Mathematical Modeling of Cancer Treatment Cultured with Chemo-Immunotherapy by Cytokine Interleukin IL-12

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Abstract: Interleukin IL-12 being heterodimeric pro-inflammatory cytokine has potential to enhance the anti-tumor immune responses. In this paper we have developed a new mathematical model for tumor regression by using this important immunoregulatory cytokine interleukin IL-12 in the form of coupled ordinary differential equations. We have formulated our model focusing on cellular populations of tumor cells, NK cells, CD8+T cells and circulating lymphocytes scheduled with chemo-immunotherapy under the impact of IL-12. Our model has extensive applications in cancer treatment therapies and exhibit improved control on tumor regression. Experimental verification of our model in the form of simulation is devoted to future work.

Key words: Interleukin IL-12 • Immunotherapy • Chemotherapy • Cancer Model • Immunoregulation

INTRODUCTION

Interleukin IL-12 is an important immunoregulatory cytokine with unique heterodimeric structure [1-4]. It was discovered in 1989 by Trinchieri and colleagues [5, 6]. In 1990, Gately and colleagues called it as “Natural killer-stimulating factor” and “cytotoxic lymphocytes maturation factor” [3, 4, 7, 8]. It was firstly identified as Epstein Barr Virus transformed human B cell Lines. It is produced from antigen presenting cells and is secreted from TH1 cells which are subtype of CD4+T cells. It includes other family members IL-23, IL-27 and IL-35 [1]. Initially it was known as T Cell Differentiator Factor(TCDF). It enhances the expansion, activation and killing functions of NK and T cells [2, 4, 6, 9, 10]. It has shown antitumor activity in various murine models of melanoma, mammary carcinoma, colon carcinoma and sarcoma. It is known as a therapeutic cytokine for cancer. It has potential to induce counter regulatory cytokines such as IL-10 [2]. It is a multifunctional cytokine and regulates the cellular immunity [3, 6, 9-12]. The effective antitumor responses produced from IL-12 supported its clinical applications [6, 10-12]. National Cancer Institute (NCI) has recommended it as a high potential anticancer cytokine [6]. It enhances the IFN-γ secretion which produces antitumor effects and it also increases the recruitment of TH1 cells and decreases the recruitment of TH2 cells [3, 6]. In 1993, Hsieh et al. discovered that it produced differentiation of TH1 T cells [3]. It has shown potent antitumor effects in preclinical studies [4, 13].

Tumor is the mass of tissue formed due to uncontrolled proliferation of abnormal, excessive and purposeless cells [14]. Surgery, radiotherapy, chemotherapy and biotherapy (based on oncolytic virus) [29] are among the current approaches to eradicate tumor. Out of these techniques, chemotherapy is the conventional tool for fighting against cancer and possesses side effects because it destroys the normal cells of the body along with killing cancerous cells [15-18]. Recently immunotherapy is playing an essential role to eliminate tumors. Therefore, in order to cope with tumors many strategies to strengthen the immune system have been used by the clinicians, scientists and researchers like vaccination, monoclonal antibodies, lymphocytes and cytokines [14, 19]. Because biological
systems are complex in nature therefore they must be treated and analyzed through some mathematical and computation modeling methodologies [19].

Historically a great number of clinicians, scientists and researchers have adopted mathematical modeling techniques under the impact of different cytokines to cope with this fatal disease. Antonio Cappuccio and colleagues model the tumor-immune interaction under the influence of interleukin-21. De Pillis developed his model under the impact of IL-2 for tumor regression then Mustafa Mamat extended the de Pillis model by incorporating Interferon-α (IFN-α) to enhance the tumor regression efficiency. We have developed a new mathematical model describing the tumor-immune interaction cultured with chemo-immunotherapy under the influence of interleukin IL-12. We want to investigate the behavior of our formulated model under this immunoregulatory cytokine for better tumor regression efficiency.

**Biological Assumptions:** Our model is based on some biological assumptions that have also been narrated in [16, 20, 21, 22, 23, 24] and we have rewritten here for our convenience.

