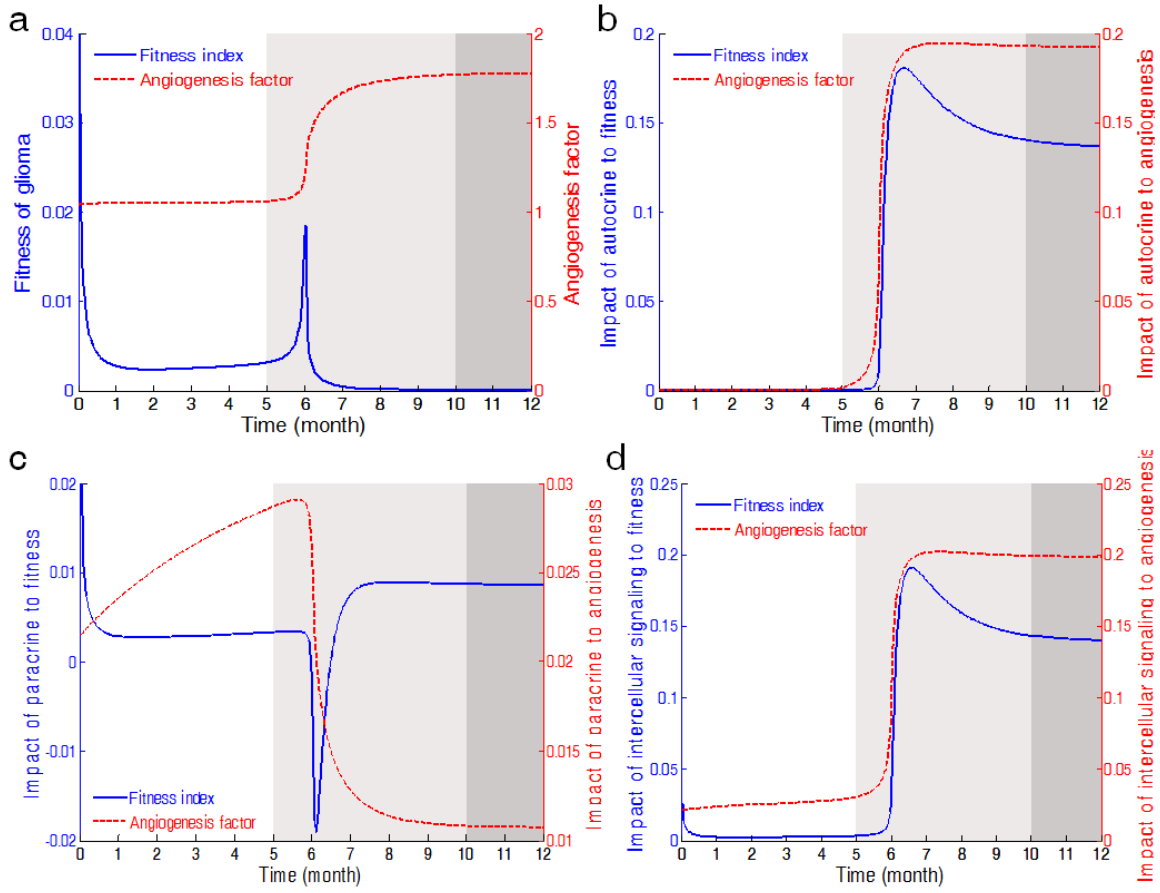
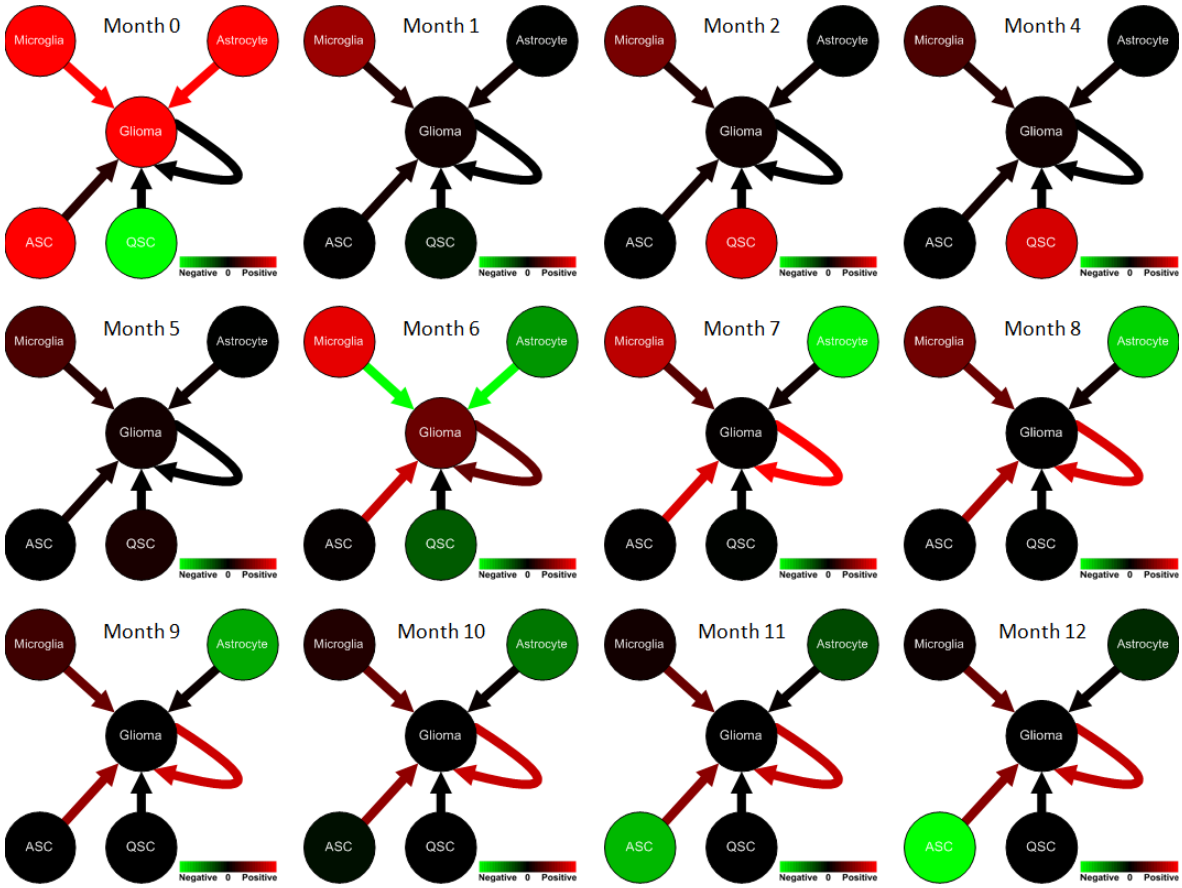
Supporting Information

