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Lrig1 and CD44v3 Expression in the Human Folliculosebaceous Unit

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Key Words

Lrig1 expression · CD44v3 expression · Human folliculosebaceous unit

The expression of Lrig1 in human epidermis has been described as clusters of Lrig1-positive keratinocytes in the basal layer of the interfollicular epidermis (IFE) [1, 2]. Giving that Lrig1 is a

functional inhibitor of EGFR, the basal layer of the IFE appears as a patch of neighboring Lrig1+/EGFR- and Lrig1-/EGFR+ expressing clusters [3]. In addition, Lrig1 and c-myc are believed to form an autoregulatory loop, as Lrig1 inhibits c-myc while c-myc activates Lrig1 [1, 4].

In contrast to humans, the expression of Lrig1 in the resting mouse is located in the isthmus connecting the infundibulum, isthmus and the sebaceous glands (SGs) of the folliculosebaceous unit (FSU) [1, 2]. These Lrig1+ cells located in the isthmus were shown by lineage tracing to feed, in homeostatic conditions, the isthmus itself, the infundibulum and the SGs. However, upon injury they were able to repopulate interfollicular epidermal compartments [5].

We have now observed similar Lrig1+ clusters in the isthmus and SGs of the human FSU. We next studied the expression of EGFR and CD44v3 in these clusters, since CD44v3 has been shown to modulate EGFR signaling [6–8]. Two human skin serial sections from the scalp and from the retroauricular area were stained with antibodies directed against the human form of Lrig1 [1, 9, 10], EGFR (Cell Signaling, #4267, Danvers, Mass., USA) and CD44v3 (BMS144, Bender MedSystems, Vienna, Austria). The previously

Fig. 1. Lrig1 (**a**) and EGFR (**b**) expression in human scalp epidermis. The analyzed sample was taken from the scalp of a 54-year-old male donor. Lrig1 and EGFR (D38B1 XP™ polyclonal rabbit antibody, Cell Signaling, #4267) were stained in two serial human sec-

tions of a human skin biopsy from scalp origin. DNA was counterstained with DAPI. Arrows indicate the Lrig1+/EGFR- clusters. Pictures were acquired with a panoramic digital slide scanner 250 (3DHISTECH). Bars = 100 μm.

described clusters of Lrig1+ cells in the IFE were detected in the basal layer, and these clusters were negative for EGFR (fig. 1) and CD44v3 (data not shown). In addition, we found Lrig1 highly positive clusters in the isthmus and also in the SGs (fig. 2). EGFR and CD44v3 expression was reduced in these clusters (fig. 2).

This staining pattern suggests that at least two clusters of Lrig1+ keratinocytes are present in human epidermis: (i) the epidermal interfollicular cluster involved in the homeostasis of the epidermis, as previously described [2], and (ii) a second follicular cluster, similar to the murine follicular Lrig1 niche, which may

have similar functions, i.e. feeding of the upper FSU, the infundibulum and the SGs [5].

In the mouse skin the Lrig1 niche feeds the upper FSU and only contributes to the regeneration of all epidermal compartments in case of injury [5]. Indeed in homeostatic conditions, the mouse IFE appears to self-renew autonomously, according to stochastic asymmetric divisions giving one differentiated cell and one basal undifferentiated cell, under the regulation of an autocrine Wnt signaling pathway [11, 12]. The human epidermis may have evolved towards a different model with two distinct epidermal

Fig. 2. Lrig1, EGFR and CD44v3 expression in human epidermis from a retroauricular and scalp zone. The analyzed samples were taken from the retroauricular area of a 34-year-old male donor and from the scalp of the patient described in figure 1; DNA was counterstained with DAPI. Pictures were acquired with a microscope confocal system Leica SP5. **a** Staining of Lrig1 with DNA counterstained with DAPI. **b** Co-staining of EGFR and CD44v3. **c** Co-staining (left) of CD44v3 and EGFR in an SG with a serial section of the same gland with a staining of Lrig1 (middle), and co-staining of Lrig1 and CD44v3 on a distinct SG (right). Arrows indicate the exclusion between the Lrig1 staining (isthmus) and EGFR/CD44v3 staining (germinal/mature sebocytes) in the two serial sections. Bars = 100 μ m.

Lrig1 niches, an epidermal Lrig1 niche and a follicular one. Hair follicles are much more scattered in human skin; this may be an explanation for the need of an additional reservoir of Lrig1+ quiescent cells in the IFE epidermis.

The distribution of Lrig1+ cells in the human follicular isthmus and some undifferentiated SG cells questions their contribution to the maintenance of SG homeostasis. The fine regulation of the EGFR/Lrig1 loop, putatively tuned by CD44v3, may be involved in acne and comedogenesis [13], the acneiform eruptions associated with EGFR inhibitors [14] and sebaceous neoplasia [15, 16].

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Disclosure Statement

The authors declare no conflict of interests.

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