

Exogenous Mitochondrial Transfer and Endogenous Mitochondrial Fission Facilitate Resistance to OxPhos Inhibition in AML

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Abstract

Oxidative phosphorylation (OxPhos) inhibition induces mitochondrial trafficking from BM stromal cells to AML and is accompanied by mitochondrial fission and mitophagy. The mitochondrial coupling and crosstalk with BM stromal cells facilitate the development of resistance to OxPhos inhibition in AML cells.

Background

AML cells are highly dependent on OxPhos for survival and continually adapt to fluctuations in nutrient and oxygen availability in the environment.

Objective

We investigated how the BM microenvironment affects the response to OxPhos inhibition in AML by using a novel complex I OxPhos inhibitor, IACS-010759.

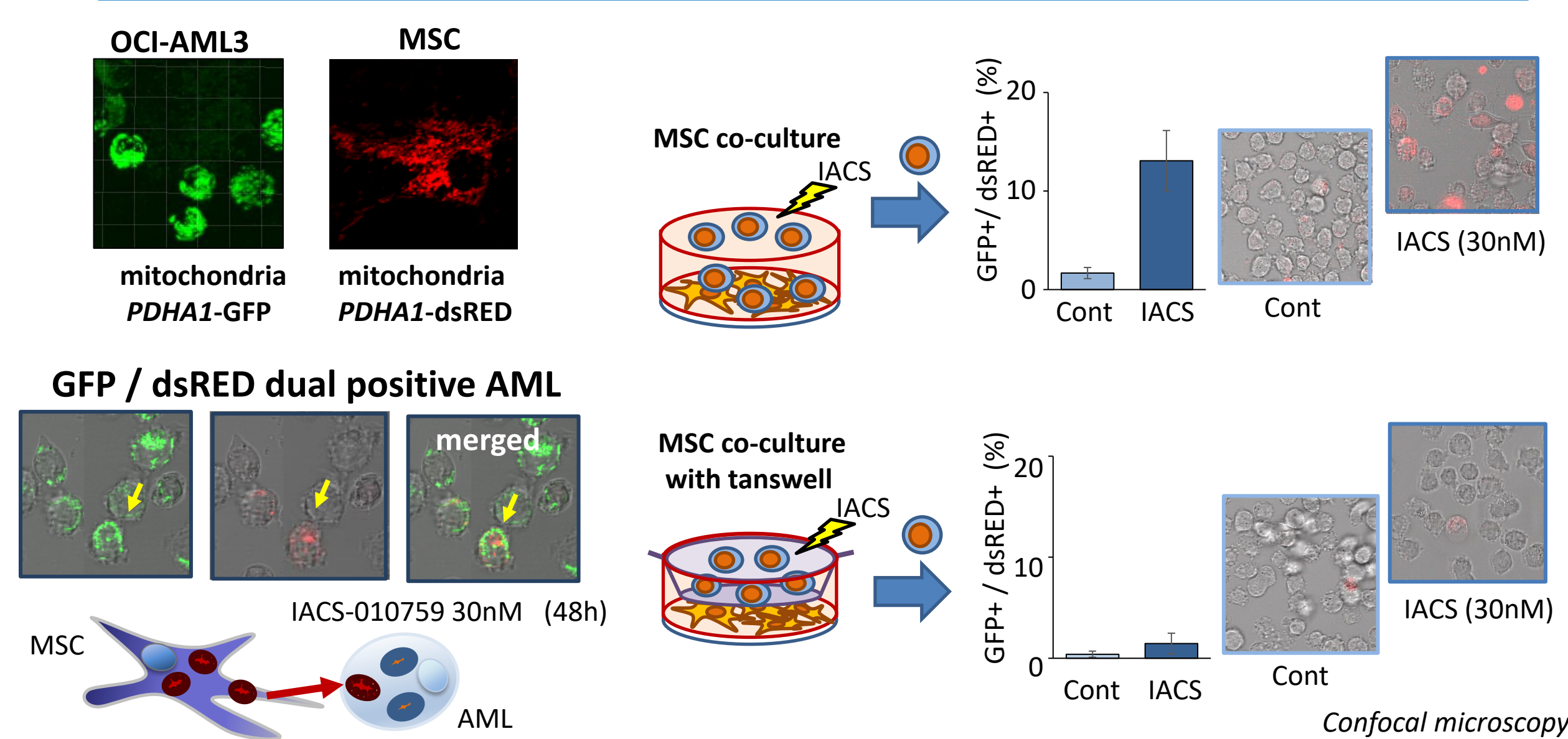
Materials & Methods

Primary AML cells (26 patients), primary MSCs, AML cell lines and AML PDXs were treated with the OxPhos inhibitor IACS-0107598 and/or cytarabine. Cap analysis of gene expression (CAGE) transcriptome analysis was performed.

