Mitochondrial Function and Bioenergetics During Malignant Transformation and Metastasis

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Introduction: The classic bioenergetic phenotype of cancer cells of enhanced glycolysis was described by Otto Warburg approximately 90 years ago. However, the Warburg hypothesis does not necessarily imply in mitochondrial dysfunction. Current thinking envisages tumor cells as compliant to an oxygen gradient within the tumor mass. Those cells on the periphery utilize Oxygen whereas those found in hypoxic regions display metabolic symbiosis with the adjacent stromal cells. Essentially metabolic reprogramming means up-regulation of pathways that increase the rate of ATP production, synthesis of lipids and redox balance. Furthermore, as shown by us, progression to metastasis requires mitochondrial function.

Material and Methods: The experimental model consisted of murine melanoma cells. A melanocyte cell line was subjected to several cycles of adhesion impediment, producing stable cell lines exhibiting phenotypes representing a progression from non-tumorigenic to metastatic cells. These were: non-tumorigenic cells melan-a (ma); non-tumorigenic cell line 4C (obtained after 4 cycles of adherence abrogation); non-metastatic 4C11- and metastatic 4C11+ melanoma cell lines. The metabolic profile of each cell line was investigated by measuring expression and enzyme activities of the glycolytic and oxidative pathways.

Results and discussion: Our results showed that metastatic cell line (4C11+) released the highest amounts of lactate and LDH activity, typical of the Warburg effect. In contrast, high-resolution respirometry showed that 4C11+ intact cells had 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 also observed an increase (1.5X) in succinate dehydrogenase (Complex II) activity in these cells. There was no increase in mitochondrial content and biogenesis, but we observed an increase (2X) in fission. Conclusion: These results suggest enhanced OXPHOS associated to metastasis. Detailed analysis of other models of tumor progression may reveal whether the modulation of the oxidative metabolism is a feature of the metastatic process.