RESEARCH HIGHLIGHT OPEN

Bone morphogenetic protein signaling drives rete ridge morphogenesis: a distinct epidermal appendage program

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In a recent publication in *Nature*, Thompson et al.[1] delineated that rete ridge morphogenesis in mammalian skin is governed by a BMP (bone morphogenetic protein)-dependent developmental program evolutionarily distinct from the LEF1/WNT- and EDA/EDAR-mediated placode pathways controlling hair follicle, sweat gland, and fingerprint ridge formation.[1–3] Rete ridges are undulating projections of the basal epidermis enveloping vascularized dermal pockets are defining architectural features of human skin, yet the timing and molecular underpinnings of their development have remained obscure despite well-established clinical links to skin aging, scarring, and dermatologic disease.[1,4]

By integrating single-cell RNA sequencing (scRNA-seq) across porcine developmental stages from embryonic day 90 (E90) to six months postnatally, and spatial enhanced resolution-omics sequencing (Stereo-seq) at postnatal days 3 and 10 (P3, P10) and six months, the authors reconstructed the spatiotemporal dynamics of epidermal architecture.[1] They complemented these data with a systematic reanalysis of previously published human fetal, neonatal, and adult skin transcriptomic datasets, thereby establishing that rete ridges initiate perinatally in both species.[1] In pigs, nascent rete ridges first become discernible at gestational weeks 15–16 (perinatal period) as regions of thickened, undulating epidermis enclosing small dermal pockets, subsequently peaking of active morphogenesis during the first postnatal week (P3–P7) and reaching a plateau of density by P10.[1] This temporal framework closely parallels human skin development, in which rete ridges likewise emerge within several months of birth, positioning porcine skin as an experimentally tractable and ethically accessible proxy for detailed investigation of human rete ridge biology.[1,4] Furthermore, a comprehensive cross-species histological survey spanning cetaceans (bottlenose dolphins), North American grizzly bears, domestic and miniature pigs, non-human primates (rhesus macaques, common marmosets), naked mole rats, and mice revealed a striking inverse correlation between hair follicle density and epidermal thickness across the surveyed mammalian species.[1] However, loss of fur alone does not lead to rete ridge formation, as evidenced by the presence of similar rete ridges in pigs (hairless miniature and domestic) and the absence of rete ridges in mice and naked mole rats. Rete ridge-bearing species universally exhibited approximately two-fold epidermal hypertrophy in ridge versus inter-ridge domains, and, critically, no species with a thickened epidermis lacked rete ridges. Taken together, rete ridge formation is a process distinct from the modulation of hair density and is closely associated with the stable increase in epidermal thickness (Fig. 1).[1,4]

The central mechanism underlying rete ridge morphogenesis indicates that it is driven by pathways fundamentally distinct from those governing other epidermal appendages.[2,3] Integrated scRNA-seq analysis showed that epidermal placode cells, defined by high LEF1 and EDAR co-expression, formed a transcriptionally distinct cluster from postnatal basal cells engaged in rete ridge formation. In contrast, postnatal KRT15-positive basal keratinocytes strongly expressed BMP ligands, including BMP2 and BMP7, NOTCH ligands, and downstream transducers SMAD1 and SMAD5. Notably, this BMP signaling was broadly active across the basal layer rather than being compartmentalized into distinct spatial domains. Spatial CellChat analysis of Stereo-seq data and CellChat analysis of scRNA-seq data together highlighted BMP signaling-mediated epidermal-dermal crosstalk during rete ridge formation and maturation, with predicted signaling via PDGF, VEGF, and ANGPTL pathways being associated with dermal fibroblast and vascular recruitment and maturation within the dermal pocket niches (Fig. 1).[1,4]

