenitor cells, which are label-retaining and keratin 15+ (7,8), and pluripotent, non-epithelial skin stem cells (e.g. nestin) (6, s7). Importantly, under regenerative conditions, human ESG epithelial progenitor cells can not only differentiate into epidermal keratinocytes, but may also be capable of generating new HFs (8). In addition, the close proximity of the non-epithelial ESG stem cells to the HF may also facilitate regeneration after injury (Text S6). Thus, our hypothesis can be further tested by probing whether selective HF wounding can recruit ESG stroma-associated nestin+ cells and/or keratin 15+ ESG stem cells facilitating HF repair.

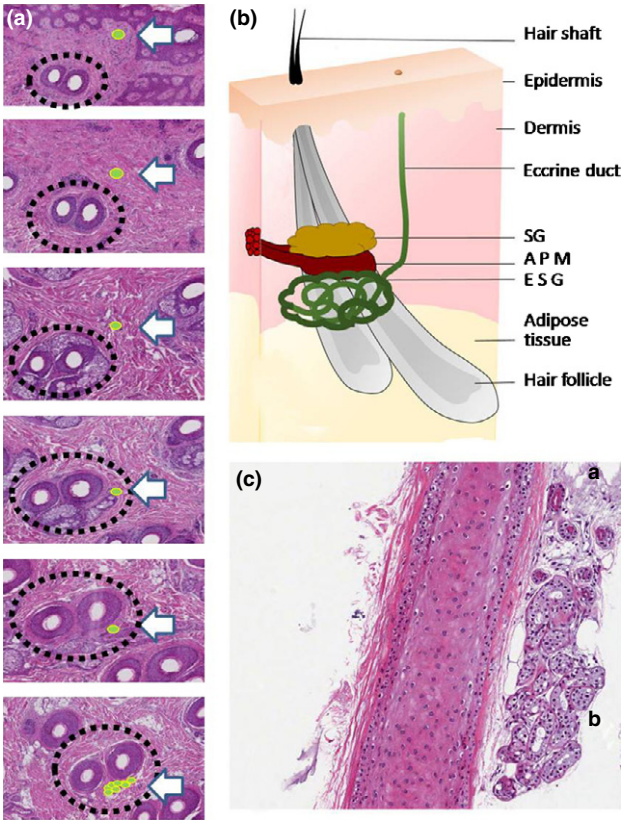

Figure 1. (a) H&E-stained serial horizontal sections following the complete trajectory of an eccrine gland from the epidermis to the deep dermis. Eccrine ducts and glands are coloured in yellow and are pointed out by white arrows. Follicular units are demarcated with a dashed black circle. Localization of these structures in serial sections permits the demonstration that the eccrine duct approximates the hair follicle, and that the secretory part of the eccrine gland closely approaches the hair follicle below the insertion of the arrector pili muscle (25× magnification). (b) Computer-assisted illustration that reproduces in a three-dimensional perspective the histological observations (without striving to accurately represent lengths or proportional sizes). (c) HE stained longitudinal section of a follicular unit harvested with a 1 mm punch from the adult human occipital scalp skin used for follicular unit hair transplantation. Note that both components of the secretory segment of the ESG, i.e. the coiled duct (a) and the secretory gland (b), are located so closely to the hair follicle that they are clearly visible even in a slim 1 mm biopsy punch tissue column. It cannot be excluded with certainty that the eccrine gland might have been compressed within the small tissue volume of this skin punch, thus moving artificially closer to the HF as is physiologically the case. However, this close proximity can also be seen in large biopsy specimens (Figure S4). SG: sebaceous gland; APM: arrector pili muscle; ESG: Eccrine sweat gland.

Relevance and perspectives

If this hypothesis is confirmed, primate scalp skin may best be thought of as being organized into numerous complex tissue districts, similar to the historical 'skin unit' or 'hair field' concepts envisioned by early morphologists (1, s8). As has recently been documented for entire fields of interacting murine HFs *in vivo* (9), the proposed HCs may engage in coordinated interactions over large stretches of primate integument, thus impacting on overall skin physiology in large territories (Text S7).

Currently, we cannot exclude that the much-ignored close spatial association of the ESG with the HF is a mere morphological peculiarity limited to the scalp skin without functional relevance. Yet, as biology makes sense in the light of evolution (s9), one is inclined to believe that this association has survived environmental selection pressures by providing significant, but as yet unclear selection advantages. In fact, phylogenetically, ESGs may have replaced the allegedly more primitive HF-associated apocrine glands (Text S8).

The HC concept proposed here may also be clinically relevant, namely in ESG-associated pathology (e.g. hyperhidrosis, neutrophilic eccrine hidradenitis or syringometaplasia), where ESGs may impact on hair growth and HF function in subtle, as yet unrecognized ways. *Vice versa*, hair diseases may affect ESG function as a result of a disturbed HC homeostasis. Moreover, the ESG and its stem cell populations may be more important for epidermal and skin appendage repair/regeneration after skin wounding than previously appreciated (Text S6). Therefore, systematic exploration of the HC concept is likely to redefine our understanding of the functional anatomy of human skin in health and disease.

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Conflict of interest

None declared.

Supporting Information

Additional supporting data may be found in the supplementary information of this article.

Figure S1. Illustration of the methodology used, that permits to infer the three-dimensional reconstruction shown in Fig. 1.

Figure S2. Images obtained with the methodology described in Fig. S1 were serially assembled in layers using Adobe Photoshop software (CS2 version).

Figure S3. 3D reconstruction of ESGs following their complete trajectory shows that the secretory portion of two glands converges on the same three hairs follicular unit.

Figure S4. H & E-stained section of normal skin shows the intimal association of the secretory coil (a) and the coiled duct (b) of a secretory gland with the outer root sheath of two hair follicles from the same follicular unit.

Data S1. Supplementary text.

Data S2. Supplementary References.

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