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Progetto Ematologia Romagna

Le vescicole extracellulari ed il metabolismo energetico nella leucemia acuta mieloide

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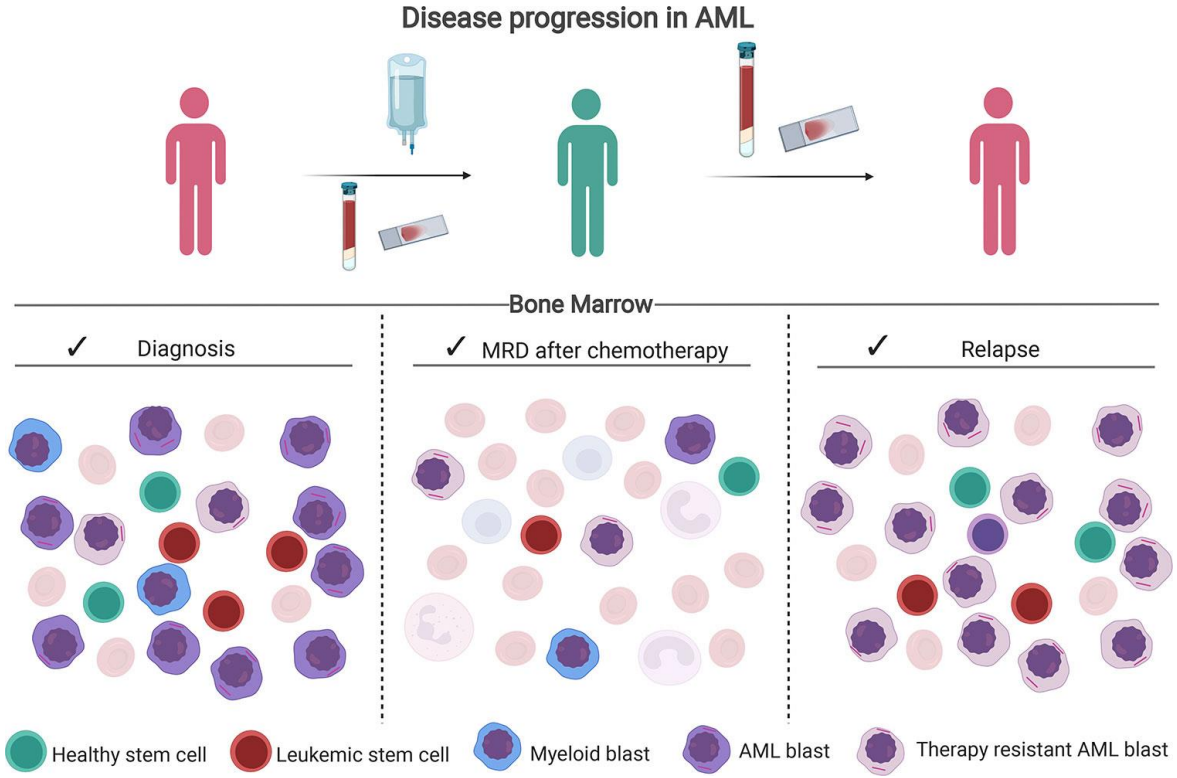
Disclosure statement

Dorian Forte, Ph.D.

