New Structured Materials in the Study of the Mechanobiological Processes Related to the Heart Failure

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Cardiovascular diseases (CD) are the number one of death globally. Considering its high prevalence, which will increase the next years, high cost, poor predictions and high hospitalisation rate, it is important to study the mechanisms involved in its development in order to identify new therapeutic targets and non invasive markers.

The heart is a dynamic, mechanically active organ that self-generates contractile forces and stretching strains (1). Preservation of cardiac structure and function depends on a balance between the extracellular matrix and cells. The cardiac extracellular matrix (ECM) provides not only the *biochemica*l environment but also a natural scaffold surrounding and connecting cardiac cells and distributing *mechanical* forces throughout the organ (2). The ECM also provides *topographic* simuli by proteins with micro and nano scale features (3). Thus, the properties of the ECM are essential for the maintenance of the functional myocardium. Alterations in cardiac ECM structure associated with heart failure influence cell-matrix and cell-cell adhesions modifying cell shape and mechanotransduction.

The need to understand the cardiac ECM remodelling mechanisms lead us to create biomimetic scaffolds which emulate the structure, topography, mechanics and chemical composition of ECM. This work presents the development of new strategies for the manufacturing of materials with myocardium properties of stiffness and elastic modulus in physiological and pathological conditions.

In CD of different etiologies, the cardiac homeostasis is disrupted by a non-appropriate myocardium remodelling promoting structural and functional damage, denominated *myocardial fibrosis* (1). Myocardial fibrosis consists on an excessive deposition of collagen fibers and an increase in their cross-linking that affects ECM stiffness. This phenomenon heads us to create materials with the same chemical composition but different stiffness. Methacrylated gelatin (GelMA) hydrogels are a biocompatible and versatile platform which allows us to modulate physical properties by photoinitiated radical photopolymerization in order to resemble the characteristics of native ECM (4) (Fig 1). Different crosslinking degree emulates different ECM conditions.

While the magnitude of elastic modulus can be easily reproduced in artificial polymeric scaffolds by proper selection of monomers and crosslinking degree, control of Poisson ratio or anisotropy of the elastic modulus, present in many biological tissues such as myocardial tissue, is far more complex to replicate and it has been less explored requiring the use of structured materials (5)(6). Here, we propose the manufacturation of auxetic structures by using laser writting (Fig 2).

On the other hand, by pulsed photoembossing we have created biocompatible micropatterned

structures which lead to better cell alignment (Fig 3).

All these technologies approach us to develop new strategies to study the cell responses behind mechanical stimuli.

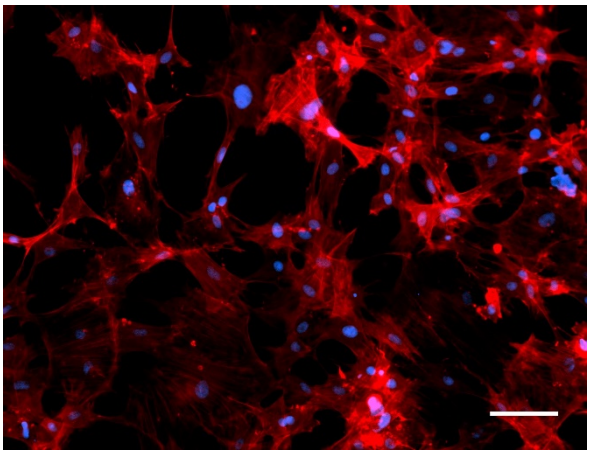

Fig 1. Mesenchymal cells on GelMA surface. Nuclei (blue) and actin (red). Scale bar= 100µm

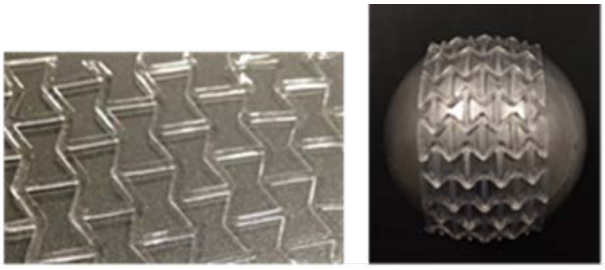

Fig 2. Re-entrant honey comb structure on photopolymerizable hidrogel.

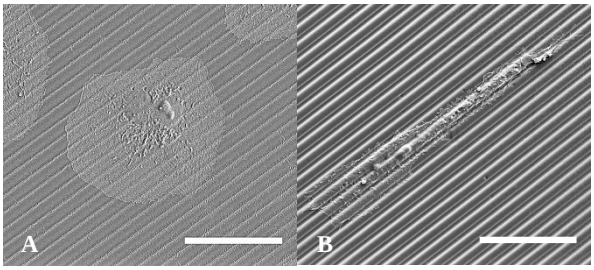

Fig 3. SEM images of cell morphology on photoembossing patterned substrates. A) Kidney epithelial cells cultured on low aspect ratio structures. B) high aspect ratio structures. Scale bars = 30 µm.

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