FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinica e Terapia delle Sindromi Mielodisplastiche

28 maggio 2022

La ferrochelazione nelle MDS (15 min)

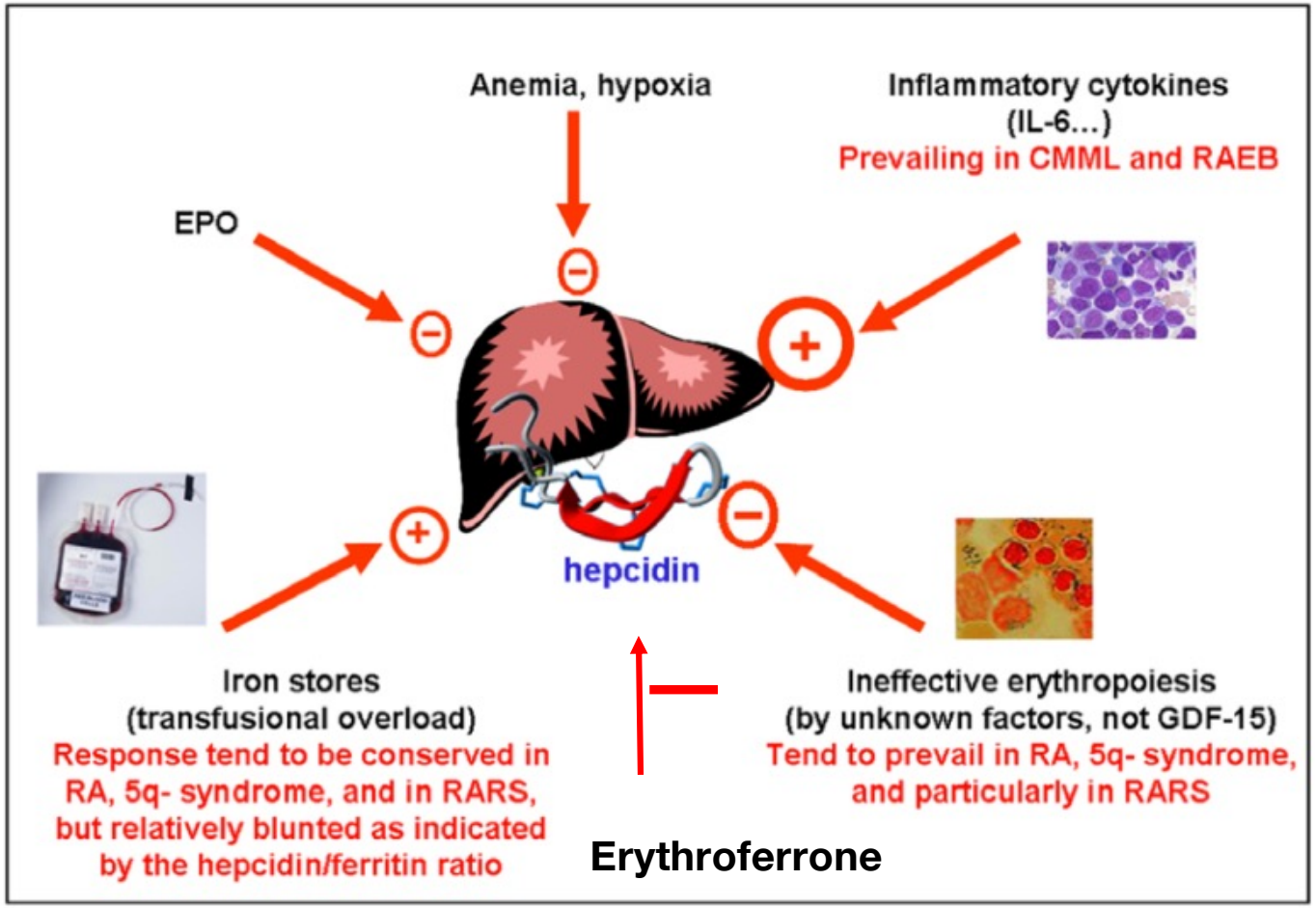
Daniela Cilloni

Università degli Studi di Torino

SCDU Ematologia, Ospedale Umberto I Ordine Mauriziano-Torino

- Perché il ferro si accumula nelle MDS
- Quali sono i meccanismi di tossicità
- Azioni antileucemiche della ferrochelazione
- Azioni antileucemiche del ferro

Proposed Mechanisms Controlling Hepcidin Production in Different MDS Types



Santini *et al. PLoS ONE* (2011) 6(8): e23109.

Some genetic lesions interfere with iron metabolism

SF3B1 mutations

- dysregulate the RNA splicing of the erythroid transcription factors TAL1 and GATA1, resulting in increased but ineffective erythropoiesis.
- SF3B1-mutated patients present mitochondrial iron accumulation
- Increased expression of a specific isoform of SLC25A37 , an important transporter of Fe(2+) into the mitochondria
- Splicing alterations have been observed in the key genes associated with iron accumulation.

5q deletion

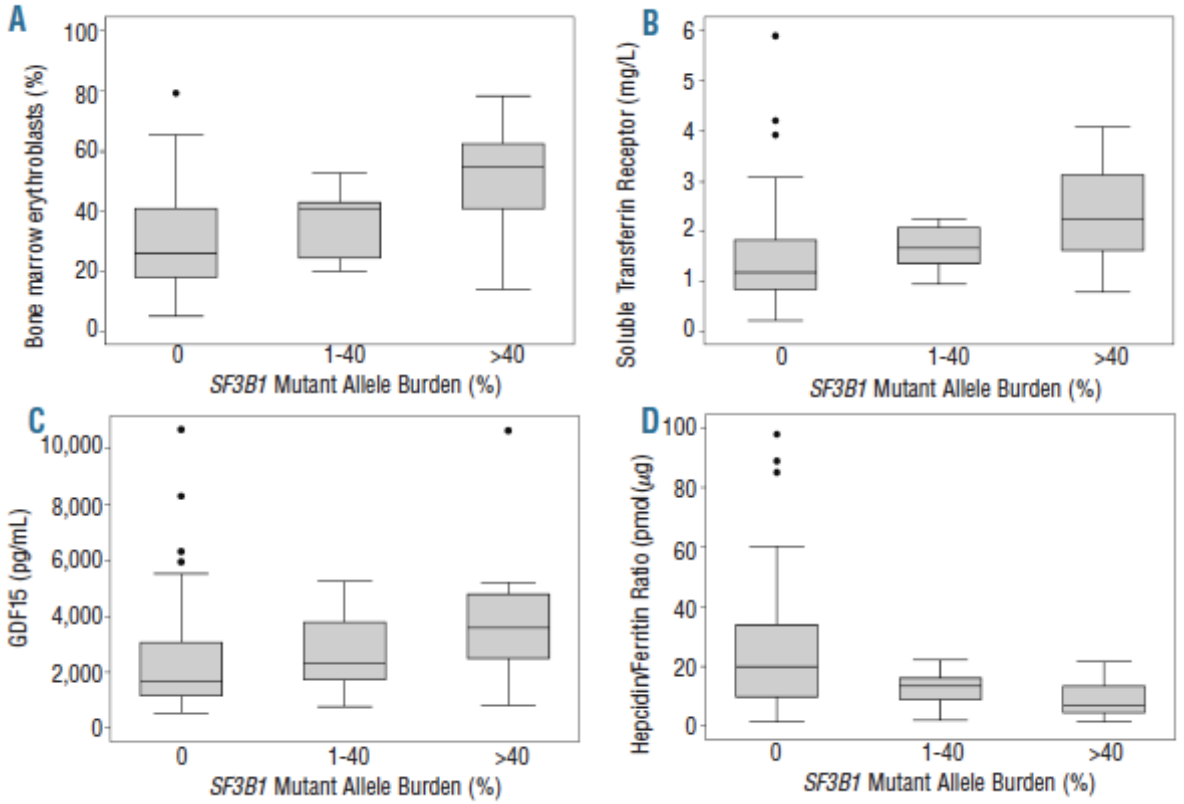
- considerable ineffective erythropoiesis associated with the heterozygous deletion of RPS14.
- RPS14 haploinsufficiency increases the expression of S100A8-S100A9, resulting in p53-dependent erythroid differentiation defects.