- Nothing to disclose

Of what remains… in AML



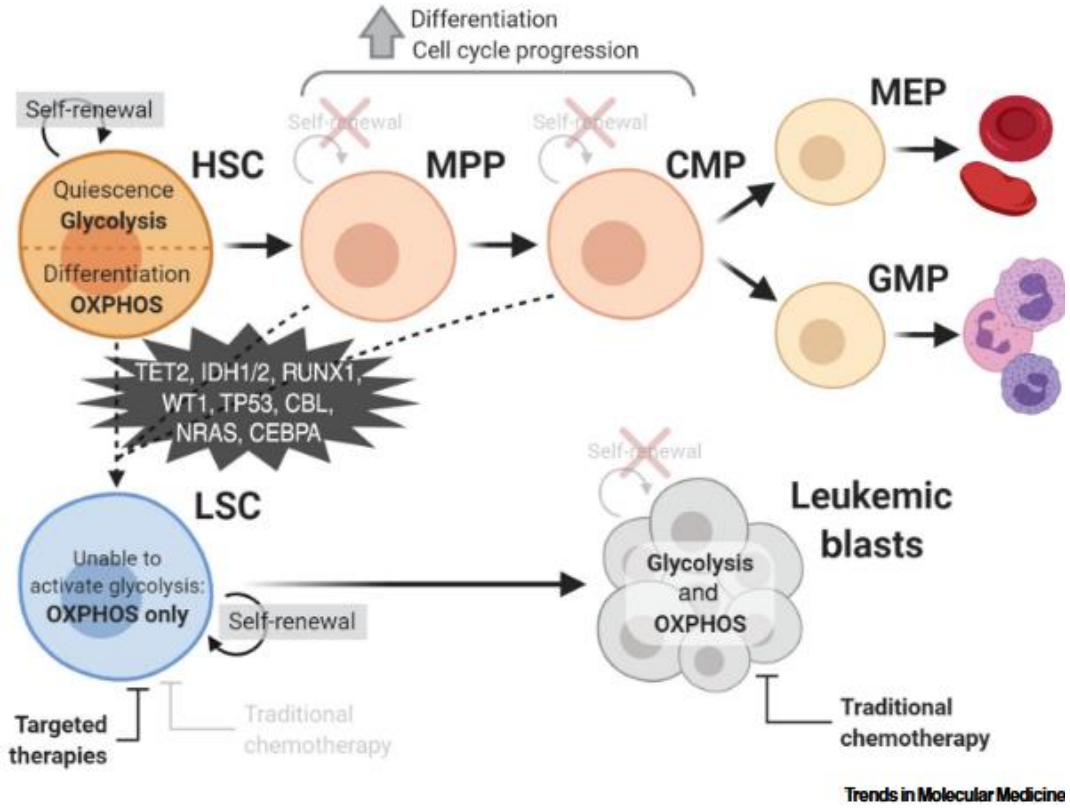
Acute Myeloid Leukemia (AML) is a heterogeneous disease characterized by the proliferation of clonal stem-cell like blasts in the bone marrow (BM).

↘ The presence of **leukemia stem cells (LSC)** has prognostic relevance as they are presumed to initiate the relapse.

↘ Measurable Residual Disease (MRD) is the assessment of the percentage of residual leukemia cells after chemotherapy

Huntly BJ et al. Nat Rev Cancer, 2005/ LL Ngai et al. Front. Oncol., 2021

Snapshot on Normal and Leukemic Myeloid Hematopoietic Hierarchies: know (metabolically) your enemy!



HSCs differentiate into multipotent progenitors (**MPPs**)

⇩

MPP differentiates to a common myeloid progenitor (**CMP**)

⇙ ⇘

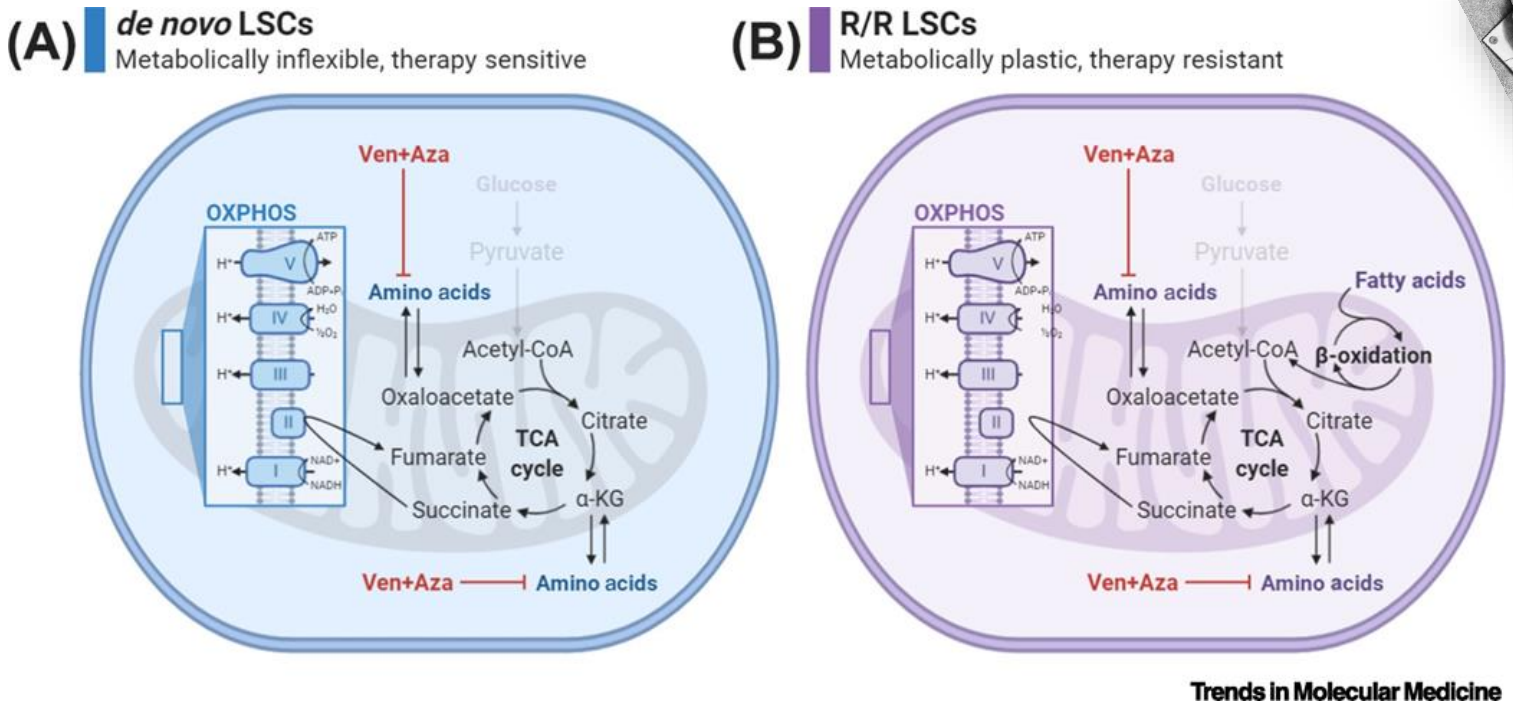
megakaryocyte–erythroid progenitor (**MEP**)

