HAEMATOLOGY 436

MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
شوق الأحمري & عبدالعزيز العقري

Polycythemia

Objectives:

-To understand the meaning of myeloproliferative neoplasm (MPN) and its clinical presentation.
-To differentiate between primary and secondary polycythemia.
-To obtain an overview about primary myelofibrosis and essential thrombocythemia.
-To appreciate the importance of genetic abnormalities (clonality) in these hematological neoplasms and the idea of targeted therapy.

Important.
Extra.
Notes

References:

436 girls & boys' slides
435 teamwork slides

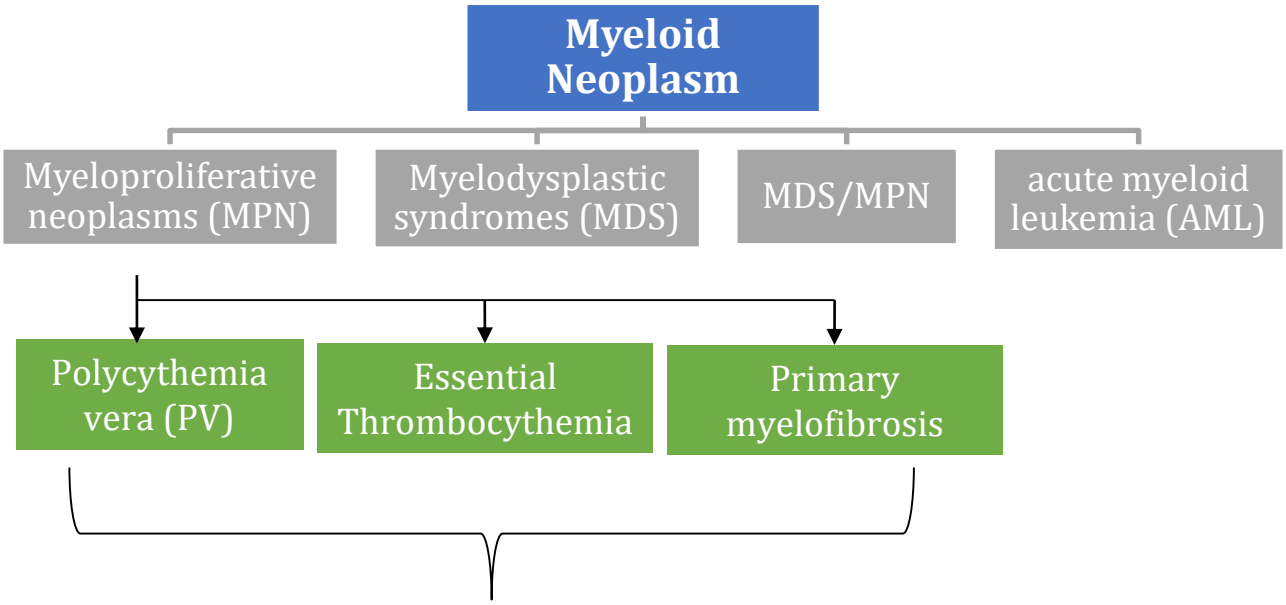
Editing file

Do you have any suggestions? Please contact us!

@haematology436 E-mail: Haematology436@gmail.com

or simply use this form

Classification:- تكملة للتقسيم في محاضرة الكرونيك لوكيميا ولا يناقضه



BCR-ABL Must be –ve

Positive BCR-ABL1 is a characteristic feature of chronic myeloid leukemia (CML)

That is why in any myeloproliferative disease the BCR-ABL1 must be negative

قبل بدايتك في المحاضرة ننصحك بمشاهدة هذا الفيديو من عمل التيم فيه شرح عام للمحاضرة ممكن يسهل عليك

Myeloproliferative neoplasm (MPN) features:

