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Simulation-Based Software Modeling of CAR T Cell Therapy Efficacy Against Solid Malignant Tumors

Daivat Bhavsar[1*], Yu Jun Li[2]

[1]Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada
[1]Faculty of Science, McMaster University, Hamilton, ON, Canada
[2]Faculty of Arts and Sciences, Harvard University, Cambridge, MA, USA

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***Correspondence:**
daivat25@student.ubc.ca

ABSTRACT

Genetically engineered T cells with Chimeric Antigen Receptors, CAR T cells, are a revolutionary immunotherapy used to treat advanced blood cancers. The purpose of this experiment was to model the destruction process of tumor cells with CAR T cell therapy using Complexity and Organized Behaviour Within Environmental Bounds (COBWEB), an agent-based simulation software. We designated parameter values for abiotic factors, agents (i.e. tumor cells, T cells) and the general environment in our immunotherapy simulation model to illustrate the interactions between tumor cells and cytotoxic components, which described the binding of innate CD8+ T cells or CAR T cells to tumor antigens. The models were used to observe and comparatively analyze the rate of destruction of a solid tumor by CAR T cells and innate CD8+ T cells. The solid tumor developed in a circular island for 60 ticks, representing days; innate CD8+ or CAR T cells were then able to infiltrate the island and the tumor cell population was monitored over 500 days. The CAR T cells exhibited a significantly powerful, efficient immune response against a general solid tumor relative to the innate CD8+ T cells, yet relapse occurred in both models albeit to a lesser extent with CAR T cells. However, further investigations are required to adequately simulate the side effects and realistically-limiting factors of CAR T cell therapy. Similar comparative analyses may help measure and compare the potency of the immune response of CAR T cells compared to standard, or lack of, treatments.

The intricate explorations of the immune system have allowed for the rapid rise in popularity and potential of cancer immunotherapy. Immunotherapy is a recently, but already widely-recognized domain of cancer immunology that involves programming the body's immune components to direct the war against growing metastatic and malignant tumors [1].

Immunotherapy allows the body to optimize its innate and adaptive defense systems, often with the help of genetic engineering. Tumor cells have unique antigens on their surfaces that are not expressed on healthy cells, and these antigens can be specifically targeted by T cells for tumor growth inhibition and regression [2]. However, the natural adaptive immune response is often lacking effectiveness when it has to destroy the tumor.

Tumor cells may learn to evade immune surveillance mechanisms as a form of natural selection, or alternatively may hijack T regulatory cells to halt innate antitumor response [3]. The inability of innate CD8+ T cells to recognize and attack tumors leads to uncontrolled tumor growth and metastasis. CD8+ T cells are innate killer T cells, whose primary function is to launch a cytotoxic response against virus-infected or cancerous cells. Chemotherapy is often used as a general therapeutic to treat various types of cancer by eliminating the rapidly-proliferating cancer cells directly. However, the rise of immunotherapies in cancer therapeutics has allowed for a more selective and relatively more patient-friendly treatment wherein the body's immune system can recognize and destroy tumor cells of specific cancers such as blood, bladder, prostate, and skin [5].

One renowned form of immunotherapy is CAR T cell therapy. The breakthrough design of modified T cells with Chimeric Antigen Receptors (CAR T cells) has led to a revolutionary form of immunotherapy that involves the genetic engineering of T cells to better recognize the specific antigens of tumor cells for destruction. This design of Chimeric Antigen Receptors involves extracting and purifying a patient's T cells from blood. In these cells, the specific CAR gene is inserted to produce additional chimeric antigens on the surface of T cells, now termed 'CAR T cells', which efficiently recognize tumor cells [4]. Millions of CAR T cells can be grown in the laboratory and inserted back into the patient via the bloodstream. These CAR T cells show stronger binding affinity and recognition ability for the specific antigens of tumor cells on macrophages [6]. Once they recognize these specific macrophages, the cytotoxic response is induced by the CD8+ T cell to vigorously damage or eliminate the tumor cell with the release of toxins such as cytokines. Compared to other immune approaches, the strategy of reprogramming T cells is a highly-specific emerging biotherapeutic that can effectively target and overcome the deceptive nature of tumor cells [5] (Table 1).