granulocyte-macrophage progenitor (**GMP**)

HSCs, MPPs, and CMPs can all potentially become a leukemic stem cell (LSC)

R Culp-Hill et al. Trends Mol Med 2021

Metabolic Features mirrored by Leukemic Stem Cells (LSCs)



(ven+aza): combination of venetoclax, a B cell lymphoma2 (BCL-2) inhibitor, and azacitidine, a DNA methyltransferase inhibitor

R Culp-Hill et al. Trends Mol Med 2021

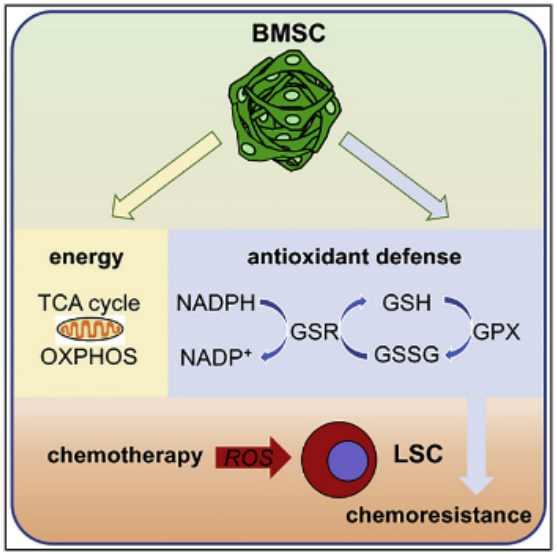
Bone Marrow Microenvironment in Acute Myeloid Leukemia: novel metabolic players

Article

Cell Metabolism

Bone Marrow Mesenchymal Stem Cells Support Acute Myeloid Leukemia Bioenergetics and Enhance Antioxidant Defense and Escape from Chemotherapy

