Enhancer evolution in mammals

Widespread changes in regulatory genomic regions have underpinned mammalian evolution, but our knowledge about these regions is still incomplete. Paul Flicek, Duncan Odom and colleagues have now contributed to a better understanding of how the noncoding portions of mammalian genomes have been reshaped over the last 180 million years (*Cell* 160, 554–566, 2015). They characterized active promoters and enhancers in liver samples from 20 mammalian species—from Tasmanian devil to human—by examining the genome-wide enrichment profiles of H3K4me3 and H3K27ac, two histone modifications associated with transcriptional activity. Their analyses suggest that rapid enhancer evolution and high promoter conservation are fundamental traits of mammalian genomes. Intriguingly, they find that the majority of newly evolved enhancers originated via functional exaptation of ancestral DNA and not through clade-specific expansions of repeat elements. Their data also indicate that this class of putative enhancers is often associated with genes under positive selection. Future studies could extend these analyses to distinct subtypes of enhancers, to different developmental stages and to additional organs, taking into account tissue and cell heterogeneity. Moreover, as our understanding of chromatin biology deepens, it will be interesting to have a closer look at the evolution of other regulatory elements. ***TF***

Long-term memory genes in *C. elegans*

The cAMP-response element (CRE)-binding protein CREB is a transcription factor that regulates multiple cellular processes, including long-term memory, in organisms ranging from *Aplysia* to humans. However, the specific transcriptional programs related to long-term memory that are regulated by CREB are unknown. Coleen Murphy and colleagues conducted the first *in vivo* genome-wide screen for CREB transcriptional targets involved in regulation of long-term memory (*Neuron* **85**, 330–345, 2015). The authors compared transcriptional profiles between *CREB*-null and wild-type *Caenorhabditis elegans* before and after training for olfactory long-term associative memory. They identified 757 transcripts that were induced in a CREB- and training-dependent manner. Only 37 of the corresponding genes contained CRE sequences. Thus, most of the CREB/training-regulated genes are likely indirect targets of CREB and would not have been identified through *in vitro* binding assays. This gene set was distinct from non-training-induced CREB targets and was enriched for neuronal transcripts and gene ontology terms including behavior, ion channel activity and intracellular signaling. Many of these genes are also known to function in neuronal processes, including memory, in mammals. Previously uncharacterized genes in the gene set may point to new memory components. *BL*

Rb links reprogramming and cancer

RB1 (retinoblastoma) was the first tumor-suppressor gene to be described and is often mutated in many human cancers. Its product, Rb protein, is well known for its negative regulation of the cell cycle and, more recently, for its accessory role in chromatin remodeling. Julien Sage, Marius Wernig and colleagues investigated the function of Rb in reprogramming, leading to new insights into tumorigenesis (*Cell Stem Cell* **16**, 39–50, 2015). They discovered that inactivating Rb facilitates reprogramming of fibroblasts to a pluripotent state. Surprisingly, their data indicate that this does not involve interference with the cell cycle but instead that Rb directly binds to and represses pluripotency-associated loci such as *Oct4* (*Pou5f1*) and *Sox2*. Loss of Rb seems to compensate for the omission of *Sox2* from the cocktail of reprogramming factors. Furthermore, genetic disruption of *Sox2* precludes tumor formation in mice lacking functional Rb protein. This study positions Rb as a repressor of the pluripotency gene regulatory network and suggests that loss of Rb might clear the path for Sox2, or other master regulators of stem cell identity, to induce cancer. It will be interesting to analyze the potential role of Rb in other types of *in vitro* reprogramming. *TF*

Micropeptide regulates muscle performance

It is becoming increasingly recognized that some transcripts annotated as long noncoding RNAs (lncRNAs) contain short ORFs that encode functional proteins. Eric Olson and colleagues now report the discovery and functional characterization of a micropeptide, termed myoregulin, that is translated from an annotated lncRNA and that alters the contractile properties of skeletal muscle (*Cell* doi:10.1016/j.cell.2015.01.009; 28 January 2015). The authors show that this 46-residue peptide is expressed specifically in skeletal muscle and has structural similarity to phospholamban and sarcolipin, two proteins that interact with the calcium pump SERCA in the sarcoplasmic reticulum of striated muscle cells and inhibit its pump activity. They further show that myoregulin colocalizes with the skeletal muscle–specific SERCA1 protein in the sarcoplasmic reticulum membrane and inhibits its calcium reuptake, similarly to phospholamban and sarcolipin. They subsequently engineered mice lacking myoregulin function and found that these mice exhibited increased muscle performance on a running endurance test. The partially overlapping expression patterns of phospholamban, sarcolipin and myoregulin suggest that this family of proteins contributes to the unique contractile properties of different striated muscle types. *KV*

Stem cell metabolic and epigenetic reprogramming

Stem cells undergo metabolic reprogramming and use different metabolic substrates during differentiation. Now, Vittorio Sartorelli and colleagues report that proliferating skeletal muscle stem cells (called satellite cells) shift from fatty acid oxidation to glycolysis, with downstream effects on epigenetic states and gene expression (*Cell Stem Cell* 16, 171–183, 2015). The authors analyzed the transcriptomes of quiescent and proliferating mouse satellite cells and observed transcriptional activation of the glycolytic program. They found that the shift to glycolysis was accompanied by a decrease in the levels of NAD+, a corresponding decrease in the activity of the NAD+-dependent enzyme SIRT1 and an increase in H4K16ac, the substrate of SIRT1-mediated deacetylation. The authors generated a skeletal muscle–specific knockout of Sirt1, which exhibited defects in skeletal muscle development and regeneration following injury. They used RNA-seq and ChIP-seq to profile gene expression and SIRT1 and H4K16ac localization across the genome to determine links between SIRT1, H4K16ac and gene expression. This work connects metabolic shifts with epigenetic regulation in tissue stem cells. ***EN***

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