solution that is solidified by ultraviolet-light-initiated polymerization — a process that stabilizes the assembled construct. Although not demonstrated, the method should also be able to control the assembly of components that provide different stiffnesses, biochemical cues or other biologically relevant features. Such generality is important for tissue-engineering applications.

Although tissues are inherently 3D, most microgel-assembly methods have been limited to manipulation in two dimensions. By contrast, the authors demonstrate that they can levitate many microgel components, and simultaneously drive the assembly of truly 3D structures of up to a few millimetres across by arranging external magnets in appropriate orientations. Massively parallel assembly in three dimensions will be needed to achieve the formation of larger tissue constructs.

In principle, the new method addresses several major challenges in tissue engineering. However, practical applications will be realized only when guided assembly of constructs can occur on the tissue scale. Incorporating molecular recognition between hydrogel subunits[9], to automate the stabilization of 3D assemblies, might help to achieve this. Moreover, it will probably be necessary to pattern multiple cell types and to introduce a means of perfusing thicker constructs to provide oxygen and nutrients for long-term cell viability.

Nevertheless, Tasoglu and colleagues' method is likely to stimulate the growing interest in guided micro-assembly. The use of external driving forces, such as magnetism, allows previously inaccessible levels of parallel assembly and might therefore propel this bottom-up approach to clinical use. Before then, however, the method will probably have a more direct impact on the formation of smaller assemblies, such as lab-on-a-chip devices for diagnostic applications and organized co-culture systems for studies of cell–cell interactions. ■

Christopher B. Rodell *and* **Jason A. Burdick** *are in the Department of Bioengineering, School of Engineering and Applied Science, University of Pennsylvania, Philadelphia 19104, USA.*
e-mail: burdick2@seas.upenn.edu

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CARDIAC BIOLOGY

Cell plasticity helps hearts to repair

Fibroblast cells are known as key players in the repair of damaged heart structures. New findings show that injury also induces fibroblasts to become endothelial cells, helping to mend damaged blood vessels. SEE ARTICLE P.585

TORU MIYAKE & RAGHU KALLURI

Heart attacks caused by a blockage in the coronary artery induce severe injury to cardiac muscle cells, leading to cell dysfunction and death. The damage elicits repair and regenerative responses that provoke the removal of dying cells and cell debris, recruit immune cells and initiate the formation of new blood vessels to recover blood supply. Fibroblast cells play a central part in this repair response. In this issue, Ubil *et al.*[1] (page 585) describe how the plasticity of cardiac fibroblasts contributes to this process, by showing that fibroblasts can, in response to the activity of the transcription factor p53, convert into the endothelial cells that line the interior surface of blood vessels.

The heart consists of myocytes (muscle cells) and non-myocytes, which include cardiac fibroblasts and endothelial cells. The fibroblasts produce growth factors and extracellular matrix (ECM) proteins to maintain proper cardiac architecture, contraction and function[2]. They also interact with endothelial cells and myocytes to aid angiogenesis (blood-vessel formation) and maintain physiological homeostasis[3]. Following heart damage, cardiac fibroblasts are activated to produce ECM proteins and soluble factors to compensate for structural defects, contain the spread of damage, reinforce cardiac stiffness and prevent cardiac rupture. These activities, collectively referred to as fibrosis, aid in remodelling the heart musculature. Controlled fibrosis is crucial for restoring cardiac function after injury. However, excessive fibrosis is considered a pathological process that can lead to adverse effects, including reduced cardiac stiffness (diastolic dysfunction) and irregular electrical connectivity (arrhythmia).

Although endothelial cells in blood vessels are typically thought of as terminally differentiated cells, they can take on the characteristics of mesenchymal cells[4,5], which are generally mobile cells surrounded by interstitial ECM proteins. During this endothelial-to-mesenchymal transition (EndMT), the endothelial cells lose the tight junctions that hold neighbouring cells together, and gain the ability to move, produce ECM proteins and contribute to excessive fibrosis, while also depleting functional capillaries and the endocardium tissue layer. EndMT is induced in cardiac endothelial cells by signalling pathways that depend on the growth factor TGF-β1 and that can be reversed by the activity of the protein BMP7 (ref. 4).