Graphical Abstract



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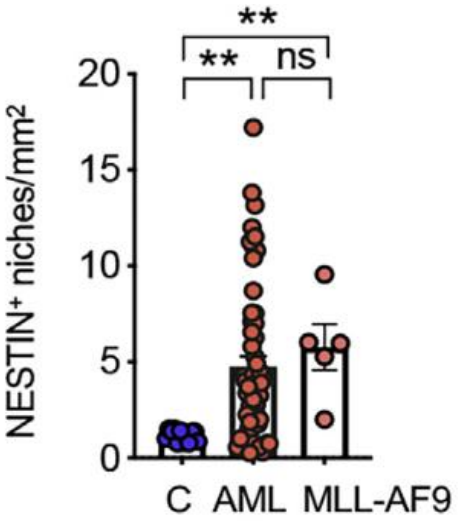
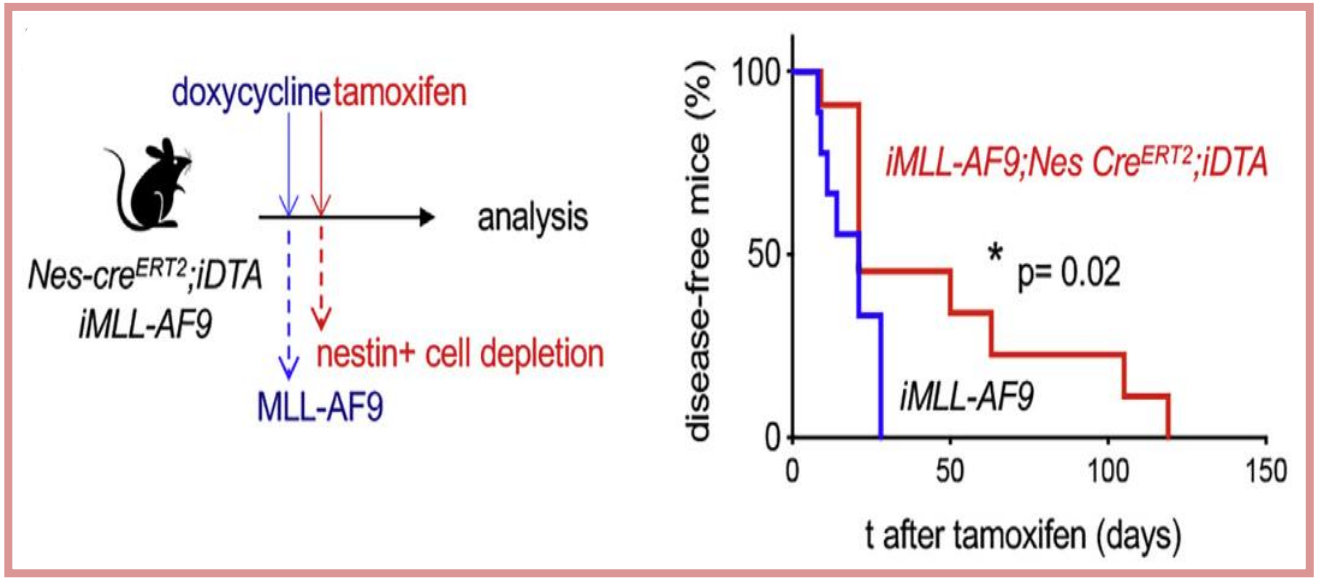
In Brief

Forte et al. reveal that nestin+ bone marrow stromal cells directly contribute to leukemogenesis and chemotherapy resistance in an *in vivo* model of acute myeloid leukemia. Nestin+ BMSCs support leukemic stem cells through a dual mechanism of increased bioenergetic capacity through OXPHOS and TCA and glutathione-dependent antioxidant defense.

AML Cells Hijack Nestin+ Niche Cells to Promote Leukemogenesis

Nestin+ cells represent a rare stromal population
Nestin+ cells co-localize near HSCs
Nestin+ cells are required for HSC homing and maintenance