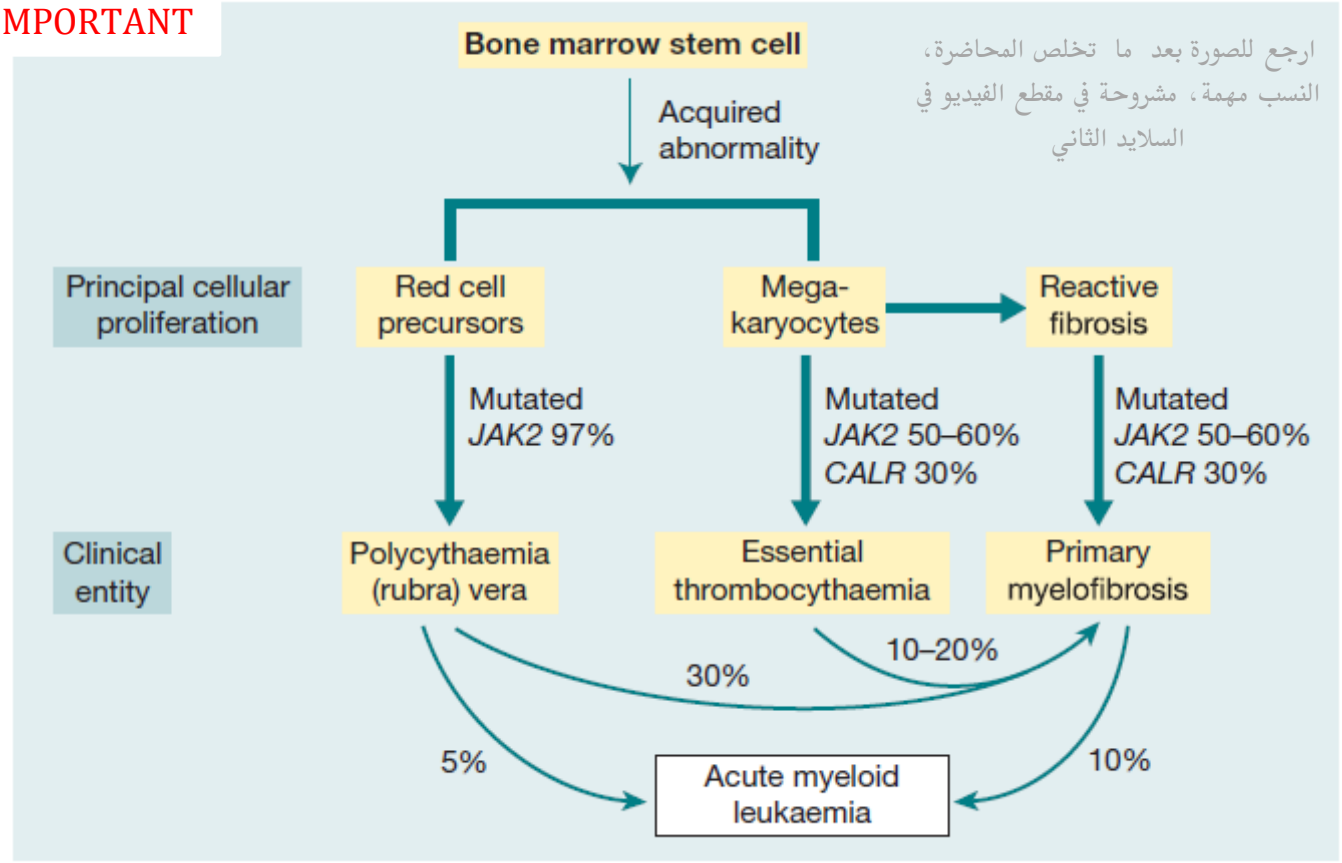
- Cytosis.
- Organomegaly (mainly splenomegaly).
- High uric acid. Because of increased turnover of these cells - may cause gout
- Hypercellular bone marrow.
- Clonal evolution.
- Progression to acute leukemia ,mainly (Acute Myeloid Leukemia).

Myeloproliferative neoplasm (MPN) is a group of interacting diseases where bone marrow stem cells are affected (by an acquired abnormality) which result in **increase proliferation**

It can affect any cell lineage:

- When red cells' precursor is affected ← polycythemia Vera
- When platelets are affected ← essential thrombocytosis
- When all three lineages are affected← primary myelofibrosis

