Physiology Undergraduate League of Students

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set #3

lecture #:	date:	professor:
8	Monday, January 22nd	Dr. Ponka
9	Wednesday, January 24th	Dr. Ponka

announcements:

- *Good luck on the midterm!*
- ***Class test on Wednesday January 31*** *(blood), will <u>now</u> be held* ***during class*** *time, 10:35am-11:25am in <u>2</u> rooms:*
  Room G-10, Macdonald Harrington Bldg: Afshar -Kyriacou
  Lyman Duff Amphitheatre in the Duff Medical Bldg: Laneuville-Zummer

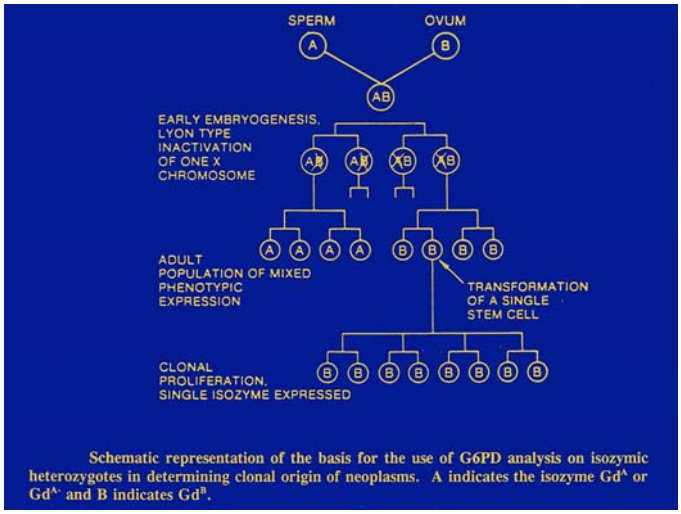
Pathology:
1) To study, describe, and attempt to understand the functions of the disease
2) To understand the mechanism of the disease and the events that occur during the development of certain types of diseases. One point mutation in a single gene may disturb an organism on many different levels.

It is important to distinguish between
- Etiology = the primary cause: infection, genetic events etc
- Pathophysiology/pathogenesis= chain of events that follow

Many diseases affect the hematopoietic stem cell system, which can thus affect the cells that are produced from it.
- Some diseases are due to specific abnormalities of the stem cell; one of the main abnormalities has a **clonal** origin.

For many years, people have asked whether hematopoietic malignancy is considered polyclonal (derived from many cells) or clonal (derived from one cell).
Virtually all of them are clonal- indicating that the entire tumor (collection of cells) is derived from a single cell.

Clonality (proposed by geneticist Mary Lyon in 1972):



Schematic representation of the basis for the use of G6PD analysis on isozymic heterozygotes in determining clonal origin of neoplasms. A indicates the isozyme Gd^{A} or Gd^{A-} and B indicates Gd^{B}.

Lyonization- a phenomenon that explains clonality:

- Inactivation of one X chromosome during the early stage development of embryogenesis
- The X chromosome is randomly chosen
- One of the two X chromosomes is inactivated in approximately half of the cells and the other X chromosome is inactivated in the other half of the cells.
- The X chromosome inactivated in the progeny at the beginning of development remains inactivated throughout the entire life of the individual.
- There is a need for a marker that will show us what proteins the X chromosome codes for and what products come from the gene.
  - G6PD (glucose-6-phosphate dehydrogenase) gene was found on the X chromosome. It is used as a marker for the X chromosome.
    - Common G6PD isozyme is **Gd-B**. More black people are affected with the disorder by having G6PD isozyme **Gd-A** instead. ****Remark: Isozyme= 2 enzymes that differ in amino acide sequence but catalyze the same chemical reaction.**
    - Approximately 1/3 of black women are heterozygote: tissues where half the cells express A and half the cells express B.
      - If such an individual develops leukemia, the cell will only have one isoform present in the tumor.
      - The reason for this is that there is clonal development
      - By using G6PD as a marker, it has been demonstrated that many hematologic malignancies (acute leukemia, acute anemia, polycythemia vera…) **arise from single cells.**

What is anemia?

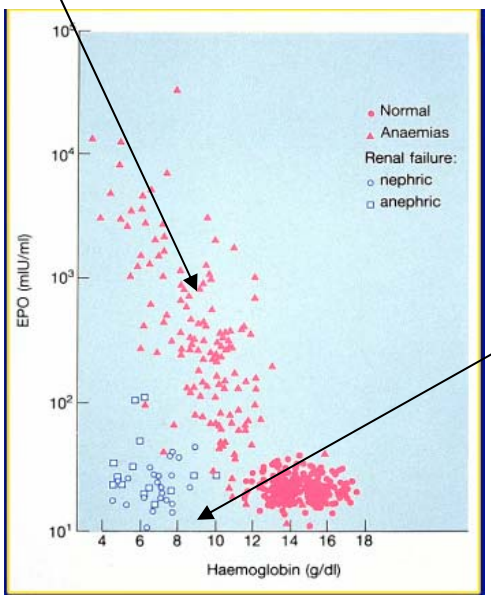
- Decreased supply of O_2 to tissues
- Low [hemoglobin] concentration in the circulation which leads to low hematocrit (Ht)
- Normal range for men: 14 -18 g/ dL; for women: 12-16 g/dL
- Can occur when red blood cell (RBC) levels containing hemoglobin (Hb) is significantly lower. **The RBC production is not capable of keeping up with the RBC destruction, or the destruction of circulating RBC is so fast the production cannot keep up.**

Anemia due to **erythrocytes** can occur for two reasons:

1) *Loss of erythrocytes (hemolytic anemia)*
   - Enzymatic defect, membrane defect in the cell, shortened lifespan
2) *Decreased in production of erythrocytes:*
   - Defect in bone marrow (aplastic anemia), which can be caused by a viral infection or other etiologic functions, defect in vitamin B_{12}…

Anemia due to **hemoglobin** can occur because of:

1) *Anemia (any type- aplastic, hemolytic, iron deficiency…)*
   - Hb cannot be synthesized at a normal efficiency → decreased supply of regulatory factors or cofactors needed for formation (eg, defect in B_{12}, or Vitamin B_6 which is needed for synthesis of heme…)
   - At a certain point, when there is a decreased Hb level, it will lead to a dramatic increase of erythropoietin (EPO). This is a compensatory mechanism in response to tissue hypoxia which increases erythrocyte production.

