OPTIMAL CONTROL APPLIED TO CELL PROLIFERATION AND MIGRATION IN GLIOBLASTOMA

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ABSTRACT

Glioblastoma, the most aggressive type of brain cancer is characterized by alternating phases of rapid proliferation and aggressive invasion in response to metabolic stress in the microenvironment. Its median survival time is one year after diagnosis. It has been reported that miR-451 and AMPK complex form a core control system determining a balance between cell growth and migration regulated by fluctuating glucose levels in the microenvironment. Low levels of glucose affect metabolism and activate cell migration through the miR-451–AMPK control system inducing migratory cells which are beyond detection even using conventional imaging techniques such as MRI. Under the assumption that infiltrative tumor cells are restricted near the surgical site, the objective is to localize glioblastoma cells for a second surgery and prevent their migration to the tissue. We apply optimal control theory to maintain up-regulated miR-451 levels keeping cancer cells in proliferative mode and restraining them from invading the brain tissue. Using glucose levels as regulator of miR-451 activity, optimal control strategies are identified to confine miR-451 concentration above a threshold through administration of glucose intravenous infusion. The effect of drug that blocks the inhibitive pathways of miR-451 from AMPK complex is also considered assuming that it can be administered concomittantly with glucose as a secondary infusion . Thus, controls are given by dose rates of glucose and drug intravenous infusions. Different strategies under various circumstances are analyzed to minimize the cost of administrations.

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