EXTRA IMPORTANT



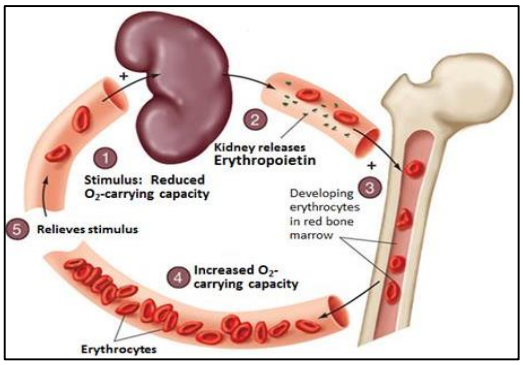
ارجع للصورة بعد ما تخلص المحاضرة، النسب مهمة، مشروحة في مقطع الفيديو في السلايد الثاني

Relationship between the three myeloproliferative diseases. They may all arise by somatic mutation in the pluripotential stem and progenitor cells. Many transitional cases occur showing features of two conditions and, in other cases, the disease transforms during its course from one of these diseases to another or to acute myeloid leukaemia. The three diseases, polycythaemia rubra vera, essential thrombocythaemia and primary myelofibrosis, are characterized by *JAK2* or *CALR* mutation in a varying proportion of cases.

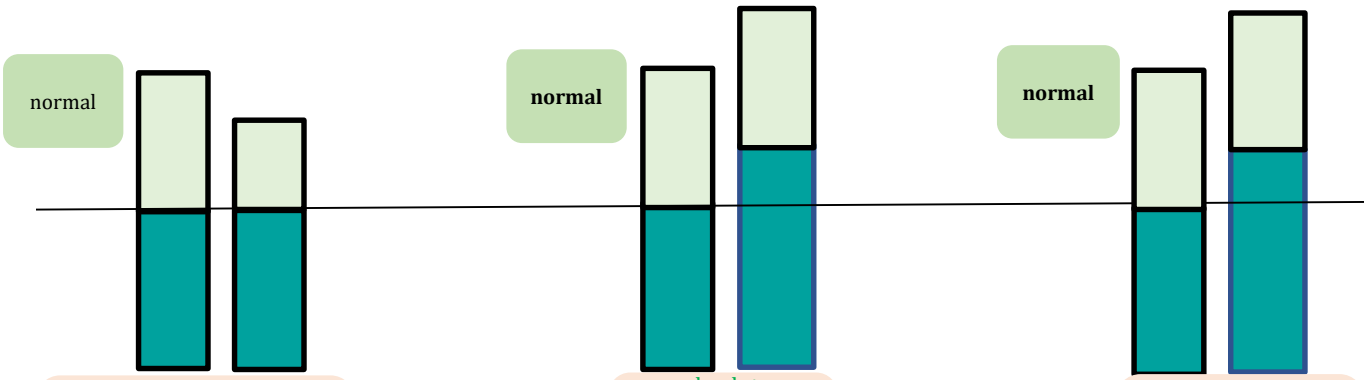
Polycythemia

- In Greek, “too many cells in the blood.”.
- Absolute increase in total body red cell volume (or mass).
- Manifests itself as a raised hemoglobin or packed cell volume (PCV), maybe masked by other disorders like iron deficiency.
- Almost always, accompanied with JAK2 mutation.

Regulation of Erythropoiesis by erythropoietin: مشروحة في الفيديو



Calcification of polycythemia. Important! مشروحة في الفيديو



Relative or pseudo or stress Polycythemia	absolute Secondary polycythemia	absolute Polycythemia Vera
Decreased plasma volume due to severe dehydration RBCs mass in NOT increased but in comparison to the decreased plasma the RBCs are a lot	Increased RBC mass due to high EPO (erythropoietin) : 1-COPD, Sleep apnea, (smoking most common) 2-High altitude 3-High affinity HB (hard release of oxygen to tissue leading to more O2 demand) 4-Renal disease 5- EPO secreting tumor (Parathyroid adenoma)	Increased RBC mass due to malignant proliferation

2ry polycythemia: Any cause that interrupt with EPO production or affect kidneys may cause more RBCs and this is not a clonal disease

Polycythemia vera:

It is a type of MPN characterized by increased red blood cell production independent of the mechanisms that normally regulate erythropoiesis (intrinsic proliferation and anti-apoptotic).

Diagnostic features of polycythemia vera:

- HB >16.5g/dl in men, 16.0g/dl in women. (raised Hb).
- Hypercellular bone marrow (pan-myelosis all myelo cell lineages may be increased).
- JAK2 mutation in >95% of cases.
- No increase in serum erythropoietin level. Because it is not the cause.

