and noticed a SATB1-dependent pattern of histone modifications confined to a 10-kb, SBS-containing region that covered genes positively regulated by SATB1. Acetylation of histone H3 at lysine (Lys) 9 and Lys14 peaked in wild type, whereas in *Satb1*$^{-/-}$ chromatin H3 methylation at Lys9 peaked. So, SATB1 mediates the histone modification pattern, which causes remodelling of the chromatin structure in a restricted region containing SATB1-dependent genes. Kohwi-Shigematsu and colleagues also reported recently that SATB1 recruits chromatin-remodelling enzymes to SBSs to regulate chromatin structure over a large distance.

The authors concluded that the SATB1 network organizes DNA sequences in a cell-type-specific manner by tethering specialized DNA sequences onto its network and providing a landing platform for chromatin-remodelling/modifying factors.

Arianne Heinrichs

References and links

ORIGINAL RESEARCH PAPER Cai, S., Han, H.-J. & Kohwi-Shigematsu, T. Tissue-specific nuclear architecture and gene expression regulated by SATB1. *Nature Genet.* **34**, 42–51 (2003)

FURTHER READING Yasui, D. *et al.* SATB1 targets chromatin remodelling to regulate genes over long distances. *Nature* **419**, 641–645 (2002)

disturbed. In *fkh1Δ*, Ser5 phosphorylation was reduced in the promoter region and low throughout the coding region, and Ser2 phosphorylation was almost undetectable.

Mellor and colleagues then decided to look at pre-mRNA 3′-end formation in *fkh1Δ* strains, because increased Ser2 phosphorylation in wild-type strains is associated with pre-mRNA 3′-end processing. Indeed, they found that 3′-end formation was defective in *fkh1Δ*. Then, using a transcription run-on assay, they showed that RNAPII in *fkh1Δ* was defective in pre-mRNA 3′-end formation and predicted that "…much of the RNAPII at the 3′ end is not actively engaged in transcription, a likely consequence of the lack of Ser5 and Ser2 phosphorylation".

So, the authors suggest that the opposing actions of Fkh1 and Fkh2 at the beginning of genes might be part of an early elongation checkpoint mechanism that has been proposed to coordinate transcription and pre-mRNA processing through phosphorylation of the CTD of RNAPII. And the evolutionary conservation of the Fkh factors indicates that this "…may reflect a general feature of gene regulation in eukaryotes".

Natalie Wilson

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ADHESION

Getting to the root of the problem

Signals that are transmitted through cell junctions can transform epithelial layers into three-dimensional structures such as hair follicles. Desmosomes, which are specialized cell junctions that make up much of the cell surfaces in mature hair follicles, contribute — in part through desmosomal cadherins — to cell–cell adhesion. Kljuic *et al.*, reporting in *Cell*, have identified desmoglein 4 and report its function in epidermal adhesion and hair-follicle differentiation.

None of the known desmosomal cadherins are expressed in the inner layers of the hair shaft despite the abundance of desmosomes here. So the authors carried out a classical genetic approach using patients with localized autosomal-recessive hypotrichosis (*LAH*), a condition in which hair is less dense, and located a candidate gene close to a desmosomal cadherin gene cluster.

Further analysis showed synteny with the mouse *lanceolate hair (lah)* mutation — which impairs hair growth — which is also near the desmosomal cadherin gene cluster. During this genomic analysis, a previously uncharacterized cadherin gene — designated desmoglein 4 (*Dsg4*) — was identified in the cluster. Desmoglein 4 was highly expressed in human and mouse skin, and colocalized with the *lah* and *LAH* linkage intervals, making *Dsg4* a candidate for both phenotypes. The authors then showed *Dsg4* to be mutated in *LAH* humans and *lah* mice. A second *lah* allele, *lah*^{J}, causes a more severe phenotype, and further sequence analysis showed that *lah*^{J}/*lah*^{J} mice are null (*lah*/*lah* mice are hypomorphic).

Dsg4 was shown to be the main desmosomal cadherin in hair follicles, and analysis of the epidermis and hair follicles from *lah*^{J}/*lah*^{J}-mutant pups showed that Dsg4 had a central role in cell–cell adhesion — desmosomes were sparse, poorly formed and often detached or torn away from their neighbours. Kljuic *et al.* then proposed, when assaying the expression of several epidermal markers, that the keratinocytes of *lah*^{J}/*lah*^{J} mice exited the basal compartment of the epidermis — in which keratinocytes proliferate — earlier or faster than normal, thereby expanding the proliferative compartment. Indeed, ectopically proliferating cells were found in the suprabasal layers, as shown by the expression of β1 integrin and the epidermal growth factor receptor (EGFR). In the context of *lah* mutants, this increased expression of β1 and EGFR correlated with enhanced keratinocyte–substrate adhesion and spreading *in vitro*.

In wild-type hair formation, keratinocytes in the lowest part of the hair follicle proliferate rapidly until they pass through a 'critical region', in which mitosis stops and the cells start to differentiate. The transition through the critical region is usually gradual, but *lah*^{J}/*lah*^{J}-mutant hair follicles abruptly stop proliferating and start differentiating. The authors propose that this abrupt transition might arise from, or be precipitated by, the defective cell–cell adhesion that impairs the transduction of signals that are important in survival and the full execution of cell-fate determination.

This is one of the first reports of a defect in a structural component — Dsg4 — of the epidermis and hair follicle that causes corresponding mouse and human phenotypes. In addition, as the authors also showed that Dsg4 functions as an autoantigen in patients with pemphigus vulgaris (an autoimmune skin disease characterized by outbreaks of blisters), the relevance of the findings extends to skin autoimmunity.

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Kljuic, A. *et al.* Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. *Cell* **113**, 249–260 (2003)