Creating a Tissue Engineered Tumor Microenvironment System Using Cell Encapsulation with MAP Gel

(Technical Paper)

Disparities in Cancer Research Funding

(STS Paper)

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

With and incidence of 3.23 in 100,000, glioblastomas make up a majority of the malignant brain tumors diagnosed in the United States (54%), and are the most fatal with a 5-year survival rate of 7% compared to 36% overall for malignant brain tumors (Miller et al., 2021). There is currently no cure for glioblastoma, with challenges in research and treatments including: the blood-brain barrier impeding drug delivery, the heterogeneity of the tumors limiting long term success of treatments, and the infiltrative nature of the tumor into healthy brain tissue (Gilbert & Armstrong, 2017). These factors and more contribute to the difficulties in studying glioblastoma behavior in vivo, as well as increasing the required complexity of in vitro models to accurately recreate the tumor microenvironment (TME). The TME is made up of the cells, tissues, blood vessels, and acellular substances that surround the tumor and interact with it as it grows and proliferates.

Due to the dangers of studying glioblastomas in vivo, the most promising method of researching glioblastoma behavior is creating an in vitro model. Current in vitro models often lack the complexity and other properties to properly sustain in vivo glioblastoma behavior. As such, I have aimed to develop a tissue engineered system using microporous annealed particle hydrogel (MAP gel) with encapsulated neural cells to mimic the TME of glioblastomas and brain tissue in order to study glioblastomas in vitro.

Despite the high level of fatality of glioblastomas, they receive significantly less funding per person years of life lost than less fatal cancers such as prostate and breast cancer (Spencer et al., 2019). This is a trend across many other types of cancer in which the less fatal cancers often receive significantly more funding than more fatal types of cancer (Samuelson, 2019). Similar disparities exist among racial and sex groups. Specifically, cancers with higher incidences among

black populations compared to those with higher incidences among white populations, and gynecological cancers receive disproportionately lower funding (*Disparities Found in Funding of Cancer Research*, 2022; Spencer et al., 2019). These disparities within funding can have massive impacts on the trajectory of the disease, from awareness, to diagnosis, to research, to access to treatment, and more.

My technical topic is the creation of a MAP gel system with encapsulated cells to recreate the brain tumor microenvironment in order to better study the behavior of glioblastoma. To compliment glioblastoma research, my STS topic is the discrepancies within cancer research funding.

Technical Topic

One of the characteristic elements of glioblastoma behavior, is its invasiveness into surrounding brain tissue (Seker-Polat et al., 2022). This along with the sensitive nature of brain tissue makes it incredibility difficult to study and/or treat glioblastoma in vivo. As a result, in vitro models have become vital to researching glioblastoma behavior and possible (non-surgical) treatment options. In the past five years, the vast majority of glioblastoma models that have had papers published have been 2D cell culture models (Paolillo et al., 2021). However, it was found that glioblastoma-derived cancer stem cells (GSCs) more closely resemble the structure of glioblastoma in vivo when developed in 3D, due to the tumor microtubes that support cell invasion and proliferation, the brain specific extracellular matrix (ECM), and the closer to in vivo behavior shown in 3D cultures compared to 2D cultures (Paolillo et al., 2021). Additionally, recent developments have shown 3D models could more closely replicate the TME which is important for including things such as immune responses and microglia facilitated tumor growth

in glioblastoma treatment studies (Kim et al., 2017). Despite the importance of mimicking the TME, some 3D models do not include certain aspects such as the blood brain barrier, substrate simulating extracellular matrix, and/or interactions with nontumor cells. The hydrogel-based system created in this technical project could make up for what other models lack.

This system uses MAP gel with encapsulated neural cells to mirror the TME creating a 3D in vitro model to study glioblastoma. The system is made by resuspending astrocytes, microglia, and endothelial cells in gel precursor and run through a microfluidic device (Figure 1) with oil-based surfactant to create uniform microparticles with evenly dispersed cells. Due to the plug and play nature of this system, the parameters are highly manipulatable allowing them to be adjusted for the desired traits such as matching the gels mechanical properties (stiffness) to that of brain tissue. Additionally, the customizable hydrogel system could make up for the aforementioned pitfalls of current in vitro models. First, the blood brain barrier issue could be solved by the use of astrocytes and endothelial cells in hydrogel which has been successfully used to recreate the blood brain barrier for models of other cancers(Augustine et al., 2021). Second, the gel particles will be seeded with ECM proteins such as laminin and collagen to help with cell viability and simulate extracellular matrix. Third, the encapsulation of the gel with neural cells specifically astrocytes, microglia, and endothelial cells allows for important interactions between tumor and non-tumor cells that are key in the TME(Kim et al.,

