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Impact of Simulated Brain Interstitial Fluid Flow on the Chemokine CXC-Chemokine-Ligand-12 Release From an Alginate-Based Hydrogel

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Abstract : The high infiltrative pattern of glioblastoma multiforme cells (GBM) is the main cause responsible for the actual standard treatments failure. The tumor high heterogeneity, the interstitial fluid flow (IFF) and chemokines guides GBM cells migration in the brain parenchyma resulting in tumor recurrence. Drug delivery systems emerged as an alternative approach to develop effective treatments for the disease. Some recent studies have proposed to harness the effect CXC-lchemokine-ligand-12 to direct and control the cancer cell migration through delivery system. However, the dynamics of the brain environment on the delivery system remains poorly understood. Nanoparticles (NPs) and hydrogels are known as good carriers for the encapsulation of different agents and control their release. We studied the release of CXCL12 (free or loaded into NPs) from an alginate-based hydrogel under static and indirect perfusion (IP) conditions. Under static conditions, the main phenomena driving CXCL12 release from the hydrogel was diffusion with the presence of strong interactions between the positively charged CXCL12 and the negatively charge alginate. CXCL12 release profiles were independent from the initial mass loadings. Afterwards, we demonstrated that the release could tuned by loading CXCL12 into Alginate/Chitosan-Nanoparticles (Alg/Chit-NPs) and embedded them into alginate-hydrogel. The initial burst release was substantially attenuated and the overall cumulative release percentages of 21%, 16% and 7% were observed for initial mass loadings of 0.07, 0.13 and 0.26 µg, respectively, suggesting stronger electrostatic interactions. Results were mathematically modeled based on Fick's second law of diffusion framework developed previously to estimate the effective diffusion coefficient (Deff) and the mass transfer coefficient. Embedding the CXCL12 into NPs decreased the Deff an order of magnitude, which was coherent with experimental data. Thereafter, we developed an in-vitro 3D model that takes into consideration the convective contribution of the brain IFF to study CXCL12 release in an in-vitro microenvironment that mimics as faithfully as possible the human brain. From is unique design, the model also allowed us to understand the effect of IP on CXCL12 release in respect to time and space. Four flow rates (0.5, 3, 6.5 and 10 µL/min) which may increase CXCL12 release in-vivo depending on the tumor location were assessed. Under IP, cumulative percentages varying between 4.5-7.3%, 23-58.5%, 77.8-92.5% and 89.2-95.9% were released for the three initial mass loadings of 0.08, 0.16 and 0.33 µg, respectively. As the flow rate increase, IP culture conditions resulted in a higher release of CXCL12 compared to static conditions as the convection contribution became the main driving mass transport phenomena. Further, depending on the flow rate, IP had a direct impact on CXCL12 distribution within the simulated brain tissue, which illustrates the importance of developing such 3D in-vitro models to assess the efficiency of a delivery system targeting the brain. In future work, using this very model, we aim to understand the impact of the different phenomenon occurring on GBM cell behaviors in response to the resulting chemokine gradient subjected to various flow while allowing them to express their invasive characteristics in an in-vitro microenvironment that mimics the in-vivo brain parenchyma.

Keywords : 3D culture system, chemokines gradient, glioblastoma multiforme, kinetic release, mathematical modeling
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