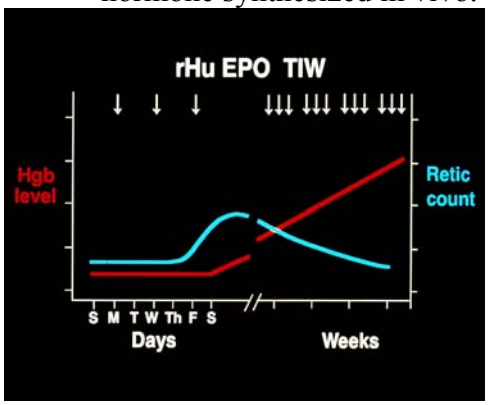


2) *Renal Failure*
   - Lack of tissues that produce EPO; cannot respond by increasing EPO levels when there is an Hb decrease. EPO levels are too low.

3) *Anemia of chronic disease:* causes low EPO levels as well (not shown on the graph)

EPO therapy:

- EPO also increases Hb levels in non-erythropoietic tissues; there is evidence that it is helpful in restoring functions in the brain following a stroke. Receptors on non-erythroid tissues are either slightly or completely different from the classical receptors on hematopoietic cells.
- Today, we have recombinant urinary EPO (purified in vitro), which is practically identical to the hormone synthesized in vivo.



- Recently, pharmaceutical firms have started to generate EPO with a long lifespan.
- The sugar dose on the hormone was increased, which increased the lifespan of RBC in circulation.
- First response after EPO administration leads to an increase of reticulocytes.
- This is a major achievement in medicine in the past 30 years, and has become a very useful drug in EPO stimulating activity.

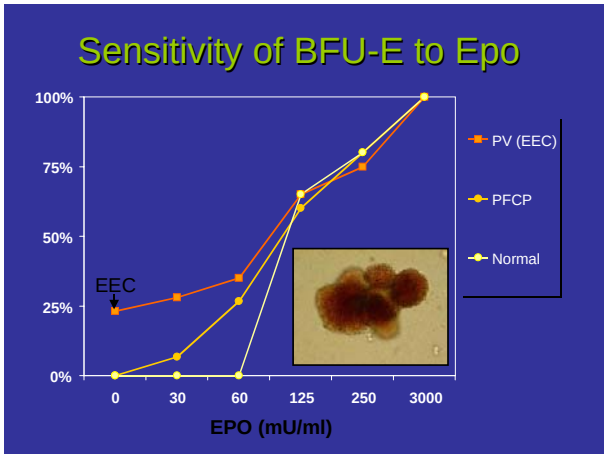
- As the reticulocyte count increases, this also leads to an increase of Hb, but there is a delay in the Hb increase.

Polycythemia (erythrocytosis) → when there is an increase in RBC count
- The normal Ht is about 45%.
- "Relative" polycythemia (~53%) is when there is a greater Ht due to an increase of plasma volume in the circulation (we are not interested in this).
- "Absolute" polycythemia (~53%) is when there is an actual increase in total blood volume; there is a huge increase in circulating RBCs and plasma together, to give an overall total increase of RBCs.

Erythrocytosis
- Relative erythrocytosis
- Absolute erythrocytosis – 2 levels:
  - **Secondary level- two reasons for EPO increase:**
    - Increase in EPO due to tissue hypoxia, caused in expected situations (EPO level appropriate)
      - When going from Montreal to Machu Pichu, there is a decrease in oxygen partial pressure.
      - If Hb has a high affinity for oxygen due to a mutation, causing a reduced capacity to release O_2 from the blood
      - Lung Disease
    - Increase in EPO not caused by hypoxia (EPO level inappropriate)
      - Can be due to EPO-producing lesions: renal cysts, tumors…
      - The tumor apparently induces EPO
  - **Primary level- Polycythemia Vera:**
    - Increase in erythropoiesis without EPO production increase
      - Not only increase in Ht but an increase in all circulating elements as well (leukocytes etc…)
      - If the situation is chronic, it can potentially slip into leukemia, as this is a pre-leukemic condition.

Measurement of EPO is essential for separating primary levels from secondary levels.

BFU-E and EPO Sensitivity:
- Normal situation: need EPO to have development of BFU-E colony growth.
- Polycythemia Vera: growth of erythroid colonies possible without EPO. Erythroid colonies can grow in vitro without EPO autonomously.
- However, we **cannot assume EPO is not used at all** because all colonies contain serum, so the colonies are still responding to EPO, but the amount of it is very low.

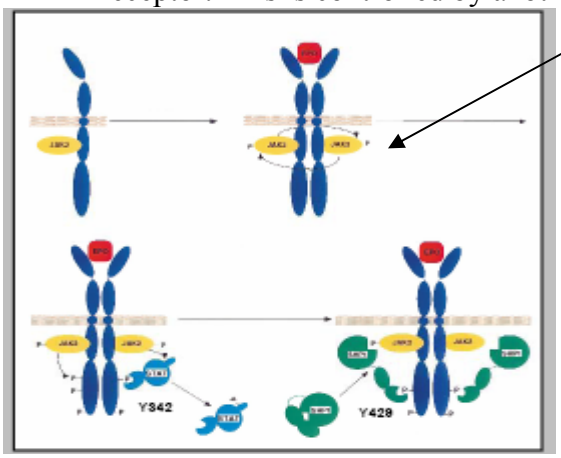


Primary Polycythemia
- Can be due to an acquired mutation of a hematopoietic single stem cell. If BFU-E colonies are grown in the presence of EPO, the number of colonies will be larger.
- Clonal hematopoiesis: if BFU-E colonies from polycythemia vera patients are grown without EPO, all of the colonies will show clonality. When EPO is added, it revives the (normal) suppressed phenotypes
- JAK-2 mutation in myeloid cells
  - All patients of polycythemia vera had JAK-2 mutations.

