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Shape of tissues influences stem cell growth

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In the field of developmental biology, and now recently in stem cell biology, it has long been thought that small molecules called morphogens control the fate of cells. These morphogens decide when an embryonic stem cell becomes a muscle cell or brain cell or any other type of cell.

New research shows these molecules have other roles as well. Sami Alom Ruiz, then at Hopkins and now at the University of Pennsylvania, and Chris Chen of U. Penn., have shown that morphogens play a role not only in determining cell fate, but also in the response to mechanical stresses such as stretching.

The goal of the work was simple: "To understand how tissue form can lead to differentiation of cells in the appropriate locations," Ruiz said.

"Understanding how differentiation is tied to tissue form will provide a better appreciation of how cells orchestrate morphogenetic processes as well as a roadmap for directing stem cell fates in regenerative therapies."

Using mesenchymal stem cells (MSCs) to study the effects of mechanical forces on stem cell fate, the researchers look at several different geometries to test growth of cells. MSCs are a multipotent stem cell, capable of forming cells involved in the formation of fat, cartilage and bone.

The researchers grew the MSCs in media that help to turn these cells into either adipocytes (fat cells) or osteoclasts (bone cells). They found that when they grew the MSCs on a flat surface so that the cells grew into what is known as a monolayer, or single layer of cells, the MSCs differentiated into both types of cells.

The interesting part is that the adipocytes preferentially grew in the center of the layer, whereas the osteocytes grew around the outside. This shows that cells can undergo cell determination based on the geometry of the structure in which they are growing.

They then asked what effect the structure had on the cell-fate determination. They grew cells on many different shapes, including a rectangle, square, annulus or ring, ellipse and sinusoidal bands. Each time they found that cells in the high stress regions - for instance, at the corner of a square - form osteocytes and those in the low stress regions form adipocytes.

"The concavity of an edge, rather than its presence inside or outside a monolayer, determined the mechanical forces, and therefore the cell type, present at that edge," Ruiz said.

This was proven by plating the cells on a pad that has little micro needles which detect tiny changes in forces. The tension in the cells which directed the MSCs to the osteocyte linege could be removed with these devices.

Feeding the cells a small molecule that blocks cell tension should stop this process, and that is exactly what

was observed. Adding this molecule stopped the MSCs from turning into the osteocytes, which instead became adipocytes.

Other research into cell biology has shown that genes expressed in the two-dimensional cell cultures is not the same as the genes expressed in three dimensions. So, the U. Penn. team created 3D cell structures and looked for the same cell-lineage patterning they had seen in the 2D cell culture.

Even in these 3D blocks of cells, the outside of the box would be osteocytes and the inside of the box would be adipocytes. This mimics what is seen in actually structures in the body. Cells in the body form a hollow bone structure, which is filled with fat cells.

The novel work by this team has enormous implications for the future of stem cell biology research, especially for regenerative medicine. This emerging medical field works on creating tissue-specific cells and structures that can aid in the regeneration of damaged tissues in the body.

This research could help define limits on what structures could actually be made. Also, it illuminates a new role for mechanical forces in cell lineage specification and how it contributes with chemical morphogens to create the tissues of the body. Future work in this research will look more directly at the possibility that geometric abnormalities contribute to diseases.

"[The] most interesting question that remains to be understood is how mechanical force is transduced to the chemical signals that bring about the gene expression changes required for differentiation," Ruiz said.
