

Iron Deficiency Anemia and Thrombocytosis: An Increasingly Unsurprising Duo

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IRON DEFICIENCY AND THROMBOCYTOSIS

Presentation Goals

Overview:

- ✓ Iron Deficiency Anemia
- ✓ Thrombocytosis

Current Literature Findings:

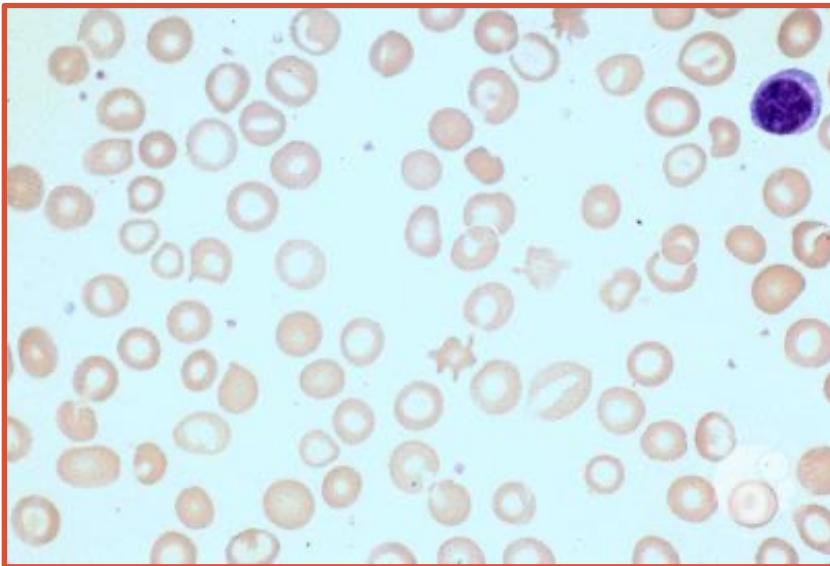
- ✓ Documented severity and incidence
- ✓ Possible mechanistic causes
- ✓ Resolution and possible complications

Self-Study Findings

Iron Deficiency Anemia (IDA)

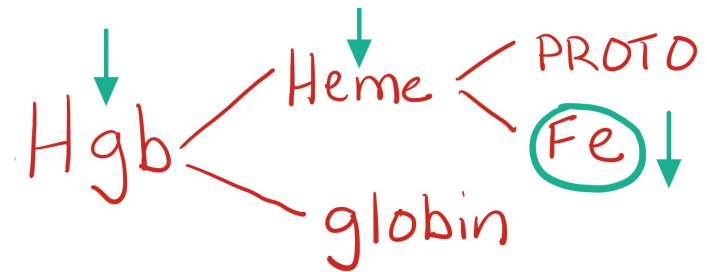
- Statistics

- ✓ Affects > 1.2 billion world-wide
- ✓ Most common type of anemia!



- Characteristics

- ✓ Decreased iron which affects hemoglobin synthesis
 - Dietary
 - Chronic Bleed



- ✓ Microcytic Hypochromic Anemia

Iron Deficiency Anemia (IDA)

- Correlating Laboratory Data

- ✓ Microcytic Hypochromic Anemia

↓ Hgb/Hct
↓ MCV
↓ MCHC

Severity	Hemoglobin (g/dL)
Mild	↓ than normal but > 10
Moderate	10 - 7
Severe	< 7

- ✓ Altered Iron Panel

Serum Iron	TIBC	%SAT	Ferritin
↓	↑	↓	↓

Iron Deficiency Anemia (IDA)

- Correlating Laboratory Data

- ✓ Altered Platelet Results?!

Severity	Hemoglobin (g/dL)
Mild	↓ than normal but > 10
Moderate	10 - 7
Severe	< 7



Thrombocytosis (↑ Platelet #)



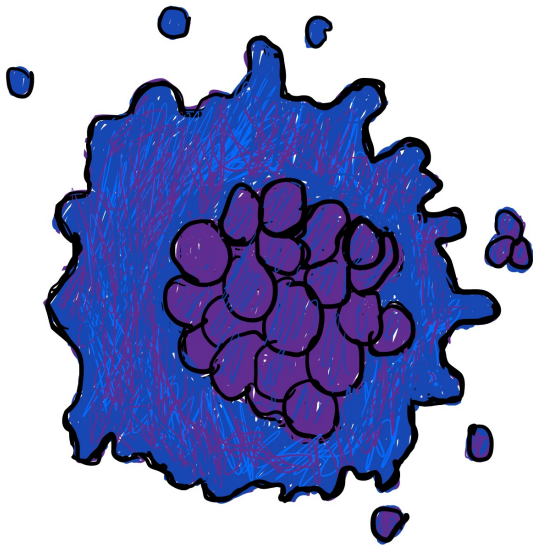
Thrombocytopenia (↓ Platelet #)

IDA + THROMBOCYTOSIS

Definition

Thrombocytosis: Definition

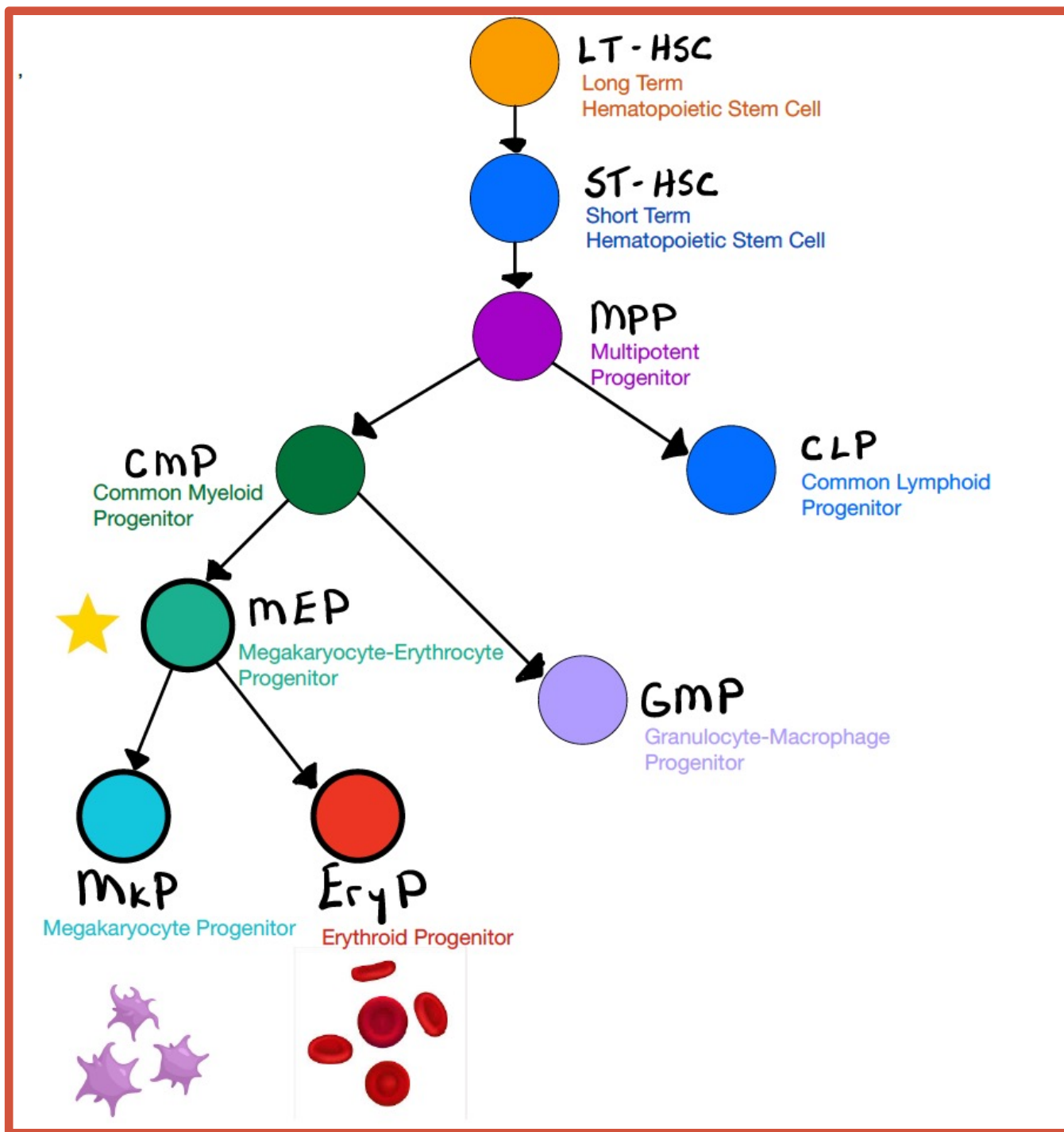
Platelets are cytoplasmic fragments of megakaryocytes



