ElectroForce® BioDynamic® Instruments Drive Stem Cell Differentiation

The Challenge:

Direct Stem Cell Differentiation in 3D Matrices

Background

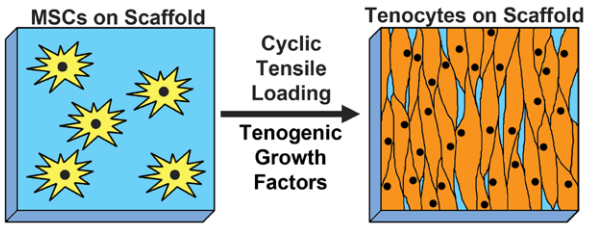
Mesenchymal stem cells (MSCs) are present throughout the body and naturally renew tissues.[1] MSCs have widely been targeted as therapeudic agents for a number of medical ailments because they have two key characteristics:

- Self-renewal
- Multi-lineage differentiation

To take advantage of these properties, researchers seek to expand MSCs in vitro and direct their differentiation into particular cell types. By culturing MSCs in controlled conditions, stem cell fate can be directed with biochemical and mechanical cues such as:

- Soluble factors in the culture media
- Tensile load
- Compressive load
- Torsion
- Shear stress

Cells of each tissue type are exposed to a unique, dynamic combination of these loads, so the correct replication of these biochemical and mechanical factors must be precisely controlled to duplicate physiological conditions.[2] When the native environment of a particular tissue is successfully replicated in vitro, MSCs will differentiate into that tissue's cell type. For example, when a scaffold containing MSCs is subjected to cyclic tension in the presence of particular biochemical factors, the MSCs differentiate into tenocytes.[3]



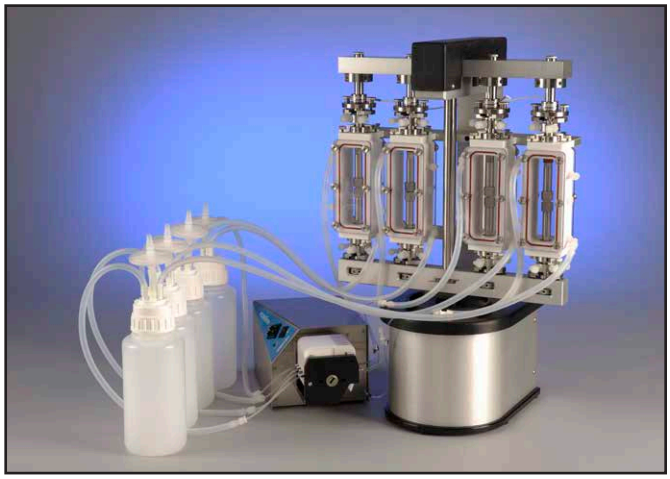
When MSCs are subjected to cyclic tensile loading of the supporting scaffold, they differentiate into tendon cells (tenocytes). This differentiation can be further directed by the addition of tenogenic factors to the culture media.

Control of stem cell fate is facilitated by an in vitro system that is as complex as the physiological environment it is meant to mimic. Bose Corporation ElectroForce® BioDynamic® test instruments offer the versatility, precision, and control required to biomechanically direct stem cell differentiation.

Meeting the Challenge

To apply environmental cues, MSCs are first seeded into a 3D matrix, or scaffold. The MSCs are then stimulated to differentiate into a specific cell-type. The expanded, transformed MSCs can then be delivered to target tissues via direct injection or through implantation of a carrier (scaffold).[1]

One application area for MSC differentiation is in fibrous tissues, such as tendons. Tendons must withstand and transfer high tensile loads, leaving them vulnerable to failure. Researchers are now looking at MSCs to develop better treatments for tendon injuries. Dr. Wan-Ju Li's lab at the University of Wisconsin-Madison has developed a braided nanofibrous scaffold to tissue-engineer tendons.[3] Dr. Li's group cultures human MSCs on the collagen fibril-like scaffold and uses an ElectroForce 5210 BioDynamic system to mimic the physiological environment of a tendon. During a 10-day culture period, cyclic tensile strain of 10% is applied at a frequency of 1 Hz for 2 hours each day. In addition to axial loading, media containing tenogenic growth factors is actively perfused to the MSCs at 20 mL/min. After conditioning with the 5210 system, the MSC population successfully differentiates into tenocyte-like cells expressing tendon-related markers.