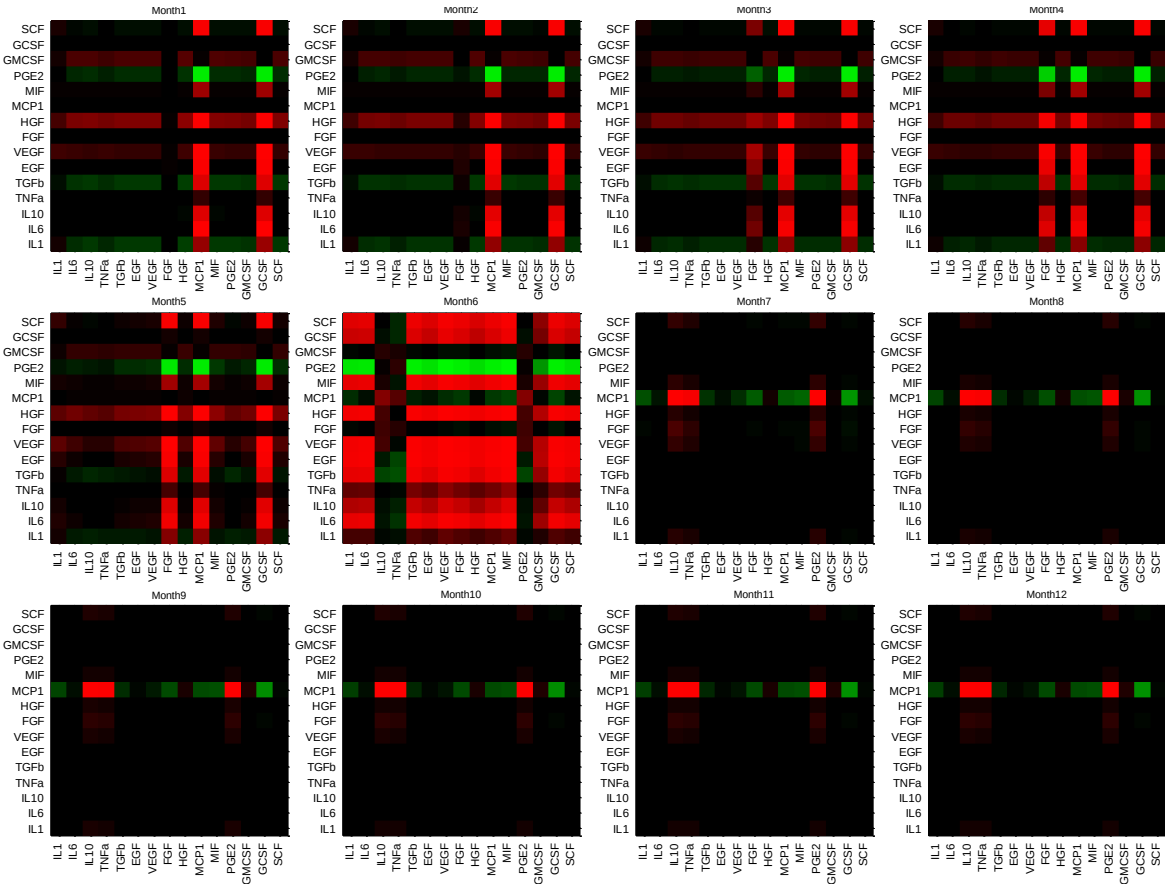
Supporting Figures



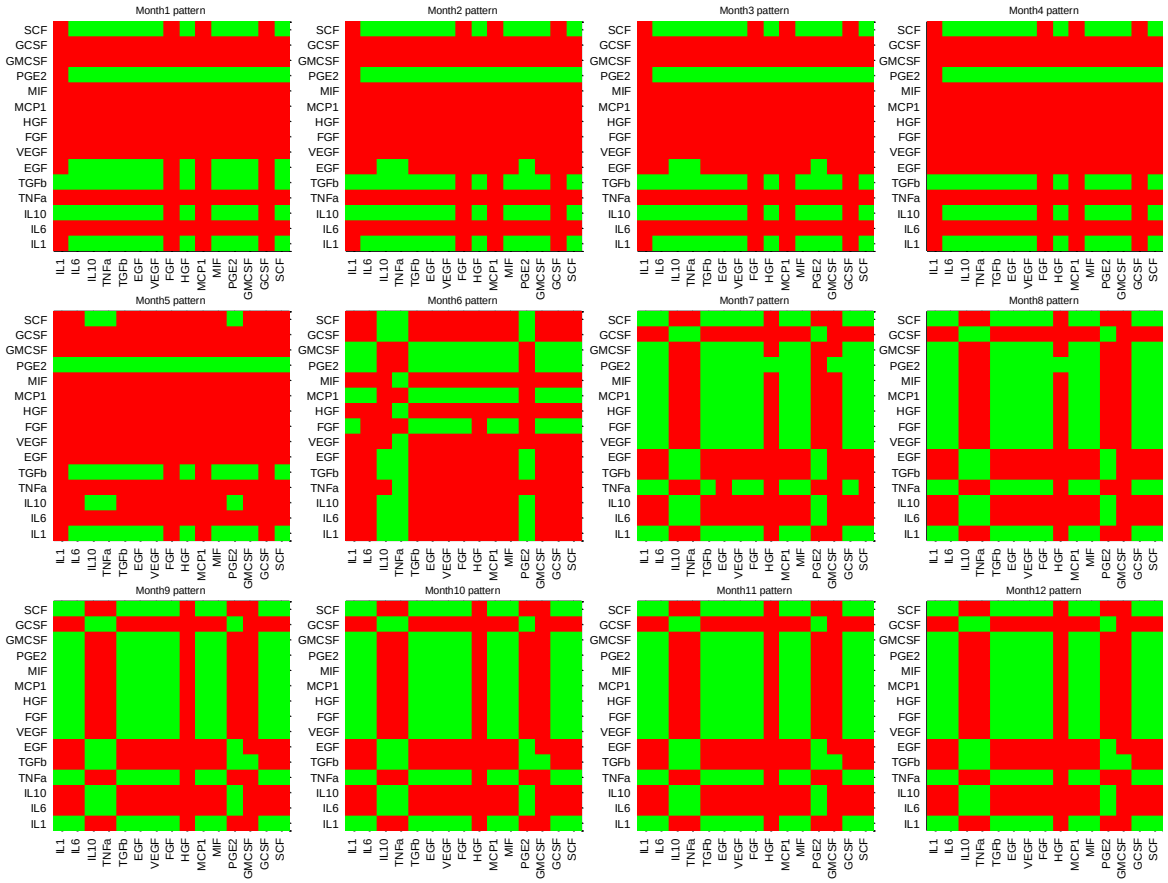
Supporting Fig. S1. a. One year evolution of fitness and angiogenesis factor of glioma. b. The contribution of autocrine to fitness ($A_{\text{glioma}}^{\text{fitness}}$) and angiogenesis ($A_{\text{glioma}}^{\text{angio}}$). c. The contribution of paracrine to fitness ($P_{\text{glioma}}^{\text{fitness}}$) and angiogenesis ($P_{\text{glioma}}^{\text{angio}}$). d. The collective contribution of intercellular signaling to fitness ($T_{\text{glioma}}^{\text{fitness}}$) and angiogenesis ($T_{\text{glioma}}^{\text{angio}}$).



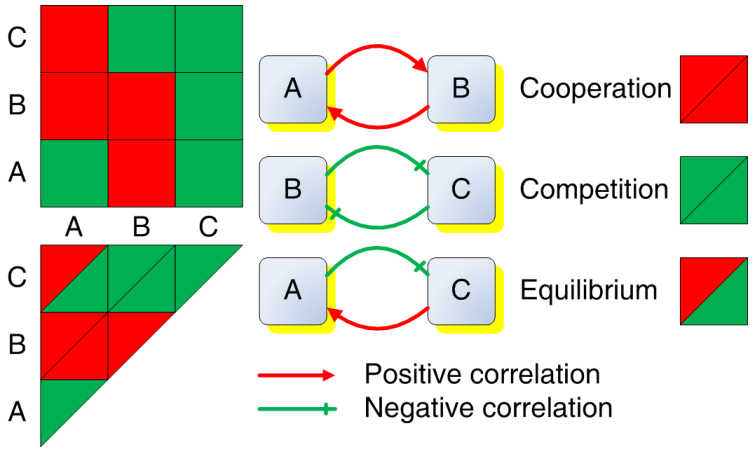