Functional validation used complementary cross-species genetic models and yielded highly consistent results. Conditional epidermal *Lef1* knockout (*Lef1*-eKO) mice showed a marked reduction in hair follicle density yet developed fingerpad rete ridges normally, indicating that *LEF1*-WNT signaling is dispensable for rete ridge formation. In parallel, the authors demonstrated that *EDA*-KO pigs formed rete ridges that were indistinguishable from those of wild-type littermates at both neonatal (P5) and adult (5-month) stages, arguing against a requirement for EDA/EDAR signaling in this process. By contrast, *K14*-Noggin transgenic mice, which constitutively overexpress the BMP antagonist Noggin in the epidermis, displayed significantly reduced fingerpad rete ridge density, and tamoxifen-induced postnatal ablation of the BMP receptor *Bmpr1a* (*K14-Cre*^{ERT}; *Bmpr1a*$^{fl/fl}$) before ridge onset markedly impaired their formation. Furthermore, BMP signaling activity, reflected by SMAD1/5 phosphorylation, was sustained in the postnatal mouse fingerpad basal epidermis during rete ridge formation. Taken together, these studies across two mammalian species identify epidermal BMP signaling through the BMPR1A-SMAD1/5 axis as an essential morphogenetic driver of rete ridge development. Additionally, the study showed that neonatal porcine dorsal skin wounds can regenerate rete ridges and re-establish vascularized dermal pockets de novo, revealing an intrinsic regenerative capacity within the neonatal signaling

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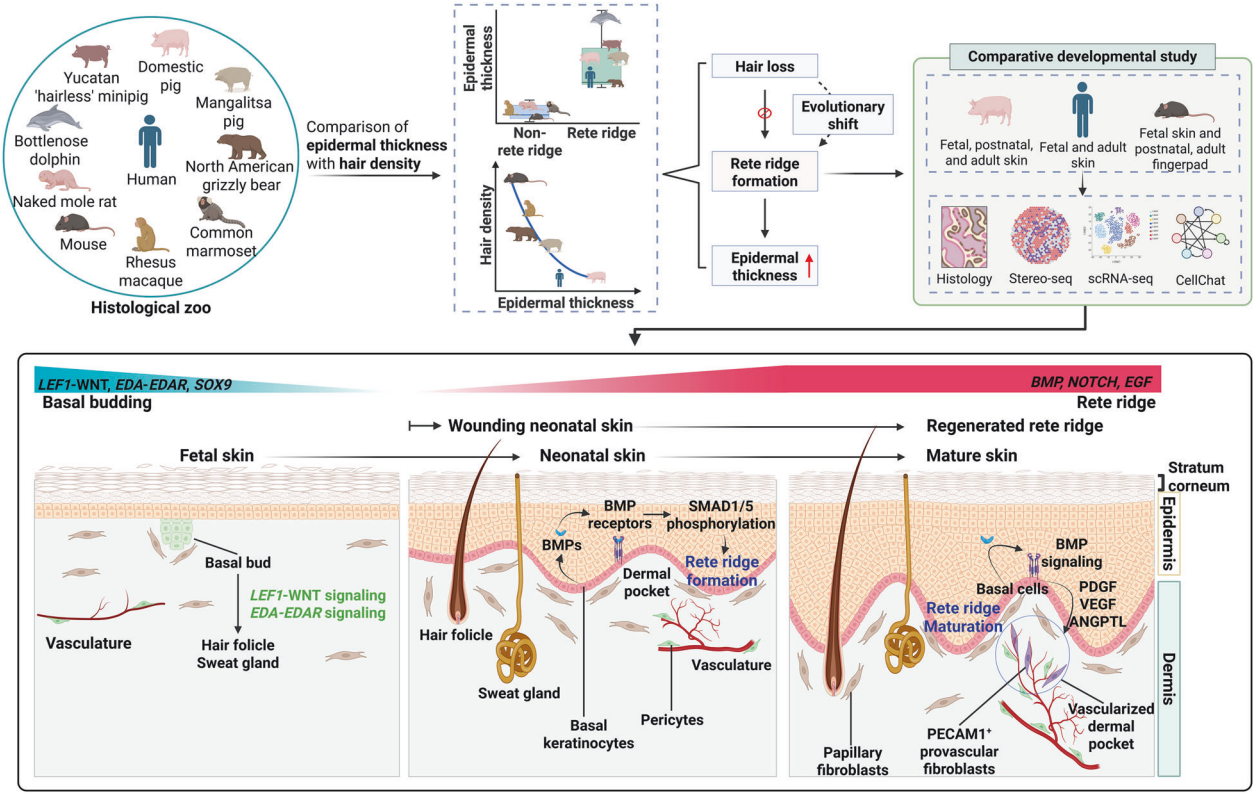

