ID: 02496
Type: Oral Comunication
Topic: Mechanism of tumour initiation and progression

AMPK as a potential regulator of glioblastoma metabolism

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Background: Glioblastoma is the most prevalent and aggressive primary brain tumor. AMP-activated kinase (AMPK), the main energy sensor of the cell, has been previously described by our group as a key factor in glioblastoma oncogenesis and proliferation and is known for taking part in tumoral metabolic transformation. Our group has also formerly reported how AMPK regulates the expression of lipoprotein receptors and alters lipid reliance of glioblastoma cells, suggesting AMPK orchestrates nutrient dependency and flexibility on glioblastoma. Overall, this evidence positions AMPK inhibition as a promising antitumoral therapy for glioblastoma.

Methods: To further study the role of AMPK in glioblastoma bioenergetics, we used the human glioblastoma cell lines U87 and U373 and silenced AMPK transfecting the cells with a siRNA for AMPK?1/2. To assess mitochondrial function, fuel oxidation, and glycolytic parameters, we carried out Seahorse extracellular flux analyses. The expression of genes related to mitochondrial energetics in these cells was studied using RT-qPCR. Protein levels were analyzed by Western blot. We are currently carrying out experiments with glutamine and fatty acids metabolic pathways as the focal subject.

Results: Our data show that silencing of AMPK?1/2 reduces basal and maximum mitochondrial respiration, as well as decreases the expression of CPT1C, PPARGC1A, and PPARA genes. AMPK silencing increases GLS1 expression in both cell lines, although glutamine dependency is only observed in U373 cells. Altogether, these results suggest alterations in mitochondrial energetic pathways. We did not record a significant effect of AMPK on the glycolytic activity of these glioblastoma cell lines.

Conclusion: Even though in glioblastoma cells there is an increment in aerobic glycolysis (Warburg effect), these tumoral cells still maintain an elevated mitochondrial activity and a great capacity to use glutamine and lipids as fuel. AMPK plays an important role in regulating glioblastoma mitochondrial activity and bioenergetics.

Grants and fellowships: Funding for the Consolidation of Competitive Groups of Research: ED431B 2020/26, Xunta de Galicia (2020-2022).