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A Spatio-Temporal Model of Macrophage-Mediated Drug Resistance in Glioma Immunotherapy

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Abstract

The emergence of drug resistance is often an inevitable obstacle that limits the long-term effectiveness of clinical cancer chemotherapeutics. Although various forms of cancer cell-intrinsic mechanisms of drug resistance have been experimentally revealed, the role and the underlying mechanism of tumor microenvironment in driving the development of acquired drug resistance remain elusive, which significantly impedes effective clinical cancer treatment. Recent experimental studies have revealed a macrophage-mediated drug resistance mechanism in which the tumor microenvironment undergoes adaptation in response to macrophage-targeted colony-stimulating factor-1 receptor (CSF1R) inhibition therapy in gliomas. In this study, we developed a spatio-temporal model to quantitatively describe the interplay between glioma cells and CSF1R inhibitor-targeted macrophages through CSF1 and IGF1 pathways. Our model was used to investigate the evolutionary kinetics of the tumor regrowth and the associated dynamic adaptation of the tumor microenvironment in response to the CSF1R inhibitor treatment. The simulation result obtained using this model was in agreement with the experimental data. The sensitivity analysis revealed the key parameters involved in the model, and their potential impacts on the model behavior were examined. Moreover, we demonstrated that the drug resistance is dose-dependent. In addition, we quantitatively evaluated the effects of combined CSF1R inhibition and IGF1 receptor (IGF1R) inhibition with the goal of designing more effective therapies for gliomas. Our study provides quantitative and mechanistic insights into the microenvironmental adaptation mechanisms that operate during macrophage-targeted immunotherapy and has implications for drug dose optimization and the design of more effective combination therapies.

Introduction

As a microenvironment-targeted immunotherapy, colony-stimulating factor-1 receptor (CSF1R) inhibition is expected to be a promising therapeutic strategy for high-grade gliomas (1, 2). Although multiple clinical trials testing the efficacy of CSF1R inhibition have been conducted in glioma patients, it is unclear whether and how resistance emerges during this therapy. Recently, a preclinical study using a genetic mouse model (3) showed that a high percentage (>50%) of glioblastoma multiformes (GBM) recur in the mice following treatment via long-term CSF1R inhibition, although overall survival is significantly prolonged. Therefore, it is important and timely to investigate the mechanisms underlying the acquisition of resistance to CSF1R inhibition and quantitatively determine the key biological parameters involved in this process.

Many types of tumor cell-intrinsic mechanisms, including genetic mutations and epigenetic modifications (4), signaling network rewiring (5–7), cellular heterogeneity involving cancer stem cells (8, 9), and drug metabolism and pharmacodynamics (10), have been studied widely. Distinct from the above mechanisms, the roles of tumor microenvironment in driving and facilitating tumor growth and drug resistance have been revealed and acknowledged with increasing attention in recent years (3, 11–13). Actually, the tumor microenvironment involves multiple cell types, such as fibroblasts, endothelial cells and immune cells, that can interact with tumor cells (14). For example, immune cells, including macrophages, dendritic cells, neutrophils, Treg cells, T effector cells, natural killer cells, etc. (15), can interact with tumor cells either via direct cell–cell contacts or via soluble factors such as secreted cytokines or growth factors (16). Such cross-talk between immune and tumor cells plays substantial roles before and during tumor growth as well as the in the development of drug resistance (17).

To investigate the dynamic interactions between cancer cells and the associated microenvironment in the context of therapeutic intervention, the traditional experimental approach requires multiple experimental conditions and time points and, thus, is time consuming and expensive. Therefore, a computational systems biology approach is necessary to address this issue. Mathematical modeling is a powerful tool for the quantitative investigation of dynamic biological systems that can provide insights...
into underlying mechanisms and experimentally testable predictions. From a quantitative biology perspective, we can ask questions regarding the effects of dose on drug resistance and the influence of critical parameters on the evolution of drug resistance. Driven by the hypothesis that an appropriately simplified mathematical model is able to capture the key kinetics of microenvironment-mediated drug resistance, we seek to mechanistically model the spatio-temporal evolution of interactions within the tumor-microenvironment system during drug treatment.

In the past decade, several theoretical models have been developed to investigate the role of the microenvironment in tumor growth [e.g., refs. (18–21)]. Moreover, some efforts using modeling approaches to investigate the role of the microenvironment in drug resistance have also been conducted recently. For instance, Lindsay and colleagues (22) developed a stochastic model to simulate the effect of oxygen on the growth kinetics of cancer cells and to investigate the potential benefits of combining hypoxia-activated produgs with standard targeted therapy to prevent drug resistance in non–small cell lung cancer. In addition, our previous study (23) designed a modeling framework using stochastic differential equations to simulate the therapy-induced microenvironmental adaptation that promotes the growth and metastasis of resistant tumor cells and, therefore contributes to the development of the acquired drug resistance. However, no modeling work has been dedicated to investigating the kinetics of drug resistance driven by the immune microenvironment, particularly involving macrophages, in cancer therapy.

Recently, the experimental studies have revealed a macrophage-mediated drug resistance mechanism in glioma immunotherapy (3). Specifically, in the absence of CSF1R inhibition, tumor-associated macrophages exhibit a protumorigenic M2 phenotype and contribute to glioma progression. However, when targeted by CSF1R inhibitors, macrophages switch to an antitumorigenic M1 phenotype with enhanced phagocytosis, thereby promoting tumor cell death. Following prolonged treatment with CSF1R inhibitors, accumulated IL4 from other cell types (e.g., T cells) stimulates macrophages to secrete insulin-like growth factor 1 (IGF1) into the microenvironment, which in turn sustains the survival and growth of glioma cells (3).

On the other hand, certain mathematical models have also recently been developed to describe the interactions between cancer cells and macrophages during cancer progression. For example, Szomolay and colleagues (24) proposed a system of partial differential equations (PDE) to simulate the macrophages-mediated interactions among tumor cells and endothelial cells through several cytokines, including M-CSF1, GM-CSF1, VEGF, and MCP-1, as well as oxygen. Their model simulations are consistent with the in vivo data obtained under different conditions of GM-CSF (granulocyte/macrophage colony-stimulating factor) exposure, allowing the model to predict treatment outcomes. Knudtöö and colleagues (25) described paracrine and autocrine signaling (i.e., CSF1/CSF1R and EGF/EGFR pathways) between tumor cells and macrophages using both PDEs model and cell-based discrete 3D simulation. The authors identified parameters responsible for the observed ratio of tumor cell to macrophage and demonstrated how CSF1/CSF1R autocrine signaling in tumor cells affect this ratio. These works provided the modeling basis and implicated potential values of theoretically investigating the interactions between tumor cells and macrophages.

In this study, based on the above experimentally validated mechanism (3), we developed a spatio-temporal model to quantitatively describe the interplay between glioma cells and CSF1R inhibition-induced transition of macrophage M2 and M1 phenotypes through dynamic CSF1/CSF1R and IGF1/IGF1R pathways. Our model was used to investigate the response of glioma cells to macrophage-targeted CSF1R inhibition therapy and the associated dynamic adaptation of the tumor microenvironment.

