Investigation of metabolic crosstalk and reprogramming in the leukemic niche and its impact on drug sensitivity

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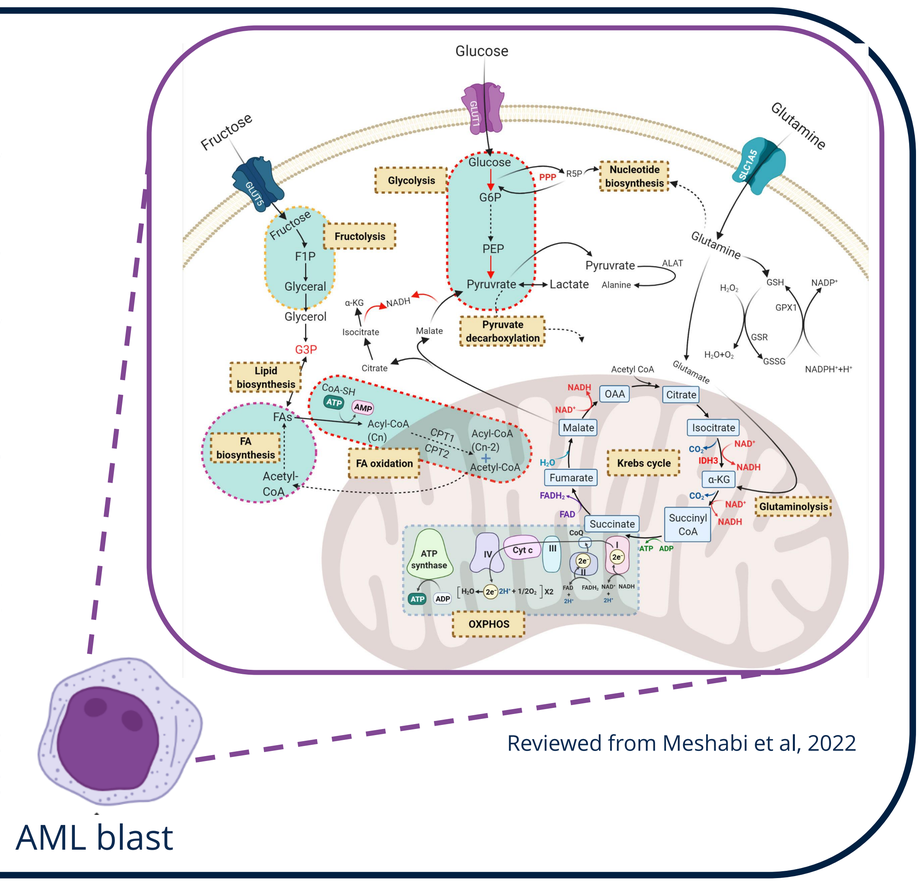
Abstract

Acute myeloid leukemia (AML) is a group of malignant disorders characterized by accumulation immature myeloid blasts due to genetic mutations in hematopoietic and progenitor stem cells. Despite advancements in treatment, a significant number of AML cases relapse due to drug resistance. This resistance is partially attributed to dysregulated metabolism in AML cells, which enhances energy production to counteract drug cytotoxicity [1]. The two major energy-production pathways are cytosolic glycolysis and mitochondrial oxidative phosphorylation (OXPHOS). According to Otto von Warburg, tumors often switch to glycolysis regardless of oxygen availability – the Warburg Effect. However, recent findings suggest that some cancer cells exhibit metabolic flexibility, adapting both glycolysis and OXPHOS to meet metabolic challenges and local nutritional conditions [2,3]. Moreover, the tumor microenvironment plays a crucial role in cancer cell metabolic dependency. AML resides in the bone marrow microenvironment, characterized by a complex cellular structure. Among these, mesenchymal stromal cells (MSCs) are notable for their ability to support AML development [4]. Numerous studies have shown that MSCs contribute to chemoresistance by altering AML cell metabolism [5,6]. However, the role of metabolic dependency and the impact of MSCs on it among AML cases with different genetic backgrounds remains unknown.

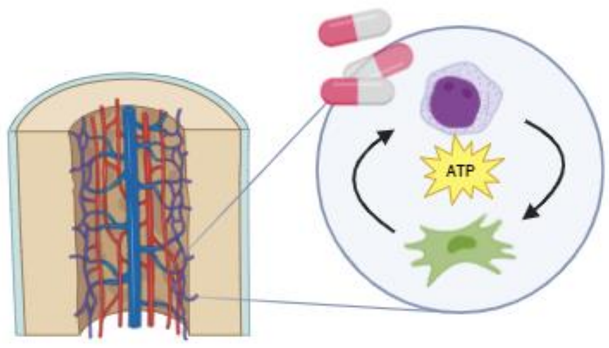


Reviewed from Meshabi et al, 2022

AML blast

Objective

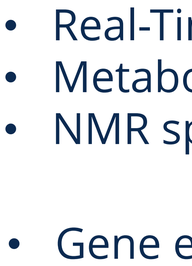
To characterize metabolic reprogramming and crosstalk in the leukemic bone marrow niche and examine its impact on AML response to anti-cancer therapy.



Prelimenary work

Real-time metabolic profiling of AML cells

Seahorse analyzer



KG1 (complex karyotype)
K562 (bcr/abl)
HL-60 (t(5;17))
Kasumi-1 (RUNX1/RUNX1T)
Molm-13, MV 4-11 (FLT3-ITD)
OCI AML-2 (DNMT3a)
OCI AML-3 (NPM1/DNMT3A)

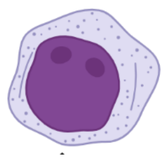
metabolically plastic

metabolically commmited

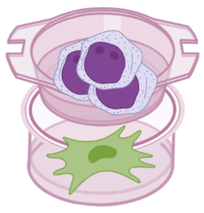
Working program

Cytarabin
Daunorubicin
Targeted drugs (Bcl-2, Flt-3)

a. AML monoculture



b. AML and MSC co-culture



indirect

direct

Methods

Flow cytometry

- Viability (PI staining)
- Apoptosis (Annexin V assay)
- Cell cycle analysis

Metabolomics

- Real-Time metabolic analysis
- Metabolic imaging
- NMR spectroscopy

DNA analysis

- Gene expression analysis
- Epigenetic analysis

References

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6. You, Ruolan, et al. "Bone marrow microenvironment drives AML cell OXPHOS addiction and AMPK inhibition to resist chemotherapy." *Journal of Leukocyte Biology* 112.2 (2022): 299-311.

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ONCOnnect

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