Now, Ubil and colleagues show that, following acute cardiac injury, fibroblasts (which belong to the mesenchymal cell lineage) can undergo a reverse conversion — from mesenchymal to endothelial cells (MEndT) — and become components of blood vessels (Fig. 1). To study this plasticity, they used mice in which cells that gain or lose expression of cell-type-specific markers can be tracked by fluorescence, a technique called genetic fate mapping.

The authors induced ischaemia-reperfusion injury by blocking the coronary artery and then restoring blood flow in the hearts of these mice. Three days later, they found that 35% of fibroblasts in the injury zone expressed the endothelial marker VECAD and were located in the interior of the vessel. Of these fibroblast-derived endothelial cells, 41% took up acetylated low-density lipoprotein, which is suggestive of endothelial-cell functionality. Most of the cells undergoing this transition expressed the fibroblast markers Col1α2 or FSP1, whereas very few expressed αSMA, a marker shared by a subset of cardiac fibroblasts (myofibroblasts) and the mesenchymal cells generated through EndMT (Fig. 1). This finding highlights a functional heterogeneity of recruited fibroblasts in injured cardiac tissue with respect to their plasticity. Understanding this heterogeneity will require future studies using fate mapping of myofibroblasts[6].

Ubil and co-workers also found that the fibroblast-derived endothelial cells in the mice express increased levels of p53, a transcription factor known for its multiple functions, including regulation of the cell cycle, apoptotic cell death and DNA repair. To investigate the involvement of the p53 signalling pathway

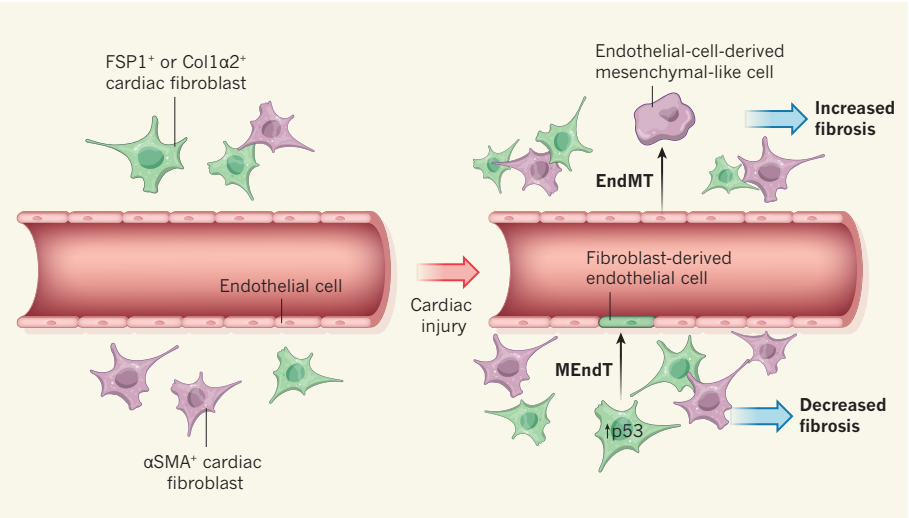

Figure 1 | Cardiac-cell conversions. The heart's response to injury involves the proliferation and activation of cardiac fibroblasts (a type of mesenchymal cell). Although this fibrosis is essential for repair, an excessive response can lead to cardiac dysfunction, and evidence is building that this balance is regulated by transitions between cell types. Previous studies[4,5] have shown that endothelial cells lining blood vessels can convert to mesenchymal-like cells in a process called the endothelial-to-mesenchymal transition (EndMT). These cells, which express αSMA, a marker shared by a subset of cardiac fibroblasts (myofibroblasts), contribute to increased fibrosis. Now, Ubil *et al.*[1] show that some cardiac fibroblasts (distinguished by the markers FSP1 or Col1α2) can undergo a reverse, mesenchymal-to-endothelial transition (MEndT). This conversion is induced by activity of the transcription factor p53, and leads to reduced fibrosis and increased blood-vessel formation.