Table 1. A comparison of the various immune approaches in cancer treatment

Approach	Description	Advantages	Disadvantages
CAR T cell therapy	Engineering patients' T cells to express receptors to target a specific cancer antigen [1, 2].	Highly specific to the cancer as they are reprogrammable; highly effective in treatment of blood cancers (i.e. leukemia) [4].	Can cause cytokine release syndrome and severe toxicities [6].
Checkpoint inhibitors	Block the proteins on T cells (i.e. PD1, CTLA-4) that tumor cells use to evade the immune response [3].	Relatively few toxicities, broad applicability to various cancers [3].	Not as effective if T cells and other immune cells are unable to infiltrate tumors; tumors can develop resistance through mutation [3].
Cancer vaccines	Simulating immune cells to detect and infiltrate tumors [7].	Highly specific to cancer, similar to CAR T cells [7].	More prone to resistance and evasion; relatively costly to design and distribute [7].
Natural killer (NK) cell therapy	Isolation and expansion of NK cells to target and destroy tumors [7].	Broad applicability to various cancers; patient response rates greatly vary [7].	Low specificity as NK cells are part of the innate immune system; can cause cytokine release syndrome [7].
Bispecific antibodies	Antibodies that recognize both tumor and immune cells, promoting the anti-tumor immune response [7].	Highly specific; can be used in combination with other immunotherapies [7].	Tumors are constantly mutating and can learn to evade newly-developed antibodies, leading to relapse [7].

However, some immune approaches to treating cancer, including CAR T cells, have the drawback of causing severe toxicities through cytokine release syndrome (CRS) [7] (Table 1). CRS is an inflammatory process often characterized by acute dysfunction of multiple organs due to high levels of circulating cytokines, such as interleukin-6 (IL-6) [1]. Nevertheless, novel strategies that can minimize the CRS effect without reducing the efficacy of CAR T cell treatment have emerged, such as administering a combination of corticosteroids and tocilizumab, which blocks the inflammatory IL-6 protein, to reduce CRS toxicity [8]. There are also general safety approaches to cancer treatment, such as administering patients with gradual increases in immunotherapy dose and careful monitoring for adverse effects, as well as the use of predictive patient biomarkers to personalize treatment decisions after hypothesizing the likely outcomes [7, 8]. In this study, potential CRS associated with CAR T cells will be considered negligible and will not be programmed into the simulation models.

The COBWEB Program is a simulation software created by Dr. Brad Bass [9]. COBWEB is used to model the immune response with and without CAR T cells to provide a learning aid for the general public and elucidate the effectiveness of this immunotherapy. As an agent-based model, tumor cells and T cells are replicated as separate agent types in a simulated environment representing the biological immune system. Essentially, one model will be designed for the interaction between innate CD8+ cells and tumor cells, and another will be created similarly with enhanced CD8+ T cells (CAR T cells). Parameters within the model induce interactions between tumor cells and CAR T cells; deceptive and deflective characteristics of the tumor and CAR T cells are embedded in the simulation to emphasize and illustrate the efficiency of the developing CAR T cell therapy. The simulation of the immune system's response to CAR T cell therapy depicting the interactions between treatment cells and tumor cells may help to propel research directions in quantifying the effectiveness of cancer immunotherapies.

Methodology

Using the COBWEB Program

COBWEB models are built around independent agents, grouped into types that are designed to represent system components. COBWEB also offers resources for each agent type and "stones" that can be used as barriers. Agents disappear from the COBWEB grid when they run out of energy, and every action requires energy. Energy is gained from resource consumption. The number of agent and resource types, agent and resource properties and features to control interactions are found under multiple tabs in the COBWEB software. Time is measured by an arbitrary unit called a tick. A tick is counted when every agent makes one move on the grid.