Supporting Fig. S2. Evolution of cell fitness and proliferation driving force. Red is positive, green is negative (see color bar). The color of cell node indicates the fitness of cell (Red means good, green means bad). The color of straight arrow indicates the paracrine strength, while the curved arrow indicates the autocrine strength.



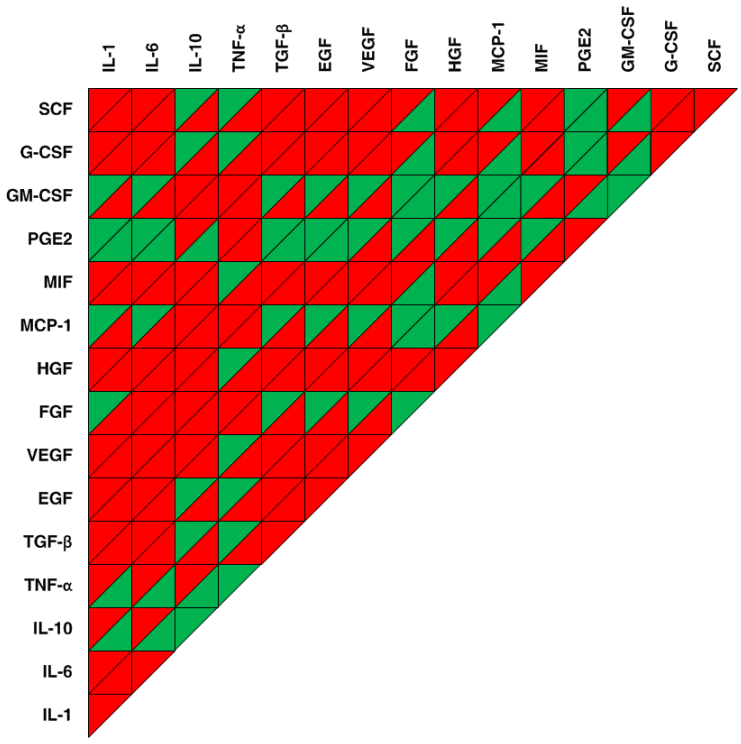
Supporting Fig. S3. Heat map of the correlation of cytokines in network level. The correlation factors are calculated at the end of each month. The cytokines highly correlated with others can be recognized as the important factors whose fluctuation can effectively rewire the network. The one year evolution shows a significant change of correlation during the sixth month. The ultimately high sensitivities also highlight the sixth month as the most active phase.