The oxygen consumption rate was measured by an extracellular flux assay. AML cell lines and MSCs were stably transfected with mitochondria-targeted PDHA1-GFP and -dsRed, to visualize mitochondria. Electron microscopy and immunoelectron microscopy analysis were performed.

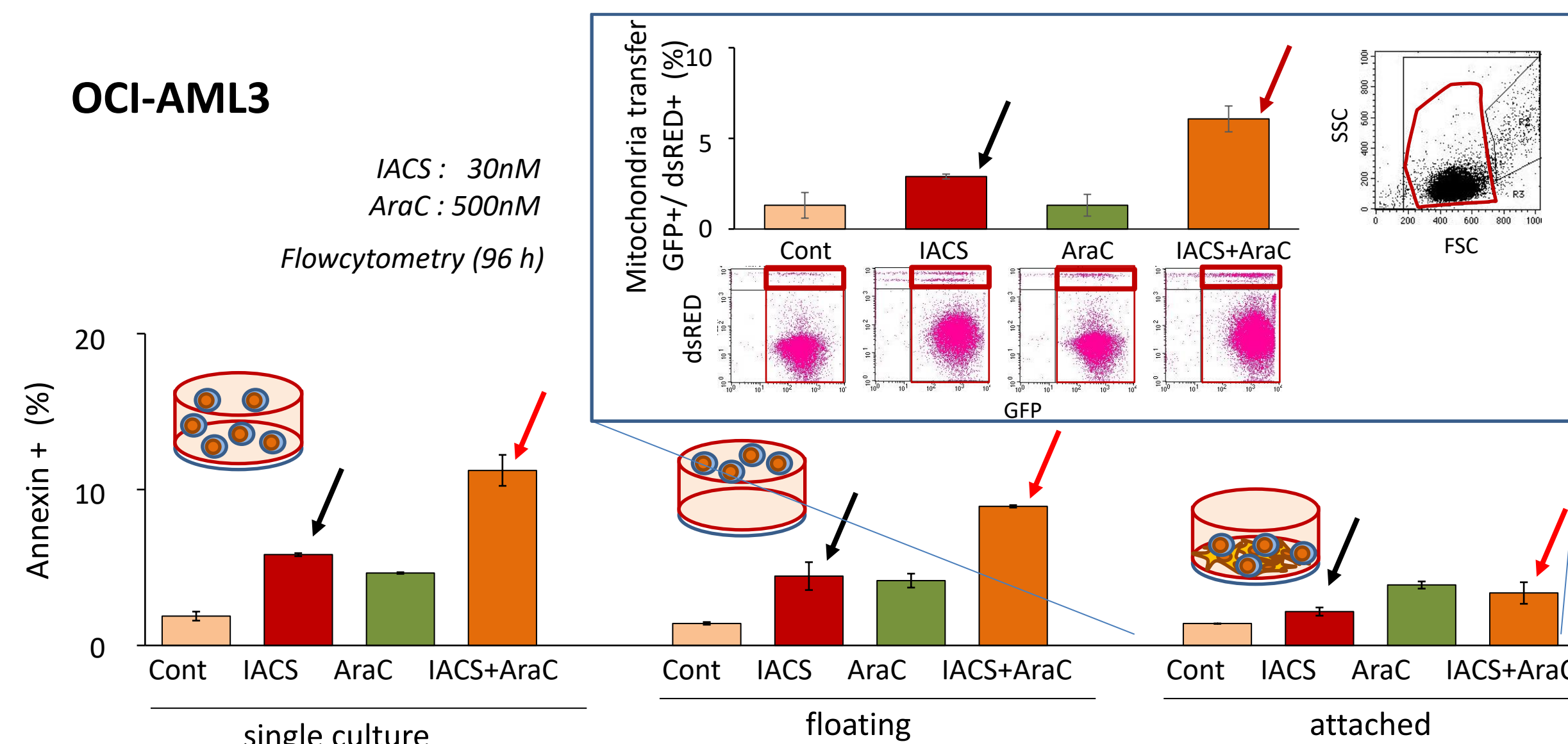
Results

IACS induces mitochondrial transfer from MSC to AML



