Bio Focus

Taking heart in gelatin for tissue engineering

The use of animals for drug testing remains a critical component of biomedical progress. However, materials advances might eventually render such tests obsolete. Apart from complex bioethical issues, animal testing suffers from a number of major scientific drawbacks, including slow experimental cycle times and species-dependent response variations; for example, observations in mice do not necessarily predict corresponding effects in humans. As an exciting alternative to animal models, Kit Parker and colleagues at Harvard University envision one day growing small-scale samples of relevant human tissues for high-throughput drug response assays, bypassing the need for live animals. Specifically, Parker's team has focused on culturing cardiac muscle cells toward the development of "Heart on a Chip" technologies.

A few years ago, the team demonstrated biocomposite materials dubbed "muscular thin films" (MTFs) that were comprised of cardiac muscle tissue grown in thin layers on the surfaces of silicone polymer (polydimethylsiloxane, PDMS); the polymer could then be pushed and pulled by voltage-induced cellular muscle contractions. In a contribution in the July issue of *Biomaterials* (DOI: 10.1016/j.biomaterials.2014.03.052; p. 5462), Parker's team demonstrated improved MTF platforms that support healthier heart tissues than previously possible and which permit mechanical probing of important tissue qualities. The key advance involves the exploration of gelatin hydrogels as new substrates for cardiac tissue growth.

Gelatin's advantages over previously used scaffold materials stem from its softness and its surface chemistry. Gelatin's low elastic modulus more closely mimics that of a living heart (10–15 kPa) in comparison to PDMS (which is stiffer). Furthermore, gelatin is mainly composed of collagen, the major constituent of the heart's extracellular matrix. Heart cells thus readily adhere to gelatin *in vitro* without the need for surface treatment, as required for both PDMS and alginate substrates.

The researchers used micropatterning techniques to grow cardiac muscle tissue on the surfaces of gelatin cantilevers. During gelatin hydrogel casting, a PDMS stamp was used to produce arrays of linear trenches, 10 μm × 10 μm in cross section, patterned in relief into the gel's top surface. Such trenches promote anisotropic myocardial growth into aligned structures that mimic native heart tissue. Cantilevers with these micropatterned surfaces are then carved by laser etching through the gel thickness, with cuts made into gelatin regions that are only weakly bound to a supporting glass substrate; the cantilevers are chemically anchored to the glass at their base.

Heart muscle tissue grown on these cantilever surfaces can induce cantilever curling in response to muscle cell contractions (see Figure), induced with an applied voltage. As the extent of cantilever curling is a function of contractile force, the researchers can quantify contractile strength versus electric pacing of the heart tissue.

Cardiac tissues grown on surface-micropatterned gelatin are found to display the same contractility response after 4 and 25 days, whereas PDMS supports culture lifetimes of only 7 days. Furthermore, measurement of oxygen consumption rates showed that cells grown on micropatterned gelatin exhibit a surplus of respiratory capacity versus PDMS-supported cells. Extending the health and function of muscle tissue cultures in this way is an important step toward making *in vitro* systems a viable option for long time-course drug toxicity studies.

The introduced mechanical cantilever assay and associated insights gained for scaffold material design may also be valuable for engineering cardiac tissue *in vitro*. For example, while the majority of experiments conducted in this study utilize cardiac cells taken from adult rats, the researchers also showed that human stem cell-derived cardiac muscle cells can be cultured and assayed in the cantilever MTF format. These human cells were found to be less robust than the rat cells, as might be expected for muscle cell lines derived *in vitro*. However, as techniques for deriving muscle from stem cells improve, a platform is now in place for spring-boarding such cells into Heart-on-a-Chip applications.

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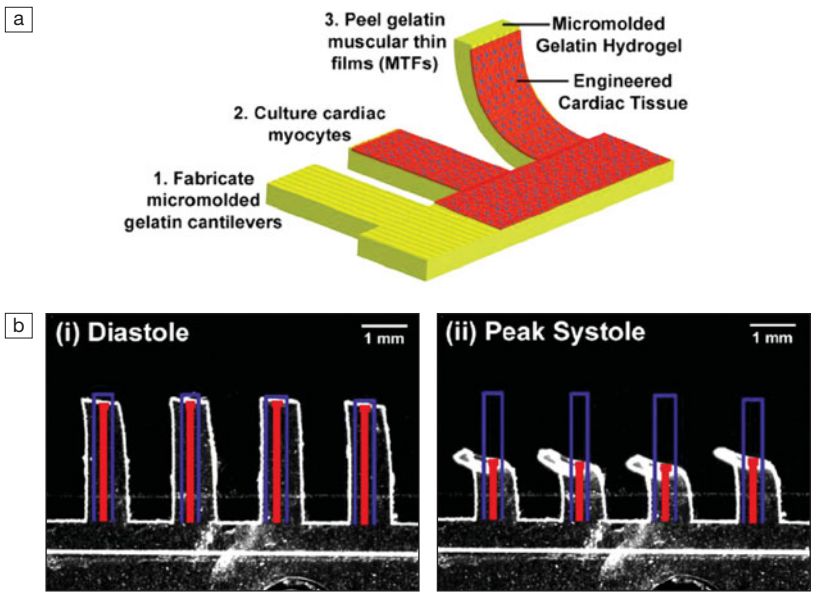

(a) Fabrication of gelatin muscular thin films; (b) Optical micrographs of voltage-paced muscular thin film cantilevers in which the muscle tissue is either in a relaxed ("diastole") or contracted ("systole") state. Reproduced with permission from *Biomaterials* **35** (2014) DOI: 10.1016/j.biomaterials.2014.03.052; p. 5462. © 2014 Elsevier Ltd.

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