Supporting Text

I. Supporting Figure Legends

Supporting Figure S1 The growth rare of glioma tumor is dictated by ASC differentiation and astrocyte mutation to glioma cells. The contributions of these two factors are comparable in the first pre-cancer phase. However, neoplastic transformation of astrocytes directly to glioma cells contributes little to tumor development in the rapid expansion and malignant phases.

Supporting Figure S2 Influence of initial conditions to tumorigenesis time is demonstrated by perturbing the initial concentration of QSC and microglia. (**a**) Three different initial concentration of QSC are compared. With a higher initial QSC concentration, the patient will get faster progression. However, the influence is not significant. (**b**) The initial concentration of microglia has a striking effect on tumorigenesis time.

Supporting Figure S3 Virtual therapy of patient #3 demonstrates the difference of therapeutic efficacy between single-targeted and combination-targeted. The monotherapy targeted at even the most significant signaling cannot arrest the rapid progression, while the combinational therapy leads to a significant synergistic effect on tumor suppression.

Supporting Figure S4 Virtual therapies of two patients demonstrate the therapeutic efficacy of combination-targeted therapy. Concomitant improvement of patient survival is observed during expansion of targeted cytokine. (**a**) Virtual treatment for patient #1, up to four cytokine combination is adopted. (**b**) Treatment for patient #3. The expected therapeutic effect is achieved by targeting five signaling simultaneously.

Supporting Figure S5 Three patients are treated with the same protocol, which is personalized according to the cytokine secretion profile of patient #3. Patient #3 receives expected therapeutic effect, while the progression of patient #2 also slows down. However, the failure of patient #1 suggests missing the target. (**a**) Patient #1. (**b**) Patient #2. (**c**) Patient #3.

Supporting Figure S6 Inter-patient heterogeneity was demonstrated by sensitivity analyses of signaling-related parameters for tumorigenesis time. a. Sensitivity factors of cytokine secretion rates. Four patients with difference in six parameters (Supporting Table S3) are compared. The x-axis parameter panels are listed in Supporting Table S6. b. Sensitivity factors of receptor signaling regulation ratios. Twenty nine parameters are analyzed and four patients with difference in six parameters (Supporting Table S4) are compared. The x-coordinate parameter panels are listed in Supporting Table S7.

II. Supporting Methods

1. Deterministic description of the intercellular signaling network.

We translated the intercellular signaling network Fig. 1a into mathematical format by employing population dynamics and introducing stochastic mechanism. The deterministic descriptions are dozens of ordinary differential equations as follows. The meanings of parameters are listed in Supporting Table S1. The computational codes are available upon request, which should be addressed to R.F. or Y.W.

Quiescent glioma stem cell (QSC)

FGF (FGF7 and FGF10) signaling contributes to the telogen to anagen transition, adding new insights into the process of stem cell activation[1].

$$\dot{x}_{QSC} = c_{QSC} + K_{QSC\_ASC} - K_{ASC\_QSC} - d_{QSC}x_{QSC} \quad (1)$$

where

$$K_{QSC\_ASC} = k_{QSC\_ASC}x_{ASC}$$

$$K_{ASC\_QSC} = k_{ASC\_QSC}\left(1 + \frac{u_{QSC\_FGF}y_{FGF}}{s_{FGF} + y_{FGF}}\right)x_{QSC}$$

K_{QSC_ASC} is the increase due to deactivation/quiescence of ASC, and K_{ASC_QSC} describes the decrease because of activation of QSC.

Activated glioma stem cell (ASC)

EGF and FGF2 enhanced GBM brain tumor stem cells survival, proliferation, and subsequent sphere size [2].

Virtually all neural stem cells maintain an undifferentiated state and the capacity to self-renew in response to FGF2 [3].

IL6 signaling contributes to glioma malignancy through the promotion of GSC growth and survival [4].

Up-regulation of FGF5 during malignant progression might reflect dedifferentiation and acquisition of stem cell-like properties [5].

