Cell metabolomics: a strategy to study crucial pathways in glioma development

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Glioblastoma (GBM) is the most common and primary brain tumors in adults.[1] Despite the available multimodal therapies, glioma patients appear to have a poor prognosis. The Hedgehog (Hh) signaling is involved in tumorigenesis and emerged as a promising target for brain tumors.[2] Glabrescione B (GlaB) has been recently identified as the first direct inhibitor of Gli1, the downstream effector of the Hh pathway.[3,4] It is known that several malignant tumors, including GBM, consume high amounts of glucose at fast rate, with the production of lactic acid, even in the presence of oxygen ("Warburg effect"). To promote the high exploitation of glucose for rapid energy production through glycolytic flux and to avoid intracellular acidosis, cancer cells rapidly wipe out the lactic acid to the extracellular environment by the plasma membrane mono-carboxylate transporters (MCTs). Accordingly, targeting lactate metabolism and transport can represent a promising approach to counteract cancer growth and progression. In this study, we found that GlaB treatment of GL261 glioma cells inhibits Gli1 transcription, reducing glioma cell growth.[5] Using an untargeted ^{1}H-NMR metabolomic approach, we also demonstrated that GlaB treatment increases both intra- and extracellular levels of lactate in GL261 cells, promoting the glycolytic process over the tricarboxylic acid cycle (TCA). Consistently, GlaB treatment induced the phosphorylation of a key protein involved in anabolic-catabolic transition, namely AMPK. The simultaneous blockade of lactate efflux with α-cyano-4-hydroxycinnamic acid (ACCA), a specific MCT inhibitor, further reduced glioma cell growth. These results were confirmed by an *in vivo* mouse model of glioma, thereby opening new perspectives for combination therapy in the treatment of this lethal tumor.

References

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