The simulation result obtained using this model is in agreement with the experimentally observed regrowth phenomenon of resistant gliomas and quantitative survival times (3). Moreover, we demonstrated that the drug resistance is dose-dependent. In addition, we quantitatively evaluated the effects of combined CSF1R inhibition and IGF1 receptor (IGF1R) inhibition with the goal of designing more effective therapies for gliomas.

### Materials and Methods

#### PDE model

We model the spatio-temporal evolution of cancer cells and their microenvironment during CSF1R inhibition based on the experimentally validated mechanism [ref. 3; Fig. 1]. The major assumptions of our model include:

- a) The numbers of cancer cells and macrophages as well as levels of secreted soluble factors including CSF1, IGF1, and IL4 are large enough such that they can be treated as continuous variables. So, the numbers of cells and levels of cytokines are described by their densities and concentrations, respectively.
- b) Glioma cells, macrophages, CSF1, IGF1, and drugs are subject to diffusion; glioma cells and macrophages are also subject to chemotaxis in response to IGF1 and CSF1, respectively.
- c) The proliferation rate and the death rate of tumor cells are regulated by IGF1 and CSF1R inhibitor. Specifically, by regulating the phenotype transition between M1 and M2 macrophages, CSF1R inhibition does not only increase apoptosis rate of glioma cells but also decreases their proliferation.

![Figure 1](image-url)  
Schematic representation of how adaptation of the tumor microenvironment contributes to acquired drug resistance during CSF1R inhibition therapy of gliomas (3). Macrophages and glioma cells can interact through the CSF1/CSF1R and IGF1/IGF1R pathways. CSF1R, a critical receptor on macrophages, is a promising immunotherapeutic target in gliomas and is undergoing clinical evaluation. In the absence of CSFIR inhibition, macrophages exhibit a protumorigenic M2 phenotype that promotes glioma progression. When targeted by a CSFIR inhibitor, macrophages switch to an antitumorigenic phenotype that promotes tumor cell death. On the other hand, following prolonged treatment, elevated macrophage-derived IGF1, which is promoted by IL4 secreted by other cell types (e.g., T cells), in turn sustains the survival and growth of glioma cells.
rate (26). Meanwhile, the CSF1R inhibitor-induced IGF1 secretion from macrophages through IL4 signaling could, in turn, sustain the proliferation of glioma cells (3).

d) The CSF1R inhibitor treatment does not significantly affect the number of tumor-associated macrophages, as experimental studies indicated (27). As such, the total density of tumor-associated macrophages is assumed to be constant during CSF1R inhibitor treatment.

We used a set of PDEs to model the growth, death, and migration of cancer cells and tumor-associated macrophages and the diffusion/secretion/degradation of CSF1, IGF1, and drugs. The time scale of this entire mechanism is about 200 days in accordance with the experimental study (3).

The migration of glioma cells consists of random diffusion and chemotaxis toward the chemical gradients of signals. We assumed a logistic growth rate and a linear death rate of cancer cells. The migration of glioma cells is modeled by the following equation:

\[
\frac{\partial C}{\partial t} = D_T \Delta C_T - d_T \nabla \cdot (C_T \nabla [IGF1]) + \tau_I C_T \left(1 - \frac{C_T}{C_T^{max}}\right) - d_T C_T, \quad (1)
\]

where \(D_T\) is the diffusion coefficient of glioma cells and \(\tau_I\) is the chemotaxis coefficient for glioma cells with respect to IGF1. \(C_T^{max}\) represents the maximal carrying capacity of the cancer cells. \(\tau_I\) and \(d_T\) are the proliferation rate and the death rate, respectively, which are regulated by the IGF1 and CSF1R inhibitor. Experimental data (3, 26) have revealed that CSF1R inhibition does not only increase apoptosis of glioma cells but also decreases their proliferation. Although the CSF1R inhibitor-induced IGF1 secretion from macrophages could promote the proliferation of glioma cells (3). Therefore, the regulated proliferation rate of glioma cells is modeled by the following equation:

\[
\dot{r}_T = \tau_I \cdot H_1([IGF1]) \cdot (\alpha \cdot C_T \cdot H_2([CSF1R\_I])), \quad (2)
\]

where \(\tau_I\) is the basic proliferation rate of tumor cells and \(\alpha\) is a regulatory coefficient for the macrophage density \(C_T\) corresponding to M2 macrophages' protumorigenic function. Hill functions (30–32) were used to describe the roles of IGF1 and CSF1R inhibitors (CSF1R_I) in regulating the proliferation rate of glioma cells as follows:

\[
H_1([IGF1]) = \frac{[IGF1]}{K_I + [IGF1]},
\]

\[
H_2([CSF1R\_I]) = \frac{1}{1 + [CSF1R\_I]/K_2},
\]

where \(K_I\) and \(K_2\) are Michaelis–Menten constants.

The apoptosis of glioma cells is accelerated by treatment with a CSF1R inhibitor (3, 26), as described above, therefore, the regulated death rate of glioma cells is described by the following equation:

\[
\dot{d}_T = d_T \cdot (1 + \beta \cdot C_T \cdot H_3([CSF1R\_I])), \quad (3)
\]

where \(d_T\) is the basic death rate of glioma cells and \(\beta\) is a regulatory coefficient corresponding to M1 macrophages' antitumorigenic function. The pro-apoptotic role of the CSF1R inhibitor was modeled as

\[
H_3([CSF1R\_I]) = \frac{[CSF1R\_I]}{K_3 + [CSF1R\_I]},
\]

where \(K_3\) is a Michaelis–Menten constant.

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\]

where \(K_3\) is a Michaelis–Menten constant.
immune cells (e.g., neutrophils, monocytes, dendritic-like cells, B cells, helper T cells and regulatory T cells) in drug-resistant group of mice are not significantly different from that in control group. As such, we do not explicitly describe the densities of IL4-secreting cells in the model for simplicity. We assume that the rate of change in the concentration of IL4 is proportional to the concentration of the CSF1R inhibitor with a coefficient of $S_{IL4}$; that is, the secretion of IL4 can be modeled by the following equation:

$$\frac{\partial [IL4]}{\partial t} = S_{IL4} \cdot [CSF1R \cdot f].$$  \hspace{1cm} (7)

Solving this equation and substituting it into Eq. (6) yields the following equation:

$$\frac{\partial [IGF1]}{\partial t} = D_{IGF1} \Delta [IGF1] + S_{IGF1} \cdot [IL4] \cdot (1 + S_{IL4} \int_0^L [CSF1R \cdot f] \cdot (s) \cdot ds) - d_{IGF1} \cdot [IGF1],$$ \hspace{1cm} (8)

where $[IL4]_0$ is the initial concentration of IL4 in the absence of treatment with the CSF1R inhibitor.

