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BIOENERGETICS AS A THERAPEUTIC TARGET IN HUMAN MELANOMA AGGRESSIVENESS CELL MODEL

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Background: Metabolic reprogramming is a hallmark of cancer and the existence of an oxidative slow-cycling phenotype in melanomas has drawn attention to the field. Previously our group developed several clones with distinct aggressiveness profiles derived from A357 a melanocytic melanoma cell line (PCDNA3, G10, and A7). We have already determined that G10 cells, the most aggressive clone, are more oxidative while A7 cells, the less aggressive clone, presented a more glycolytic profile. G10 cell line has also presented mitochondrial dysfunction, in comparison to the other cell lines.
Aims: Here, we aimed to further characterize these different phenotypes focusing on bioenergetic parameters.
Methods: Exponentially growing cells were cultivated in DMEM/F12 medium supplemented with insulin, ascorbic acid, pyruvic acid, and galactose. Sulforhodamine B assay was used to assess doubling time and the cytotoxicity of metabolic modulators and chemotherapeutic drugs. One-way ANOVA and *Tukey* test were used for data analysis, $p<0.05$ considered significant. Differentially expressed genes from melanoma cells microarray data were obtained using the *limma* package in *R* statistical environment.
Results: Differentially expressed genes analysis showed that G10 has higher expression of cytochrome *c* related proteins, glycolytic control enzyme (*PFKL*) and enolase, while A7 has higher expression of proteins related to glucose phosphorylation such as hexokinase-1 and ADP-dependent glucokinase. There was no significant difference between the groups when treated with oligomycin, indicating that the cell lines do not depend as much on oxidative phosphorylation as on other ATP producing pathways. However, G10 presented greater sensitivity to 2-deoxyglucose. Preliminary results indicate differences between control cell lines, G10 and A7 growth patterns as well as sensitivity to chemotherapeutic drugs.
Conclusion: Altogether these results suggest that G10 cells present features of a slow-cycling phenotype, which has been clinically associated with drug resistance and aggressiveness in melanomas. These metabolic alterations could be applied as novel therapeutic targets for melanoma management. Furthermore, we believe that understanding how cell lines presenting different bioenergetic parameters respond to drug challenge would be of great importance to the field.
Perspectives: In addition, we will perform a time-lapse experiment of each cell line aiming to understand the migratory behavior of slow-cycling phenotype.