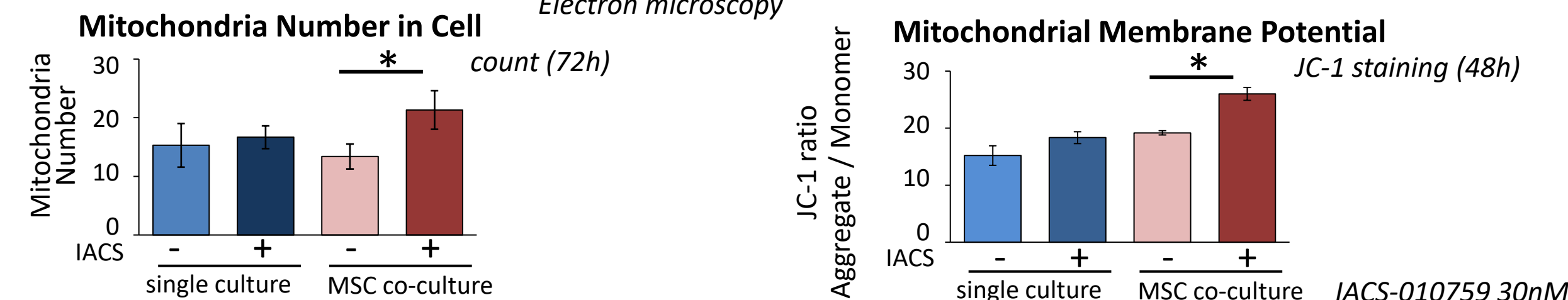
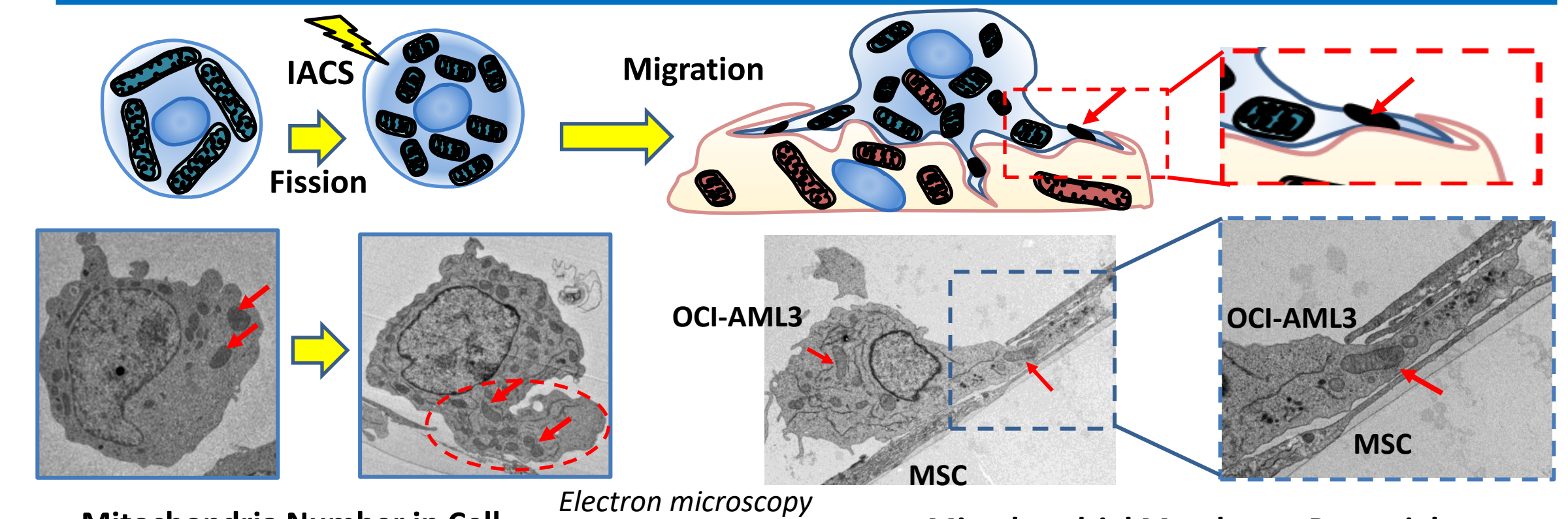
Under co-culture condition, IACS treatment induced significant increase of GFP and dsRed dual positive OCI-AML3 cells, indicating mitochondrial transfer from MSC to AML cells. IACS treatment increased dsRed positive OCI-AML3 cells only under conditions of direct cellular contact, indicating that mitochondria requires cell adhesion.

