PROGETTO

Supervisore::	Dr. Andrea Domenico Menegon
Titolo/*Title:*	Acid Sensing Ion Channel isoform 3, role in glioblastoma (GBM) and as drug target for GBM treatment
Curriculum:	*Neuroscience and Experimental Neurology*
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	**https://research.hsr.it/en/centers/experimental-imaging-center/drug-screening-technologies.html and https://research.hsr.it/en/core-facilities/alembic/andrea-menegon.html**

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge Glioblastoma multiforme (GBM) is the most common tumor of the brain accounting for more than 50% of total gliomas, characterized by a high proliferation and infiltration capabilities. Despite recent advances GBM remains incurable and has a poor prognosis with a mean median survival time of 15 months. One of the GBM most infamous trait is its resistance to conventional therapies and the absence of a valuable anti-tumor strategy. As many tumors, GBM contains a small subpopulation of cells with stem cell-like properties called Cancer Stem Cells (CSCs). Several studies have demonstrated that CSCs are resistant to conventional chemotherapy and radiation, possibly contributing to tumor growth and therapy resistance, thus representing important target cells for novel anti-cancer therapies. Proton sensing receptors expressed by CSCs represent important factors involved in their stemness phenotype and contribute to their adaptation to the tumor acidic environment. Acid-sensing ion channels (ASICs) are proton-gated sodium channels, associated with the peripheral (PNS) and central nervous system (CNS) and mainly expressed in neurons. Surprisingly, the expression of ASICs has been described in several tumors and has been linked to an increase in cell migration and proliferation.

Rationale and hypothesis We discovered that the Acid sensing ion channel isoform 3 (ASIC3), usually absent in the CNS and present in the PNS, is expressed at high levels in Human GBM CSCs primary lines of all the GBM subtypes studied, the proneuronal (PN), the mesenchymal (MES) and the classical (CLA),while poorly expressed in the biopsy of the same patients as well as in the human healthy brain. Based on these observations, we suggest a role for ASIC3 in GBM CSCs physiology to be further studied at the molecular and functional levels. In addition, we propose ASIC3 as a new druggable target for GBM treatment and a medicinal chemistry program to identify new ASIC3 modulators. Our strategy is based on solid

preliminary results demonstrating the detrimental effects induced by both genetic and pharmacological ASIC3 modulation on GBM CSCs growth and survival both "*in vitro"* and "*in vivo"*.

Objectives and specific aims

Aim1) Generation and characterization of a library of parental and ASIC3 downregulate GBM CSCs of the three main GBM types PN, MES and CLA.

Aim2) "In vitro" study of the role of ASIC3 in GBM CSCs physiology.

Aim3) "in vivo" study of the role of ASIC3 in GBM progression

Aim4) Set up of a phenotypic assays to study the effect of the new ASIC3 modulators.

Aim5) Design, synthesis and test of new ASIC3 modulators to control CSCs growth.

Expected outcomes These project aims at studying the role of ASIC3 in GBM CSCs physiology as well as its potential as a target for GBM therapy. Our preliminary results suggest a potential relevant role of ASIC3 in GBM tumor by the exposition of the CSC population to an acidic environment. IN addition, we have preliminary results demonstrating the potential specific detrimental effect on GBM CSCs that can be induced by ASIC3 modulation. Based on these observations, we expect a specific role of ASIC3 in GBM progression and as a new potential target for GBM treatment.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

The student will acquire the following skills: basic molecular biology for cloning LV (lentiviral) vectors encoding ASIC3 as well as ASIC3 shRNAs for its downregulation. Cell biology techniques for in vitro validation of LV and ASIC3 subcellular distribution studies. Generation of a GBM CSCs bank and its validation. Study of neurospheres growth. Study of GBM CSCs migration in a 2D assay. Cell cycle analysis of parental and ASIC3 downregulated cells. Set up of a phenotypic assay for pharmacological studies. Immunohistochemistry to perform pathology studies in GBM CSCs injected mice.

Bibliografia (max. 15)

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