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Compartmental Mathematical Modelling of Immune System-Melanoma Competition

Marzio Pennisi[1], Carlo Bianca[2], Francesco Pappalardo[1] and Santo Motta[1]

[1] *Dipartimento di Matematica, Politecnico di Torino*

[2] *Dipartimento di Matematica & Informatica, Università di Catania*

emails: mpennisi@dmi.unict.it, carlo.bianca@polito.it, francesco@dmi.unict.it, motta@dmi.unict.it

Abstract

This paper deals with a preliminary model developed to sketch the immune response stimulated by the administration of OT1 activated cytotoxic T cells with Anti-CD 137 immunostimulatory monoclonal antibodies against melanoma cells. We model two compartments: the injection point compartment where the treatment is administered and the skin compartment where melanoma tumor cells proliferate. To model the migration of OT1 T cells and Antibodies from the injection to the skin compartment we use delay differential equations (DDE). We then present preliminary results showing the immune response entitled with the use of the treatment.

1 Introduction

Melanoma represents one of the most aggressive malignant tumors and it is due to the mutation of cells that produce the melanin (melanocytes). Many approaches in clinical and preclinical studies are actually based on the use and stimulation of cytotoxic T lymphocytes against melanoma cells. Immunological rejection of progressive tumors requires not only activation and expansion of tumor specific cytotoxic T lymphocytes (CTL), but also an efficient effector phase including migration of CTL in the tumor followed by conjugation and killing of target cells.

Accumulating evidence suggests that tumor-infiltrating lymphocytes are rendered anergic through the actions of co-inhibitory molecules expressed on the surface of tumor and stroma cells. Successful immunotherapy requires combined strategies that are able to

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turn-off deleterious signals while enhancing CTL migration and overall killing capacity [1]. CD137, also known as 4-1BB, is a co-stimulatory protein expressed on activated T, NK, B-lymphocytes, dendritic cells and tumor endothelium [2]. CD137 natural ligand, CD137L is present on the surface of activated antigen presenting cells [3]. Recently, in vivo experiments executed in B16-OVA mice models [2] revealed that the combination of in vitro Activated-OT1 cytotoxic T cells with Anti-CD137 immunostimulatory monoclonal antibodies that improve cytotoxicity, duplication rate and chemotaxis sensitivity of activated cytotoxic T cells are able to prevent the melanoma formation.

To catch-up the dynamics of this biological process we sketched a two-compartments model. We used Delay Difference Equations to model two different compartments: the injection point compartment where both antibodies and OT1 cells are injected and the Skin compartment where melanoma develops.

2 The Model

The experiment runs for 30 days. At day 0 B16-OVA mice receive one injection of melanoma malignant cells. The therapeutic treatment is administered at day 3. We built a mathematical model describing the biological process.

Equation 1 and 2 refer to first compartment and simulate the time evolution of both injected activated OT1 cytotoxic T cells (E) and antibodies (Ab) where kin(t; r) is a known function that represents the number of inoculated entities r at the scheduled injection time t. Both the entities migrate to the skin compartment with given rates (terms $-a_{11}E$ and $-a_{11}Ab$) and are subject to death or natural degradation (terms $-a_8E$ and $-a_{12}Ab$). Equation 3 describes the melanoma cells (C) behavior in the skin compartment. The first term $((a_1 - a_2 \ln(C)) \cdot C)$ represents a gompertizan growth whereas the second term denotes killing of C by Activated OT1 T cells that are already in the skin compartment (E_s). With equation 4 we describe the tumor associated antigen (A) dynamics. Antigens are released in the skin compartment by killed melanoma cells ($a_4 \cdot (a_3 C E_s)$) and are subject to natural degradation ($-a_5 A$).

Activated OT1 T cells that have migrated to the skin compartment (E_s) are described by equation 5. The term $a_7 A_s E_s$ is used to model duplication of OT1 T cells. Anti CD-137 antibodies that reached the skin compartment (A_s) are able to boost OT1 T cells duplication rates. The term $a_{11}E(t-\tau)$ models migration of OT1 T cells from the injection point to the skin compartment. OT1 T cells in the skin compartment are supposed to be proportional to the number of OT1 T cells in the injection point compartment with a proportionality constant a_{11} and a time delay of τ. Some antigens released by killed melanoma cells may be captured by presenting cells such as macrophages and dendritic cells and presented to Naive cytotoxic T cells (N). After the right chain of steps (i.e. stimulation by T helper cells) these cells may become active and then able to kill melanoma tumor cells. This process

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is not modeled since it involves to model other entities that are not essential at this first stage. We then estimate the number of newly activated OT1 cytotoxic T cells on the basis of released antigens with the term a_6NA. The last term $(-a_8E_s)$ reproduces natural death of OT1 T cells. Equation 6 models the behavior of Naive OT1 T cells that are already in the skin compartment. The term $h(M-N)$ models homeostasis. M is the number of circulating naive T cells under safe conditions given by the leukocyte formula. The second term (a_6NA) models the cytotoxic T cells state changing from naive to activated (E_s).

Antibodies that have reached the skin compartment (A_s) are modeled and described by equation 7. Antibodies in the skin compartment are supposed to be proportional to the number of antibodies in the injection point compartment (Ab) with a proportionality constant a_{11} and a time delay of τ. They also disappear by stimulating OT1 cells activities and are subject to a natural degradation (terms $-a_{12}A_s$ and $-a_9A_sE_s$).

