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Tuning tissue growth with scaffold degradation in enzyme-sensitive hydrogels: a mathematical model

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Despite tremendous advances in the field of tissue engineering, a number of obstacles remain that hinder its successful translation to the clinic. One challenge that relates to the use of cells encapsulated in a hydrogel is identifying a hydrogel design that can provide an appropriate environment for cells to successfully synthesize and deposit new matrix molecules while providing a mechanical support that can resist physiological loads at the early stage of implementation. A solution to this problem has been to balance tissue growth and hydrogel degradation. However, identifying this balance is difficult due to the complexity of coupling diffusion, deposition, and degradation mechanisms. Very little is known about the complex behavior of these mechanisms, emphasizing the need for a rigorous mathematical approach that can assist and guide experimental advances. To address this issue, this paper discusses a model for interstitial growth based on mixture theory, that can capture the coupling between cell-mediated hydrogel degradation (i.e., hydrogels containing enzyme-sensitive crosslinks) and the transport of extracellular matrix (ECM) molecules released by encapsulated cells within a hydrogel. Taking cartilage tissue engineering as an example, the model investigates the role of enzymatic degradation on ECM diffusion and its impact on two important outcomes: the extent of ECM transport (and deposition) and the evolution of the hydrogel's mechanical integrity. Numerical results based on finite element analysis show that if properly tuned, enzymatic degradation yields the appearance of a highly localized degradation front propagating away from the cell, which can be immediately followed by a front of growing neotissue. We show that this situation is key to maintaining mechanical properties (e.g., stiffness) while allowing for deposition of new ECM molecules. Overall, our study suggests a hydrogel design that could enable successful tissue engineering (e.g., of cartilage, bone, etc.) where mechanical integrity is important.

1. Introduction

EC [9,10]

[11 13]

[14,15]

47640( ) 5( ) 4.6(4 417) 9(3(-319.3( )–6(( )-5.9( )-280.3(3( )( )0(283.6(9-2 31.8(.5(6.6(-.4 2( )1 6( )-440.338)-46

$$\frac{Dr}{Dt} = -k' c_e \frac{r}{r + k''} \quad (2.1)$$

$_a/x$ ... a ... x ... :[35]

... (F . 1).

... [35] ... $_a/x$

:

$$D_a(r_a, r, J) = D_a^1 f(J, J_0)\left(1 - \frac{r_a}{x(r, J)}\right); \quad r_a < x < x_c \quad (2.2)$$

... x ... r ... $x = x(r,)$ ...

(, $_0$) ...

E , [37] ...

... C ... [38] ... [39] ...

(, $_0$) = (□1/ ($_0$ □ 1)).

... $r \to r$, ...

... , ... (, $_0$) ... $r = r$ . ...

(2.2) ... $_a < x < x$; ... , $x <$ $_a$, ... $_a \to 0$. x 4 x , ... , ... $(x \to \infty)$ ...

... , $_a = \ _a^{\infty}$ ... E ... .[40] ...

$$x(r, J) = \ell J^{\frac{1}{3}}\sqrt{\frac{r_0}{r}}; \quad r_c < r$$

( ) . 56. B EC :

$$q_a j_{S_{cell}} = q_a^0 \left(1 - \frac{c_a}{c_a^0}\right) \tag{4.3}$$

c_a^0 a (= ,). EC c_a^0.[28]

:

$$x^* = \frac{x}{L}, \quad t^* = \frac{t D_m^1}{L^2} \tag{4.4}$$

, :

$$u^* = \frac{u}{L}, \quad c_a^* = \frac{c_a}{c_a^0}, \quad p^* = \frac{p}{RT}, \quad r^* = \frac{r}{r_0} \tag{4.5}$$

, c_a^0 (4.2). ,

(3.3) (3.6), . F , ∞ EC , :

D_a^*

EC

5.1 Degradation around a single cell

$r^* = 0.99$. ... 33.

Diffusion-dominated and diffusion-limited systems. F . 5 ... k^* ... *. F ... (F . 5). B ... (F . 5).

Characterization of the degradation dynamics. A ...

6. Discussion and concluding remarks

$$\int_V w_2^T \frac{\partial c_e}{}$$

$$C_{eu} = \sum_{1}^{\#el} \int$$

37 . . , . J . . . E ,