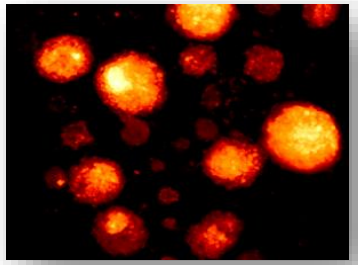


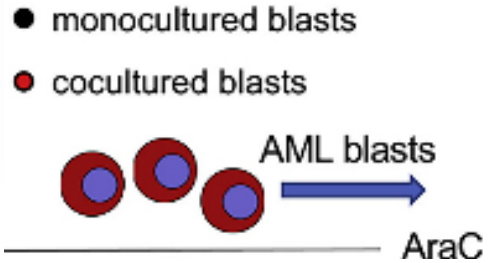


BMSCs Support Leukemic Blast Survival and Chemoresistance In vitro

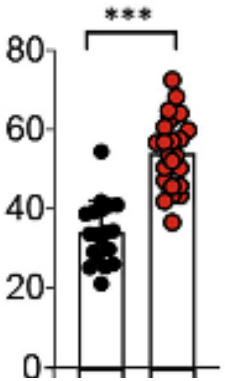
nestin –
MSC adherent

nestin+ Dsred+
mesenspheres

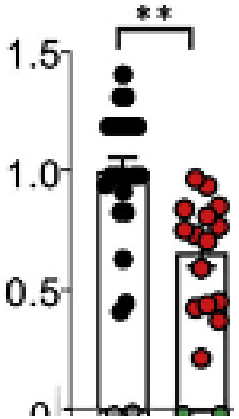




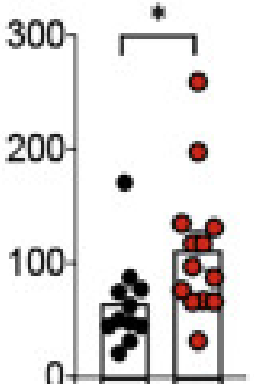
Survival



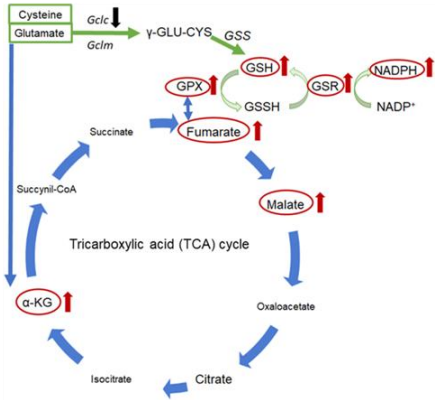
ROS

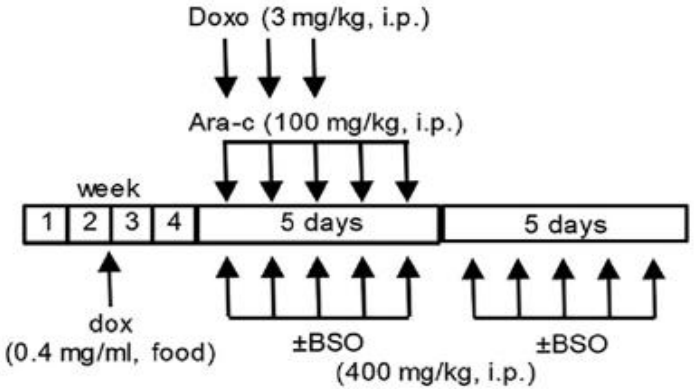


GSH



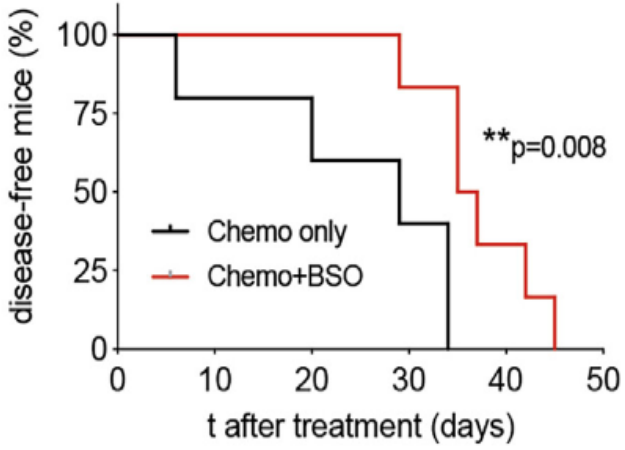
Targeting BMSCs-induced Antioxidant Defense improves antileukemic chemotherapy in vivo

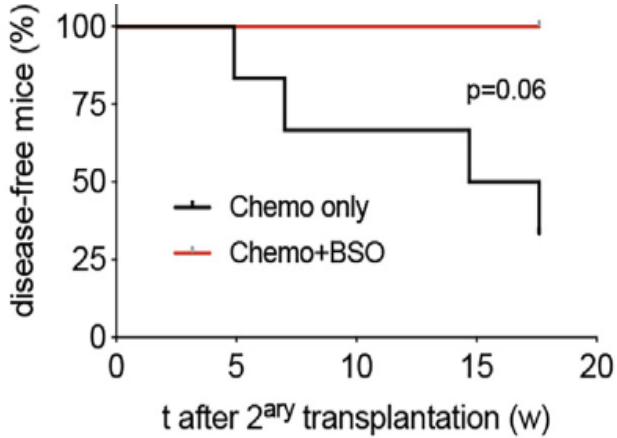




Buthionine sulfoximine (BSO) is a sulfoximine which reduces the levels of glutathione (GSH)

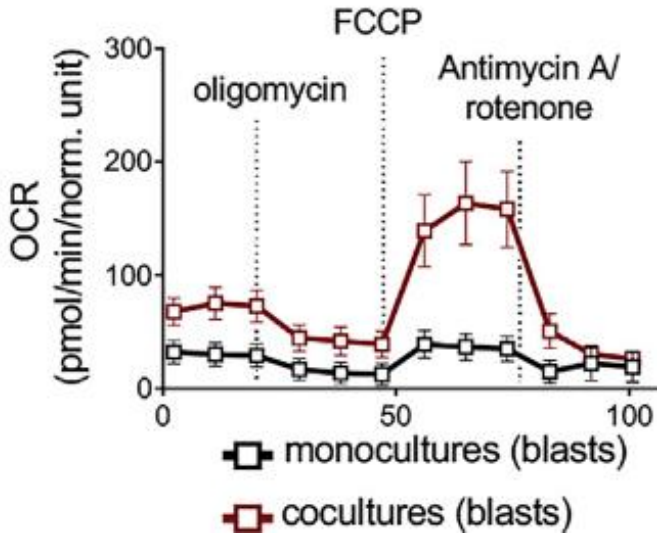
Chemo = "5+3" i.p. injections of cytarabine (100 mg/kg/day over 5 days) and doxorubicin (3 mg/kg/day over 3 days)



