Infectious retrovirus and prostate cancer

The R462Q variant of the endoribonuclease RNase L has been reported to be associated with familial prostate cancer, albeit with mixed support in follow-up studies. As RNase L functions in the interferon antiviral response, it had been proposed that a virus might be associated with some cases of prostate cancer, and a recent study identified a gammaretrovirus in prostate tumors from men carrying the R462Q variant. A new study shows that a full-length clone of this virus, xenotropic murine leukemia virus–related virus (XMRV), is replication competent (*Proc. Natl. Acad. Sci. USA* 104, 1655–1660; 2007). Beihua Dong and colleagues constructed a full-length XMRV clone and showed that it can infect and replicate in the LNCaP cell line, a prostate cancer line that is partially deficient in RNase L. Treatment of infected cells with interferon-β reduced viral yields, but this reduction was inhibited in LNCaP cells or in other cells in which RNase L levels were knocked down by short hairpin RNAs. The authors also identified viral integration sites in DNA isolated from human prostate tumors, confirming *bona fide* infection of humans by XMRV and strengthening the case for its relevance in prostate cancer. *AP*

Familial chilblain lupus

Biallelic mutations in *TREX1*, encoding a key 3′→5′ exonuclease, were recently shown to underlie some cases of Aicardi-Goutières syndrome (*Nat. Genet.* **38**, 917–920; 2006), a recessive encephalopathy sharing clinical similarities with systemic lupus erythematosus. Now, Yanick Crow and colleagues (*Am. J. Hum. Genet.*, in the press) report the identification of a heterozygous frameshift mutation in *TREX1* segregating with familial chilblain lupus, a monogenic form of cutaneous lupus previously linked to the interval on 3p harboring *TREX1*. Lymphoblastoid cell lines derived from the affected individuals showed a 65%–85% reduction in exonuclease activity, consistent with the dominant presentation of the disease phenotype. The authors also report the identification of a *de novo* heterozygous missense mutation in an individual with classical features of Aicardi-Goutières syndrome. Notably, the exonuclease activity measured in a lymphoblastoid cell line derived from this individual was comparable to that seen in clinically unaffected heterozygous carriers of known loss-of-function *TREX1* mutations, leading the authors to speculate that this *de novo* mutation affects TREX1 activity in a manner not detectable by standard exonuclease assays. These findings strengthen the link between *TREX1* mutations and lupus-associated phenotypes and suggest further insights into disease pathogenesis. *KV*

Choosing odor receptor genes

The expression of a single odor receptor gene in olfactory receptor neurons (ORNs) poses a considerable challenge to an organism. A recent report suggests that in mammals, a stochastic mechanism may be in place that relies on negative feedback to prevent expression of more than one gene. A new study suggests that the situation in *Drosophila melanogaster* is different, relying on a combination of deterministic mechanisms to generate its highly stereotyped array of ORNs (*Neuron* **53**, 353–369; 2007). The mechanisms underlying odor receptor gene choice in *Drosophila* must account for regulated gene expression at the level of the individual neuron, the level of the sensillum (where neurons expressing one particular receptor are always paired with neurons expressing another) and the level of the organ (maxillary palp versus antenna). Anandasankar Ray and colleagues show that neuron-specific alternative splicing, cell-specific transcription factors and organ-specific *cis*-regulatory elements combine to control odor receptor gene expression in ORNs. Moreover, when individual odor receptor genes are ectopically expressed in the maxillary palp, they do not prevent the expression of other odor receptor genes, suggesting that expression of these genes in *Drosophila* is permissive and does not involve negative feedback. *AP*

Research Highlights written by Emily Niemitz, Alan Packer and Kyle Vogan.

Tumor suppressor role for Chd5

Loss of heterozygosity at 1p36 occurs at high frequency in many human cancers, including neuroblastomas and several other malignancies of the nervous system, suggesting the existence of an important tumor suppressor gene in this region. A new study by Alea Mills and colleagues (*Cell* **128**, 459–475; 2007) now identifies *CHD5*, which encodes a protein implicated in chromatin remodeling, as a strong candidate for the long-sought-after 1p36 tumor suppressor. Mills and colleagues engineered mice with either a duplication or a deletion of a chromosome 4 region syntenic to human 1p36. Cells heterozygous for the duplication showed reduced proliferation and increased apoptosis, whereas cells heterozygous for the deletion showed enhanced proliferation and increased sensitivity to immortalization. By screening candidate genes from the interval using short hairpin RNA constructs, the authors found that knockdown of Chd5 phenocopied the effects of the deletion allele. Notably, both Chd5 knockdown and the deletion allele resulted in reduced expression from the *Ink4* (*Arf*) locus and compromised p53 function. Chd5 knockdown cells, like cells with the deletion, readily formed tumors when injected into immunocompromised mice. As spontaneous tumors in mice with the deletion retained the wild-type allele, the data suggest that Chd5 functions as a dosage-sensitive tumor suppressor. *KV*

Lesson on muscle regeneration

Although Marfan syndrome is best known for cardinal features in the cardiovascular, skeletal and ocular systems, myopathy and inability to increase muscle mass are also common features. Increased TGF-β signaling, caused by genetic deficiency of fibrillin-1, has been implicated in the pathogenesis of many Marfan phenotypes. Now Hal Dietz and colleagues report that TGF-β signaling also contributes to myopathy in Marfan syndrome, and they implicate TGF-β signaling in failure to regenerate muscle in Duchenne muscular dystrophy (*Nat. Med.* advance online publication 21 January 2007; doi:10.1038/nm1536). Using a mouse genetic model of Marfan syndrome, the authors showed that treatment with TGF-β-neutralizing antibody restored the ability to regenerate muscle after injury. Moreover, long-term treatment with losartan, an angiotensinogen II type 1 receptor blocker that also antagonizes TGF-β, led to both improved muscle function and restoration of muscle regeneration after injury. Losartan is an FDA-approved drug widely used for hypertension. In order to investigate whether TGF-β signaling may be involved more generally in impairment of muscle regeneration, the authors used a dystrophin-deficient mouse model of Duchenne muscular dystrophy. Treatment of these mice with TGF-β-neutralizing antibody or losartan improved muscle regeneration after injury, and long-term treatment with losartan attenuated disease progression. *EN*