Stimulating β cell proliferation

Doug Melton and colleagues (*Cell* 153, 747–758, 2013) report the discovery of a secreted peptide produced by liver and fat cells that stimulates the proliferation of pancreatic β cells. The authors discovered this putative hormone, which they call betatrophin, by studying a new mouse model in which insulin resistance is induced by administering the insulin receptor antagonist S961. They found that mice infused with S961 showed a striking increase in β cell proliferation, whereas mouse β cells treated directly *in vitro* with S961 showed no effect. To look for potential mediators of the *in vivo* stimulatory activity of S961, the authors performed an expression screen in tissues involved in metabolic regulation and found that the gene encoding betatrophin was upregulated in liver and fat cells following S961 treatment in the insulin resistance model as well as in other diabetic models. They further showed that betatrophin is a secreted protein that is conserved in mammals and detectable in human serum. Notably, when they injected betatrophin expression constructs into mouse liver, they observed a dramatic increase in β cell proliferation, β cell mass and insulin production. Future work will now be aimed at testing the activity of recombinant betatrophin protein and elucidating downstream signaling mechanisms. ***KV***

SETD2 and mismatch repair

Inactivation of mismatch repair (MMR) complexes causes susceptibility to certain cancers and a cellular mutator phenotype characterized by microsatellite instability and increased frequency of spontaneous mutation. However, not all cancers with a mutator phenotype have defects in MMR machinery. Now, Liya Gu, Guo-Min Li and colleagues report a new regulator of MMR, shedding light on how seemingly MMR-proficient tumors can have a mutator phenotype (*Cell* **153**, 590–600, 2013). The authors show that the DNA mismatch repair protein hMSH6 interacts with histone H3 trimethylated at lysine 36 (H3K36me3) and that H3K36me3 recruits hMSH6 to chromatin. They also show that the H3K36 methyltransferase SETD2 is required for DNA mismatch repair, as loss of SETD2 causes a mutator phenotype with microsatellite instability and increased rates of spontaneous mutation. They further show that tumor cell lines with loss of *SETD2* have loss of H3K36me3 marks, loss of hMSH6 recruitment to chromatin and a mutator phenotype. This work suggests a molecular mechanism to explain *SETD2* tumorigenic driver mutations. *EN*

Somatic *GNAQ* mutation

Jonathan Pevsner, Douglas Marchuk, Anne Comi and colleagues report whole-genome sequencing of three individuals with Sturge-Weber syndrome, a neurological and skin disease characterized by abnormal blood vessel development, glaucoma, seizures, intellectual disability and port-wine stain of the skin (*N. Engl. J. Med.* doi:10.1056/NEJMoa1213507, 8 May 2013). They identified a missense mutation, encoding p.Arg183Gln, in the *GNAQ* gene in affected skin or brain tissue from all three individuals, whereas the mutation was not present in tissue taken from unaffected areas. They looked for the mutation in additional individuals with Sturge-Weber syndrome and in total identified the mutation in affected tissues from 23 of 26 tested individuals. They also identified the same mutation in affected tissues from 12 of 13 tested individuals with nonsyndromic port-wine stain. *GNAQ* encodes $G\alpha_q$, a G protein subunit involved in G protein–coupled receptor signaling. The authors further determined that the p.Arg183Gln substitution causes modestly elevated activation of downstream mitogen-activated protein kinase (MAPK) signaling. They hypothesize that early developmental origin of the somatic mutation causes Sturge-Weber syndrome, whereas later origin causes nonsyndromic port-wine stain. *EN*

Written by Pamela Feliciano, Emily Niemitz & Kyle Vogan

Malaria gene allows infection

It was previously known that some strains of the malaria parasite *Plasmodium falciparum* can evade the immune system of the mosquito vector *Anopheles gambiae*. A new study from Carolina Barillas-Mury and colleagues (*Science* doi:10.1126/science.1235264, 9 May 2013) identifies the first *P. falciparum* gene that enables the parasite to infect mosquitoes without activating their immune system. The authors analyzed a genetic cross between two *P. falciparum* lines that differed in their ability to infect w*A. gambiae* and mapped a quantitative trait locus (QTL) to a 172-kb region that encompassed 41 genes. Analysis of gene expression and sequencing reduced the number of candidates, and the authors made knockouts of the two top candidate genes, *Pfs47* and *Pfs48/45*, which both encode 6-cysteine protein family members. Parasites with *Pfs48/45* knockout that invaded the midgut of the mosquito had a similar phenotype to wild-type parasites, showing that this gene is not needed to evade the mosquito immune system. In contrast, *Pfs47* knockout parasites invaded the midgut but were eliminated by mosquitoes, showing that this gene is essential in evading the mosquito's immune system. The authors were also able to complement *Pfs47* knockout with different *Pfs47* alleles, suggesting that this gene's function increases parasite survival in *A. gambiae*. *PF*

Interneurons from pluripotent cells

Previous studies have successfully differentiated human pluripotent stem cells into several neuronal subtypes, but no effort has been able to generate cortical interneurons, which are involved in neuropsychiatric diseases such as schizophrenia and autism. Lorenz Studer, Stewart Anderson and colleagues (*Cell Stem Cell* 12, 559–572, 2013) now report a method for deriving human cortical interneurons from a human embryonic stem cell line. The authors first identified conditions that would generate NKX2.1$^+$ forebrain progenitors and tested whether these putative interneuron precursors showed the typical migratory potential seen in primary interneurons in mice. Indeed, they identified conditions in which robust migration of these cells occurred in the neocortex in mice. The authors then plated these cells over feeder cultures of mouse cortical pyramidal neurons and glia and compared them to cells grown on feeder cultures enriched for human cortical projection neurons. They found a consistent difference between NKX2.1$^+$ cells plated on mouse and human cortical feeders, suggesting that the maturation of NKX2.1$^+$ progenitors depends on local cellular context. Future work should investigate the functional mechanisms that determine species-specific maturation rates. The authors also suggest that studies involving transplantation of these derived interneurons into mouse models of neurological disease should be explored. ***PF***