The simulations involve two agent types in COBWEB defined to represent tumor cells (Agent 1) and T cells (Agent 2). The model simulates the engineered CAR T cells and innate CD8+ T cells, against a solid malignant tumor. The CD8+ T cells simulation was used as a control group because the CD8+ T cells represent the standard immune response to cancerous cells without treatment. The T cells are to attack the tumor cells by directly feeding on them, which is set up in COBWEB under the 'Food Web' tab. Under the 'Food Web' tab, Agent 2 was programmed to feed on Agent 1 (tumor cell) upon contact. An island of tumor cells was created for establishing the congregated tumor in one location before T cells launched a cytotoxic response, which occurred once the island was offset after 60 ticks. The food resources grew in and around the islands to feed the appropriate agents (i.e. yellow food congregates at

the same location as the yellow agents (tumor agents) to fuel their growth). The total length of each simulation is 500 ticks with each tick representing approximately one day[1]. Therefore, the immunotherapy was introduced 60 days (2 months) after the tumor was first detected and continued for 17 months (500 days). This timescale is arbitrary, but the rate of tumor growth in 60 ticks is similar to what can be inferred from the literature for 60 days.

Innate CD8+ T Cell Model Methods

The normal tumor model was designed as the control group. The tumor cells (Agent 1) were located in the circular islands and parameter values were selected to represent its characteristics. The parameters under the Agents tab were altered to create the interaction between normal T cells and tumor cells. The 'initial count' of tumor cells (Agent 1) was set at 35 tumor cells and a T cell (Agent 2) initial count of 20 T cells. These numbers are relative estimates of the ratio between normal tumor cells to T cells in the cancer patient's system. To ensure the tumor cell was appropriately fed, the parameter: 'Agent eating efficiency' was set at 100%. For Agent 2, the 'Agent eating efficiency' was set to be 50%. These two parameters arbitrarily regulate the feeding behavior of Agents 1 and 2 in the presence of one another.

The parameter values for 'Step energy', 'Agent bump energy', 'Food Web' were altered to illustrate the ability for T cells to detect the antigen of tumor cells using their antigen receptors. Under the 'Food Web' parameter, Agent 2 or the T cells are programmed to feed on the tumor cells upon direct contact. 'Step energy' is representative of the effectiveness of T cells against tumor cells and the tumor cells' response to attacking T cells. 'Step Energy' is 5 units for T cells to ensure T cells will detect tumor antigens and release enzymes upon detection accordingly. The 'Step Energy' for Agent 1 was 2 units, to ensure the tumor cells adequately detect the antigen receptor of T cells and facilitate a response. The 'Agent bump energy' parameter forces Agent 1 and 2 to lose energy upon contact with one another. When the T cell detects and attacks tumor cells, both agents will lose energy. Agent 1 was set at 5 units, and Agent 2 was set at 40 units to generate a more rapid growth of tumor cells in comparison to T cells. For Agent 2, specifically, breed energy was set at 80 units to generate T cells as the tumor cells exponentially grew between 0 to 60 ticks. The T cells will experience aging, so the T cell will expire after 300 ticks. All other parameters remain unchanged.

At the end of 60 ticks, the agent abiotic factors are manipulated to the same preference value and preference difference factor so that Agent 2 is the same as Agent 1 (tumor cell) so the T cells can infiltrate the island and generate a cytotoxic response against the tumor cells. The simulation is run for a total of 500 ticks and another screenshot is taken to use as a comparison against the CAR T cell model. The populations of general tumor and innate CD8+ T cells are plotted against the number of ticks as a double line graph (Figure 1A).

