Understanding the tumor microenvironment in glioblastoma for the development of focused therapies

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CHAPTER 7

SUMMARY AND DISCUSSION

SUMMARY

Glioblastomas (GB) are one of the most aggressive cancers in the brain and are resistant to therapy. GBs are known for their rapid and diffuse growth. This lethal malignancy can be attributed in most part by the tumors advanced stage at the time of diagnosis and the heterogeneity of the tumor cells and the cells in the tumor vicinity which together with the vasculature and extracellular matrix make up the TME. In this thesis we have aimed to develop therapeutical strategies targeting tumor cells directly or cells of the TME to combat GB progression. Three therapeutical approaches have been tested in preclinical GB mouse models and showed prolonged survival outcomes.

The first part of **Chapter 1** focusses on the importance of communication between GB cells and cells of the TME and evaluates the tumor suppressing and tumor supportive role of astrocytes and their changes mediated by extracellular vesicle crosstalk. Next, the ability of GB to change microglia cells into tumor supportive phenotype. The second part introduces the different therapeutic strategies that are being developed to reduce GB progression and highlights the different therapy approaches that have been assessed throughout this thesis.

Chapter 2 characterizes a mouse model that could help future studies to understand the interaction between astrocytes and GB cells and its potential effect on GB progression. A transgenic mouse model encoding the EV marker hCD81-mNeonGreen lox-stop-lox transgene was crossed with GFAP-Cre transgenic mouse. Here Cre recombinase is driven by GFAP promoter which resulted in a mouse strain where GFAP positive astrocytes that secrete EVs that are labeled with hCD81-mNeonGreen. This mouse model serves as a tool to study EV-mediated crosstalk between astrocytes and GB cells *in vivo.*

Chapter 3 focusses on the role of microglia in the TME. Microglia have an early exposure to GB cells, since they are the first to arrive at the tumor site. Their initial cytotoxic and tumor killing functions alter in the presence of GB. This study indicates that the transformation of tumor-associated microglia is

driven by increased ApoE levels. The hijacked microglia in the TME are not able to clear the brain from tumor cells causing sustained tumor growth. Here we show that deleting the ApoE gene or blocking ApoE function using therapeutic anti-ApoE antibodies hampers glioma growth in mice.

Chapter 4 demonstrates the potential of local administration of recombinant IL-12 to accumulate $CD8^{POS}$ T cells at the tumor site in preclinical GB mouse models. In addition to the direct stimulation of $CD8^{POS}$ T cells by rIL-12, specialized DCs are recruited and activated at the tumor site, further enhancing the $CD8^{POS}$ T cell activity. We show that the rIL-12-driven effect was assisted by its co-stimulatory factor, 41BBL, delivered through AAV vector in the TME. This study provides evidence that 4-1BBL acts both on $CD8^{POS}$ T cells and DCs. These recruited and activated DCs, in turn, direct the T cell response and further activated the $CD8^{POS}$ T cells in the TME effectively enhancing anti-GB immunity. In conclusion, we have demonstrated an immune-gene therapy combination strategy whereby $CD8^{POS}$ T cells were activated at the tumor site with limited cues from tumor-associated DCs, leading to increased survival in GB tumor-bearing mice.

In **Chapter 5** it was shown that targeting miR-21 directly in GB cell lines reduces cell migration, invasion, and proliferation *in vitro*. Implanting GB cell lines (mouse and human) lacking miR-21 intracranially reduces tumor growth and improves survival of mice. Downstream miR-21 targets involved in regulating cell proliferation such as Cdc25a and Cdk6 were shown to be upregulated in miR-21 knockout GB cells. **Chapter 6** utilizes the findings in chapter 5 and served as a proof-of-concept for the application of AAV vector-mediated delivery of CRISPR-SaCas9-KKH in GB-bearing mice, targeting miR-21 at the tumor site as a therapeutical intervention.

In **Chapter 7** a summary of all these findings is listed and future prospect for therapeutic approaches in the treatment of GB are discussed.

