

How can a failure in immune balance(Th17, Neutrophil, Tregs) lead to tumor invasion in lung cancer development : A Mathematical model

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ABSTRACT

Cancer cell invasion is a complex process that involves mutual interactions between a tumor and tumor microenvironment (TME)[1,2]. In the lung, the T helper cells (Th1/Th2/Th17) play a significant role in regulation of many diseases such as asthma and lung cancer [3,4,5]. In this study we consider complex interactions between a lung tumor and immune cells such as N1 and N2 neutrophil, T helper cell (Th1, Th2, Th17), T regs, and other T cells. There are two types of neutrophils, N1 and N2 phenotype. The N1 phenotype acts as classical immune cells, i.e, they attack and kills the tumor cells but the other type (N2 phenotype) is highly associated with other proactive tumor promotors to enhance the tumor activities [6]. Of course, there is a continuous spectrum between these types but these types at the end of the spectrum ray play a significant role in regulating tumor cell invasion through the extracellular matrix within the lung tissue by modifying the surrounding microenvironment and interacting with many other regulating cells such as Tregs and Th17 cells. We study this complex interaction by considering a system of partial differential equations and identify the key interacting components for cancer cell invasion. We find that tumor cell invasion can be controlled by modulating the inhibition components, indicating an anti-invasion strategies. The system shows the bistability behaviors in response to high and low signaling strength of both IL-6 and TGFbeta. These bistability can be perturbed by movement of the cancer cells and diffusion coefficient of immune cell-secreting molecules. We also develop several hypotheses on anti-cancer strategies in the presence of these immune cells in TME.

REFERENCES

1. Yangjin Kim, Ji Young Yoo, Tae Jin Lee , Joseph Liu, Jianhua Yu, Michael A Caligiuri, Balveen Kaur, and Avner Friedman, 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. Yangjin Kim, Seongwon Lee, You-Sun Kim, Yoon-Keun Kim, Yong Song Gho, Hyung Ju Hwang, Sean Lawler, Regulation of Th1/Th2 cells in asthma development: A mathematical model, Math. Bios. Eng., 10(4), 1095-1133, (Aug, 2013).
4. Seongwon Lee, Hyung Ju Hwang, Yangjin Kim, Modeling the role of TGF- β in regulation of the Th17 phenotype in the LPS-driven immune system, Bull Math Biol., 76 (5), 1045-1080 (May, 2014).
5. Ji Sun Lim, Seongwon Lee, and Yangjin Kim, Hopf bifurcation in a model of TGF- β in regulation of the Th 17 phenotype, Discrete and Continuous Dynamical Systems-B, 21(10), 3575-3602, Dec 2016.
6. A.D. Gregory and A.M. Houghton. Tumor-associated neutrophils: new targets for cancer therapy. Cancer Res, 71(7):2411-2416, 2011.
7. A. Mantovani, M.A. Cassatella, C. Costantini, and S. Jaillon. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol, 11(8):519-531, 2011.