CAR T Cell Model Methods

The 'Agents' parameters for the Agent 2, representing the CAR T cells, were manipulated on the COBWEB model to represent a higher efficiency of these engineered cells. The efficiency of the immune response elicited by the innate or engineered T cells was measured using the number of tumor cells surviving after 500 ticks. Specifically, the 'breed energy' of Agent 2 was

[1] Ticks are arbitrary time units. Given the prognosis of cancers being one to five years, one tick appropriately represents one day.

decreased from 80 to 60 units, agent eating efficiency was doubled, and agent bump energy, turn left and right energy were halved. Although the relative factors of these energy expansions are an estimation, these alterations serve to depict the CAR T cells as the basis of a more energy-efficient powerful immune system with increased longevity and vigorous attack.

Similar to the normal T cell model, all other parameters are unchanged and the program is first run for 60 ticks to create an island of congregated tumor in a certain area of the body as in the innate T cell model. The T cells approach and surround the tumor. The number of tumor cells was observed at the end of 60 ticks. To stimulate the attack of CAR T cells against a solid tumor, the simulation file is modified, so all the CAR T cells can access the tumor to begin their cytotoxic response. The simulation is run for a total of 500 ticks. The populations of general tumor and CAR T cells are plotted against the number of ticks as a double line graph (Figure 1B).

AI Seed

When investigating the efficiency of CAR T cell response against a solid tumor response, the Artificial Intelligence (AI) parameter was utilized to randomize the tumor and CD8+ population count. Each experimental trial was performed with a new "seed" (population) to generate random populations and the impact of CD8+ and CAR T cells against the tumor. This parameter allowed five trials to be performed for each type of T cell (normal vs. CAR T cell) to minimize random errors for a more valid comparison of the T cell therapy (Table 2).

Results

Cytotoxic Response of Normal/Innate CD8+ T cells Against Tumor at 60 ticks

Tumor cells are concentrated in the island illustrated by the yellow particles of food (source of energy) and yellow agents within a definable circle. The immune-response components, T cells, are located in the areas surrounding the island, but are not yet able to enter the island region yet (Figure 2A). This is the developing stage of the tumor. The population of T cells represents the innate number of CD8+ T cells in a patient's body before immunotherapy.

Cytotoxic Response of Normal/Innate CD8+ T cells Against Tumor at 500 ticks

Tumor cells have evidently decreased in number as the normal T cells begin to detect and infiltrate the island of tumor and launch an attack, as seen by the cyan agents entering the island space. However, the tumor population has had enough time to replenish at the end of the simulation and remain concentrated within the island at the end of 500 ticks (Figure 3A). This concentration of tumor cells may allow for a relapse of the tumor which is observed by a second wave, as would be expected without immunotherapy treatment or other interventions (Figure 1A).

Cytotoxic Response of CAR T cells Against Tumor at 60 ticks

In the CAR T cell model, the tumor cells are concentrated on the island, as illustrated by the yellow particles of food (source of energy) (Figure 2B). The CAR T cells are illustrated by the cyan agents surrounding the island filled with tumor cells. The number of T cells has increased

significantly due to the insertion of CAR T cells into the patient's body after immunotherapy (Figure 1B).

Cytotoxic Response of CAR T cells Against a Tumor at 500 ticks

In direct comparison to the response of innate CD8+ T cells at 500 ticks, there is a dramatic decrease in tumor cells (Figure 1B). Again, the T cells surround the island and have evidently infiltrated, as was observed by the cyan agents (Figure 3B). The island consists of primarily CAR T cells rather than tumor cells, whereas few tumor cells remain on one edge, and each cell (yellow agent) is heavily surrounded by CAR T cells.