- Disease has been known for many years, but took 20-25 years to detect molecular defect

Eero Mantyranta has won many Olympic medals in the past but his hemoglobin level was about 23.1 g/dL, which is very high compared to 15 g/dL in normal males. His hematocrit level was also very high; it was 68%. This value is almost 50% higher than in normal individuals.
This phenomenon intrigued interest in scientists as to why this happened; EPO doping was ruled out because EPO did not exist at the time as a purified substance. However, it turned out to be a mutation in JAK-2 Kinase.

- A tyrosine kinase called JAK-2 associated with region near plasma membrane undergoes autophosphorylation and phosphorylates the EPO-R.
- Aside from the JAK kinase phosphorylation, there is a need for the removal of JAK kinase from the receptor. This is controlled by another system. In the patient shown here, his receptor is truncated so dephosphorylation could not occur, causing EPO-R to be hyperactive → **an increase in erythrocyte production.** (This produces similar effects as polycythemia vera, but it is not the same mechanism!)

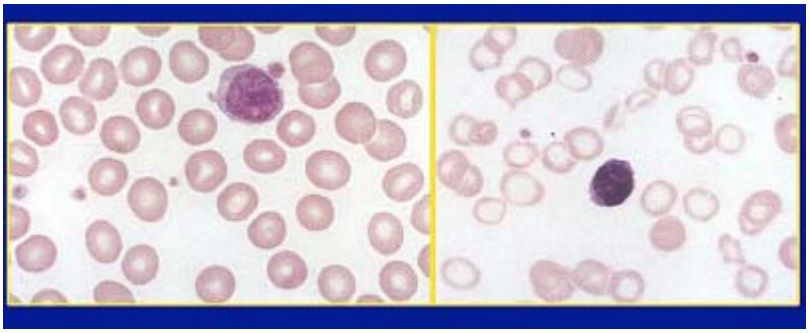


Polycythemia

- Not advantageous
  - EPO-R mutation can lead to increase in EPO production. This can be harmful because EPO increases RBC count, which increases blood viscosity, and leads to a high hematocrit. It is used as a doping agent and has caused death due to high EPO levels.
- Can be detrimental
  - Increases hypertension and atherosclerosis (hardening of the arteries).
- Transgenic mice
  - Overproduction of EPO has led the mice to become feeble (lacking physical strength). They are in bad shape and they have bad Ht (~60%).

Hypochromic microcytic anemia: caused by quantitative defects in the production of Hb.

- Hypochromic:
  - Less hemoglobin, which makes the cell paler
- Microcytic
  - Smaller
- 3 important players are necessary for Hb formation:
  - **Protoporphyrin IX** (tetrapyrolles), Fe from the environment and **globin synthesis pathway** (if there is a *defect* in globin synthesis, it is *quantitative*, not structural.)



On the right, there is Fe deficiency. The cells are smaller, paler and there is less pigment. The cell on the right is morphologically normal.

Iron Deficiency:

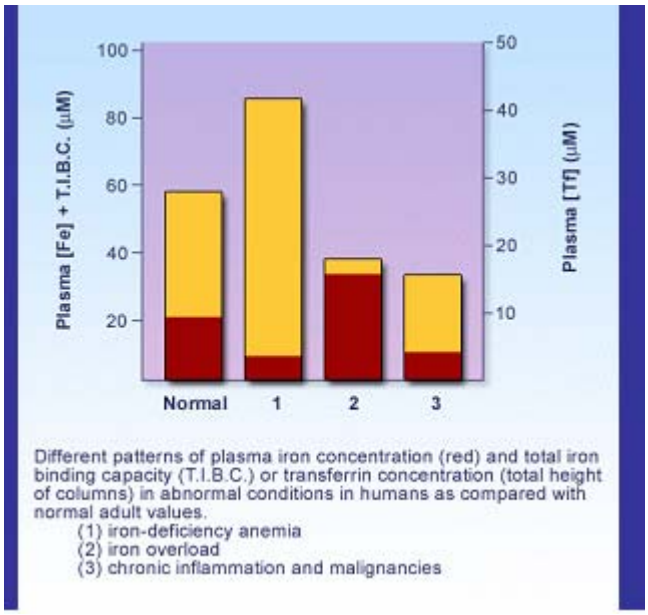
- Most common cause of anemia: ~500-600 million people worldwide affected.
- Not common in developed countries.

- In developing countries, the major groups affected are:
  - Women during the reproductive phase of life
  - Premature infants
  - Young children with poor dietary iron intake
  - Elderly
- In northern parts of South America, hookworms (parasites found in the GI tract that drink people's blood) are very common.
- Main causes in developed countries
  - Acute bleeding
  - Chronic blood loss
  - Tumors: it is very important to seek out tumors because they are not always easily detectable. If there is an iron deficiency and a tumor, it could become very dangerous.

The diagnosis for iron deficiency should not be made solely on looking at blood morphology (such as examining the cells in hypochromic microcytic anemia) but ALSO by measuring the concentration of iron in the circulation.