In addition, we model the diffusion and degradation of drugs (including CSF1R inhibitors and IGF1R inhibitors) as follows:

$$\frac{\partial [Drug]}{\partial t} = D_{drug} \Delta [Drug] - \eta_{drug},$$ \hspace{1cm} (9)

where $D_{drug}$ is the diffusion rate of the drug and $\eta_{drug}$ is the degradation rate or the uptake rate of the drug by cells.

**Non-dimensionization and radial symmetry simplification**

To reduce the number of parameters, we simplify the PDE model by rescaling the equations into a dimensionless form (Supplementary Text S1). Furthermore, for simplicity, we assumed a spherical model for the tumor and its microenvironment. Therefore, the domain we consider is a spheroid. Assuming radial symmetry, the cell density and cytokine concentration evolve in the domain [0, L]. The details of radial symmetry simplification are provided in Supplementary Text S2.

**Initial and boundary conditions**

The initial and boundary conditions are given in Supplementary Text S3. In particular, the addition of the drug is modeled with a Dirichlet boundary condition $[Drug]_{|L} = \eta_{drug}$.

**Numerical simulation**

We solve the system of the dimensionless PDEs (Eqs. Supplementary S11–S15) numerically using the pdepe solver in MATLAB R2007b (MathWorks), which automatically and dynamically selects time steps and is capable of solving PDEs with multiple temporal orders (38). The length of the simulation domain ($L$) is approximately 4 cm. The numerical simulation results are evaluated at locations with spatial step of 0.08 cm and time points with step of 1 day.

**Parameter sensitivity analysis**

Most parameters in the model are obtained from experimental measurements, whereas some others are estimated or calibrated. The details of parameter estimation were described in Supplementary Text S4. Supplementary Tables S1 and S2 list the original parameters and the dimensionless parameters, respectively, used in the simulation. To examine whether the parameter variations significantly affect the model output of interest, we implement sensitivity analyses of the most relevant parameters, i.e., $A_{phi}, A_p, r_p, d_1, B_1, B_2, c, D_{drug}$ and $S_{IL4}$.

A sampling-based global sensitivity analysis (39) is performed. For each parameter, we use Latin hypercube sampling to generate 1,000 samples in the range of $[1/5p_0, 5p_0]$, where $p_0$ is the baseline value of the parameter. All parameters are varied simultaneously for the simulations.

For the varied parameters, we choose the killing rate and the regrowth rate of cancer cells as model outputs to evaluate the long-term effects of parameter variations on the drug response and resistance. The killing rate of cancer cells is defined as

$$R_{k} = \frac{C_{G}(0) - C_{G}(t_f)}{t_f},$$ \hspace{1cm} (10)

where $C_{G}$ represents the average cancer cell density and $t_f$ is the time at which the minimal average cancer cell density is achieved. Similarly, the regrowth rate of cancer cell density is defined as

$$R_{r} = \frac{C_{G}(t_s) - C_{G}(t_i)}{t_s - t_i},$$ \hspace{1cm} (11)

where $t_s$ is the length of time over which the simulation performed. For each parameter, the partial correlation coefficient between the simulated model output ($R_{k}$ or $R_{r}$) and the sampled parameter values is calculated and is defined as a global sensitivity coefficient in this study.

A local parameter sensitivity analysis (Supplementary Text S5) is also performed to investigate the dose-dependent sensitivities of parameters and to assess the combinatorial effects of the parameters on drug resistance.

**Results**

The evolution profiles of the tumor and microenvironment in response to CSF1R inhibitor treatment

We used our mathematical model to investigate the evolution profile of the tumor and the associated microenvironment under the condition of treatment with a CSF1R inhibitor. The drug response of a high-grade glioma tumor (with a radius of approximately 4 cm) to treatment with a CSF1R inhibitor (1 dose) was simulated (Fig. 2). As shown in Fig. 2A, at the early stage, the cancer cell density decreased dramatically after a dozen days. However, the tumor regrew after a long-term dormancy period of approximately 150 days. At day 200, the cancer cell density was restored to nearly the level that was comparable before the treatment. The changes in macrophage density and the concentrations of CSF1 and IGF1 in the tumor microenvironment during the CSF1R inhibitor treatment were also examined (Fig. 2B–D). As expected, the change in the CSF1 concentration exhibited similar pattern with the evolution of the cancer cell density, whereas the IGF1 concentration kept increasing over
Drug response of cancer cells and adaptation of the tumor microenvironment in the context of therapeutic intervention with CSF1R inhibition. The spatio-temporal distributions of (A) cancer cell density, (B) macrophage density, (C) CSF1 concentration, (D) IGF1 concentration, and (E) drug concentration. (F) Curves of time course of average cancer cell density and average drug concentration.
A key parameter affecting the dynamics of drug resistance is the secretion rate of IGF1. The secretion rate of IGF1 (\( \beta_1 \)) is a critical parameter for the macrophage-mediated drug resistance as described above. Heterogeneous drug resistance under treatment of CSF1R inhibitor as previously reported (Fig. 1B in ref. 3).

To determine which parameters are more sensitive and critical for the killing rate and the regrowth rate of cancer cells during treatment with a CSF1R inhibitor, we performed a global parameter sensitivity analysis (see Supplementary Text S3). Figure 3 shows the results of the global sensitivity analysis. The killing rate (Fig. 3A) and the regrowth rate (Fig. 3B) display different sensitivities with respect to variations in the parameters. The significant sensitive parameters for the killing rate are \( \tau_2 \), \( d_2 \), \( B_2 \), and \( D_B \) whereas the significant sensitive parameters for the regrowth rate are \( \lambda_0 \), \( \tau_2 \), \( B_2 \), \( D_B \), and \( \eta_2 \).

To confirm that the emergence of the regrowth of the cancer cells is not caused by the decreased drug concentration due to drug degradation or consumption, we examined the spatio-temporal profiles of cancer cells and their microenvironment using the model with increased drug consumption rate (10-fold of \( \eta_{ag} \); Supplementary Fig. S1). The simulation results showed that increasing the drug consumption rate did not significantly influence the emergence of drug resistance, compared with Fig. 2.

We also examined the behavior of the model using different values of certain important parameters (\( \tau_2 \), \( d_2 \), \( B_2 \), and \( D_B \); Supplementary Fig. S2). A decrease in the value of \( \tau_2 \) (growth rate of tumor cells) and an increase in \( d_2 \) (death rate of tumor cells), as well as a decrease in \( B_2 \) (secretion rate of IGF1), resulted in the disappearance of the emergence of drug resistance. In addition, the diffusion rate of the drug (\( D_B \)) also affected the killing and regrowth rates of the resistant cancer cells.