Table 2. Investigating the impact of CAR T cell treatment using the artificial intelligence (AI) tab to randomize the immune response

Type of T Cell and Trial #	Tumor population 60 Days	Tumor Population 500 Days	Tumor Reduction Percentage
Normal 1	758	258	65.96%
Normal 2	533	138	74.11%
Normal 3	388	138	64.43%
Normal 4	495	200	59.59%
Normal 5	406	136	66.50%
Average	66.12%		
CAR 1	430	17	96.05%
CAR 2	691	89	87.12%
CAR 3	417	37	91.13%
CAR 4	608	48	92.11%
CAR 5	487	57	88.30%
Average	90.94%		

Figure 1. Modeling the cytotoxic response of innate CD8+ T cells (A) and CAR T cells (B) against a general solid tumor. The graph illustrates the average population of tumor cells (blue line) and either normal/innate CD8+ T cells or CAR T cells (red line) over the period of 500 ticks. The simulation was modified at 60 ticks (days) to allow the T cells to begin infiltrating the island to attack the tumor cells. Data represents the mean of five trials.

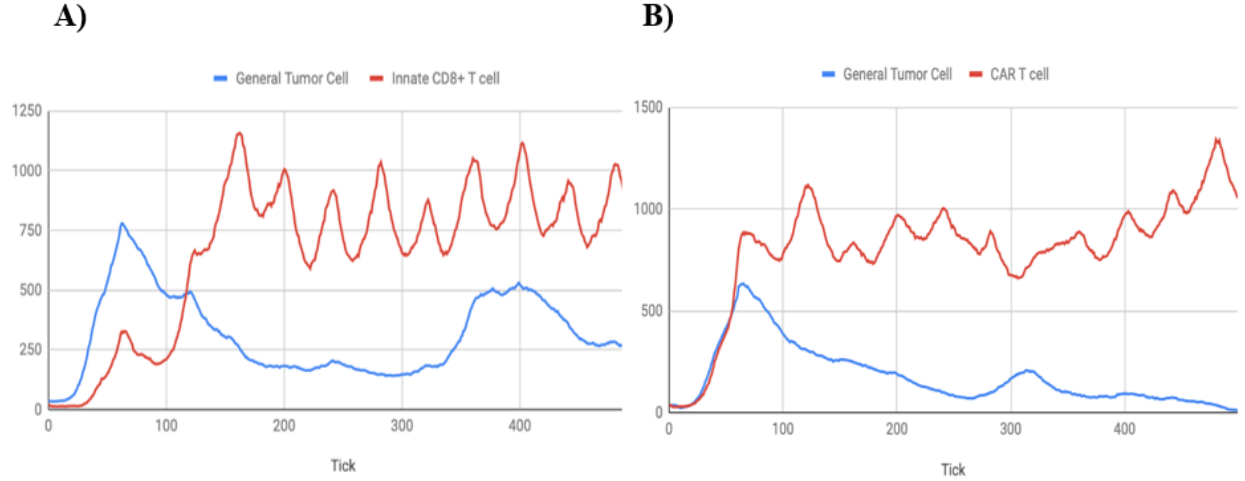

Figure 2. Cytotoxic response of innate CD8+ T cells (A) and CAR T cells (B) at 60 ticks. The yellow-dotted triangles are agents that represent the tumor cells that have grown over 60 ticks (days). The yellow-filled squares represent the resources of tumor cells occupying the tumor microenvironment, represented by the circular yellow island. The cyan-dotted triangles are agents that represent the T cells that begin surrounding and targeting the tumor microenvironment at 60 ticks.