Clinical feature of polycythemia vera :

1-Increased blood viscosity due to increase the number of RBCs related to plasma.

- Hypertension
- Headache, dizziness, visual disturbances & paresthesia
- pruritus.

2- Thrombosis

- Deep vein thrombosis
- Myocardial infarction
- Mesenteric, portal or splenic vein thrombosis

3-Splenomegaly in 70% most important feature due to Extra destruction of RBCs in the spleen, because of its high number

4-Hepatomegaly in 40%

When do we say that this patient has PV? Important!

- When he has 3 Major criteria or First 2 Major and the Minor criteria.

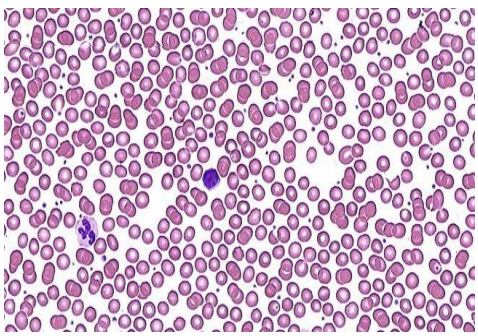
- **Major criteria**

1. Hb> 16.5 g/dl in men or Hb>16.0 g/dl in women
Or Hematocrit > 49% in men or >48% in women
Or Increased Red Cells Mass (RCM).
2. Bone Marrow biopsy shows (panmyelosis).
3. Presence of JAK2V617 or JAK2 exon12 Mutation.

- **Minor criteria**

- Subnormal serum erythropoietin level.

Investigations of polycythemia vera :



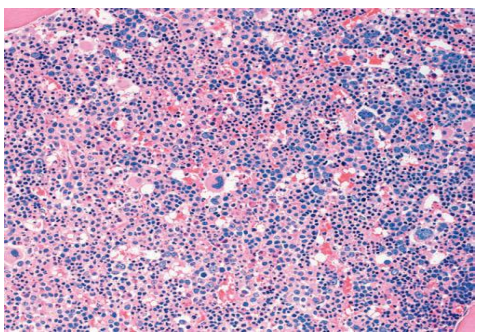
CBC:

*RBC: increased *Hb: increased

*WBC&PLT (platelets) :mildly increased (usually).

Blood smear:

- Excess of normocytic normochromic RBC.
- ± Leukocytosis &thrombocytosis.



Bone marrow

- Hypercellular.
- Predominant erythroid precursors.
- ± Increased megakaryocytes & myeloid precursors.

Blasts → AL transformation

Complication and treatment of polycythemia vera:

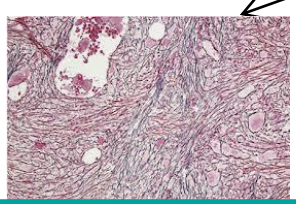
Treatment: Not important

- Venesection + Aspirin to prevent thrombosis
- ± Myelo-suppressive drugs (hydroxyurea) it's a chemotherapy

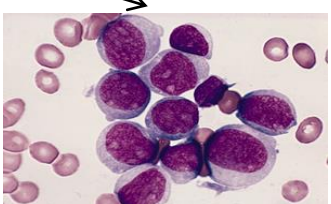
Complications:

10-15 years

20-30% → Myelofibrosis



5-10% → Acute leukemia



Primary myelofibrosis

- It is a clonal MPN characterized by a proliferation of megakaryocytes & granulocytes in the bone marrow that associated with deposition of fibrous connective tissue and extramedullary hematopoiesis

Clinical feature of primary myelofibrosis :

•Anemia

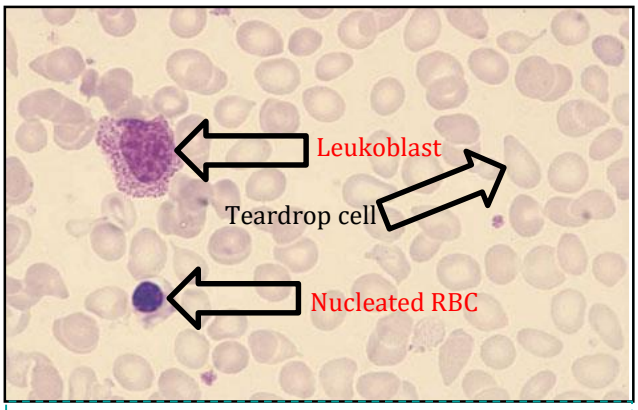
• Leukoerythroblastic blood picture. Due to bone marrow stress from fibrosis

