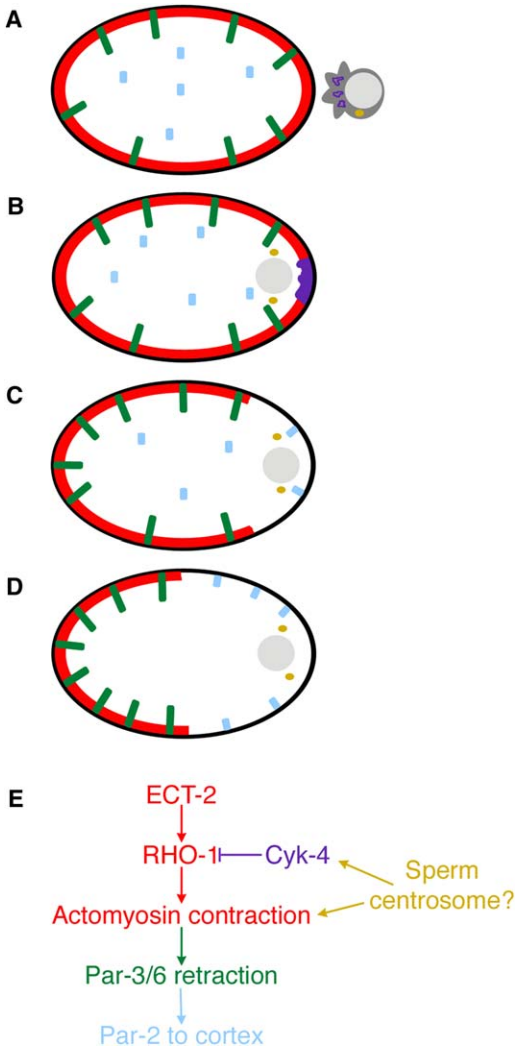

Figure 1. Polarization of *C. elegans* by Sperm-Contributed Cues

Fertilization (A) imparts two sperm-derived components that are essential for polarization (B), CYK-4 (purple) and the pair of centrosomes (orange) derived from the single sperm centrosome. The sperm nucleus (gray) is dispensable for polarization. Polarization signals lead to contraction of the actomyosin network (red), which carries the anterior PAR proteins (green) (C). This allows access to the cortex for the posterior PAR complex (blue) (D). (E) diagrams the regulatory pathway involved in this process.

systems, although exactly how this works has never been completely clear. In *C. elegans* embryo polarization, the centrosome or associated microtubules might act in parallel with CYK-4, or they might act as an integral part of a CYK-4 mechanism. For example, CYK-4 is known to be recruited to microtubules during cytokinesis by the kinesin-like protein ZEN-4 (Mishima et al., 2002). While ZEN-4 is not required in polarization, it is possible that alternative or redundant partners may link CYK-4 to microtubules after fertilization. This might enable centrosomes to temporally regulate polarization of the embryo, waiting to drive polarization until meiosis completes by delaying delivery of CYK-4 to the cell cortex until centrosome maturation.

With two symmetry-breaking cues contributed by the sperm in *C. elegans*, which one acts as a positional cue, or do both share this job? Does one act as a positional cue and the other as a temporal cue? Rho activity and centrosomes have both been recognized as important players in cell polarization in a variety of systems. The new results suggest that changing the position or timing at which both centrosomes and CYK-4 function in *C. elegans* may help determine how these cues function in cell polarization.

Daniel J. Marston and Bob Goldstein
Biology Department
The University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599

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Smad7: Licensed to Kill β-Catenin

Elevated levels of inhibitory Smad7 are detected in several pathologic skin conditions; however the functional consequences of this expression have been unclear. A recent study shows that Smad7 overexpression in transgenic mouse epidermis at levels comparable to those seen in pathologic states is insufficient to block TGFβ or BMP signaling, but instead produces striking phenotypes due to degradation of β-catenin through a novel mechanism involving Smad7 and Smurf2.

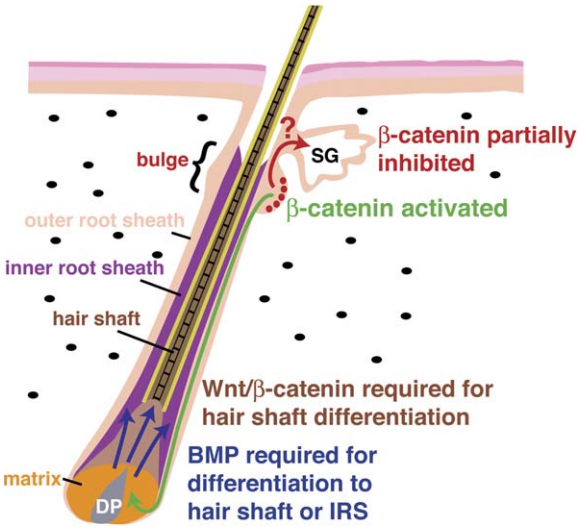

Figure 1. Model of Potential Roles for BMP and Wnt/β-Catenin Signals during the Anagen Growth Phase in Postnatal Hair Follicles