Normal platelet count: 140,000 – 440,000 cells/ μ L

- Thrombocytosis > 450,000 cells/ μ L
- Thrombocytopenia < 100,000 cells/ μ L

Hematopoiesis: Classical Pathway



LT-HSC
Long Term
Hematopoietic Stem Cell

ST-HSC
Short Term
Hematopoietic Stem Cell

MPP
Multipotent
Progenitor

CLP
Common Lymphoid
Progenitor

CMp
Common Myeloid
Progenitor

mEP
Megakaryocyte-Erythrocyte
Progenitor

GMP
Granulocyte-Macrophage
Progenitor

MkP

EryP

Megakaryocyte Progenitor

Erythroid Progenitor



TPO

Thrombopoietin

IL-3

IL-6

IL-11

Interleukin

CCL-5

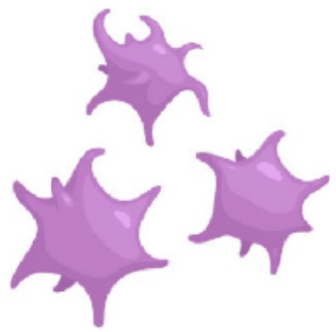
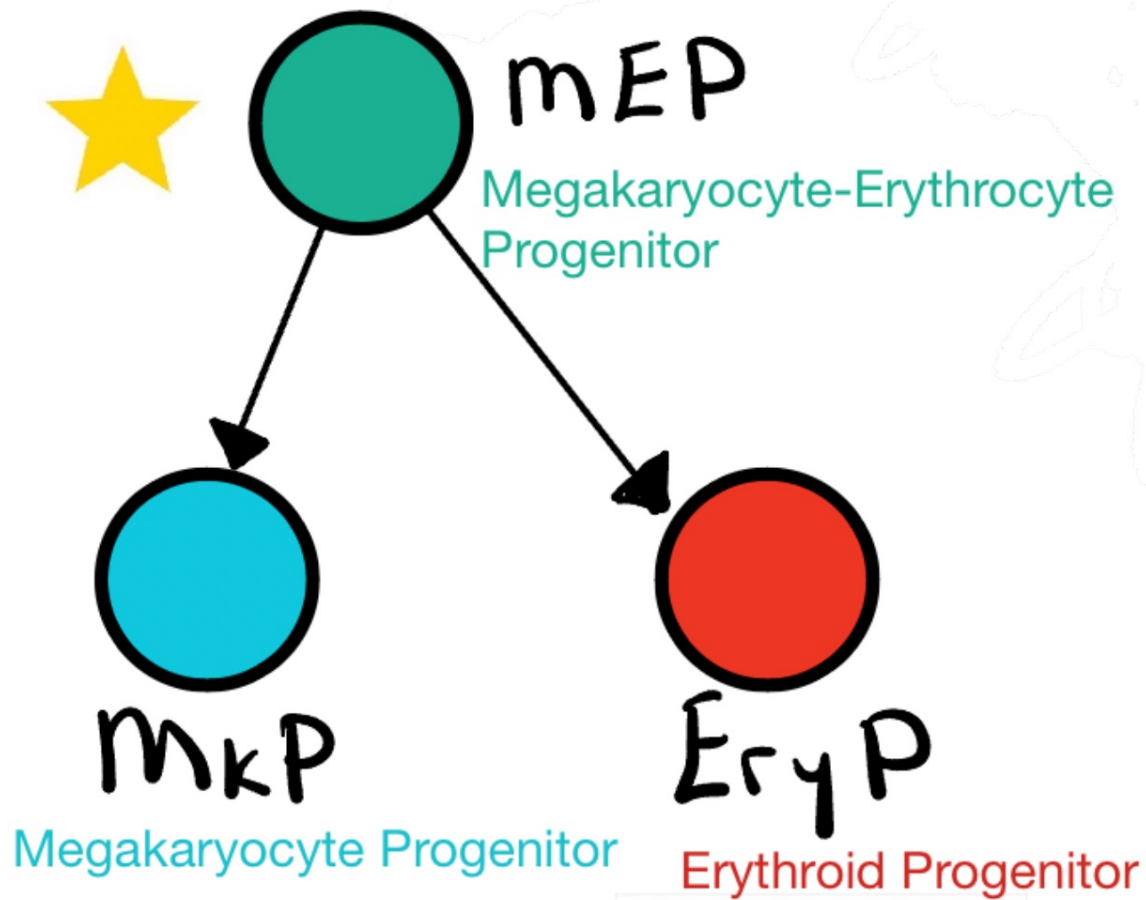
CC Chemokine Ligand

IGF-1

Insulin Growth Factor

X

Many Others

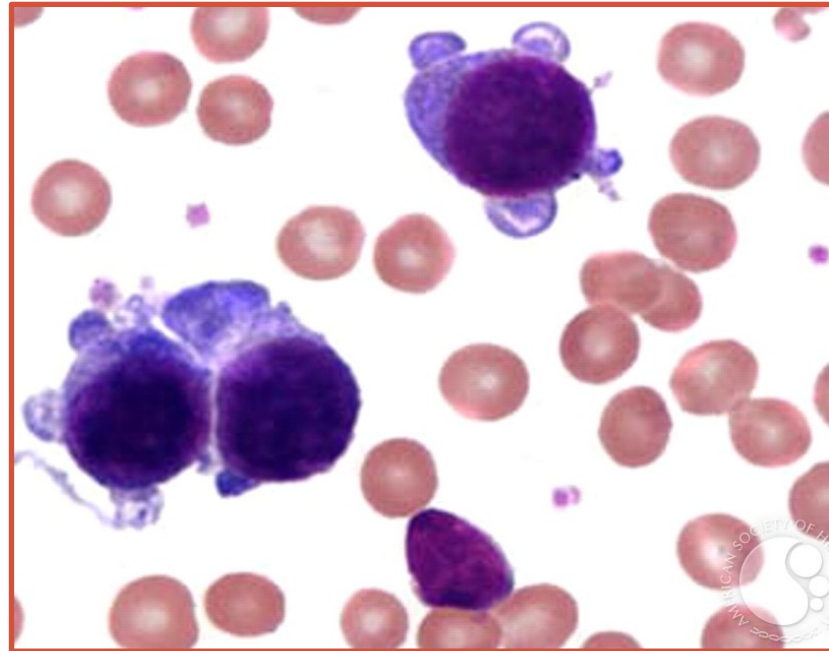


Megakaryopoiesis



MkP

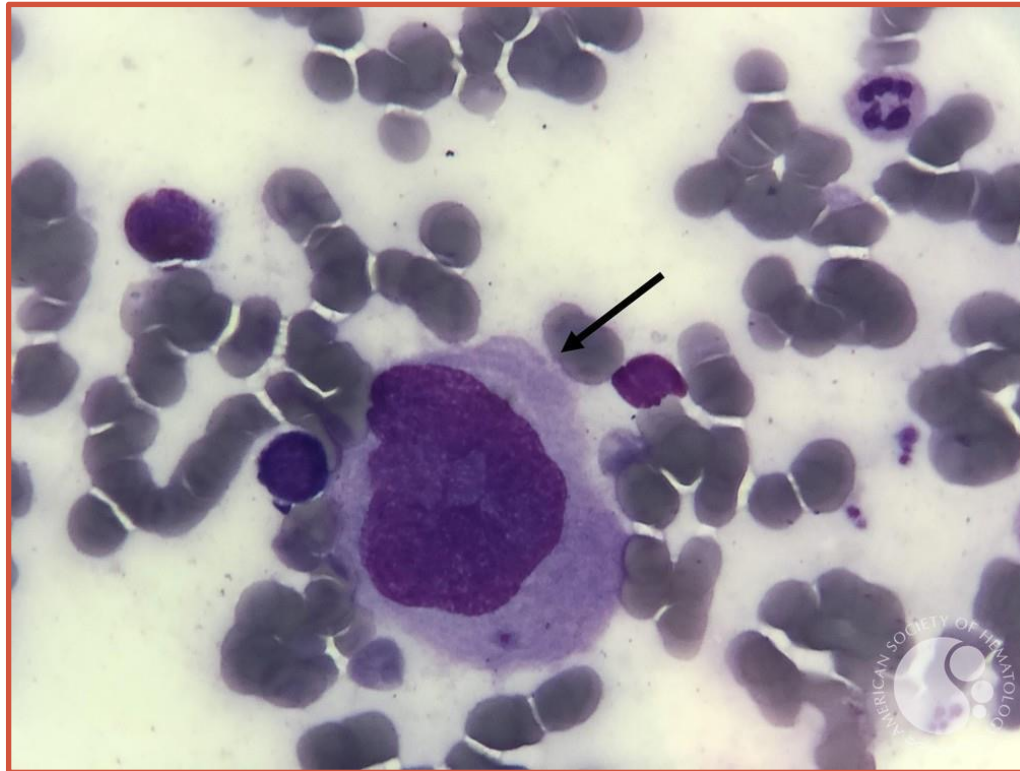
Megakaryocyte Progenitor



Megakaryoblast



Megakaryopoiesis



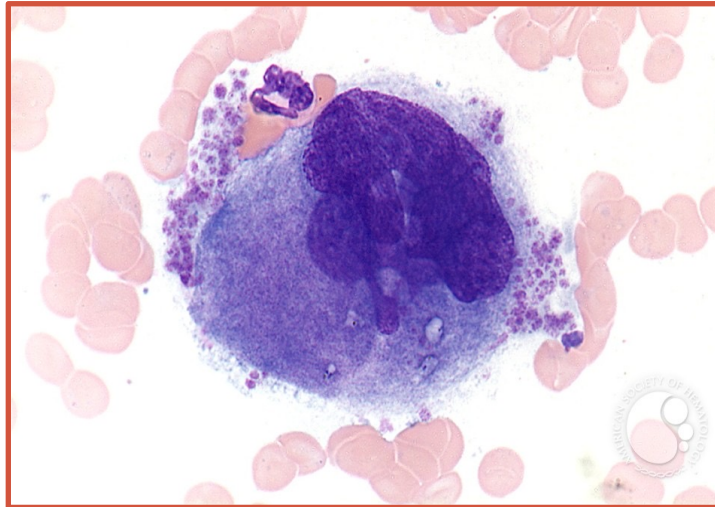
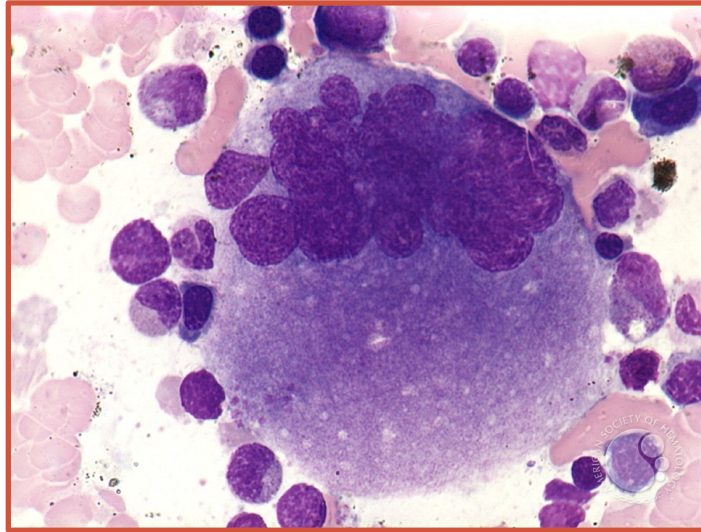
Promegakaryocyte
(Immature Megakaryocyte)