- A tumor grows logistically in the absence of immune response.
- Both NK cells and CD8+T cells can kill tumor cells.
- IL-12 depends on dosage because it is introduced through the administration of vaccine.
- Natural Killer (NK) cells being part of the immune system are always present even no tumor cells exist.
- Active tumor specific cells as being part of the immune system are present only when tumor cells are present.
- Each of the NK and CD8+T cells become inactive after some number of encounters with the tumor cells.
- Despite the activated CD8+T cells and NK cells, the action of all other lymphocytes including circulating lymphocytes C (t), has been included.
- Effects of IL-12 are considered on NK, CD8+T and circulating lymphocytes cells. Major focus of the model is on the contribution of IL-12 to the cellular immunity. Moreover we consider only the exogenous IL-12 i.e. externally concentrated.
- CD4+T helper cells are also neglected because they have minor contribution to anticancer response and also have low secretion as compared to the other therapeutic doses.
- NK and CD8+T cells respond with tumor cells by expanding and increasing metabolic and catalytic activity.
- IL-12 causes inactivation of tumor cells.
- The fraction of the tumor cells killed by the chemotherapy depends on the amount of the drug in the system and this killed fraction is always less than one.
- Chemotherapy also kills some fraction of the NK, C(t) and CD8+T cells.
- Immune system possesses self-regulatory nature because activated effector cells i.e. NK and CD8+T cells form the cyclic process of stimulation and decay.

**Model Populations:** Our model carries the following cellular populations such that each cell population represents one state variable represented below

- $T(t)$ Tumor cell population
- $N(t)$ Natural Killer cell (NK cell) population
- $L(t)$ CD8+T cell population
- $C(t)$ Circulating lymphocytes
- $M(t)$ Chemotherapy concentration drug
- $IL-12$ Interleukin concentration drug

Besides considering assumptions and populations our model carries the four types of actions which are described below.

- Natural growth
- Natural decay
- Death of mediated cells
- Recruitment
- Exogenous drug

Each term in the ordinary coupled differential equations represents a single action like reproduction of population growth, natural elimination death and death of one cell population from another cell population, cell being recruited and external drug intervention [21]. The function and interaction of cell populations with drug concentrations are depicted in schematic diagram Fig.1.

**Schematic Diagram:** The above discussion can be formulated in the form of two generalized equations (A-1) and (B-1) [22] which are given below

(A-1) Rate of change of tumor cell population = (growth and death rate term) – (cell- cell kill rate term).
Fig. 1: Schematic diagram of the tumor-immune interaction. Cell populations have been represented by circles and ellipse. Small rectangles with downward arrow show the impact of IL-12. Left and right arrows show the chemotherapeutic effect on cellular populations. Other interactions among the cellular populations have been shown by vertical and curved arrows.

(B-1) Rate of change of active effector cell population = (growth and death rate term) + (recruitment rate term) - (Inactivation rate term).

Now we are able to develop the growth equations and explaining core theory involved in our models.

Theory and Calculations: All the above stated physical assumptions, cell populations, schematic representation and generalized equations [1, 2, 13, 19, 21] constitute a concise mathematical model comprising of coupled ordinary differential equations (A-G) given below

\[
\frac{dT}{dt} = aT[1 - bT] - cNT - DT - k_T(1 - e^{-M})T - C_{\text{CTL}}[2 - e^{\frac{LT}{N}}]
\]

(A)

\[
\frac{dN}{dt} = eC - fN - pNT + \frac{pN}{N + H_{12}} - k_N(1 - e^{-M})N
\]

(B)

\[
\frac{dL}{dt} = -mL + \frac{e\text{IL-12}}{K_r + \text{IL-12}} - qLT + rNT + lT_C - k_L(1 - e^{-M})L + V_L(t)
\]

(C)

\[
\frac{dC}{dt} = \alpha - \beta C - k_C(1 - e^{-M})C
\]

(D)

The parameters used in this model vary from patient to another however, some particular experimental and clinical studies agree with the arbitrary values of these parameters which are given in Table-1. Now we justify dynamics involved in our model.

Justification of Terms of Model

Tumor Cell Dynamics Eq (A): On R.H.S of equation (A) the first term \(aT[1 - bT]\) represents the tumor growth that grows logistically. This logistic law is based on the immunodeficient mice data that has been collected from [25]. Tumor growth is influenced by the cytotoxic, NK cells and CD8+T cells exhibiting antitumor response. Second term \(-cNT\) is the tumor cells killed by the activated NK cells. The term \(-DT\) where the value of \(D\) has been given separately in equation (G) is the tumor cells killed by the activated CD8+T cells. The term \(-k_T(1 - e^{-M})T\) indicates the chemotherapeutic effect on tumor cells. It represents the fraction of the tumor cells killed by the chemotherapy \(M(t)\). Last term \(C_{\text{CTL}}[2 - e^{\frac{LT}{N}}]\) of the equation (1) gives the influence of the IL-12. IL-12 is inculcated through the vaccine. \(C_{\text{CTL}}\) is the rate of tumor cells inactivated by cytotoxic lymphocytes (CTLs). The addition of growth term, cell kill terms along with chemotherapeutic and IL-12 effects gives net tumor growth on R.H.S while on L.H.S the term \(\frac{dT}{dt}\) represents the rate of change of tumor

