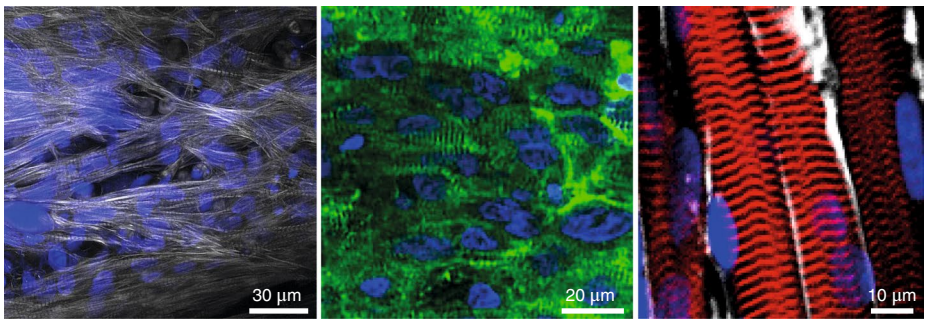
Tissue-engineered disease models

Research on disease mechanisms will increasingly be supported by progressively more sophisticated engineered tissues serving as in vitro models of human disease.

Small-animal models are a cornerstone of biomedical research. Yet their limitations become apparent when the research is geared towards detecting, alleviating or understanding human disease. Genetic, phenotypic and physiological differences between animals and humans can often be large enough that biomedical results based on animal models are insufficiently representative of the disease in humans. And if the condition is highly dependent on the genetic or epigenetic make-up of the individual, or on their immune status or characteristics of their microbiome, even genetically engineered animal models can fail to recapitulate critical biological aspects of the patient's diseased cells and their microenvironment, their diseased tissue or organs, or their physiology.

Notwithstanding the shortcomings, for the study of most diseases and for the testing of many treatments, there are no alternatives to the use of animal models of disease. Human tissue explants can be scarce and may not be viable for long-term experimentation, and cells on tissue-culture plastic, softer flat substrates or suspended in culture medium are often too simplistic. Organoids can more faithfully recapitulate the biology of specific tissue and can be used for longer periods, yet they lack proper vasculature and immune cells; and as with animal models, they do not offer the simplicity and controllability of minimalist in vitro systems, such as transwell inserts.

Yet it is possible to engineer increasingly sophisticated models of human tissues and organs that permit the study of the effects of specific molecular factors, cell types (such as parenchymal, vascular and immune cells) and microphysiological configurations (such as geometry, and the presence of dynamic flow or mechanical forces) on functional responses. Such engineered tissue models and microphysiological systems incorporating them (such as tissues on chips) can complement animal models because the engineered models offer a higher degree of controllability, repeatability and reproducibility. Although, compared to organoids and ex vivo tissues, engineered in vitro tissues can be too simplistic, they can benefit from the increased modularity, flexibility and scale-up advantages of microfabrication methods.



Credit: Engineered cardiac tissues showing sarcomere striation patterns. Images reproduced from the Articles by Kevin Kit Parker and colleagues (left), Kevin Healy and colleagues (middle), and Nenad Bursac and colleagues (right), Springer Nature Ltd

In this issue, four Articles provide examples of such tissue-engineered models. Kevin Kit Parker and colleagues made scale models of the human left heart ventricle (250 times smaller by volume) by pull-spinning nanofibres made of polycaprolactone and gelatin onto a rotating ellipsoidal collector and then seeding the casted nanofibrous scaffold with cardiomyocytes derived from human induced pluripotent stem cells. Although the ventricle tissue models are avascular and much smaller than the human ventricle, they reproduced the architecture and functional output (in particular, contractile work and the effect of drugs on it) of real human ventricles, owing to the recapitulation of the fibrillar and anisotropic characteristics of the myocardial extracellular matrix. Also, the model ventricles can be interrogated using catheters, and used to study arrhythmia caused by structural defects (in the case of the model vesicles, punched holes).

Kevin Healy and co-authors also developed cardiac-tissue models made of cardiomyocytes derived from human induced pluripotent stem cells and filamentous matrices. They used the engineered tissues to study whether external mechanical stresses regulate the sensitivity of cardiomyocytes to the loss of myosin-binding protein C (MYBPC3), caused by a genetic mutation in the *MYBPC3* gene (which can induce hypertrophic cardiomyopathy and dilated cardiomyopathy). The engineered tissues, which recapitulated the synergistic effects of the genetic defect and environmental stresses (via the tissue's mechanical resistance to contraction), allowed the authors to conclude that the genetic deficiency and external stresses synergistically lead to contractile deficits characteristic of the cardiomyopathies.

In contrast with heart tissue, adult skeletal muscle can self-repair after minor injury; yet such regenerative capacity cannot overcome severe damage, for example resulting from major muscle loss. By making cylindrically shaped tissues made of adult rat myogenic cells in a hydrogel of fibrinogen and matrigel, Nenad Bursac and colleagues show that the incorporation of macrophages derived from rat bone marrow or human blood into the tissues boosted structural and functional self-repair after tissue injury induced by exposure to cardiotoxin (a snake-venom polypeptide toxin), both in culture and when the tissues where implanted in mice through a dorsal-skinfold window chamber.

Implantable, engineered tissues can also address a few limitations of mouse models in the study of cancer metastasis in humans, such as the inability to recapitulate the role of the immune system and to manipulate properties of the pre-metastatic niche, as well as impracticalities in the detection of metastatic recurrence, which is driven by dormant disseminated tumour cells. In this respect, Jungwoo Lee and collaborators studied how disseminated tumour cells that are dormant can become active — the main cause of metastatic relapse and of mortality for most cancers. The team created a humanized tissue-engineered model

of a pre-metastatic niche in mice, via the subdermal implantation of microfabricated porous hydrogel scaffolds coated with collagen and pre-seeded with human bone-marrow stromal cells. The implanted biomaterial recruited human circulating tumour cells released from an orthotopic tumour xenograft. Serial transplantation of these niches into syngeneic naive mice enabled the study of the kinetics of metastatic relapse.

As exemplified by these four advances, it is the relative biological simplicity and controllability of tissue-engineered models that makes it possible, or easier, to unveil individual and combined contributions of the genetics, microstructure, architecture, biological make-up and mechanical properties of the tissue microenvironment to human disease. The incorporation of primary cells isolated from patients or of cells differentiated from patient-specific human induced pluripotent stem cells should help accelerate the development of personalized medicine, as engineered tissue models can in principle be used for testing the response of patients to individualized treatments, at least when the key biological aspects to be modelled involve specific tissues and tissue architectures rather than complex interactions between different tissues and organs. Yet at present it is still largely unclear how similar engineered tissues and native tissues are, and whether the former can faithfully and robustly recapitulate the hallmarks of most human diseases. Although for most preclinical studies, small animals need to stick around, further scientific and technological developments should increasingly replace, reduce or refine their use in research. ❐

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