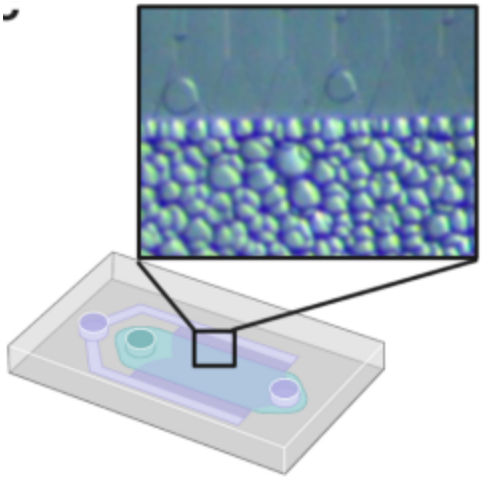

Figure 1- Microfluidic device

2017). Moreover, the customizability of system could allow for the addition of other cell types in the future should it be deemed beneficial to the promotion of TME interaction.

The first stage of the project is developing the engineered system such that glioblastoma cell behavior reflects cell behavior seen in vivo. Milestones for development are the system sustaining non-tumor (neural) cell life and function, eliciting the same glioma cell behavior as in vivo, and establishing a protocol that can be easily reproduced. The second stage of the project is creating protocol that allows for the safe transport of the system from The Griffin Lab at UVA to the collaborating Munson Lab at Virginia Tech. Current plans for this protocol are freezing and thawing the scaffold, which will require testing for maintenance of cell viability and function following transport.

STS Topic

Despite the fatality of the glioblastoma, it receives disproportionately less funding than other more common or less fatal cancers. However, this disparity is not limited to brain cancers nor just more fatal cancers. Cancers that have disproportionately higher incidences among black populations compared to cancers with high incidences among white patients, cancers with higher mortality rates, and cancers related to highly stigmatized behaviors and body parts, all receive disproportionally low funding (*Disparities Found in Funding of Cancer Research*, 2022; Spencer et al., 2019). The types of cancer that exemplify these disparities are colorectal, pancreatic, liver and bile duct, brain, lung, ovarian, cervical, and endometrial cancers. These cancers have significantly lower funding per person-years of life lost per 100 cases scores than prostate and breast cancer with colorectal at .442, brain/ONS at .110, ovary at .097, compared to prostate at 1.812, and breast at 1.803(Spencer et al., 2019).

Cancer research is funded both by the federal government, mainly through the National Cancer Institute (NCI), and through non-profit organizations such as the American Cancer Society. The NCI budget is determined by US Congress in appropriations for National Institutes of Health and the Department of Health and Human Services (*NCI Budget and Appropriations - NCI*, 2015). Proposals undergo a scientific peer review process to determine if they should be funded; however, as there is no predetermined target for disease areas, they are also evaluated by NCI leadership for scientific novelty, public health significance, and representation on the topic within the NCI portfolio. Although non-profit organizations are funded primarily by personal donors, grants are similarly awarded by peer review committees which include scientists, clinicians, and other volunteer stakeholders (*How American Cancer Society Research Funding Works*, n.d.). For general organizations, the number of grants given to a certain topic depends on the number of researchers for that area. There are also many organizations that focus on a specific cancer type or disease area, that are similarly funded by personal donations.

Regardless of the different sources of funding, disparities in funding between cancer types exist for within the NCI and non-profit organizations. The amount of funding directly correlates with the number of clinical trials, and for certain cancers such as pancreatic cancer, increased NCI funding has been shown to correlate with increased survival ("Urge Congress to Make Pancreatic Cancer Research a National Priority!," n.d.). The current funding process has lots of room for human bias from the people who approve funding proposals, to the dedicated non-profits for which less fatal cancers have more survivors to advocate for increased funding and research. Changing the way cancer research is funded could potentially save millions of lives of those afflicted with cancer.

Research question and methods

For my STS research, I aim to answer how current cancer research funding structures can lead to inequalities. My research will include the current funding structure, and possible alternatives to current funding structures to reduce the magnitude of funding disparities. This will be done by first breaking down how the current funding structure originated, who the major research funders and stakeholders are and how they interact, and how different types of funding affect research and disease progression. Next, policy alternatives or other possible changes to funding structure will be analyzed and compared to determine what improvements can be made and how they will be able to decrease the disparities between cancer types. Through this process, various metrics will be determined to evaluate how fairly funding is allocated, such as based on lethality, incidence, or social factors.

Conclusion

In order to improve in vitro models and better study glioblastoma behavior by recreating the tumor microenvironment I will design and create a tissue engineered system using microporous annealed particle hydrogel seeded with neural cells. This system will be an improvement on current models and make progress on glioblastoma treatment research towards the goal of a reliable therapy to implemented with patients. Funding for research of this and other types of underfunded cancers will be analyzed for current effects and implications of future funding changes. Evaluating how current cancers are funded, and how that can be improved to better serve those being affected by cancer, can change the way cancer behavior and treatments are researched in addition to saving lives.

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