Supporting Fig. S4. Pattern map of the correlation of cytokines in network level. The positive correlations are in red, while the negative ones are in green. The correlations during first five months demonstrate similar pattern, whereas the last six months show a different pattern with more negative correlations than positive ones. The sixth month is recognized as the transition phase.

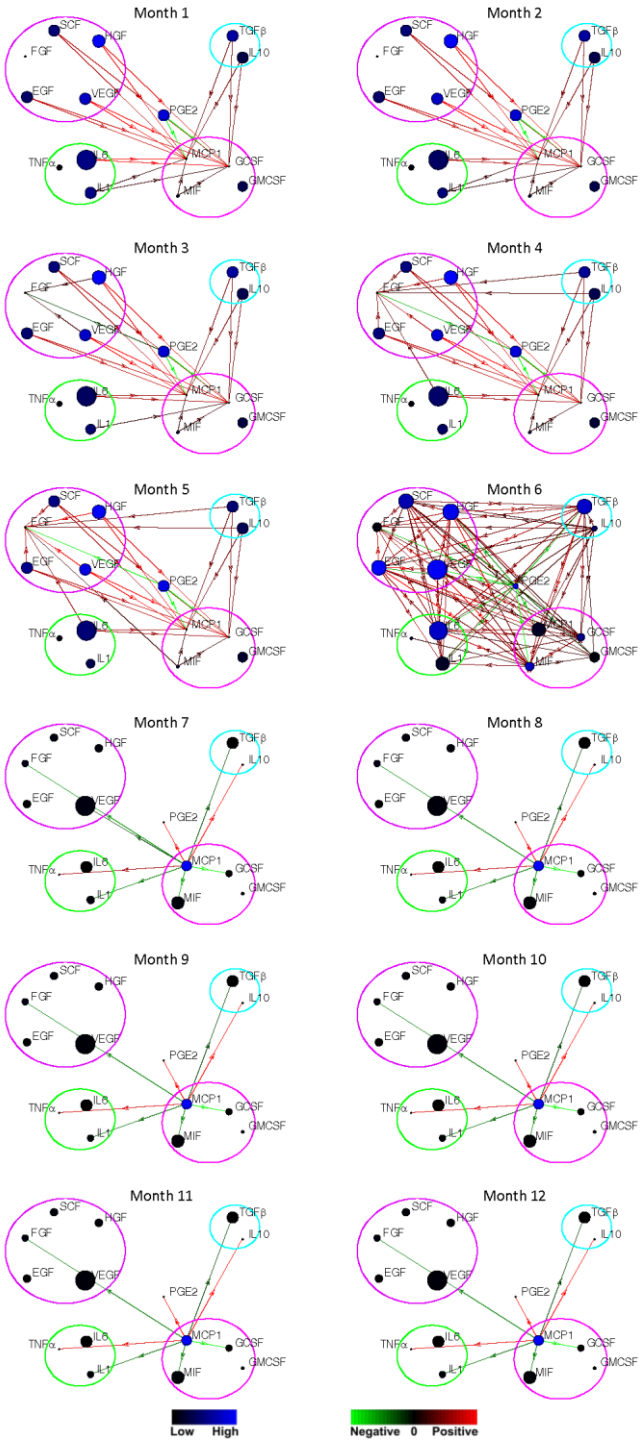


(a)



(b)

Supporting Fig. S5. Network level cytokine correlation pattern sketch map. a. The correlations of cytokines are generalized into cooperation, competition, and equilibrium, according to the positive or negative correlation. b. The correlation pattern at the sixth month has been illustrated.



Supporting Fig. S6. One year evolution of grouped signaling protein correlation network. Fifteen signaling proteins are classified into five sub-sets, including growth factors (purple circle group), proinflammatory cytokines (yellow), anti-inflammatory cytokines (cyan), chemokines (magenta), and PGE2. Each blue circle (node) represents a cytokine. The diameter of the circle is proportional to the cytokine concentration, and the color indicates the impact factor of the cytokine according to the blue color bar. The arrow link between two nodes represents the directional regulation of two cytokines. The green-red color bar shows the strength of the up-regulation (red) and down-regulation (green).

Supporting Methods

1. Deterministic description of the intercellular signaling network.

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

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

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

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).

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

where

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

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

R_{ASC} is the logistic proliferation term. Parameter $x_{\max}$ is the saturating concentration factor, whereas $A_{a\mathrm{ngiogenesis}}$ is the angiogenesis factor. So the product $x_{\max}A_{a\mathrm{ngiogenesis}}$ 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).