Stochasticity in the secretion rate of IGF1 results in heterogeneous drug resistance. The secretion rate of IGF1 (\( \beta_1 \)) is a critical parameter for the macrophage-mediated drug resistance as described above (Fig. 3). Therefore, we then examined whether stochasticity in IGF1 secretion rate could result in heterogeneous drug resistance. We assumed a bimodal distribution of \( \beta_2 \) and used the Monte Carlo method to simulate the stochastic temporal evolution of cancer cell density in a population of \( N \) glioma patients. The details of the stochastic simulation and the computation of the distribution of survival times were described in Supplementary Text S6.

Figure 4A shows the heterogeneous evolution of cancer cell density in different patients in response to drug treatment. Each curve represents one patient. The simulation demonstrated that the cancer cell density was reduced in some patients but some tumors regrew. Furthermore, Fig. 4B shows the theoretical survival curves, representing the changes of survival percentages over time, of the glioma patients with and without CSF1R inhibition treatment (red line and gray line, respectively). The predicted significant difference between these two curves and their trends are in good agreement with the preclinical data (Fig. 1D in ref. 3). Moreover, we quantified the survival percentage, \( SP(t) \), from the experimental data (Fig. 1D in ref. 3) and calculated the corresponding survival frequency according to \( f(t) = SP(t) - SP(t_h) \), with results shown in Fig. 4C and D. The comparison between the simulated survival frequency and experimental data shows a good agreement between them.

Dose-dependent drug resistance

We further investigated the effect of dose on the drug response and resistance. Figure 5A displays curves for the time course of cancer cell density under conditions of treatment with different doses (0, 0.1, 0.5, 1, 2, and 3) of a CSF1R inhibitor. A low dose (e.g., less than 0.1) had a slight inhibitory effect on tumor growth. High doses killed cancer cells at the early stage but did not prevent tumor recurrence at a later stage. As the dose was increased, the rate of cancer cell death increased; however, the regrowth rate also increased due to drug resistance. A more comprehensive illustration of the "dose-temporal drug response" (Fig. 5B) demonstrated that different drug doses resulted in differential temporal evolutions of cancer cell density. The emergence of drug resistance, as well as its extent, depended on the dose of CSF1R inhibitor used.

Quantitative evaluation of the effect of combination drug therapy

To determine how the combined parameters affect the killing and regrowth rates of cancer cells during drug treatment, we performed a 2-parameter sensitivity analysis (see Supplementary Text S5). The results revealed that variations in the parameters \( \tau_1 \), \( \tau_2 \), \( d_1 \), \( d_2 \), \( B_1 \), \( B_2 \), and \( B_3 \) influenced the killing rate of cancer cells more than other combinations.
(Supplementary Fig. S3A). For the regrowth rate, the most sensitive parameter combination was $r_1&B_2$ (Supplementary Fig. S3B). These results indicate that combination therapy using drugs that both prevent cancer cell growth and inhibit the IGF1 signaling axis might be more effective than single CSF1R inhibition therapy.

Therefore, we evaluated the results of combination therapy using a CSF1R inhibitor and an IGF1R inhibitor (Fig. 6). The effect of IGF1R inhibition was incorporated into the model using the following equation:

$$R = \frac{\hat{R} - \frac{1}{1 + [\text{IGF1R}] / K_1}}{B}.$$  

where $K_1$ is a half-constant that was used to normalize the drug concentration of the IGF1R inhibitor. Therefore, $K_1$ was set to 1 in the simulation.

To quantitatively evaluate the synergy of the CSF1R-I and IGF1R-I co-treatment, a combination index based on Bliss independence (40, 41) was defined as follows:

$$CI(x_1, x_2) = E_2(x_1, x_2) - [E_1(x_1) + E_2(x_2) - E_1(x_1) \cdot E_2(x_2)].$$  

where $E_i(x) = R_i(x) - R_i(0)$ quantifies the drug efficacy of the single CSF1R inhibitor ($i = 1$) or IGF1R inhibitor ($i = 2$) alone at dose $x$, $E_i(x) = R_i(x) - R_i(0)$ in Eq. (13) is the expected efficacy of the combination drug, and $E_{11}(x_1, x_2)$ is the actual outcome produced by the combination. Hence, the combination of CSF1R-I with IGF1R-I is synergistic if $CI > 0$, antagonistic if $CI < 0$, and additive if $CI = 0$.

Figure 6 demonstrates the dose-dependent effects of a combination therapy using a CSF1R inhibitor and an IGF1R inhibitor simultaneously. Figure 6A shows the time course of cancer cell density under conditions of treatment with single or combined CSF1R and IGF1R inhibitors. The combined intervention significantly reduced the resistance of the glioma to CSF1R inhibition. This prediction is consistent with experimental results (fig. 7 in ref. (3)) that the combination of BLZ945 [CSF1R inhibitor] and OSI906 [IGF1R inhibitor] significantly improved outcome in preclinical models. Figure 6B and C further shows the dependence of the killing and regrowth rates of the cancer cells on the drug dose. The regrowth rate decreased as the dose of IGF1R inhibitor was increased. In particular, at a dose of $1$, the killing rate was high, and the
and/or clinical trials aiming to investigate resistance mechanisms and/or multiple doses should be considered in experimental designs. The killing rate was also increased. These results imply that resistance to CSF1R inhibition. Higher doses induced a greater dose-dependent mechanism of inhibition and the associated dynamic adaptation of the tumor microenvironment. The model simulations of tumor evolution to mechanistically describe the response of glioma cells to CSF1R inhibition and the associated dynamic adaptation of the tumor microenvironment. The model simulations of tumor evolution and drug resistance are consistent with experimental results (3). The modeling framework provides a basis for the further investigation of tumor microenvironment-mediated drug resistance, provided that patient-specific data are available in future studies. Moreover, our results revealed a dose-dependent mechanism of resistance to CSF1R inhibition. Higher doses induced a greater regrowth rate of cancer cells compared with lower doses, although the killing rate was also increased. These results imply that multiple doses should be considered in experimental designs and/or clinical trials aiming to investigate resistance mechanisms and optimize drug doses.

Discussion

The tumor microenvironment plays multiple indispensable roles in cancer progression, and as such, targeting the tumor microenvironment has been proposed as a promising strategy for treating cancers (1, 2). Macrophages are of the most abundant immune cell types in the tumor microenvironment, and the accumulation of which has been associated with the progression and high grade of various tumors, including gliomas (42, 43). Preclinical experiments using genetic mouse models have been conducted to demonstrate that macrophages can be targeted by inhibiting CSF1R to regress high-grade gliomas (3). However, like other targeted therapies, acquired resistance to CSF1R inhibition also occurs following long-term treatment (3).

In this study, we developed a simplified spatio-temporal model to mechanistically describe the response of glioma cells to CSF1R inhibition and the associated dynamic adaptation of the tumor microenvironment. The model simulations of tumor evolution and drug resistance are consistent with experimental results (3). The modeling framework provides a basis for the further investigation of tumor microenvironment-mediated drug resistance, provided that patient-specific data are available in future studies. Moreover, our results revealed a dose-dependent mechanism of resistance to CSF1R inhibition. Higher doses induced a greater regrowth rate of cancer cells compared with lower doses, although the killing rate was also increased. These results imply that multiple doses should be considered in experimental designs and/or clinical trials aiming to investigate resistance mechanisms and optimize drug doses.