TET2 mutations

- Only in a subset of patients with MDS may be involved in iron metabolism and in heme biosynthesis in the erythroblasts.
- TET2 knockdown mouse models have shown high serum and mitochondrial ferritin levels and dysregulation in a number of genes involved in iron metabolism

Inappropriately low hepcidin levels in patients with myelodysplastic syndrome carrying a somatic mutation of *SF3B1*

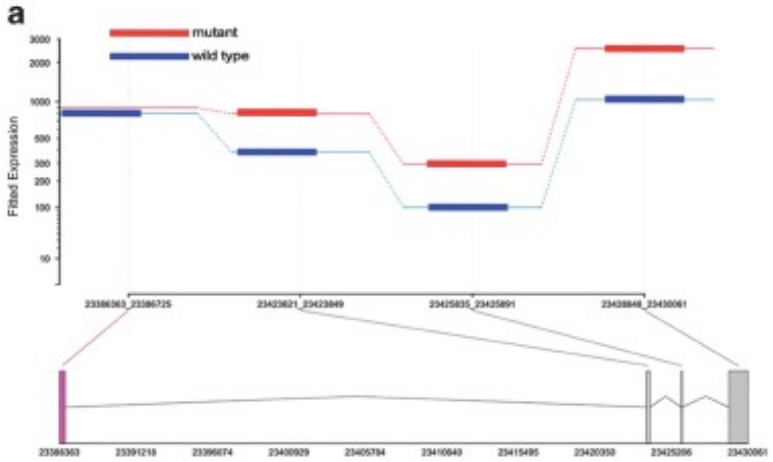
Ilaria Ambaglio,[1] Luca Malcovati,[1,2] Elli Papaemmanuil,[3] Coby M. Laarakkers,[4,5] Matteo G. Della Porta,[1] Anna Gallì,[1,2] Matteo C. Da Vià,[1,2] Elisa Bono,[1,2] Marta Ubezio,[1,2] Erica Travaglino,[1] Riccardo Albertini,[6] Peter J. Campbell,[3] Dorine W. Swinkels,[4,5] and Mario Cazzola[1,2]

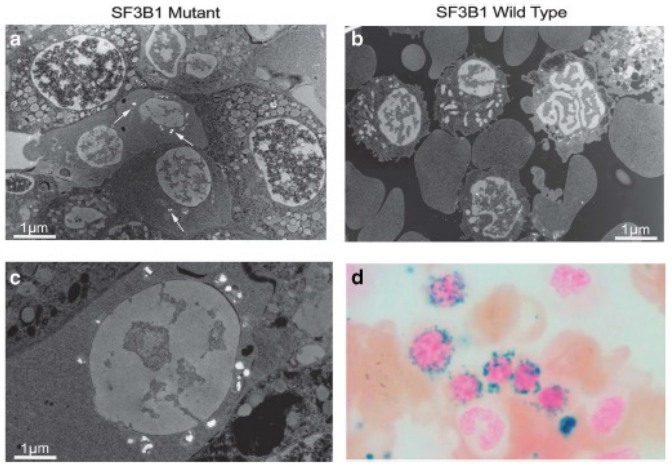


haematologica | 2013; 98(3)

Distinct iron architecture in *SF3B1*-mutant myelodysplastic syndrome patients is linked to an *SLC25A37* splice variant with a retained intron

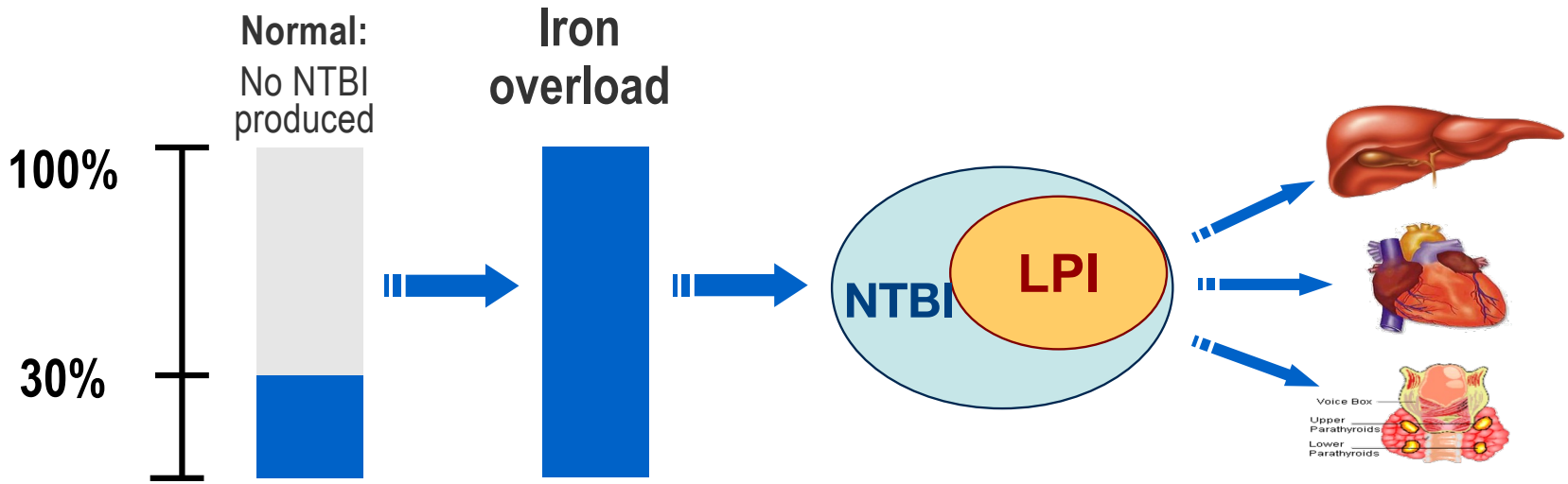
V Visconte[1], N Avishai[2], R Mahfouz[1], A Tabarroki[1], J Cowen[2], R Sharghi-Moshtaghin[2], M Hitomi[3], HJ Rogers[4], E Hasrouni[1], J Phillips[1], MA Sekeres[1,5], AH Heuer[2], Y Sauntharajah[1,5], J Barnard[6] and RV Tiu[1,5]





SF3B1 mutations lead to a different iron pattern in cells from MDS-RS patients.
There is an abundant iron deposits in an SF3B1 mutant

Non-transferrin-bound iron (NTBI) and labile plasma iron (LPI)

