

SPOTLIGHT

Skin without fibroblasts: Rethinking epidermal-dermal dependence

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Epidermal stem cell maintenance depends on complex niche signalling. In this issue Gaeta, Du et al. (<https://doi.org/10.1083/jcb.202507165>) show that substantial dermal fibroblast depletion has surprisingly minimal effects on epidermal proliferation and skin function during development and adult homeostasis.

The skin is our most important protective barrier and is composed of two main layers: the outer epidermis and the underlying dermis. The epidermis consists of tightly packed keratinocytes anchored to the dermis via the basement membrane, while the dermis is primarily composed of diverse fibroblast subpopulations and extracellular matrix (ECM) components that provide structural support (1).

During early skin development, there is a complex signalling cross talk between epidermal and mesenchymal cells, particularly fibroblasts, which supports epidermal stratification, skin appendage development, and formation of distinct dermal layers including the papillary, reticular, and adipocyte layer. Epidermal cells progressively establish a basal stem cell-rich layer, where cells continue to proliferate and subsequently delaminate to form the cornified skin barrier. Similarly, multipotent dermal fibroblasts differentiate into distinct subpopulations that give rise to the various dermal sublayers. These mechanistic insights into skin development have emerged from elegant lineage-tracing and transcriptomic studies, which have not only elucidated the cellular dynamics but also dissected the intricate signalling interactions at spatial single-cell resolution (2).

The importance of epidermal-mesenchymal cross talk is particularly evident during the formation of skin appendages such as hair follicles and sweat glands (3, 4). For example, deletion or

inhibition of specific cell populations or key signalling pathways (e.g., Wnt, SHH) in dermal condensate fibroblasts impairs hair follicle formation and growth (5, 6). However, how dermal fibroblasts influence epidermal stem cells in the interfollicular epidermis and skin function later in development remains poorly understood.

In cell culture systems, the role of fibroblasts in promoting epithelial stem cell proliferation and differentiation is well established. But the extent to which this interaction is essential in vivo, beyond hair follicle formation, has remained unclear.

Interestingly, while epidermal cells maintain a highly proliferative state during development, dermal fibroblasts are initially proliferative but rapidly transition to a quiescent state postnatally, with dermal expansion occurring primarily through ECM deposition (7). During this process, distinct tissue niches are established with defined cellular and molecular microenvironments that regulate epidermal stem cell function, hair follicle formation, and vascular development (8).

This raises a key question: how critical is epidermal-dermal signalling cross talk during dermal maturation, particularly once the epidermis has established its niche microenvironment?

Using state-of-the-art transgenic models and innovative labelling approaches to track proliferating cells, Gaeta, Du, and colleagues addressed this question by examining the effects of genetic depletion of dermal

fibroblasts in neonatal and adult skin (9). They focused on paw skin, which is hairless and has a multilayered epidermis, thereby more closely resembling key features of human skin. Surprisingly, substantial fibroblast depletion (~70% reduction across all fibroblast subpopulations) for periods of 1 wk to 1 mo had only minimal effects on epidermal proliferation, ECM organization, and overall skin structure, while skin barrier function remained intact (Fig. 1). This is particularly striking in neonatal skin, where dermal expansion must support rapid organismal growth of the skin.

Due to systemic health effects, the study in neonatal skin was limited to short-term fibroblast depletion and local depletion approaches in the paw were less efficient. Future studies investigating long-term consequences on skin health and regeneration to explore potential changes in wound closure and scar formation will be important. Similarly, identifying which dermal signals persist or are lost after fibroblast depletion would further elucidate how the epidermal-dermal signalling cross talk is perturbed after fibroblast depletion.

Closer examination of structural and mechanical properties of the connective tissue 1 wk after fibroblast depletion revealed no significant changes in collagen density, organization, or basement membrane morphology. However, basement membrane stiffness was significantly reduced. Additionally, basal epidermal cell detachment was delayed in neonatal skin

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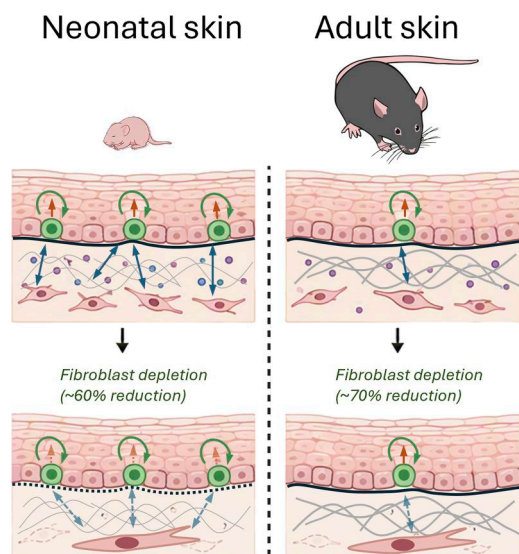


Figure 1. Disruption of epidermal–dermal signalling through genetic depletion of dermal fibroblasts has minimal effects on neonatal and adult skin homeostasis. Basal epidermal stem cells actively proliferate and progressively delaminate to drive epidermal stratification, particularly during neonatal stages when the skin undergoes rapid expansion. Unexpectedly, substantial depletion of dermal fibroblasts had minimal impact on epidermal cell proliferation in both neonatal and adult skin. The remaining fibroblasts exhibited an increase in nuclear area and cell size, potentially compensating for the loss of neighboring cells. Although overall skin architecture was preserved, fibroblast depletion reduced basement membrane stiffness and decreased basal cell delamination in neonatal skin.

following fibroblast depletion. These observations suggest that dermal fibroblasts, particularly papillary fibroblasts in the upper dermis, may contribute to basement membrane maturation during postnatal growth. Whether the delayed detachment of basal cells is directly linked to reduced basement membrane stiffness, potentially through altered cell anchorage as observed in ageing skin (10), remains an intriguing question for future investigation.

Using a dual in vivo reporter system labelling fibroblast nuclei and membranes, Gaeta, Du, and colleagues further demonstrated that although most fibroblasts were depleted (as indicated by loss of nuclear labelling), membrane coverage remained largely intact. Moreover, the nuclei of persisting fibroblasts were enlarged, indicating potential changes in tissue mechanics or cell state. These findings highlight the remarkable adaptability of fibroblasts, which can extend their membranes to compensate for

reduced cell numbers and maintain dermal structural integrity.

Whether this reduced fibroblast population can sustain epidermal function and overall skin resilience over the long term, particularly during injury or environmental stress, remains to be determined.

Interestingly, similar compensatory mechanisms have been observed in ageing skin (11) and following UV-induced damage (12). Here in addition to epidermal cell damage, UV exposure caused a transient reduction in dermal fibroblast density in the upper dermis, which is restored through a combination of fibroblast proliferation and membrane expansion. Chronic UV exposure further enhances fibroblast membrane expansion, correlating with dermal changes associated with photoaging and reduced skin function. These observations suggest that while short-term compensation of fibroblast loss is able to preserve tissue

integrity, long-term consequences may include premature skin ageing and functional decline.

Overall, the study by Gaeta, Du, and colleagues reveals an unexpected resilience of the skin to the loss of dermal fibroblasts, even in neonatal stages. This work provides important new insights into the skin cell dynamics and niche function, suggesting that reduced dependence on fibroblast-derived signals may represent an adaptive mechanism that enables the skin to better withstand environmental and mechanical challenges throughout postnatal life.

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