MDM2 variant in tumorigenesis

MDM2 is a well-known negative regulator of the p53 tumor-suppressor pathway. Arnold Levine and colleagues (*Cell* 119, 591–602; 2004) now show that a common functional variant in the *MDM2* promoter is associated with accelerated tumor formation in humans. The variant allele, present at a frequency of ~30% in the study population, produces elevated levels of MDM2, resulting in an attenuated p53 DNA-damage response. Levine and colleagues examined 88 individuals from families with Li-Fraumeni syndrome and germline mutations in *TP53* to determine whether the presence of the *MDM2* variant allele had any effect on tumor occurrence or age of onset. They found that individuals carrying the variant allele developed tumors at a significantly earlier age and showed a higher incidence of multiple, subsequent tumors. They also examined several sporadic cases of soft tissue sarcoma and again found a significant correlation between the presence of the variant *MDM2* allele and an earlier age of tumor onset. These findings implicate this common *MDM2* promoter variant as a key modulator of the p53 pathway and an important risk factor for cancer in humans. ***KV***

Worn down by stress?

Elissa Epel and colleagues (*Proc. Natl. Acad. Sci. USA* **101**, 17312–17315; 2004) found that mothers caring for a chronically ill child had telomeres as short as those of mothers a decade older with a healthy child. The lengths of the telomeres and caregiving period were negatively correlated. Caregiving is stressful; this was measured both in a questionnaire reporting subjective experience and by the ratio of objective markers of oxidative stress (F2-isoprostanes) in urine to vitamin E (antioxidant defense) in peripheral blood mononuclear cells. Telomere length was negatively correlated with perceived stress in both groups tested, making it unlikely that there was an underlying biological difference between mothers of healthy and chronically ill children, although to judge by the r^2 values of these correlations, neither stress nor time spent caregiving explains even a fifth of the variance in telomere length. But it is notable that across the sample, the quartile reporting the highest perceived stress had about half the telomerase activity of the quartile reporting the lowest stress. Although it is conceivable that longer telomeres buffer against the effects of stress, the authors argue that they can rule out the unlikely idea that telomere length determines the years spent caring for a sick child, leaving an unexplained correlation or a causal effect of stress on telomere length. *MA*

Salt of the earth

The cytochrome P450 (*CYP*) genes have important roles in the metabolism of a variety of endogenous substrates as well as prescription drugs. One key factor in regulating CYP expression is the *CYP3A5* intron 3 polymorphism, which results in the production of a nonfunctional protein. The frequency of this 'nonexpressor' variant varies between different populations, and E.E. Thompson and colleagues now show that this variation correlates with distance from the equator (*Am. J. Hum. Genet.* **75**, 1059–1069; 2004). The frequency of the nonexpressor allele is at its lowest in sub-Saharan Africa and at its highest in Europe and East Asia. Given that the expressor allele may be associated with increased systolic blood pressure in African Americans, the new data support a previous proposal that this allele confers a selective advantage in equatorial populations where salt and water are scarce (possibly becoming deleterious at high latitudes). Moreover, Thompson *et al.* report that the angiotensinogen M235T variant, which is associated with hypertension, has a similar geographic distribution, suggesting that unlinked variants influencing salt homeostasis are the targets of a shared selective pressure. *AP*

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

Ancient population genetics

Diverse clades of bison, sharing a most recent common ancestor ~136,000 years ago (~136 kya), migrated and mated across an ice-free refugium in the Pleistocene land of Beringia, comprising northeastern Asia, northwestern North America and the surmised land bridge between them. Beth Shapiro and colleagues (*Science* **306**, 1561–1565; 2004) sequenced a 685-bp region of mitochondrial replication origin from 442 of these fossil bison and used radiocarbon dates ranging over the last 60,000 years to calibrate the within-species nucleotide substitution rate and phylogenetic analysis to estimate an evolutionary rate similar to the fossil-calibrated rates for cattle. North American bison migrated from the Beringian population between 130 and 75 kya, with gene flow persisting until they were separated by the Canadian glacial ice sheet 25–13 kya. This conclusion replaces a previous hypothesis that the North American population migrated south after the last ice age. Coalescent theory best supported a demographic model in which the population rose to a peak ~37 kya and subsequently declined. Thus, although human depredation was responsible for the severe population bottleneck in the North American population in the last bicentennium, it seems that humans, arriving in Alaska ~12 kya, were too late to witness the main rise and fall of the eastern Beringian population. Eastern Beringian bison populations hung on until a few hundred years ago before becoming extinct. *MA*

Exon skipping to the rescue

There are two different forms of muscular dystrophy caused by mutations in the gene encoding dystrophin (*DMD*). The more severe of these, Duchenne muscular dystrophy, is caused by mutations that interrupt the translational frame, resulting in complete loss of function. Internal deletions that do not disrupt the reading frame result in partially functional protein and cause milder Becker muscular dystrophy. This difference in severity suggests that partially functional dystrophin may have therapeutic potential. Olivier Danos and colleagues (*Science* 306, 1796–1799; 2004) used a new combination of gene therapy techniques to rescue dystrophic muscle in the *mdx* mouse, which carries a frame-disrupting nonsense mutation in *Dmd*. They used antisense oligonucleotides, commonly used to inhibit gene expression by inducing degradation of double-stranded RNA, to induce specific skipping of the mutation-carrying exon. This resulted in the expression of dystrophin proteins that were shortened but still capable of functional rescue. To enhance the activity of the antisense sequences, they linked them to the U7 small nuclear RNA to promote inclusion into mRNA-processing machinery. To achieve stable, long-term expression, they used adeno-associated virus–based gene transfer. The end result of these engineering efforts was sustained production of dystrophin *in vivo*, detected up to 13 weeks after treatment. The treated muscles had essentially normal histology and contractile and mechanical properties. It is estimated that 50–75% of individuals with Duchenne muscular dystrophy could benefit from exon-skipping therapy. ***EN***