VEGF, FGF, SCF, IL1, HGF, and MIF are recognized as major factors that induce angiogenesis within GBM [6-21].

$$\dot{x}_{ASC} = K_{ASC\_QSC} - K_{QSC\_ASC} + R_{glioma} p_{ASC\_glio}\left(\frac{y_{FGF}}{s_{FGF} + y_{FGF}}\right) + R_{ASC}\left(1 - p_{glio\_ASC}\left(\frac{s_{FGF}}{s_{FGF} + y_{FGF}}\right)\left(\frac{u_{glio\_ASC\_IL6} y_{IL6}}{s_{IL6} + y_{IL6}}\right)\right) - d_{ASC} x_{ASC} \quad (2)$$

where

$$R_{ASC} = r_{ASC} x_{ASC}\left(1 - \frac{x_{QSC} + x_{ASC} + x_{glioma} + x_{astroglia} + x_{microglia}}{x_{\max} A_{angiogenesis}}\right)\left(1 + \frac{u_{ASC\_EGF} y_{EGF}}{s_{EGF} + y_{EGF}}\right)$$

$$A_{angiogenesis} = \left(1 + \frac{u_{cell\_IL1} y_{IL1}}{s_{IL1} + y_{IL1}}\right)\left(1 + \frac{u_{cell\_VEGF} y_{VEGF}}{s_{VEGF} + y_{VEGF}}\right)\left(1 + \frac{u_{cell\_HGF} y_{HGF}}{s_{HGF} + y_{HGF}}\right)\left(1 + \frac{u_{cell\_MIF} y_{MIF}}{s_{MIF} + y_{MIF}}\right)\left(1 + \frac{u_{cell\_SCF} y_{SCF}}{s_{SCF} + y_{SCF}}\right)\left(1 + \frac{u_{cell\_FGF} y_{FGF}}{s_{FGF} + y_{FGF}}\right)$$

R_{ASC} is the logistic proliferation term. Parameter $x_{\max}$ is the saturating concentration factor, whereas $A_{\mathrm{angiogenesis}}$ is the angiogenesis factor. So the product $x_{\max} A_{\mathrm{angiogenesis}}$ represents the carrying capacity. The first term of the right-hand side of Eq. (2) is the activation term, and the second term is the deactivation term. The third term is the dedifferentiation from glioma cells to ASC, while the fourth term is the result of proliferation minus differentiation. The last term is the decay of ASC.

Glioma

The experimental glioma genesis models indicate that when sufficient numbers of critical pathways are disrupted, glioma can originate from cells at all differentiation stages during glial cell development. In addition, progenitor cells appear to be more susceptible to transformation compared to the mature glial cells [22,23].

The Fibroblast Growth Factor (FGF) signaling pathway is reported to stimulate glioblastoma (GBM) growth [24,25]. Autocrine FGF5 is predominantly a survival and migration factor for GBM cells [5].

EGF receptor signalling promotes proliferation, tissue invasion, increases chemoresistance and inhibits apoptosis of glioma cells [26-28].

IL-1, IL-6, IL-10, TGFβ and their receptors were strongly expressed in nearly all glioblastomas and cell lines tested, and have been postulated to promote glioma cell proliferation [29,30,31-33].

The overexpression of EGF receptors suggests the potential for autocrine/paracrine proliferation in response to EGF and Hb-EGF [34-40].

TNF-α increases EGF receptor expression in glioma cells in vitro [41].

A decrease in tumor-cell proliferation was observed in *vivo* by systemic treatment with a monoclonal antibody against VEGFR-2 [42].

TNF-α increases VEGF expression in glioma cells in vitro [43].

HGF and its receptor, Met, have been found in gliomas [44], where they are thought to be involved in cell motility, chemoattraction, and tumor invasion [45,46].

G-CSF/G-CSFR is expressed constitutively in some glioma cell lines [47,48] and in human gliomas, where it has been postulated to promote in an autocrine fashion glioma cell proliferation [49].

SCF and its receptor c-kit, are highly expressed in glioma cell lines [50,51], and SCF can mediate the proliferation of glioma cells in vitro [52].

MIF plays a particularly critical part in cell cycle regulation and therefore in tumorigenesis as well. [10,20,53,54]. Recent studies have suggested a potentially broader role for MIF in growth regulation because of its ability to antagonize p53-mediated gene activation and apoptosis [55].

