COMMENTARY

In summary, Kosumi et al. (2021) have identified COL17 displacement from HDs that occurs with inhibition of Wnt/β-catenin signaling. This phenotype was concurrent with aPKC-induced reduction of plectin in HDs. Although causality remains to be conclusively demonstrated, existing literature suggests that several physiological and pathological events can be influenced by Wnt/β-catenin signaling—induced COL17 stabilization in the epidermis. Because recent studies have elucidated the novel functions of COL17, exploring upstream signaling pathways that regulate COL17 localization or expression is gaining importance. Kosumi et al. (2021) propose a possible upstream pathway of COL17 regulation that may be involved in physiological or pathological events in the skin.

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Dermal Hedgehog Signaling in Papillary Fibroblasts: An Emerging Key Player in Skin Regeneration

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Skin morphogenesis and regeneration require the coordinated function of two layers: the outer epidermis and the underlying dermis. The epidermis is built of tightly packed keratinocytes, and the most common cells in the dermis are fibroblasts that are essential for structural integrity and are best known for their ability to deposit and remodel the extracellular matrix (ECM). Recent advances in single-cell RNA sequencing (scRNA-seq) and lineage tracing technologies have revealed impressive fibroblast heterogeneity in the skin and other organs (Shaw and Rognoni, 2020). However, our understanding of the functions of these subpopulations and how they are regulated by different signaling pathways is largely unknown.

During skin development, multipotent fibroblasts differentiate into distinct subpopulations that create the dermal sublayers: papillary dermis, reticular dermis, and dermal white adipose tissue (DWAT) (Rognoni and Watt, 2018). These fibroblast subpopulations differ in location and function, and their cell identity and composition change with age. Although papillary fibroblasts immediately beneath the basement membrane have an active Wnt signaling signature, show high Hedgehog (Hh) target gene expression, and are required for hair follicle (HF) formation, fibroblasts in the reticular dermal layer express genes associated with ECM and immune signaling at high levels and mediate the initial phase of wound repair. Dermal maturation is governed by a tight balance of fibroblast proliferation, quiescence, and ECM deposition during development. Notably, there is a coordinated switch in fibroblast behavior from highly proliferative in embryonic development to postnatal quiescence, allowing
Clinical Implications

- Hedgehog (Hh) signaling in papillary fibroblasts is essential for hair follicle regeneration.
- Hh signaling activation induces a dermal papilla fate in papillary fibroblasts in scarring wounds.
- Expressing developmental signals in selected fibroblasts holds therapeutic potential for skin regeneration.

for efficient ECM deposition/remodeling. The quiescent state can be maintained long term in postnatal skin, but upon wounding, different fibroblast lineages become activated at the wound site. α-SMA-positive fibroblasts quickly resume proliferation and migrate into the wound bed. Intriguingly, besides depositing/remodeling ECM, wound bed fibroblasts are able to acquire a dermal papilla or adipocyte fate in response to distinct developmental signals, which are still under investigation, promoting de novo HF and DWAT regeneration (Rognoni and Watt, 2018).

Hh signaling in papillary fibroblasts promotes HF morphogenesis

In their article in the Journal of Investigative Dermatology, Frech et al., (2021) explore the role of dermal Hh signaling in different fibroblast lineages during HF development and regeneration. Previous in vivo studies indicated a central role of the Wnt and Hh signaling pathways for HF development and regeneration, but their specific contribution in different fibroblast populations remained elusive (Rognoni and Watt, 2018). Using state-of-the-art transgenic mouse models to genetically deplete or activate SMO, a seven-transmembrane domain protein controlling Hh pathway activity, in either papillary (Blimp1-Cre) or all dermal (Dermo1-Cre and PDGFRe-CreER) fibroblasts, Frech et al., (2021) showed that dermal Hh signaling in papillary fibroblasts is essential for HF morphogenesis. In line with the importance of papillary fibroblast for HF formation, heterozygote Smo depletion in this fibroblast population led to reduced HF density in neonatal skin. Interestingly, only modulation of Hh signaling in all fibroblasts was able to influence HF growth postnatally. Because neither HF Wnt signaling, proliferation, or collagen deposition were significantly affected, it is likely that Hh signaling–induced changes in the DWAT layer, which is tightly linked with the hair cycle regulation (Kruglikov et al., 2019), are responsible for the observed phenotype. Dissecting the role of Hh signaling in specialized fibroblast populations such as dermal papilla cells, pericytes, and adipocytes during skin development warrants further investigation.