A) **B)**

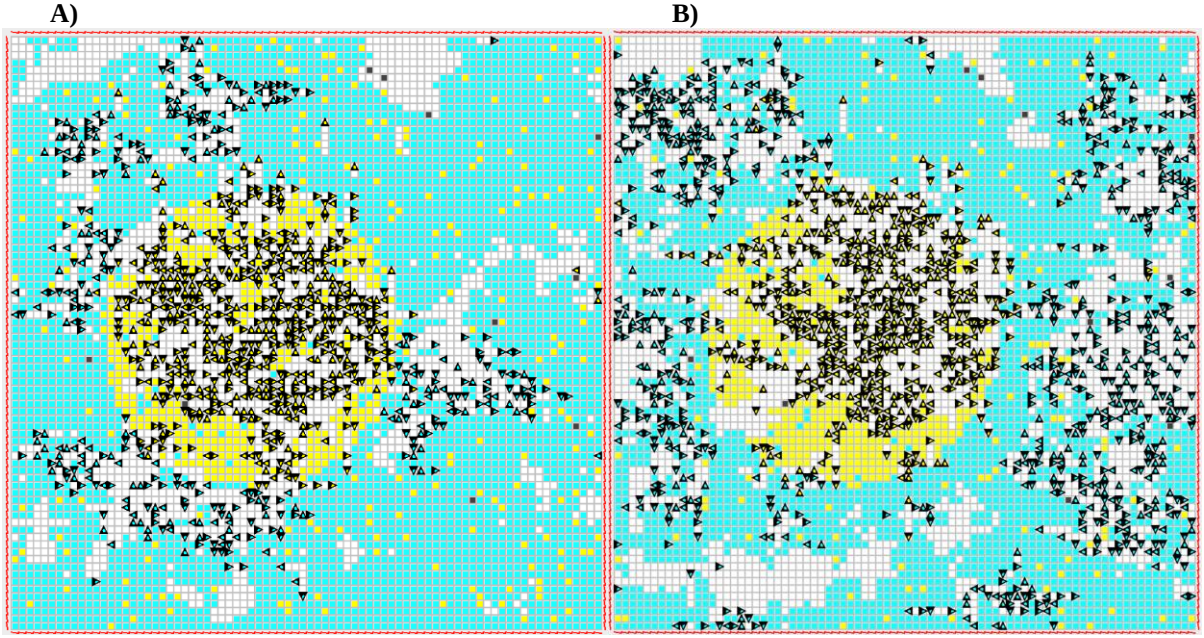

Figure 3. Cytotoxic response of innate CD8+ T cells (A) and CAR T cells (B) at 500 ticks. The yellow-dotted triangles are agents that represent the tumor cells that have grown over 500 ticks (days). The yellow-filled squares represent the resources of tumor cells occupying the tumor microenvironment, represented by the circular yellow island. The cyan-dotted triangles are agents that represent the innate CD8+ T cells that target the tumor microenvironment at 500 ticks.

