Heterochromatin and human aging

The molecular events that lead to human aging are poorly understood. Werner syndrome, which is characterized by premature aging, is caused by recessive mutations in the WRN gene. Juan Carlos Izpisua Belmonte, Guang-Hui Liu, Fuchou Tang and colleagues derived human embryonic stem cells that lack WRN protein to model Werner syndrome *in vitro* and to illuminate the mechanisms that underlie precocious aging (*Science* doi:10.1126/science.aaa1356; 30 April 2015). The authors differentiated WRN-null embryonic stem cells to mesenchymal stem cells and observed several signs of premature cellular aging, a global reduction in H3K9me3 histone methylation and alterations in heterochromatin patterns. They demonstrated that WRN associates with the heterochromatin proteins SUV39H1 and HP1α as well as with LAP2β, a nuclear lamina–heterochromatin anchoring protein. Indeed, knocking in a catalytically inactive form of SUV39H1 in wild-type mesenchymal stem cells accelerated cellular senescence and resulted in a phenotype mimicking that of WRN-null mesenchymal stem cells. Interestingly, mesenchymal stem cells from older individuals showed a reduction in WRN expression and heterochromatin marks. Taken together, these findings show that WRN helps maintain heterochromatin stability and suggest a role for heterochromatin disorganization in human aging. It will be interesting to study the function of WRN in diverse cell lineages, particularly *in vivo*. ***TF***

Fibrogenic lineage identified

The deposition of extracellular matrix (ECM) components by fibroblasts is important for normal organ development and wound healing but also contributes to the pathology of many disease states. To gain insight into the developmental origins of fibroblasts, Yuval Rinkevich, Irving Weissman, Michael Longaker and colleagues (*Science* doi:10.1126/science.aaa2151; 17 April 2015) performed lineage tracing in mouse dorsal skin and identified a cell population with intrinsic fibrogenic potential. Specifically, they identified a population of cells marked by transient embryonic expression of *En1* that migrated from the somites into the dorsal trunk dermis and persisted into adulthood. This *En1*-positive lineage expressed classical fibroblast markers and colocalized with regions marked by ECM deposition. Following cutaneous wounding, this cell population was closely associated with the ensuing scar tissue and collagen type I expression. The authors also observed similar findings in fibrotic skin regions induced by melanoma or radiation. Furthermore, they identified CD26 as a specific marker of this cell population in adult mice and showed that CD26 inhibition could reduce scarring during wound healing. Altogether, these findings provide valuable insights into fibrogenic cell populations and suggest possible avenues for modulating their activity for therapeutic benefit. *KV*

Spermatogenic signaling through *Rarg*

Shosei Yoshida and colleagues report that differential expression of the retinoic acid (RA) receptor γ gene (*Rarg*) between two self-renewing subpopulations of undifferentiated spermotogonia controls the response to differentiation signals (*Development* **142**, 1582–1592, 2015). In mouse seminiferous tubules, differentiating and undifferentiated, self-renewing germ cells comingle. This is in contrast to closed stem cell niches, such as the *Drosophila* testicular hub, in which undifferentiated and differentiating cells are spatially separated. Using a vitamin A–deficient mouse model, Yoshida and colleagues found that the GFRα1$^+$ stem cell population does not depend on RA signaling for self-renewal or differentiation into NGN3$^+$ cells, a poised cell population that normally differentiates further into KIT$^+$ spermotogonia and finally into spermatocytes. However, NGN3$^+$ cells cannot differentiate into KIT$^+$ cells in the absence of vitamin A. The authors found that *Rarg* was differentially expressed between the NGN3$^+$ and GRFα1$^+$ subpopulations and that *Rarg* expression was necessary for the response of NGN3$^+$ cells to RA. Finally, they showed that enforced expression of *Rarg* was sufficient to cause the stem cell population to differentiate directly into KIT$^+$ cells, skipping the NGN3$^+$ stage. These results provide insight into how cell fate decisions can be regulated within open stem cell niches. *BL*

Modeling *NOTCH1* haploinsufficiency

Heterozygous nonsense mutations in *NOTCH1* cause bicuspid aortic valve and aortic valve calcification. Now, Deepak Srivastava and colleagues report the use of human induced pluripotent stem cell (iPSC) models to investigate how *NOTCH1* haploinsufficiency causes aortic valve calcification (*Cell* **160**, 1072–1086, 2015). The authors derived human endothelial cells *in vitro* and characterized them using RNA sequencing and ChIP-seq for H3K4me3, H3K27ac, H3K4me1 and H3K27me3 histone modifications. They also generated iPSC-derived endothelial cells from three individuals with heterozygous nonsense mutations in *NOTCH1* and created isogenic control lines by correcting the mutations using TALENs. They found that exposure to shear stress, which is known to protect against aortic valve calcification *in vivo*, alters the epigenetic state and suppresses the expression of components of osteogenic and inflammatory pathways when applied *in vitro* to normal human endothelial cells. In contrast, exposure to shear stress dysregulated the epigenetic state and caused aberrant upregulation of components of osteogenic and inflammatory signaling pathways in *NOTCH1*-mutated cells. Finally, the authors used network modeling to identify three putative regulatory node genes aberrantly upregulated by *NOTCH1* heterozygosity and showed that siRNA-mediated downregulation of these targets restored gene expression in *NOTCH1*-heterozygous cells toward the normal state. *EN*

Regulatory rewiring

Stefan Mundlos and colleagues report that disruption of genomic topologically associated domains (TADs) can result in new regulatory architecture, leading to disease phenotypes (*Cell* doi:10.1016/j.cell.2015.04.004; 7 May 2015). The authors identified patients with brachydactyly who carried heterozygous deletions effectively removing the boundaries between the TADs encompassing *EPHA4*, a gene expressed during limb development in mice, and *PAX3*. Similar alterations to this region, including an inversion and two duplications, were found in families affected by two other limb malformation syndromes. Mundlos and colleagues generated mice carrying the analogous alterations for two of the above syndromes using CRISPR/Cas9 and found that they recapitulated the human phenotypes. RNA sequencing analysis of the limbs of wild-type and mutant embryos showed specific upregulation of *Pax3* in the brachydactyly model and *Wnt6* in the F-syndrome model. A previously described model for polydactyly, Doublefoot, showed upregulation of *Ihh*. In the mutants, *Pax3*, *Wnt6* and *Ihh* adopted spatial expression patterns similar to that of wild-type *Epha4*, which had been disrupted by the mutations. 4C-seq experiments confirmed that the *Epha4* TAD interacted with *Pax3*, *Wnt6* and *Ihh* in mutant but not wild-type mice. Finally, the authors showed that similar aberrant interactions were present in patient-derived cells. ***BL***

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