Dermal Hh signaling enables regenerative wound healing

HF regeneration is usually restricted to embryonic and early neonatal wounds in mice and other mammals (Rognoni and Watt, 2018). Small skin wounds in adult mice contract and form a scar, but large wounds (>1 cm²) induce Hh signaling in the central area, leading to localized regeneration of HFs (Lim et al., 2018). The appearance of HF neogenesis predominately in the central wound bed area suggests the presence of distinct tissue repair zones with differential regenerative capacity (Figure 1). By combining scRNA-seq and assay for transposase-accessible chromatin using sequencing, a recent study by Abbasi et al. (2020) revealed that the wound bed microenvironment induces significant chromatin rearrangement in recruited fibroblasts generating more central, upper dermal regenerative and peripheral, lower dermal scarring zones, which can be modulated by pharmacological intervention.

The recent study by Frech et al. (2021) explored how modulation of dermal Hh signaling in different fibroblast subpopulations affects skin regeneration in nonregenerative (small adult wounds) and regenerative (neonatal wounds) wound healing models. Hh signaling inhibition in all fibroblasts delayed wound closure and impaired angiogenesis and HF regeneration, whereas Hh activation accelerated wound healing and promoted HF neogenesis and angiogenesis throughout the wound bed, coinciding with increased VEGFα expression, PDGFα-positive fibroblast proliferation, and increased density. It remains unclear whether dermal Hh activation led to a selective increase in papillary wound bed fibroblasts, which was previously shown to increase HF regeneration upon dermal Wnt signaling inhibition (Rognoni et al., 2016).

In addition to inhibiting HF regeneration, selective Hh signaling inhibition in papillary fibroblasts significantly impaired angiogenesis in wounds, pointing to a new emerging function of papillary fibroblasts. There is accumulating evidence that papillary fibroblasts have a higher angiogenic potential than reticular fibroblasts owing to their proangiogenic gene expression signature of secreted and ECM-bound factors (Mauroux et al., 2020). Furthermore, it was recently shown that in contrast to reticular fibroblasts, papillary lineage–derived fibroblasts strongly contribute to the regeneration of blood vessel–associated pericytes (Goss et al., 2021), which may influence angiogenesis during wound healing.

Of note, the reported findings by Frech et al. (2021) are in contrast to those of a previous study in which activating Hh signaling in myofibroblasts showed no alterations in cell proliferation or angiogenesis (Lim et al., 2018), reflecting potential differences in Hh signaling in heterogeneous wound bed fibroblasts as well as the timing of Hh signaling modulation during the wound healing process (Guerrero-Juarez et al., 2019). Furthermore, the mechanism of how Hh signaling in lower dermal fibroblasts specifically influences wound closure remains to be investigated. In future studies, it will be important to specifically activate Hh signaling in papillary and other fibroblasts (reticular fibroblasts, pericytes, adipocytes, etc.) to dissect its relevance in different fibroblast subpopulations during the wound repair process.

Hh signaling induces a dermal condensate phenotype in papillary fibroblasts

A crucial function of Hh signaling in wound bed fibroblasts is to induce a dermal papilla fate, enabling HF regeneration. In the recent scRNA-seq analysis of aSMA-positive fibroblasts, Lim et al. (2018) identified two Hh-active myofibroblast populations with distinct dermal condensate gene signatures. Although most dermal condensate genes were expressed in both populations, genes highly expressed in developing HFs such as \( \text{Lef1} \) and \( \text{Alpl} \) were limited to a small subpopulation of Hh-active fibroblasts. Frech et al. (2021) elegantly revisited this transcriptomic dataset and explored the gene expression changes in papillary and reticular fibroblasts identified by BLIMP1\(^+\)/SCA1\(^-\) and BLIMP1\(^-\)/SCA1\(^+\) expression, respectively. Besides the genes associated with epithelial development, wound healing, and vascularization, Hh signaling–induced dermal condensate signature genes were specifically enriched in papillary wound bed fibroblasts (Figure 1). This suggests that the two previously described Hh-active myofibroblast populations indeed represent papillary fibroblasts, promoting HF regeneration and angiogenesis. Further analysis of identified dermal condensate genes in wounded skin from their genetically depleting or activating \( \text{Smo} \) transgenics revealed that their expression correlated with the Hh signaling activity in papillary fibroblasts and observed HF regeneration.