Figure 5.
Dose-dependent drug resistance. A, Time courses of the average cancer cell density under conditions of treatment with various doses (0, 0.1, 0.5, 1, 2, and 3) of a CSF1R inhibitor. B, Dose-temporal drug response of cancer cell density. Average density of cancer cells in the whole domain was shown.
that this drug combination exhibited a pattern of dose-dependent synergy and that the synergy decreased as the drug doses increased. This indicates that the efficiency of high drug doses in combination was reduced due to antagonistic effects, although high doses of combined drugs might produce higher killing rates or lower regrowth rates compared with low doses of combined drugs. Considering the increased side effects induced by high doses of drugs, information on how to optimize the doses of combined drugs in combination therapy is very important, especially in the era of precision medicine. In addition, cancer cell populations are heterogeneous and they might react differentially to immune cells. The model could be extended to include cancer stem cells to investigate the heterogeneous response of cancer cells to immunotherapies. Moreover, the in vivo data used to estimate the model parameters are indispensable to a more realistic model because the previous relevant works have showed that the slight changes in the model parameter might significantly influence the prediction results (47–49). In future work, we will develop data-driven methods to construct the signaling pathways involved in cross-talk interactions between gliomas and their microenvironments using single cell RNA-seq data and proteomics data. Furthermore, we will build multiscale agent-based models (50) of cell-microenvironment interactions to investigate the intracellular and intercellular mechanisms underlying the drug resistance of cancer cells.

In summary, in this study, we developed a PDE model to quantitatively investigate the mechanisms of interaction between...
Disclosure of Potential Conflicts of Interest  
No potential conflicts of interest were disclosed.

Authors’ Contributions  

Conception and design: Y. Zheng, X. Sun
Development of methodology: Y. Zheng, X. Sun
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Zheng
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Zheng, J. Bao, X. Sun
Writing, review, and/or revision of the manuscript: Y. Zheng, Q. Zhao, T. Zhou, X. Sun

References


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Zheng, X. Sun
Study supervision: Y. Zheng, X. Sun

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Supplementary Information

A Spatio-temporal Model of Macrophage-mediated Drug Resistance in Glioma Immunotherapy

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Table S1. Values of dimensional parameters.

Table S2. Values of dimensionless parameters.
Text S1. Dimensionless equations

To reduce the number of parameters, we simplify the PDE model by rescaling the equations into a dimensionless form. We make the following variable substitutions:

\[
\hat{x} = x \cdot \hat{x}, \quad \hat{t} = t \cdot \hat{t}, \quad C_T = C_T^* \cdot \hat{C}_T, \quad C_\phi = C_\phi^* \cdot \hat{C}_\phi, [IGF1] = [IGF1]^* \cdot [IGF1]_s, \quad [CSF1] = [CSF1]^* \cdot [CSF1]_s, \quad \text{and} [Drug] = [Drug]^* \cdot \hat{[Drug]}_s,
\]

(S1)

where * denotes the dimensional variables.

The scaling parameters are set as follows:

\[
\hat{T}_D = \frac{D_{IGF1}}{d_{IGF1}}, \quad \hat{\phi} = \frac{D_{IGF1}}{d_{IGF1} \cdot \hat{T}_D}, \quad \hat{C}_\phi(x,0) = C_\phi^0, \quad \hat{T}_T = C_T^\text{max}, \quad [CSF1]_s = \frac{S_{CSF1} \cdot C_{CSF1}^\text{max}}{d_{IGF1}}, \quad \text{and} \quad [Drug]_s = 1.
\]

(S2)

With the above scaling, the dimensionless equations are obtained as follows:

\[
\frac{\partial C_T}{\partial \hat{t}} = \Delta C_T - A_T \nabla \cdot (C_T \nabla [IGF1]) + \tilde{\gamma}_T C_T (1 - C_T) - \tilde{\mu}_T C_T,
\]

(S3)

\[
\frac{\partial C_\phi}{\partial \hat{t}} = \Delta C_\phi - A_\phi \nabla \cdot (C_\phi \nabla [CSF1]),
\]

(S4)

\[
\frac{\partial [CSF1]}{\partial \hat{t}} = \frac{1}{\epsilon} \Delta [CSF1] + \frac{B_1}{\epsilon} (C_T - [CSF1]),
\]

(S5)

\[
\frac{\partial [IGF1]}{\partial \hat{t}} = \frac{1}{\epsilon} \Delta [IGF1] + \frac{1}{\epsilon} \left( C_\phi - [IGF1] \right) + \frac{B_2}{\epsilon} C_\phi \int_0^\infty [CSF1(t,s)](\hat{t} \cdot s)ds,
\]

(S6)

\[
\frac{\partial [Drug]}{\partial \hat{t}} = D_d \Delta [Drug] - \eta_d \cdot C_T.
\]

(S7)

The new dimensionless parameters are derived from the original parameters as follows:

\[
A_T = \frac{a_T}{D_T}, \quad A_\phi = \frac{a_\phi}{D_\phi}, \quad B_1 = \frac{d_{CSF1}}{d_{IGF1}}, \quad B_2 = \hat{\nu} \cdot S_{ILA}, \quad D_d = D_{IGF1}, \quad \text{and} \quad \eta_d = \hat{C}_\phi \eta_{davg} = \frac{1}{\epsilon} C_T^\text{max} \cdot \eta_{davg}.
\]

(S8)

Note that \( \epsilon \) is a small parameter because the molecular diffusion rate (\( D_{IGF1} \)) is much greater than the cell migration velocity (\( D_T \)). In addition, the dimensionless regulatory functions of the proliferation and death rates in the above dimensionless equations are as follows:

\[
\tilde{\gamma}_T = \frac{D_{IGF1}}{d_{IGF1} \cdot D_T} \cdot \gamma_T H_T^*(IGF1) \cdot \left( \alpha^* \cdot C_\phi \cdot H_\phi^*(CSF1R_I) \right),
\]

(S9)

\[
\tilde{\mu}_T = \frac{D_{IGF1}}{d_{IGF1} \cdot D_T} \cdot \mu_T \cdot \left( 1 + \beta^* \cdot C_\phi \cdot H_\phi^*(CSF1R_I) \right),
\]

(S10)

where \( H_T^*(IGF1) = \frac{[IGF1]}{K_T^* + [IGF1]} \), with \( K_T^* = K_T / [IGF1]_s \) and \( \alpha^* = \alpha \cdot \hat{C}_\phi \),
$H_2^*(CSF \ I, R) = \frac{1}{1 + \frac{[CSF \ I, R]}{K_2}}$, with $\beta^* = \beta \cdot \hat{C}_\phi$.

and $H_3^*(CSF \ I, R) = \frac{[CSF \ I, R]^*}{K_3 + [CSF \ I, R]^*}$.

