Mathematical model for BMP4 induced differentiation therapy in combination with radiotherapy in glioblastoma

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INTRODUCTION

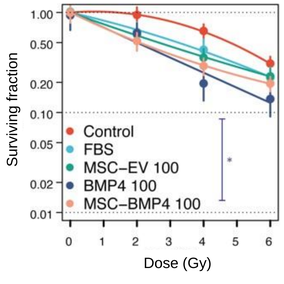
Glioblastoma (GBM) is the most aggressive and most common primary brain tumour in adults and is uniformly fatal, with a poor median survival time of 15 months. Radiotherapy forms an integral part in standard of care treatment, despite this radio-resistance almost always occurs leading to recurrent disease. Glioma stem cells (GSCs) are a special subpopulation, functionally defined as tumour cells (TCs) that can self-renew and initiate a tumour. Treatment cannot be successful unless all GSCs are eliminated. However, GSCs are known to be highly resistant to radiotherapy, and complete surgical removal is usually impossible in GBM. Therefore, new treatments that specifically target the GSCs could have a large benefit. BMP4 has been shown to induce differentiation of GSCs towards a less malignant astrocytic-like (ALCs) lineage[1]. New delivery systems (nano particles) provide a mechanism by which BMP4 could be successfully administered to reverse the GSC state and reduce radio resistance in a patient.

We develop a previously published cancer stem cell model[2] to further incorporate the effects of BMP4 therapy and radiotherapy, specifically in the case of GBM. Analysis of our model reveals the importance of how several key parameters, including: radiosensitivity of all populations and the effect of BMP4 on differentiation rate, impact treatment outcomes.

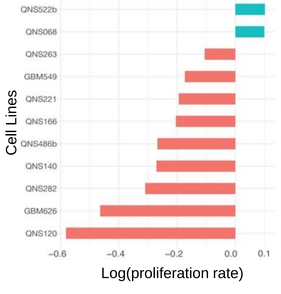
BIOLOGICAL DATA

Exposure of patient derived GSCs to BMP4 causes GSCs to differentiate into ALCs, this has two key effects:

BMP4 Increases radiosensitivity



BMP4 decreases proliferation rate

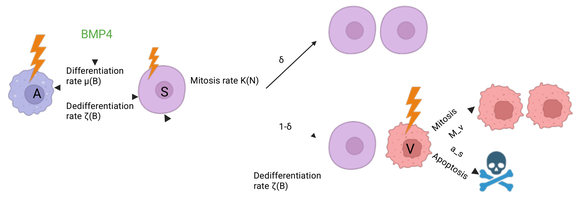


MATHEMATICAL MODEL

Based on the biological data we make the following key model assumptions:

- GSCs are immortal, while TCs have a limited capacity for proliferation. This ensures that GSCs are tumor propagating while TCs cannot survive without GSCs.
- Proliferation rate of GSCs, TCs and ALCs depends on the total tumor density (N) via K(N), which is a strictly decreasing function, reflecting competition for resources.
- BMP4 causes differentiation of GSCs into ALCs and a decrease in dedifferentiation rate of both ALCs and TCs.
- GSCs are highly resistant to radiotherapy, compared to both TCs and ALCs.

Model schematic



Stem cell model

$$\frac{ds}{dt} = \underbrace{\delta m_s K(N) s}_{\substack{\text{Symetric division} \\ \text{of GSCs}}} + \underbrace{2\zeta(B) a}_{\substack{\text{Dedifferentiation} \\ \text{of TCs and ALCs}}} - \underbrace{\mu(B) s}_{\text{Differentiation}}$$

$$\frac{dv}{dt} = \underbrace{(1-\delta) m_s K(N) s}_{\substack{\text{Asymetric division} \\ \text{of GSCs}}} + \underbrace{m_v K(N) v}_{\substack{\text{Mitosis} \\ \text{of TCs}}} - \underbrace{a_v v}_{\substack{\text{Apoptosis} \\ \text{of TCs}}} - \underbrace{\zeta(B) v}_{\text{Dedifferentiation}}$$

$$\frac{da}{dt} = \underbrace{\mu(B) s}_{\text{Differentiation}} - \underbrace{\zeta(B)}_{\text{Dedifferentiation}}$$