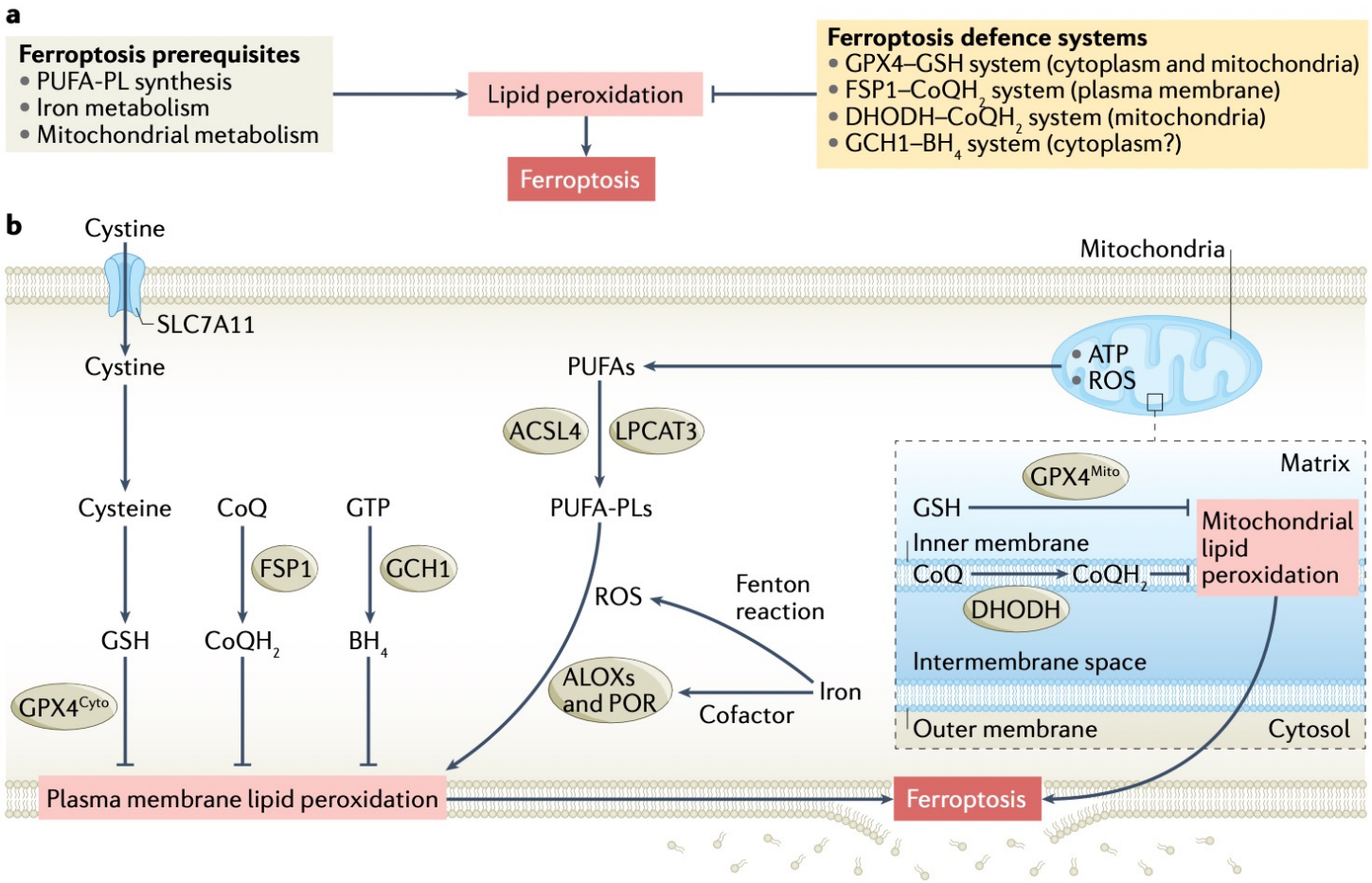


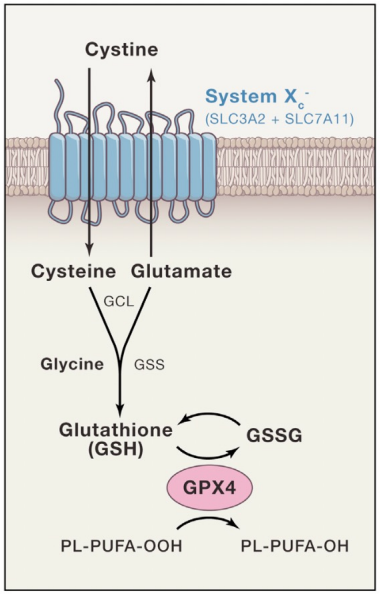
NTBI appears when plasma iron exceeds transferrin binding capacity (saturation > 60–70%)

LPI is a chelatable redox-active component of NTBI

1. Hershko C, Peto TE. Br J Haematol. 1987;66:149-51.
2. Cabantchik ZI, et al. Best Pract Res Clin Haematol. 2005;18:277-87.

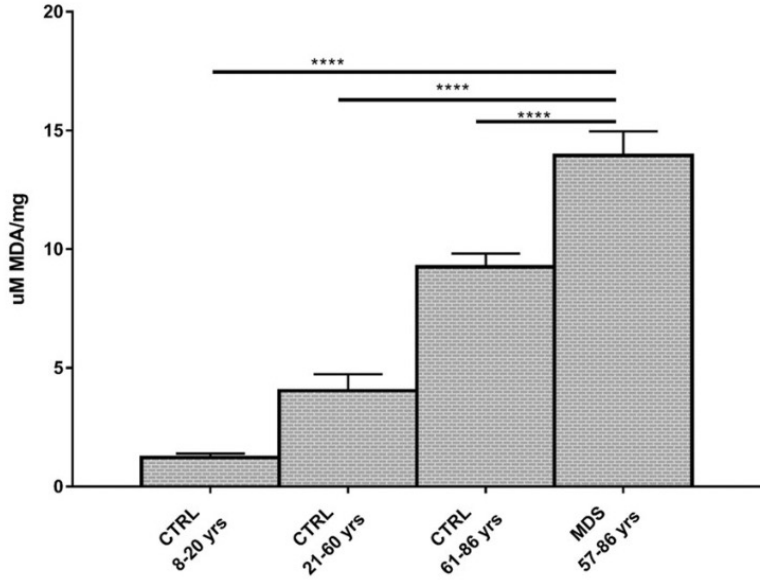
Ferroptosis is a form of regulated cell death that occurs as a consequence of lethal lipid peroxidation