TPO

IL-6

Megakaryopoiesis



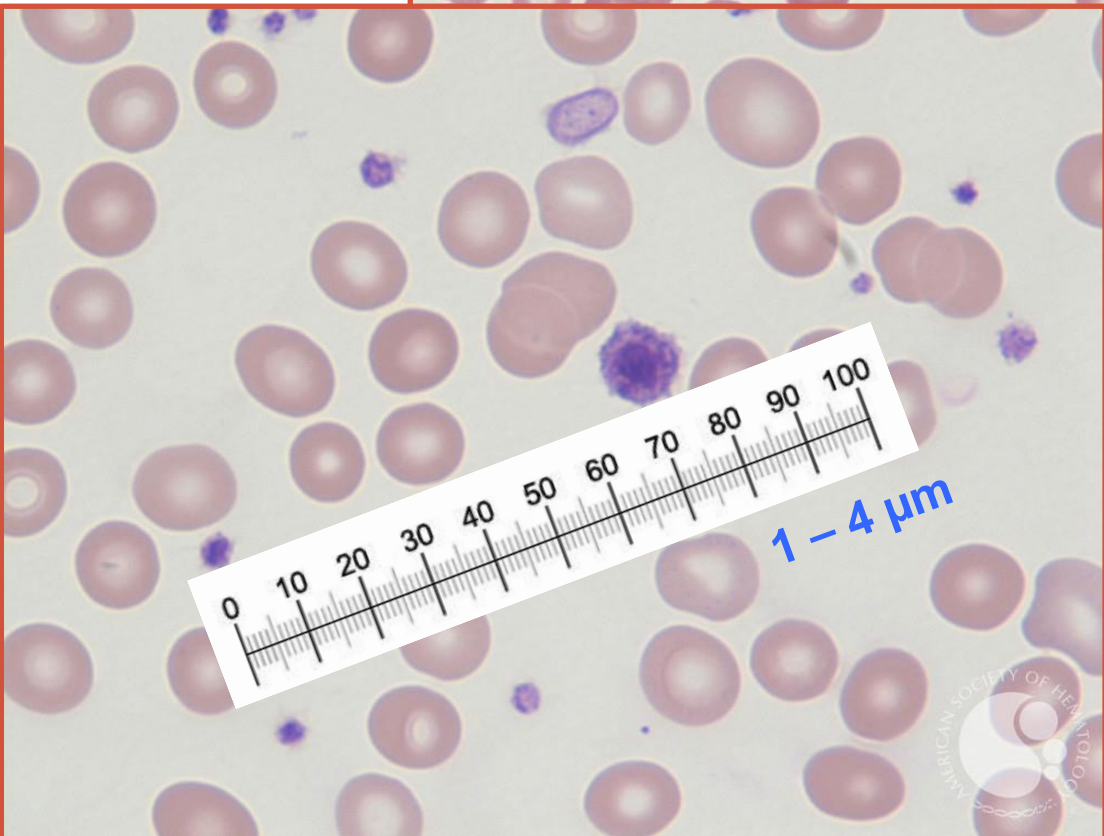
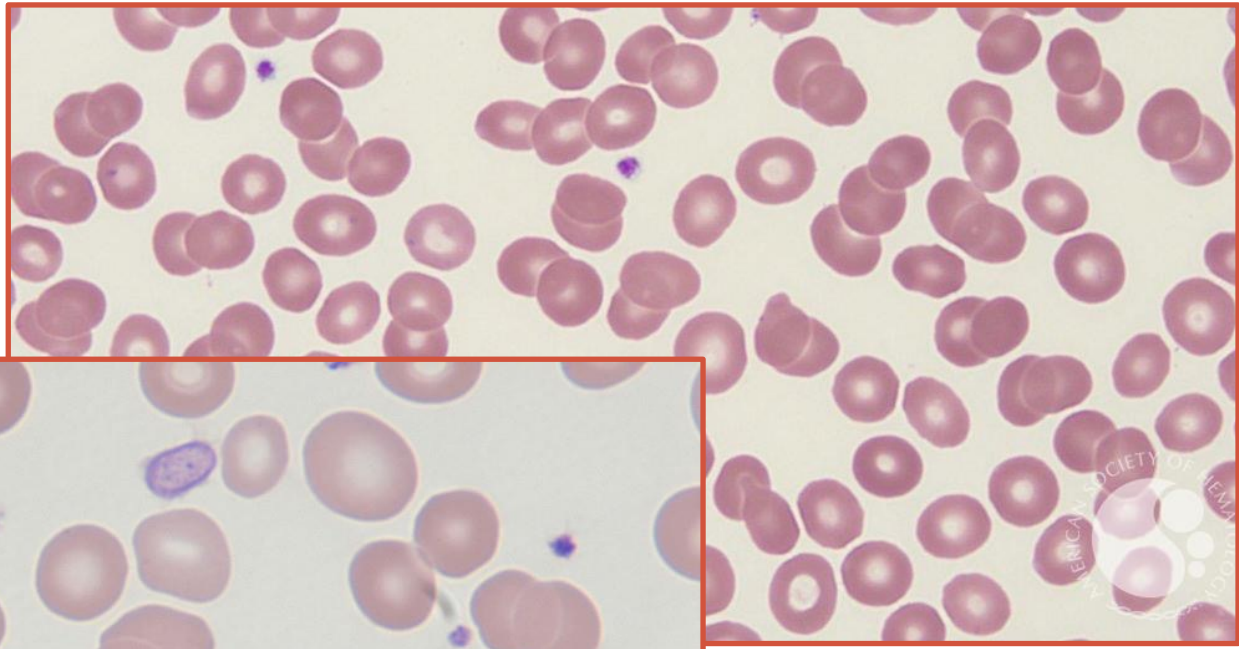
Megakaryocyte

TPO





1×10^{11} platelets released from each megakaryocyte
1,000 – 3,000 platelets enter the blood



Mature Platelet (Thrombocyte)

Thrombocytosis: Classification

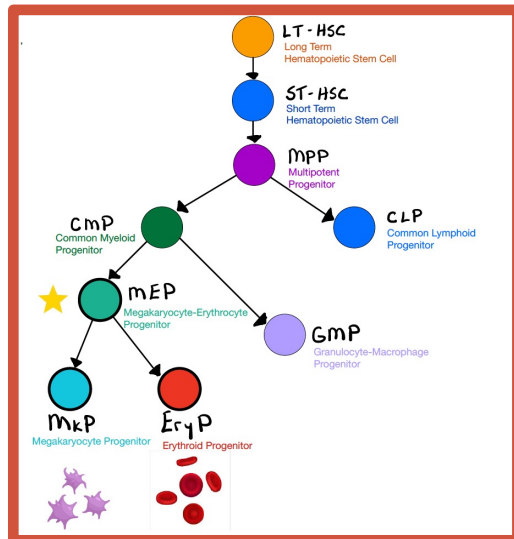
Thrombocytosis > 450,000 cells/ μ L

Thrombocytosis

1°
CLONAL

2°
REACTIVE

Myeloproliferative Process



Uncontrolled Proliferation (Leukemia)

Response to:

- Acute infection**
- Inflammation
- Post-operative stress
- Post-splenectomy
- Iron deficiency anemia!!

IDA + THROMBOCYTOSIS

Correlation Data

IDA and Thrombocytosis: DATA

- # of IDA subjects with thrombocytosis

Source	% Patients
Li, X., et al	8.1%
Kuku, I., et al	13.3%
Song, A., et al	32.6%

8 – 33%

88.1% of subjects with IDA were female



90.2% of IDA subjects with thrombocytosis were female

Kuku, I., et al

- (1) Li, X., et al (2022) Effect of iron supplementation on platelet count in adult patients with iron deficiency anemia, *Platelets*
- (2) Kuku, I., et al (2009) Platelet counts in adults with iron deficiency anemia, *Platelets*
- (3) Song, A., et al (2020) Characterization of the rate, predictors, and thrombotic complications of thrombocytosis in iron deficiency, *Am J Hematology*

IDA and Thrombocytosis: DATA

- Average platelet counts of IDA subjects with thrombocytosis

Source	Ave PLT Count
Dan, K.	499,000 cells/ μ L
Kuku, I., et al	469,000 cells/ μ L
Li, X., et al	521,670 +/- 98,720 cells/ μ L

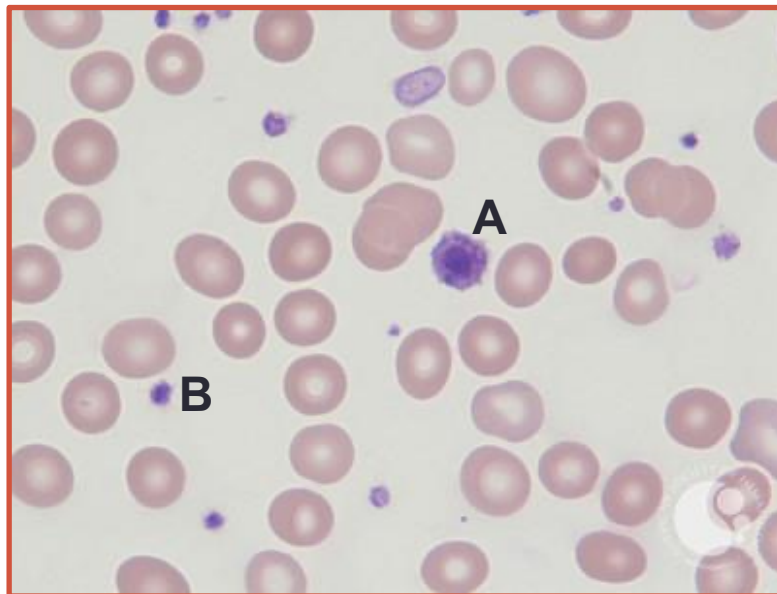
Mild Thrombocytosis
Typically < 1,000,000 cells/ μ L

