

## **Myoferlin Regulates Endosomal Trafficking and Tunes Cancer Cell Metabolism**

Arnaud Blomme<sup>1</sup>, Brunella Costanza<sup>1</sup>, Marc Thiry<sup>2</sup>, Pascal de Tullio<sup>3</sup>, Ana Perez-Palacios<sup>1</sup>, Ange Mouithys-Mickalad<sup>4</sup>, Eric Lifrange<sup>5</sup>, Philippe Delvenne<sup>6</sup>, Vincent Castronovo<sup>1\*</sup> & Andrei Turtoi<sup>1\*</sup>

<sup>1</sup>Metastasis Research Laboratory, GIGA Cancer, University of Liège

<sup>2</sup>Laboratory of Cell Biology, Faculty of Sciences, University of Liège

<sup>3</sup>Laboratory of Drug Research Centre, CIRM, University of Liège

<sup>4</sup>Center for Oxygen Research and Development, University of Liège

<sup>5</sup>Department of Senology, University Hospital (CHU), University of Liège

<sup>6</sup>Department of Anatomy and Pathology, Faculty of Medicine, University of Liège, Liège, Belgium

Myoferlin is a member of the ferlin protein family that have key physiological functions in plasma membrane fusion, repair and endocytosis events. High-throughput genomic and proteomic studies have repeatedly found myoferlin as overexpressed in cancer. However, only few reports thus far associate a particular function to myoferlin in cancer. We have recently reported myoferlin as overexpressed in human breast adenocarcinoma and identified its important role in regulating EGFR function in the triple negative breast cancer (TNBC) cells.

In the current study we show for the first time that myoferlin modulates cancer cell metabolism through its involvement in endocytosis. Using transmission electron microscopy we demonstrate that myoferlin is an essential component of the endosomal system of TNBC cells, whose depletion severely impairs vesicle trafficking. Loss of myoferlin *in vitro* causes impaired mitochondrial function resulting in lowered oxygen consumption, ROS and ATP production.

Correspondingly, mitochondria are found frequently depolarized and the cells are prone to apoptosis. The resulting metabolic imbalance provokes *in vitro* a shift towards glycolysis resulting in increased lactate production. The metabolic sensor AMPK escorts this adaptation process and its activation is dependent on caveolin-1 expression. Myoferlin depletion *in vivo* significantly suppresses tumor development in mouse xenograft model of TNBC. Post-tumorectomy follow-up shows that animals bearing myoferlin-deficient tumors develop significantly fewer and smaller lung metastases. In line with this is the histological analysis demonstrating that these tumors display no necrosis and less tumor cell invasion compared to their control counterparts. Further functional insights based on histology and NMR-based metabolomics prove a dramatic decrease in the lipid content of myoferlin-silenced tumors. Current efforts in our lab aim at in clarifying which metabolic path is actively used by the myoferlin-depleted tumors and how can this be therapeutically exploited.

\* Contributed equally

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