A continuum mechanics model of enzyme-based tissue degradation in cancer therapies

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Abstract

ECM degrading enzymes can degrade some constituents of the ECM. They are used to enhance gene transfection or penetration of drugs into tumors. Our goal is to evaluate the effect of an injection of ECM degrading enzymes on the porosity of a biological tissue.

We developed a poroelastic macroscopic model of biological tissue based on:
- Balance laws
- Constitutive relations

We consider that the changes of porosity are due to:
- the elasticity of the medium
- the fact that cells are slightly compressible
- the effect of an ECM degrading enzyme

Mathematical Model

Assumptions: saturated medium, incompressible liquid phase, slightly compressible solid phase, negligible inertia

\[ \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0 \]  

\[ \frac{\partial \rho_f}{\partial t} + \nabla \cdot (\rho_f \mathbf{u}) = 0 \]  

\[ \frac{\partial \rho_s}{\partial t} + \nabla \cdot (\rho_s \mathbf{u}) = 0 \]  

\[ \frac{\partial \mathbf{u}}{\partial t} + \left( \rho \mathbf{u} \cdot \nabla \right) \mathbf{u} = -\nabla P + \nabla \left( \mu \nabla \mathbf{u} \right) + \rho_g \mathbf{g} + \mathbf{f} \]  

\[ \frac{\partial \mathbf{u}_c}{\partial t} + \left( \rho_c \mathbf{u} \cdot \nabla \right) \mathbf{u}_c = -\nabla \mathbf{P}_c + \nabla \left( \mu_c \nabla \mathbf{u}_c \right) + \rho_c g \mathbf{g}_c \]  

\[ \frac{\partial \mathbf{u}_m}{\partial t} + \left( \rho_m \mathbf{u} \cdot \nabla \right) \mathbf{u}_m = -\nabla \mathbf{P}_m + \nabla \left( \mu_m \nabla \mathbf{u}_m \right) + \rho_m g \mathbf{g}_m \]  

\[ \frac{\partial \rho_f}{\partial t} + \nabla \cdot (\rho_f \mathbf{u}_f) = \rho_f \mathbf{f} \]  

\[ \frac{\partial \rho_s}{\partial t} + \nabla \cdot (\rho_s \mathbf{u}_s) = \rho_s \mathbf{f} \]  

\[ \frac{\partial \mathbf{u}_c}{\partial t} + \left( \rho_c \mathbf{u} \cdot \nabla \right) \mathbf{u}_c = \left( \rho_c g \mathbf{g}_c \right) \]  

\[ \frac{\partial \mathbf{u}_m}{\partial t} + \left( \rho_m \mathbf{u} \cdot \nabla \right) \mathbf{u}_m = \left( \rho_m g \mathbf{g}_m \right) \]  

\[ \frac{\partial \mathbf{u}_e}{\partial t} + \left( \rho_e \mathbf{u} \cdot \nabla \right) \mathbf{u}_e = \left( \rho_e g \mathbf{g}_e \right) \]  

\[ \frac{\partial \mathbf{u}_l}{\partial t} + \left( \rho_l \mathbf{u} \cdot \nabla \right) \mathbf{u}_l = \left( \rho_l g \mathbf{g}_l \right) \]  

\[ \frac{\partial \mathbf{u}_g}{\partial t} + \left( \rho_g \mathbf{u} \cdot \nabla \right) \mathbf{u}_g = \left( \rho_g g \mathbf{g}_g \right) \]  

Drugs penetration in tumors

An injection of matrix degrading enzymes removes diffusive hindrance to the penetration of therapeutic molecules.

The distribution of therapeutic agents is wider when the spheroid was previously incubated into an ECM degrading enzyme, thereby improving the diffusion process.

Interstitial Fluid Pressure may be temporarily reduced by degrading the tumor ECM thus improving the transcapillary transport of therapeutic agents.

Without pretreatment, the drugs stay at the periphery. An enzyme pretreatment permits to obtain a wider distribution.

Conclusion

An injection of ECM degrading enzyme enhances the distribution of drugs by improving both diffusion and convection

Calibration with additional experimental data is needed

References

1. Hyaluronidase induces a transcapillary pressure gradient and improves the distribution and uptake of liposomal doxorubicin (Caelyx) in human osteosarcoma xenografts, Ellington, Tari, Tutto, Brueland and De Lange Davis (2010)
2. Effects of hyaluronidase on doxorubicin penetration into squamous carcinoma multicellular tumor spheroids and its cell lethality, Kohno, Ohnuma, Tsuru (1994)

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