Table 1: Parameters used in model

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Parameter</th>
<th>Values</th>
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<td>(a)</td>
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<td>[21]</td>
<td>(q)</td>
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<td>[20]</td>
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<tr>
<td>(b)</td>
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<td>[21]</td>
<td>(r)</td>
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<tr>
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<tr>
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<td>(k_c)</td>
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<tr>
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<td>(J)</td>
<td>(1.245\times10^2)</td>
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</table>
cell population. Thus all constituents involved in tumor cell dynamics satisfy equation (A) by following the equation A-1. Similarly we justify the other equation of our model by taking into consideration the equations A-1 and B-1 as follows.

**Natural Killer (NK) Cell Dynamics Eq (B):** NK cell population follows the logistic growth law \( eC - fN \) whose further justification is given in Chang et al. [26]. The contribution of IL-12 is given by the term \( \frac{PN \cdot IL_{12}}{\gamma N + IL_{12}} \) through the activation term [19]. The inactivation term \(-pNT\) represents the NK cell death by tumor killing and the last term of this equation \(-k_c(1 - e^{-u_t})N\) indicates the NK cell death by chemotherapy. Thus the sum of self growth, decay rates and inactivation terms constitute the net growth rate of NK cells.

**CD8+T Cell Dynamics Eq (C):** Here \(-mL\) represents natural growth of CD8+T cells which is proportional to the death rate [22]. IL-12 is partially absorbed by the stimulation signals through the recruitment term \( \frac{jIL_{12}}{k + T} \).

CD8+T cells death by tumor killing resources is given by the inactivation term \(-qLT\). The cells killed due to recruitment are proportional to \( rN \). The term \( r_c CT \) represents the presence of tumor cells given by the encounters between circulating lymphocytes and the tumor [22]. The chemotherapeutic effect on CD8+T cells is given by \(-k_c(1 - e^{-u_t})L\). \( V(t) \) gives the CD8+T cell injected drug concentration. Thus all the terms added to given net rate of change of CD8+T cells \( \frac{dT}{dt} \) satisfying the equation (B-1).

**Circulating Lymphocytes Dynamics Eq (D):** Here the term \( \alpha - \beta C \) has been explained in depth in [21, 26]. There is no apparent interaction of IL-12 with circulating lymphocytes. The last term \( k_c (1 - e^{-u_t})C \) gives the chemotherapeutic impact on circulating lymphocytes.

**Chemotherapeutic Dynamics Eq (E):** The rate of change of chemotherapy is equal to decay or elimination of chemotherapy drug \(-\gamma M\) plus chemotherapy drug intervention \( V_{sd}(t) \).

**Interleukin IL-12 Dynamics Eq (F):** Here the rate of change of IL-12 is equal to decay of IL-12 i.e. \(-\mu IL_{12}\) plus administration of IL-12 given by the term \( V_{IL_{12}}(t) \) in the form of dosage infusion.

Eq (G): Represents killing of tumor cells by the activated CD8+T cells.

**DISCUSSION AND ANALYSIS**

For analysis we consider our model in the absence of treatment [22] i.e. when we eliminate chemoinmunotherapeutic effect and external administration from our model we get the following system of equations

\[ \frac{dT}{dt} = aT[1 - bT] - cNT - DT \]  
\[ \frac{dN}{dt} = eC - fN - pNT \]  
\[ \frac{dL}{dt} = -mL - qLT + rNT + r_c CT \]  
\[ \frac{dC}{dt} = \alpha - \beta C \]  
\[ D = d(L/T)^{1/2}/(s + (L/T)^{1/2}) \]

By non-dimensionalizing the above equations we have the following system of equations [22] while quotation (5) remains the same.

\[ \frac{dT}{dt} = T[1 - T] - cNT - DT \]  
\[ \frac{dN}{dt} = C - fN - pNT \]  
\[ \frac{dL}{dt} = -mL - qLT + rNT + r_c CT \]  
\[ \frac{dC}{dt} = 1 - \beta C \]

In order to find the equilibria of the system of equations (1-4) we put all the equations simultaneously equal to zero [22].

\[ 0 = T[1 - T] - cNT - DT \]  
\[ 0 = C - fN - pNT \]  
\[ 0 = -mL - qLT + rNT + r_c CT \]
resistance of adaptive and innate mechanism against
tumor. In vitro IL-12 has enhanced the cytoxicity of
healthy cells against colon carcinoma and neuroblastoma
cell lines. Animal studies have shown that IL-12 had
dramatic impact in decreasing the tumor growth and
delaying death [5]. The delay growth property of IL-12
has also been observed with reticulum cell sarcoma
M5076 and with renal cell adenocarcinoma renca [5]. Due
to delay of tumor growth property encouraged its
utilization for preparation of cancer vaccine. IL-12 acts like
a bridge between innate resistance and adaptive immune
response. It becomes central cytokine against cancer.