Plasma Iron Concentration *(aside: Tf=transferrin [x]= concentration)*

- Situation 1: Iron deficiency anemia; this is due to a low level of Tf receptors. Plasma [Fe] decreases. Tf binding capacity increases, which dramatically decreases the Tf saturation.
- Situation 2: Iron overload- there is a dramatic increase in plasma [Fe] levels with low total iron binding capacity. This leads to high saturation of Tf receptors, which indicates iron overload.
- Iron-loading anemia have fully saturated transferrin (Tf). There is a small fraction of iron not bound to Tf, and it seems to be a major cause behind iron toxicity in iron overload.



Different patterns of plasma iron concentration (red) and total iron binding capacity (T.I.B.C.) or transferrin concentration (total height of columns) in abnormal conditions in humans as compared with normal adult values.
(1) iron-deficiency anemia
(2) iron overload
(3) chronic inflammation and malignancies

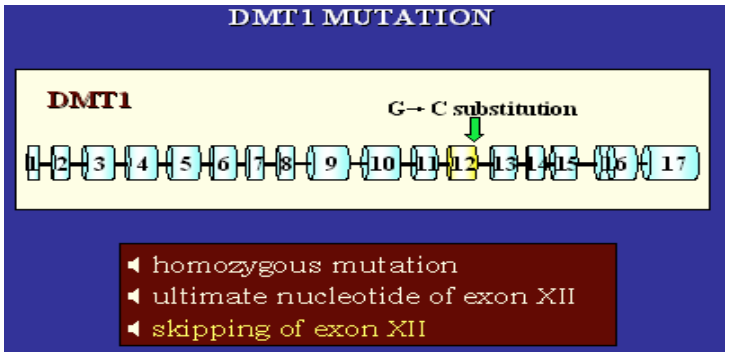
Anemia of Chronic Disorders

- The anemia seen in chronic infection, inflammatory disorders, malignancy etc…
- Pathogenesis:
  - There is an overall decrease in the red cell life-span.
  - There is a decrease in Fe release from macrophages.
    - Ferritin production in macrophages diverts Fe from its pathway in the cell.
    - **Why?** This is caused by increased levels of inflammatory cytokines, which stimulate ferritin synthesis.
  - Inflammatory cytokines also stimulate the production of hepcidin, which binds to ferroportin, causing its internalization and degradation. This also results in a decrease of iron release from macrophages.
  - Inflammatory cytokines also decrease the ability of bone marrow to respond to EPO.

In recent years, iron deficient erythropoiesis occurs due to:

- A genuine defect in generating RBCs that affect iron formation and decrease iron supply
- A lack of iron either in the diet or its delivery across a cell membrane

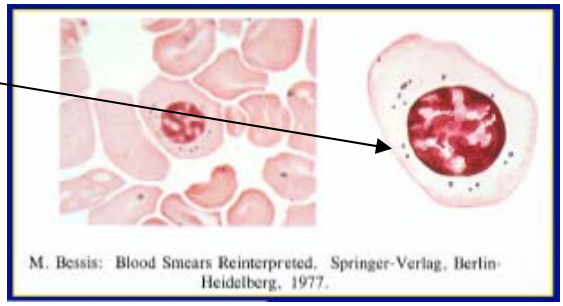
DMT 1 (Divalent Metal Transporter 1)



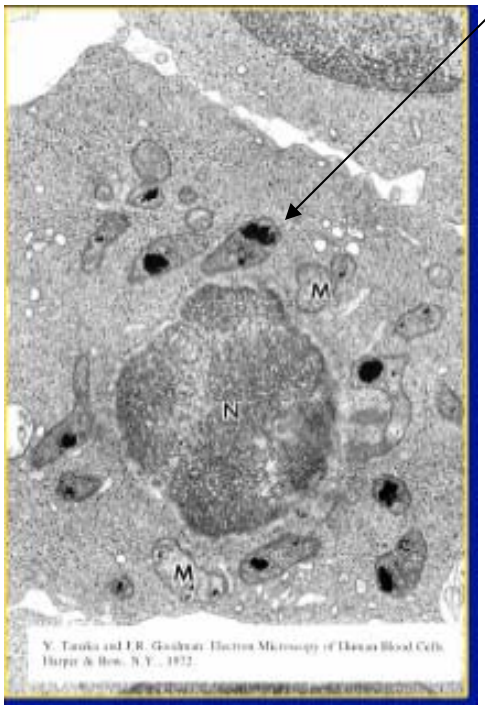
- MK mice and Belgrade rats were mutated for the DMT1 gene. They both had hypochromic microcytic anemia.
- Severe hypochromic microcytic anemia was diagnosed in a woman who was a product of consanguineous marriage (genetic).
    - Iron overload was discovered
    - When studied, DMT-1 was not included at the beginning because of iron-overload in the patient.
    - Several genes were cloned, nothing was found with regard to defect.
    - DMT-1 finally cloned, and that was where the mutation was located.
- When it was first cloned, DMT-1 reveal mutations of both **decrease in transferrin** and **decrease in iron absorption in the intestine.**
- How can this cause iron overload? It was predicted that there was an increase in the heme iron transporters, which increased the iron in the patient.

In the duodenal enterocyte (epithelial cell of the superficial layer of the large and small intestine tissue), there is increased absorption of heme iron. There is probably some kind of compensatory up-regulation of heme iron receptors or transporters, which increase Fe absorption.

In this cell, there are decreased levels of protoporphyrin IX, caused by alcohol. Protoporphyrin IX was affected because there was a decrease in ALA synthase activity. It does not affect the iron acquisition of the cell.