The ElectroForce 5210 BioDynamic system can be used to direct stem cell differentiation through culture media perfusion and compressive (or tensile) loading.

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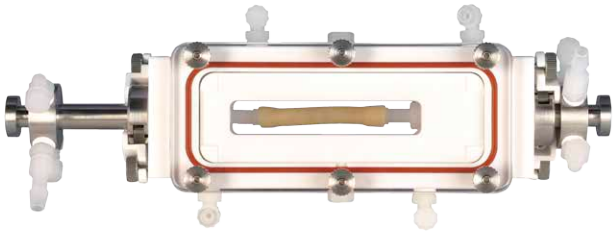
At the University of Sheffield (U.K.), Dr. Gwendolen Reilly and collaborators are using an ElectroForce® 3200 biomaterials test instrument with a media-filled BioDynamic® chamber to examine the effects of dynamic compression on stem cell differentiation.[4] By applying a cyclic compressive load to an MSC-seeded scaffold, they are able to induce MSC differentiation into osteocyte-like cells, providing valuable insight to future treatment options for weakened bone. After a 9-day static culture period, a 5% compressive strain is applied to the scaffold at a frequency of 1 Hz for 2 hours. This loading protocol is repeated two more times at 5-day intervals. After the 19-day total culture period, the loading regimen drives osteogenic differentiation, even in the absence of biochemical stimulation.

A BioDynamic chamber can be added to the ElectroForce 3200 Biomaterials test instrument to apply compressive (or tensile) loading on biological samples.

In cardiovascular applications, fluid shear stress has been shown to drive MSC differentiation into vascular endothelial cells. Additionally, when fluid shear stress is coupled with cyclic strain, MSCs differentiate into cardiomyocytes (heart muscle cells).[5] To replicate the complex and dynamic nature of the cardiovascular system, each mechanical factor must be precisely defined and integrated into a single system. For vascular specimens, BioDynamic systems can be used to apply pulsatile (dynamic) flow, along with axial loading, while monitoring vessel pressure and distension. In this way, ElectroForce BioDynamic instruments can mimic the physiological cardiovascular waveforms that are associated with cardiac contraction and hemodynamics, making them optimal for the differentiation of MSCs into cardiomyocytes and other cardiovascular cells.



Vascular BioDynamic Chamber

In addition to vascular constructs, cardiac loading waveforms are suitable for regenerative medicine treatments of cardiac infarction. Stem cell injection at the infarction site has been proposed to stimulate myocyte regeneration. To investigate this potential therapy, an in vitro study can be performed to physiologically condition infarcted tissue that has been injected with stem cells in a BioDynamic system. The damaged muscle and injected cells can be mechanically loaded using waveforms that mimic cardiac contraction, and stem cell tissue penetration and homing can be assessed. Using this in vitro approach, researchers can identify the appropriate conditions to optimize mechanically-induced stem cell differentiation into cardiac myocytes for repair of infarcted heart muscle.

There are several BioDynamic configurations that can be tuned to direct stem cell differentiation in various physiological environments:

- Tensile loading for tendons and ligaments
- Compressive loading for bone and cartilage
- Fluid shear stress for arteries

Combinations of these mechanical factors can be easily customized to meet the needs of each application that seeks to control stem cell fate. The ElectroForce BioDynamic systems take advantage of MSC environmental responsiveness, allowing the user to direct stem cell differentiation with precisely controlled biochemical and mechanical cues.

References

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