Inhibition of intracellular Ca^{2+} channels as a strategy to control glioma

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Abstract:

Tumours of the brain and nervous system (BNS) represent a particular diagnosis and therapeutical challenge. The estimated cumulative risk of mortality associated with BNS cancers is particularly high in countries such as Portugal and Brazil. BNS cancers rank 8th and 9th in the list of cancers with higher mortality in Portugal and Brazil, respectively. The poor survival rate of glioma patients is mostly attributed to the high genetic heterogeneity and invasive properties of the tumour. Inevitably, this leads to invasion of adjacent tissues and resistance to the therapies. Tumour invasion is a key hallmark of high-grade gliomas such as glioblastoma (GB) and a determinant for patient outcome. The current therapies rarely result in remission or meaningful improvement of life expectancy. Therefore, the development of alternative therapeutic approaches against gliomas is urgent. Despite this, no approved drugs target cell invasion.

Calcium ion (Ca2+) signalling dynamics and subcellular localization are tightly regulated. The dysregulation of Ca2+ homeostasis is crucial in cancer initiation and progression. Cancer cells can establish cancer hallmark features, by manipulating the expression or activity of Ca2+ modulators, including pumps, channels, and exchangers. Thus, our main goal is to explore the modulation of intracellular Ca2+ fluxes as a therapeutic strategy to inhibit glioma progression.

As an innovative approach, we propose to reprogram Ca2+ intracellular fluxes/homeostasis by inhibiting specific endoplasmic reticulum (ER) or Golgi apparatus (GA) Ca2+ channels to control glioma progression. Ca2+ release to the cytoplasm can control processes essential for glioma progression. Increasing evidence associates intracellular Ca2+, redox and thiol homeostases with glioma progression. The mechanisms linking these key aspects of glioma cell biology and how they impact cell invasion or proliferation are unclear and no approved glioma therapeutics target these processes. We propose to modulate the activity of specific intracellular ER and GA Ca2+ channels to control glioma progression.

As proof of principle, we demonstrated that manipulating the GA Ca2+ channel TMBIM4 expression impacts glioma cell invasion and in vivo tumour growth. We herein propose to identify other ER and GA Ca2+ channels that affect glioma progression and to find pharmacological inhibitors to TMBIM4.

To identify the first inhibitors of the GA Ca2+ channel TMBIM4, a virtual screening will be conducted from libraries of compounds that will include natural compounds and derivatives. The impact of the identified molecules on GB 3D invasion and redox status will be evaluated in vitro.

The search for additional ER and GA Ca2+ channels that may constitute therapeutic targets will start with a bioinformatic approach based on glioma gene expression and patient survival data, to identify those associated with glioma patient outcome. The effects of expression manipulation of identified channels on cell viability, proliferation, invasion, and redox status will be analysed. To survive in adverse conditions, cancer cells undergo deep metabolic reprogramming. Here, thiol homeostasis the availability of cysteine are central for glioma progression. Searching for additional mechanistic clues, we propose to identify the subset of ER and GA Ca2+ channels that act on glioma cell phenotype in a cysteine-dependent manner. Here, our findings will break the ground on the combined effects of Ca2+ intracellular fluxes deregulation and cysteine availability in glioma.

This project will allow the identification of drug-like copounds able to inhibit TMBIM4, which could constitute potential drugs and mechanistic tools for cell biology studies, and the identification and validation of additional ER or GA Ca2+ channels that affect glioma progression. The data generated will pave the way for subsequent lines of research in pharmacology and drug delivery systems against glioma invasion.

Partners:

Alignment with SDGs:

This application fits in different Sustainable Development Goals, but it is particularly relevant for **SDG 3** - **Good Health and Wellbeing**. The project's objective to identify and modulate the activity of intracellular calcium ion channels to control glioma progression directly contributes to SDG 3 by addressing the critical need for advancements in the diagnosis, treatment, and management of brain tumours. Gliomas are a type of brain tumour associated with significant morbidity and mortality worldwide. Despite advances in medical science, the prognosis for patients with gliomas remains poor, highlighting the urgent need for innovative approaches to improve outcomes and quality of life for affected individuals. By unravelling the intricate molecular mechanisms underlying glioma progression, including the role of intracellular calcium channels, the project aims to provide crucial insights into the pathobiology of these tumours. This deeper understanding has the potential to revolutionise current therapeutic strategies by identifying novel targets for intervention. Moreover, the project's focus on glioma biology aligns with broader efforts to address non-communicable diseases (NCDs), such as cancer, as outlined in SDG 3.4. By advancing knowledge in this field, the project contributes to reducing the global burden of NCDs and achieving targets related to reducing premature mortality from these diseases. Furthermore, the outcomes of the project have the potential to improve health equity by enhancing access to innovative treatments for glioma patients worldwide. As new therapeutic targets emerge from the

research findings, there is an opportunity to develop more personalised and effective treatment approaches, tailored to the specific molecular characteristics of individual tumours. This personalised medicine approach aligns with the principles of SDG 3, which emphasise the importance of ensuring universal access to quality healthcare services and promoting health equity for all.

Besides SDG3, this project also contributes to SDGs 9 and 17. The project fosters innovation in biomedical research and contributes to the development of novel therapeutic targets. This innovation in scientific knowledge and technology infrastructure fits in **SDG 9 - Industry, Innovation, and Infrastructure**, and is essential for addressing complex health challenges, such as gliomas, and driving progress toward sustainable development.

Moreover, this project strengthens collaborations between research institutions, healthcare professionals, and other stakeholders, which are crucial for advancing knowledge and translating research findings into clinical practice. By fostering partnerships and knowledge-sharing within the scientific community, the project contributes to the collective effort to tackle the global burden of gliomas and achieve sustainable development goals related to health and innovation. The application is thus fully aligned with **SDG 17 - Partnerships for the Goals**.