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

where

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

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).

$$\dot{y}_{TGF\beta} = k_{TGF\beta\_ASC} x_{ASC} + k_{TGF\beta\_glio} x_{glioma} \left(1 + \frac{u_{TGF\beta\_IL1} y_{IL1}}{s_{IL1} + y_{IL1}}\right) + k_{TGF\beta\_micro} x_{microglia} - d_{TGF\beta} y_{TGF\beta} \quad (10)$$

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).

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

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).

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

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).

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

SCF

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

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

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}, $r_{\mathrm{astrocyte}}$, $r_{\mathrm{microglia}}$, $p_{\mathrm{glio\_astro}}$, $p_{\mathrm{glio\_ASC}}$, $p_{\mathrm{ASC\_glio}}$).

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

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

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

and the auto correlation function

$$R(\tau) = \frac{1}{2}\exp\left(-\frac{\sigma^2}{2}|\tau|\right)\cos\Omega\tau = \begin{cases} \frac{1}{2}\delta_{\tau,0} & \sigma\to\infty \\ \frac{1}{2}\cos\Omega\tau & \sigma\to 0 \end{cases} \tag{23}$$

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 $r_{\mathrm{stochastic}}(t)$ describes a stochastic fluctuation around the average rate $r_{\mathrm{deterministic}}$, 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.

Supporting Tables

Supporting Table S1. Deterministic Parameters

Variable	Description	Value	Dimension	Reference	Comment
x_{QSC}	Concentration of quiescent glioma stem like cell	1E4	ml^{-1}	(120, 121)	Initial density
x_{ASC}	Concentration of activated glioma stem like cell	0	ml^{-1}		Initial density is zero
x_{glioma}	Concentration of glioma cell	0	ml^{-1}		Initial density
$x_{microglia}$	Concentration of microglia	2E6	ml^{-1}	(122-125)	Initial density
$x_{astrocyte}$	Concentration of astrocyte	2.8E7	ml^{-1}	(123, 126-130)	Initial density
y_{IL1}	Concentration of IL1	150	pM	Estimated	Initial Concentration
y_{IL6}	Concentration of IL6	250	pM	Estimated	Initial
y_{IL10}	Concentration of IL10	150	pM	Estimated	Initial
$y_{TNF\alpha}$	Concentration of TNFα	80	pM	Estimated	Initial
$y_{TGF\beta}$	Concentration of TGFβ	150	pM	Estimated	Initial
y_{EGF}	Concentration of EGF	150	pM	Estimated	Initial
y_{VEGF}	Concentration of VEGF	150	pM	Estimated	Initial
y_{FGF}	Concentration of FGF	0	pM	Estimated	Initial
y_{HGF}	Concentration of HGF	150	pM	Estimated	Initial
y_{MCP1}	Concentration of MCP1	0	pM	Estimated	Initial
y_{COX2}	Concentration of COX2	40	pM	Estimated	Initial
y_{PGE2}	Concentration of PGE2	150	pM	Estimated	Initial
y_{GMCSF}	Concentration of GMCSF	150	pM	Estimated	Initial
y_{GCSF}	Concentration of GCSF	0	pM	Estimated	Initial
y_{SCF}	Concentration of SCF	150	pM	Estimated	Initial
c_{QSC}	Rate of supply of quiescent glioma stem cell from normal neural stem cell	1	$ml^{-1}\ h^{-1}$	Estimated	
$c_{microglia}$	Rate of replenishment of microglia from monocytes	800	$ml^{-1}\ h^{-1}$	(57)	
$c_{astrocyte}$	Rate of supply of astrocyte from progenitors	2000	$ml^{-1}\ h^{-1}$	Estimated	
r_{ASC}	Average basal proliferation (including self-renewal and differentiation) rate of activated glioma stem cell obtained in the absence of population limitation and cytokine stimulus	5E-4	h^{-1}	(131)	$\frac{\ln 2}{\text{cell cycle period}}$ Cell cycle ~58 days
r_{glioma}	Average basal proliferation rate of glioma cell obtained in the absence of population limitation and cytokine stimulus	0.0174	h^{-1}	(132)	Cell cycle ~40 hours

$r_{microglia}$	Average basal proliferation rate of microglia obtained in the absence of population limitation and cytokine stimulus	0.0174	h^{-1}	(133-135)	Cell cycle ~40 hours
$r_{astrocyte}$	Average basal proliferation rate of astrocyte obtained in the absence of population limitation and cytokine stimulus	0.0174	h^{-1}	(130)	Cell cycle ~40 hours
x_{max}	Maximum cell population (including QSC, ASC, glioma, microglia, astrocyte) level due to limited nutrition and space	3E7	ml^{-1}	(122, 124, 135-137)	Density-dependent inhibition of cell growth
u_{cell_IL1}	Maximum up-regulation ratio of maximum cell concentration due to angiogenic effect of IL1	0.1		(7, 8, 11)	
u_{cell_VEGF}	Maximum up-regulation ratio of maximum cell concentration due to angiogenic effect of VEGF	0.2		(6, 12-14)	
u_{cell_FGF}	Maximum up-regulation ratio of maximum cell concentration due to angiogenic effect of FGF	0.2		(6, 15-18)	
u_{cell_HGF}	Maximum up-regulation ratio of maximum cell concentration due to angiogenic effect of HGF	0.1		(6, 9, 138)	
u_{cell_MIF}	Maximum up-regulation ratio of maximum cell concentration due to angiogenic effect of MIF	0.1		(10, 19, 20)	
u_{cell_SCF}	Maximum up-regulation ratio of maximum cell concentration due to angiogenic effect of SCF	0.15		(21)	
u_{QSC_FGF}	Maximum up-regulation ratio of QSC activation rate by FGF	2		(1)	
u_{ASC_EGF}	Maximum up-regulation ratio of ASC proliferation rate by EGF	2		(2)	
$u_{glio\_ASC\_IL6}$	Maximum up-regulation ratio of differentiation rate from ASC to glioma by IL6	2		(4)	
u_{glio_IL1}	Maximum up-regulation ratio of glioma proliferation rate by IL1	2		(113, 139, 140)	
u_{glio_IL6}	Maximum up-regulation ratio of glioma proliferation rate by IL6	2		(29)	
u_{glio_IL10}	Maximum up-regulation ratio of glioma proliferation rate by IL10	2		(33)	
$u_{glio\_TGF\beta}$	Maximum up-regulation ratio of glioma proliferation rate by TGFβ	2		(113, 141-143)	
u_{glio_EGF}	Maximum up-regulation ratio of glioma proliferation rate by EGF	3		(24, 36, 39, 40)	
u_{glio_VEGF}	Maximum up-regulation ratio of glioma proliferation rate by VEGF	3		(42)	
u_{glio_HGF}	Maximum up-regulation ratio of	3		(46)	

