Synergetic effect of bortezomib on oncolytic virus: signaling pathways

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ABSTRACT

Tumor growth is a complex evolutionary process driven by dynamic feedback between a heterogeneous cell population and selection pressures from the tumormicroenvironment (TME) [2]. Glioblastoma is also characterized by tumor cells that hijack immune system cells in a deadly symbiotic relationship [1]. In this paper we consider bortezomib-induced ER stress, appotosis and synergetic cell killing in oncolytic viral therapy. Using a multi-scale PDE model, we first develop an ODE model for the IkB-proteasome- NFkB -Bcl-2- BAX intracellular signaling network in response to various levels of bortezomib in the absence and presence of oHSV. This will determine the cell fate of glioma cell, i.e., anti-apoptosis, apoptosis, and necroptosis from the IkB-proteasome- NFkB -Bcl-2- BAX core control system. In a series of experiments by Yoo et al (2014, 2016, Clinical cancer research [3,4[), experimentalists found that the combination therapy (bortezomib+oHSV) can significantly reduce the tumor size. Therefore, we study the detailed dynamics of the core control system and overal dynamics of the combination therapy so that we can better control the aggressive tumor, glioblastoma. We consider the densities of uninfected tumor cells, infected tumor cells, necrotic tumor cells, and oncolytic viruses (oHSV), and concentration of diffusible bortezomib and intracellular molecules (NFkB, IkB, BAX, and RIP2). We first compare our simulation results with experimental data and test several hypotheses on anti-cancer strategies.

REFERENCES

[1] Yangjin Kima, Ji Young Yooc, Tae Jin Leec , Joseph Liue, Jianhua Yuf, Michael A Caligiurif, Balveen Kaurc, and Avner Friedmana, Complex Role of NK cells in regulation of OV-Bortezomib therapy, PNAS, in revision (2017)

[2] Yangjin Kim, Hyejin Jeon, and Hans Othmer, The role of the tumor microenvironment in glioblastoma: A mathematical model, IEEE Trans Biomed Eng (IF 2.347), 64(3):519-527, March 2017.

[3] Yoo J, et al. (2014) Bortezomib-induced unfolded protein response increases oncolytic hsv-1 replication resulting in synergistic antitumor effects. Clin Cancer Res 20(14):3787-3798.

[4] Yoo J, et al. (2016) Bortezomib treatment sensitizes oncolytic hsv-1 treated tumors to nk cell immunotherapy. Clin Cancer Res pii: clincanres.:1003.2016.