GENE THERAPY

Heartening news

Although bone marrow-derived mesenchymal stem cells (MSCs) have been shown to develop into cardiac muscle *in vivo*, their potential as a treatment for cardiac disease is limited, in part, by their poor viability after transplantation.

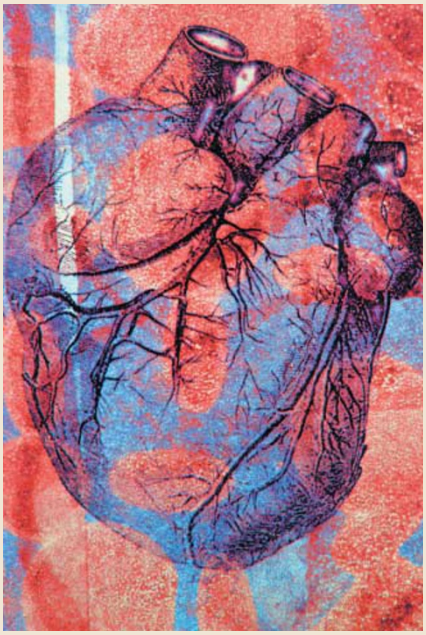
Victor Dzau and colleagues proposed that by engineering MSCs to overexpress Akt — a serine threonine kinase that is necessary for cell survival — they would be more resistant to cell death and so enhance cardiac repair when transplanted into an ischaemic rat heart.

To genetically modify purified rat MSCs, the authors transduced them with retrovirus that carried the mouse *Akt1* cDNA in a stem-cell virus vector. The significant increase in the total Akt signal showed that *Akt1* was successfully incorporated and expressed. Akt activity in these transgenic MCSs (Akt-MSCs) was greater than in controls, and the activity increased further in response to hypoxia. This increased activity coincided with an 80% decrease in the apoptosis of Akt-MCSs *in vitro* and *in vivo*.

Next, Dzau and co-workers injected Akt-MSCs into the heart of adult female rats, 60 minutes after heart attack. Not only did they find that the MSCs migrated to the injured site and developed into cardiac myocyte-like cells that formed connections with existing cardiac myocytes, but also the volume of the affected area in these rats was dramatically reduced, the cardiac function was normalized and cardiac remodelling was prevented. Interestingly, these cellular responses were not seen when Akt-MCSs were transplanted into uninjured normal myocardium, and, encouragingly, the authors were only able to induce the Akt-MSCs to develop into cardiac myocyte-like cells.

Questions still remain about the mechanism by which MSCs develop into cardiac myocyte-like cells — by fusion with existing native cells or by differentiation — and research is needed to define exactly how MSCs exert their therapeutic effect. Nonetheless, the authors believe that this approach is the way forward for cardiac repair and regeneration: "This novel, cell-based, gene-therapy approach has the potential … to make cell-based therapy an effective treatment for human cardiac disease".

Natalie Wilson



References and links

ORIGINAL RESEARCH PAPER Mangi, A. A. *et al.* Mesenchymal stem cells modified with Akt prevent remodeling and restore performance in infarcted hearts. *Nature Med.* **9**, 1195–1201 (2003).

WEB SITE

Victor J. Dzau's laboratory: http://bwheart.partners.org/content/ourresearch/cardiosystemandgene.htm

GENE EXPRESSION

Grand masters of diversity

Phenotypic diversity is crucial for many biological processes, from antibody production to the evolution of species. Possibly the best-known source of such variation is the modification through mutation of many different genes; however, Resnick and Inga now show that individual 'master genes' could also have the potential to generate enormous amounts of genetic-based phenotypic diversity.

To test this theory, the authors investigated human and murine *p53*, the product of which is a transcription factor that controls the expression of more than 50 downstream genes through direct binding to response elements (REs). These target genes are involved in a wide range of processes, including apoptosis, growth arrest, DNA repair and checkpoint responses.

The authors compared the *in vivo* transactivation capacity of wild type and mutant *p53* using an isogenic yeast-based system that measures the activity of target REs upstream of the colour-marker reporter gene *ADE2*. Varying the levels of *p53* expression allowed Resnick and Inga to identify mutants with altered binding affinities through changes in colony colour, which indicated differences in the patterns of target-gene activation and transcription.

The partial-function mutants were found to differ greatly in their ability to induce transcription from the target REs. This confirms that single amino-acid changes in a sequence-specific transcription factor can act as a potential source of rapid phenotypic diversification.

On the basis of their results, the authors propose a master gene hypothesis and use a piano analogy to explain their model. The master gene (the hand) is a single transcriptional activator or repressor that controls the expression of many target genes (the keys). Null mutations correspond to non-functional hands, whereas partial mutants lead to a range of different effects. For example, new notes are struck if different but related REs are recognized, and the intensity of individual notes can vary according to different levels of transactivation. Such changes could lead to a vast array of potential outcomes, which correspond to different biological responses.

Resnick and Inga have established that mutations in a single master gene can lead to a range of simultaneous changes in both the selection and the extent of transcriptional modulation at individual targets. Moreover, this process creates phenotypic diversity without the constraints of altering protein–protein interactions and thereby provides opportunities for accelerated evolutionary change.

Victoria Kitchener

References and links

ORIGINAL RESEARCH PAPER Resnick, M. A. & Inga, A. Functional mutants of the sequence-specific transcription factor p53 and implications for master genes of diversity. *Proc. Natl Acad. Sci. USA* **100**, 9934–9939 (2003)

WEB SITE

IARC TP53 Mutation Database: http://www.iarc.fr/p53/Index.html