A) **B)**

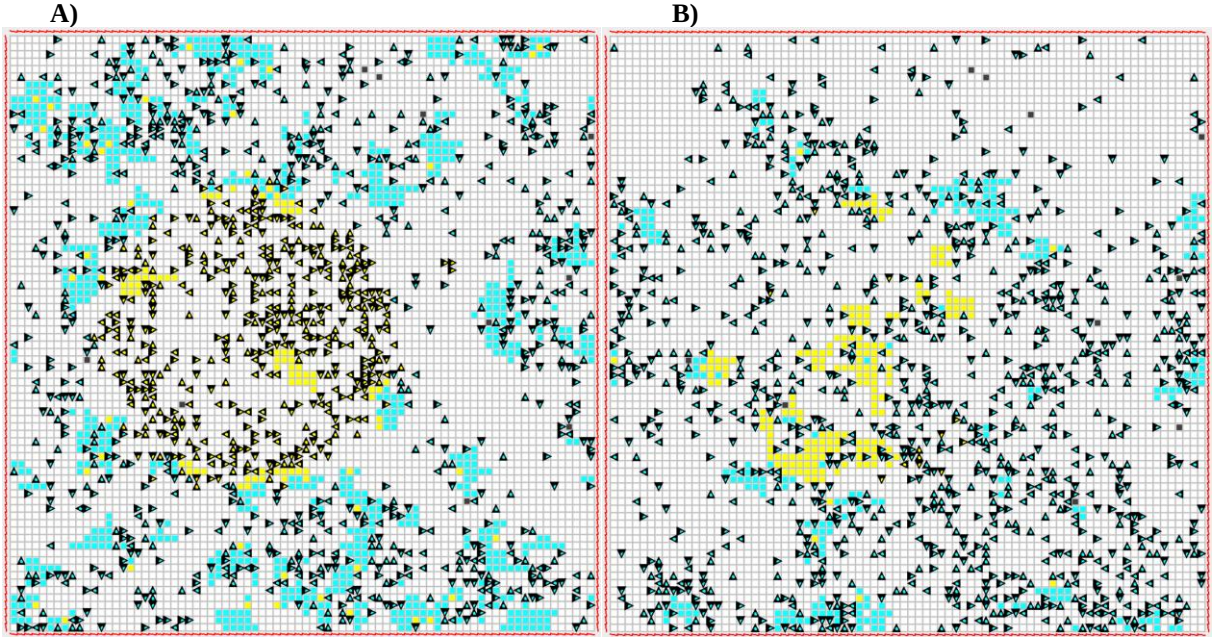

Table 3. A Comparative Summary of the Main Results Derived from the Models for the Cytotoxic Responses of Innate CD8+ and CAR T cells

Comparison Criteria	Innate CD8+ T cell	CAR T cell
Cytotoxic response at 60 ticks	Fewer number of innate CD8+ T cells prepared to invade tumor island and launch cytotoxic response (Figure 2A, refer to Online Supplemental section)	Greater number of CAR T cells prepared to invade tumor island and launch cytotoxic response (Figure 2B, refer to Online Supplemental section)
Peak tumor population	~750 cells at 75 days (Figure 1A)	~650 cells at 75 days (Figure 1B)
Peak T cell population	~1125 at 160 days (Figure 1A)	~1350 cells at 480 days (Figure 1B)
Tumor relapse	150 to 500 tumor cells (233% increase)	100 to 225 tumor cells (125% increase)
Cytotoxic response at 500 ticks	Average number of tumor cells left: 143 Average tumor reduction: 66% (Figure 1A, Table 2)	Average number of tumor cells left: 50 Average tumor reduction: 91% (Figure 1B, Table 2)

Discussion

The normal/innate CD8+ model exhibits tumor cells concentrated in an island and T cells surrounding the island. The T cells were programmed to begin infiltrating the tumor at 60 ticks. From 60 ticks to 500 ticks, the response of the innate CD8+ T cells against the tumor exhibited a steady decline in the number of tumor cells from 60 to 500 ticks. The average efficiency rate of natural CD8+ T cells is 66.12% reduction of tumor cells, as calculated in Table 2. The innate CD8+ T cells increased in population until a 'carrying capacity' was reached at approximately 800 agents as the attack against the tumor progressed. The population of T cells began to oscillate in population count after reaching 'carrying capacity', which indicates the death of innate CD8+ T cells and regeneration within the span of 40 to 50 ticks. As the attack proceeds, a relatively significant relapse occurs in tumor population count at approximately (Figure 1A) with the tumor population surging from 150 to 500 cells, a 233% increase in tumor size or cell population. As the tumor population count experiences a relapse, the innate CD8+ T cell population count sharply oscillates to maintain the ferocity of attack against the tumor, which indicates the success of the innate CD8+ T cell's response against tumor cells. This oscillation pattern is evident in all of the CD8+ T cell's response against tumor cells across the randomized AI seed trials performed. The tumor population count tends to relapse at around 300 days. The population count of tumor cells exhibits a steady decline until it begins to stabilize at 250 agents and increases again before declining by the end of 500 ticks, which indicates the immune system's innate response to potential threats.