IL-12 has productive effects on the immune system.
IL-12 has proven very effective for the treatment of
leukemia in animals. And human trials are under progress.
A recent research at University Health Network (UHN)
shows that IL-12 administered through transduced
leukemia cells has strong anticancer effects. In mouse
Acute Lymphoblastic leukemia (ALL) model IL-12 has
demonstrated long lasting anticancer effects (J. Medin
and C. Paige, IL-12 Immunotherapy for the Treatment of
cancer, Technology Development & Commercialization,
University Health Network UHN Reference # 8062). Also
the studies [27, 28] confirmed the suggestion of IL-12 as
antitumor cytokine but prohibited the high dosage. IL-12
has shown therapeutic efficacy in many solid tumors like
hematological leukemias and lymphomas. Intra tumoral
injection of IL-12 produces significant anti-tumor effects
in mice. Heinzerling at al., in two animal models first B16
melanoma in C57BL6 mice and secondly human melanoma
xenografts in nude mice showed significance tumor
regression [13]. All the studies till now demonstrated the
antitumor effects of IL-12.

Our developed model may compensate the two drugs
IL-2 and INF-α in M. Mamat’s model because from
theoretical modeling process we observe from the terms
involved that our model is comparable to that with model
[20]. Now it depends on the simulation of our model that
our model is better than M. Mamat’s model or than De
Pillis model. IL-12 proteins have completely eradicated the
murine breast cancer. Currently IL-12 is under human
clinical trials alone and with combination of other
cytokines to eradicate solid tumors at National Institute
for Health (NIH), National Cancer Institute (NCI)
(Bethesda, MD) and Beth Israel Deaconess Medical
Centre (BIDMC) (Boston, MA). IL-12 and INF-α both are
derived from macrophages and have same antitumor
effects. Eguchi et al. has showed IL-12 as additive
antitumor effects in MC38 colorectal cancer. As both
cytokines IL-2 and INF-α are involved in M. Mamat’s

\[ 0 = 1 - \beta C \]  
\[ \text{So at equilibria we have} \]
\[ C_{\text{equilibria}} = \frac{1}{\beta} \]  
\[ \text{Solving equation (10) for} \ N \]
\[ N = \frac{c}{f+pT} \]  
\[ \text{Substituting the equations (15) and (5) in equation} \ (10) \ \text{and solving for} \ L \]
\[ L_{1} = \frac{s\left(\frac{T}{T(1-\frac{e^{-\mu T}}{T})}\right)}{d-T(1-\frac{e^{-\mu T}}{T})} \]  
\[ \text{Now substituting the value of equation (15) in} \ (12) \ \text{and solving for} \ L \]
\[ L_{2} = \frac{r\left(\frac{c}{f+pT}\right)^{T}+r_{2}CT}{m+qT} \]  
\[ \text{Equilibriums points of equations (5-9) can be} \]
\[ \text{obtained by intersection of the equations (16) and (17).} \]
model therefore under the above stated circumstances IL-12 may produce better tumor regression efficiency through our developed model. IL-21 plays an active role to enhance the IL-12 induced production of IFN-γ [13]. We conjecture that our developed model produces the antitumor efficiency between IL-21 induced and IL-2 plus IFN-γ induced antitumor efficiencies or it may be better than the both cases.

CONCLUSION

Mathematical modeling of the immune system is an active research topic carrying a few practical applications. In this paper we have formulated a new mathematical model for cancer treatment focusing on the cellular population of the immune system cultured with chemo-immunotherapy under the impact of heterodimeric cytokine IL-12. IL-12 remains unique and promising antitumor cytokine. Our model may have better tumor regression efficiency. It needs experimental verification in the form of simulation. Future perspective of the modeling involves the discovery of new medical knowledge, developments of new devices and new simulation softwares. Emerging area of research is the investigation of IL-12 family members IL-23 and IL-27 for tumor regression through mathematical modeling techniques and their immunomodulatory along with antitumor effects both In vitro and in vivo suggest their future immunotherapy protocols. Combing IL-12 with other cytokines i.e. combined therapies for cancer treatment have also become active approach for the researchers.

REFERENCES