

Enhanced OXPHOS, Glutaminolysis and Beta-oxidation Constitute the Metastatic Phenotype of Melanoma Cells.

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Many tumor cells show enhanced aerobic glycolysis, even in the presence of oxygen (Warburg effect). This pathway provides substrates for the synthesis of lipids, proteins and DNA. However, the Warburg effect does not necessarily imply mitochondrial dysfunction. Research currently pictures tumors as compositions of different populations of cells with distinct metabolic phenotypes, which are able to adjust to oxygen and nutrient gradients within the tumor mass. Not all cancer cells display a high glycolytic flux as proposed by Warburg. Our results indicate that progression to metastasis requires mitochondrial function. Our research, centered on cell lines that display increasing degrees of malignancy, focuses on metabolic events, especially those involving mitochondria, which could reveal which stages are mechanistically associated to metastasis. The experimental model consisted of murine melanocytes. These cells were subjected to several cycles of adhesion impediment, producing stable cell lines exhibiting phenotypes representing a progression from non-tumorigenic to metastatic cells (ma). These were: non-tumorigenic 4C, non-metastatic 4C11- and metastatic 4C11+. The metabolic profile of each of these different cell lines was investigated by evaluating enzymatic activities and expression of members of the glycolytic and oxidative pathways. Our results show that only metastatic cell line (4C11+) released the highest amounts of lactate may derived from glutamine catabolism. Results from measurements with high-resolution respirometry show that 4C11+ intact cells increased (2.8x) oxidative metabolism, with enhanced (2.6x) rates of oxygen consumption coupled to ATP synthesis, when compared to the other pre-malignant stages. We did not observe an increase in mitochondrial content, mitochondrial biogenesis and alterations of mitochondrial morphology. In addition, in 4C11+ cells, we observed an increase in ATP content, complex II activity and fatty-acid oxidation. Furthermore we were able to show that the migration of cells depended on glutaminase activity. The results presented here have centered on how the multiple metabolic inputs of tumor cells may converge to compose the so called metastatic phenotype.

Keywords: mitochondria, metabolic profile, metastatic phenotype.

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