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Analyzing the effects of mechanical and osmotic loading on glycosaminoglycan synthesis rate in cartilaginous tissues

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ABSTRACT

The glycosaminoglycan (GAG) plays an important role in cartilaginous tissues to support and transmit mechanical loads. Many extracellular biophysical stimuli could affect GAG synthesis by cells. It has been hypothesized that the change of cell volume is a primary mechanism for cells to perceive the stimuli. Experimental studies have shown that the maximum synthesis rate of GAG is achieved at an optimal cell volume, larger or smaller than this level the GAG synthesis rate decreases. Based on the hypothesis and experimental findings in the literature, we proposed a mathematical model to quantitatively describe the cell volume dependent GAG synthesis rate in the cartilaginous tissues. Using this model, we investigated the effects of osmotic loading and mechanical loading on GAG synthesis rate. It is found our proposed mathematical model is able to well describe the change of GAG synthesis rate in isolated cells or in cartilage with variations of the osmotic loading or mechanical loading. This model is important for evaluating the GAG synthesis activity within cartilaginous tissues as well as understanding the role of mechanical loading in tissue growth or degeneration. It is also important for designing a bioreactor system with proper extracellular environment or mechanical loading for growing tissue at the maximum synthesis rate of the extracellular matrix.

1. Introduction

The glycosaminoglycan (GAG) plays an important role in cartilaginous tissues to support and transmit mechanical loads, and the decrease of GAG content is a sign of tissue degeneration (Antoniou et al., 1996; Maroudas, 1979). The negatively charged groups on the GAG impart a high extracellular osmolarity and hence high swelling pressure to the extracellular matrix (ECM) (Lai et al., 1991; Maroudas, 1979). GAG acts in concert with collagen to give cartilage the capacity to support and transmit mechanical loads (Maroudas, 1976). The GAG is produced and maintained by cells which live in a very complex mechno-electrochemical environment within the tissue (Maroudas, 1979; Setton and Chen, 2004; Snowden and Maroudas, 1972; Urban, 2002). A change in cell shape or volume has been known as a mechanism to perceive the alteration of extracellular environment by mammalian cells (Benzeev, 1991; Folkman and Moscona, 1978; Sarkadi and Parker, 1991). Currently, it has been found that direct membrane stretch has little or no influence on chondrocyte metabolic activities (O'Conor et al., 2014), which indicates cell volume change may play a role in regulating the synthesis activities. It was hypothesized that the change of cell volume could be a factor in mediating mechanotransduction in cartilaginous tissues (Guilak et al., 1995; Wong et al., 1997).

Osmotic loading and mechanical loading have been shown to affect the synthesis of GAG in vitro in both explant and cell culture experiments (e.g., Bush and Hall, 2001; Gray et al., 1988, 1989; Guilak et al., 1994; Johnson et al., 2014; Maroudas and Evans, 1974; O'Conor et al., 2014; Sampat et al., 2013; Schneiderman et al., 1986; Urban et al., 1993). For example, the extracellular osmolarity has been found to have a dose-dependent effect on GAG synthesis rate by isolated cells (Ishihara et al., 1997; Negoro et al., 2008); the cells in the NP explant exhibit a higher synthesis rate of GAG at the osmolarity level close to the in situ value (van Dijk et al., 2011, 2013); the GAG synthesis rate has been observed to decrease in osmotic loaded articular cartilages (Bayliss et al., 1986; Schneiderman et al., 1986); a static compression has been shown to suppress GAG synthesis in articular cartilage (Kim et al., 1994; Schneiderman et al., 1986), whereas the GAG synthesis rate in bovine tail disc was found to be elevated if the static loading is less than 5 kg (Ohshima et al., 1995). However, there is no adequate theoretical model in the literature for the quantitative analysis and prediction of the effect of mechanical loading and/or osmotic

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loading on the synthesis rate of GAG in the cartilaginous tissues. Thus, the objective of this study was to develop a mathematical model to quantitatively investigate GAG synthesis rate by cells in cartilaginous tissues (or in a culture) under the mechanical and/or osmotic loading.

2. Model development

It has been found that cells of cartilaginous tissues exhibit maximum synthesis rate (R_0, mole or mass per unit cell per unit time) of GAG at an in vivo state (refer to the optimal state, denoted by subscript 0) as mentioned in Section 1. Ishihara et al. (1997) experimentally revealed that the change of GAG synthesis rate (R) is proportional to the relative change of a cell volume. Based on their findings, in this study, we proposed a mathematical model for the relationship between GAG synthesis rate and cell volume:

$$\frac{R-R_0}{R_0} = -\alpha\left|\frac{V-V_0}{V_0}\right|, \tag{1}$$

where V_0 and V are the cell volumes at the optimal state and current state, respectively, and α is a positive parameter characterizing the effect of cell volume change on GAG synthesis rate. Curve-fitting of Eq. (1) to the experimental results (Ishihara et al., 1997) of GAG synthesis rate versus the volume changes of the cells from bovine nucleus pulposus (NP), yielded $\alpha = 2.41$ ($R^2 = 0.94$), see Fig. 1a.

The alteration of the cell volume can be attributed to its passive or active responses to biophysical stimuli. In this study, we focused only on the passive response of cell volume to osmotic loading and/or mechanical loading.