- (1) Dan, K. (2005) Thrombocytosis in Iron Deficiency Anemia, *Internal Medicine*
- (2) Li, X., et al (2022) Effect of iron supplementation on platelet count in adult patients with iron deficiency anemia, *Platelets*
- (3) Kuku, I., et al (2009) Platelet counts in adults with iron deficiency anemia, *Platelets*

IDA and Thrombocytosis: DATA

- Mean Platelet Volume (MPV)

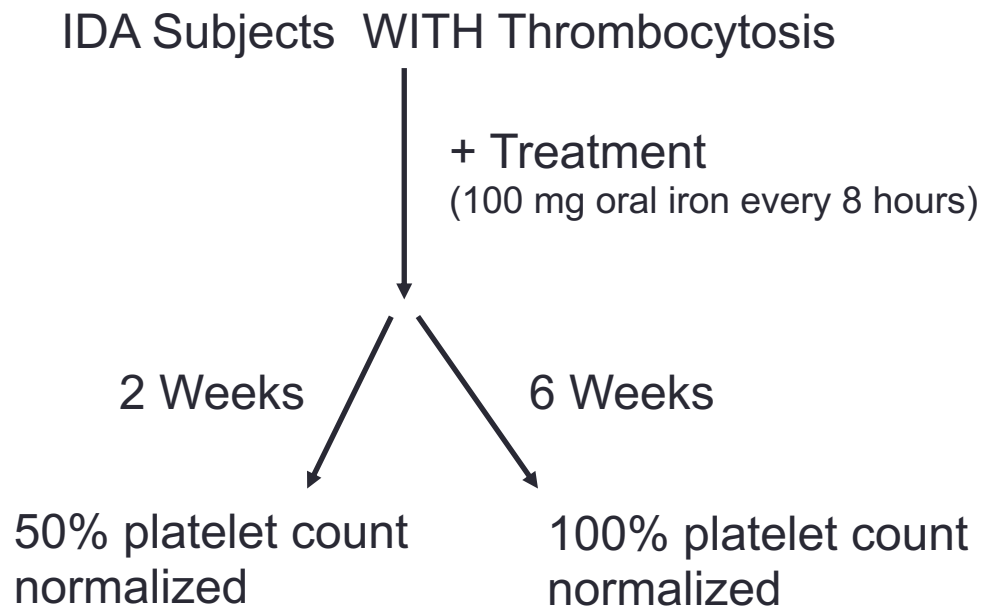
IDA with \uparrow PLT	IDA without \uparrow PLT	Reference Range
11.2	9.5	7.4 – 10.4



Source: ASH Image Bank

IDA and Thrombocytosis: DATA

- Mean time to resolve thrombocytosis



Thrombocytosis can be resolved within 6 weeks with oral iron treatment

IDA and Thrombocytosis: DATA

- Mean time to resolve IDA

IDA Subjects



+ Treatment
(100 mg oral iron every 8 hours)

Average time to resolve IDA = 8 weeks

and... IDA resolved faster if the subject initially had thrombocytosis

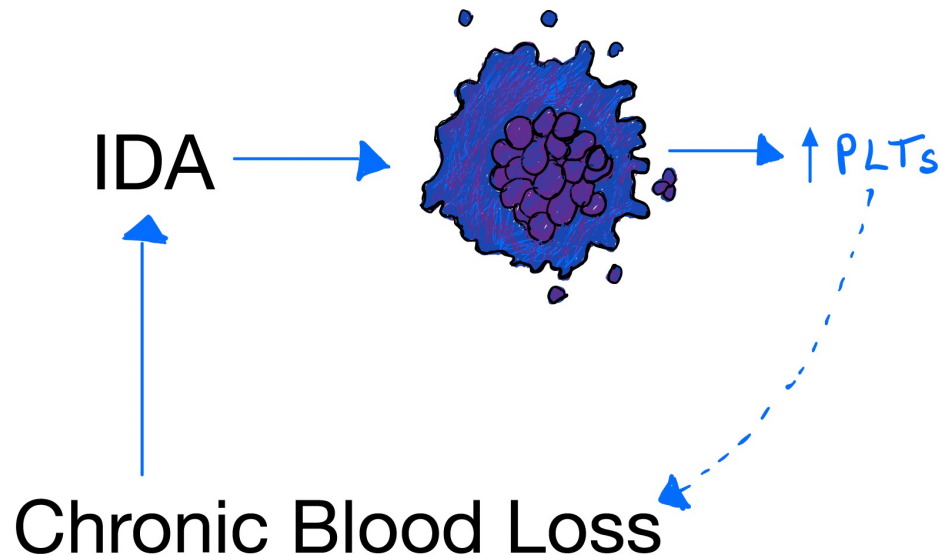
IDA + THROMBOCYTOSIS

Reasoning

IDA + Thrombocytosis = WHY?

What is the clinical significance of thrombocytosis 2° to IDA?

“IDA-induced thrombocytosis can be an adaptive mechanism to counter potential blood loss”



IDA + Thrombocytosis = WHY?

Why do only a subset of IDA patient's develop thrombocytosis?

Development may correlate with severity of iron deficiency!

	IDA with ↑ PLT	IDA without ↑ PLT	Reference Range
Hgb (g/dL)	7.975	8.860	12 – 16 (f) 13.5 – 18 (m)
MCV (fL)	70.01	73.31	80 - 100
PLT # (cells/ μ L)	521,670	291,390	140,000 – 440,000
Serum Ferritin (μ g/L)	5.05 ↓	5.59	24 – 336
% SAT (%)	4.33 ↓	5.61	29 – 50
Serum Iron (μ mol/L)	3.63 ↓	4.22	10 – 30
TIBC (μ mol/L)	80.69 ↑	75.71	43 – 81

