Mitochondria in human acute myeloid leukemia cell lines have ultrastructural alterations linked to deregulation of their respiratory profiles

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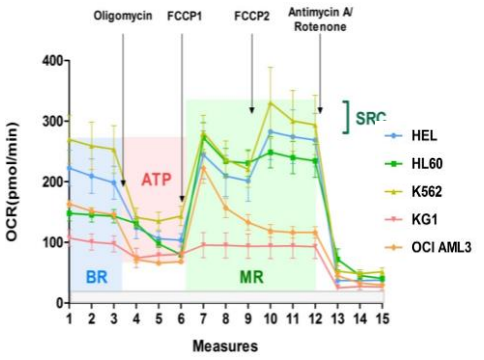
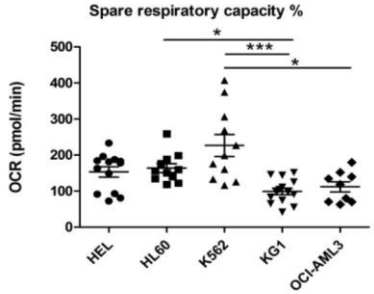
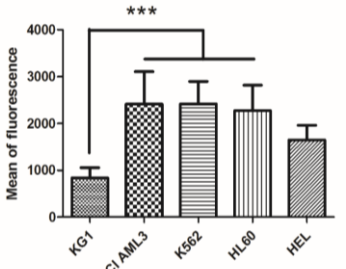
Compared to normal cells, leukemic cells are known to have a lower respiratory chain complex activity and a lower spare reserve capacity in the respiratory chain balanced by an increase in mitochondrial biogenesis[1]. Parallel to these functional deregulations, morphological alterations of mitochondria have been reported in cancers[2]. Few data are available on the deregulation of the number and/or shape of mitochondria in leukemia cells, despite the evident link between ultrastructure and function. In this context, we correlated functional and ultrastructural analysis of the mitochondria from 5 leukemia cell lines (HEL, HL60, K562, KG1, OCI-AML3).



Functional respiratory profiles of leukemia cell lines using Seahorse Mito stress test kit (Agilent Technologies) identified **two subgroups of "low "and "high" respiration leukemia cell lines**



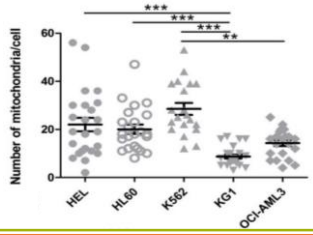
KG1 and to less level OCI-AML3 displays a **reduced percentage of spare respiratory capacity** and maximal respiration compared to K562, HEL, HL60 that could be considered as a "high respiration" leukemia cell line



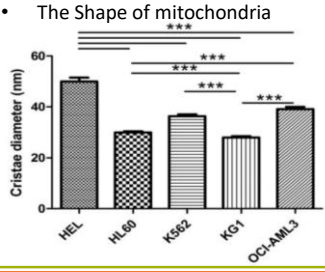
Furthermore, we observed alterations of **ROS production (DHE probe)** that were correlated to the respiratory profiles of leukemic cells.

Functional diversity between cell lines is associated with ultrastructural inter-leukemia variability

