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Hypoxic Migratory Cell Waves around Necrotic Cores in Glioblastomas: A Mathematical Model

Malignant gliomas are the most common and deadly brain tumors. Survival for patients with glioblastoma (GBM), the most aggressive glioma, although individually variable, is in the range of 10 months to 14 months after diagnosis, using standard treatments which include surgery, radiotherapy, chemotherapy (temozolamide and antiangiogenic drugs such as bevacizumab) [1]. GBM is a rapidly evolving astrocytoma that is distinguished pathologically from lower grade gliomas by the presence of necrosis and microvascular hyperplasia. Interestingly, necrotic foci are tipically surrounded by a population of rapidly moving tumor cells that superimpose themselves on a more stationary population, causing increased cell density, known as "pseudopalisades" [2, 3]. Evidence suggests that this tumor cell migration is caused by a vaso-occlusive event where the local tumor blood vessels no longer provide the necessary oxygen supply. This leads to the formation of a wave of tumor cells actively migrating away from central hypoxia (oxygen deprivation) that arises after a vascular insult. Indeed, pseudopalisading cells show nuclear expression of hypoxia-inducible factor 1α, consistent with their hypoxic nature [2, 3].

We have developed a mathematical model that incorporates the spatio-temporal interplay among two tumor cell phenotypes, a necrotric core and the oxygen distribution. Our scenario consists of the tumor cells embedded within two blood vessels. We will assume that the hypoxic phenotype is the migratory one but non-proliferative, whereas the normoxic is less migratory but proliferative [4, 5]. In addition, our model takes into account the switching mechanisms between both phenotypes when the local oxygen levels cross a threshold value characteristic of hypoxia. Our numerical simulations reveal the formation of a superimposed travelling wave of hypoxic cells that qualitatively reproduces the experimentally observed patterns. This suggest that our model could be further extended to include the selective action of radiotherapy on the tumor cells depending on their oxic state.

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