IDA + THROMBOCYTOSIS

Possible Mechanisms

Mechanistic Cause #1

Increased Platelet Lifespan

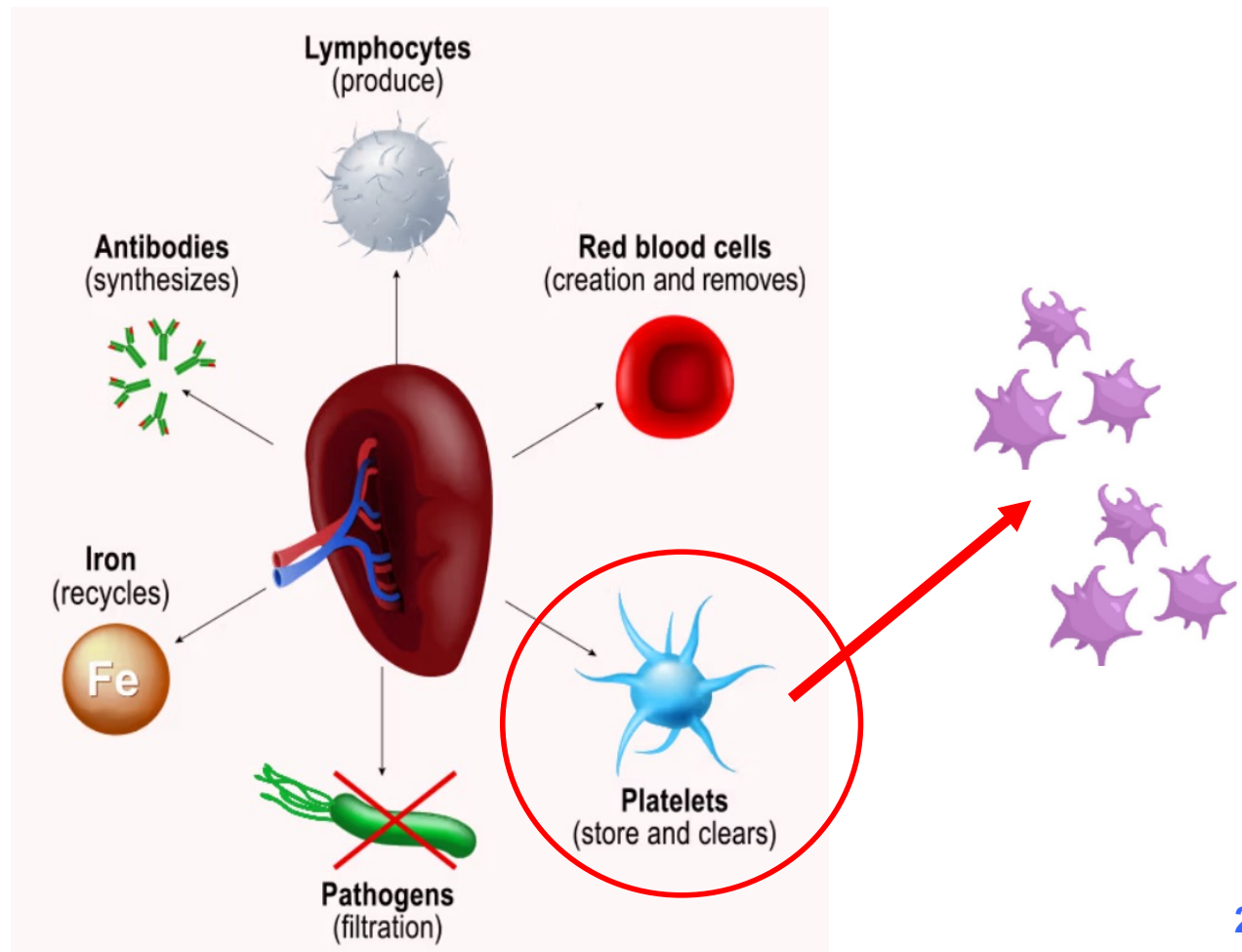


7- 10 day ~~lifespan~~

Prolonged lifespan

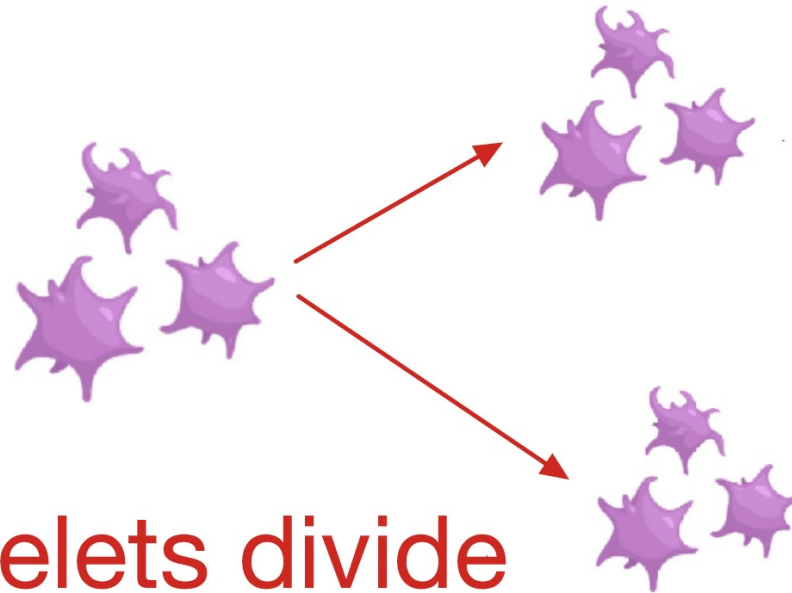
Mechanistic Cause #2

Increased Spleen Release



Mechanistic Cause #3

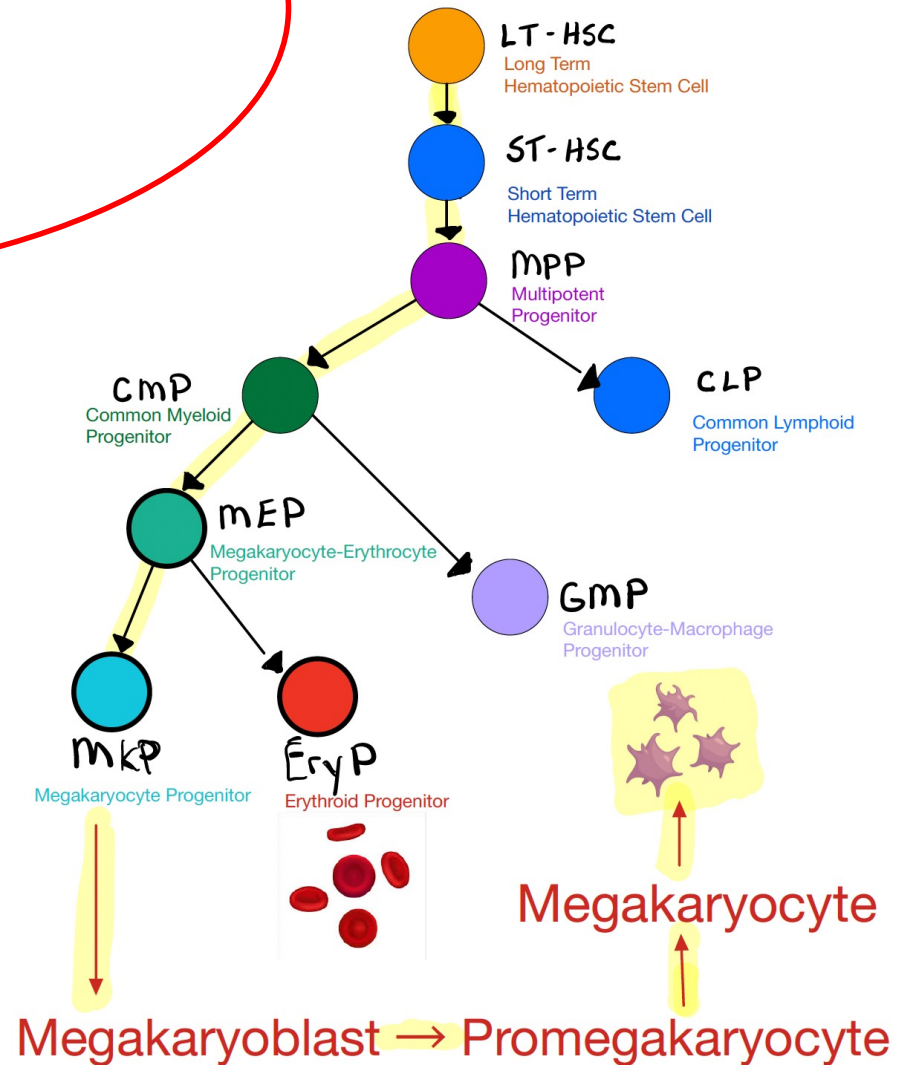
Increased Circulatory Division



Platelets divide
in circulation

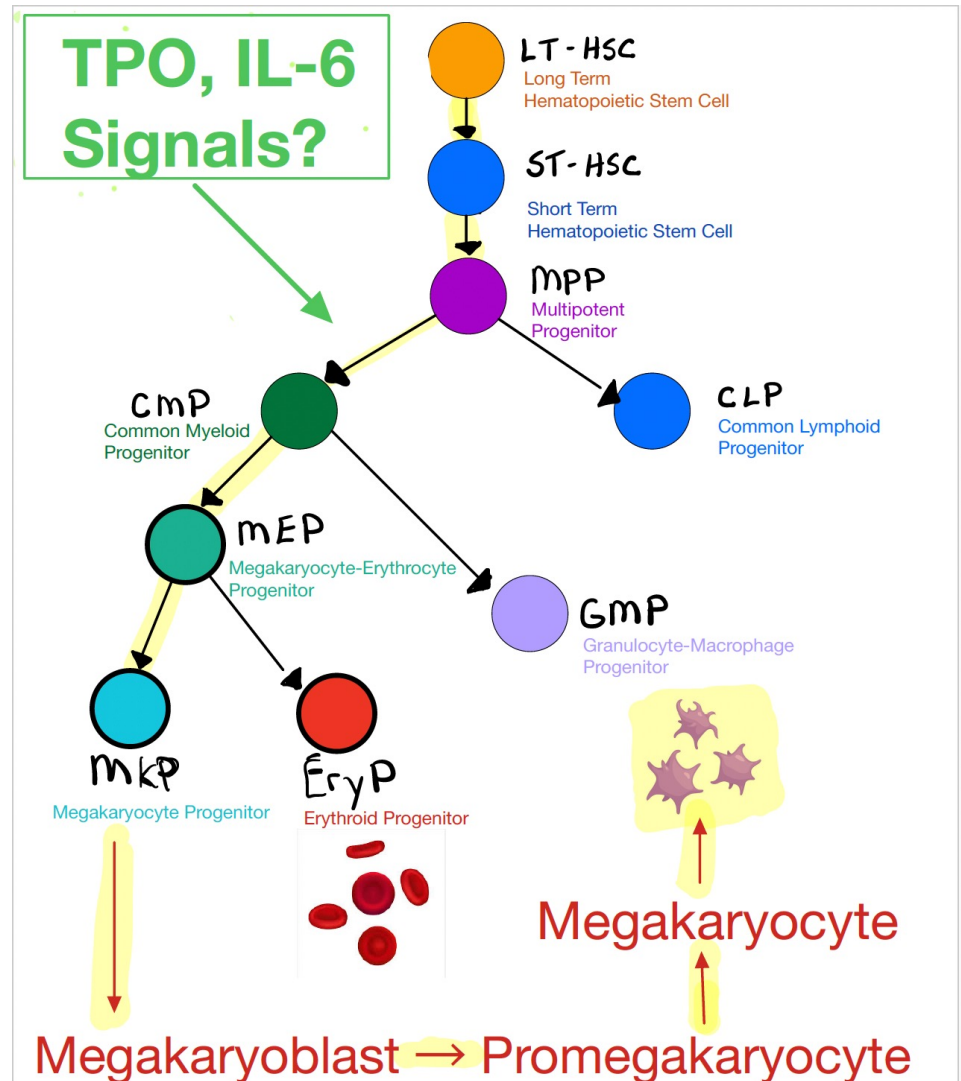
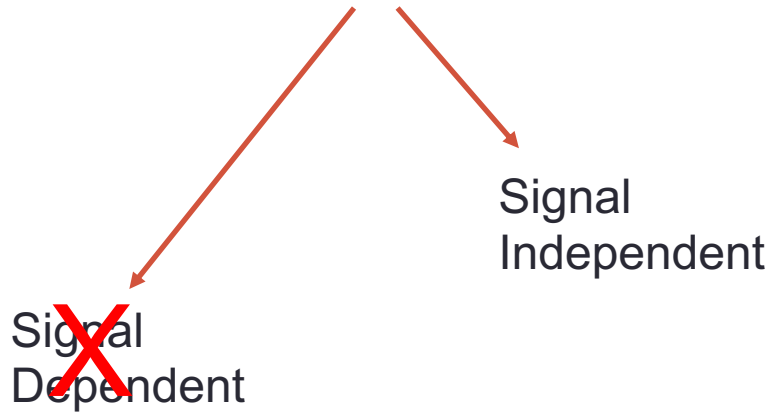
Mechanistic Cause #4

