Large-scale dendrimer-based uneven nanopatterns of RGD towards improved architectural networks in chondrogenesis

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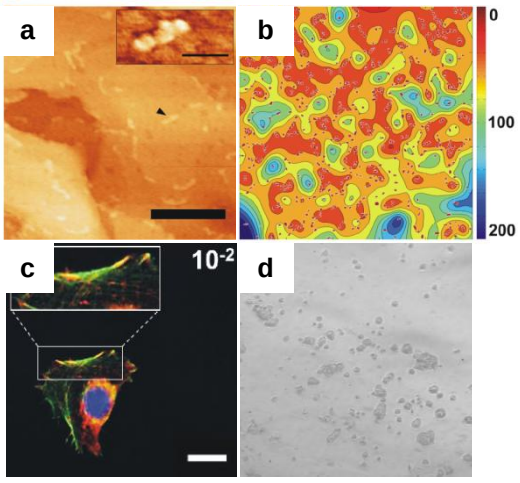
Cartilage damage is the main cause of joint disorders, having a huge impact on an increasingly ageing population. Cartilage inability to spontaneous repair and regenerate has stimulated clinical and experimental work towards optimal cartilage regeneration. Transplantation of mesenchymal stem cells (MSCs), which have a vast proliferative capacity and differentiation potential, has emerged as a promising strategy to treat joint defects. However direct implantation of undifferentiated MSCs without any preconditioning lead to calcification of the implanted cells, fibrogenesis and heterotopic tissue formation in the cartilage.[1]

As in most biological systems showing multi-level organization with cross-level interdependence, extensive cell-cell communication networks are formed during cartilage development. In the initial stages of chondrogenesis MSCs condensation takes place, leading to a marked decrease of the intercellular space, and the occurrence of a large number of cell-to-cell contacts of the gap-junction (GJ) type. Signaling in multi-cellular networks is strongly influenced by the system architecture: in conventional culture systems of chondrogenic differentiation of MSCs, a hyaline-like, zonal-distributed cartilage structure, in which nearly cylindrical cells are aligned and connected side-by-side and end-to-end along the proximal-distal axis of the limb, is not sustained; instead, irregularly shaped cells spread randomly, resulting in randomly distributed cell junctions.

In this sense it is of crucial importance to provide an appropriate cell environment that allows the establishment and maintenance of cell-to-cell interactions during the different stages of MSCs differentiation, and that while still favoring strong cell anchorage, allows the subsequent transplantation and release in the injured area. Taking advantage of a recently developed dendrimer-based large-scale nanopatterning approach,[2] surfaces of poly-L-lactic acid (PLA) nanopatterned with cell adhesive dendrimers, at different initial bulk concentrations, were used as substrates for chondrogenesis. Surface nanopatterning is applied to modulate cell-biomaterial interaction in order to better mimic cartilage architecture.



(a) AFM image (scale bar = 250 nm) of nanopatterned dendrimers. Inset: magnified phase image of one of the nanodomains (scale bar = 50 nm). (b) d_{min} probability contour plot showing regions of high local ligand density. Color scale: d_{min} values in nm. (c) Fluorescent micrograph of a fibroblast after 4.5 h in culture on the nanopatterns. Inset: magnified portion of FAs formed at the cell periphery. Scale bar = 20 µm. (d) Optical microscope image showing early hMSCs cell condensation on nanopatterns (chondrogenesis, day 3).

[1] Cui, J. H., Park, S. R., Park, K., Choi, B. H., Min, B. H. Preconditioning of mesenchymal stem cells with low-intensity ultrasound for cartilage formation in vivo. Tissue Eng. 2007; 13: 351-60.

[2] Lagunas, A., Castaño, A. G., Artés, J. M., Vida, Y., Collado, D., Pérez-Inestrosa, G., Gorostiza, P., Claros, S., Andrades, J. A., Samitier, J. Large-scale dendrimer-based uneven nanopatterns for the study of local RGD density effects on cell adhesion. Nano Research 2014; 7: 399-409.