Global epistasis

Michael Desai and colleagues examine the influence of epistatic interactions between mutations on the patterns of evolution in *Saccharomyces cerevisiae* (*Science* **344**, 1519–1522, 2014). They began with 432 independent *S. cerevisiae* lines from a single haploid clone and evolved each line separately for 240 generations. From the resulting lines, they selected 64 clones that were representative of a range of fitness levels to use as founders in the next adaptation phase of the experiment, in which 10 replicate populations from each founder were each adapted for 500 generations. They found marked differences in the adaptation rate between populations and attribute a substantial proportion of these differences to the identity and fitness of the founder. Further, populations with lower initial fitness showed a more rapid rate of adaptation. The authors sequenced the whole genomes of 104 clones that evolved from 13 founders, characterizing the mutations that arose during the evolution experiment. Although the majority of mutations were unique, the authors did identify genes in which there were recurrent mutations, and they found that these mutations were more frequent in lines that showed a greater increase in fitness during adaptation. Their analysis provides support for a global diminishing-returns epistasis model in which beneficial mutations across a range of biological processes are globally coupled and interact for a combined effect on fitness. *OB*

Intergenerational epigenetic inheritance

Some prenatal exposures are known to affect offspring and subsequent generations through non-mendelian epigenetic inheritance. Now, Mary-Elizabeth Patti, Anne Ferguson-Smith and colleagues shed light on the epigenetic mechanisms of intergenerational inheritance following *in utero* undernourishment in mice (*Science* doi:10.1126/science.1255903, 10 July 2014). The authors imposed maternal nutritional restriction during the time when male primordial germ cells are epigenetically reprogrammed in developing embryos and assessed the whole-genome distribution of methylation in the sperm of F_1 animals using immunoprecipitation of methylated DNA followed by high-throughput sequencing. They identified 166 differentially methylated regions (DMRs), most of which were hypomethylated and were preferentially located in intergenic regions and CpG islands. The authors found that differential methylation was not present in liver and brain samples from F_2 generation animals, although they did observe changes in the expression of genes neighboring DMRs. This work shows that *in utero* exposure to an adverse environment can affect genome-wide patterns of methylation in the male germ line. *EN*

Host microbiome signature of Crohn's disease

Lee Denson and colleagues report the identification of a Crohn's disease–specific gene signature that distinguishes Crohn's disease from another form of inflammatory bowel disease (IBD), ulcerative colitis (*J. Clin. Invest.* doi:10.1172/JCI75436, 8 July 2014). The study used 359 samples from the RISK cohort to compare the ileal biopsies of treatment-naive pediatric cases from 3 groups—Crohn's disease with ileal inflammation (iCD), colon-only Crohn's disease (cCD) and ulcerative colitis—with non-IBD controls. In total, 1,281 genes were differentially expressed in 2 independent iCD groups in comparison to controls, making up the core iCD gene signature. In addition, 82% of genes in the core signature were also differentially expressed in cCD versus control biopsies, in comparison to just 18% in the ulcerative colitis versus control comparison. The authors used measures of microbial abundance from the ilea of additional RISK case samples to show that shifts in the microbial community were similar in the ilea of both iCD and cCD cases, identifying the ileum as the likely primary tissue of induction for Crohn's disease. Finally, the authors identified gene coexpression signatures characterized by the upregulation of *DUOX2* and downregulation of *APOA1* that distinguished both forms of Crohn's disease from ulcerative colitis. A model including these two coexpression signatures and microbial composition data was more predictive of 6-month steroid-free remission than a model including only clinical parameters. *BL*

iPSC models of retinitis pigmentosa

Hideyuki Okano and colleagues report increased expression of endoplasmic reticulum (ER) stress and apoptotic markers in an induced pluripotent stem cell (iPSC) model of retinitis pigmentosa (*Mol. Brain* **7**, 45, 2014). The authors derived iPSCs from an affected individual carrying a mutation encoding p.Glu181Lys in the rhodopsin gene. Control iPSCs were obtained by reverting the mutation to the normal allele. Upon differentiation into rod receptors, the cells with mutant rhodopsin had decreased survival and increased expression of transcripts for the ER stress markers BiP and CHOP as well as for the apoptotic markers BID and NOXA. The results were confirmed in an independent iPSC line in which the authors replaced the normal rhodopsin gene with the allele encoding p.Glu181Lys. They further demonstrated that the effects on cell survival and expression of ER stress and apoptotic markers could be attenuated by treatment with drugs that inhibit the mTOR pathway, ASK1 or protein synthesis, or that activate AMPK. *BL*

Developmental origins of coronary vessels

Lineage tracing is a powerful approach for studying the origins and fates of individual cell populations during development. Using an inducible lineage tracing system, Bin Zhou and colleagues (*Science* **345**, 90–94, 2014) have mapped the developmental origins of the coronary vasculature in mice. The authors used tamoxifen-inducible Cre under the control of the *Apln* promoter to drive expression in coronary vascular endothelial cells. In treating the mice with a single dose of tamoxifen at embryonic day 10.5 and following the fate of the labeled cells postnatally, they found that the labeled cells were restricted to the outer half of the myocardial wall. Conversely, applying single doses of tamoxifen at later time points resulted in progressive labeling of the interventricular septum and the inner myocardial wall. Additional lineage tracing experiments using a promoter expressed selectively in the endocardium showed that these latter waves of vascular endothelial cells emerged directly from the endocardium via lineage conversion during periods of myocardial compaction. The authors propose that this mechanism of lineage conversion allows for more rapid vascular and myocardial growth during the early postnatal period and might provide a new entry point for studying cardiovascular regeneration. *KV*

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