

Polarity signaling ensures epidermal homeostasis by coupling cellular mechanics and genomic integrity

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Epithelial homeostasis requires balanced progenitor cell proliferation and differentiation, whereas disrupting this equilibrium fosters degeneration or cancer. Here we studied how cell polarity signaling orchestrates epidermal self-renewal and differentiation. Using genetic ablation, quantitative imaging, mechanochemical reconstitution and atomic force microscopy, we find that mammalian Par3 couples genome integrity and epidermal fate through shaping keratinocyte mechanics, rather than mitotic spindle orientation. Par3 inactivation impairs RhoA activity, actomyosin contractility and viscoelasticity, eliciting mitotic failures that trigger aneuploidy, mitosis-dependent DNA damage responses, p53 stabilization and premature differentiation. Importantly, reconstituting myosin activity is sufficient to restore mitotic fidelity, genome integrity, and balanced differentiation and stratification. Collectively, this study deciphers a mechanical signaling network in which Par3 acts upstream of Rho/actomyosin contractility to promote intrinsic force generation, thereby maintaining mitotic accuracy and cellular fitness at the genomic level. Disturbing this network may compromise not only epidermal homeostasis but potentially also that of other self-renewing epithelia⁽¹⁾.

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