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Numerical modeling of cell differentiation and proliferation in force-induced substrates via encapsulated magnetic nanoparticles

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ABSTRACT

Background and objective: Cell migration, differentiation, proliferation and apoptosis are the main processes in tissue regeneration. Mesenchymal Stem Cells have the potential to differentiate into many cell phenotypes such as tissue- or organ-specific cells to perform special functions. Experimental observations illustrate that differentiation and proliferation of these cells can be regulated according to internal forces induced within their Extracellular Matrix. The process of how exactly they interpret and transduce these signals is not well understood.

Methods: A previously developed three-dimensional (3D) computational model is here extended and employed to study how force-free substrates and force-induced substrate control cell differentiation and/or proliferation during the mechanosensing process. Consistent with experimental observations, it is assumed that cell internal deformation (a mechanical signal) in correlation with the cell maturation state directly triggers cell differentiation and/or proliferation. The Extracellular Matrix is modeled as Neo-Hookean hyperelastic material assuming that cells are cultured within 3D nonlinear hydrogels.

Results: In agreement with well-known experimental observations, the findings here indicate that within neurogenic (0.1–1 kPa), chondrogenic (20–25 kPa) and osteogenic (30–45 kPa) substrates, Mesenchymal Stem Cells differentiation and proliferation can be precipitated by inducing the substrate with an internal force. Therefore, cells require a longer time to grow and maturate within force-free substrates than within force-induced substrates. In the instance of Mesenchymal Stem Cells differentiation into a compatible phenotype, the magnitude of the net traction force increases within chondrogenic and osteogenic substrates while it reduces within neurogenic substrates. This is consistent with experimental studies and numerical works recently published by the same authors. However, in all cases the magnitude of the net traction force considerably increases at the instant of cell proliferation because of cell–cell interaction.

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Conclusions: The present model provides new perspectives to delineate the role of force-induced substrates in remotely controlling the cell fate during cell–matrix interaction, which open the door for new tissue regeneration methodologies.

1. Introduction

The ability of Stem Cells (SCs) to differentiate into multiple cell types allows multiple tissues to be generated and reconstituted from a single cell source. Despite the advantages, the results may sometimes be disastrous if SCs differentiate at an inappropriate place and time or into undesirable phenotypes. This can lead to a pathological state or non-functional tissue construction. To avoid such abnormal conditions, cells have to be particularized in such a way as to differentiate or proliferate in response to appropriate biological stimuli.

Experiments have shown that, besides other factors [58,59], the mechanical structure of cellular micro-environments plays an important role in cell differentiation and proliferation [21,22,31,71]. For instance, Mesenchymal Stem Cells (MSCs) differentiate into specific phenotypes with high sensitivity to the tissue rigidity where they reside in. The mechanical interaction between a cell and its Extracellular Matrix (ECM) is considered symbiotic. Although cells are able to remodel their surrounding micro-environment, the mechanical structure and characteristics of their surroundings can also regulate intracellular signaling. This mutually dependent relationship between cells and their surrounding matrices is often referred to as dynamic reciprocity [13]. Consequently, besides other cell reactions [38,39,41], cells may respond to changes in their mechanical environment, such as changes in matrix rigidity, by undergoing differentiation and/or proliferation [13,43]. For instance, experiments have demonstrated that for soft matrices that resembling brain tissue (0.1–1 kPa) SCs differentiate to neurogenic cells, for intermediate matrices that mimicking cartilage tissue (20–25 kPa) they differentiate into chondrogenic cells, and comparatively hard matrices that mimic the tissue of collagenous bone (30–45 kPa) they differentiate into osteogenic cells [13,26,40,56]. Although MSCs have demonstrated quicker differentiation and an increase in the proliferation rate when cultured on osteogenic substrates [40,42], mechanical forces induced into their micro-environment can actively accelerate these processes [34,35]. This has been attributed to protein anchorage densities and configurations which are proportional to substrate stiffness and rigidity [69]. However, the process of how exactly mechanical force regulates the MSC lineage specification is not well-known [40].

The findings of Kurpinski et al. [34] indicate that mechanical strain due to force inducement increases MSC proliferation and plays an important role in MSC differentiation. They show that the differential cellular responses to an anisotropic mechanical environment in a force-induced micro-environment have important implications in tissue engineering and remodeling due to alterations in the signaling pathway. In another study, the same group demonstrates that these mechanical stimulations play unique and important roles in the regulation of MSCs at both transcriptional and post-transcriptional levels. In addition, they suggest that an accurate combination of micro-environmental cues may promote MSC differentiation [35].

Previous observations concerning cell differentiation and proliferation at the SC-material interface may assist to control a broader range of stem cell behaviors. Murphy et al. [52] have documented a series of diverse work reporting that inherent material properties, such as chemical functionality, adhesivity, binding affinity, nanostructure or degradability, can be engineered to dictate stem cell fate decisions due to dynamic micro-environment of the SC-material interface. In other words, materials can send signals to SC micro-environment by their nano-structural properties, such as surface topographies, and also receive signals from cells by means of molecular sequestering, as in the binding and unbinding of growth factors through material-associated ligands. Therefore, the cell fate and behavior can change due to this dynamical variation of cell-material adhesiveness, nano-structure, stiffness and ECM degradability. For instance, switching of degradable hydrogels into non-degradable ones demonstrates that cell-traction forces are crucial for osteogenic lineage specification of human MSCs in 3D substrates. Although, it is proved that substrate stiffness lead to stem cell differentiation [13,26], it is not yet well-known how extent “switching” material stiffness can trigger broad phenotypic changes, or how the rate of change in material stiffness can influence cell behavior. Therefore, emerging material-screening strategies may quickly improve our mechanistic knowledge about effects of distinct inherent material properties. Beyond the available investigations that considering the effect of elastic modulus on MSC differentiation, many experimental investigations reviewed by Murphy et al. [52] confirm that the inherent material properties, such as dynamic changes in stiffness and frequency-dependent stress responses, may also regulate the MSC lineage specification.

Among the wide range of biomaterials employed as cell substrate for *in vitro* investigations, hydrogels are a relevant option. These are composed of water-swollen networks of cross-linked polymer chains. While hydrogel stiffness depends on factors such as its concentration and cross-linking, due to its nonlinear behavior, the stiffness can be altered as a result of internal contractile forces exerted by cells or by another internal compressing and/or stretching forces exerted within it [1,2]. Several approaches have been proposed in the literature to enhance the local stiffness of the hydrogel, including plastic compression [6], cross-linking techniques [3] and magnetic field alignment of collagen-based hydrogels [1]. A helpful alternative approach to remotely induce an internal force within hydrogels and to change their relative local stiffness is to incorporate magnetic nanoparticles within them. Inducing magnetic force on these magnetic nanoparticles causes compression and/or stretching of the hydrogel,