In this way, we reduce the number of key parameters from 15 in the original equations to 9 in the dimensionless model.
Text S2. Radial symmetry simplification of the system

For simplicity, we assumed a spherical model for the tumor and its microenvironment. Therefore, the domain we consider is a spheroid. Assuming radial symmetry, the cell density and cytokine concentration evolve in the domain \([0, L]\). The original model (Eqs. S3-S7) is transformed into the following equations:

\[
\frac{\partial C_r}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial C_r}{\partial r} \right) - A_r \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 C_r \frac{\partial [IGF1]}{\partial r} \right) + \tilde{\gamma}_r C_r (1 - C_r) - \tilde{\mu}_r C_r, \tag{S11}
\]

\[
\frac{\partial C_\phi}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial C_\phi}{\partial r} \right) - A_\phi \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 C_\phi \frac{\partial [CSF1]}{\partial r} \right), \tag{S12}
\]

\[
\frac{\partial [CSF1]}{\partial t} = \frac{1}{\epsilon} \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial [CSF1]}{\partial r} \right) + \frac{B_r}{\epsilon} \left( C_r - [CSF1] \right), \tag{S13}
\]

\[
\frac{\partial [IGF1]}{\partial t} = \frac{1}{\epsilon} \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial [IGF1]}{\partial r} \right) + \left( C_\phi - [IGF1] \right) + \frac{B_\phi}{\epsilon} \int_0^1 [CSF1] ds, \tag{S14}
\]

and

\[
\frac{\partial [Drug]}{\partial t} = D_d \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial [Drug]}{\partial r} \right) - \eta_s C_r. \tag{S15}
\]
Text S3. Initial and boundary conditions

Initial conditions

We assume the following initial conditions:

\[
C_T(r, 0) = C_0 \times (1 + 0.1 \cdot r_{\text{rand}}), \quad C_\phi(r, 0) = 1 + 0.1 \cdot r_{\text{rand}},
\]

\[
[IGF1](r, 0) = 1 + 0.01 \cdot r_{\text{rand}}, \quad [CSF1](r, 0) = f_0 \cdot (1 + 0.01 \cdot r_{\text{rand}}),
\]

\[
[\text{Drug}](r, 0) = d_{\text{max}} \cdot r,
\]

where \( r_{\text{rand}} \) is a random number subject to the standard normal distribution as in Ref. [1]. For the initial tumor (grade II), \( C_0(r, 0) = 0.5 \), if \( r < 0.1 \cdot L \); otherwise, \( C_0(r, 0) = 0 \). For high grade tumor, \( C_0(r, 0) = 0.5 \), for all \( r \leq L \). \( f_0 \) is a Heaviside function of \( C_T(r, 0) \). \( d_{\text{max}} \) is the dose of the drug delivered at the boundary of the tumor. Macrophages and IGF1 are assumed to pre-exist in the entire region.

To investigate the effect of spatial distribution of macrophages on the resistance dynamics, we also tested the following initial conditions for macrophages:

(a) \( C_\phi(r, 0) = (r/L + 0.5) + 0.1 \cdot r_{\text{rand}} \);

(b) \( C_\phi(r, 0) = 2 \cdot r/L + 0.1 \cdot r_{\text{rand}} \).

These conditions ensure the equal total density of macrophages. The results were shown in Fig S3-S4.

Boundary conditions

At \( r=0 \), zero flux boundary conditions are imposed for \( C_T, \ C_\phi, \ [CSF1], \ [IGF1] \) and \( [\text{Drug}] \), and at \( r=L \), zero flux boundary conditions are imposed for \( C_T, \ C_\phi, \ [CSF1] \) and \( [IGF1] \), except that \( [\text{Drug}](L, t) = d_{\text{max}} \). Therefore,

\[
\left. \frac{\partial C_T}{\partial r} - A_T C_T \frac{\partial [IGF1]}{\partial r} \right|_{0, \ L} = 0, \quad \left. \frac{\partial C_\phi}{\partial r} - A_\phi C_\phi \frac{\partial [CSF1]}{\partial r} \right|_{0, \ L} = 0,
\]

\[
\left. \frac{\partial [CSF1]}{\partial r} \right|_{0, \ L} = 0, \quad \left. \frac{\partial [IGF1]}{\partial r} \right|_{0, \ L} = 0, \quad \left. \frac{\partial [\text{Drug}]}{\partial r} \right|_0 = 0, \quad \text{and} \quad [\text{Drug}]_L = d_{\text{max}}.
\]
Text S4. Parameter estimates

(1) Diffusion rates. The diffusion rates of cancer cells and macrophages are assumed to be the same (1.0×10⁻⁹ cm²/s [2]), since cancer cells and macrophages move with similar velocities as observed in the experiments [1,3]. The molecular weights of IGF1 and CSF1 are \( M_1 = 7649 \) Da [4] and \( M_2 = 60179 \) Da [1], respectively. The diffusion rates of IGF1 and CSF1 should therefore be scaled by a factor of \( \left( \frac{M_2}{M_1} \right)^{1/3} \approx 2 \), indicating that these rates are of the same order of magnitude and are therefore assumed to be equal. The diffusion rate of CSF1 has been estimated to be \( 2 \times 10^{-9} \) cm²/s [5-7], which is comparable to the diffusion rate of EGF in rat brain extracellular space (5.18×10⁻⁹ to 16.6×10⁻⁹ cm²/s) measured by integrative optical imaging since they have similar molecular weights [7]. A similar assumption is made for the diffusion rate of the CSF1R inhibitor BLZ945 (molecular weight: 398.48 Da).

(2) Chemotaxis coefficients. The chemotaxis coefficient of CSF1 for macrophages is set to be \( 1.7 \times 10^{-3} \) cm²/(s nM), which is taken from the previous works [1,2]. The chemotaxis coefficient of IGF1 for cancer cells is assumed to be the same with that of CSF1 for macrophages, since the tumor cells and macrophages move alongside one another as experiments observed [8,9].

(3) Growth/death rates. Based on the results of experimental measurements [10], the basic coefficient of the growth rate of cancer cells is set to \( 2.41 \times 10^{-3} \) s⁻¹, a typical value also used in previous works [5,6]. The basic death rate is estimated to be \( 2.886 \times 10^{-7} \) s⁻¹, by calibrating the sum of the death rates of cancer cells due to both necrosis and apoptosis [5,6].

