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STEM CELLS

Stem cells follow the clock

> the molecular clock controls the temporal behaviour of stem cells

Epidermal stem cells, which ensure skin homeostasis, exist as heterogeneous populations — some stem cells respond to stimulating signals (such as WNT signals) to start proliferating, whereas others remain dormant. Janich *et al.* now show that such heterogeneity depends on the circadian clock.

The authors studied the bulge, a structure which contains stem cells that contribute to hair follicle growth and which alternates between phases of growth and dormancy. Only a subset of bulge cells responds to growth-activating stimuli to proliferate and migrate out of the niche.

To assess the activity of the clock in bulge cells, the authors used transgenic mice containing a reporter in which the expression of fluorescent Venus was under the regulation of the period 1 (*Per1*) gene promoter. *Per1* encodes a clock protein that is under the control of the core clock transcription factors BMAL and CLOCK, and thus its expression reflects clock activity. They found that, when dormant, only half of the bulge cells expressed Venus at high levels. When entering an active phase of growth, the proportion of cells expressing high levels of Venus increased to 90%. Thus, when dormant, bulge stem cells are heterogeneous in the clock phase.

But how does the clock phase affect stem cells? The authors compared the transcriptome of dormant cells with high Venus levels with that of dormant cells with low Venus levels. They found that bulge stem cells expressing high levels of Venus also expressed higher levels of genes related to bulge stem cell activation, including several factors of the WNT signalling pathway and inhibitors of transforming growth factor-β (TGFβ) signalling, among others. Furthermore, BMAL–CLOCK bound to the promoters of these genes, which suggests that factors that control bulge stem cell proliferation are directly controlled by the circadian clock.

Next, the authors assessed the biological significance of this regulation by the clock. They hypothesized that the clock controls the predisposition of stem cells to dormancy or activating stimuli, such as TGFβ and WNT. To test this, they analysed BMAL-knockout mice, which have an arrhythmic clock that tends towards permanently low levels of BMAL–CLOCK-controlled genes (and, consistently, low levels of WNT-signalling and TGFβ-inhibitory factors). Indeed, BMAL-knockout mice were more responsive to TGFβ treatment. Furthermore, bulges in BMAL knockouts had fewer proliferative cells and the hair follicles were less efficient in becoming active after depilation. These mice also showed inefficient epidermal self-renewal and premature signs of skin ageing. Finally, deletion of BMAL in mice that spontaneously develop cutaneous squamous tumours considerably reduced the appearance of neoplastic lesions.

These results show that the molecular clock controls the temporal behaviour of stem cells, as it prevents all stem cells within a niche from becoming simultaneously responsive, and this seems to be crucial for maintaining homeostasis. When and how stem cell heterogeneity is established remains to be determined.

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ORIGINAL RESEARCH PAPER Janich, P. *et al.* The circadian molecular clock creates epidermal stem cell heterogeneity. *Nature* 9 Nov 2011 (doi:10.1038/nature10649)