



“
actomyosin
remodelling is
important for
transmitting
mechanical
cues”

Cells respond to various mechanical cues, with implications for fundamental cellular processes, such as cell fate determination. However, the mechanisms through which mechanical signals affect cell fate decisions are poorly understood. *Le et al.* now show that, in epidermal stem cells, mechanical forces induce silencing of differentiation-associated genes, thereby influencing mammalian skin morphogenesis.

To study how mechanical cues influence genetic regulation of cell fate, the authors used *in vitro* propagated human epidermal progenitor cells (EPCs). Subjecting these cells to physiologically relevant levels of mechanical strain and analysing their transcriptional profiles revealed that physical strain led to the downregulation of nearly 4,000 genes, including various genes that regulate EPC differentiation. Many of these genes are known targets of Polycomb repressive complex 2 (PRC2), which silences genes through the trimethylation of histone 3 Lys27 (H3K27me3). In line with this, following strain, the levels of H3K27me3 were increased both globally as well as specifically at the promoters of genes associated with EPC differentiation. This indicated that applying mechanical strain on EPCs leads to PRC2-mediated transcription silencing, including of genes involved in lineage commitment.

To address how mechanical cues are transmitted to the chromatin, the authors investigated changes in the actomyosin skeleton — a key player in mediating cellular

mechanotransduction. In response to strain, extensive actin polymerization was observed, particularly in the perinuclear region. Importantly, interfering with this perinuclear actin formation by inhibiting non-muscle myosin II (NMII) or depleting Emd, which is a nuclear membrane protein that links actomyosin to chromatin, abrogated the strain-induced increase in the levels of H3K27me3 and prevented the silencing of differentiation genes. This indicates that actomyosin remodelling is important for transmitting mechanical cues onto chromatin and consequently for regulating gene expression and cell fate commitment in response to strain.

Actin shuttles between the cytoplasm and the nucleus, and nuclear actin has been shown to enhance transcription by associating with RNA polymerase II. As a result of this shuttling, strain-induced increase in perinuclear actin polymerization could affect the pool and functions of nuclear actin. Indeed, in strained EPCs, the nuclear actin pool was decreased. Furthermore, experimental manipulation of actin levels was sufficient to drive changes in gene expression: increasing nuclear actin pools reversed the silencing of differentiation genes in strained EPCs, whereas decreasing nuclear actin in unstrained cells could mimic strain-induced gene silencing. This collectively implied that, in strained EPCs, transcription levels decrease as a result of actin remodelling and the depletion of the nuclear

actin pool. As a decrease in transcription levels consistently preceded the deposition of H3K27me3 marks, the authors also concluded that attenuation of transcription upon nuclear actin depletion promotes PRC2 recruitment, leading to more-stable repression of gene expression.

To delineate the importance of this mechanosensory circuit *in vivo*, knockout mice with epidermis-specific defects in NMII activity were generated, thereby impairing the transmission of mechanical signals in epidermal stem cells. These stem cells exhibited premature differentiation, leading to perturbed epidermal development. Importantly, this precocious differentiation was associated with decreased H3K27me3 levels, increased nuclear actin levels and a concomitant dramatic increase in the expression of differentiation genes.

Together, these results provide important insights into the mechanisms of cellular mechanosensory networks and reveal that sensing external forces can be directly linked — through actomyosin cytoskeleton remodelling — to gene expression during fundamental processes, such as cell fate determination. It would be interesting to study these mechanosensory circuits in diverse cell types and in different *in vivo* contexts.

Paulina Strzyz

ORIGINAL ARTICLE Le, H. Q. *et al.* Mechanical regulation of transcription controls Polycomb-mediated gene silencing during lineage commitment. *Nat. Cell Biol.* <http://dx.doi.org/10.1038/ncb3387> (2016)