THE WARBURG EFFECT AT THE STEERING WHEEL OF CANCER CELL MIGRATION

Steven Wink, Hans de Bont, Bob van de Water and Sylvia Le Dévédec
Leiden Academic Centre of Drug Research
Leiden University, Einsteinweg 55, 2333CC Leiden, The Netherlands
s.e.ledevedec@lacdr.leidenuniv.nl

KEY WORDS: live cell imaging, FRET, cell migration, metabolism

Introduction: Enhanced migratory behaviour of tumour cells in metastasis is a critical hallmark of cancer progression. Cell migration is driven by dynamic changes in matrix adhesions, complexes that regulate the linkage between the actin cytoskeleton and the extracellular matrix. Aerobic glycolysis or the Warburg effect is another important hallmark of cancer. Little is known on the role of the Warburg effect in tumour cell migration. In particular the spatiotemporal relationships between energy supply and the dynamics of matrix adhesion and actin are unclear. Recently, we discovered that several enzymes of the glycolytic program are central regulators of the migratory phenotype and matrix adhesion dynamics. Therefore we hypothesize that the Warburg effect is critical to control the migratory behaviour of tumour cells and hence metastasis formation.

Method: To fully understand the relationship between the Warburg effect and tumour cell migration, we aim at developing a quantitative and predictive *in silico* model that integrates the relationships between matrix adhesions/actin dynamics, glucose/ATP concentration/fluxes and the migratory phenotype of tumour cells. Using high-end microscopy and available genetically-encoded optical biosensors, we monitor both matrix adhesions/actin dynamics and the concentration of metabolites in real-time and in single migrating tumor cells.

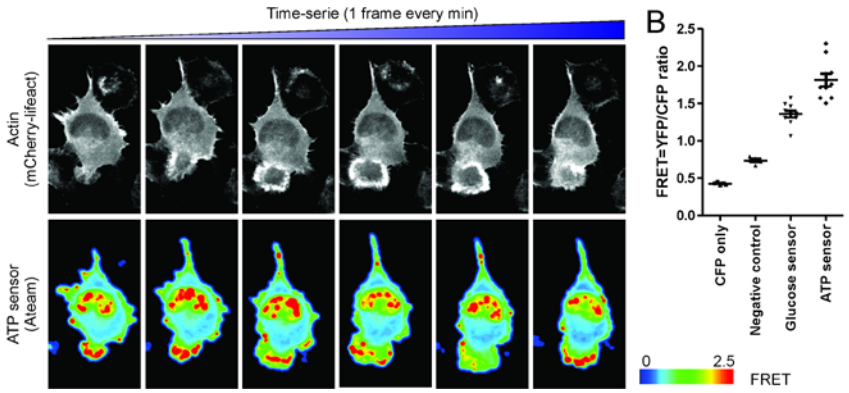

Figure: A) Simultaneous live imaging of actin dynamics and the ATP levels in a migrating tumor cell. B) YFP/CFP emission ratios of glucose and ATP FRET biosensors.

Results: We established a multi-parametric image analysis pipeline to systematically quantify matrix adhesion and actin dynamics, intracellular glucose and ATP concentrations and cell migration. As a next step, the obtained data of this single-cell metabolic analysis will be integrated in an *in silico* model for glycolysis-driven cell migration that will be tested by genetic manipulations of the glycolytic program using siRNA approaches.

Conclusion: Such approach will be a unique tool for the future efficient design and development of anti-metastatic drugs in relation to cancer metabolism.