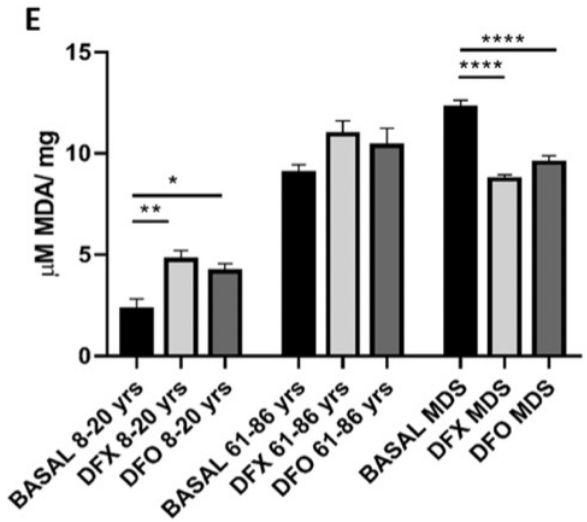




Lei G. et al. Nat Rev 2022

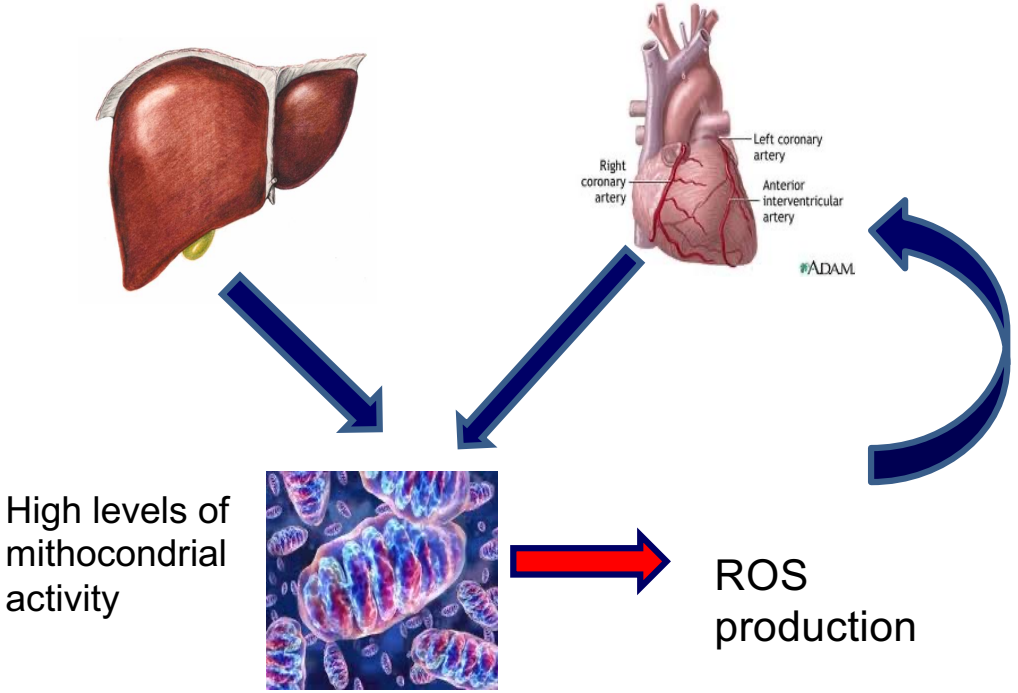
Iron overload alters the energy metabolism in patients with myelodysplastic syndromes: results from the multicenter FISM BIOFER study





Cilloni D et al Sci Rep 2020

Iron accumulation is tissue specific
The damage of iron is different in different tissues



Type of ferritin: L-ferritin is better suited to iron storage compared to H-ferritin

Concentration of transferrin receptor

Antioxidant capacity

$$\text{Fe toxicity}_{\text{tissue}} \cong \Sigma\ \text{tissue iron concentration} \times \text{genetics} \times \text{environmental factors} \times \Delta\text{time}.$$

Genetic:

genetic differences in:

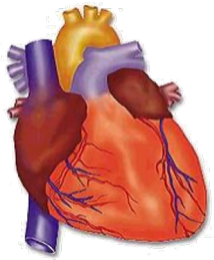
- Antioxidant defense mechanisms
- iron transport
- Marrow pathology (i.e β-thalassemia vs SCD)

- **Environmental factors**
- nutritional status deficiency (thamine deficiency, vit D, Vit C, etc)
- Blood transfusions
- Iron chelation
- Concomitant drugs

Chronic exposure to NTBI

From iron overload to chronic exposure

detectable only after 75-100 units of RBC,

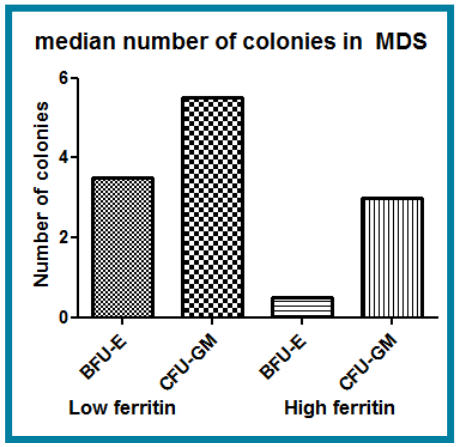


but ...

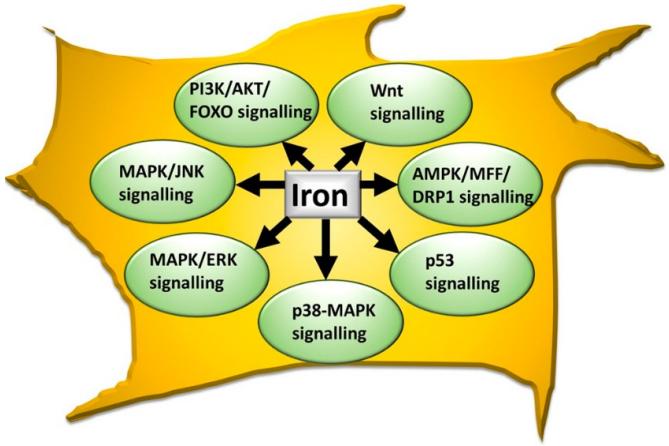
cardiac function may be more vulnerable than liver function

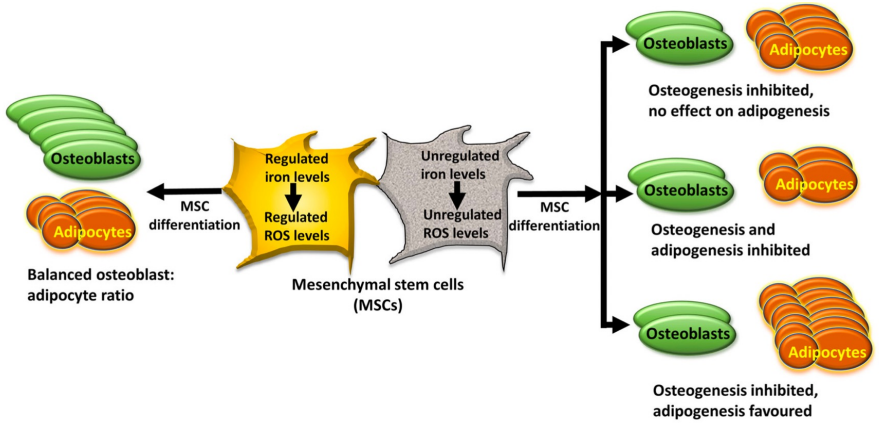
- **... may not only depend on the degree of tissue iron accumulation**
- **... but may also be related to chronic exposure to NTBI/LPI ROS**

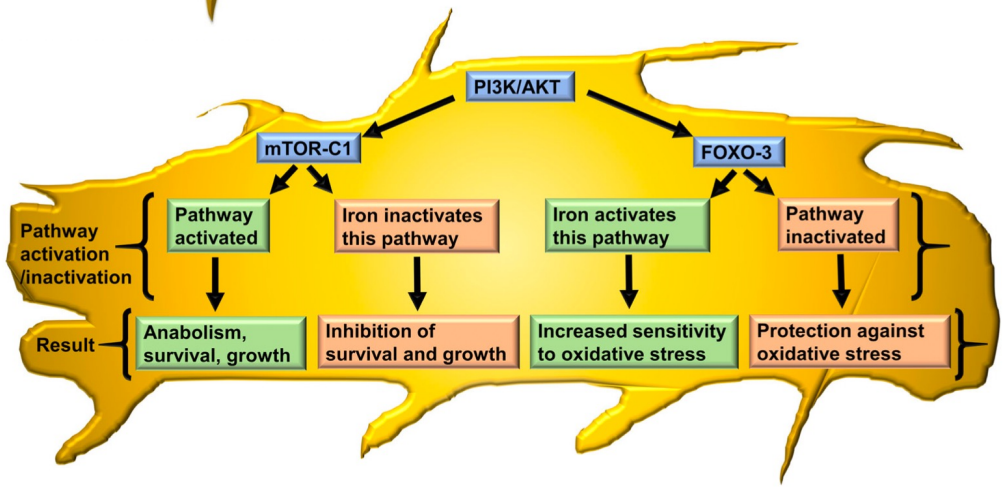
Role of iron in hematopoietic and mesenchymal stem cells