Adhesion to MSC protects AML cells from IACS/cytarabine induced apoptosis with mitochondrial transfer



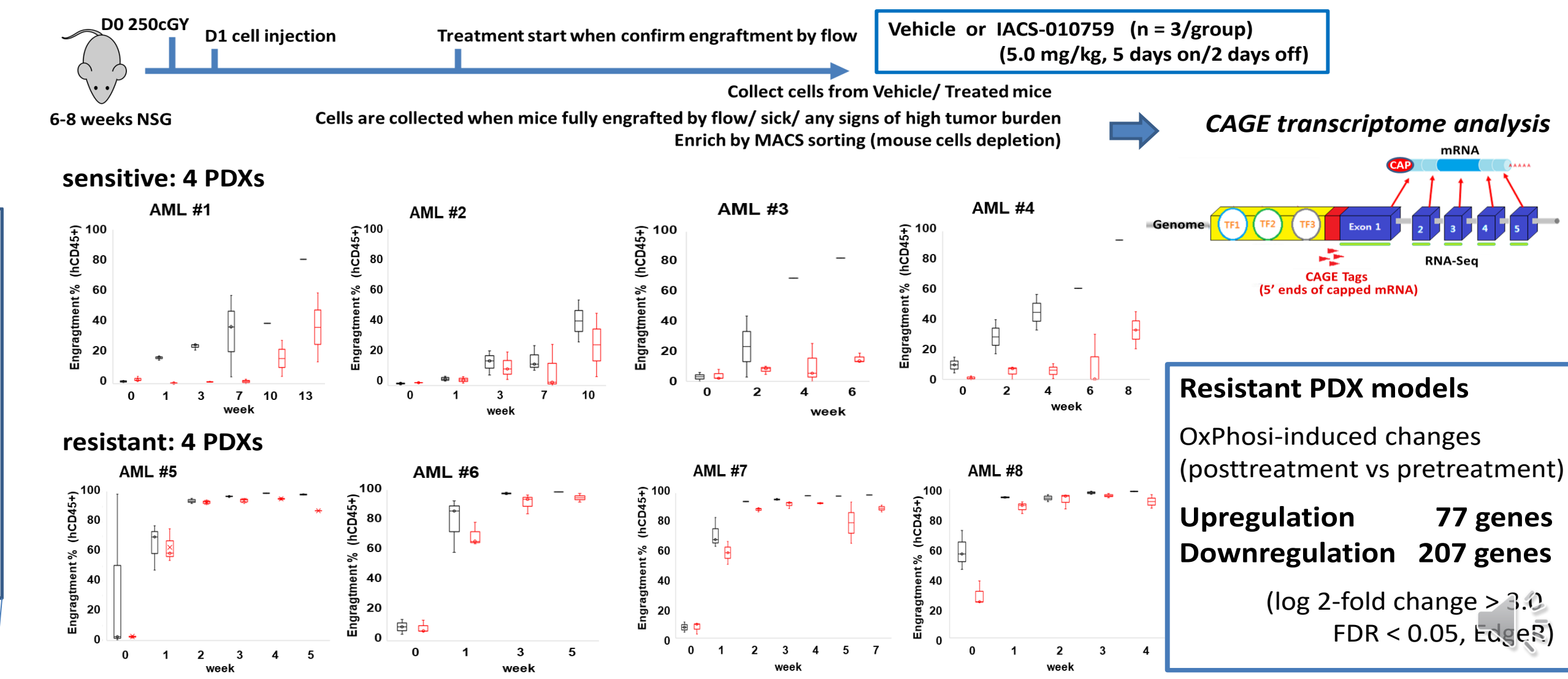
Adhesion to MSC protected AML cells from IACS induced apoptosis and more prominently IACS and AraC combination induced apoptosis. In these cells, mitochondrial transfer from MSC to AML cells was triggered by IACS treatment, and further increased by IACS and AraC co-treatment.

