
Shh maintains dermal papilla identity and hair morphogenesis via a Noggin-Shh regulatory loop.

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Public Summary:

Sonic hedgehog (Shh) is a secreted protein that elicits cellular signaling response essential for the development and regeneration of a number of organs in mammals. Shh deficiency in humans can lead to developmental defects such as holoprosencephaly, a series of malformations of the brain and face. Conversely, aberrantly activated Shh response results in a number of cancers including glioma in the brain and basal cell carcinoma in the skin. In mammalian skin, hair follicle is a mini-organ that can regenerate itself throughout the adult life. The hair follicle proper is a columnar structure mainly composed of epithelial cells, and is associated with a specialized group of dermal cells from the stroma, named dermal papilla. During hair follicle development, as the hair follicle epithelial progenitor cells proliferate and differentiate, dermal papilla co-develops with this epithelial tissue. The dermal papilla functions as a signaling center that supports and regulates hair follicle epithelial progenitor cell proliferation and differentiation, yet relatively little is known about the molecular basis of dermal papilla formation. Shh is secreted by hair follicle epithelial cell while Shh responses are received and detected in both the epithelial and dermal papilla cells. While we know Shh signaling response in the epithelial progenitor cells drives cell proliferation, the role of Shh response in the dermal papilla cells is less clear. In this study we investigate the role of dermal Shh response in dermal papilla formation and hair growth. Our strategy is to inhibit Shh response by blocking a Shh signal transducer called Smoothed, a membrane protein, focused only in the dermal cells. We used mouse genetics to remove Smoothed gene in the dermal cells and analyze the mutant mouse hair follicles. We complemented and extended this study by using a hair follicle reconstitution assay, a tissue regeneration model in which hair follicles are generated from extracted mouse skin dermal and epithelial cells. In this case we used lentivirus delivered short hairpin RNA (shRNA) in extracted mouse skin dermal cells to block Smoothed expression, and examined hair follicle regeneration from combination of these Smoothed deficient dermal cells and normal, untreated epithelial cells. We found that loss of dermal Smoothed leads to the loss of the early stage dermal papilla, and hair follicle development arrest as evident with stunted early stage hair follicles. These abnormalities were not due to any defects in cell proliferation or survival. Using microarray profiling and skin tissue staining studies, we show that dermal Smoothed controls the expression of a subset of dermal papilla signaling molecules, including nuclear proteins Sox2 and Sox18, and Noggin, which is a secreted protein and a BMP antagonist. Using lentivirus delivered shRNA and cDNA in dermal cells in hair follicle reconstitution assays, we demonstrated that dermal Noggin expression, but not Sox2 or Sox18, increases epithelial Shh protein expression and partially rescues dermal Smoothed knockdown hair growth defect. These data suggest dermal Shh response regulates specific set of dermal papilla molecules to maintain dermal papilla development and functions, and reveal that the epithelial-secreted Shh maintains its own expression via a reciprocal Shh – Noggin signaling loop to support the epithelial progenitor cells and hair follicle development.

Scientific Abstract:

During hair follicle morphogenesis, dermal papillae (DPs) function as mesenchymal signaling centers that cross-talk with overlying epithelium to regulate morphogenesis. While the DP regulates hair follicle formation, relatively little is known about the molecular basis of DP formation. The morphogen Sonic hedgehog (Shh) is known for regulating hair follicle epithelial growth, with excessive signaling resulting in basal cell carcinomas. Here, we investigate how dermal-specific Shh signaling contributes to DP formation and hair growth. Using a Cre-lox genetic model and RNAi in hair follicle reconstitution assays, we demonstrate that dermal Smoothed (Smo) loss of function results in the loss of the DP precursor, the dermal condensate, and a stage 2 hair follicle arrest phenotype reminiscent of Shh(-/-) skin. Surprisingly, dermal Smo does not regulate cell survival or epithelial proliferation. Rather, molecular screening and immunostaining studies reveal that dermal Shh signaling controls the expression of a subset of DP-specific signature genes. Using a hairpin/cDNA lentiviral system, we show that overexpression of the Shh-dependent gene Noggin, but not Sox2 or Sox18, can partially rescue the dermal Smo knockdown hair follicle phenotype by increasing the expression of epithelial Shh. Our findings suggest that dermal Shh signaling regulates specific DP signatures to maintain DP maturation while maintaining a reciprocal Shh-Noggin signaling

loop to drive hair follicle morphogenesis.

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