Hartmann J, et al. Blood. 2008;112



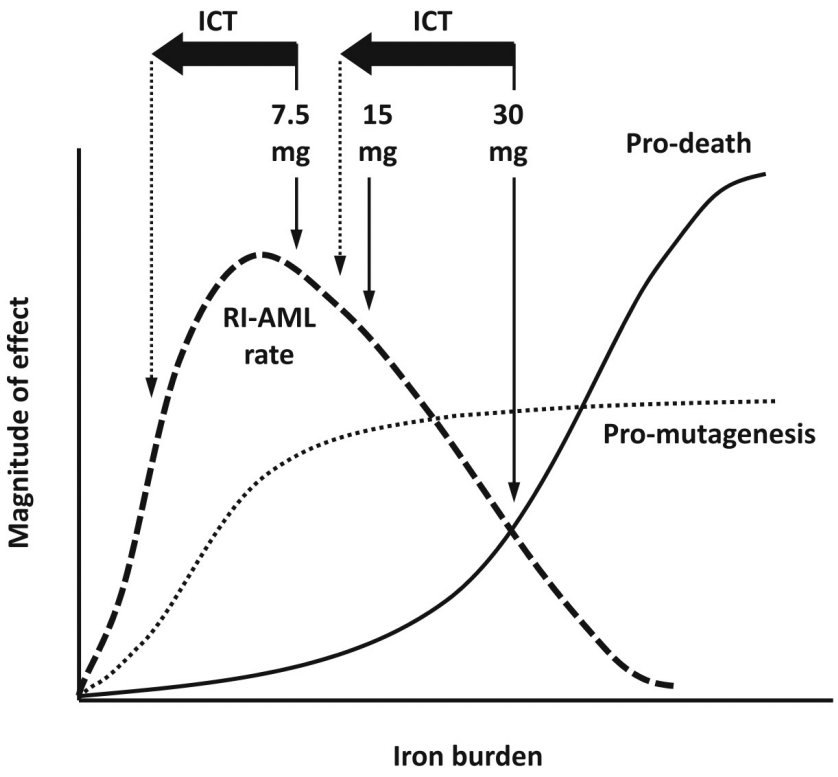




Mehta KJ. J Cell Physiol. 2021;236:7266–7289.

The effects of secondary iron overload and iron chelation on a radiation-induced acute myeloid leukemia mouse model

Lap Shu Alan Chan[1,2*], Lilly ChunHong Gu[1] and Richard A. Wells[1,2,3,4]

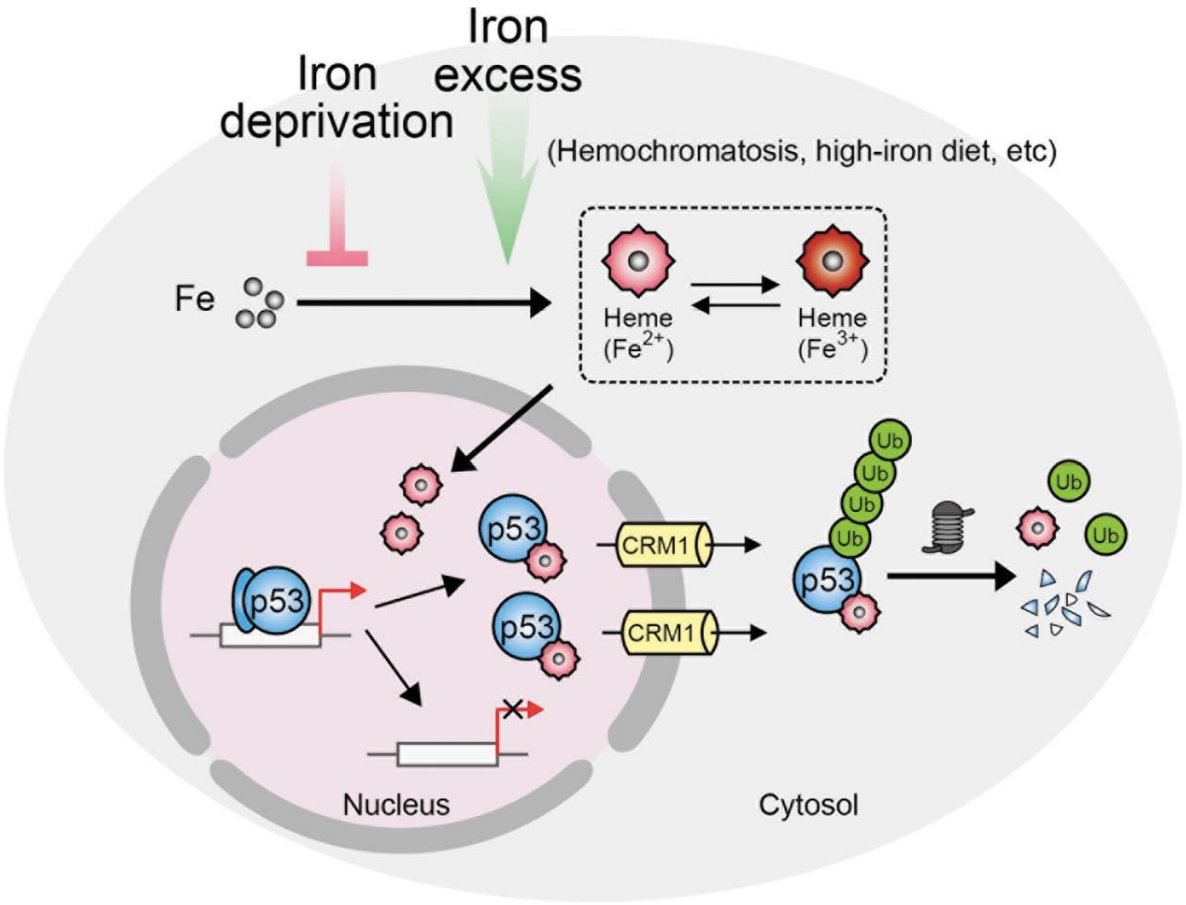


Iron is a promoter of leukemogenesis in vivo up to a peak iron dose, but further iron loading decreases AML risk by increasing cell death.

ICT can partially mitigate the adverse effects of iron overload, and to maximize its benefit this intervention should be undertaken prior to the development of extreme iron overload.

