Cells 2025 Conference

The 3rd International Online Conference on Cells

25–27 March 2025 | Online

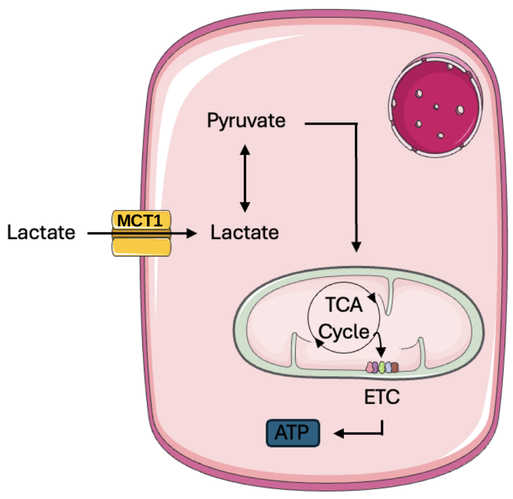
MDPI

Impact of MCT1-Mediated Lactate Uptake on Melanoma Cancer Stem Cells

Gaia Giannitti, Alyssa J.J. Paganoni, Sara Marchesi, Riccardo Garavaglia, Ivan Preosto, Fabrizio Fontana
Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan

INTRODUCTION & AIM

Lactate significantly influences the metabolism of melanoma by promoting tumor development and progression. The aim of this project is to investigate the role of this metabolite and of its main transporter MCT-1 in driving the propagation of melanoma stem cells (SCs).



METHOD

Experiments were conducted on A375 melanoma cells. Cell quiescence was assessed by Trypan blue exclusion assay, cell cycle analysis (flow cytometry) and Western blot. Spherogenic ability of tumor cells was evaluated by sphere formation assay. The metabolic consequences of lactate and AZ3965 treatment were analyzed by flow cytometry and Western blot.

RESULTS & DISCUSSION

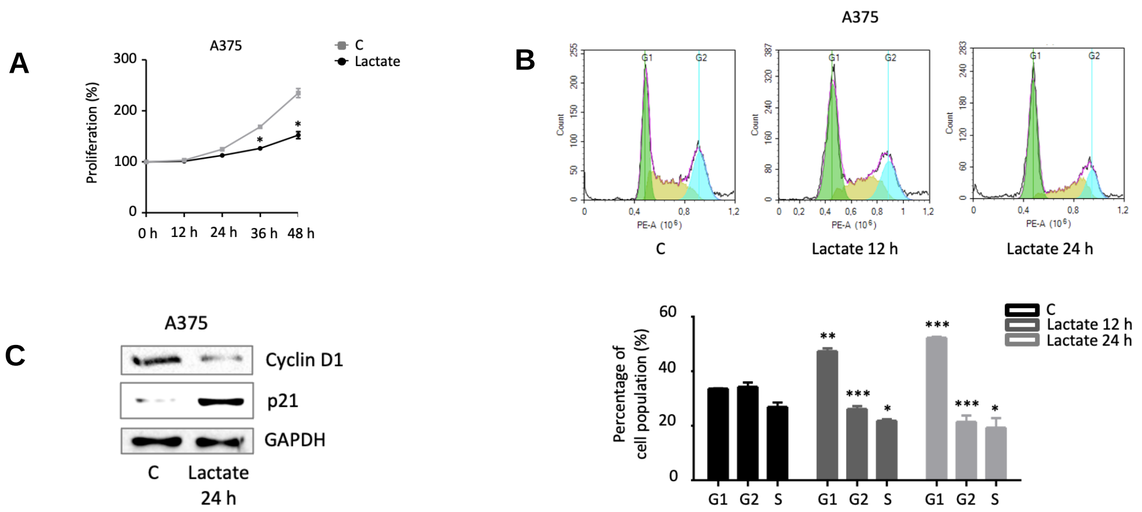


Fig. 1. Lactate affects melanoma cell proliferation and cell cycle regulation.
A decrease in the number of cells was found in melanoma cells treated with lactate **(A).** Of note, tretament with lactate appears to significantly block cell cycle **(B)**, as also indicated by reduced expression of Cyclin D1 and increased p21 levels **(C)**

