Integrin β3 in MLL-AF9 leukemia

In vivo **RNA interference screens are an approach for identifying genes required for leukemia in the physiologically relevant microenvironment. Using such an approach, Benjamin Ebert and colleagues now report that *Itgb3* (encoding integrin β3, Itgb3) is required for MLL-AF9 acute myeloid leukemia in mice (*Cancer Cell* 24, 45–58, 2013). Using a known model of leukemia with 100% penetrance, the authors targeted 268 genes with small hairpin RNAs (shRNAs), looking for targeted genes that would become highly depleted. The top three hits included two genes with known roles in MLL-AF9 leukemia as well as *Itgb3*. The number of leukemia cells harboring *Itgb3* shRNAs was reduced over time, and mice transplanted with leukemia with *Itgb3* shRNAs survived longer than control mice, showing that *Itgb3* shRNAs affect the growth of leukemia cells *in vivo*. Using a human cell line transduced with the *MLL-ENL* oncogene and primary acute myeloid leukemia samples expressing *ITGB3*, the authors showed that *ITGB3* shRNAs inhibited human leukemia growth. Further experiments established a role for Syk in mediating Itgb3 activity in leukemia. Finally, the authors expressed MLL-AF9 in mouse cells lacking Itgb3 and found that mice transplanted with $Itgb3^{-/-}$ bone marrow lived longer than those transplanted with $Itgb3^{+/+}$ cells.** ***PF***

DNA methylation and the brain

Genomic patterns of DNA methylation are known to dynamically change during mammalian brain development. Now, Ryan Lister, Margarita Behrens, Joseph Ecker and colleagues report profiling at single-base resolution of DNA methylation in the mouse and human frontal cortex at multiple points during development to gain insight into potential functions (*Science* doi:10.1126/science.1237905, 4 July 2013). The authors found an accumulation of hydroxymethylcytosine (hmC) and non-CG methylation over the course of development. They also profiled isolated neurons and glia from human and mouse adult frontal cortex and found differences in both the amount and localization of methylcytosine (mC) in these cell types, showing that non-CG methylation is more abundant than methylation of CG dinucleotides in neurons. By analyzing profiles on the X chromosome, the authors determined that both promoter CG hypomethylation and intragenic non-CG hypermethylation mark genes that escape X-chromosome inactivation in human females. The authors discerned a pattern in the fetal brain of enrichment of hmC at CG sites in genomic regions that show dynamic changes in mC at CG sites during development, and they propose that hmC at CG sites might mark these regions for DNA demethylation later during development. *EN*

Microbial stability in the human gut

Jeffrey Gordon and colleagues sequenced fecal microbiota sampled from 37 healthy adult individuals over time (*Science* **341**, 1237439, 2013). The authors used a newly developed LEA-seq method for amplicon sequencing of bacterial 16S rRNA that has been demonstrated to have higher precision than existing methods. They compared the bacterial composition of the gut microbiota within an individual across time points for a collection of 33 individuals from whom samples were obtained 2–13 times over the course of 5 years. They found that, although the bacterial composition did change, over 70% of the same strains were present after 1 year, and a core set remained constant over longer time scales. Strains present in greater abundance were more likely to remain constant over time, as were members of the Bacteroidetes and Actinobacteria phyla. The authors also sequenced fecal microbiota from four individuals participating in an in-patient weight-loss study, from whom samples were obtained every 16 d for 32 weeks while patients were on a controlled liquid diet. These individuals showed reduced bacterial strain stability over time. They also showed a negative correlation between weight stability, as measured by absolute change in body mass index (BMI) between time points, and bacterial strain stability. Finally, the authors found enrichment of shared strains in fecal microbiota for related individuals. *OB*

Written by Pamela Feliciano, Emily Niemitz & Orli Bahcall

Evolution of human limb development

Changes in gene regulation are thought to contribute to morphological adaption in human evolution. In an effort to identify candidate genes that regulate human-specific anatomical features, James Noonan and colleagues studied the evolution of *cis*-regulatory elements in developing human, rhesus and mouse limb development (*Cell* **154**, 185–196, 2013). The authors profiled the genomic location of acetylation of histone H3 at lysine 27 (H3K27ac) as a proxy for promoter and enhancer activity in human, rhesus and mouse embryonic limb tissues at multiple stages of development. They identified genomic regions with potential gains in activity since human-rhesus divergence by focusing on sites that showed an increase in H3K27ac levels in humans compared to the orthologous sites in rhesus and mice. They identified over 5,000 putative promoters and enhancers with increased H3K27ac levels in the human lineage and determined that these regions, on average, had a more recent evolutionary origin and were less conserved than loci with similar levels of H3K27ac in all 3 species. By integrating gene expression profiles from developing human and mouse limbs, the authors identified 302 genes with both increased expression in the human limb and increased H3K27ac levels at nearby regulatory elements. *EN*

Oncogenic microRNA

In two recent publications, Pier Paolo Pandolfi and colleagues report that the microRNA miR-22 has oncogenic activities in hematological malignancies (*Cell Stem Cell* 13, 87–101, 2013) and in breast cancer (*Cell* 154, 311–324, 2013). The authors showed that miR-22 expression is often higher in myelodysplastic syndrome (MDS) and is correlated with poor survival rate. They generated transgenic mice expressing miR-22 in the hematopoietic compartment; these mice developed MDS and hematological malignancies. The authors identified *TET2*, which encodes an enzyme that catalyzes the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), as a direct target of miR-22 and showed that miR-22 overexpression reduced global 5hmC levels. Separately, the authors showed that high expression of miR-22 associates with advanced breast tumor stage and poor survival rate. The authors generated transgenic mice expressing miR-22 in mammary glands; these mice developed mammary hyperplasia and mammary tumor formation with lung metastases. The authors showed that miR-22 directly targets TET enzymes for repression, resulting in reduced global 5hmC levels. Specifically, miR-22 overexpression and TET repression caused reduction of promoter 5hmC and reduced expression of miR-200, a microRNA with known tumor suppressor functions. Together, these papers identify oncogenic functions for miR-22 and a tumorigenic pathway involving the deregulation of TET enzymes. ***EN***