PGE2 has been shown to transiently prevent glioma cell proliferation in vitro [56].

$$\dot{x}_{glioma} = R_{ASC} p_{glio\_ASC}\left(\frac{s_{FGF}}{s_{FGF}+y_{FGF}}\right)\left(\frac{u_{glio\_ASC\_IL6}\, y_{IL6}}{s_{IL6}+y_{IL6}}\right) + p_{glio\_astro} R_{astroglia} + R_{glioma}\left(1 - p_{ASC\_glio}\left(\frac{y_{FGF}}{s_{FGF}+y_{FGF}}\right)\right) - d_{glioma}\frac{s_{EGF}}{s_{EGF}+y_{EGF}}\frac{s_{FGF}}{s_{FGF}+y_{FGF}}\frac{s_{MIF}}{s_{MIF}+y_{MIF}} x_{glioma} \tag{3}$$

where

$$R_{glioma} = r_{glioma} x_{glioma}\left(1 - \frac{x_{QSC}+x_{ASC}+x_{glioma}+x_{astroglia}+x_{microglia}}{x_{\max} A_{angiogenesis}}\right)$$
$$\left(1+\frac{u_{glio\_IL1}\, y_{IL1}}{s_{IL1}+y_{IL1}}\right)\left(1+\frac{u_{glio\_IL6}\, y_{IL6}}{s_{IL6}+y_{IL6}}\right)\left(1+\frac{u_{glio\_IL10}\, y_{IL10}}{s_{IL10}+y_{IL10}}\right)\left(1+\frac{u_{glio\_TGF\beta}\, y_{TGF\beta}}{s_{TGF\beta}+y_{TGF\beta}}\right)$$
$$\left(1+\frac{u_{glio\_EGF}\left(1+\frac{y_{TNF\alpha}}{s_{TNF\alpha}+y_{TNF\alpha}}\right) y_{EGF}}{s_{EGF}+y_{EGF}}\right)\left(1+\frac{u_{glio\_VEGF}\left(1+\frac{y_{TNF\alpha}}{s_{TNF\alpha}+y_{TNF\alpha}}\right) y_{VEGF}}{s_{VEGF}+y_{VEGF}}\right)$$
$$\left(1+\frac{u_{glio\_HGF}\, y_{HGF}}{s_{HGF}+y_{HGF}}\right)\left(1+\frac{u_{glio\_GCSF}\, y_{GCSF}}{s_{GCSF}+y_{GCSF}}\right)\left(1+\frac{u_{glio\_SCF}\, y_{SCF}}{s_{SCF}+y_{SCF}}\right)\left(1+\frac{u_{glio\_MIF}\, y_{MIF}}{s_{MIF}+y_{MIF}}\right)\left(\frac{s_{PGE2}}{s_{PGE2}+y_{PGE2}}\right)$$

R_{glioma} is the logistic proliferation term. The product $x_{\max} A_{\text{angiogenesis}}$ indicates the carrying capacity. The first term of the right-hand side of Eq. (3) represents the differentiation from ASC to glioma cells. The second term describes the mutation from astrocytes to glioma cells. The third term is the result of proliferation minus dedifferentiation. The last term is the death of glioma cells due to life span.

Activated Microglia

It is generally accepted that monocytes are the most likely source of all brain macrophages. These cells, which begin their migration into normal brain during embryogenesis, can differentiate into microglia [57].

Glioma cells express the microglia chemoattractant, MCP-1, at the mRNA and protein levels [58-60], and microglia possess the specific MCP-1 receptor, CCR2 [61]. Thus, recruitment of microglia to the site of gliomas may in part result from the local production of MCP-1 [58,62].

Microglia express receptors for EGF that enable them to proliferate in response to local release of this growth factor [63].

In vitro, VEGF can also induce the proliferation and migration of microglia [64].

HGF and its receptor, c-Met, have been found in microglia [65], where they are thought to be microglial chemoattractant and inducer of proliferation in vitro [66].

GM-CSF is potent mitogen for microglia [67].

TGF-β inhibits the proliferation of microglia as well as their production of cytokines in vitro [68].