- Number of mitochondria

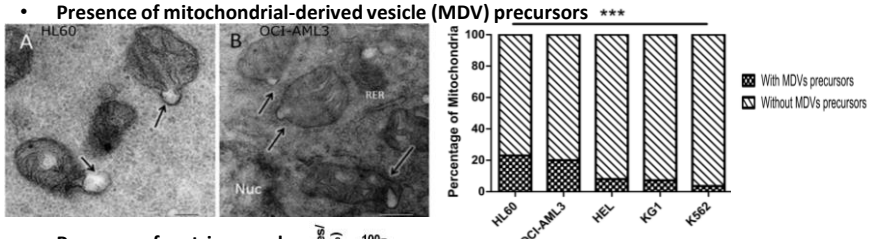


- The Shape of mitochondria

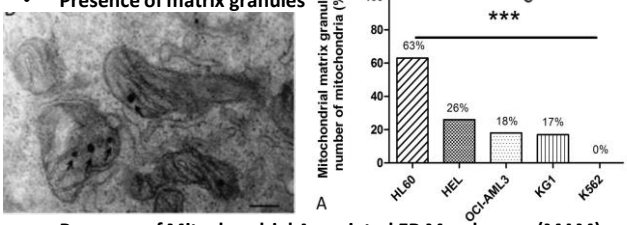


Analysis of mitochondria by electron microscopy also depicted disparities in :

- **Presence of mitochondrial-derived vesicle (MDV) precursors** ***



- **Presence of matrix granules**



- **Presence of Mitochondrial Associated ER Membranes (MAM)**

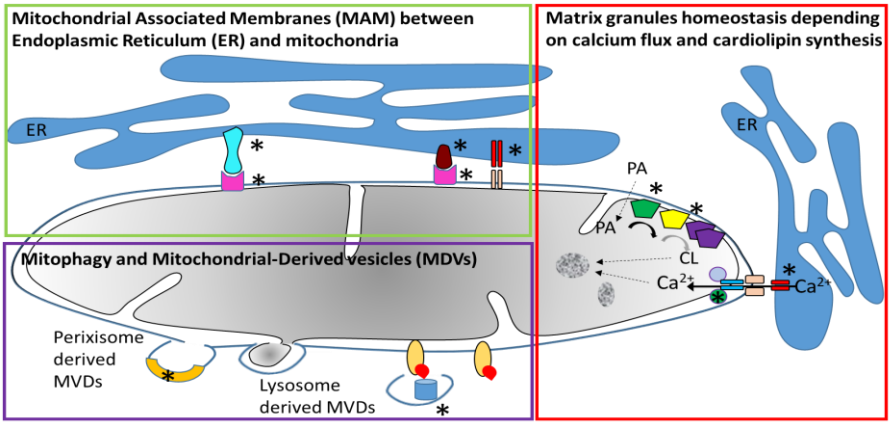
MAMs were more abundant in HL60 than in K562 cells, where RER was less extensive

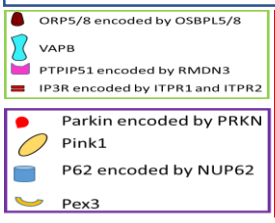
- K562, carrying the *ASXL1* mutation, presents a mitochondria–Endoplasmic Reticulum deficiency.
- Less sensitivity to drugs targetting mitochondria (compared to HL60)

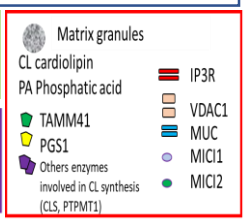
Is the ASXL1 mutation associated to mitochondria-ER deficiency?

Transcriptomic analysis from public data (cbioportal) (n=415 patients)

Significant reduction of the *VAPB, RMDN3, OSBPL5, ITPR1, ITPR2, MICU2, TAMM41, PGS1, NUP62, PEX3* transcripts according to *ASXL1* status implicated in the ER-mitochondrial communication







Conclusion : Our study shows new and original data on the shape and quantitative alterations in AMLs mitochondria together with bioenergetics modifications. In particular, we observe that the *ASXL1* mutation was associated to a mitochondria-ER deficiency, suggesting that novel strategies targeting the ER-mitochondria interface to potentiate the cytostatics could be less effective[3].

These data suggest that leukemic cells could modulate their energetic metabolism through modification of mitochondria shape and/or number and/or integrity of endoplasmic reticulum and, thereby, regulate or adapt their proliferative potential and their chemosensitivity

References : 1 *Sriskanthadevan S* et al, Blood, 2015, 2 *Wallace* DC, Nat Rev Cancer 2012; 3 Koczian et al, Haematologica, 2019