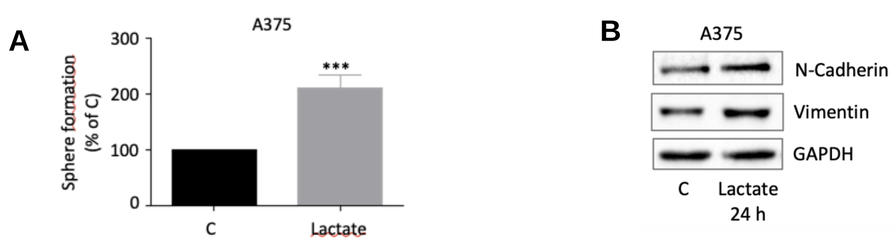


Fig.2. Lactate promotes the stem-like features of melanoma cells.
Lactate was shown to promote the stem-like traits of melanoma cells, determining an increase in tumor cell spherogenic ability **(A)** as well as the activation of EMT, as indicated by the upregulation of N-Caderin and Vimentin **(B)**.

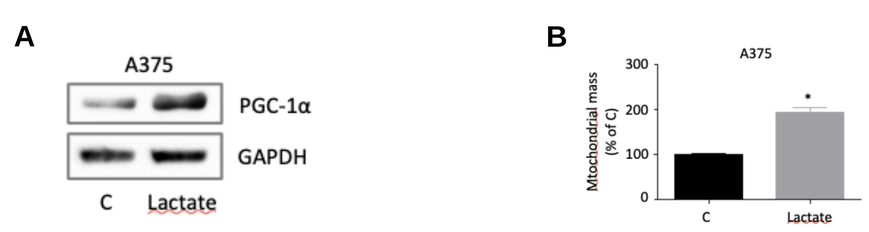


Fig. 3. Lactate fuels melanoma SC mitochondrial metabolism.
An increase in the protein levels of the PGC-1α was found in melanoma cells treated with lactate (**A**), leading to increased mitochondrial biogenesis (**B**).

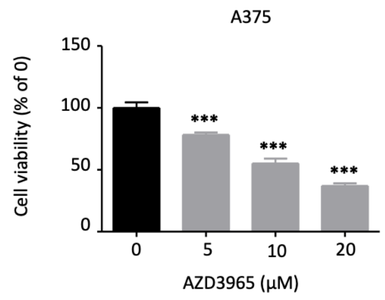


Fig.4. MCT1 inhibitor (AZ3965) reduces melanoma cell viability.
A progressive decrease in cell viability was observed when melanoma cells were treated with increasing AZ3965 concentrations, indicating a dose-dependent cytotoxic effect.

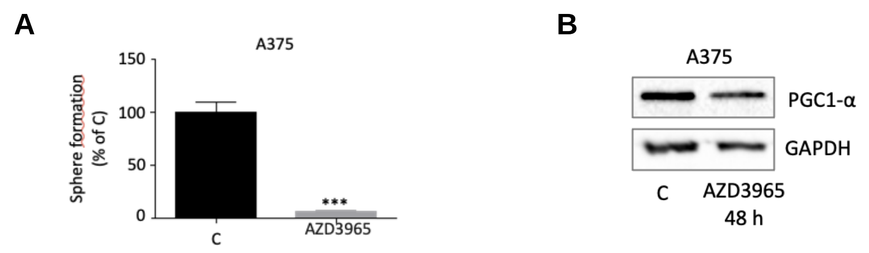


Fig.5. AZ3965 severely alters melanoma stem-like traits and mitochondrial metabolism.
Treatment with AZ3965 led to a suppression in tumor cell spherogenic ability **(A)** as well as to a downregulation of PGC-1α expression **(B)**.

CONCLUSION

Our results indicate that lactate plays a key role in sustaining melanoma SC proliferation and survival. In particular, it promotes the stem-like features of tumor cells, supporting a profound reprogramming of mitochondrial metabolism. Blocking MCT1-dependent lactate uptake with AZ3965 completely prevented these effects, suggesting that MCT1 might represent a new therapeutic target for tumor eradication.

FUTURE WORK

Our future experiments will be directed at targeting melanoma lactate metabolism *in vivo*, in order to develop novel anti-cancer therapies. Optimizing the use of MCT1 inhibitors in combination with other therapies could represent a promising strategy to overcome melanoma drug resistance.

UNIVERSITÀ DEGLI STUDI DI MILANO
DEPARTMENT OF PHARMACOLOGICAL AND BIOMOLECULAR SCIENCES "RODOLFO PAOLETTI" - DiSFeB