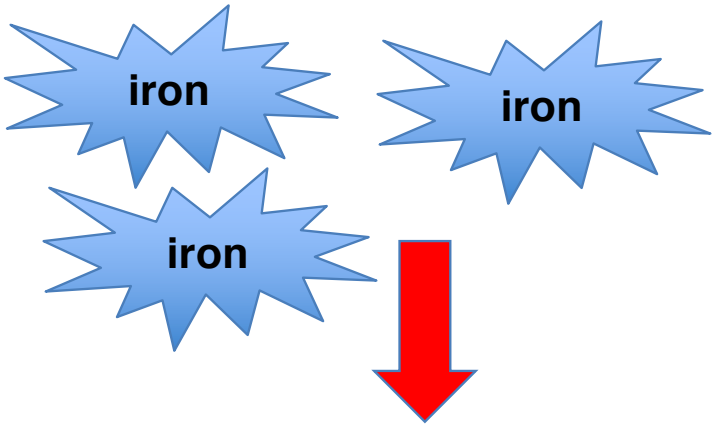
BMC Cancer 2021:21:509

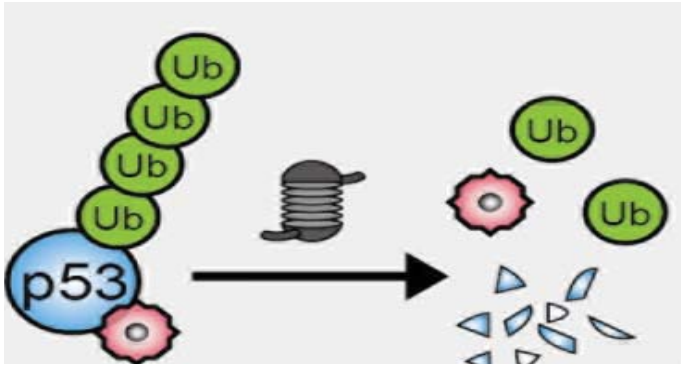
Iron excess favors p53 degradation



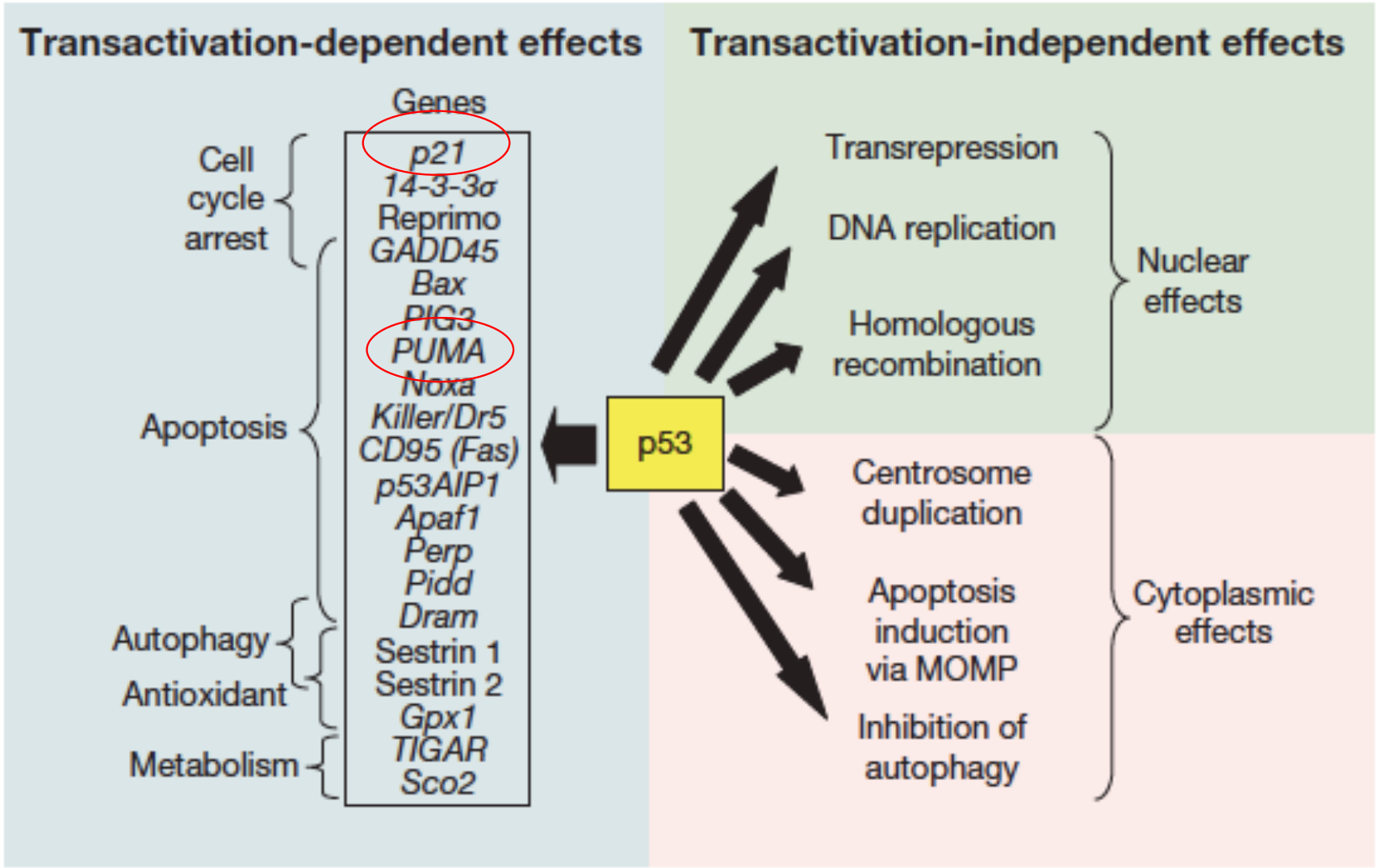
Shen J, et al. Molecular and cellular oncology 2014

P53 è un potente oncosoppressore



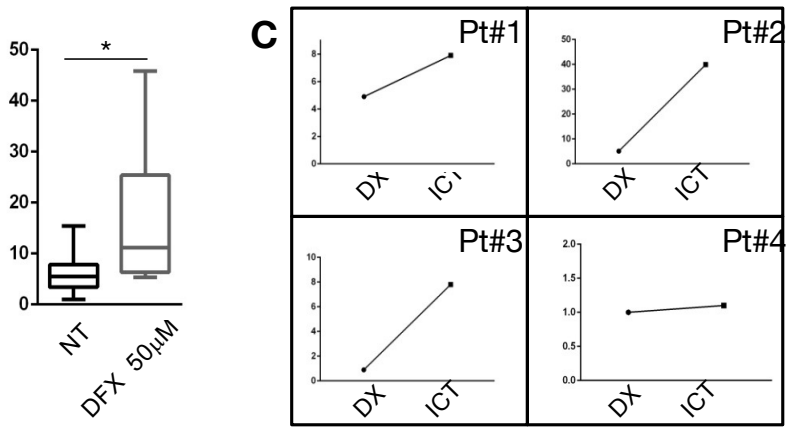


P53 deficiency

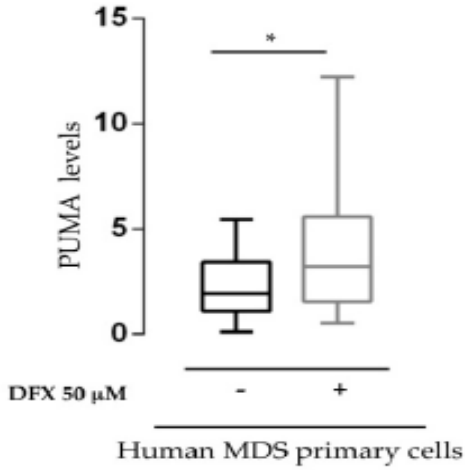

Transactivation-dependent effects
Transactivation-independent effects
Genes
Cell cycle arrest
p21
14-3-3σ
Reprimo
Apoptosis
GADD45
Bax
PIG3
PUMA
Noxa
Killer/Dr5
CD95 (Fas)
p53AIP1
Apaf1
Perp
Pidd
Autophagy
Dram
Antioxidant
Sestrin 1
Sestrin 2
Gpx1
Metabolism
TIGAR
Sco2
p53
Transrepression
DNA replication
Homologous recombination
Nuclear effects
Centrosome duplication
Apoptosis induction via MOMP
Inhibition of autophagy
Cytoplasmic effects