In vitro, SCF inhibits microglial proliferation and their expression of the inflammatory cytokines TNFa and IL-1b [69].

$$\dot{x}_{microglia} = c_{microglia}\left(1+\frac{u_{micro\_MCP1}y_{MCP1}}{s_{MCP1}+y_{MCP1}}\right)+r_{microglia}x_{microglia}\left(1-\frac{x_{QSC}+x_{ASC}+x_{glioma}+x_{astrocyte}+x_{microglia}}{x_{\max}A_{angiogenesis}}\right)$$
$$\left(1+\frac{u_{micro\_EGF}y_{EGF}}{s_{EGF}+y_{EGF}}\right)\left(1+\frac{u_{micro\_VEGF}y_{VEGF}}{s_{VEGF}+y_{VEGF}}\right)\left(1+\frac{u_{micro\_HGF}y_{HGF}}{s_{HGF}+y_{HGF}}\right) \quad (4)$$
$$\left(1+\frac{u_{micro\_GMCSF}y_{GMCSF}}{s_{GMCSF}+y_{GMCSF}}\right)\left(\frac{s_{TGF\beta}}{s_{TGF\beta}+y_{TGF\beta}}\right)\left(\frac{s_{SCF}}{s_{SCF}+y_{SCF}}\right)-d_{microglia}x_{microglia}$$

The first term of the right-hand side of Eq. (4) is the replenishment of microglia from monocytes. The second term is logistic proliferation.

Astrocyte

Astrocytes have been shown to originate from progenitors, and can migrate radially [70].

IL-1 has been shown to stimulate the growth of astrocytes in vitro [71-73]. The duration of survival of GBM patients is enhanced when levels of intratumoral IL-1β, not necessarily produced by microglia, are elevated [74].

PGE2 released from activated microglia enhances astrocyte proliferation in vitro [75].

$$\dot{x}_{astrocyte} = c_{astrocyte} + R_{astrocyte}(1-p_{glio\_astro}) - d_{astrocyte}x_{astrocyte} \quad (5)$$

where

$$R_{astrocyte} = r_{astrocyte} x_{astrocyte} \left(1 - \frac{x_{QSC} + x_{ASC} + x_{glioma} + x_{astrocyte} + x_{microglia}}{x_{\max} A_{angiogenesis}}\right)\left(1 + \frac{u_{astro\_IL1} y_{IL1}}{s_{IL1} + y_{IL1}}\right)\left(1 + \frac{u_{astro\_PGE2} y_{PGE2}}{s_{PGE2} + y_{PGE2}}\right)$$

The first term of the right-hand side of Eq. (5) represents supply of astrocytes from progenitors. The second term is the result of proliferation minus mutation.

IL-1

Ameboid microglia, when activated, release significant quantities of IL-1 [76-78]. Astrocyte is observed to release IL-1 in culture [76,79]. Malignant glioma cells also secrete or express IL-1 [80-82].

In vitro, SCF inhibits microglial proliferation and their expression of the inflammatory cytokine IL-1β [69].

$$\dot{y}_{IL1} = k_{IL1\_glio} x_{glioma} + k_{IL1\_micro} x_{microglia} \frac{s_{SCF}}{s_{SCF} + y_{SCF}} + k_{IL1\_astro} x_{astrocyte} - d_{IL1} y_{IL1} \quad (6)$$

IL-6

Glioma secretes IL-6 [29,83-86].

When cultured in the presence of IL-1β, the human glioma cell lines U251 and HP591 demonstrated a marked increase in IL-6 production [83].

IL-1β has been shown to exert a strong inducing signal for IL-6 in primary human/rat astrocytes [78,87].

IL-6 also released by microglia [78,88,89]

$$\dot{y}_{IL6} = k_{IL6\_glio} x_{glioma}\left(1 + \frac{u_{IL6\_IL1} y_{IL1}}{s_{IL1} + y_{IL1}}\right) + k_{IL6\_astro} x_{astrocyte}\left(\frac{y_{IL1}}{s_{IL1} + y_{IL1}}\right) + k_{IL6\_micro} x_{microglia} - d_{IL6} y_{IL6} \quad (7)$$

IL-10

Microglia are the major source of IL-10 in gliomas [33,90].

$$\dot{y}_{IL10} = k_{IL10\_micro} x_{microglia} - d_{IL10} y_{IL10} \quad (8)$$

TNF-α

TNF-α is one of the products of activated microglia [30,78,91-93].

In vitro, SCF down-regulates microglial expression of TNF-α [69].