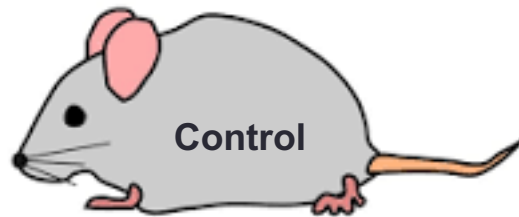
Increased Megakaryopoiesis



Current Mechanism

Increased Megakaryopoiesis





<input checked="" type="checkbox"/> Signals	Results
Thrombopoietin (TPO)	No difference
IL-3, IL-6	No difference
Erythropoietin (EPO)	Increased in ID mice



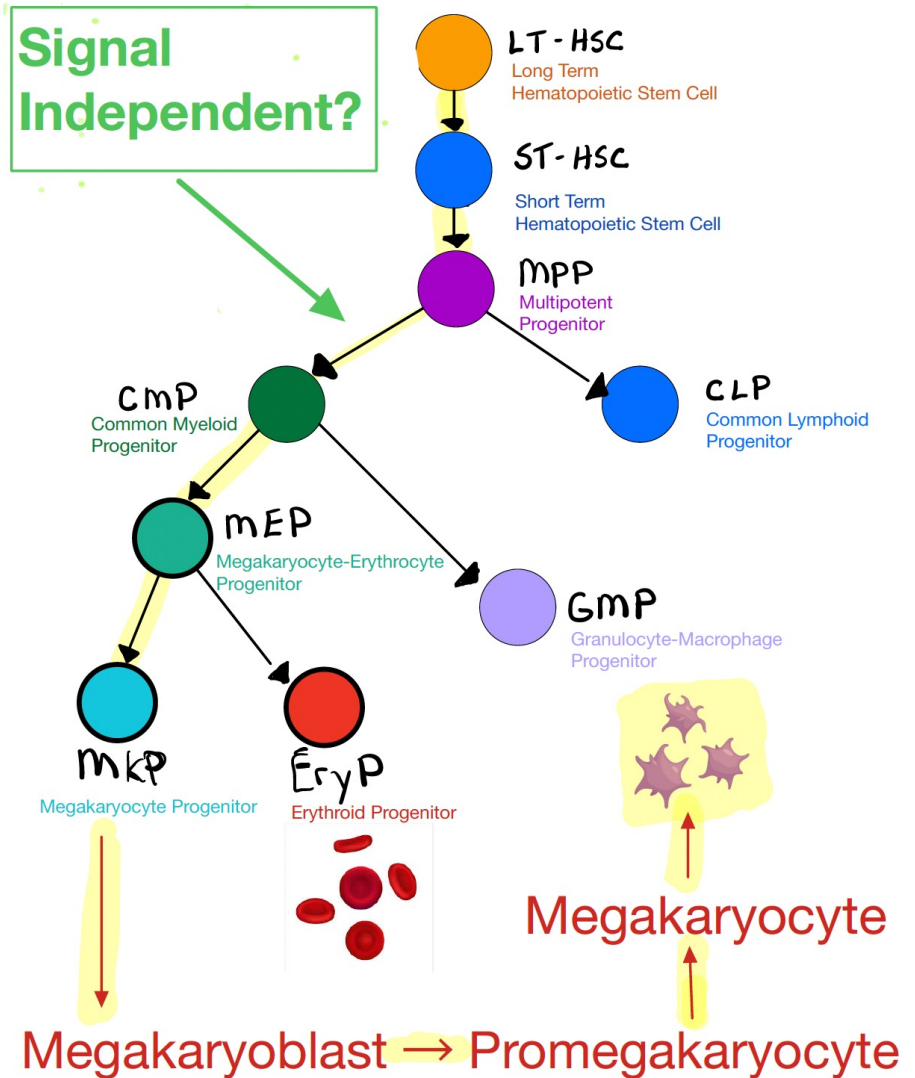
To resolve anemia!
Unlikely inducing megakaryopoiesis

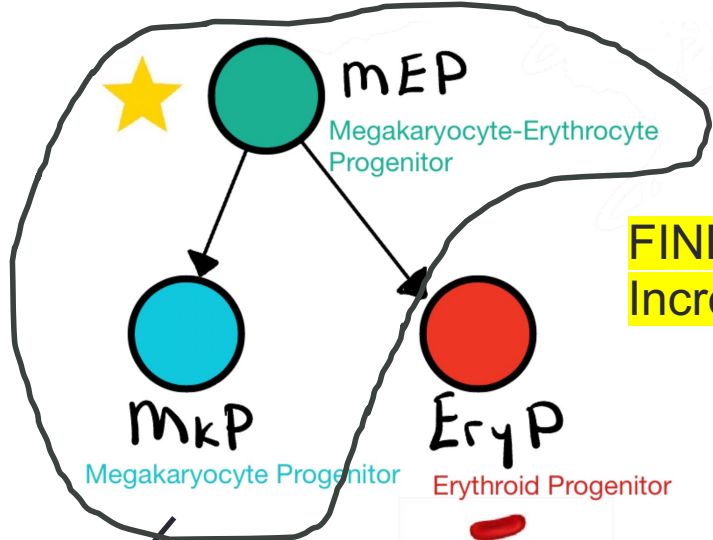
Current Mechanism

Increased Megakaryopoiesis

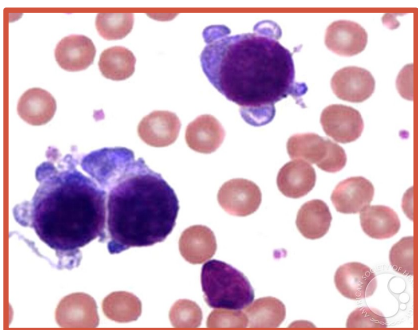
~~Signal
Dependent~~

Signal
Independent
Iron-Deficiency!





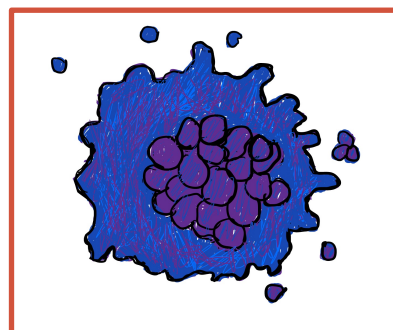
FINDING #1:
Increased MkP vs. EryP commitment