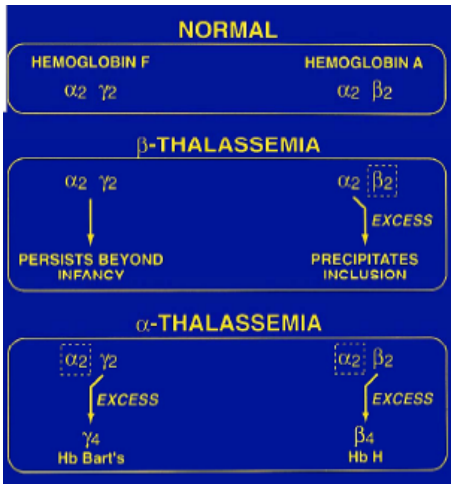
It is also possible to have an overload of erythroblast mitochondric iron in the cell.



- Iron is targeted to the mitochondria. However, even though the second substrate for heme is not present, the iron will still be around. However it will simply accumulate in non-heme form.

Thalassemia:

- Type of inherited blood disorder causing anemia. It affects a person's ability to produce Hb.
- Defects in globin synthesis are quantitative, they are not structural. The Hb that is made is normal.
- Thalassemia Major (β-Thalassemia): β chains are mutated. It is very severe- low Hb and low Ht. There is an increase in erythropoiesis in bone tissues. There are also facial changes, which are due to activation of bone marrow in facial bones, such as the cheekbone.

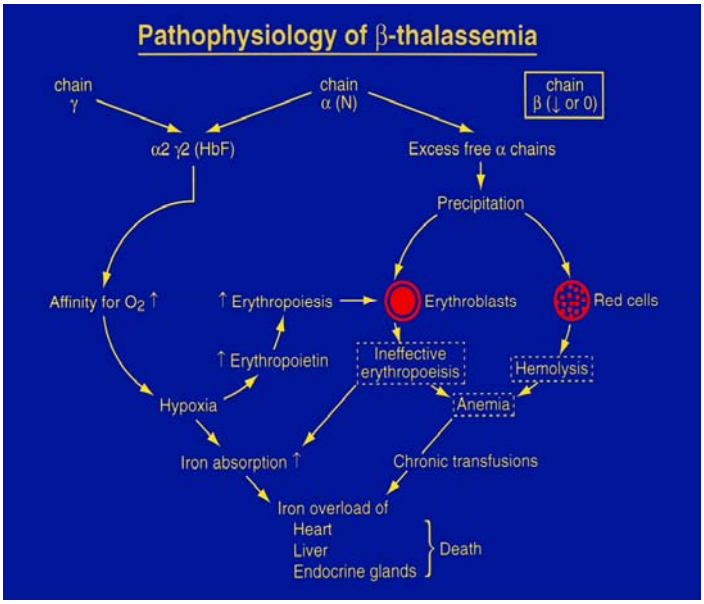


- Hemoglobin consists of two α-chains and two β chains.

- α-Thalassemia:
  - Mutation in α chains during adult development
  - Leads to excess of β of chains.
  - If γ tetrameric= Hb-Bart's will form. This is toxic.
  - In adulthood, it can lead to the formation of β tetrameric, which causes the formation of Hemoglobin-H.
  - Thus, there are 2 types of unstable hemoglobin: γ chain and β chain

Pathophysiology of β - Thalassemia:
  - Mutations in the β- chain
  - There is excess of α- chains
    - Damages and lyses RBCs → anemia
    - EPO stimulated, and will lead to expansion of developing RBC
    - But RBCs are sick, some die before making it to circulation

Anemia can also cause iron overload by itself, and thus, increase iron absorption from food.



Many patients can only survive if given chronic RBC-formation from chronic transfusions. This can lead to iron overload in the heart, in the liver, in the endocrine glands because of increase of Fe formation. This can eventually cause death.
Most children die at the age of 3. Chronic transfusions can prolong life to teenage years.
To prolong one's lifespan, one must be given iron-chelating agents, which can be very cumbersome (inefficient), and daily infusions of blood for 5-6 days a week is also required. This is the only way to save the lives of these individuals.

Thalassemia is prevalent in Southeast Asia and the Mediterranean. It seems that the gene of thalassemia is also used as protection against malaria, for the heterozygotes.

Granulopoiesis

Macrophage

•Monocyte when in peripheral blood
•Ubiquitous, found in almost all tissues and organs

Tissue/Organ	Tissue specific Macrophage
kidney	intraglomerular mesangial cells
brain	microglial component
serous surfaces	serosal macrophages
lung	lung alveolar macrophages (key to primary defense against pathogens)
liver	Küpffer cells
spleen	spleen sinus macrophages
bone marrow	bone marrow macrophages
lymph nodes	lymph node macrophages

•Performs diverse functions:
-Combats pathogens (by phagocytosis)
-Act as scavengers that removes dead cell debris and unwanted foreign material
-Küpffer cells and spleen sinus macrophages phagocytose old erythrocytes and efficiently recycle hemoglobin iron

The other cell type to be discussed is the **polymorphonuclear (PMN) granulocyte**

CFU_{GM} or granulocyte monocyte progenitor

-Common origin of macrophages and granulocytes
-Committed cell
-No morphological characteristics of granulocytes or monocytes are present yet
-Can't meet body's requirement for granulocytes or macrophages since it doesn't proliferate, stem cells are needed for this

•Aside: Stem cells are now a household term, greatly due to the ability of injected/transplanted embryonic stem cells to regenerate damaged tissue

