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MEK Inhibition May Prevent the Recruitment of NK Cells in the Tumor Microenvironment: A Mathematical Model of Glioma Treatment

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Abstract In this paper, we analyze the dynamics of oncolytic virotherapy combined with MEK inhibitors for the treatment of glioma. Although the therapeutic effect of oncolytic viruses (OV) depends on the recruitment of NK cells, these viruses are frequently subject to NK cell clearance, which may reduce the efficacy of oncolytic virotherapy. Furthermore, it is more challenging for OV to enter glioma cells because these cells lack Coxsackievirus and Adenovirus Receptors (CAR). MEK inhibitors, however, are able to compensate for this deficiency in CAR molecules. Herein, we propose and analyze a mathematical model of the dynamics of cancer cells, oncolytic viruses, activated NK cells, and CAR molecules while combining oncolytic virotherapy with MEK inhibition. Our goal is to identify the circumstances in which the treatment may be effective. In this research, we investigated the existence of equilibrium points. The two endemic equilibriums and the virus infection-free equilibrium stability conditions are given. The findings demonstrate that, in a dynamical system, NK cell activation can either establish or destroy equilibrium points and that substantial recruitment of activated NK cells might have detrimental effects on oncolytic virotherapy. However, MEK inhibitors boost OV effectiveness and may prevent NK cell recruitment.

Keywords Glioma, cancer, oncolytic virotherapy, MEK inhibitors, mathematical model

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1. Introduction

In a number of preclinical and clinical tumor models, oncolytic virotherapy has demonstrated promising antitumoral effects [1–4]. An oncolytic virus (OV) that selectively replicates to kill cancer cells while preserving healthy normal cells is used in this therapy strategy. Additionally, oncolytic virotherapy promotes a strong immune response to both infected and uninfected tumors [2, 5, 6]. However, oncolytic viruses are frequently susceptible to immune cell clearance when supplied through a

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vein to immunocompetent hosts. This lowers the chances of virotherapeutic success [7, 8].

Natural killer (NK) cells and T lymphocytes are well-known to have a significant role in oncolytic virotherapy. Wodarz et al. [9] demonstrated that for OV to have a therapeutic impact, NK cells and T cells are necessary. Senekal et al. [10] investigated how oncolytic virotherapy was affected by the recruitment of NK cells. Their findings demonstrate the critical functions that OV infection plays in reducing tumor growth and activating a potent NK cell response to achieve tumor remission. However, other studies [11–13] showed that the impact of virotherapy on the eradication of tumor cell populations may be diminished. Virus-induced immune responses may also destroy virus-infected tumor cells prematurely, before viruses have a chance to produce new progeny.

In our research, we are interested in the dynamics of OV therapy for glioma and how it interacts with NK cell recruitment. We only take into account the newly emerging function of NK cells in oncolytic virotherapy due to the need for a more thorough investigation of their dual and counter-intuitive contributions [8].

Gliomas are a type of brain cancer that arise from cells that help support the brain's neurons [14]. Major research on the use of several oncolytic viruses in the treatment of gliomas has been done [15, 16]. Adenoviral vectors have an edge over other viral vectors because they are comparatively non-toxic and do not integrate into the genome [17]. However, the lack of Coxsackievirus and Adenovirus Receptors (CAR) on the surface of gliomas makes it difficult for wild-type adenoviral vectors to effectively transduce in these tumors [18]. Studies from clinical trials have demonstrated that the absence or diminished expression of CAR in tumor cells, particularly in glioma cells, complicates the entry of an adenovirus into these cells [18]. Targeting the adenovirus to gliomas remains difficult because the CAR levels in gliomas are low [16].

Mitogen-activated protein kinase kinase (MEK) inhibitors have been shown to increase CAR expression [19]. However, MEK inhibitors may limit the replication of the virus. This requires finding an optimal balance between the positive effect of MEK inhibitors and their negative effect. This makes the dynamics of the group consisting of tumor cells, viruses, and MEK inhibitors more complicated. Zurakowski and Wodarz [19] proposed an ODE model to describe the effects of MEK inhibitors and viruses on tumor cells. They used it to investigate whether the combined therapy may reduce the size of the tumor. More recently, Camara et al. [20] analytically demonstrated the conditions that lead to optimal therapy in minimizing glioma cells proliferation using a spatiotemporal mathematical model that describes the interaction between tumor cells and oncolytic viruses. They stated that when the amount of MEK inhibitors is high, virotherapy always fails. However, the dynamics of CAR expression on the cells' surface were not included in their model. Recently, Nono et al. [21] proposed a nonlinear mathematical model of brain tumor control through regulating the growth of cancer cells by employing conditionally replicative adenoviruses (CRAds) and MEK inhibitors in combination therapy. But they didn't take into account the recruitment of NK cells into the tumor microenvironment.

In this paper, we propose a mathematical model of the dynamical interactions among cancer cells, oncolytic viruses, virus-induced NK cells, and CAR molecules. Particularly, our study aims to analyze how the combination of MEK inhibitors and activated NK cells affects oncolytic virotherapy.