BMP4 therapy model

BMP4 is administered at a set time and then exponentially decays.

$$B(t) = \begin{cases} 0, & t < t_{treat} \\ e^{-h(t-t_{treat})}, & t \geq t_{treat} \end{cases}$$

BMP4 both increase the differentiation rate (to ALCs) and decrease the dedifferentiation rate (of both ALCs and TCs)

$$\mu(B) = \frac{\psi B}{1+B}, \qquad \zeta(B) = \frac{\zeta_{max}}{1+\omega B}$$

RADIOTHERAPY MODEL

Radiotherapy is modelled according to the LQ model, for the GSCs the surviving fraction after a single dose of d grays is given by

$$\gamma_s(d) = \exp(-\alpha d - \beta d^2)$$

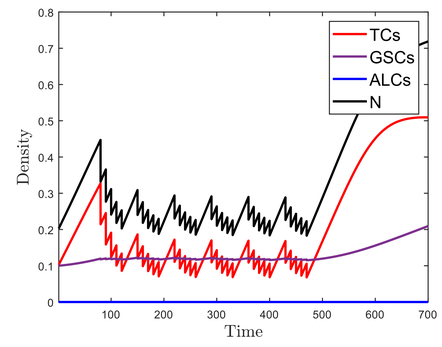
We can then calculate the surviving fraction of TCs by multiplying γ_s by the radiosensitivity factor (F)

$$\gamma_v = \mathrm{F}\gamma_s$$

MODEL SIMULATIONS

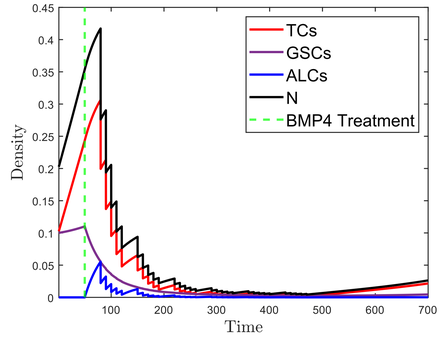
When no BMP4 is applied radiotherapy has little effect on the GSC compartment, this allows for rapid regrowth after treatment is stopped.

No BMP4



When BMP4 is applied before radiotherapy it reduces the GSC compartment (turning them into ALCs), radiotherapy is then applied reducing the TC and ALC populations. The reduced number of GSCs as well as TCs means that recurrence takes much longer.

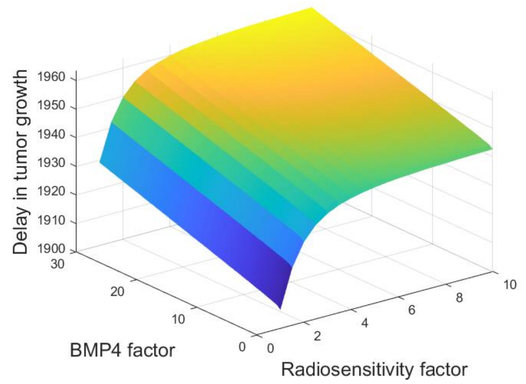
BMP4 + radiotherapy



MODEL PARAMETERS

Two key parameters for determining the success of treatment are the difference in radiosensitivity between GSCs and TCs (radiosensitivity factor) and the effectiveness of BMP4 (BMP4 factor).

Radiosensitivity and BMP4 factor surface plot



DISCUSSION

- New treatments that specifically target GSCs could improve survival times.
- A combination of BMP4 therapy and radiotherapy can provide superior outcomes than either one individually..

FUTURE WORK

- Simulate virtual clinical trail.
- Sensitivity analysis of the model.
- Optimizing combination therapy.

REFERENCES

1. Nayak et al. Cancers, 2020
2. Hillen and Enderling, Bull of Math Biol, 2012

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