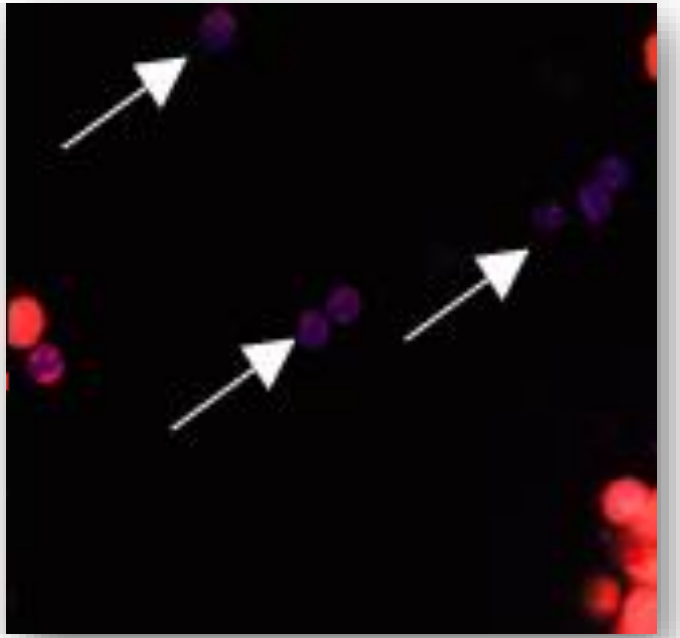


BMSCs increase transfer protective mitochondria in AML

Mitochondrial Respiration
using Seahorse Extracellular Flux (Agilent)



Mitochondria transferred
from **MitoTracker CMXRos red^{+} BMSCs**
in **GSH^{+} leukemic blasts**



OCR= Oxygen consumption rate

Functional gift exchange between BMSCs and Leukemic cells

Article

Cell Metabolism

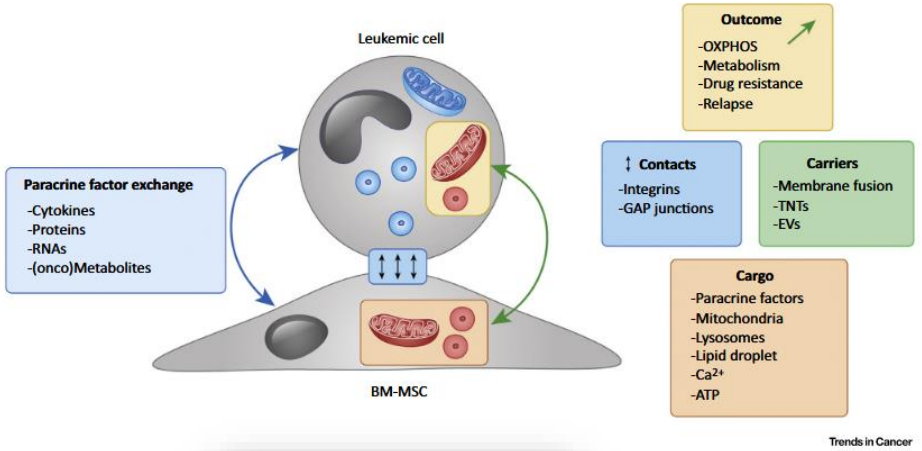
Bone Marrow Mesenchymal Stem Cells Support Acute Myeloid Leukemia Bioenergetics and Enhance Antioxidant Defense and Escape from Chemotherapy

Highlights

- Nestin$^+$ BMSCs support leukemogenesis and chemoresistance
- BMSCs support metabolic requirements of LSCs
- BMSCs provide LSCs with essential antioxidant defense from chemotherapy
- GSH and GSH peroxidases underlie BMSC-derived antioxidant AML protection