Stem cells in the bulge region are colored red. Stem cell activation by β-catenin signaling results in their transient proliferation and migration of stem cell progeny to the matrix (green arrow). Matrix cells proliferate rapidly. BMP signals induce cessation of proliferation and differentiation toward hair shaft or inner root sheath (blue arrows). Wnt/β-catenin signaling is implicated in hair shaft differentiation. Inhibition of β-catenin signaling by expression of dominant negative Lef1 promotes sebocyte rather than matrix cell fate. This might involve direct contribution of bulge cell descendants to the sebaceous gland (red arrow). SG, sebaceous gland; DP, dermal papilla; IRS, inner root sheath.

Hair follicle development is initiated in embryogenesis and results in the formation of a mini-organ with a dermal papilla core surrounded by proliferating epithelial matrix cells. Differentiation of the matrix results in formation of a hair shaft, surrounded by an inner root sheath that molds the hair shaft as it emerges from the skin (Figure 1). Sebaceous glands develop just before birth from follicular epithelial cells. Hair follicles undergo cycles of growth and regression throughout life that depend on a population of epithelial stem cells in the permanent, bulge region of the follicle. At the start of periods of follicular regrowth, stem cells proliferate transiently, give rise to descendants that repopulate the matrix, and may also replenish the sebaceous gland (Morris et al., 2004; Tumbar et al., 2004).

Wnt/β-catenin signaling is required for initiation of hair follicle morphogenesis in embryonic skin and for onset of the growth phase in postnatal hair follicles (Andl et al., 2002; Huelsken et al., 2001). Wnt pathway activity is controlled in part by regulation of cytoplasmic β-catenin protein levels. In the absence of a Wnt signal, cytoplasmic β-catenin is phosphorylated and bound by β-transducin repeat-containing protein (βTrCP) and the associated RING-type ubiquitin ligase (E3) complex SCF (Skp1, Cullin, F-box) (Wu et al., 2003), resulting in ubiquitination of β-catenin and its degradation by the proteasome. Wnt ligands act via their receptors to inactivate the phosphorylation complex, resulting in accumulation of cytoplasmic β-catenin, its translocation to the nucleus, and activation of target gene transcription by complexes of β-catenin with LEF/TCF family members (Logan and Nusse, 2004).

The importance of Wnt signaling in skin homeostasis is underscored by the discovery that activating mutations in β-catenin cause hair follicle tumors (Chan et al., 1999). In contrast, mutations in Lef1 that interfere with β-catenin-dependent transcriptional activation result in formation of sebocytes at the expense of hair follicle matrix cells and are associated with sebaceous gland tumorigenesis in mice and humans (Takeda et al., 2006). Thus, additional signaling pathways that regulate β-catenin stability are likely to impact skin development and homeostasis.

TGFβ signaling is mediated by intracellular receptor-regulated Smad (RSmad) proteins that become phosphorylated following binding of TGFβ ligands to type I and type II receptors, complex with common partner (Co) Smad4 and translocate to the nucleus where they bind to transcriptional coactivators or corepressors and regulate transcription. Smad7, an inhibitory (I) Smad that is a target of TGFβ signaling, acts in a negative feedback loop to inhibit TGFβ activity by preventing phosphorylation of Smad proteins. Smad7 also inhibits TGFβ signaling by targeting TGFβ receptors for proteasomal degradation via recruitment of the HECT-class ubiquitin ligases Smurf1 and Smurf2.

Elevated levels of Smad7 are detected in several pathologic skin conditions including during carcinogenesis and in aged skin (He et al., 2002). However the functional consequences of Smad7 overexpression have not been clear. This is in part because Smad7 can inhibit signaling by multiple TGFβ superfamily members, including BMPs that utilize different sets of RSmads from those activated by TGFβ1 and TGFβ2, and whose effects on skin biology differ. For instance, loss of epithelial BMPR1A causes failure of hair follicle matrix cell differentiation and matrix tumors, while null mutations in TGFβ1 and TGFβ2 result in delayed hair follicle regression, and retarded or arrested embryonic hair follicle development, respectively.