Injection point compartment

$$\frac{dE}{dt} = kin(t,p) - a_{11}E - a_8E \quad (1)$$

$$\frac{dAb}{dt} = kin(t,k) - a_{11}Ab - a_{12}Ab \quad (2)$$

Skin compartment

$$\frac{dC}{dt} = (a_1 - a_2\ln(C))\cdot C - a_3E_sC \quad (3)$$

$$\frac{dA}{dt} = a_4\cdot(a_3CE_s) - a_5A \quad (4)$$

$$\frac{dEs}{dt} = a_7A_sE_s + a_{11}E(t-\tau) + a_6NA - a_8E_s \quad (5)$$

$$\frac{dN}{dt} = h(M-N) - a_6NA \quad (6)$$

$$\frac{dA_s}{dt} = a_{11}Ab(t-\tau) - a_9A_sE_s - a_{12}A_s \quad (7)$$

3 Preliminary Results and Conclusions

According to in vivo data from literature, our past experience in this field [4, 5] and experimental data coming from the experiment, we were able to find a preliminary tuning of the model able to qualitatively reproduce the time evolution of the system. In absence of therapy there is no induced immune response and thus melanoma cells grow up to their saturation threshold. In figure 1 we show the system behavior when the treatment is administered. Antibodies (Ab) and activated OT1 cells (E) are injected at day three and then migrate to the skin compartment (see fig.1 (g) and (d)). At the same time Antibodies (As) and activated OT1 cells (Es) in the skin compartment (fig.1 (f) and (c)) growth up to their maximum and cooperate to kill the melanoma cells (fig.1 (a)) entitling almost complete

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eradication before day 20. Note here that the number of activated OT1 cells in the skin (E_s) is also boosted by (previously) naive OT1 T cells (N) (see fig.1 (e)) that are recruited thanks to killed melanoma cells antigens (A) (fig.1 (b)). As an initial conclusion we can therefore say that the treatment acts in two ways: directly by activated OT1 cytotoxic T cells that are able to kill melanoma and Antibodies that boost T cells activities, and indirectly by promoting recruitment of naive OT1 cytotoxic T cells thanks to the releasing of melanoma cells antigens captured by presenting cells and then presented to these.

Further improvement to the tuning as well as deeper analysis of the model are on the way and will be presented in due course.

4 Figures

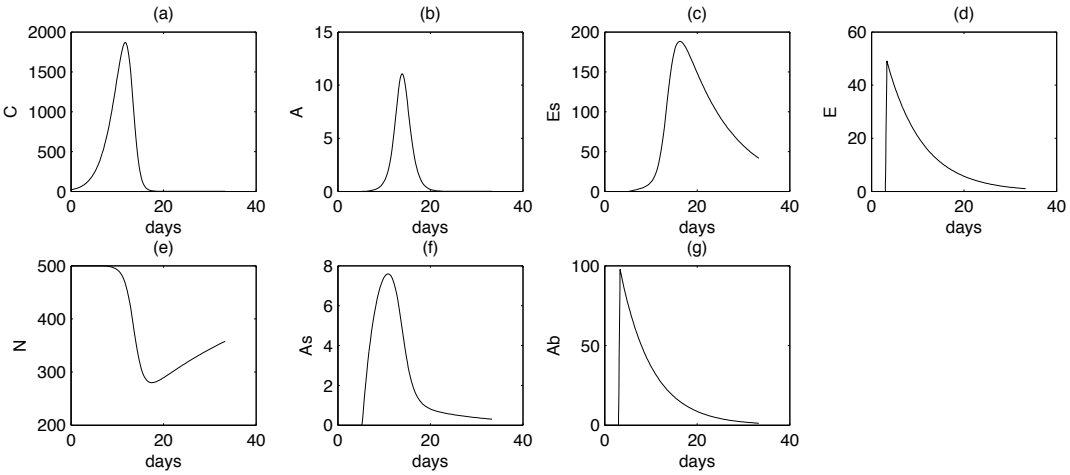

Figure 1: System behavior entitled with the use of activated OT1 cytotoxic T cells + AntiCD-137 monoclonal Antibodies.

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References

[1] Perez-Gracia JL, Berraondo P, Martinez-Forero I, Alfaro C, et al. *Clinical development of combination strategies in immunotherapy: are we ready for more than one investigational product in an early clinical trial?* Immunotherapy, 1:845-853 (2009).

[2] Palazon A, Teijeira A, Martinez-Forero I, Hervas-Stubbs S, et al. *Agonist anti-CD137 mAb act on tumor endothelial cells to enhance recruitment of activated T lymphocytes,* Cancer Res, 71:801-811 (2011).

[3] Melero I, Murillo O, Dubrot J, Hervas-Stubbs S, Perez-Gracia JL *Multi-layered action mechanisms of CD137 (4-1BB)-targeted immunotherapies,* Trends Pharmacol Sci, 29:383-390 (2008).

[4] Pennisi M, Bianca C, Pappalardo F, Motta S. *Modeling artificial immunity against mammary carcinoma,* CMMSE 2010, ISBN 978- 84-613-5510-5, 753-756 (2010).

[5] Pennisi M, Pappalardo F, Palladini A, Nicoletti G, Nanni P, Lollini P-L, Motta S *Modeling the competition between lung metastases and the immune system using agents,* BMC Bioinformatics, 11(Suppl 7):S13 (2010).