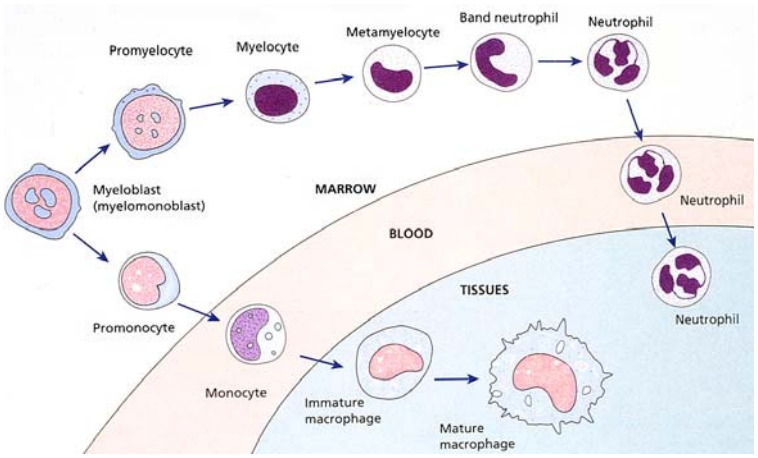
Developmental Path

•The macrophage and granulocyte have a common precursor → myeloblast

Granulocyte development:
•Myeloblast→promyelocyte→myelocyte→metamyelocyte→band or band neutrophil→ polymorphonuclear (PMN) neutrophil
•At the PMN neutrophil stage, morphological changes include indentation and segmentation of the nucleus

•Neutrophil:
-Leaves bone marrow and enters circulation
-Has short life span (1/2 life approximately 7 hours)
-Is called out of circulation into tissues in order to combat pathogens

Macrophage development:

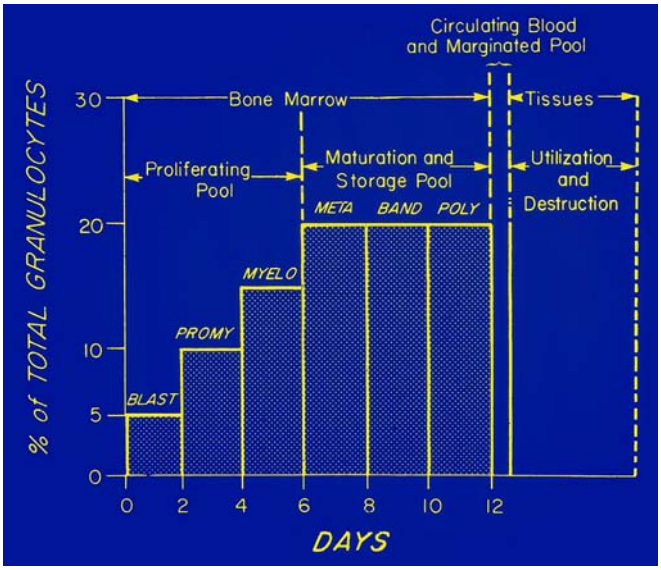


•Similar to granulocyte development, shorter pathway
•Myeloblast →promonocyte →monocyte (circulation) →macrophage (tissue)

•Released from bone marrow as a monocyte
•Develops into macrophage when fixed in a tissue

Examining granulocyte development from a staining perspective:
•The least mature cells show strongest basophilic staining
-Basophilia caused by high nucleic acid and ribosomal RNA content
•Capacity to divide is only up to and including the myelocyte stage
•2 types of granules
-Formed during development and maturation in bone marrow
-Primary/azurophilic and secondary/specific-staining granules
-Contain combating elements involved in destruction of bacteria

Examining granulocyte development from a quantitative perspective
• Cells in the proliferating pool are present in lower numbers:
-Myeloblast, promyelocyte and myelocyte

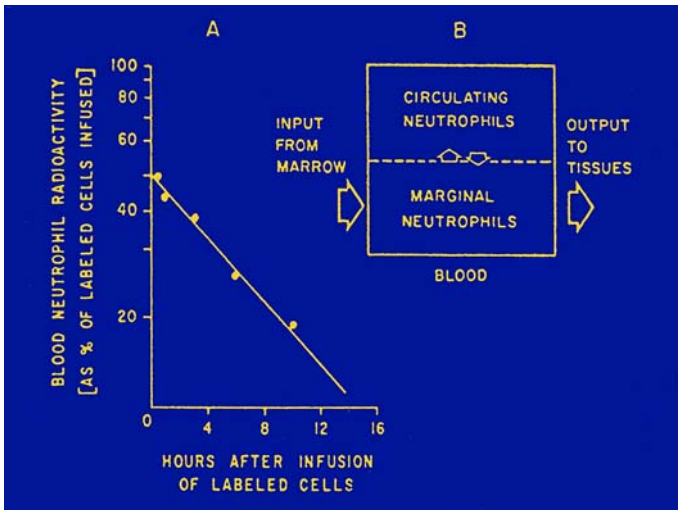


•Most abundant are the cells in the maturation and storage pool:
-Metamyeloctyes, band neutrophils and PMN neutrophils
-Nonproliferating cells
-Not normally released from marrow until PMN neutrophil stage is reached
-**Following infection, cells can be released from the storage pool earlier → provides weaponry to deal with pathogens quickly →** this phenomenon interferes with studies of granulopoiesis (see problem 1 below)

Investigations into Granulopoiesis
•Problems:
1) # of circulating neutrophils doesn't reflect their rate of production because of fluctuations in their release
2) No experimental technique to suppress granulopoiesis or macrophage formation (unlike for erythropoiesis by polycythemia)
3) Equipment of these cells is much more diverse than that of erythrocytes; no marker to label them endogenously (label erythrocytes with Fe59)

•Studies of granulopoiesis are difficult
•However, can take advantage of granulopoietic kinetics:
-Remove sample of blood from animal or human
-Isolate mononuclear cells or granulocytes
-Label the cells in vitro (radioactively labeled P32 diisopropyl sticks to the membrane)
-Measure radioactivity and inject cells into experimental animal
-Assess radioactivity in circulation:

▫It's rate of decay is exponential (semi log graph yields a straight line)
▫Decay represents removal of cells from circulation into tissues
▫About 50% of radioactivity disappears after only minutes
▫Half of the cells disappear almost immediately after injection → there's a dynamic equilibrium between granulocytes free in circulation and those crawling along endothelial cell walls



