STEM CELLS

Boosting myocardial repair

Stem-cell-based therapy is a promising approach for restoring cardiac function following myocardial infarction and heart failure, with initial trials supporting its feasibility, although efficacy has been limited. Understanding the factors that influence the differentiation of stem cells into desired cardiac cell types is a key challenge to fulfilling the potential of this approach. Schneider and colleagues now report sulphonyl-hydrazone (Shz) small molecules that are capable of inducing mRNA and protein expression involved in cardiac fate in stem cells. They also show that stem cells treated in this way can enhance myocardial repair in rats.

To identify molecules capable of promoting the cardiac fate of pluripotent cells, the authors performed a cell-based screen of ~147,000 small molecules to identify chemical activators of *Nkx2-5*, one of the earliest lineage-restricted genes to be expressed in cardiovascular progenitor cells. Approximately 1,600 hits were clustered into ten chemically distinct families using chemoinformatics, and one of the most promising lead families, the Shz small molecules, was selected for further investigation.

Initial studies of the Shz small molecules showed that they activated only a limited set of cardiac reporter genes, and could not activate the neuronal gene programme in stem cells, excluding at least one alternative fate. Furthermore, the Shz small molecules were shown to activate several early markers of cardiac progenitor cells in pluripotent mouse stem cells. These include myocardin, a serum-response factor co-activator; the mesodermal marker brachyury-T, which is upstream of both *Nkx2.5* and myocardin; and sarcomeric α-tropomyosin, a highly specific protein marker of striated muscle cells. Functional and biochemical experiments demonstrated that Shz-mediated cardiac fate is distinct from key cardiogenic signalling circuits including BMP2, FGF2 and Wnt.

Extending their findings to human stem cells, the authors studied the effects of Shz small molecules on cultured human granulocyte colony-stimulating factor (G–CSF)-stimulated peripheral blood mononuclear cells, and found that expression of cardiac marker mRNAs and proteins were increased. Next, they tested Shz-enhanced stem cells on the cryoinjured rat heart and demonstrated a significant improvement in cardiac function by day 7, which returned to normal by day 21. By contrast, untreated rats did not regain their pre-injury function.

Overall, these results indicate that the Shz class of compounds can enhance the cardioregenerative potential of adult stem cells, as well as providing tools to further understand pathways underlying cardiac cell-fate decisions.

Bethan Hughes

ORIGINAL RESEARCH PAPER Sadek, H. *et al.* Cardiogenic small molecules that enhance myocardial repair by stem cells. *Proc. Natl Acad. Sci.* **105**, 6063–6068 (2008)