	glioma proliferation rate by HGF				
u_{glio_GCSF}	Maximum up-regulation ratio of glioma proliferation rate by GCSF	2		(49)	
u_{glio_SCF}	Maximum up-regulation ratio of glioma proliferation rate by SCF	2		(50, 52)	
u_{glio_MIF}	Maximum up-regulation ratio of glioma proliferation rate by MIF	2		(10, 20, 53, 54)	
u_{MIF_glio}	Maximum up-regulation ratio of secretion rate of MIF from glioma due to hypoxia and hypoglycemia	6		(10)	
u_{micro_MCP1}	Maximum up-regulation ratio of replenishment rate of microglia due to chemotaxis	5		(58, 62)	
u_{micro_EGF}	Maximum up-regulation ratio of microglia proliferation rate by EGF	2		(63)	
u_{micro_VEGF}	Maximum up-regulation ratio of microglia proliferation rate by VEGF	2		(64)	
u_{micro_HGF}	Maximum up-regulation ratio of microglia proliferation rate by HGF	2		(65, 66)	
u_{micro_GMCSF}	Maximum up-regulation ratio of microglia proliferation rate by GMCSF	2		(67, 135)	
u_{astro_IL1}	Maximum up-regulation ratio of astrocyte proliferation rate by IL-1	2.5694		(71, 72)	
u_{astro_PGE2}	Maximum up-regulation ratio of astrocyte proliferation rate by PGE2	2		(75)	
u_{IL6_IL1}	Maximum up-regulation ratio of IL-6 production by glioma in the presence of IL-1β	2		(83)	
$u_{TGF\beta\_IL1}$	Maximum up-regulation ratio of TGF-β production by glioma in the presence of IL-1β	2		(98, 99)	
u_{GMCSF_IL10}	Maximum up-regulation ratio of decay rate of GM-CSF in the presence of IL-10	1		(115-117)	
u_{GCSF_IL10}	Maximum up-regulation ratio of decay rate of G-CSF in the presence of IL-10	1		(115, 116)	
$u_{VEGF\_TNF\alpha}$	Maximum up-regulation ratio of VEGF production by glioma in the presence of TNFα	2		(43)	
$u_{MIF\_TNF\alpha}$	Maximum up-regulation ratio of MIF production by microglia in the presence of TNFα	2		(20, 111)	
u_{VEGF_MIF}	Maximum up-regulation ratio of VEGF production by glioma in the presence of MIF	2		(54, 106)	
u_{HGF_PGE2}	Maximum up-regulation ratio of	2		(65)	

	HGF production by microglia in the presence of PGE2				
s_{glioma}	Half max concentration of glioma cell in hypoxia dependent MIF production	1.5e7	ml^{-1}	(10)	
s_{IL1}	Saturation concentration of IL-1 producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{IL6}	Saturation concentration of IL-6 producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{IL10}	Saturation concentration of IL-10 producing half max regulation effect to cellular activity	2200	pM	Estimated	
$s_{TGF\beta}$	Saturation concentration of TGFβ producing half max regulation effect to cellular activity	2200	pM	Estimated	
$s_{TNF\alpha}$	Saturation concentration of TNFα producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{EGF}	Saturation concentration of EGF producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{VEGF}	Saturation concentration of VEGF producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{FGF}	Saturation concentration of FGF producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{HGF}	Saturation concentration of HGF producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{GCSF}	Saturation concentration of G-CSF producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{SCF}	Saturation concentration of SCF producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{PGE2}	Saturation concentration of PGE2 producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{MCP1}	Saturation concentration of MCP1 producing half max regulation effect to cellular activity	1100	pM	Estimated	
s_{GMCSF}	Saturation concentration of GM-CSF producing half max regulation effect to cellular activity	2200	pM	Estimated	
s_{MIF}	Saturation concentration of MIF producing half max regulation effect to cellular activity	2200	pM	Estimated	