IACS induces mitochondrial transfer from MSC to AML



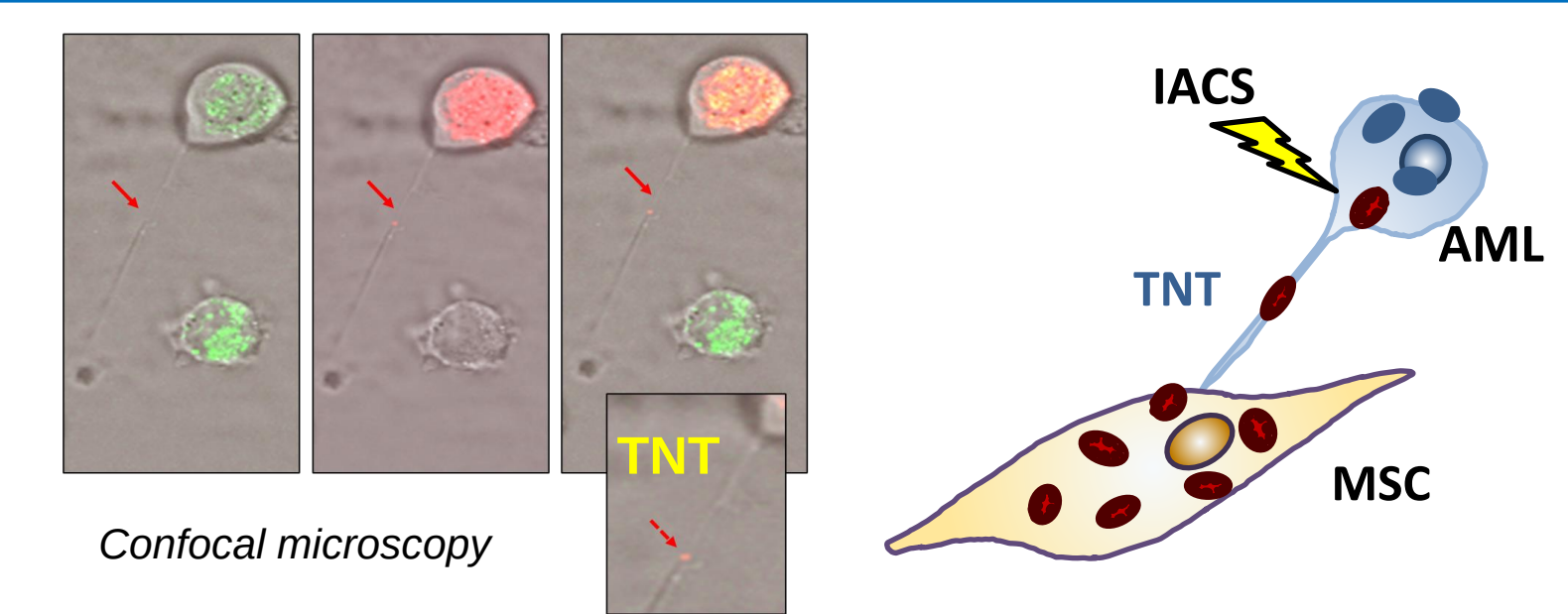
The number of mitochondria was significantly increased by IACS treatment in MSC coculture condition, which accompanied with mitochondria fission and mitochondria transport to the leading edge of the migrating AML cells. Mitochondria membrane potential was increased in the IACS treated cells under MSC co-culture condition.