Conclusion and outlook

Pathological scarring of the skin affects >100 million people every year, and it presents a significant healthcare burden. Currently, there are no efficient therapies to prevent, halt, or reverse scar formation in the skin and any other organs, emphasizing the great clinical need to develop new strategies to improve tissue regeneration. Skin appendage (including HFs and sweat glands) regeneration is a key hallmark of regenerative wound healing. In this study, Frech et al. (2021) elucidated for the first time how Hh signaling modulation in different fibroblast subpopulations influences HF development and regeneration in wounded skin. Their findings emphasize the importance of Hh signaling in papillary fibroblasts to increase the regenerative zone in scarring wounds (Figure 1), which may open new therapeutic opportunities. A major challenge will be to selectively activate and balance Hh signaling in dermal fibroblasts to induce a dermal papilla fate and prevent adverse effects such as tissue fibrosis and cancer caused by overactivation of Hh signaling in fibroblasts and other skin cells (Hu et al., 2015). To achieve this goal, it will be essential to further dissect the upstream and downstream Hh signaling regulators that induce a dermal papilla fate in papillary fibroblasts and promote angiogenesis. Because Hh signaling in the skin appears to be well-conserved between mice and humans, this may lead to the identification of suitable targets for selective pharmaceutical interventions that will increase regenerative healing in scarring wounds.

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It has been over a decade and a half since the first large-scale study of the accelerated risk of myocardial infarction in psoriasis (Gelfand et al., 2006). Since then, a broad range of scientific approaches has determined that psoriasis itself is associated with a higher-risk subclinical vascular disease (Naik et al., 2015), high-risk coronary plaque (Lerman et al., 2017), and major adverse cardiovascular (CV) events (Mehta et al., 2010) and mortality (Noe et al., 2018). Although these studies have established that the risk of CV disease (CVD) is independent of traditional CV risk factors, psoriasis also has complex interactions with metabolic disease. For example, for each 10% increase in body surface area affected by psoriasis, there is a 20% higher risk of developing diabetes, independent of body mass index (Wan et al., 2018). Mechanistic and preclinical studies highlight the role of systemic inflammation (Baumer et al., 2018); immune dysfunction (Teague et al., 2019); and an interplay between adiposity, inflammation, and dyslipidemia (Sajja et al., 2020) in accelerating coronary disease.

Dyslipidemia, defined as either elevated low-density lipoprotein (LDL) and triglycerides or low high-density lipoprotein, is highly prevalent in psoriasis (Neimann et al., 2006; Sorokin et al., 2018); increases with increasing body surface area affected by psoriasis (Langan et al., 2012); and is a driver of multiple systemic comorbid diseases, including stroke, heart attack, and fatty liver disease. Given the accumulation of evidence of accelerated vascular disease in psoriasis, in 2018, the American College of Cardiology/American Heart Association issued landmark guidelines (Grundy et al., 2019) identifying psoriasis as a CV risk enhancer and recommending earlier use of statins (i.e., in patients whose 10-year risk of atherosclerotic disease is ≥5%) in patients with psoriasis. Similarly, the American Academy of Dermatology/National Psoriasis Foundation 2019 guidelines (Elmets et al., 2019) recommended early and more frequent screening for dyslipidemia, especially when skin disease is severe, and recommended earlier use of statins.

Treatment with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor or statin therapy has been the cornerstone of the management of dyslipidemia associated with atherosclerotic CVD. Statins are extremely effective at LDL lowering and provide among the largest benefit in both primary and secondary risk reduction in CVD. Recently, statins were shown to have similar benefits on lipid reduction and reduction of CV events in people with psoriasis as in people without psoriasis (Masson et al., 2020), and in another posthoc analysis, statins were shown to improve LDL levels in those with psoriasis (Ports et al., 2017).