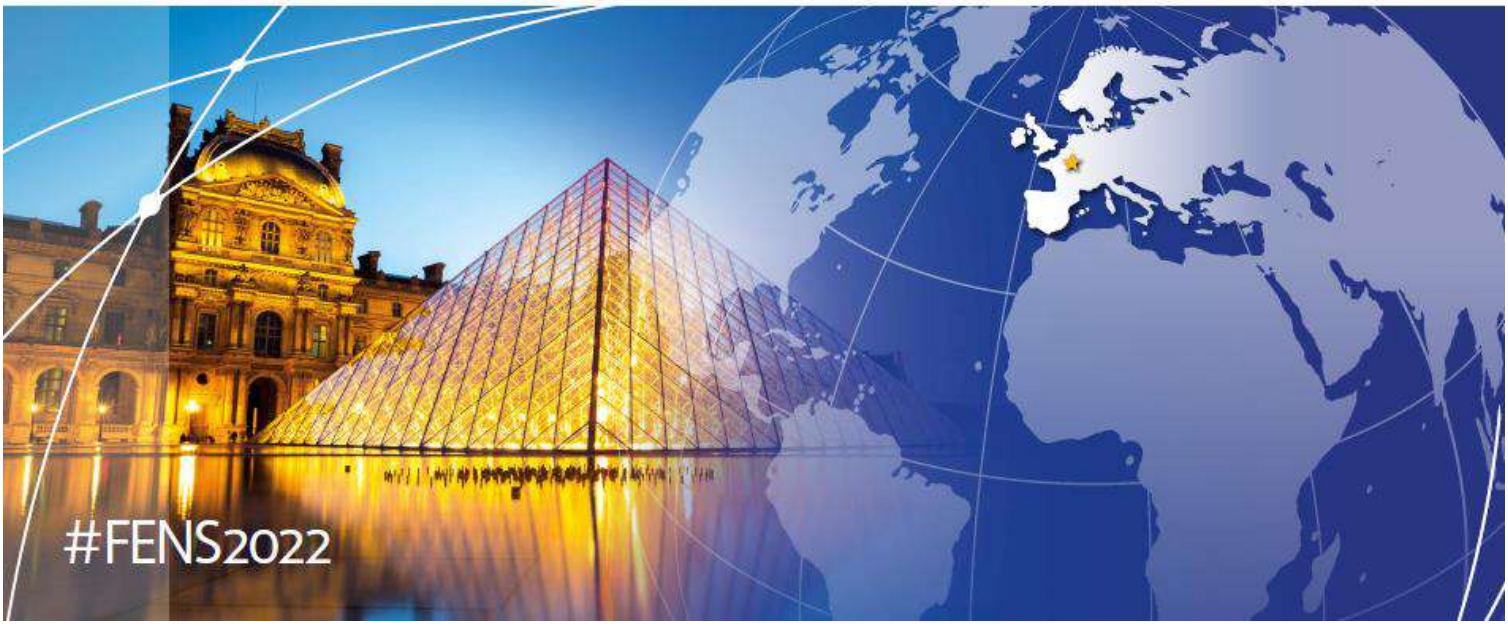
Welcome to FENS Forum 2022



E-Book of Abstracts

fens.org/2022

To search in the book please download it and use control + F

FENS Forum 2022
9-13 July 2022 | Paris, France

BOARD NUMBER: S07-534

ALTERATION OF THE MITOCHONDRIAL ACTIVITY AND LIPIDIC METABOLISM CAUSED BY THE SELECTIVE STIMULATION OF M2 MUSCARINIC RECEPTORS IN HUMAN GLIOBLASTOMA CELLS

POSTER SESSION 07 - SECTION: NEURO-ONCOLOGY

Claudia Guerriero[1], Michael Salazar Intriago[2], Anna Giudetti[3], Marianna Manfredelli[1], Maria Petrone[1], Stefano Tacconi[1], Teresa Rinaldi[1], Carlo Matera[4], Sergio Visentin[5], Angela Iuzzolino[1], Clelia Dallanoce[4], Luciana Dini[1], Ada Maria Tata[1]
[1]La Sapienza, University of Rome, Biology And Biotechnologies "c. Darwin", Rome, Italy, [2]La Sapienza, University of Rome, Biology And Biotechnologies C. Darwin, Rome, Italy, [3]University of Salento, Biological And Environmental Sciences And Technologies, Lecce, Italy, [4]University of Milan, Department Of Pharmaceutical Sciences, Medicinal Chemistry Section “pietro Pratesi”, Milan, Italy, [5]Istituto Superiore di Sanità, Neuroscience, Rome, Italy

Background and aims: Glioblastoma is the most malignant human brain tumor characterized by heterogeneous cell populations, including undifferentiated cells defined Glioblastoma Stem cells (GSCs), responsible for the beginning of neoplastic process and recurrence formation. Previous studies demonstrated how the activation of M2 muscarinic receptor by orthosteric agonist Arecaidine Propargyl Ester (APE) and dualsteric agonist N-8-Iper caused a significant decrease of cell proliferation and survival both in GSCs and in glioblastoma cell lines. Interestingly N8-Iper is capable to activate M2 receptor with higher affinity and at a lower concentration than APE. The aim of this work was to investigate the mechanisms downstream of M2 receptor activation by both agonists responsible of the cytotoxic and pro-apoptotic effects both in U251 cell line and in GSCs. Methods: mitochondrial functionality was evaluated by MITO ID assay, TMRE staining and oxygen consumption measurement by oxygraph. Lipid homeostasis was analyzed by Oil Red O staining, TLC and WB analysis. Autophagy was analyzed by WB analysis and LC3-GFP construct transfection. Results: our results demonstrate the ability of the M2 agonists to induce oxidative stress, alteration of the mitochondrial morphology and activity with consequent alteration of cellular respiration, lipid homeostasis and lipid droplets formation. M2 agonists also induce autophagy, as demonstrated in U251 cells. Conclusions: these results suggest that the selective activation of M2 receptor in particular by N-8-Iper may be a promising therapeutic strategy for the glioblastoma treatment, reducing the possible side effects that may be caused by the high doses of the orthosteric agonist.