Effect of OxPhox inhibition in a mouse xenograft model



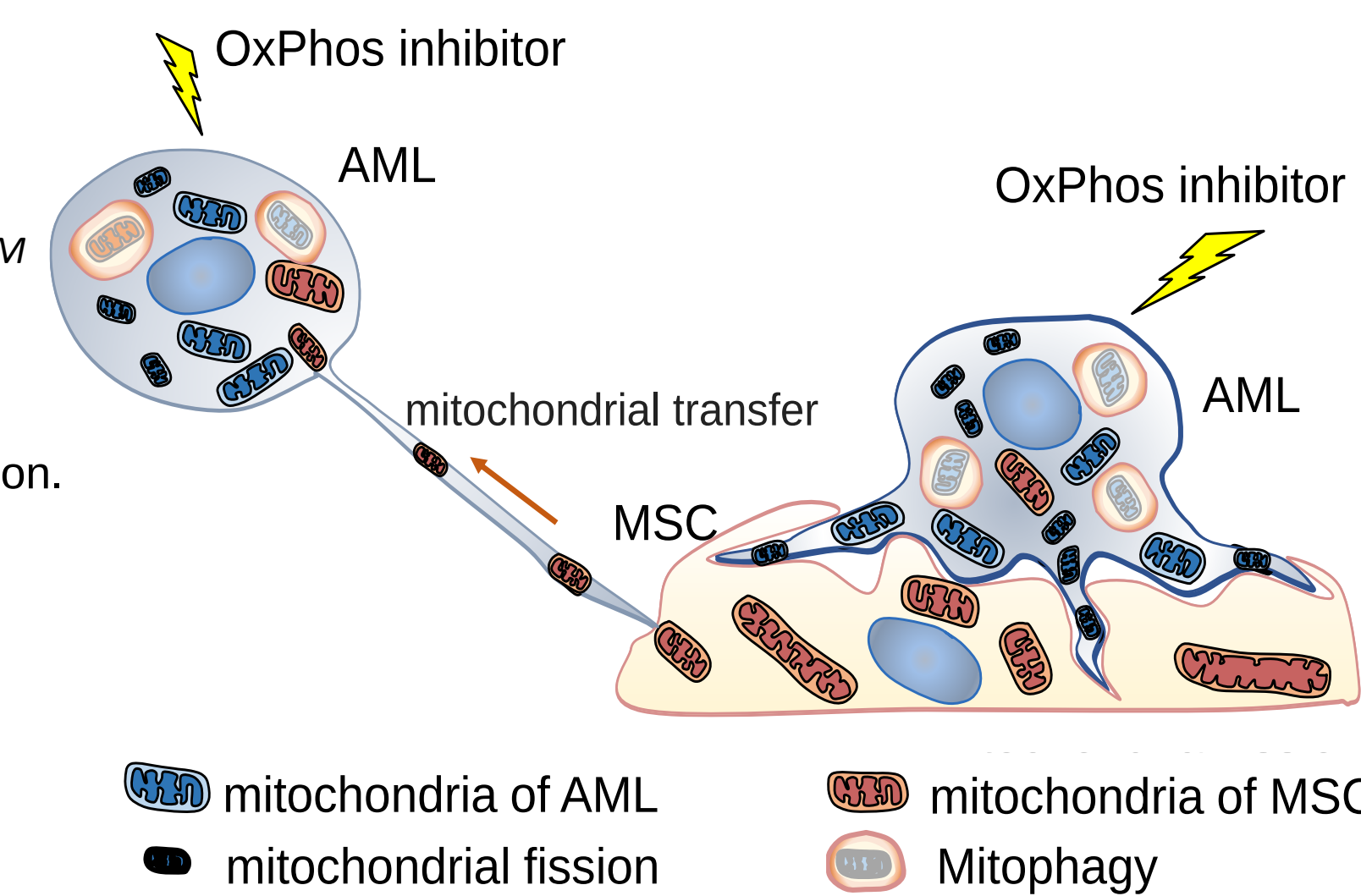
In the resistant PDX, CAGE identified Oxphosi induced 77 upregulation and 207 downregulation of promoters.

Formation of Tunneling Nano Tubes (TNT)



TNT formation of AML cells that formed a direct contact with MSCs.

Summary



OxPhos inhibitor treatment induces AML cells to adhere and migrate to BM stromal cells and stimulates mitochondrial transport to the leading edge of the migrating AML cells. OxPhos inhibition also causes mitochondrial fission and mitophagy in AML cells and induces mitochondrial transfer from MSCs to AML cells via adhesion and tunneling nanotube formation.

Conclusions

The findings indicate an important role of exogenous mitochondrial trafficking from BM stromal cells to AML cells and of endogenous mitochondrial fission and mitophagy in the compensatory adaptation of leukemia cells to energetic stress in the BM microenvironment.