•The pool of neutrophils is divided into two rough halves:
-Circulating neutrophils and marginal neutrophils
-In constant equilibrium

•Physiological implication of having a marginal pool: neutrophils can readily enter tissues on demand (to serve an immune role)
•The Curve allows for calculation of neutrophile ½ life
-Radioactivity decays to half of original after about 7 hours

Interactions with Pathogens
•Neutrophils extend pseudopods to capture pathogens
-Adhere to pathogens and bring them back to the nest within the cell
•Basic scheme used by the cell to clear itself of the pathogen:
-After phagocytosis and formation of the nest
-Phagosomes merges with primary and secondary granules
-Debris extruded from cell by exocytosis or, alternatively, the cell dies
•Enzymes present in primary and secondary granules:
•Primary:
-Myeloperoxidase – enhances H_2O_2's ability to kill bacteria
-Lysozyme – hydrolyses bacterial cell walls, digests bacterial debris
-Hydrolases:
▫Elastase and cathepsins
-Various other proteins

•Secondary:
-Lysozyme
-Collagenase – Digestion of pathogenic macromolecules
-Lactoferrin – Slows down bacterial growth by chelating iron
– High homology to circulating transferrin
▫Similarities: structure, capacity to bind up to 2 Fe^{2+}, capacity to oxidize iron
▫Differences:
▪lactoferrin binds iron more tightly (at pH 7.4)
▪Lactoferrin can bind iron at relatively low pH (pH 5.0) → believed to be responsible for denying bacteria iron in the acidic environment around infected loci

▪Transferrin synthesized in liver, lactoferrin in granulocytes (but not macrophages)

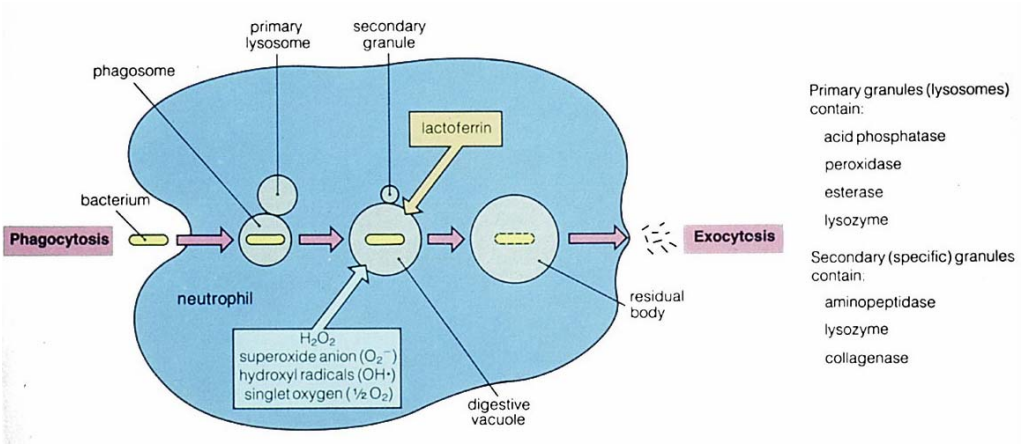
–Lactoferrin is present in tears, colostrums, milk, saliva

–Very low concentrations of lactoferrin in circulation, therefore, no apparent role in iron metabolism

–Mice heterozygous for a lactoferrin knockout had no change in iron metabolism

Microbicidal Pathways of Phagocytes:

•Cell engulfs opsonized bacteria → triggers many biochemical responses including the oxidative burst



•Oxidative burst:

-Phagocytes immediately start to consume more oxygen after pathogens are taken in

-*Respiratory burst oxidase* is the responsible enzyme:

▫7 subunits in final form

▫Some subunits are always present in the cell membrane

▫The remaining subunits are recruited to the membrane after entry of the pathogen

▫Converts molecular oxygen to superoxide (a one electron adduct of oxygen)

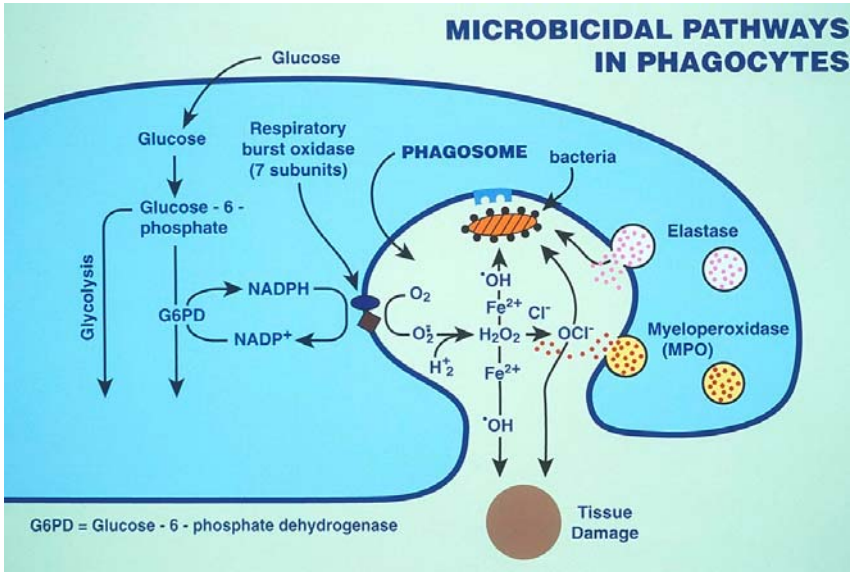
-Reaction consumes the cofactor NADPH

-NADPH can only be regenerated via reactions in glucose-6-phosphate cycle (through the formation of G6PD, an intermediate of the pentose phosphate shunt)

-In the presence of protons, superoxide is dismutated into H_2O_2

-In the presence of Fe^{2+}, H_2O_2 is catalytically split into several products including hydroxyl radical