The model for the CAR T cells shows results that agree with the hypothesis - the response of CAR T cells was much more effective than the response against normal cells. The ferocity of the attack launched and the longevity of the engineered CD8+ T cells was accurately featured in the second part of the project as suggested by the dominance of CAR T cells at the end of 500 ticks. From 60 to 500 ticks, the response of these CAR T cells against the solid tumor showed a steady decline in the number of tumor cells to nearly zero. Within this time frame, the tumor population decreased with an average tumor regression of 90.94% . This value is approximately 24% greater than that of innate CD8+ T cells. Again, the CAR T cells increased in population until a 'carrying capacity' was reached at approximately 800 cells/agents, where oscillations in population count are displayed (Figure 1B). Most importantly, the CAR T cell treatment shows a minimal relapse in tumor population count at approximately 320 ticks

relative to the standard treatment; the tumor population increased only from 100 to 225 cells, a 125% increase in tumor size or cell population. This minimal relapse is evident across the randomized population trials conducted with AI seeds. The minimal relapse had a tendency to occur at approximately 150-250 days. This emphasizes the success of the CAR T cells in delivering a rigorous immune response to the disease. Although the maximum population of both varieties of T cells are the same, the tumor cells' rapid decline shows the efficacy of immunotherapy (Figure 1B).

Although the innate model and CAR T cell model provides conclusive results, the model faces limitations as it is intended to reflect a rather simplistic version of the general adaptive immune response. Aspects in the model, such as the 'island' parameters and 'food energy', were used as vehicles to illustrate the immune response of innate CD8+ T cells and CAR T cells against a solid tumor [10]. In reality, the formation of a tumor island is not necessarily a prerequisite to a cytotoxic response; both the settlement of tumor and activation of the immune response can originate simultaneously. Background factors such as the likelihood of metastasis have been eliminated to bring focus on the anti-tumor immune response. There are various immune molecules involved in the immune response than simply T cells (i.e. cytokines, natural killer cells); however, the main focus of the model was solely revolving around two agents: T cells with their cytotoxicity and rapidly-proliferating tumor cells. Additionally, the ratios by which the CAR T cells were modified in relation to the innate CD8+ T cells was arbitrary (i.e. CAR T cells had 25% less breeding energy and the step, or movement, energy was halved). These modifications were made to reflect the efficiency of engineered CAR T cells, but the ratios of these T cell behavior parameters are highly subject to variation.

Conclusion

In conclusion, the results agree with the hypothesis as the innate model shows a significantly greater number of tumor cells than in the CAR T cell model at the end of the designated time frame (500 days) of this study. This suggests a higher relapse rate than the CAR T cell as the immune response is relatively slow and ineffective (Figure 1). The CAR T cells also had greater longevity as their peak population was 1325 cells or agents, compared to innate CD8+ T cells which peaked at 1150 cells (Figure 1). After observing both the control T cell model and CAR T cell model, the results show that engineered CAR T cells can be as much as 35% more effective, as measured by the average tumor reduction percentage (Table 2). Altogether, our model suggests that the CAR T cells can more potently infiltrate and launch a powerful immune response against the general solid tumor (Figure 2, 3).

However, the primary limitation of our study would be that the model simplifies the primary immune response by ignoring the major and more complex anti-tumor immunological aspects, other than the cytotoxicity of T cells. For example, tumors are often heterogeneous and ever-evolving; they can adapt over the course of the CAR T cell therapy to evade immune measures. However, our methodology had not programmed the solid tumor for some cells to mutate and acquire survival advantages.

Nevertheless, this model emphasizes the efficiency and high specificity of CAR T cells as a cancer immunotherapy that can lead to better health outcomes for cancer patients, in terms of tumor regression and relapse. This study should motivate future modeling efforts of immunotherapies and the adoption of CAR T cell therapy as a practical, flexible biotherapy by

care providers. Other parameter categories in the COBWEB application such as 'Artificial Intelligence' of the agents and Genetics (i.e. mutation rate) can be applied for further investigation of CAR T cell therapy to reflect additional complexities of adaptive immunity associated with other types of T cells [11].

Declarations

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