78b Gradients of Matrix-Bound Morphogens Created by Cells in 3d Dynamic Environments

Mark E. Fleury, Cara-Lynn E. Helm, and Melody A. Swartz

Introduction

Tissue morphogenesis is largely orchestrated by spatial gradients of morphogenetic proteins. Many of these morphogens (such as VEGF, bFGF, BMP and many cytokines) are secreted in a matrix-binding form to be later released proteolytically by cells. [1] The mechanisms by which such matrix-bound morphogens are mobilized to form spatial gradients are poorly understood. In this work we explore how subtle biophysical forces such as interstitial flow can be utilized by the cell to activate patterns of extracellular morphogens and demonstrate an efficient mechanism for gradient generation.

Interstitial fluid flow is the slow flow of fluid through the extracellular matrix that is driven by cell-vasculature fluid balance. This flow is present in many soft tissues and notably includes lymph. While difficult to measure exact physiological values, interstitial flow velocities have been found to range from 0-8 um/s [2].

By introducing exquisitely low levels of interstitial flow to simple models of cell-matrix interactions, the predicted extracellular gradients of liberated morphogens are amplified and can even be shown to increase relative to the cell [3]. Understanding these transport processes can lead to greater insight into physiological events such as chemotaxis and directed morphogenesis.

Methods

Mass transport is modeled using a steady-state mass transport equation and solved numerically:

where C=concentration, v=fluid velocity, D=diffusion coefficient, and R_v= generation (e.g., morphogen release from the matrix).

The cell in its extracellular matrix is modeled as flow around a sphere in a porous media. The flow profile is predicted by solution of the Brinkman equation for flow around a sphere. The resulting Brinkman velocity profile as well as the appropriate boundary conditions are incorporated into a numerical solution technique to yield the spatial solute concentration around the cell. The equation is first solved for soluble enzymes (such as MMPs) that are released from the cell surface. The resulting

enzyme concentration distribution is then utilized as the generation term (R_v) in solving the equation a second time assuming that the enzyme liberates bound morphogens (such as VEGF) from the matrix in a concentration-dependent manner. In both cases the problem is solved under both static and flow conditions.

Results

Steady-state solutions to the mass transport problem for assumed physiological conditions, where Pe=0.5, are plotted in Figure 1 showing the relative spatial distributions for enzymes and released morphogens.

Figure 1 : Concentration profiles of cell-released enzymes under static (A) and 4.2 um/s flow (B). Profiles of morphogens released from the matrix due to enzymatic action under static (C) or flow (B) conditions. Red indicates highest concentration, blue lowest, and cell location is denoted with a grey circle.

Conclusion

The evolution of morphogen gradients has long been studied in the context of diffusion and reaction only. Here we show that low levels of convection, present in almost all tissues, has a drastic influence on shaping morphogen gradients, particularly those that are liberated from the matrix. Of specific interest is that these results indicate a possible mechanism by which cells can create autologous morphogen gradients which *increase* with radial distance from the cell as opposed to autologous diffusive gradients which must necessarily *decrease* with radial distance from the cell. A clearer understanding of this mechanism may hold greater insight into many morphological events such as cell migration, lymphangiogenesis, and tumor metastasis.

References

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