Iron chelation increases the level of P21 and PUMA

P21 expression in primary cells

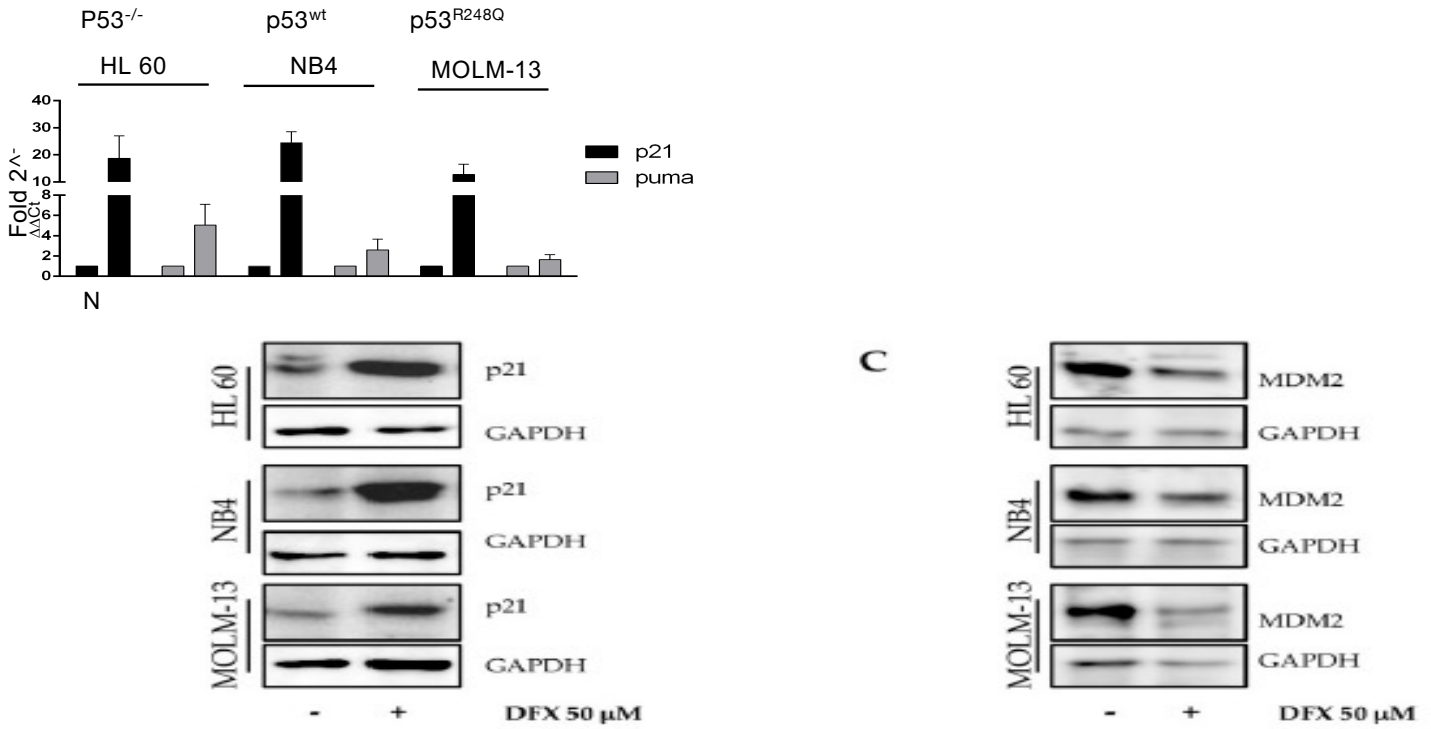


PUMA expression



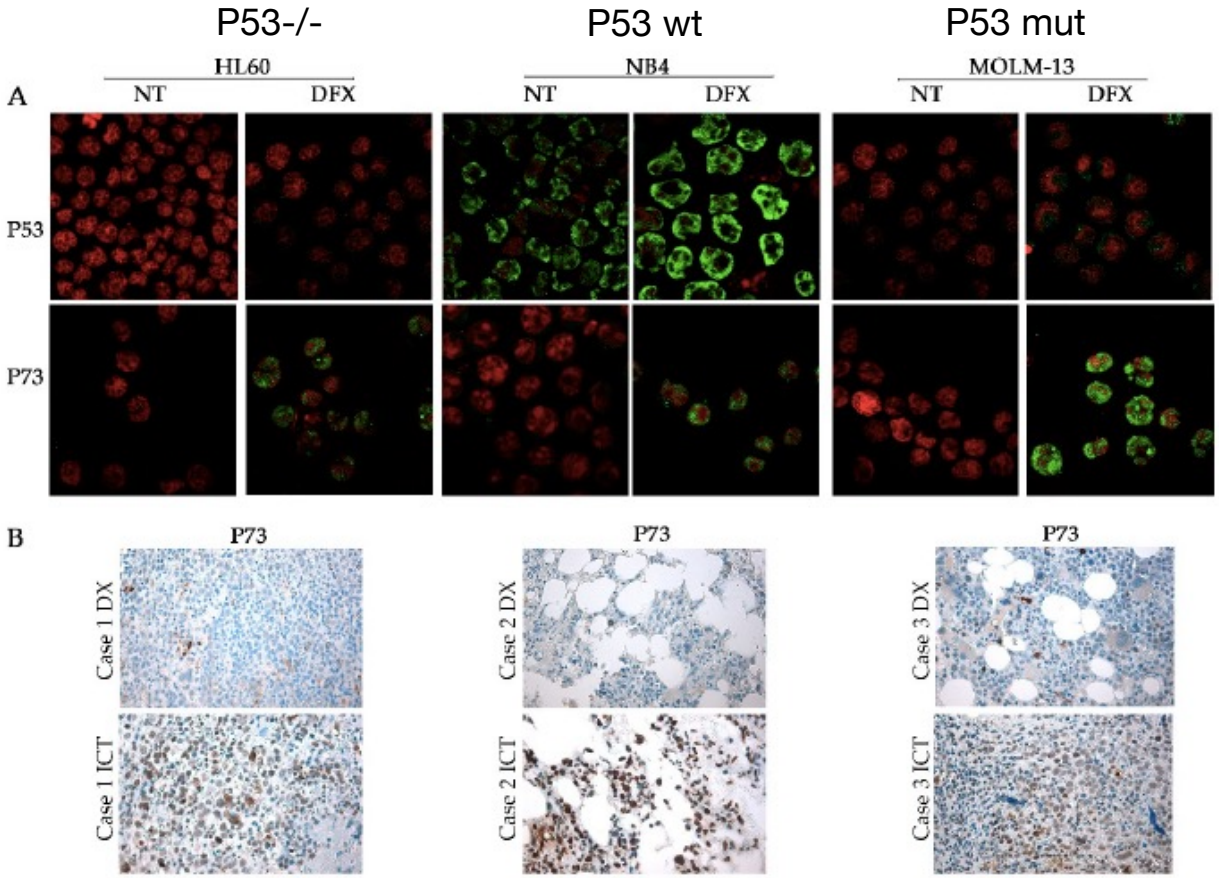
Calabrese C. et al. Int J Mol Sci 2020

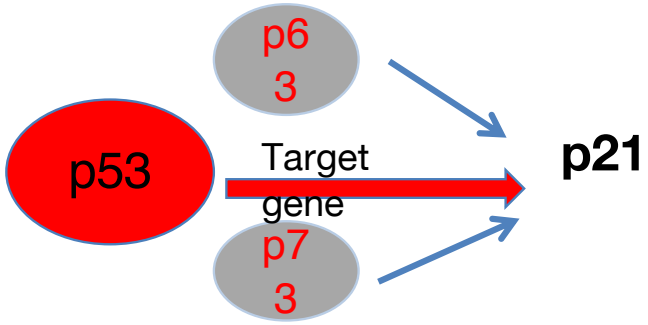
P21 e PUMA sono trascritti anche nelle cellule che non hanno p53



