Serine metabolism controls lung adenocarcinoma cells migratory ability by modulating AMP kinase activity

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Abstract

Metastases account for the great majority of cancer-associated deaths, in particular those developing in the brain. Non-small Cell Lung Cancer (NSCLC) preferentially metastasize in the brain, producing one of the most complicated metastases form threatening patient's survival. The metabolic features of the Tumor Microenvironment (TME) are a critical regulator of cancer progression in primary and metastatic malignancies and its biochemical composition is of prime importance controlling cancer cell metabolism, survival and motility. The brain TME is characterized by its unique nutrient availability and heterogeneity, in particular neurotransmitters and amino acids (1,2). Thereby, the increased metabolic demand of metastasizing cells, make them dependent on continuous uptake of certain metabolites when intracellular synthesis is not adequate to deal with their metabolic requirements (3,4). We aimed to study NSCLC metastatic potential in particular microenvironments, such as the brain where different amino acids are released, and to investigate the genetic and metabolic tools that cancer cells develop in order to invade the brain.

Material and Methods

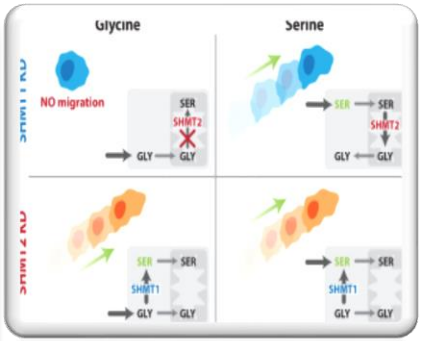
We developed an experimental procedure to mimic the situation occurring in the brain TME by collecting the brain extracellular fluid from mice using it to culture lung cancer cells. We then performed metabolic analysis by seahorse and GC-MS analysing specific metabolic parameters such as ATP and ROS production and evaluating cell migration using boyden chamber, we investigated in detail the role of amino acids, distributed in the brain microenvironment, in lung cancer cell chemo-kinesis and we characterized the resulting metabolic reshaping of NSCLC during brain metastasis formation.

Results and Discussions

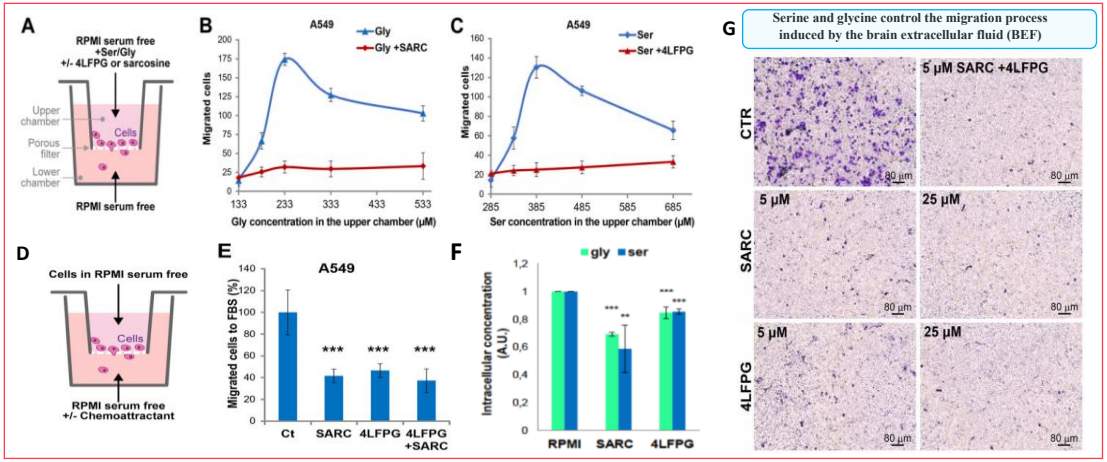
Our results indicate that serine and glycine, released in the brain TME, stimulate NSCLC chemo-kinesis and support brain invasion by NSCLC. In this context, the cytoplasmic serine hydroxymethyltransferase (SHMT1), a key enzyme in the One Carbon Metabolism, fine-tune the cytoplasmic serine level, a parameter deemed critical in controlling cancer cell energy production and redox homeostasis of metastasizing cells. A drop on intracellular serine and glycine levels, activate the cellular sensor, AMP kinase, which possibly leads metastasizing cells to switch from a more motile to a survival phenotype.