-Tissue damage if we get hydroxyl radical leakage



-Myeloperoxidase acts on H_2O_2, forming hypochloric acid

-Combo of all these oxygen species is a major weapon against pathogens

Regulators

•Different nomenclature (CSF (colony stimulating factor) vs IL (interleukin)) because hematologists and immunologists were making simultaneous discoveries

•Growth factors are divided into two classes (Note, not an official division)

•Class I growth factors: -Act on pluripotent stem cells and immature progenitor cells
-SCF (stem cell factor), GM-CSF (essential for growth of BFU-Es), Multi- CSF/IL-3 (also needed for growth of BFU-E colonies), IL-1, IL-6

•Class II growth factors: -Act on mature progenitor cells during later stages of hematopoiesis
-Act on specific cell lines
-Erythropoietin, G-CSF, M-CSF, IL-4 (mast cells), IL-5 (eosinophils), IL-6 (megakaryocyte development, but thrombopoietin is a more specific growth factor)

•No similarity in primary structure of these growth factors
•Possible similarity in the tertiary structure
•All heavily glycosylated
•Glycosylation isn't needed for function or interaction with receptors but to increase lifespan

•Erythropoietin
-One of first hematopoietic growth factors studied
-Cell specific and so others were expected to be also→ **not the case**
-Even erythropoietin influences megakaryocte development and may have extra-hematopoietic effects such as protection in brain and other tissues

•GM-CSF
-Regulatory role is even more complex than Epo's
-Acts on any type of hematopoietic cell since works on committed progenitors
-Extra-hematopoietic effects on placenta

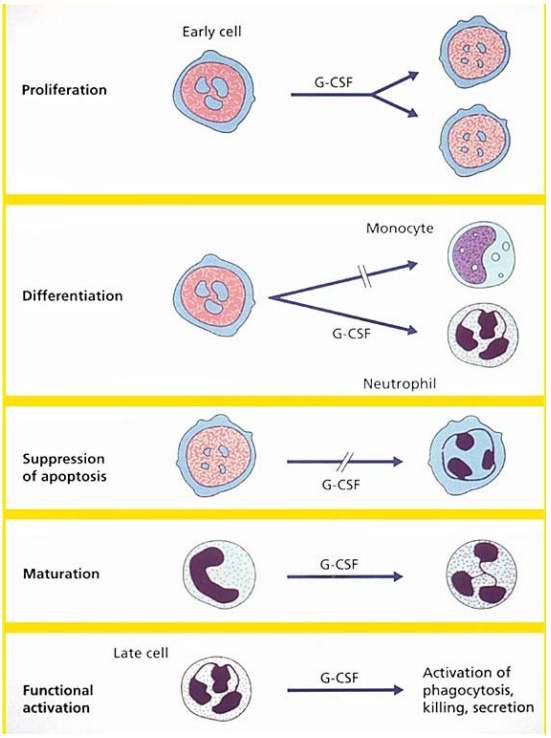
•LIF (Leukemia inhibiting factor)
-Even greater number of extra-hematopoietic effects
Ex. -Inhibits leukemic cell growth
-Action on neurons

•Three methods by which regulators manifest their functions:
1) Factor may be associated with stromal cell membrane (ex. fibroblast, osteoblast) and stimulate attached hematopoietic stem cells
2) Factor may be locally produced
3) Factor may be produced elsewhere and delivered via circulatory system (ex. erythropoietin)

•M-CSF is an example of a regulator that acts in all three ways

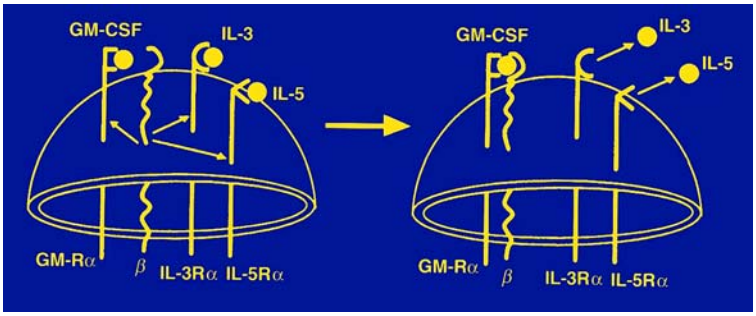
•G-CSF
-Example of a growth factor with diverse effects on cells at various stages of maturation
-In early cells, stimulates proliferation

-Later, pushes towards granulocytic path while blocking development into monocyte
-Suppression of apoptosis (like erythropoietin) → this is possibly a major role of many growth factors
-Evidence that it promotes maturation into fully differentiated cell
-Enhances activation of phagocytosis and granule secretion



Growth Factor Receptors
•Glycoproteins
•High affinity for their ligands, only low concentrations of receptors are required
•Full occupancy is not required for effect to occur

•2 groups of receptors
1) -Contain tyrosine kinase in their cytosolic tail
-Receptors for SCF (c-kit ligand) and M-CSF are the only examples of this group
2) -Lacking tyrosine kinase
-Made up of 2 types of chains: α are specific while β are shared competitively between receptors
-When ligand binds, α chain heterodimerizes with a β common chain
-ex. Receptors for GM-CSF, G-CSF, Multi-CSF (IL-3), IL-2, IL-4, IL-6



Competition for β chains explains why response of a target cell to one ligand diminishes it's response to another ligand

Recombinant CSFs
•Now available and widely used
•Used for quick recovery of granulopoiesis after transplantation
•In the course of autologous bone marrow transplantation, marrow is ablated by irradiation greatly reducing the neutrophil population
•Administer G-CSF to increase regeneration of neutrophils
•Similar treatment for patients undergoing chemotherapy (also leads to ablation of bone marrow)