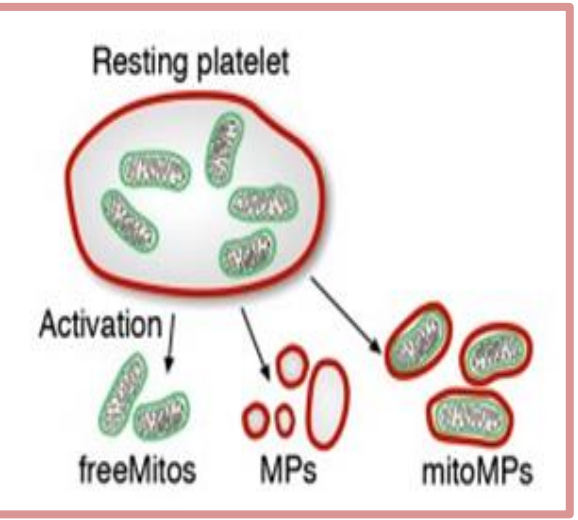
Forte et al. Cell Metabolism 2020

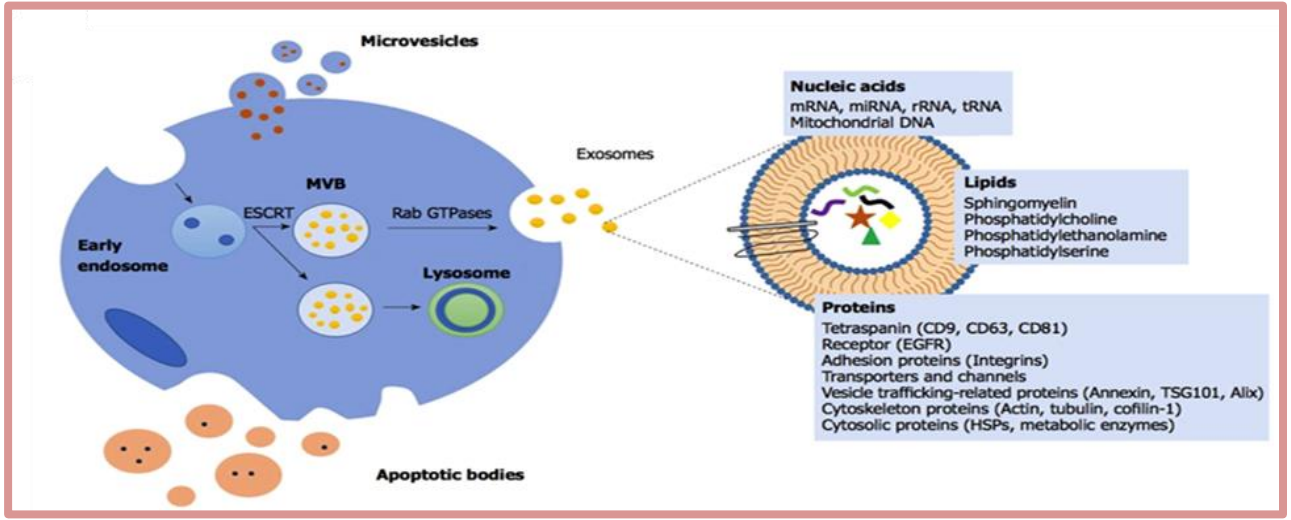
Mitochondrial uptake by leukemic cells results in augmented ATP production through increased oxidative phosphorylation (OXPHOS) and higher drug resistance



E Griessinger et al. Trends Cancer 2017

Extracellular Vesicles (EVs) as carriers of complex intercellular information within the microenvironment