d_{QSC}	Death rate of quiescent glioma stem cell based on lifespan	0.00001	h^{-1}	(144-146)	$\frac{\ln 2}{\text{cell half-life}}$ Stem cell half-life ~8 years
d_{ASC}	Death rate of activated glioma stem cell based on lifespan	0.0001	h^{-1}	(144-146)	Half-life ~9.6 months
d_{glioma}	Death rate of glioma cell based on lifespan	0.001	h^{-1}	(147)	Half-life ~29 days
$d_{microglia}$	Death rate of microglia based on lifespan	0.001	h^{-1}	(147)	Half-life ~29 days
$d_{astrocyte}$	Death rate of astrocyte based on lifespan	0.001	h^{-1}	(147)	Half-life ~29 days
d_{IL1}	Decay rate of IL-1 based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{IL6}	Decay rate of IL-6 based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{IL10}	Decay rate of IL-10 based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
$d_{TNF\alpha}$	Decay rate of TNFα based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
$d_{TGF\beta}$	Decay rate of TGFβ based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{EGF}	Decay rate of EGF based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{VEGF}	Decay rate of VEGF based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{FGF}	Decay rate of FGF based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{HGF}	Decay rate of HGF based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{MCP1}	Decay rate of MCP1 based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{MIF}	Decay rate of MIF based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{PGE2}	Decay rate of PGE2 based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{GMCSF}	Decay rate of GM-CSF based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{GCSF}	Decay rate of G-CSF based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
d_{SCF}	Decay rate of SCF based on half-life	0.6931	h^{-1}	(148-153)	Half-life ~1 hour
k_{QSC_ASC}	Deactivation rate	1e-3	h^{-1}	Estimated(1, 131, 154-156)	
k_{ASC_QSC}	Activation rate	5e-3	h^{-1}	Estimated(1, 131, 154-156)	
p_{ASC_glio}	Probability of dividing glioma	1e-4		Estimated(	

	dedifferentiate to ASC during each cell cycle			5, 157-160)	
p_{glio_ASC}	Probability of dividing ASC differentiate to glioma during each cell cycle	0.5		(161)	
p_{glio_astro}	Probability of dividing astrocyte mutate to glioma during each cell cycle	1E-6		(162-164)	
k_{IL1_glio}	Secretion rate of IL1 by glioma	60	10^{-21}mol h^{-1}	(80-82)	
k_{IL1_micro}	Secretion rate of IL1 by microglia	22.1	10^{-21}mol h^{-1}	(76, 78)	
k_{IL1_astro}	Secretion rate of IL1 by astrocyte	3	10^{-21}mol h^{-1}	(76)	
k_{IL6_glio}	Secretion rate of IL6 by glioma	40	10^{-21}mol h^{-1}	(29, 83-86)	
k_{IL6_micro}	Secretion rate of IL6 by microglia	96.2	10^{-21}mol h^{-1}	(78, 88, 89)	
k_{IL6_astro}	Secretion rate of IL6 by astrocyte	6	10^{-21}mol h^{-1}	(78, 87)	
k_{IL10_micro}	Secretion rate of IL10 by microglia	60	10^{-21}mol h^{-1}	(33, 90)	
$k_{TNF\alpha\_micro}$	Secretion rate of TNFα by microglia	29.4	10^{-21}mol h^{-1}	(30, 78, 91-93)	
$k_{TNF\alpha\_astro}$	Secretion rate of TNFα by astrocyte	2.94	10^{-21}mol h^{-1}	(78, 94-96, 165)	
$k_{TGF\beta\_ASC}$	Secretion rate of TGFβ by ASC	0.15	10^{-21}mol h^{-1}	(97)	
$k_{TGF\beta\_glio}$	Secretion rate of TGFβ by glioma	40	10^{-21}mol h^{-1}	(31)	
$k_{TGF\beta\_micro}$	Secretion rate of TGFβ by microglia	60	10^{-21}mol h^{-1}	(100-102)	
k_{EGF_glio}	Secretion rate of EGF by glioma	60	10^{-21}mol h^{-1}	(104)	
k_{EGF_micro}	Secretion rate of EGF by microglia	60	10^{-21}mol h^{-1}	(103)	
k_{VEGF_ASC}	Secretion rate of VEGF by ASC	30	10^{-21}mol h^{-1}	(14, 105)	
k_{VEGF_glio}	Secretion rate of VEGF by glioma	60	10^{-21}mol h^{-1}	(12, 13, 166)	
k_{VEGF_micro}	Secretion rate of VEGF by microglia	60	10^{-21}mol h^{-1}	(13)	
k_{FGF_ASC}	Secretion rate of FGF by ASC	60	10^{-21}mol h^{-1}	(107, 108)	
k_{FGF_glio}	Secretion rate of FGF by glioma	60	10^{-21}mol h^{-1}	(5)	
k_{HGF_glio}	Secretion rate of HGF by glioma	60	10^{-21}mol h^{-1}	(44, 109)	
k_{HGF_micro}	Secretion rate of HGF by microglia	60	10^{-21}mol h^{-1}	(65)	
k_{MCP1_glio}	Secretion rate of MCP1 by glioma	90	10^{-21}mol h^{-1}	(58-60)	
k_{MIF_glio}	Secretion rate of MIF by glioma	20	10^{-21}mol h^{-1}	(110)	
k_{MIF_micro}	Secretion rate of MIF by microglia	15	10^{-21}mol h^{-1}	(20)	
k_{PGE2_micro}	Secretion rate of PGE2 by microglia	60	10^{-21}mol h^{-1}		
k_{GMCSF_glio}	Secretion rate of GM-CSF by glioma	60	10^{-21}mol h^{-1}	(47, 49)	
k_{GMCSF_micro}	Secretion rate of GM-CSF by microglia	60	10^{-21}mol h^{-1}		
k_{GCSF_glio}	Secretion rate of G-CSF by glioma	60	10^{-21}mol h^{-1}	(47, 49)	
k_{SCF_glio}	Secretion rate of SCF by glioma	60	10^{-21}mol h^{-1}	(50, 51)	

k_{SCF_micro}	Secretion rate of SCF by microglia	60	10^{-21}mol h^{-1}	(118, 119)	