• Massive splenomegaly. (The bone marrow is filled with fibrosis so extramedullary hematopoiesis is required and splenomegally is massive because the spleen not only filter but also makes new cells so even bigger than in polycythemia Vera or Essential thrombocythemia)

• Fibrotic bone marrow.

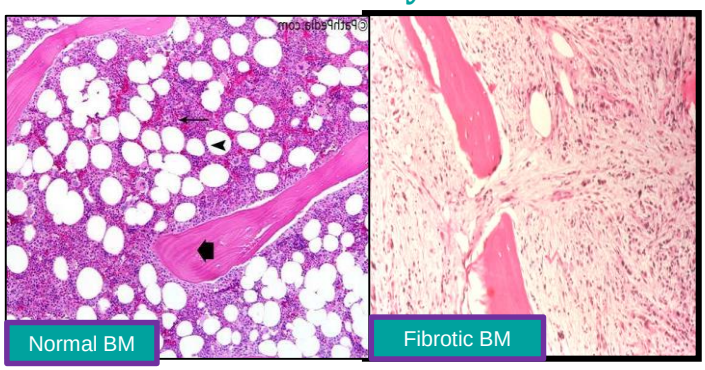
• JAK2 mutation (50%-60%).

• Risk of AML transformation (10-20%).

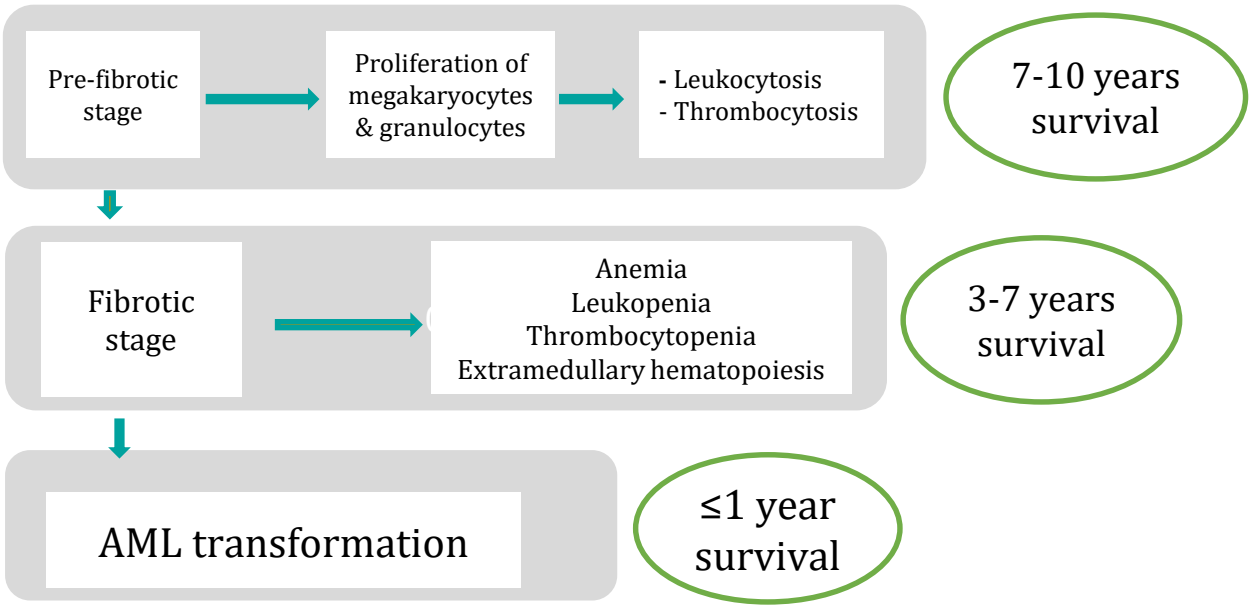


Leukoerythroblastic blood picture. مهمة ومشروحة في الفيديو
Blast cells seen in peripheral blood because bone marrow is filled with fibrosis
- Nucleated RBCs (immature) -Blast WBS -Tear drop cells