Consistent with Smad7's known roles, high levels of constitutive Smad7 overexpression in a transgenic model resulted in inhibition of TGFβ and BMP signaling (He et al., 2002). In the current issue of *Developmental Cell*, Han et al. describe an inducible model for Smad7 overexpression that permits control of the levels as well as the timing of Smad7 overexpression (Han et al., 2006). The big surprise of this new work is that, when expressed at levels comparable to those seen in pathologic conditions, Smad7 only partially reduced TGFβ and BMP signaling activity in postnatal skin, but nevertheless produced striking phenotypes. Induction in embryogenesis inhibited hair follicle development but accelerated formation of sebaceous glands, while postnatal Smad7 expression blocked hair follicle entry into a new growth phase, and resulted in sebaceous gland enlargement and hair follicle degeneration.

These unexpected results were explained by the authors' finding that β-catenin protein levels were markedly reduced in Smad7 overexpressing skin. Investigation of the underlying molecular mechanism revealed that Smad7 complexes with both β-catenin and the E3 ligase Smurf2. This results in proteasomal degradation of β-catenin and loss of β-catenin/LEF/TCF-mediated signaling activity. Overexpression of Smurf2 in vitro increased β-catenin ubiquitination and the effects of

Smad7 on β-catenin expression levels, and overexpression in vivo enhanced the phenotypes produced by Smad7 expression. Conversely, depletion of endogenous Smad7 in cultured keratinocytes resulted in elevated levels of β-catenin protein and enhanced β-catenin/LEF signaling. Interestingly, in aged skin, elevated Smad7 correlated with decreased levels of β-catenin, suggesting that this novel mechanism might be important pathologically.

While postnatal phenotypes caused by Smad7 overexpression are consistent with prior reports of the effects of Wnt/β-catenin inhibition, embryonic Smad7 overexpression surprisingly was not accompanied by failure of hair follicle placode development. This observation suggests that residual epithelial β-catenin protein levels in Smad7-expressing embryonic skin at the time of hair follicle initiation were sufficient to permit this process. The embryonic hair follicle defects may be due to failure of maintenance of Wnt signaling in the placodes. Alternatively it is possible that RSmad phosphorylation is more sensitive to low levels of Smad7 in embryonic than in postnatal skin, and that the embryonic defects are in part due to loss of TGFβ2 signaling. Analysis of phospho-Smad levels in Smad7 overexpressing embryonic skin should resolve this issue.

The HECT-class Smurf2 E3 ligase that complexes with β-catenin via Smad7 ubiquitinates its substrates by a different mechanism than that employed by RING-type E3 ligases such as SCF (Wu et al., 2003). It will be interesting to investigate whether similar domains of β-catenin are required for both degradation mechanisms. If not, this would raise the possibility that β-catenin that is mutated to a constitutively active form by deletion of N-terminal phosphorylation and β-TrCP1 binding sites, as occurs in colon and other tumors, still remains susceptible to Smad7-mediated degradation.

This work also raises questions about the endogenous roles of Smad7 and Smurf2 in the epidermis and hair follicles. It will be important to determine whether depletion of Smad7 causes β-catenin accumulation in vivo as well as in vitro, and whether this has functional consequences for hair follicle development, cycling and tumorigenesis. As with the overexpression model, depletion of Smad7 in skin epithelial cells is expected to impact multiple signaling pathways. Inducible Smad7 deletion, and phenotypic and functional analyses similar to those performed by Han et al. will likely be necessary to dissect out the mechanistic details. In light of the critical roles played by Wnt and TGFβ pathways in skin development and homeostasis, the potential new mechanism for pathway cross-talk described by Han et al. has important implications for our understanding of development and disease mechanisms in the skin.

Sarah E. Millar[1,2]
[1]Departments of Dermatology and Cell and Developmental Biology
University of Pennsylvania
[2]Department of Dermatology
University of Pennsylvania School of Medicine
M8D Stellar-Chance Laboratories
422 Curie Boulevard
Philadelphia, Pennsylvania 19104

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From Pore to Kinetochore and Back: Regulating Envelope Assembly

Reassembly of the nuclear envelope following mitosis is a fundamental process that remains only partially understood. Two recent reports by Fernandez and Piano (2006) and Galy et al. (2006) in the September 5 issue of *Current Biology* identify a novel protein, MEL-28, that shuttles between the nuclear pore complex and kinetochore and is essential for envelope assembly in *C. elegans* early embryos.

The acquisition of membrane bound organelles has provided eukaryotes with unique opportunities for the regulation of multiple cellular activities. Nowhere is this more obvious than the in nucleus, where chromosomes are enclosed by a selective barrier, the nuclear envelope (NE). However, compartmentalization of cellular activities comes at the price of complicating cell division.