MODELLING BIOLOGICAL GEL CONTRACTION BY CELLS: MECHANOCellular FORMULATION AND CELL TRACTION FORCE QUANTIFICATION

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ABSTRACT

Traction forces developed by most cell types play a significant role in the spatial organisation of biological tissues. However, due to the complexity of cell-extracellular matrix interactions, these forces are quantitatively difficult to estimate without explicitly considering cell properties and extracellular mechanical matrix responses. Recent experimental devices elaborated for measuring cell traction on extracellular matrix use cell deposits on a piece of gel placed between one fixed and one moving holder. We formulate here a mathematical model describing the dynamic behaviour of the cell-gel medium in such devices. This model is based on a mechanical force balance quantification of the gel visco-elastic response to the traction forces exerted by the diffusing cells. Thus, we theoretically analyzed and simulated the displacement of the free moving boundary of the system under various conditions for cells and gel concentrations. This model is then used as the theoretical basis of an experimental device where endothelial cells are seeded on a rectangular biogel of fibrin cast between two floating holders, one fixed and the other linked to a force sensor. From a comparison of displacement of the gel moving boundary simulated by the model and the experimental data recorded from the moving holder displacement, the magnitude of the traction forces exerted by the endothelial cell on the fibrin gel was estimated for different experimental situations. Different analytical expressions for the cell traction term are proposed and the corresponding force quantifications are compared to the traction force measurements reported for various kind of cells with the use of similar or different experimental devices.

KEYWORDS: Extracellular matrix mechanical response, mathematical model, cell-matrix interactions, parameter identification, viscoelasticity, fibrin gel, endothelial cells.

1. INTRODUCTION

Among the various aspects of cell-extracellular matrix interactions, mechanical interactions are fundamental in many physiological and pathological situations ranging from embryogenesis and connective tissue morphogenesis to tumour invasion and wound healing (Stopak & Harris, 1982; Trinkaus, 1984). In the latter case, wound contraction is a particularly clear manifestation of the mechanical forces that can be generated by nonmuscle cells (McGrath & Simon, 1983; Harris, 1984; Ehrlich, 1988; Clark et al., 1988).

Several studies have demonstrated the existence of cell traction forces in vitro since the pioneering work of Harris and co-workers, who proposed that fibrils reorganization around cells embedded in a reconstituted collagen gel results from cell traction forces (Harris et al., 1981; Yamato et al., 1995). For example, Guidry and Grinnell (1986) showed that cells can reduce gel thickness, as it is obtained by centrifugation only.

Beyond these phenomenological observations, several studies have tried to quantitatively estimate the force produced in vitro by various kind of cells on extracellular matrix. The most common in vitro assay is based on the compaction of disks or spheres, made of biological gels, under the influence of the mechanical forces exerted by cells dispersed into the gel (Bell et al., 1979; Ehrlich et al., 1990; Moon & Tranquillo, 1993). A measure of the cell traction magnitude is then provided by the amount of diameter reduction of the gel.

More recently, cell traction forces have been measured in assays where the contraction of a free-floating gel held in place between two holders is recorded as a function of time (Delvoye et al., 1991; Kolodney et al., 1992; Chapuis et al., 1992; Eastwood et al., 1994, 1996). The traction force generated by the cells is then estimated from the value of the force measured at the end of the gel contraction and by evaluating the ratio between this final force value and the time needed to reach it (Delvoye et al., 1991; Kolodney & Wysolmerski, 1992).

Despite the characterisation of the cell-extracellular matrix (ECM) mechanical interactions provided, these studies suffer from severe limitations since the force measurements depend on the cell and gel concentrations. Indeed, it is not the cell traction per se which is calculated but the balance between cell traction forces and the viscoelastic resistance of the gel, which is known to undergo drastic changes in nature and amplitude according to the gel concentration (Ferry, 1988; Guenet, 1992; Djahouri & Guenet, 1995).

Moreover, these measurements can also be significantly affected by any modifications of cell activity, including mitosis, migration or extracellular secretion factors. Let us briefly recall from biological studies that the production of traction forces is the result of the interplay of various biological processes involving at least the pulsatile extension and retraction of cell pseudopods, the rearrangement of the cell cytoskeleton and cell adhesion onto the ECM mediated by transmembrane proteins like integrins (Ingber, 1991; Hynes, 1992). More generally, the cell-ECM composite medium can be viewed as a self-organised mechanical continuum in which traction forces have a pivotal role: cell migration and adhesion to the ECM fibers modulate the strain level of the ECM, while in turn cells can respond to the mechanotransduction of extracellular signals (Ingber, 1993; Juliano et al., 1993).

As a result, a true quantification of cell traction forces based on gel contraction experiments could not be undertaken without modelling the mechanical behaviour of the gel through explicit stress-strain relationships in conjunction with a modelling of the cell dynamics.