DISCUSSION

GBs are embedded in a dynamic TME formed by the tumor cells and the organismal milieu that consists of an adapted blood vessel structure, suppressed immune cells, hijacked glial cells, and an extracellular matrix which varies across tumor areas (Sharma et al. 2023; Quail and Joyce 2017; Baghban et al. 2020). Over the past decades, GBs have been primarily viewed as a single entity thereby not fully recognizing the role of the TME in tumor progression (Ayuso and Ochoa Garrido 2022). Through the tumor cell centric perspective research efforts, focusing mostly on genetics through single cell RNA sequencing, the dynamic plasticity and heterogeneity of GB has been elucidated (Neftel et al. 2019; Greenwald et al. 2024). Recent spatial transcriptomic analysis pointed to the role of local TME, the interactions of tumor cells entangled with neighboring cells help determining the cancer cell fate (Greenwald et al. 2024; Ravi et al. 2022; Moffet et al. 2023). In this thesis we aimed to utilize therapeutic strategies that could help combatting GB and together better understand components of its extensive TME (Laplane et al. 2019).

The GB TME harbors a wide range of cells, such as neurons, macrophages, microglia, endothelial cells, pericytes, dendritic cells, oligodendrocytes, and a variety of immune cells (Sharma et al. 2023). In the first part of this thesis, we focused on astrocytes with the emphasis on the role of EVs in GB progression. Based on previous literature, the field leans towards a pro-tumorigenic role of astrocytes in the TME, with GB-derived EVs involved in astrocyte activation. However, more studies are necessary to better understand astrocyte-derived EVs and their function in GB development and progression. We therefore characterized a transgenic mouse model that allows tracking of EVs secreted by astrocytes. We showed direct transfer of EVs from astrocytes to GB cells and this mouse model could serve as a platform to study EV crosstalk between astrocytes and other cells in their surrounding such as GB cells. Future studies could use this tool track astrocytes-derived EVs and show the effect of astrocyte-derived EV uptake by other cells such as GB cells. This will aid the field in understanding the EV trafficking between astrocytes and other cells including tumor cells and this model could provide insights in the intercellular

communication of astrocytes through EVs *in vivo*. Specifically, gaining knowledge about the content that is being transferred between astrocytes and GB cells could provide potential therapeutic targets. Future studies could aim in interfering in the GB-astrocyte communication by either blocking or enhancing certain genetic material and other cargo that is involved in tumor progression. Understanding the EV communication between GB and the TME may yield in mechanistic insights with the goal to re-enforce control over the TME from GB cells and could potentially lead to novel therapeutic approaches.

Another type of glial cell are microglia, they act as first when irregularities are observed within the CNS. A variety of microglia subtypes have been identified in the context of brain pathologies such as Alzheimer's Disease (AD) and GB. GAMs, are microglia located in the tumor vicinity and display a cancer supportive phenotype. Here we characterized tumor associated microglia and aimed to inhibit reprogrammed microglia located in the TME. The transcriptomic profile of GAMs showed elevated expression of ApoE, compared to microglia not exposed to GB cells. ApoE is an apolipoprotein involved in transporting lipids, including cholesterol, implicated in AD (Raulin et al. 2022) and cardiovascular disease (Mahley 2016). We showed that reduction of ApoE in the TME results in smaller tumor volumes and lower number of tumor cells in GB mouse models. Importantly, human GB tissue also showed high levels of ApoE in GAMs, we therefore anticipate the potential of ApoE targeted therapy into the clinic. This study shows the transformation of microglia in the presence of GB, that is partially driven by elevated ApoE levels. Understanding the role of ApoE in dysregulating microglia may not only hold potential in GB context but could also aid in understanding other disorders in the CNS. Future directions should therefore focus on the mechanisms and underlying pathways of ApoE related to microglia dysfunction and study its potential effect on other cell types in the brain, such as astrocytes. Additionally, scientists should aim to validate our current findings in human GB as a step towards clinical translation.

Besides targeting the innate immune cells present in and around the tumor we have also attempted to design a therapeutic approach towards the adaptive immune cells. The immune landscape is an important element of the TME