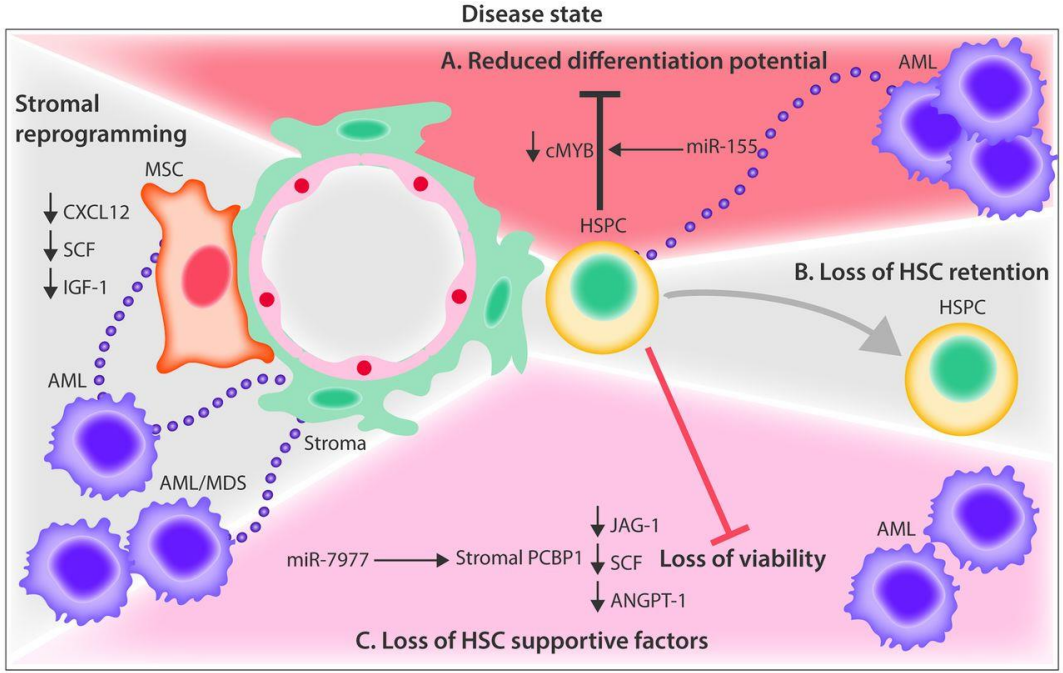


The most abundant type of EVs in circulation are platelet-derived extracellular vesicles

EVs may also be considered a promising tool for liquid biopsy in routine clinical practice

CZJ Lim et al. ACS Sens. 2019/
Luc H Boudreau et al. Blood 2014

Extracellular vesicle crosstalk in the leukemic microenvironment



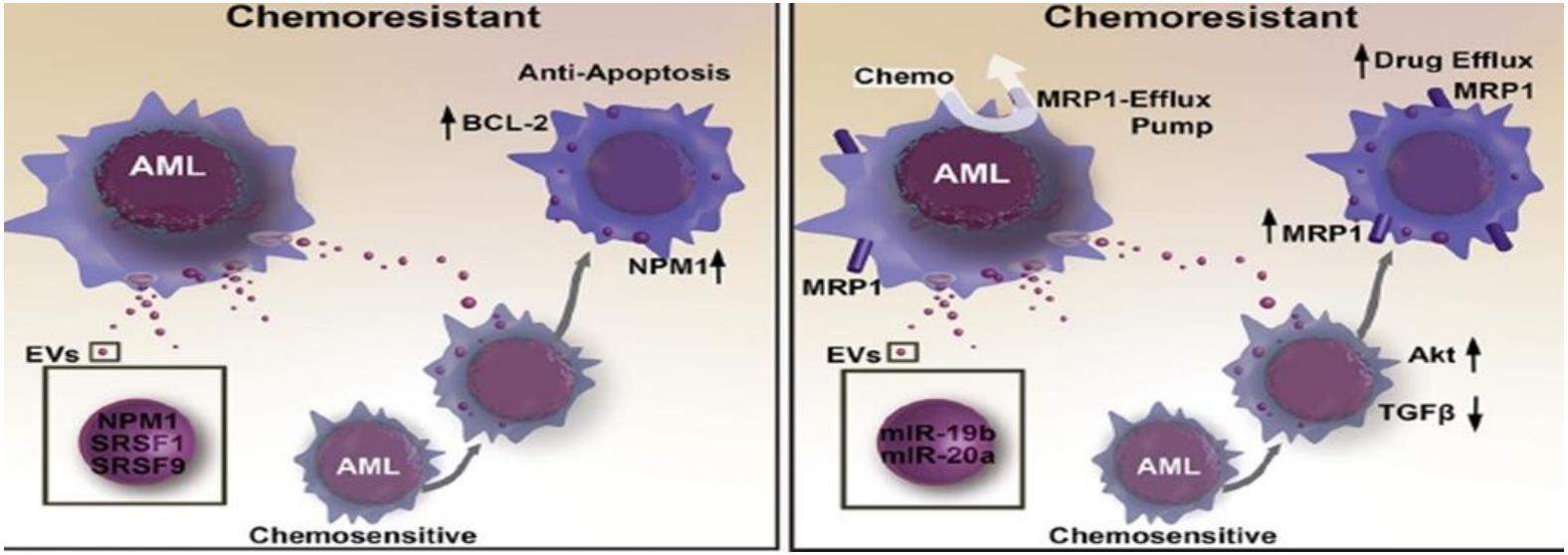
(A) EVs from AML blasts reduced differentiation potential;

(B) AML EVs reprogram MSCs and stromal cells;

(C) AML and MDS EVs promote the loss of HSPC supportive factors;

JT Butler et al. Haematologica. 2018

Extracellular Vesicles and Chemotherapy Resistance in the leukemic microenvironment



EV trafficking between AML cells transfers regulatory factors that induce resistance to chemotherapy

J Nehrbas et al. Front. Oncol., 2020

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Beat-Leukemia.org
Multi language resources for leukemia fighters.

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