Fig. 1 BMP signaling drives evolutionarily distinct rete ridge morphogenesis in mammalian skin. Comparative histological overview (histological zoo) summarizes that mammalian epidermal thickness correlates with hair density and rete ridge formation, but hair loss does not induce rete ridge formation, indicating that rete ridge formation arose as a result of evolutionary shift. To investigate the mechanism of rete ridge formation, comparative developmental study was performed by using histological examination, stereo sequencing (stereo-seq), single cell RNA sequencing (scRNA-seq), and cell-cell communication analysis (CellChat) in the skin of pigs (fetal, postnatal, and adult), humans (fetal and adult), and mice (fetal, postnatal, and adult fingerpad). During mammalian skin development, discrete epidermal appendages, including hair follicles and sweat glands, are formed prenatally through LEF1-WNT- and EDA-EDAR-mediated signaling pathways. In contrast, rete ridges develop postnatally through activation of SMAD1/5 via BMPR1A and BMPR2 receptors, which are triggered by BMP7 and BMP2 ligands produced by basal keratinocytes in the interfollicular epidermis. This BMP-dependent mechanism drives the formation of interconnected epidermal invaginations that establish dermal pockets enriched with papillary fibroblasts and vasculature. The evolutionary replacement of discrete appendage programs with the BMP-driven rete ridge network represents a fundamental shift in epidermal architecture specification in rete ridge-bearing mammalian skin. Neonatal pig wound experiments further demonstrate the intrinsic capacity for de novo rete ridge regeneration. Figure created with BioRender.com (https://BioRender.com/zltljnh)

environment that is absent in adult wound healing, where fibrotic scarring predominates and rete ridges typically fail to reform.[1]

Despite the study's considerable strengths in multispecies comparative transcriptomics and functional genetic validation, several limitations warrant careful consideration. First, the primary reliance on porcine and murine models constrains direct extrapolation to human clinical contexts, and ethical restrictions on sampling human perinatal skin complicate precise developmental mapping between gestational week 20 and early infancy, the inferred critical window for human rete ridge initiation. Second, the limitations of Stereo-seq, such as lateral diffusion and its detection of only RNA, may obscure nanoscale morphogen gradients at the protein level that are potentially critical for rete ridge pattern initiation. Moreover, potential contributions of neural innervation and resident immune cell populations to rete ridge morphogenesis remain unclear. Finally, the study does not address whether exogenous BMP activation alone is sufficient to induce de novo rete ridge formation in rete ridge incompetent species such as mice, leaving unresolved the question of how this developmental capacity was evolutionarily acquired.

The translational and evolutionary implications of this work are substantial. Clinically, rete ridge flattening is a pathological hallmark of skin aging, keloid and hypertrophic scarring, and epidermolysis bullosa, collectively affecting hundreds of millions of patients worldwide. The identification of the BMP signaling pathway as a central morphogenetic driver opens plausible therapeutic avenues for regenerative dermatological applications. The detailed molecular and cellular delineation of dermal pocket architecture, including papillary fibroblasts, pericytes, PECAM1-positive provascular fibroblasts, and organized microvasculature, provides a critical architectural reference for designing next-generation tissue-engineered skin substitutes, which currently lack this microstructural component.[4] From an evolutionary perspective, this demonstration challenges the prevailing assumption that the formation of rete ridges has been regarded as a passive consequence of hair loss by redefining their developmental program as uncoupled from the follicular program, thereby reframing mammalian skin diversification.[3] Thompson et al. establish rete ridges as a molecularly and developmentally distinct, BMP-dependent appendage class, presenting comprehensive cross-species developmental atlases with rigorous functional genetic validation and demonstrating neonatal wound regeneration as evidence of their intrinsic regenerative ability (Fig. 1).[1,2,5] Taken together, this study provides a strong mechanistic framework for future work in regenerative dermatology, tissue engineering, and the evolutionary developmental biology of the mammalian integument.

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ADDITIONAL INFORMATION

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