(Arifianto et al. 2023). In a GB context, the immune response is suppressed allowing tumor cells to escape detection by the adaptive immune cells such as CD4 and CD8 T cells. Due to this immunosuppressive nature of GB, adaptive immune cells have low infiltration capacity (REF). Although recent efforts have tried to activate the limited number of T cells present at the tumor border, current immunotherapy strategies including immune checkpoint inhibitors have shown minimal efficacy in GB compared to other cancers (REF). We hypothesized that addressing the immunosuppressive nature of GB requires a multifaceted approach, potentially augmenting immunotherapy with other strategies to overcome the immunosuppressive TME. In the context of GB, T cells are not only deprived but are also remain inactivated. DCs can convert information from their surroundings to guide the T cell response (Cabeza-Cabrerizo et al. 2021). However, in the presence of GB, DC function and numbers are suppressed (Friedrich et al. 2023), inhibiting their anti-tumor immunity function. We therefore provided both IL-12 and 4-1BBL at the tumor site, these stimulatory signals activate DCs which then instruct T cells to become functional. Here, a preclinical evaluation of a combined therapeutical strategy was conducted. In detail, a low dose of the cytokine recombinant (r)IL-12, able to activate $CD8^{POS}$ T cells and DCs was administered, followed by the co-stimulative factor, 4-1BBL. The dendritic cell regulatory factor 4-1BBL has shown to enhance the rIL-12-driven immunology effect. In our study, 4-1BBL was delivered through an AAV vector specifically targeting astrocytes by using the GFAP promoter. Astrocytes located at the tumor border were transduced with AAV vector, prior to administration of rIL-12 intratumorally. Upon transduction astrocyte produce 4-1BBL directly at the side of the tumor. Delivering AAV vector at the vicinity of the tumor rather than directed at the tumor, enforces an indirect therapeutic effect, and reduces transgene dilution due to the high proliferative nature of the tumor cells. However, intracranial injections are invasive and present limitations in delivery strategy, including risks of infection, tissue damage, and difficulty in achieving uniform distribution of therapeutic agents across the brain. Using this delivery approach, also limits the amount of transgene that can be delivered at the tumor site. Ideally, one would prefer to control the desired dosage of therapeutic transgene delivered into the brain. Scientists have developed methods that regulate transgene

expression through the implementation of a drug inducible promoter which allows for specific delivery at the tumor sites upon oral delivery of the blood-brain barrier permeable drug (Chiocca et al. 2019). Moreover, potential leakage of AAV vector post intra-tumoral injection into the bloodstream would increase the possibility of systemic toxicity and off-target effects. To overcome this challenge sophisticated AAV vector capsids and improved promoters targeting specifically the cell of interest are being developed. Additionally, different methods to deliver 4-1BBL into the tumor should be considered, such as the use of retroviruses, EVs or lipid nanoparticles.

An alternative strategy to hamper tumor growth is through knocking out oncogenes in the tumor cells or cells of the TME. A well-studied driver of tumor progression in cancer is miR-21, and it has been reported that miR-21 is abundantly expressed in GB cells. Recent studies have shown that miR-21 is an important factor that shapes the TME into a more tumor-suppressive environment. Interestingly, miR-21 is found in GB-derived EVs and is reported to reprogram microglia in the TME (Abels et al. 2019a). These hijacked microglia lose their immunology role and instead support tumor growth. Microglia that take-up tumor-derived miR-21 show increased proliferation which re-shape a tumor favorable TME beneficial for tumor growth (Abels et al., 2019). This direct transfer of miR-21 from tumor cells to microglia in the TME opens new options to therapy strategies aiming to disrupt or inhibit the transfer of GB-derived miR-21 to the TME. MiR-21 is important in tumor progression therefore, impeding miR-21 in tumor cells has been an important strategy to combat tumor growth throughout the cancer field, including GBs (Aloizou et al. 2020). Besides targeting the TME, we also attempt to target the tumor cells directly by using CRISPR tools. miR-21 was first discovered to be elevated in glioblastoma patient-derived tumor tissue by Chan et al. and many other studies have found upregulated miR-21 levels in patient derived samples and CSF (Chan, Krichevsky, and Kosik 2005; Lakomy et al. 2011; Gabriely et al. 2008; Wu et al. 2013; Baraniskin et al. 2012). miR-21 levels have been correlated to GB grades and prognosis supporting its potential diagnostic value (Silantyev et al. 2019; Jiang et al. 2020) (Ma et al. 2018). Here we have shown that a complete knockout of miR-21 in GB cells mediated by the CRISPR technology reduces tumor

growth in mice. A complete knockout of miR-21 resulted in reduced migration, invasion, and progression *in vitro*. Implanting GB cells lacking miR-21 into mice hampered tumor grow as compared to GB cells with elevated expression of miR-21 (Nieland et al. 2022). Although many studies have tried to inhibit miR-21 in multiple cancer types, a direct translation to the clinic has yet to be developed (Corsten et al. 2007; Lee et al. 2017; Belter et al. 2016; Seo et al. 2019). Realizing the full potential of CRISPR-based genome editing requires a safe and efficient gene transfer delivery approach. Here we used AAV vector-mediated delivery of gene-therapy targeting miR-21 and showed a reduction of miR-21 resulting in improved overall survival in mouse GB models.