Bone marrow in myelofibrosis

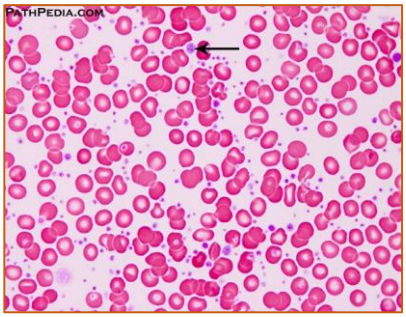


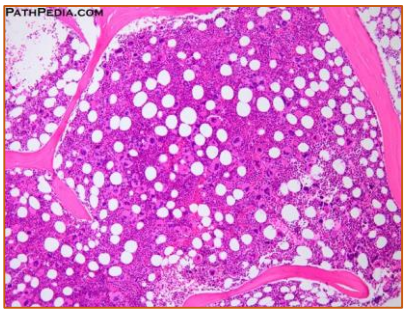
Stages of primary myelofibrosis :



Essential Thrombocythemia

- It is a MPN that involves primarily the megakaryocytic lineage and characterized by sustained thrombocytosis





Diagnostic features of Essential Thrombocythemia

- Sustained thrombocytosis ≥450×10^9/L.
- Hypercellular BM with megakaryocytic proliferation.
- Exclusion of: CML, MDS, PV &PMF. (all these diseases can cause thrombocytosis so exclude them) remember CML is excluded by a negative BCR-ABL
- JAK2 V617F mutation (50-60%), CARL or MPL mutations, If negative; no evidence of reactive thrombocytosis which is : Iron deficiency, splenectomy, surgery, infection ,autoimmune disease…. The causes of reactive thrombocytosis should be also excluded because they increase thrombocytes as well

Clinical presentation of essential thrombocytopenia

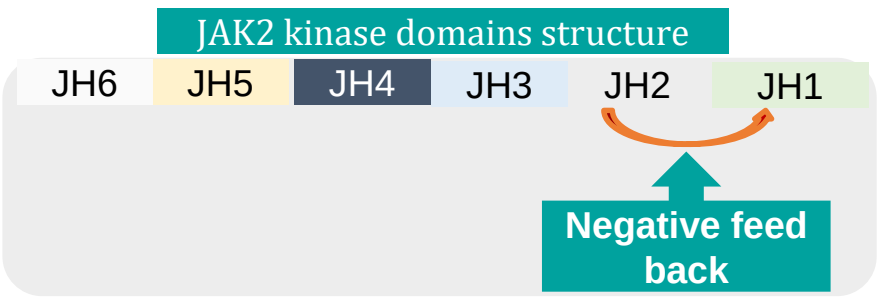
- Asymptomatic (50%)
- Thrombosis
- Bleeding (defective function of platelets)
- Mild splenomegaly (50%)
- Mild hepatomegaly (20%)

Very indolent (5% risk of AML transformation)

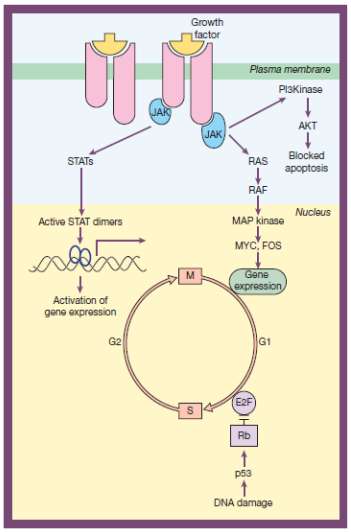
Treatment : Aspirin (to prevent thrombosis) ± Hydroxyurea