(4) Secretion/degradation rates. The experimental data [11] indicated that IL4 concentration under the treatment of CSF1R inhibitor for 16 weeks (112 days) is 3.5-fold of that before treatment. Solving Eq. (6), we have

\[
[IL4](t,x) = [IL4]_0 \left( 1 + S_{IL4} \cdot \int_0^{112} [CSF1R_I](s) ds \right).
\]

Setting \( t = 112 \) in the above equation, we can know \( S_{IL4} \cdot \int_0^{112} [CSF1R_I](s) ds = 2.5 \) and estimate that the secretion rate of IL4 (\( S_{IL4} \)) is 1.2905×10⁻⁷ s⁻¹. The secretion and degradation rates of CSF1 and IGF1 (3.2×10⁻²² g s⁻¹ cell⁻¹ and 1.92×10⁻²² g s⁻¹ cell⁻¹ respectively) are estimated from Refs [5,6], while the degradation rate of the drug is set to be \( 1 \times 10^{-17} \) s⁻¹ as reported in Ref. [12].

(4) Other parameters. Based on the experimental results [13], the maximal carrying capacity of cancer cells (\( C_T^{max} \)) and the initial value of the macrophage density (\( C_M^0 \)) are set to be \( 1.0 \times 10^9 \) cells/cm³ and \( 2.0 \times 10^6 \) cells/cm³, respectively, similar to that in Refs [5,6]. The Michaelis constant of IGF1 in the Hill function of the growth rate (Eq. (S9) in Text S1) is assumed to be comparable to the IGF1 concentration.

Table S1 and Table S2 list the original parameters and the dimensionless parameters, respectively, used in the simulation. Considering that the values of these parameters may vary over certain ranges, we perform a parameter sensitivity analysis to determine the robustness of the model prediction with such variations; the results suggest that the model is robust with respect to most parameters (see the Results section).
**Text S5. Local sensitivity analysis**

**Single-parameter sensitivity analysis.**

A local sensitivity coefficient for the killing rate of cancer cells with respect to parameter $p_j$ is calculated as follows:

$$S_k = \frac{\partial R_k}{\partial p_j} \left( \frac{R_k}{p_j} \right) \approx \frac{\Delta R_k}{R_k} \left( \frac{\Delta p_j}{p_j} \right), \text{ for small } \Delta p_j. \quad (S18)$$

Similarly, the sensitivity coefficient for the regrowth rate with respect to parameter $p_j$ was calculated as:

$$S_g = \frac{\partial R_g}{\partial p_j} \left( \frac{R_g}{p_j} \right) \approx \frac{\Delta R_g}{R_g} \left( \frac{\Delta p_j}{p_j} \right), \text{ for small } \Delta p_j. \quad (S19)$$

Each parameter is increased by 10% from its estimated value and then the relative changes in the killing rate and regrowth rate as defined by Eqs. S18-19 are obtained. Given the randomness of the initial conditions of the model, the computations of the sensitivity coefficients are repeated 20 times, and the mean value and standard deviation are calculated.

**Two-parameter sensitivity analysis**

To assess the combinatorial effects of the parameters on drug resistance, we perform a two-parameter sensitivity analysis. A local sensitivity coefficient for the killing rate of cancer cells with respect to the parameter pair $(p_i, p_j)$ is calculated as follows:

$$S_k = \frac{\partial^2 R_k}{\partial p_i \partial p_j} \left( \frac{R_k}{p_j} \cdot p_i \right) \approx \frac{\Delta R_k}{R_k} \left( \frac{\Delta p_i}{p_i} \cdot \frac{\Delta p_j}{p_j} \right), \text{ for small } (\Delta p_i, \Delta p_j). \quad (S20)$$

where $\Delta R_k$ is the relative change in the killing rate of cancer cells due to a small parameter perturbation $(\Delta p_i, \Delta p_j)$.

Similarly, the sensitivity coefficient for the regrowth rate with respect to the parameter $p_j$ is calculated as:

$$S_g = \frac{\partial^2 R_g}{\partial p_i \partial p_j} \left( \frac{R_g}{p_j} \cdot p_i \right) \approx \frac{\Delta R_g}{R_g} \left( \frac{\Delta p_i}{p_i} \cdot \frac{\Delta p_j}{p_j} \right), \text{ for small } (\Delta p_i, \Delta p_j). \quad (S21)$$

The values of each pair of two different parameters are simultaneously altered by 10% from their original values for 4 times (increased or decreased for each parameter in this pair). All other parameters remain at their base values. The relative changes in the killing and regrowth rates, as defined by Eqs. S20-S21, are then obtained. Given the randomness of the initial conditions of the model, the computations of the sensitivity coefficients are repeated 20 times, and the mean value of the results are calculated.
Text S6. Stochastic simulation and the computation of survival times

We assumed a bimodal distribution of $B_2$ and used the Monte Carlo method to simulate the stochastic temporal evolution of cancer cell density in a population of $N$ glioma patients. The bimodal distribution function of $B_2$ was set to be

$$
\rho(x) = \frac{r}{\sigma_1 \sqrt{2\pi}} \exp\left(-\frac{(x - \mu_1)^2}{2\sigma_1^2}\right) + \frac{1-r}{\sigma_2 \sqrt{2\pi}} \exp\left(-\frac{(x - \mu_2)^2}{2\sigma_2^2}\right), \quad x>0,
$$

(S22)

where $r = 0.6$, $\mu_1 = 2 \times B_2$, $\mu_2 = 0.5 \times B_2$ and $\sigma_1 = \sigma_2 = 0.5$.

The survival time ($T_s$) of each patient was calculated as the time period from the initiation of the simulation to the time at which the cell density exceeded a predefined threshold, $C_{th}$ (assumed to be 0.6 in this work), that is,

$$
T_s = \inf \{ t : C_T(t) \geq C_{th} \}.
$$

(S23)

Due to the stochastic nature of cancer progression represented by $C_T(t)$, $T_s$ is a random variable. In our simulations, the number of patients, $N$, was set to 100. We calculated the survival time for each patient, $T_s^{(i)}$, $i = 1, 2, \ldots, N$, according to Eq. (S23). The survival percentage, $SP(t)$, for the entire patient population was computed as

$$
SP(t) = \frac{\text{card}\left\{ i : T_s^{(i)} > t \right\}}{N},
$$

(S24)

