Myoferlin Regulates Endosomal Trafficking and Tunes Cancer Cell Metabolism

Blomme Arnaud (ULg Metastasis Research Laboratory), Costanza Brunella (ULg, Metastasis Research Laboratory), Thiry Marc (ULg, Laboratory of Cell Biology), de Tullio Pascal (ULg, Laboratory of Drug Research Centre), Perez Palacios Ana (Metastasis Research Laboratory), Lifrange Eric (Ulg - Department of Senology - CHU), Delvenne Philippe (Ulg - Department of Anatomy and Pathology - Faculty of Medicine), Castronovo Vincent (Ulg - Metastasis Research Laboratory), Turtoi Andrei (Ulg - Metastasis Research Laboratory)

Myoferlin is a member of the ferlin protein family that have key physiological functions in plasma membrane fusion, repair and endocytosis events. Genomic and proteomic studies have repeatedly found myoferlin as overexpressed in cancer. However, only few reports 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 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 delays 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.