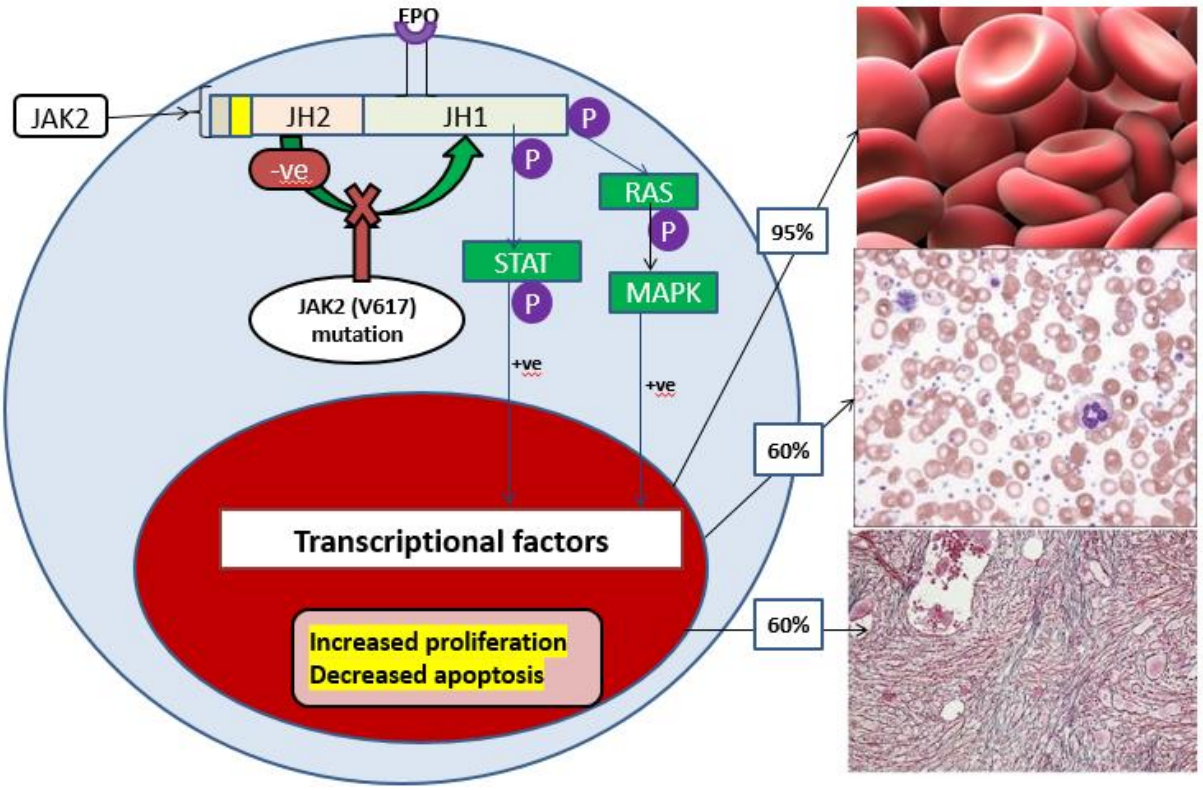
JAK2 mutation

JAK2: (Ch 9p with 26 exons), a non-receptor protein tyrosine kinase involved in signal transduction pathway.



When JAK2 get Activated it activates system called STATs by dimerizing 2 STATs Together This system will cause modulating of Gene expression To start the proliferation.





Summary

The video in slide 2 summarizes everything.

MCQs:

- Which ONE of the following is NOT a cause of polycythemia?

  A) Mutation of *JAK-2*.

  B) Renal disease.

  C) Congenital heart disease.

  D) Hemoglobin abnormality.

  E) Iron overload.

- Which ONE of these statements is TRUE about pseudo (stress) polycythemia?

  A) It is caused by a raised red cell mass.

  B) It is associated with a large spleen.

  C) It is treated with hydroxycarbamide (hydroxyurea).

  D) It is most common in young male adults.

- What is the approximate frequency of the Val617Phe mutation in *JAK2* in myeloproliferative neoplasms?

  A) 99% in polycythemia vera (PV) and 50% in essential thrombocythemia (ET) and primary myelofibrosis (PM).

  B) Approximately 50% in PV, ET and PM.

  C) 50% in PV and 25% in ET and PM.

  D) 90% in PV, rare in ET and PM.

Answers
1) E
2) D
3) A

Good Luck!

Team Members
Khalid Al-Husainan
Abdullah Al-Nasser
Dania AlKelabi

Team Leaders
Abdulaziz Al-Hussainy
Safa Al-Osaimi