PAK inhibitor in fragile X

Fragile X syndrome (FXS) is an autism-like disorder caused by mutations in the fragile X mental retardation 1 gene (*Fmr1*). Previous work has shown that dendritic spine architecture is abnormal in both humans with FXS and mice lacking *Fmr1*. Because dendritic spines require actin cytoskeleton regulation and multiple lines of evidence connect *Fmr1* to the Rac-PAK (p21-activated kinase) pathway, Susumu Tonegawa and colleagues postulated that inhibition of the PAK pathway might rescue FXS phenotypes. They now report that a small molecule PAK inhibitor, FRAX486, rescues hyperactivity, repetitive movements and seizures in *Fmr1* knockout mice (*Proc. Natl. Acad. Sci. USA* 110, 5671–5676, 2013). The authors screened a library of 12,000 small molecules, identifying a molecule that was further developed into FRAX486. FRAX486 inhibited group I PAKs at half-maximal inhibitory concentration (IC_{50}) = 8.25 nM and crossed the blood-brain barrier at levels that would inhibit group I PAKs. Treatment with FRAX486 rescued dendritic spine defects and sound-induced seizures, completely abolishing the latter at a dose of 30 mg/kg. As repetitive behavior is a major criterion in autism diagnosis, the authors tested whether FRAX486 could improve this symptom. *Fmr1* knockout mice treated with FRAX486 exhibited significantly fewer counterclockwise revolutions than controls. ***PF***

Inhibitors of mutant IDH1 and IDH2

Somatic mutations in genes encoding isocitrate dehydrogenase isoforms IDH1 and IDH2 have recently been found in 50–80% of human low-grade gliomas, whereas somatic mutations in *IDH2* are found in ~10% of acute myeloid leukemias (AMLs). Scientists now report compounds that selectively inhibit mutant IDH1 and IDH2. Ingo Mellinghoff, Katharine Yen and colleagues report a selective inhibitor (AGI-5198) of mutant R132H IDH1 (*Science* doi:10.1126/science.1236062, 4 April 2013). The compound inhibited R132H IDH1 but not wild-type IDH1 at half-maximal inhibitory concentration (IC_{50}) = 70 nM. In TS603 glioma cells carrying a heterozygous mutation for R123H IDH1, AGI-5198 decreased colony formation by 40–60%. AGI-5198 also caused 50–60% inhibition of human glioma xenograft growth in mice. Katharine Yen and colleagues identified a small molecule (AGI-6780) that selectively inhibited mutant R140Q IDH2 ($IC_{50} \leq 20$ nM) (*Science* doi:10.1126/science.1234769, 4 April 2013). They treated primary human AML cells with the mutation for R140Q IDH2 *ex vivo*, seeing a dose-dependent reduction in the levels of the metabolite 2-hydroxyglutarate and an increase in the numbers of more mature, CD45-positive cells. Their experiments showed that treatment with AGI-6780 reversed growth factor–independent growth and a block in erythroid differentiation seen in human AML cells with mutant R140Q IDH2. Both papers provide evidence that agents targeting mutant IDH1 and IDH2 should be further investigated in the clinic. *PF*

Widespread *TERT* promoter mutations

Two recent studies reported that somatic mutations in the *TERT* promoter region occur at high frequency in human melanomas (*Science* **339**, 957–959, 2013; *Science* **339**, 959–961, 2013). To extend these findings to other cancers, Bert Vogelstein, Hai Yan and colleagues assessed the prevalence of *TERT* promoter mutations in a large collection of different human tumor types (*Proc. Natl. Acad. Sci. USA* doi:10.1073/pnas.1303607110, 25 March 2013). In total, they examined 1,230 tumors representing 60 human cancers and identified 8 different tumor types, in addition to melanoma, exhibiting a high frequency of *TERT* promoter mutations, including several glioma subtypes, hepatocellular carcinoma, urothelial carcinoma and myxoid liposarcoma. Conversely, they found a low frequency of *TERT* promoter mutations in many common epithelial tumors, including breast, prostate and colon cancers, and in several leukemias. In gliomas, they found that *TERT* promoter mutations were mutually exclusive with *ATRX* alterations, which are associated with activation of the ALT pathway for telomere maintenance. Overall, these findings show that *TERT* promoter mutations are frequent driver events in many human cancers, particularly those that arise from tissues with low rates of self-renewal. *KV*

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Motif-driven enhancer assay

Manolis Kellis and colleagues systematically examined the role of specific regulatory motifs in predicted human enhancer regions using a massively parallel reporter assay to quantitatively measure enhancer activity (*Genome Res.* doi:10.1101/gr.144899.112, 19 March 2013). They screened a library of 145-bp sequences from candidate enhancers and measured reporter expression in two human cell lines. Candidate cell type–specific enhancer elements were predicted on the basis of chromatin state and searched for enrichment or depletion of specific regulatory motifs. Five predicted activator (HNF1, HNF4, FOXA, GATA, NFE2L2) and 2 predicted repressor (GFI1, ZFP161) motifs were selected, and the authors tested 2,104 wild-type sequences and 3,314 engineered sequences with targeted motif disruptions, confirming the cell type–specific enhancer activity of these elements. Scrambling, disrupting or removing the predicted activator motifs reduced reporter expression to baseline, supporting the idea that these motifs are necessary in establishing enhancer activity. The authors confirmed repressor activity for GFI1, showing that scrambling this motif resulted in increased expression in a cell line where the enhancer is not active. They also examined the sequence context for wild-type enhancer function, finding that specific features, including evidence of nucleosome exclusion, strength of motif match and evolutionary conservation, were correlated with higher expression. *OB*

Jmjd3, PHF20 and reprogramming

Transcription factor–driven reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) is inefficient, suggesting that normal cellular mechanisms act as barriers to reprogramming. Now, Rong-Fu Wang and colleagues identify a new epigenetic regulator of the reprogramming process (*Cell* 152, 1037–1050, 2013). The authors produced mouse embryonic fibroblasts (MEFs) with tetracycline-inducible transgenes of four pluripotency-inducing transcription factors and used these MEFs to screen for epigenetic factors that alter reprogramming efficiency. They found that knockdown of the histone demethylase gene *Jmjd3* increased the efficiency of reprogramming. The authors generated *Jmjd3* knockout mice and confirmed that *Jmjd3* loss enhanced efficiency and kinetics of reprogramming MEFs to iPSCs. Jmjd3 is known to modify the expression of the *Ink4a/Arf* locus, which is a known barrier to reprogramming. However, the authors found that the effects of *Jmjd3* on reprogramming could not be entirely accounted for by *Ink4a/Arf* expression. The authors subsequently identified PHF20 as a target of Jmjd3 and showed that PHF20 is required for both the reprogramming and maintenance of iPSCs. They also found that Jmjd3 has an additional activity, targeting PHF20 for ubiquitination and degradation, and showed that PHF20 is required for the reactivation of endogenous Oct4 expression during the reprogramming process. ***EN***