Astrocyte produces TNF-α in response to IL-1β [78,94-96].

$$\dot{y}_{TNF\alpha} = k_{TNF\alpha\_micro} x_{microglia} \frac{s_{SCF}}{s_{SCF} + y_{SCF}} + k_{TNF\alpha\_astro} x_{astrocyte} \left(\frac{y_{IL1}}{s_{IL1} + y_{IL1}} \right) - d_{TNF\alpha} y_{TNF\alpha} \quad (9)$$

TGF-β

The glioma cancer stem cells produce TGF-β1 [97].

Human GBM cell lines have been shown to produce TGF-β2 [31]. IL-1β also modulates the secretion of TGF-β from glioma cells in vitro, although the modulation has been shown to be both stimulatory and inhibitory, depending upon the cell line used [98,99].

Microglia has been shown to derive TGF-beta [100-102].

$$\dot{y}_{TGF\beta} = k_{TGF\beta\_ASC} x_{ASC} + k_{TGF\beta\_glio} x_{glioma} \left(1 + \frac{u_{TGF\beta\_IL1} y_{IL1}}{s_{IL1} + y_{IL1}} \right) + k_{TGF\beta\_micro} x_{microglia} - d_{TGF\beta} y_{TGF\beta}$$

(10)

EGF

EGF can be produced by activated microglia in vitro [103].

Heparin binding-EGF (Hb-EGF), a member of the EGF family, is produced by gliomas [104].

$$\dot{y}_{EGF} = k_{EGF\_glio} x_{glioma} + k_{EGF} x_{microglia} - d_{EGF} y_{EGF} \quad (11)$$

VEGF

Glioblastoma stem cells consistently secreted markedly elevated levels of VEGF [14,105].

Both microglia and gliomas secrete VEGF [12,13].

TNF-α increases VEGF expression in glioma cells in vitro [43].

MIF has been observed to induce a significant dose-dependent increase of VEGF [54,106].

$$\dot{y}_{VEGF} = k_{VEGF\_ASC} x_{ASC} + k_{VEGF\_glio} x_{glioma} \left(1 + \frac{u_{VEGF\_TNF\alpha} y_{TNF\alpha}}{s_{TNF\alpha} + y_{TNF\alpha}} \right) \left(1 + \frac{u_{VEGF\_MIF} y_{MIF}}{s_{MIF} + y_{MIF}} \right) + k_{VEGF\_micro} x_{microglia} - d_{VEGF} y_{VEGF} \quad (12)$$

FGF

FGF5 is frequently expressed in embryonic tissues and has been recently described as a stem cell marker [107]. Consequently, up-regulation during malignant progression might reflect dedifferentiation and acquisition of stem cell-like properties [5]. FGF has also been recognized as an autocrine signaling pathway in human embryonic stem cells [108].

Secreted FGF5 protein has been reported to generally present in the GBM cells *in vivo* and *in vitro* [5].

$$\dot{y}_{FGF} = k_{FGF\_ASC} x_{ASC} + k_{FGF\_glio} x_{glioma} - d_{FGF} y_{FGF} \tag{13}$$

HGF

HGF and its receptor, c-Met, have been found in microglia [65] and gliomas [44,109].

The expression of HGF in microglia is up-regulated by PGE2 in vitro and in vivo after ischemic injury [65].

$$\dot{y}_{HGF} = k_{HGF\_glio} x_{glioma} + k_{HGF\_micro} x_{microglia}\left(1 + \frac{u_{HGF\_PGE2} y_{PGE2}}{s_{PGE2} + y_{PGE2}}\right) - d_{HGF} y_{HGF} \tag{14}$$

MCP-1

Glioma cells express the microglia chemoattractant, MCP-1, at the mRNA and protein levels [58-60].

$$\dot{y}_{MCP1} = k_{MCP1\_glio} x_{glioma} - d_{MCP1} y_{MCP1} \tag{15}$$

MIF

MIF has been shown to be produced by glioma cell [110], and its expression was up-regulated under hypoxic and hypoglycemic stress conditions in vitro [10].