2.1. Effects of osmotic loading

It has been shown that the passive volumetric response of isolated chondrocytes or chondrocyte-like cells from the intervertebral disc (IVD) to osmotic loading in a culture medium can be characterized by Boyle van't Hoff equation (Guilak et al., 2002; Nobel, 1969),

$$\frac{V-V_0}{V_0} = \beta\left(\frac{\pi_0}{\pi}-1\right), \tag{2}$$

where π_0 and π are the osmolarities at the optimal state and current state, respectively. The osmolarity can be estimated by the sum of the concentration of all dissolved particles (or solutes, donated by i), that is, $\pi = \sum_i c^i$, where c^i is the concentration of solute i per fluid volume. The parameter β in Eq. (2) is positive and its value is equal to the hydration of the cell at the optimal state (Ateshian et al., 2006). Substituting Eq. (2) into Eq. (1), it yields:

$$\frac{R}{R_0} = \left(1-\gamma\left|\frac{\pi_0}{\pi}-1\right|\right), \tag{3}$$

where $\gamma = \alpha\beta$. Curve-fitting to the experimental results (Ishihara et al., 1997) on GAG synthesis rate versus extracellular osmolarity, yielded $\gamma = 1.487$ and $\pi_0 = 404$ mOsm ($R^2 = 0.91$), see Fig. 1b. Thus, the value of parameter β for bovine NP cells is 0.62, which is close to the value ($\sim$0.6) for mesenchymal stem cells (Sampat et al., 2013).

2.2. Effects of mechanical loading

The Boyle van't Hoff equation (i.e., Eq. (1)) can characterize the volume change of an isolated cell under osmotic loading, but it is no longer valid for the cells in the tissue because the cells are encapsulated by the extracellular matrix (ECM) which provides external resistance to the deformation of the cell. In order to estimate the cell volume change as a function of tissue deformation, let us consider a simple case where a spherical cell is encapsulated in a larger sphere of the ECM, see Fig. 2. The radii

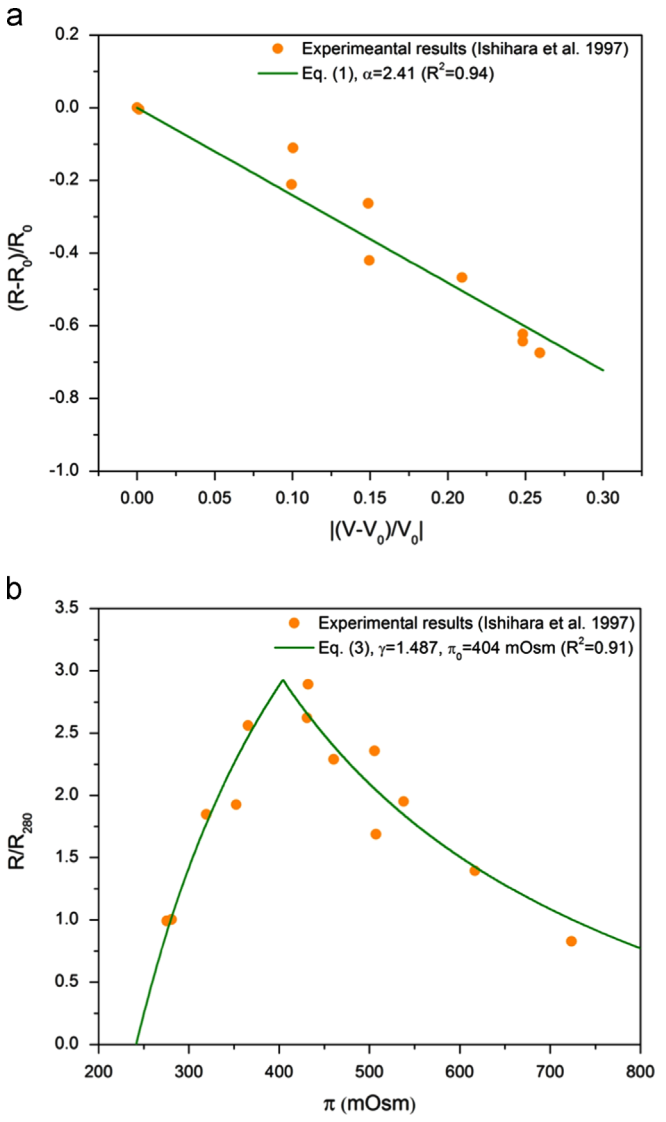

Fig. 1. (a) GAG synthesis rate versus relative volume change of cells; (b) GAG synthesis rate versus extracellular osmolarity. The synthesis rates were normalized by the rate at 280 mOsm (R_{280}) (Ishihara et al., 1997).

of a cell and matrix at the optimal state are r_c and r_m, respectively. The cell–matrix composite (Fig. 2) is assumed to be subjected to a normal stress uniformly distributed at the matrix outer boundary, and the cell be attached to the matrix perfectly. At equilibrium state (without fluid flow), the deformation of the cell–matrix composite can be estimated by a linear elasticity theory. The equation of equilibrium in the spherical coordinate system is

$$\frac{d}{dr}\left[\frac{1}{r^2}\frac{d}{dr}(r^2 u_r)\right] = 0, \tag{4}$$

where r is the radial coordinate, and u_r is the displacement in the radial direction. The relative volume change (i.e., dilatation) of the cell or composite can be obtained through calculating the change of the radius of the cell or composite using Eq. (4). Thus, the dilatation of the cell, e_c ($e_c = (V-V_0)/V_0$, where V_0 is again the volume of the cell at the optimal state for GAG synthesis), is related to the dilatation of the composite (e), through

$$e_c = f(e) = \left[1-\frac{E_m}{E_c}\frac{2(1-2\nu_c)(1-\chi^3)(\sqrt[3]{1+e}-1)}{2(1-2\nu_m)(\chi^3-\zeta)+(1-\zeta)(1+\nu_m)\chi^3}\right]^3 - 1, \tag{5}$$

where E_m and E_c are the Young's moduli of the matrix and cell, respectively, ν_m and ν_c are the Poisson's ratios of the matrix and