Megakaryoblast

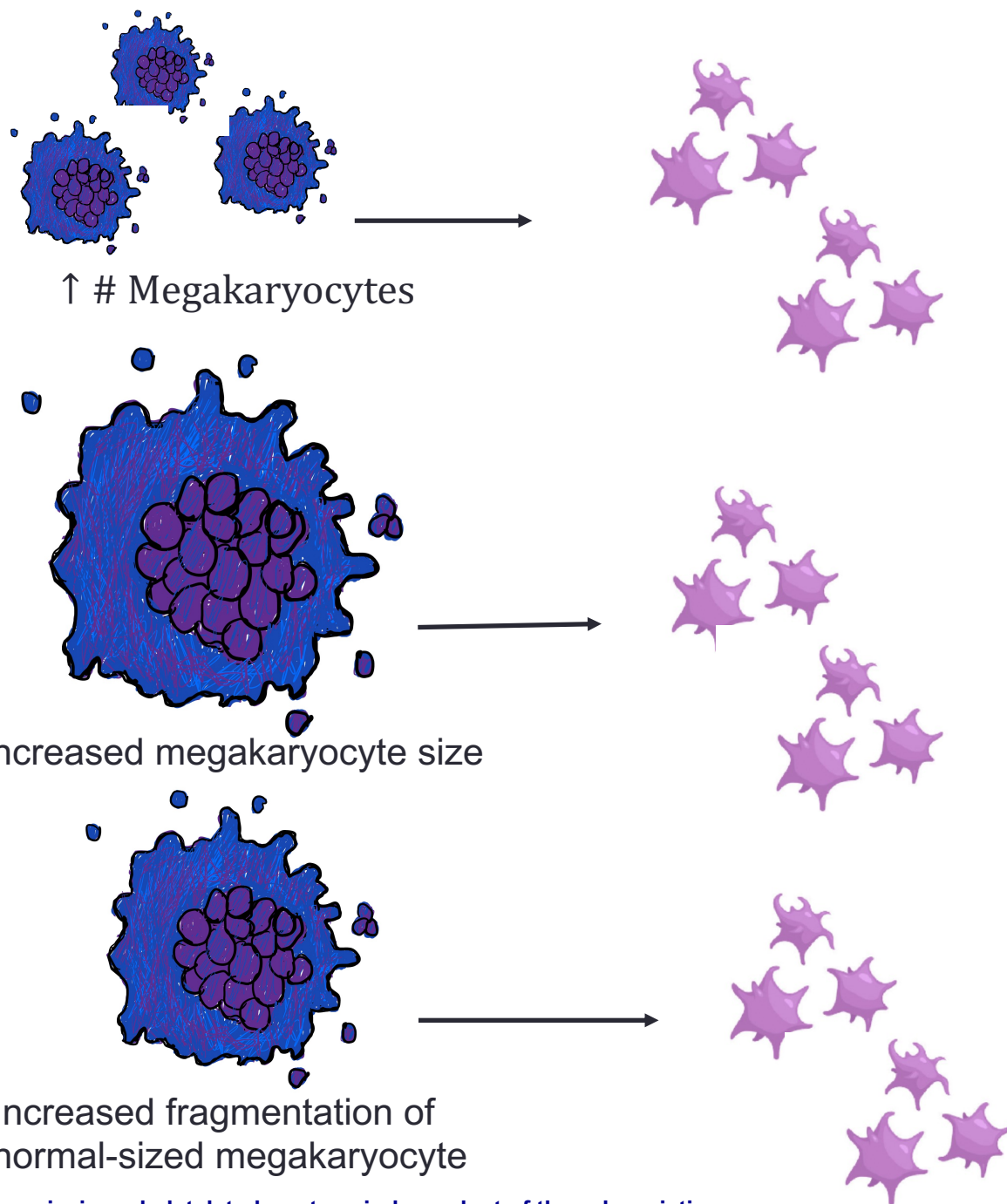


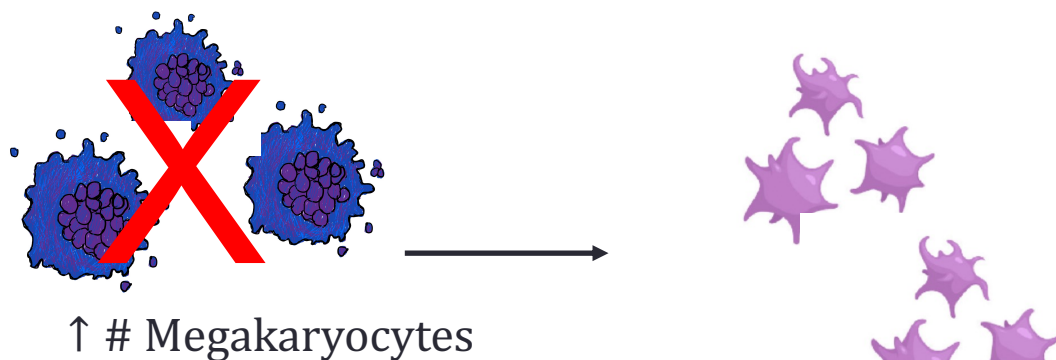
Promegakaryocyte



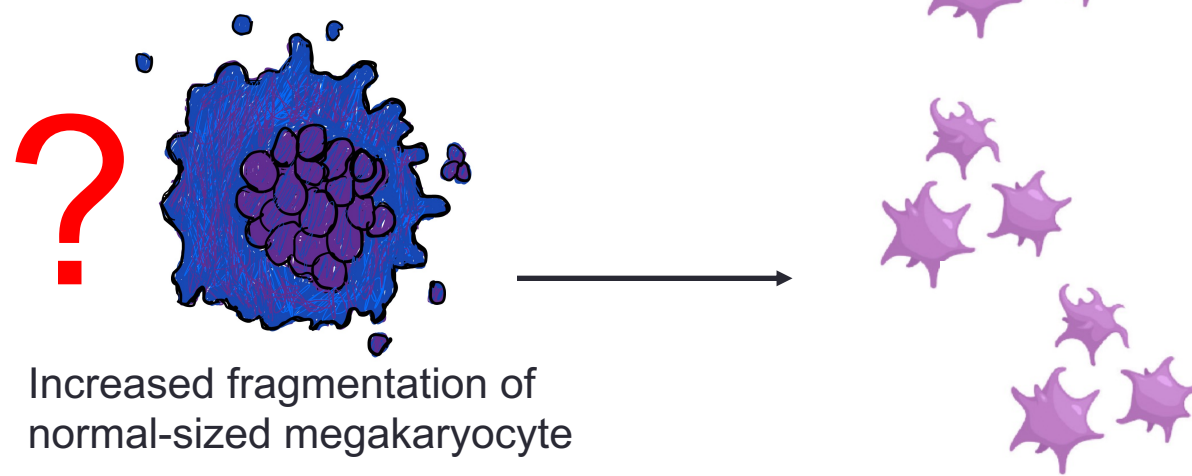
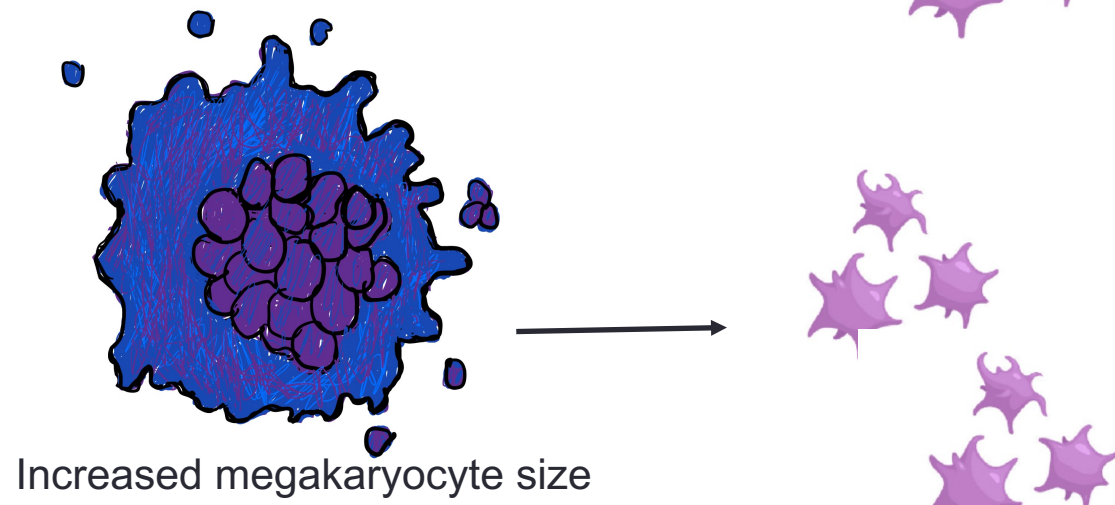
Megakaryocyte







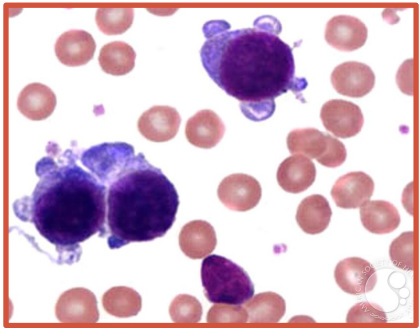
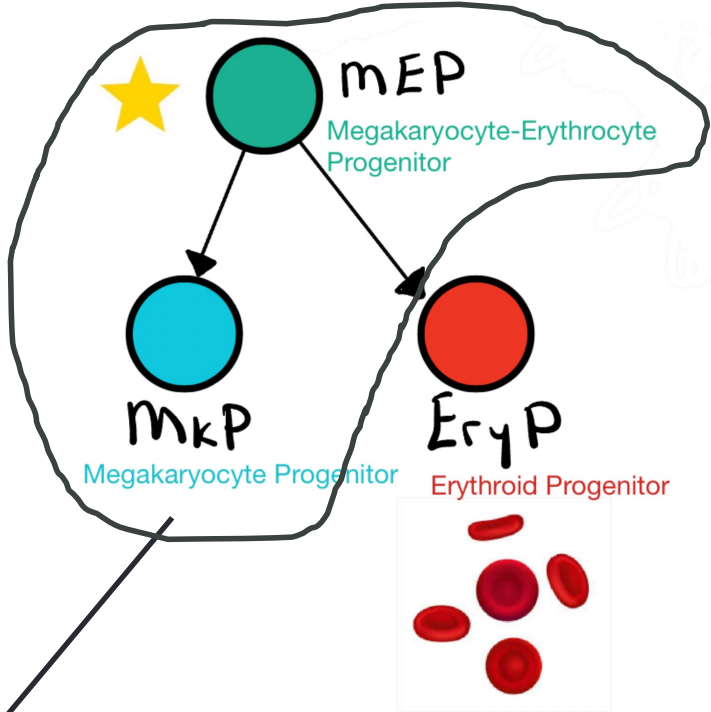
Increased size and ploidy



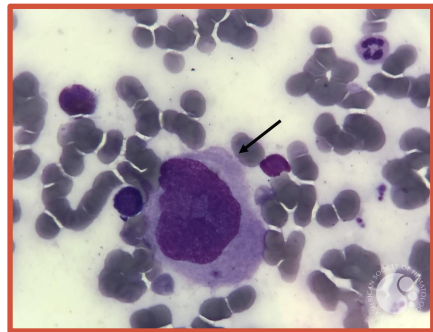
FINDING #2:

1. Proliferation not enhanced
2. Increased size
3. Increased ploidy

↑ MkP
Commitment!