MIF was also secreted by activated microglia [20], and its secretion from macrophage can be induced by TNF-α [111].

$$\dot{y}_{MIF} = k_{MIF\_micro} x_{microglia}\left(1 + \frac{u_{MIF\_TNF\alpha} y_{TNF\alpha}}{s_{TNF\alpha} + y_{TNF\alpha}}\right) + k_{MIF\_glio}\left(1 + \frac{u_{MIF\_glio} x_{glioma}}{s_{glioma} + x_{glioma}}\right) x_{glioma} - d_{MIF} y_{MIF} \tag{16}$$

PGE2

Glioma-infiltrating microglia are a major source of PGE2 production through the COX-2 pathway [112].

$$\dot{y}_{PGE2} = k_{PGE2\_micro} x_{microglia} - d_{PGE2} y_{PGE2} \tag{17}$$

GM-CSF

Glioma cell lines express GM-CSF [47,113]. TGF-β2 and PGE2 has been shown to suppress GM-CSF production by gliomas in vitro [114]. IL-10 inhibits GM-CSF[115-117].

$$\dot{y}_{GMCSF} = k_{GMCSF\_glio} x_{glioma} \frac{s_{PGE2}}{s_{PGE2} + y_{PGE2}} \frac{s_{TGF\beta}}{s_{TGF\beta} + y_{TGF\beta}} + k_{GMCSF\_micro} x_{microglia} - d_{GMCSF} \left(1 + \frac{u_{GMCSF\_IL10} y_{IL10}}{s_{IL10} + y_{IL10}}\right) y_{GMCSF} \quad (18)$$

G-CSF

G-CSF is expressed constitutively in some glioma cell lines and in human gliomas [47,49]. IL-10 inhibits G-CSF[115,116].

$$\dot{y}_{GCSF} = k_{GCSF\_glio} x_{glioma} - d_{GCSF} \left(1 + \frac{u_{GCSF\_IL10} y_{IL10}}{s_{IL10} + y_{IL10}}\right) y_{GCSF} \quad (19)$$

SCF

SCF and its receptor c-kit, are highly expressed in glioma cell lines [50,51] and microglia [118,119].

$$\dot{y}_{SCF} = k_{SCF\_glio} x_{glioma} + k_{SCF\_micro} x_{microglia} - d_{SCF} y_{SCF} \quad (20)$$

2. Stochastic description of rate parameters

2.1 Bounded noise

We use bounded noise to describe the stochastic proliferation / mutation / differentiation /dedifferentiation rate (r_{ASC}, r_{glioma}, $r_{astrocyte}$, $r_{microglia}$, p_{glio_astro}, p_{glio_ASC}, p_{ASC_glio}).

$$r_{stochastic}(t) = r_{deterministic}(1 + \varepsilon \sin(\Omega t + \sigma W(t) + \Delta)) \quad (21)$$

where $W(t)$ is a standard Wiener process. $\zeta(t) = \varepsilon \sin(\Omega t + \sigma W(t) + \Delta)$ is the so called bounded noise with the mathematical expectation at a fixed time t

$$E[\zeta(t)] = e^{-t\sigma^2/2} \sin(\Omega t + \Delta) = \begin{cases} 0 & \sigma \to \infty \\ \sin(\Omega t + \Delta) & \sigma \to 0 \end{cases} \quad (22)$$

and the auto correlation function

$$R(\tau)=\frac{1}{2}\exp\left(-\frac{\sigma^2}{2}|\tau|\right)\cos\Omega\tau=\begin{cases}\frac{1}{2}\delta_{\tau,0} & \sigma\to\infty\\ \frac{1}{2}\cos\Omega\tau & \sigma\to 0\end{cases}$$

(23)

where $\delta_{\tau,0}$ is Kronecker delta. Thus, the bounded noise $\zeta(t)$ tends to a finite power white noise as $\sigma \to \infty$, and becomes a harmonic noise as $\sigma \to 0$.

The stochastic rate term $r_{\text{stochastic}}(t)$ describes a stochastic fluctuation around the average rate $r_{\text{deterministic}}$, which should be estimated according to the experimental data. There are three critical parameters: the strength factor $0 \le \varepsilon < 1$, the bandwidth factor $\sigma \ge 0$, and the center frequency $\Omega > 0$.

The flexible and adjustable characteristics of bounded noise make it an appropriate description of the intrinsically random rates and a good approximation to cell cycles according to heterogeneous scenarios.

