Effect on tumor growth in systems of two different types of tumor-associated neutrophils : A mathematical model

Haneol Cho [1], Junho Lee [1] and Yangjin Kim [1,2]

1) *Department of Mathematics, Konkuk University, Seoul 143-701, KOREA*
2) *Mathematical Biosciences Institute, The Ohio State University, Columbus OH 43210, USA*

Corresponding Author: Yangjin Kim, ahyouhappy@gmail.com

ABSTRACT

Specific roles of Tumor-associated neutrophils (TANs) have been investigated in a tumor microenvironment: both tumor-promoting and tumor-inhibiting roles are reported. Due to technical challenges in experiments in tumor biology, the role of TANs has been underestimated, but these immune cells are being recognized as an emerging specialist in tumor invasion and metastatic regulation in recent years. In this study, we divided TANs into two different phenotypes with their respective antagonistic roles in the tumor microenvironment: (1) N1 TANs, the anti-tumor neutrophils and (2) N2 TANs, the tumorigenic neutrophils. With these two phenotypes, TGF-beta has been noticed as a major cytokine inducing N2 TAN domination, while IFN-beta and TGF-beta inhibitor enhance N1 TAN activities, suppressing tumor growth. We developed a new mathematical model to investigate the dynamics of tumor growth between tumor suppressive N1 TANs and tumor promoting N2 TANs based on partial differential equations and hybrid system. The critical, phenotypic transition between N1 TANs and N2 TANs in response to various TGF-beta, IFN-beta and TGF-beta inhibitor stimuli can be recognized in the model. We also observed how N1 TANs and N2 TANs affect tumor growth depending on which phenotype dominates. Finally, we investigated how a brain tumor may shape its growth pattern in a complex human brain structure with gray- and white- matter. This model, thus, may explain the complex dynamics of glioblastoma, a serious brain tumor with low survival rates, where recurrent tumor cells in other parts of brain kill most of cancer patients less than a year after diagnosis.

REFERENCES

1. Kim Y, Lee D, Lee J, Lee S, Lawler S. Role of tumor-associated neutrophils in regulation of tumor growth in lung cancer development: A mathematical model. PLoS One. 2019; 14(1):e0211041.

2. Shen L, Smith JM, Shen Z, Eriksson M, Sentman C, Wira CR. Inhibition of human neutrophil degranulation by transforming growth factor-beta1. Clin Exp Immunol. 2007; 149:155–161.

3. Saha S, Biswas SK. Tumor-Associated Neutrophils Show Phenotypic and Functional Divergence in Human Lung Cancer. Cancer Cell. 2016; 30(1):11–13.

4. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: N1 versus N2 TAN. Cancer Cell. 2009; 16(3):183-194.

5. Tuting T, de Visser KE. CANCER. How neutrophils promote metastasis. Science. 2016; 352(6282):145–146.