Stem cell rescue from afar

It is hoped that stem cells will be useful in therapy of genetic disease by differentiating to replace diseased tissue. A recent study suggests that stem cells may also restore normal development. Id proteins regulate differentiation in multiple tissue lineages by antagonizing basic helix-loop-helix transcription factors. Their functions are partially redundant but embryonic lethality results from the targeted homozygous deletion of any two Id genes. These mutant embryonic mice die mid-gestation and are small, with severe cardiac defects. Robert Benezra and colleagues (*Science* 306, 247–252; 2004) injected LacZ-marked Rosa26 embryonic stem (ES) cells into affected blastocysts, which rescued their embryonic viability. They observed incorporation of small clusters of ES-derived cells into the heart. The rescue depends on Id function, as ablation of Id by short interfering RNA before ES-cell incorporation blocked rescue. Partial rescue was achieved by injecting the ES cells into the peritoneum of the mother before conception. The fact that ES-cell incorporation is not required implicates long-range signals in the rescue mechanism. The authors conclude that insulin-like growth factor 1 and local WNT5a account for the restoration of the cardiac phenotype. ***MA***

Evolution of heart disease

A functional variant in the promoter of *MMP3*, encoding the matrix metalloproteinase stromelysin, has been convincingly associated with risk of coronary artery disease. Matthew Rockman and colleagues now show that this variant has been a hot spot for mutation in nonhuman primates and has been under recent positive selection in Europeans but not other human populations (*Curr. Biol.* **14**, 1531–1539; 2004). The variant in question is a poly-T tract, with either five or six Ts at position –1,608 upstream of the start site of transcription. Rockman *et al.* show that in nonhuman primates this region has been the target of insertion or deletion events at a rate 70 times higher than that of the remainder of the *MMP3 cis*-regulatory region. In European populations, but not in populations in Africa, China or New Guinea, the 5T variant seems to have undergone a partial selective sweep. The most recent common ancestor carrying the European 5T allele lived ~24,000 years ago. The 5T allele drives higher expression of *MMP3*, and the relative risk of heart disease associated with it means that, in the British population, annual mortality owing to heart disease may have been reduced by more than 50,000. *AP*

Too much calcium

Timothy syndrome is a rare disorder whose phenotypic manifestations include multiple developmental abnormalities, heart arrhythmias, cognitive deficits and autism. Igor Splawski and colleagues (*Cell* **119**, 19–31; 2004) now show that Timothy syndrome is caused by a recurrent, gain-of-function mutation in the gene encoding the cardiac L-type calcium channel, $Ca_v1.2$. Notably, the authors found the identical G406R mutation in each of the affected individuals they examined (11 sporadic cases whose mutations arose *de novo* and 2 affected siblings whose mother was mosaic for the mutation). Using whole-cell patch-clamp studies, they showed that this mutation impairs voltage-dependent inactivation of the channel, resulting in prolonged inward calcium currents. Based on these observations, the authors propose that altered calcium influx, coupled with the broad tissue distribution of $Ca_v1.2$, underlies the diverse spectrum of phenotypes associated with the syndrome. In case of cardiac tissue, the G406R mutation is predicted to result in prolonged action potentials in cardiomyocytes, consistent with the high incidence of lethal arrhythmias seen in carriers of the mutation. The study also suggests that there is a potentially important link between calcium homeostasis and autism, which opens up new avenues for exploring the etiology of this poorly understood class of disorders. *KV*

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

Size matters

In *Saccharomyces cerevisiae*, cells must reach a certain size, have sufficient nutrients and attain a minimum translation rate before they can commit to the cell cycle at 'Start', the point in G1 phase after which they are committed to divide. Nutrient availability shifts the size threshold: cells are large in rich media and small in poor media. Systematic studies in yeast deletion strains have identified many cell-size genes that are potential Start regulators; many of these genes are implicated in ribosome biogenesis. Both Mike Tyers and colleagues (*Genes Dev.* advance online publication 1 October 2004; doi:10.1101/gad.1228804) and Erin O'Shea and colleagues (*Proc. Natl. Acad. Sci. USA* **101**, 14315–14322; 2004) identify the transcription factor Sfp1 as an important mediator of nutrient state, cell-size control and expression of ribosomal proteins. Sfp1 is localized to the nucleus during optimal growth conditions, where it promotes expression of ribosomal proteins; during poor nutrient conditions, Sfp1 leaves the nucleus and expression of ribosomal proteins is downregulated. Yeast cells lacking Sfp1 do not properly downregulate expression of ribosomal proteins or reduce in size in poor nutrient conditions or during stress. The authors propose a model of nutrient-responsive cell-size control that is communicated in part by nuclear localization of Spf1 and ribosome production rate. *EN*

Out of Africa

The most prevalent strain of malaria-causing *Plasmodium* in many parts of the world is not the well characterized *Plasmodium falciparum*, but rather its less virulent and often neglected relative, *Plasmodium vivax*. Now *P. vivax* receives attention in a study of its genetic variability, reported by Francois Renaud and colleagues (*Proc. Natl. Acad. Sci. USA* 101, 14455–14460; 2004). Examining 13 microsatellite loci in *P. vivax* samples from eight locations in Asia, Africa, South America and New Guinea, the authors found low levels of variation, with nine loci monomorphic. In comparison, related *Plasmodium* species were polymorphic at many of these loci, suggesting that there is no evolutionary conservation at these sites. The authors speculate that this lack of variation may reflect selective sweeps or population bottlenecks in the recent evolutionary history of the species, and that global expansion of *P. vivax* as a human parasite from Africa occurred less than 10,000 years ago. The completion of the genome sequence of *P. vivax*, currently underway at The Institute for Genome Research, should help resolve these issues of genetic variation, particularly in comparison with *P. falciparum*, whose genome has already been sequenced. ***OB***