Calabrese C. et al. Int J Mol Sci 2020

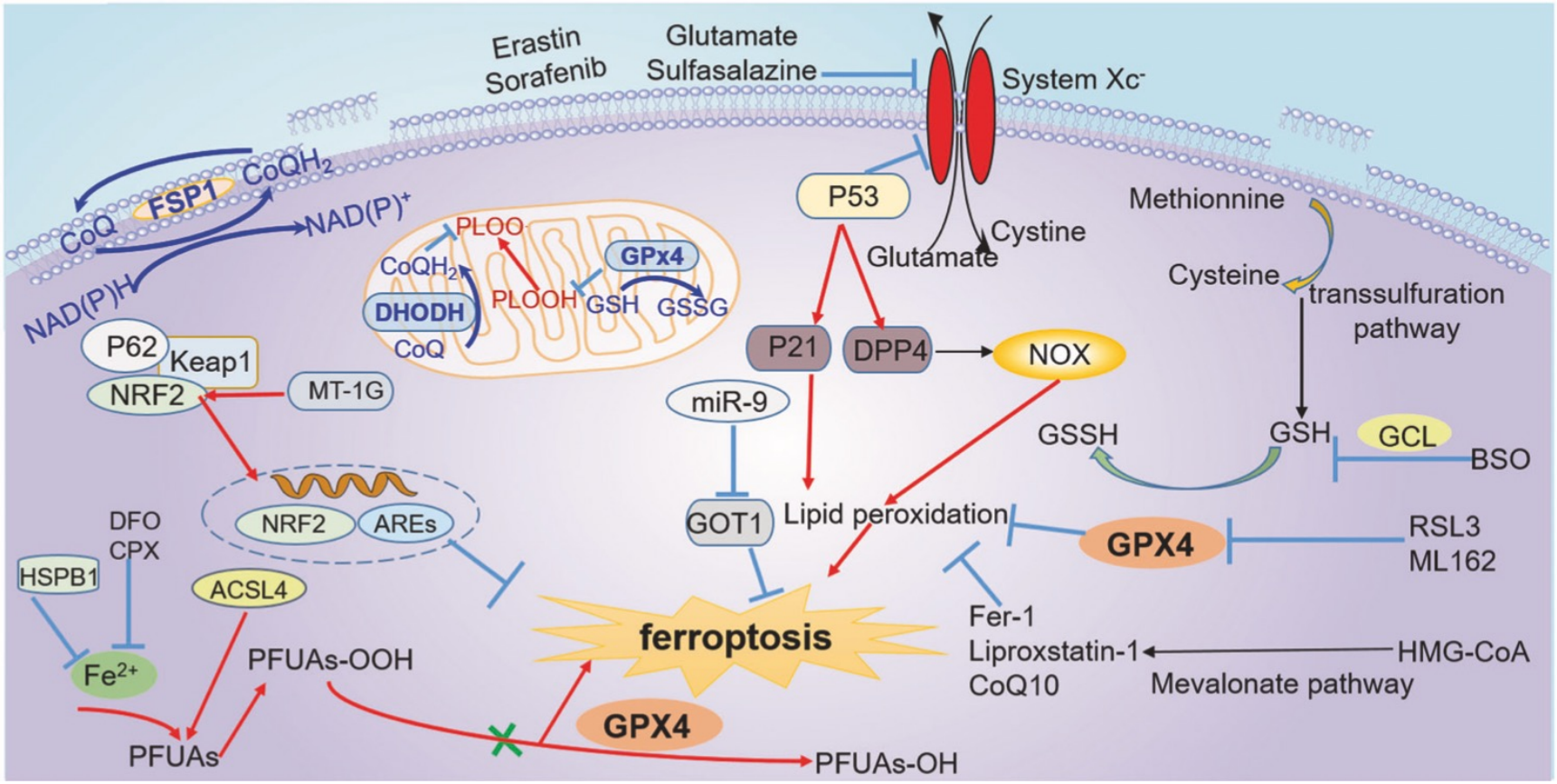
Iron chelation reactivates p53 and its family members p63 and p73



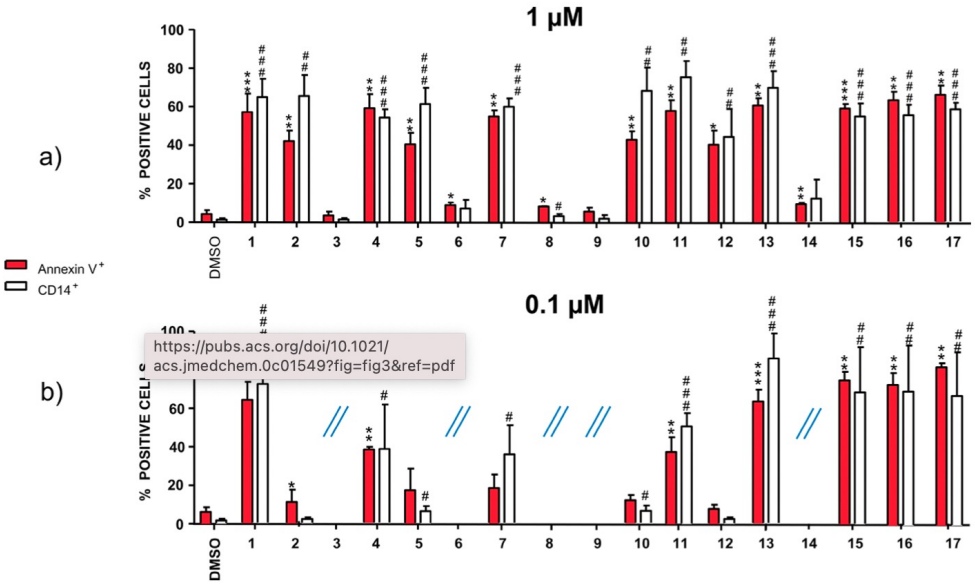


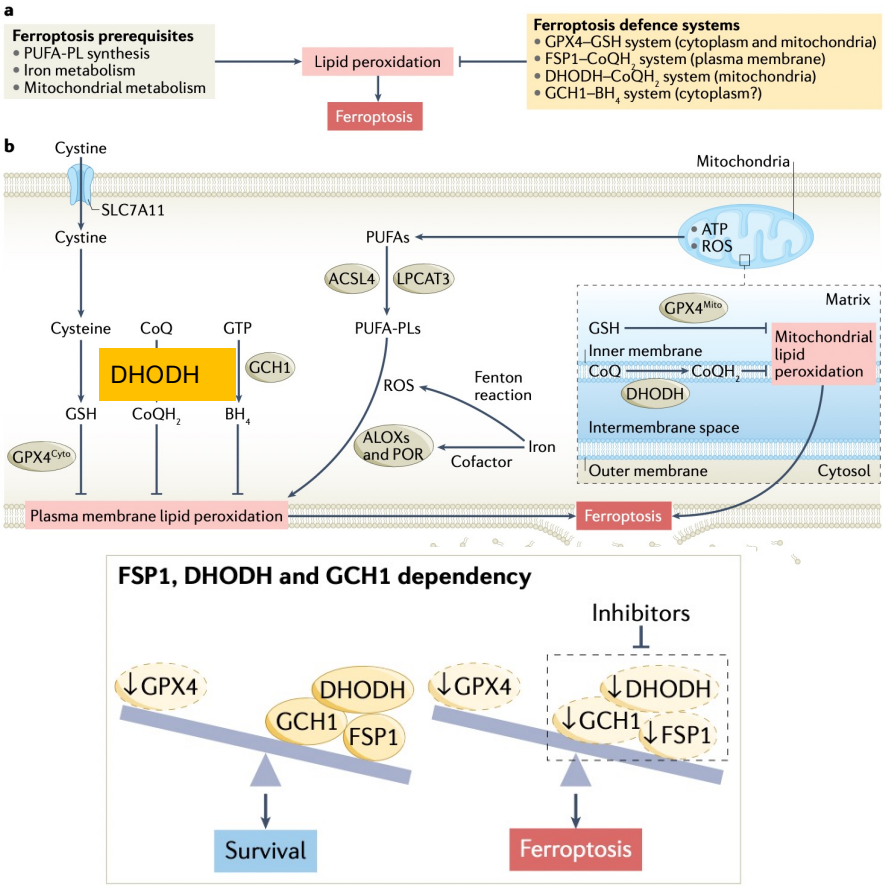
Calabrese C. et al. Int J Mol Sci 2020

Ferroptosi è sempre negativa?



DHODH inhibitors have antileukemic effects





Sainas S. et al. J. Med. Chem. 2021, 64, 5404−5428