where $\text{card}(A)$ represents the number of elements in set $A$. The frequency of survival time, $f(t)$, can also be calculated by noting that $SP(t) = 1 + \int_0^t f(s)\, ds$, or $SP(t) = 1 - \sum_{r=0}^t f(r)$ in the discrete form.
Fig S1. Simulated spatio-temporal profiles of cancer cells and their microenvironment using the model with increased drug consumption rate ($10 \times \eta_{drug}$). The spatio-temporal distributions of (A) cancer cell density, (B) macrophage density, (C) CSF1 concentration, (D) IGF1 concentration, (E) drug concentration. (F) The time courses of averaged cancer cell density and averaged drug concentration are shown. The simulation showed that increasing drug consumption rate did not significantly influence the emergence of drug resistance (compared to Fig 2 in the main text).
Fig S2. Model behavior under different values of certain critical parameters, including $r_1$, $d_1$, $B_2$, and $D_d$. (A) The decrease in the growth rate of tumor cells, $r_1$, and (B) the increase of the death rate of tumor cells, $d_1$, as well as (C) the decrease of the secretion rate of IL4, $B_2$, resulted in disappearance of the emergence of drug resistance. (D) The diffusion rate of the drug affected the killing rate and the regrowth rate of cancer cells.
Fig S3. Sensitivity analysis for parameter combination. Sensitivity of (A) the cancer cell killing rate and (B) the regrowth rate with respect to combined variations in two parameters. The treatment was conducted with 3 doses of CSF1R inhibitor.
Fig S4. Dose-dependent sensitivities of the killing rate and the regrowth rate of cancer cells under treatment with different doses of a CSF1R inhibitor [dose 1 (A, B) and dose 3 (C, D)]. Panels A and B show the sensitivity of the cancer cell killing rate (A) and the regrowth rate (B) to parameter variations during treatment with dose 1 of a CSF1R inhibitor. Panels C and D show the sensitivity of the killing rate (C) and the regrowth rate (D) to parameter variations during treatment with dose 3 of a CSF1R inhibitor.
Fig S5. The dynamics of drug response simulated from the model with initial condition (a) of macrophages as in Text S3. (A) The initial condition of macrophages. (B) Curves of time course of average cancer cell density. (C-F) The spatio-temporal distributions of cancer cell density (C), macrophage density (D), CSF1 concentration (E), and IGF1 concentration (F).
Fig S6. The dynamics of drug response simulated from the model with initial condition (b) of macrophages as in Text S3. (A) The initial condition of macrophages. (B) Curves of time course of average cancer cell density. (C-F) The spatio-temporal distributions of cancer cell density (C), macrophage density (D), CSF1 concentration (E), and IGF1 concentration.
Table S1. Values of dimensional parameters. Each parameter is listed with its symbol, value, biological description and reference.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_T$, $D_e$</td>
<td>$1.0 \times 10^{-9}$</td>
<td>cm²/s</td>
<td>Diffusion coefficient of cancer cells or macrophages</td>
<td>[1,3]</td>
</tr>
<tr>
<td>$r_T$</td>
<td>$2.41 \times 10^{-3}$</td>
<td>s⁻¹</td>
<td>Growth rate coefficient of cancer cells</td>
<td>[5,6,10]</td>
</tr>
<tr>
<td>$d_T$</td>
<td>$2.886 \times 10^{-7}$</td>
<td>s⁻¹</td>
<td>Death rate coefficient of cancer cells</td>
<td>[5,6]</td>
</tr>
<tr>
<td>$a_T$, $a_\phi$</td>
<td>$1.7 \times 10^{-3}$</td>
<td>cm²/(s nM)</td>
<td>Chemotaxis coefficient of IGF1 (or CSF1) for cancer cells (or macrophages)</td>
<td>[1,2]</td>
</tr>
<tr>
<td>$D_{CSF1}$, $D_{IGF1}$</td>
<td>$2.0 \times 10^{-6}$</td>
<td>cm²/s</td>
<td>Diffusion coefficient of CSF1 or IGF1</td>
<td>[5-7]</td>
</tr>
<tr>
<td>$S_{CSF1}$</td>
<td>$3.2 \times 10^{-22}$</td>
<td>g s⁻¹ cell⁻¹</td>
<td>Secretion rate of CSF1 from cancer cells</td>
<td>[5,6]</td>
</tr>
<tr>
<td>$S_{IGF1}$</td>
<td>$1.92 \times 10^{-22}$</td>
<td>g s⁻¹ cell⁻¹</td>
<td>Secretion rate of IGF1 from cancer cells</td>
<td>[5,6]</td>
</tr>
<tr>
<td>$d_{CSF1}$</td>
<td>$5 \times 10^{-4}$</td>
<td>s⁻¹</td>
<td>Degradation rate of CSF1</td>
<td>[5,6,14]</td>
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<tr>
<td>$d_{IGF1}$</td>
<td>$2.5 \times 10^{-4}$</td>
<td>s⁻¹</td>
<td>Degradation rate of IGF1</td>
<td>[5,6,15]</td>
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<tr>
<td>$S_{IL4}$</td>
<td>$1.2905 \times 10^{-7}$</td>
<td>s⁻¹</td>
<td>Secretion rate of IL4</td>
<td>[11]</td>
</tr>
<tr>
<td>$D_d$</td>
<td>$2.0 \times 10^{-6}$</td>
<td>s⁻¹</td>
<td>Diffusion rate of drug</td>
<td>[5-7]</td>
</tr>
<tr>
<td>$\eta_{drug}$</td>
<td>$1 \times 10^{-17}$</td>
<td>s⁻¹</td>
<td>Degradation rate of drug</td>
<td>[12]</td>
</tr>
<tr>
<td>$K_1$</td>
<td>$5 \times 10^{-9}$</td>
<td>g cm⁻³</td>
<td>Michaelis constant of IGF1 in growth rate</td>
<td>Calibrated</td>
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<tr>
<td>$\alpha$</td>
<td>$0.5 \times 10^{-8}$</td>
<td>–</td>
<td>a regulatory coefficient corresponding to M2 macrophages' function</td>
<td>Calibrated</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$0.5 \times 10^{-7}$</td>
<td>–</td>
<td>a regulatory coefficient corresponding to M1 macrophages' function</td>
<td>Calibrated</td>
</tr>
<tr>
<td>$C_{max}^T$</td>
<td>$1.0 \times 10^9$</td>
<td>cells cm⁻³</td>
<td>Maximal carrying capacity of cancer cells</td>
<td>[5,6,13]</td>
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<tr>
<td>$C_{\phi}^0$</td>
<td>$2.0 \times 10^8$</td>
<td>cells cm⁻³</td>
<td>Initial value of the density of macrophages</td>
<td>[5,6,13]</td>
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Table S2. Values of dimensionless parameters. Each parameter is listed with its symbol, value, biological description and reference.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value</th>
<th>Correspondence to biological meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_T$</td>
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<td>Chemotaxis rate of tumor cells</td>
</tr>
<tr>
<td>$A_\phi$</td>
<td>0.0109</td>
<td>Chemotaxis rate of macrophages</td>
</tr>
<tr>
<td>$B_1$</td>
<td>2</td>
<td>The ratio of degradation rate of CSF1 to that of IGF1</td>
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<tr>
<td>$B_2$</td>
<td>1.0324</td>
<td>Secretion rate of IGF1 induced by IL4</td>
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<tr>
<td>$\varepsilon$</td>
<td>$5 \times 10^{-4}$</td>
<td>Time scale parameter</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>1</td>
<td>A regulatory coefficient for M2 macrophages' function</td>
</tr>
<tr>
<td>$\beta$</td>
<td>1</td>
<td>A regulatory coefficient for M1 macrophages' function</td>
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<tr>
<td>$D_d$</td>
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<td>Diffusion rate of the drug</td>
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<tr>
<td>$\eta_d$</td>
<td>0.08</td>
<td>Degradation/uptake rate of the drug</td>
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References


