Promoter silencing by CGG repeats

Fragile-X syndrome is caused by CGG trinucleotide repeat expansion and silencing of the X-linked *FMR1* gene. Now, Samie Jaffrey and colleagues show that an RNA-directed gene silencing mechanism drives epigenetic silencing of *FMR1* (*Science* 343, 1002, 2014). The expanded CGG repeat is transcribed as part of the *FMR1* 5' UTR and forms a hairpin structure. The authors investigated the role of this transcript in *FMR1* silencing. They used human embryonic stem cells that carry an *FMR1* allele with expanded CGG repeats; these cells undergo *FMR1* silencing upon neuronal differentiation. The authors first showed that knockdown of *FMR1* mRNA inhibited *FMR1* silencing, and they then showed that altering the hairpin structure of the CGG repeats with a small molecule that selectively binds the hairpin also prevented *FMR1* silencing. In addition, the authors showed that expanded *FMR1* transcripts bind to the *FMR1* promoter and form an RNA-DNA duplex, and treatment with the small molecule that alters the hairpin structure of the *FMR1* transcript reduced binding to the promoter. This work provides a mechanism linking trinucleotide repeat expansion with promoter silencing. ***EN***

Inflammatory syndrome ADA2 deficiency

Two independent studies describe a new vascular inflammatory syndrome caused by loss-of-function mutations in *CECR1*, which encodes the extracellular adenosine deaminase ADA2. Ivona Aksentijevich and colleagues (*N. Engl. J. Med.* **370**, 911–920, 2014) performed exome sequencing of three unrelated subjects with a spectrum of phenotypes that included recurrent fevers and early-onset stroke, discovering biallelic mutations in *CECR1* in all three cases. They subsequently identified six other individuals with biallelic *CECR1* mutations and overlapping clinical features. Separately, Ephrat Levy-Lahad and colleagues (*N. Engl. J. Med.* **370**, 921–931, 2014) performed exome sequencing of several individuals of Georgian Jewish ancestry diagnosed with polyarteritis nodosa, a systemic necrotizing vasculitis, and identified a homozygous missense mutation in *CECR1* in all cases. They subsequently found compound heterozygous *CECR1* mutations in individuals of German and Turkish ancestry with similar clinical presentations. In both studies, the mutations were associated with reduced ADA2 activity in plasma. Given the known biological roles of ADA2, the disease phenotypes may result from upregulation of the adenosine inflammatory response pathway or from loss of ADA2-mediated growth factor activity. *KV*

Two pathways for courtship behavior

The male-specific product of the *fruitless* gene (fru^M) in *Drosophila melanogaster* is necessary for all aspects of male courtship. However, previous studies have reported observations of courtship-like behaviors in males lacking fru^M when these flies are housed with other males for several days. Now, Yufeng Pan and Bruce Baker report that this experience-dependent development of courtship behaviors requires the expression of male-specific *doublesex* (dsx^M) in neurons that normally express both genes (*Cell* **156**, 236–248, 2014). Males lacking fru^M that were housed for at least 1 day with other males, conspecific females or females of a different species all showed courtship behaviors toward males and females in a courtship assay. Wild-type males, however, rarely court other males, and their courtship of females is not dependent on previous social experience. The authors further demonstrated that, when dsx^M was replaced by the female-specific *dsx* in neurons that normally express both dsx^M and fru^M, all courtship behavior was lost. Finally, they demonstrated that genetic females expressing dsx^M also courted females. These data identify *Drosophila* male courtship as a genetic model for understanding the interplay between innate and acquired behavior. *BL*

Written by Orli Bahcall, Brooke LaFlamme, Emily Niemitz & Kyle Vogan

eQTL mapping for innate immunity

Two new studies report expression quantitative trait locus (eQTL) mapping of primary cells involved in innate immunity isolated from healthy humans. Julian Knight and colleagues report eQTL mapping of $CD14^+$ monocytes from 432 healthy volunteers of European ancestry (*Science* **343**, 2014, doi:10.1126/science.1246949). Monocytes were exposed to either interferon-γ or lipopolysaccharide (LPS) for a short (2-hour) or long (24-hour) duration. The majority of the *cis* eQTLs identified were specific to the condition tested. The authors also identified *trans* eQTLs and condition-specific gene networks. In a second study, Nir Hacohen and colleagues report eQTL mapping of dendritic cells isolated from the peripheral blood monocytes of 560 healthy individuals of European, Asian or African-American ancestry from the PhenoGenetic cohort (*Science* **343**, 2014, doi:10.1126/science.1246980). They identified 264 *cis* eQTLs for resting dendritic cells. By stimulating dendritic cells with LPS, influenza virus or interferon-β, they identified 121 *cis* eQTLs for the response to 1 or more of the stimulation conditions, with 57 shared by all 3 conditions. The authors also identified *trans* eQTLs of *IRF7*. The two studies show overlap of eQTLs with loci that have previously been associated with particular autoimmune or infectious diseases and suggest further studies to explore disease mechanisms. *OB*

PRKCI and *SOX2* drive lung cancer

Lung squamous cell carcinoma (LSCC) represents 30% of all lung cancers but has few effective treatments available. Now, Alan Fields and colleagues identify a novel signaling axis specific to LSCC that has implications for the development of new treatment options (*Cancer Cell* 25, 139–151, 2014). The authors previously identified *PRKCI* as an oncogene overexpressed in lung cancers with an amplification of chromosome 3q26. In this study, the authors establish that *PRKCI* is overexpressed, and its product, protein kinase Cι (PKCι), was activated in five cell cultures of isolated stem-like cells from lung cancer cell lines. They further showed that PKCι regulates the Hedgehog pathway in these cultures to stimulate proliferation and to maintain a stem-like phenotype *in vitro* and drive tumor formation *in vivo*. Further, they found that the LSCC oncogene *SOX2*, a known master regulator of stem cell maintenance, was frequently coamplified with *PRKCI* in human cancers. Through a series of meticulous experiments, they showed that PKCι phosphorylates a novel site in SOX2 (Thr118), leading to SOX2 occupancy of the *HHAT* promoter and thereby activating Hedgehog signaling. Disruption of the Thr118 phosphorylation site abolished PKCι-dependent Hedgehog signaling and diminished tumor cell proliferation *in vitro*. These results implicate PKCι and HHAT inhibitors as strong candidates for the treatment of LSCC. ***BL***