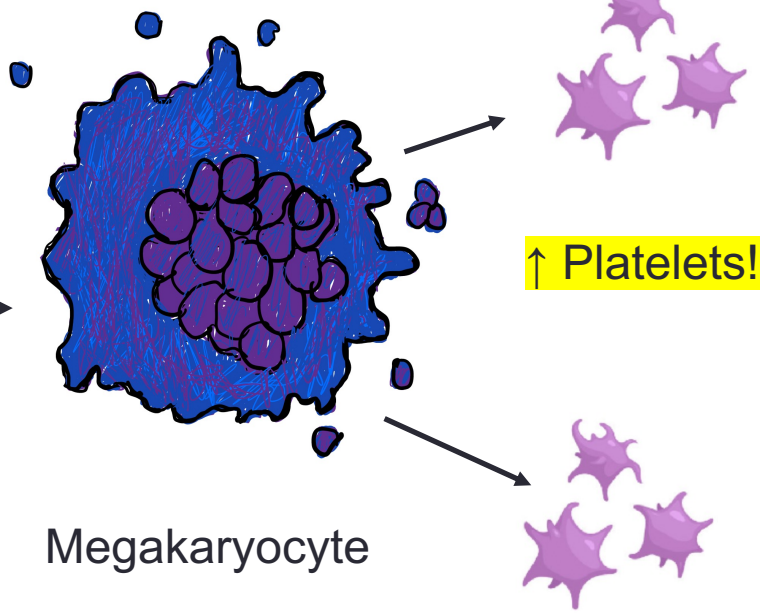


Megakaryoblast

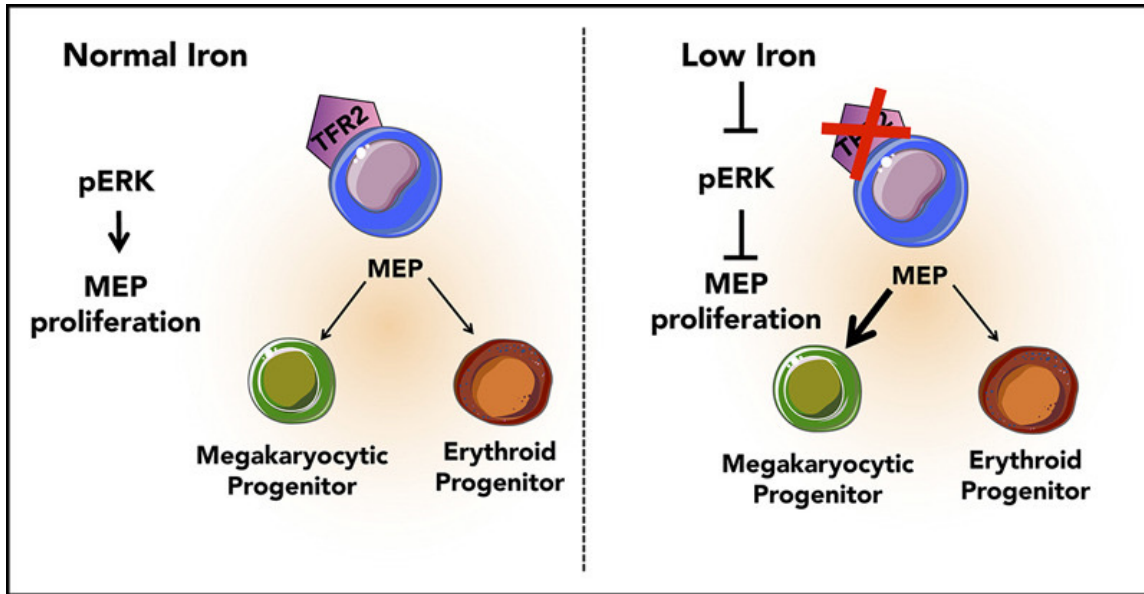
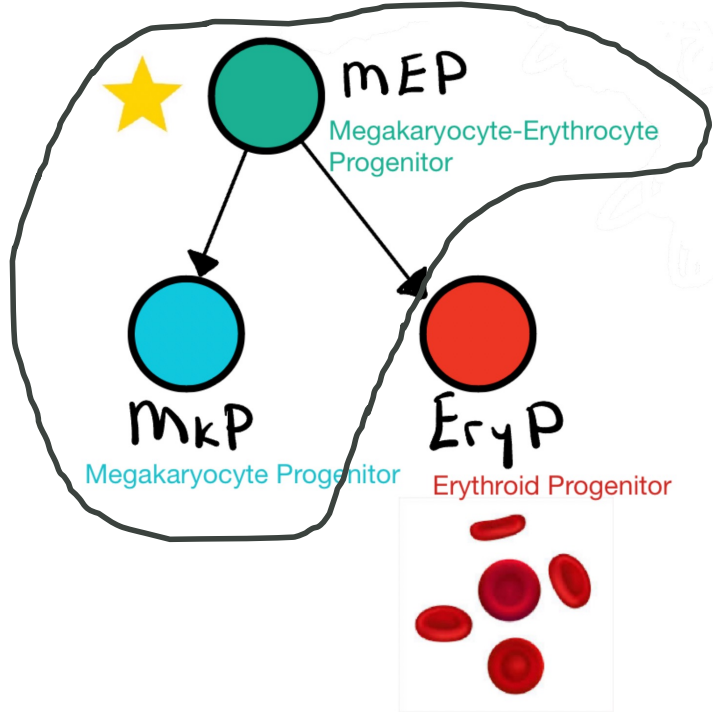


Promegakaryocyte

Large
↑ Nuclei



Megakaryocyte

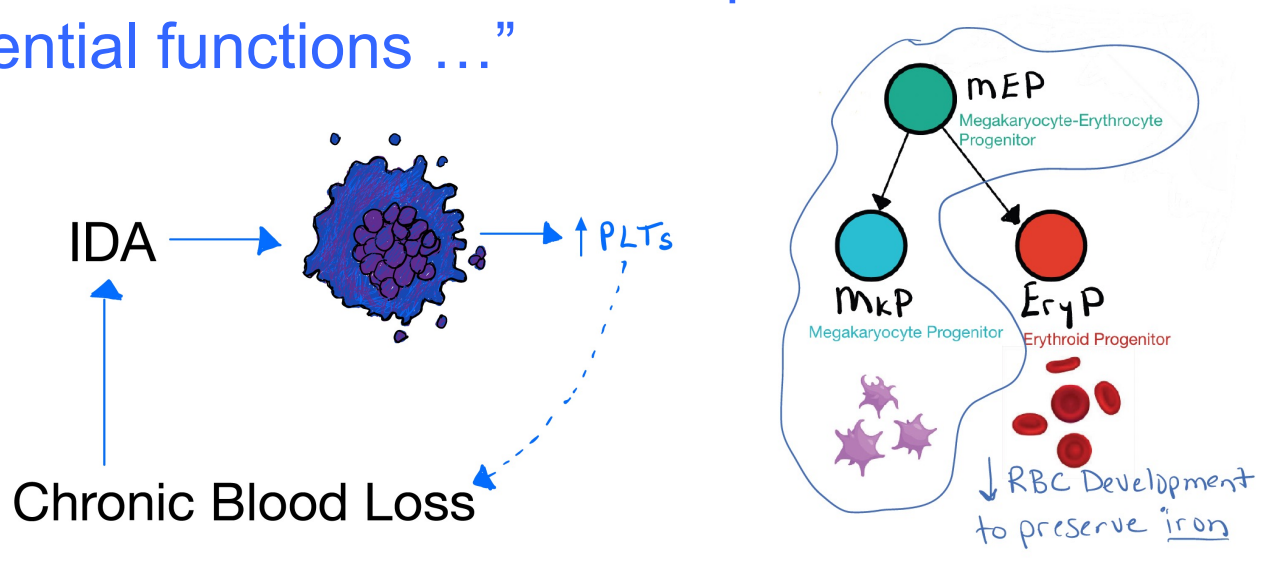


Decreased ERK signaling

IDA + Thrombocytosis = WHY?

What is the clinical significance of thrombocytosis 2° to IDA?

“...thrombocytosis might confer selective hemostatic advantage in the setting of major bleeding, whereas limiting erythroid differentiation could preserve iron stores for other essential functions ...”



IDA + THROMBOCYTOSIS

Possible Complication

Thrombosis = ISSUE!

- Thrombosis = Formation of blood clot

Source	IDA with ↑ PLT	IDA without ↑ PLT
Kuku, I., et al	0%	X
Song, A., et al	15.8%	7.8%

2 fold risk for thrombosis
(deep vein thrombosis; pulmonary embolism)

IDA + THROMBOCYTOSIS

Self-Study Findings

Date	Hgb g/dL	Hct %	PLT Count #/μL	PLT Count #/μL	PLT Morphology	Iron Therapy
			Automated	Manual		
March 3, 2023	11.5	35.7	527,000 (↑)	765,000 (↑)	Small Ave Size: 1μm	3 months no therapy
April 5, 2023	11.4	36.3	438,000 (N)	NA	*not assessed	3 weeks OTC iron supplement
August 31, 2023	12.9	33.7	440,000 (N)	465,000 (N/↑)	Normal Ave Size: 2μm	5 months OTC iron supplement
October 23, 2023	12.8	36.3	431,000 (N)	435,000 (N)	Normal Ave Size: 3μm	7 months OTC iron supplement
November 16, 2023	12.3	36.4	414,000 (N)	390,000 (N)	Normal Ave Size: 3μm	8 months OTC iron supplement
December 14, 2023	+++	+++	+++	1,572,000 (↑)	Small Ave Size: 1μm	1 month no therapy

+++ denotes inability to obtain an accurate value via the automated instrument

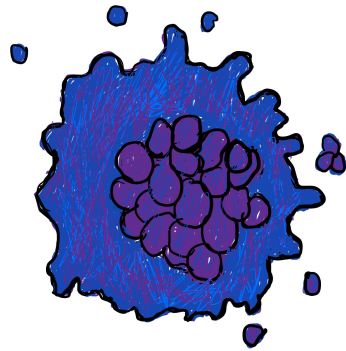
Platelet changes occurred rapidly.

- Platelets became elevated within 1 month of no therapy
- Platelets normalized within 3 weeks with therapy

MANUAL PLT # > AUTOMATED PLT # by average of 37%

Platelets varied in size with and without iron therapy.

- WITHOUT therapy: 1 μm
- WITH therapy: 3 μm



Possible!



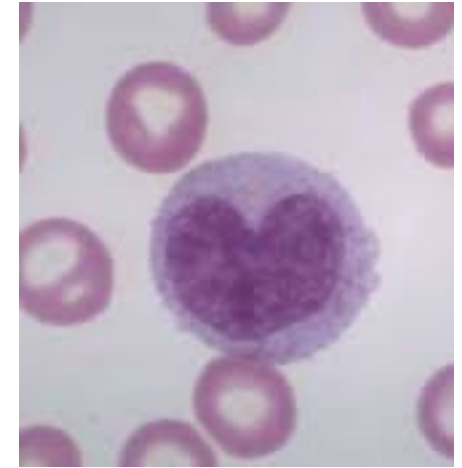
Increased fragmentation of
normal-sized megakaryocyte

IRON DEFICIENCY AND THROMBOCYTOSIS

Significance

- ✓ Educate medical laboratory of correlation
 - Understand that manual platelet counts may be useful to obtain accurate platelet counts
- ✓ Provide iron treatment to IDA patients
 - Alleviate thrombocytosis
 - Prevent possible risk of thrombosis
- ✓ Monitor IDA patients for signs of thrombosis

Thank You



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