in the MEndT program, the authors studied cardiac fibroblasts cultured *in vitro* under serum deprivation — a stress condition that induces upregulation of p53. The cells formed tubular structures reminiscent of endothelial-cell architecture and expressed endothelial markers, including VECAD and transcription factors such as HoxA9 and HoxD3. However, the fibroblasts did not generate these tubules without serum deprivation, even when p53 was artificially overexpressed, suggesting that p53 expression alone is not sufficient to induce MEndT and that other signalling pathways are involved in launching this program.

The authors went on to show that treating mice with the small molecule RITA, which enhances p53 signalling, for three days after cardiac injury increased the number of fibroblast-derived endothelial cells. The treatment also accelerated angiogenesis and decreased cardiac fibrosis, leading to an improvement in cardiac function. These *in vitro* and *in vivo* findings suggest that p53 expression in fibroblast-derived endothelial cells has a key role in the recovery of cardiac function following injury.

Administration of other p53-activator molecules has previously been shown to impair angiogenesis, increase apoptotic cell death and cause dysfunctional muscle contraction in a mouse model of a condition called cardiac hypertrophy[7]. Conversely, Ubil *et al.* show no increase in myocyte p53 expression or the number of apoptotic cells after RITA treatment compared with control mice. These contrasting results could be explained by the different cardiac-injury models and drugs used, which will need to be considered in investigations of the potential clinical application of p53-inducing drugs for targeting cardiac fibrosis.

Nevertheless, Ubil and colleagues' study provides insight into the cardiac-repair process and highlights potential new therapeutic strategies. It also adds to the debate of whether the term 'terminally differentiated' in adult tissue might be too confining when cellular plasticity is rampant and seemingly functional in situations of disease or injury, just as in embryonic development. ■

Toru Miyake *and* **Raghu Kalluri** *are in the Department of Cancer Biology, Metastasis Research Center, University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA.* **R.K.** *is also in the Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, and in the Department of Bioengineering, Rice University, Houston.*
e-mail: rkalluri@mdanderson.org

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IMMUNOLOGY

Starve a fever, feed the microbiota

A study finds that the cells lining the gut are modified in response to systemic infection, increasing the host's tolerance to infection in a manner that is dependent on the microorganisms that inhabit the gut. SEE LETTER P.638

SETH RAKOFF-NAHOUM &
LAURIE E. COMSTOCK

Mammals have a mutualistic relationship with the consortium of microorganisms that inhabit their intestines, collectively known as the gut microbiota. The microbiota profits from an environment that is rich in dietary and host-derived nutrients, and provides its host with numerous benefits, ranging from immune and digestive capabilities to resistance to pathogen colonization. On page 638 of this issue, Pickard *et al.*[1] describe another facet of this mutualism. They show that in a model of systemic infection, the host modifies the surface molecules of the epithelial cells lining its intestine, which increases host fitness in a microbiota-dependent manner.

The authors began their study with the question of how the beneficial microbiota is maintained during the period of diminished food consumption — known as anorexia — associated with systemic infection in the host. Host-derived sugars such as fucose are present on the intestinal epithelium and serve as an alternative to dietary food sources for the gut microbiota. Pickard and colleagues therefore evaluated fucosylation (the addition of fucose to molecules that are then secreted to the cell surface) of the small intestine following systemic administration of bacterial-derived molecules, such as lipopolysaccharide (LPS), which are recognized by Toll-like receptor proteins (TLRs). This administration mimics a bacterial infection and induces symptoms of sickness, including anorexia. The researchers