Pubmed:

34440646: Guerriero C, Matera C, Del Bufalo D, De Amici M, Conti L, Dallanoce C, Tata AM
The Combined Treatment with Chemotherapeutic Agents and the Dualsteric Muscarinic Agonist Iper-8-Naphthalimide Affects Drug Resistance in Glioblastoma Stem Cells.
Glioblastoma multiforme (GBM) is characterized by heterogeneous cell populations. Among these, the Glioblastoma Stem Cells (GSCs) fraction shares some similarities with Neural Stem Cells. GSCs exhibit enhanced resistance to conventional chemotherapy drugs. Our previous studies demonstrated that the activation of M2 muscarinic acetylcholine receptors (mAChRs) negatively modulates GSCs proliferation and survival. The aim of the present study was to analyze the ability of the M2 dualsteric agonist Iper-8-naphthalimide (N-8-Iper) to counteract GSCs drug resistance.
Cells, 2021; 10
34359896: Di Bari M, Tombolillo V, Alessandrini F, Guerriero C, Fiore M, Asteriti IA, Castigli E, Sciaccaluga M, Guarguaglini G, Degrassi F, Tata AM
M2 Muscarinic Receptor Activation Impairs Mitotic Progression and Bipolar Mitotic Spindle Formation in Human Glioblastoma Cell Lines.
Glioblastoma multiforme (GBM) is characterized by several genetic abnormalities, leading to cell cycle deregulation and abnormal mitosis caused by a defective checkpoint. We previously demonstrated that arecaidine propargyl ester (APE), an orthosteric agonist of M2 muscarinic acetylcholine receptors (mAChRs), arrests the cell cycle of glioblastoma (GB) cells, reducing their survival. The aim of this work was to better characterize the molecular mechanisms responsible for this cell cycle arrest.
Cells, 2021; 10
32131421: Cristofaro I, Limongi C, Piscopo P, Crestini A, Guerriero C, Fiore M, Conti L, Confaloni A, Tata AM

M2 Receptor Activation Counteracts the Glioblastoma Cancer Stem Cell Response to Hypoxia Condition.
Glioblastoma multiforme (GBM) is the most malignant brain tumor. Hypoxic condition is a predominant feature of the GBM contributing to tumor growth and resistance to conventional therapies. Hence, the identification of drugs able to impair GBM malignancy and aggressiveness is considered of great clinical relevance. Previously, we demonstrated that the activation of M2 muscarinic receptors, through the agonist arecaidine propargyl ester (Ape), arrests cell proliferation in GBM cancer stem cells (GSCs). In the present work, we have characterized the response of GSCs to hypoxic condition showing an upregulation of hypoxia-inducible factors and factors involved in the regulation of GSCs survival and proliferation. Ape treatment in hypoxic conditions is however able to inhibit cell cycle progression, causing a significant increase of aberrant mitosis with consequent decreased cell survival. Additionally, qRT-PCR analysis suggest that Ape downregulates the expression of stemness markers and miR-210 levels, one of the main regulators of the responses to hypoxic condition in different tumor types. Our data demonstrate that Ape impairs the GSCs proliferation and survival also in hypoxic condition, negatively modulating the adaptive response of GSCs to hypoxia.
Int J Mol Sci, 2020; 21
32182759: Cristofaro I, Alessandrini F, Spinello Z, Guerriero C, Fiore M, Caffarelli E, Laneve P, Dini L, Conti L, Tata AM
Cross Interaction between M2 Muscarinic Receptor and Notch1/EGFR Pathway in Human Glioblastoma Cancer Stem Cells: Effects on Cell Cycle Progression and Survival.
Glioblastomas (GBM) are the most aggressive form of primary brain tumors in humans. A key feature of malignant gliomas is their cellular heterogeneity. In particular, the presence of an undifferentiated cell population of defined Glioblastoma Stem cells (GSCs) was reported. Increased expression of anti-apoptotic and chemo-resistance genes in GCSs subpopulation favors their high resistance to a broad spectrum of drugs. Our previous studies showed the ability of M2 muscarinic receptors to negatively modulate the cell growth in GBM cell lines and in the GSCs. The aim of this study was to better characterize the inhibitory effects of M2 receptors on cell proliferation and survival in GSCs and investigate the molecular mechanisms underlying the M2-mediated cell proliferation arrest and decreased survival. Moreover, we also evaluated the ability of M2 receptors to interfere with Notch1 and EGFR pathways, whose activation promotes GSCs proliferation. Our data demonstrate that M2 receptors activation impairs cell cycle progression and survival in the primary GSC lines analyzed (GB7 and GB8). Moreover, we also demonstrated the ability of M2 receptor to inhibit Notch1 and EGFR expression, highlighting a molecular interaction between M2 receptor and the Notch-1/EGFR pathways also in GSCs.
Cells, 2020; 9