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Editorial

Quantification of Cell Generated Forces: A Tool to Assess Functionality

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Within the last decade the field of tissue engineering has expanded rapidly due to the need for studying specific tissues *in vitro* without the interference from other tissues. Investigations of tissue structure and composition can now be performed intricately with the use of new advanced microscopy techniques (e.g. electron microscopy) and proteomic analysis. Cells are critical for tissue development both *in vivo* and in tissue-engineered constructs as they not only synthesize the basic components for the extracellular matrix that governs the tissue's three-dimensional structure; they also generate forces that are responsible for the assembly and maintenance of the tissue. The cells achieve this by continually sensing external physical and mechanical stimuli and responding through a process termed 'mechanotransduction' [1]. Cell-matrix interactions play a critical role in mechanotransduction, and thus in tissue assembly and homeostasis [2]. Therefore, quantification of cell-generated forces within a matrix can provide a strong insight into cells' role in tissue's function.

The drive to study mechanical forces in biology has led to the development of new methods, including atomic force microscopy and 3D microscopy. One method worth noting is the use of force monitors based on cantilevers. introduced a cell force monitor that could detect, and record cell generated forces [3]. Briefly, fibroblasts were mixed with a collagen solution and then allowed to form a gel between two glass rods that were connected to strain gauges. The signal of the stain gauges could then be calculated into force measurements based on the known stiffness of the glass rods. As the collagen polymerized they were able to detect a rising tension over a period of 24 hours.

This type of equipment has been improved and slightly modified by other groups over the years [4, 5]. Generated a more sensitive force monitor which required fewer cells compare to previous studies [6]. In addition, it could apply tension onto the tissue construct via a controlled stepping motor and was able to detect forces simultaneously. Force recordings are made in voltage that is then converted to Newton, which is fairly simple with a detection range that is at the scale of nano- to milli-Newtons. In general, these kinds of monitors are useful tools to elucidate tissue function, having certain advantages but drawbacks as well. The main advantage is the absolute and precise measurement of the generated forces in real-time. Furthermore, the simple setup of these devices gives the freedom to transfer into cell culture incubator or adjust with a microscope to allow live imaging of the tissue during tensioning. Also, the manipulation of either the cells by providing treated medium or the matrix by length deformation are simple procedures, and calculation of forces is simple and fast. However, the properties of how the tissue relaxes over time within a cycle of tension/untension have not been assessed with these devices. In addition, the use of protocols with defined parameters, such as strain, could be used and provide more reproducible results.

The mechanical properties of the matrix can regulate cell biological processes including differentiation and so reinforces the need to develop equipment that can measure and characterize viscoelastic properties for example. The current devices either rely on pre-formed matrices with defined properties that are only able to evaluate the cellular component, or they can evaluate the mechanical properties but only by pulling the tissue to failure. In cases where the cells create their own matrix or how matrix properties may be affected by the different components of an extracellular matrix remains undefined. To partially overcome this problem researchers, prepare more samples so that they can use more replicates for all the different devices.

The major drawback of these experiments on tissue-engineered constructs is the assumption that all cells within the lattices or tissues contribute equally to produce the total force is recorded. It is more likely that specific cell types within the tissues are more active and produce higher forces. For example, myofibroblasts in connective tissues are believed to be responsible for increased contractility of the tissue [7]. In addition, it would be valuable to be able to monitor forces during the formation and

maturation of an engineered tissue, which can take several weeks, and to be able to reproducibly measure a large sample number. Cell to matrix interactions and their smooth communication are critical to tissue homeostasis and disruption of the mechanotransduction pathway can lead to pathology. As a consequence, a cell force monitor is essential for the researchers investigating tissue development and regeneration and cell-matrix interactions. For tissue engineering in particular, findings from such devices will enable the creation of more accurate, *in vivo*-like tissues.

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