Supporting Table S2. Stochastic Parameters

Deterministic variable	Stochastic description	Parameters	Dimension	Comment
r_{ASC}	$r(1+\varepsilon\sin(\Omega t+\sigma W(t)+\Delta))$ r_{ASC}=0.0005 ε_{ASC}=0.99 Ω_{ASC}=0.0045 σ_{ASC}=10	r_{ASC} is the basal proliferation rate of ASC. ε is the amplitude of stochastic fluctuation; σ is the bandwidth factor ; Δ is a random phase uniformly distributed in $[0, 2\pi]$.	Ω (h^{-1}), Others are dimensionless	$r > 0$, $0 \le \varepsilon < 1$, $\Omega = \frac{2\pi r_{ASC}}{\ln 2}$
r_{glioma}	$r(1+\varepsilon\sin(\Omega t+\sigma W(t)+\Delta))$ r_{glioma}=0.0174 ε_{glioma}=0.99 Ω_{glioma}=0.1577 σ_{glioma}=10	r_{glioma} is the basal proliferation rate of glioma.	Ω (h^{-1}), Others are dimensionless	$r > 0$, $0 \le \varepsilon < 1$, $\Omega = \frac{2\pi r_{glioma}}{\ln 2}$
$r_{astrocyte}$	$r(1+\varepsilon\sin(\Omega t+\sigma W(t)+\Delta))$ $r_{astrocyte}$=0.0174 $\varepsilon_{astrocyte}$=0.99 $\Omega_{astrocyte}$=0.1577 $\sigma_{astrocyte}$=10	$r_{astrocyte}$ is the basal proliferation rate of astrocyte.	Ω (h^{-1}), Others are dimensionless	$r>0$, $0 \le \varepsilon < 1$, $\Omega = \frac{2\pi r_{astrocyte}}{\ln 2}$
$r_{microglia}$	$r(1+\varepsilon\sin(\Omega t+\sigma W(t)+\Delta))$ $r_{microglia}$=0.0174 $\varepsilon_{microglia}$=0.99 $\Omega_{microglia}$=0.1577 $\sigma_{microglia}$=10	$r_{microglia}$ is the basal proliferation rate of microglia.	Ω (h^{-1}), Others are dimensionless	$r>0$, $0 \le \varepsilon < 1$, $\Omega = \frac{2\pi r_{microglia}}{\ln 2}$
p_{glio_astro}	$p(1+\varepsilon\sin(\Omega t+\sigma W(t)+\Delta))$; $p_{glio\_astro}=1\times10^{-6}$ ε_{glio_astro}=1 Ω_{glio_astro}=0.1577 σ_{glio_astro}=10	p_{glio_astro} is the average proportion of dividing astrocyte mutate to glioma during each cell cycle;	Ω (h^{-1}), Others are dimensionless	$0 \le p \le 1$, $0 \le \varepsilon \le \min\left(1, \frac{1}{p}-1\right)$ $\Omega = \frac{2\pi}{T_{\text{cell cycle}}} = \frac{2\pi r_{astrocyt}}{\ln 2}$
p_{glio_ASC}	$p(1+\varepsilon\sin(\Omega t+\sigma W(t)+\Delta))$; p_{glio_ASC}=0.5	p_{glio_ASC} is the average proportion of dividing ASC differentiate to	Ω (h^{-1}), Others are dimensionl	$0 \le p \le 1$, $0 \le \varepsilon \le \min\left(1, \frac{1}{p}-1\right)$

	$\varepsilon_{glio\_ASC}=1$ $\Omega_{glio\_ASC}=0.0045$ $\sigma_{glio\_ASC}=10$	glioma during each cell cycle.	ess	$\Omega=\frac{2\pi}{T_{\text{cell cycle}}}=\frac{2\pi r_{\text{ASC}}}{\ln 2}$
p_{ASC_glio}	$p(1+\varepsilon\sin(\Omega t+\sigma W(t)+\Delta))$; $p_{ASC\_glio}=1\times10^{-4}$ $\varepsilon_{ASC\_glio}=1$ $\Omega_{ASC\_glio}=0.1577$ $\sigma_{ASC\_glio}=10$	p_{ASC_glio} is the average proportion of dividing glioma dedifferentiate to ASC during each cell cycle.	Ω (h^{-1}), Others are dimensionl ess	$0\le p\le 1$, $0\le\varepsilon\le\min\left(1,\frac{1}{p}-1\right)$ $\Omega=\frac{2\pi}{T_{\text{cell cycle}}}=\frac{2\pi r_{\text{glioma}}}{\ln 2}$
c_{QSC}	$\xi(t)=\sum_{k=1}^{N(t)}Y_k\delta(t-\tau_k)$; $Y_k=1$; $\lambda=c_{QSC}=1$;	c_{QSC} is the average rate of supply of quiescent glioma stem cell from normal neural stem cell; $\xi(t)$ is Poisson white noise; $N(t)$ is Poisson counting process giving the number of pulses that arrive in the time interval $[0, t]$; λ is the mean arrival rate of $N(t)$;		
$c_{microglia}$	$\xi(t)=\sum_{k=1}^{N(t)}Y_k\delta(t-\tau_k)$; $Y_k=1$; $\lambda=$ $c_{microglia}\left(1+\frac{u_{micro\_MCP1}y_{MCP1}}{s_{MCP1}+y_{MCP1}}\right)$;	$c_{microglia}$ is the average rate of supply of microglia from monocytes;		
$c_{astrocyte}$	$\xi(t)=\sum_{k=1}^{N(t)}Y_k\delta(t-\tau_k)$; $Y_k=1$; $\lambda=c_{astrocyte}$;	$c_{astrocyte}$ is the average rate of supply of astrocyte from progenitors;		
k_i	$k_i\max(0,1+\sigma N(0,1))$	Truncated normal distribution		

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