Although mice treated with the therapeutic AAV vector stayed alive for an extra ~10 days compared to non-treated mice, they were not cured. We therefore need to optimize our current AAV vector-based therapeutical strategy by improving its capsid and promoter to increase efficiency of transducing tumor cells. Interestingly, there is an increased number of miRNAs that are identified as targets for drug discovery (Hanna, Hossain, and Kocerha 2019). This proof-of-concept study may provide opportunities to further enhance the efficiency, for example by targeting multiple miRNAs at once by including various guides into a single AAV vector. Additionally, this type of therapy could potentially be applied for a more personalized treatment strategy. Based on biopsy results, specific miRNAs that are elevated could be targeted besides miR-21 such as miR-10b. Moreover, this approach could be tested in combination with radiotherapy and/or chemotherapy to aim for prolonged survival outcomes. Verifying our current AAV vector-based strategy in human GB models is important to evaluate the translational feasibility. Overall, the development of gene therapy strategies including AAV vector-based approaches, is crucial, given that current chemotherapeutics such as Temozolomide are not selective for tumor cells only and often require frequent administration and therefore cause many side-effects. AAV vector-based gene therapy has a high degree of specificity, minimizing adverse effects and preventing random integration events that can occur with retroviral gene delivery. However, gene therapy related impediments exist, such as the overexpression of the therapeutic protein. For example, long-term expression of Cas9 nuclease is not desirable.

Moreover, expression of the transgenes in unintended cell types or tissues due to constitutive active promoters, and vector-associated immunogenicity require resolution to ensure safe clinical translation. Besides AAV vectors, a range of different gene transfer platforms have been developed and applied in cancer disease models such herpes virus (Nattress and Hallden 2018; Cao et al. 2014; Santiago-Ortiz and Schaffer 2016), but also the use of engineered EVs (Nieland et al. 2023) capable of loading the SaCas9-KKH protein would allow the delivery of CRISPR nucleotides into the tumor (Lyu et al. 2023).

Taken together, the TME is dynamic and adaptive to external factors such as cell interactions including EV-mediated communication, alterations in cellular and genetic compositions of the tumor, metabolic changes, epigenetic alterations, and other components such as oxygen, pH balance and chemical or electrical signaling. The bidirectional interaction between tumor cells and members of the TME favors tumor progression, reshapes the vascular structure, impairs the native and incoming immune cells, and builds resistance to current available therapies. A complete understanding of this complex multicellular system is necessary to be able to overcome the tumor's clever mechanisms to hijack healthy cells beneficial for tumor growth. Recent studies have gained knowledge in one-way interactions between selective members of the TME with GB cells. The next important step is to study these interactions in a connective network. Sophisticated tools are therefore necessary to understand all aspects of the TME. Most of the current knowledge has been obtained using animal models, they allow to study of tumor progression in a living organism, however, the brain is a closed system in which it is difficult to control multiple aspects of the TME at once. Therefore, the use of robust models derived from patient tissue in a 3D fashion, such as organoids, organoid typic cultures or brains on a chip may aid in studying multiple components of the TME in a controlled manner. Moreover, these models might better reflect human GB which might be the key to succeed in bridging the preclinical findings towards the patients.

CONCLUSION

Over the past years the TME has been recognized as a critical player in GB progression (Sharma et al. 2023; Bikfalvi et al. 2023). We have addressed the role of astrocytes and microglia in the TME and both glial types were observed to take a tumor supportive stand. Furthermore, we aimed to develop therapeutic strategies against GB progression activating $CD8^{POS}$ T cells and DCs in the TME. Lastly, we showed that ApoE and miR-21 are promising targets that upon inhibition prolong survival in preclinical GB mouse models. As each of these single therapeutic strategies showed improved survival in preclinical mouse model, none of the approaches cured the mice from GB tumors. Therefore, we propose a multifaced strategy directing at both the tumor cells and cells in the TME with an AAV vector unifying both miR-21 and 4-1BBL. This would even be further optimized by adding targeting ApoE for example by using the CRISPR strategy. In conclusion, future directions should shift towards targeting multiple points of interaction between GBs and its neighboring cells and external factors to comprehend the full picture of GB aggressiveness.

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