Conclusion

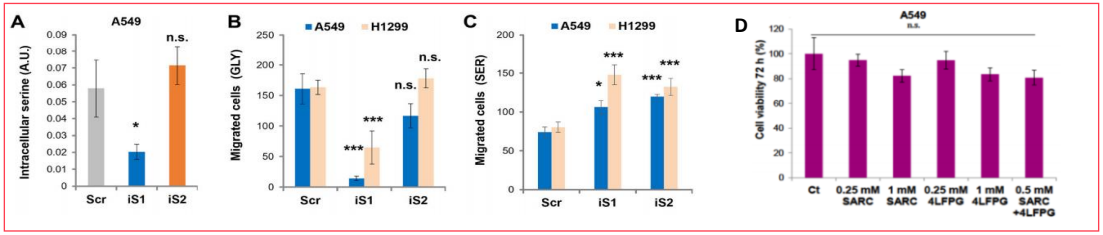
The presence of serine and glycine in the brain TME, and the metabolic and the genetic characteristics of metastasizing cells participate in the development of lung cancer derived brain metastases by providing the necessary cellular energy reserve and antioxidant power.



1. Serine and glycine intracellular levels affect the migratory properties of lung adenocarcinoma cells



2- SHMT1 controls serine/glycine cytosolic interconversion and affects cell migration



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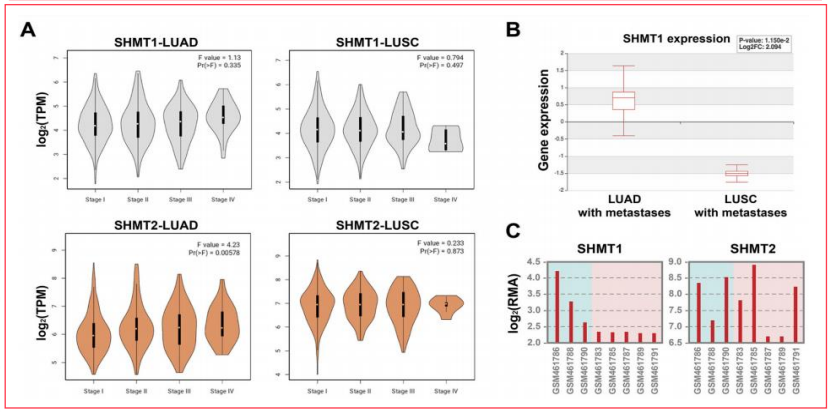
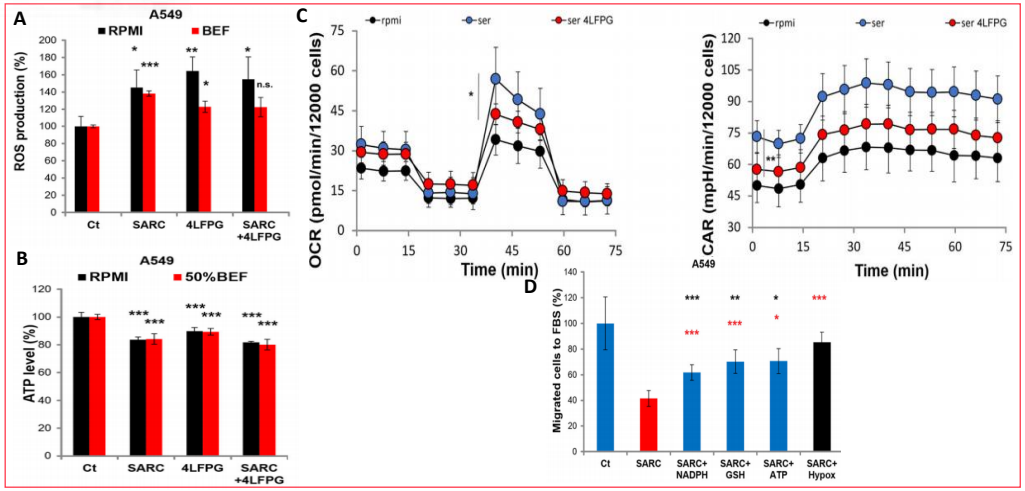
1. Bouzidi, A. et al. 2020. Cytosolic serine hydroxymethyltransferase controls lung adenocarcinoma cells migratory ability by modulating AMP kinase activity. Cell Death and Disease. 11:1012
2. Ngo B et al. 2020. Limited Environmental Serine and Glycine Confer Brain Metastasis Sensitivity to PHGDH Inhibition. Cancer Discovery.

3- Shmt1 and shmt2 expression increases in patients during lung cancer progression



4- Cytosolic serine levels controlled by SHMT1 modulate reactive oxygen species (ROS) formation and ATP production



5- AMP kinase is the sensor of serine starvation modulating cell migration