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Stem cells shape up to their surroundings

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Many scientists aspire to take control over the stem cell differentiation process, so that we can grow organs and implants perfectly matched to each patient in the future. Now research in the *Journal of Tissue Engineering* explains how engineering the topography on which stem cells grow, and the mechanical forces working on them, can be as powerful an agent for change as their chemical environment.

Stem cells respond to the stiffness, chemistry and topography of the environments they find themselves in – and scientists building their understanding of the complex signalling controlling these responses hope to harness this knowledge to take stem cell research further. As well as increasing the potential to guide stem cells to create desired materials for research and clinical applications, using nanoscale topographies could eliminate (or alternatively enhance) steps including those involving feeder layers and synthetic induction supplements currently used in stem cell culture. In addition, tomorrow's increasingly sophisticated prosthetics for regenerative medicine could feature surfaces with varied tissue zones for different purposes, thanks to this improved understanding.

In their article, Laura McNamara of the University of Glasgow, UK, Centre for Cell Engineering, together with colleagues from Columbia University, New York, Nanotechnology Centre for Mechanics in Regenerative Medicine and the Bone and Joint Research Group at the University of Southampton, UK, review the latest developments in the use of nanotopography to direct stem cell differentiation. In particular they look at skeletal (mesenchymal) stem cells.

Evidence is mounting that researchers can both maintain stem cells in the undifferentiated state, and determine the direction of their fate, by precise control of the surface features beneath them. Stem cells have an uncanny ability to detect and respond to nanoscale grooves, pits and ridges, and are particularly sensitive to the spacing and regularity of these features.

Nanotopographical responsiveness has been observed in diverse cell types including fibroblasts, osteoblasts, osteoclasts, endothelial, smooth muscle, epithelial, and epitenon cells. "This is intriguing from a biomaterials perspective," says McNamara, "as it demonstrates that surface features of just a few nanometres can influence how cells will respond to, and form tissue on, materials."

Stem cells detect surface features with a variety of mechanosensors, including integrin-linked focal adhesions. These respond to the mechanical constraints of the surface by inducing signalling cascades, such as the ERK-MAPK pathway. When the cell's rearranging cytoskeleton physically pulls on components of the cell's nucleus, this force works together with chemical signalling. Together these indirect (biochemical signal-mediated) and direct (force-mediated) factors can modulate nuclear components, altering gene expression to direct stem cell responses.

One interesting finding has been that topography can in some cases have the same effect as biochemical differentiation factors. The potential to eliminate the need for the latter opens the door to development of improved clinical prostheses with topographies that can directly modulate stem cell fate. In particular, the authors envisage applications involving engineered topography components for stem cells in regenerative medicine, for instance, in orthopaedics and dental implants. A combination of different topographies could be used to differentially functionalise implants for distinct applications, or demarcate particular "zones" within a single device.

Orthopaedic implants designed with specific regions tailored to integrate with bone and improve the chances of implant fixation might be seamlessly join other areas of the implant programmed to reduce excessive bony ingrowth, for example. Some surfaces with clinical potential include nanostructured titanium and diamond. A growing number of precision nanofabrication techniques are becoming available to help carve out the substrates needed for this research.

Skeletal stem cells have even been shown to grow into non-skeletal cells (known as transdifferentiation) on surfaces with the right groves and ridges – in some studies this has produced neural tissue.

"With the emergence of mechanical stimuli as critical modulators of cellular functionality, nanotopography should prove an excellent tool for development of novel biomaterials capable of promoting desirable cellular behaviour, discouraging unwanted cell responses, and preventing or ameliorating pathological changes," the authors suggest.

More information: Nanotopographical Control of Stem Cell Differentiation by Laura E. McNamara, Rebecca J. McMurray, Manus J. P. Biggs, Fahsai Kantawong, Richard O. C. Oreffo, and Matthew J. Dalby is published in the *Journal of Tissue Engineering*. The article is available free here: www.sage-hindawi.com/journals/jte/2010/120623.html

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