Cell cycle is obviously periodic; however, the endogenous and exogenous signals that influence the cellular activity may be aperiodic. Thus, it is reasonable to assume that the rate is a stochastic perturbation to periodic fluctuations. In case the cellular activity observed in experiment shows regular periodic fluctuations around a mean value, a small σ should be adopted. Then, the center frequency Ω is determined by the period of cell cycle $T_{\text{cell cycle}}$

$$\Omega=\frac{2\pi}{T_{\text{cell cycle}}}=\frac{2\pi\times(\text{basal proliferation rate})}{\ln 2} \tag{24}$$

Alternatively, when there do not exist regular fluctuations or a characteristic frequency band, a large σ will be chosen to capture the stochastic nature.

2.2 Poisson white noise

We introduce Poisson white noise $\xi(t)$ to describe the stochastic immigration, emigration and supply from normal neural stem cell / monocytes / progenitors (c_{QSC}, $c_{\text{microglia}}$, $c_{\text{astrocyte}}$).

$$\xi(t)=\sum_{k=1}^{N(t)}Y_k\delta(t-\tau_k) \tag{25}$$

$\xi(t)$ is the stochastic representation of discrete event type fluctuation. Y_k is the magnitude of kth discrete event, i.e., the number of cell increasing (decreasing) at time point $t = \tau_k$, $N_i(t)$ denotes a non-homogeneous Poisson counting process with arrival rate function $\lambda_i(t) > 0$ (i.e., the number of events per unit time) and gives the number of events that arrive in the time interval $[0,t]$.

$$\lambda_{QSC}(t)=c_{QSC} \tag{26}$$

$$\lambda_{astrocyte}(t)=c_{astrocyte} \tag{27}$$

$$\lambda_{microglia}(t)=c_{microglia}\left(1+\frac{u_{micro\_MCP1}y_{MCP1}}{s_{MCP1}+y_{MCP1}}\right) \tag{28}$$

2.3 Gaussian white noise

We use Gaussian white noise to describe the stochastic fluctuation of cytokine secretion rates and up-regulation ratio via receptor kinase signaling (k_i and u_i).

$$k_{\text{stochastic}}(t) = k_{\text{deterministic}} \max\left(0, 1 + \sigma_g \eta(t)\right) \tag{29}$$

$$u_{\text{stochastic}}(t) = u_{\text{deterministic}} \max\left(0, 1 + \sigma_g \eta(t)\right) \tag{30}$$

where $\eta(t)$ is a Gaussian white noise with mean zero and standard deviation 1.

3. Sensitivity analysis

To systematically evaluate the influence of each cytokine on tumorigenesis rate, we conducted a sensitivity test, in which the sensitivity factor of cytokine x_i can be calculated as

$$S_i \equiv \left.\frac{\partial F(\mathbf{x})}{\partial x_i}\right|_{\mathbf{x}=\mathbf{x}^0} \tag{31}$$

where $F(\mathbf{x})$ is the objective function (e.g. tumorigenesis time, cell density, cytokine concentration), and $\mathbf{x}^0$ is the local parameter profile. The sensitivity factor S_i can be calculated numerically. The scenarios are dependent on the choice of objective function F. In the context, we studied the parameter sensitivity for tumorigenesis time and therapeutic effect, respectively. The definition is also local-state-dependent, that is, each sensitivity factor is calculated locally at parameter profile $\mathbf{x}^0$. Thus, we showed inter-patient heterogeneity by comparison of the sensitivity analyses results with diverse individual patient profiles, and further designed patient-based cytokine-targeted therapy.

The results show marked effects of these cytokines on the development of glioma and suggests and possibility of designing therapeutic intervention by targeting cytokine signaling pathways (both cytokine production and receptor expression level) (Supplementary Fig. S9). It was also found that the quantitative results are context specific; the exact time for observing tumor formation ($1\text{x}10^6$ cells/ml) depends on the profile of all initial parameters for each patient (Supplementary Tables S3 and S4). The greater the difference between cytokine sensitivity factor landscapes, the greater the inter-patients heterogeneity. In addition to quantitative manifestation of inter-patient heterogeneity, sensitivity analysis also points to a venue to identify a cytokine profile that potentially can serve as molecule signature for tumor sub-classification, and thus provides a means to stratify patients via their cytokine profiles and to design individualized treatment.

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