Functions of The Blood

- Transport
- Defense
- Hemostasis
- Homeostasis

Genesis of Red Blood Cells

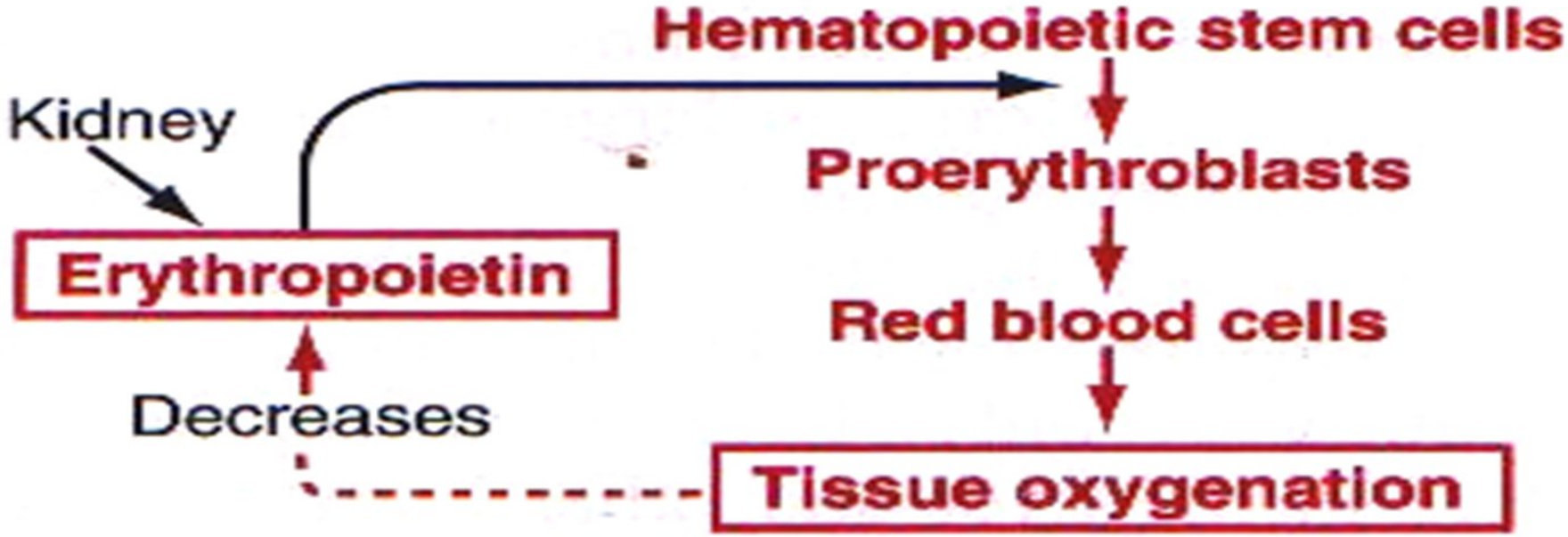
- Pluripotential Hematopoietic Stem Cells (PHSC) reproduce and give
  - Burst Forming unit Erythrocyte (BFU-E)
  - Colony-forming unit–erythrocyte (CFU-E)
- From CFU-E, other erythroid committed progenitors arise
- Growth inducers promotes growth and reproduction of cells
- Differentiation inducers promotes differentiation of cells

Erythropoietin

- The main hormone controlling RBCs production
- Increased with poor tissue oxygen delivery
  - Anemia
  - High attitudes
  - Chronic lung disease
  - Cyanotic congenital heart disease
- About 90 percent of all erythropoietin is formed in renal, peritubular fibroblast like interstitial cells
- Renal tissue hypoxia leads to increased tissue levels of **hypoxia-inducible factor–1** (HIF-1) which turns on erythropoietin gene

- The remainder is formed mainly by hepatic perisinusoidal cells
- Non renal events
  - Norepinephrine and epinephrine and several prostaglandins stimulate erythropoietin production

- Loss of renal tissue invariably leads to anemia
- Erythropoietin stimulates production of Proerythroblast and fasten their maturation



Factors that decrease oxygenation

1. Low blood volume
2. Anemia
3. Low hemoglobin
4. Poor blood flow
5. Pulmonary disease

B12 and folate

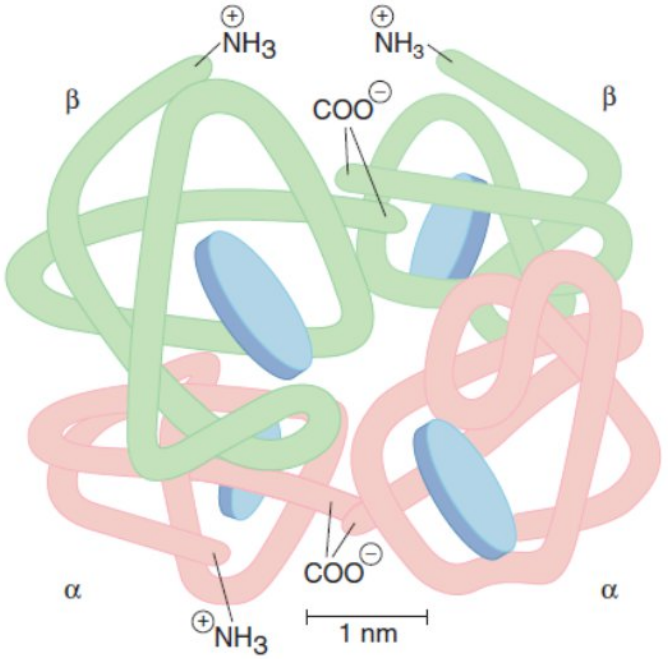
- Erythropoietic cells are rapidly reproducing
- Particular need for B12, folate for DNA building blocks
- Especiallyimportant for final maturation of the RBCs
- Deficiency
  - Reduced proliferation / maturation failure
  - Larger than normal finally differentiated cell
  - Weak irregular membrane

Hemoglobin

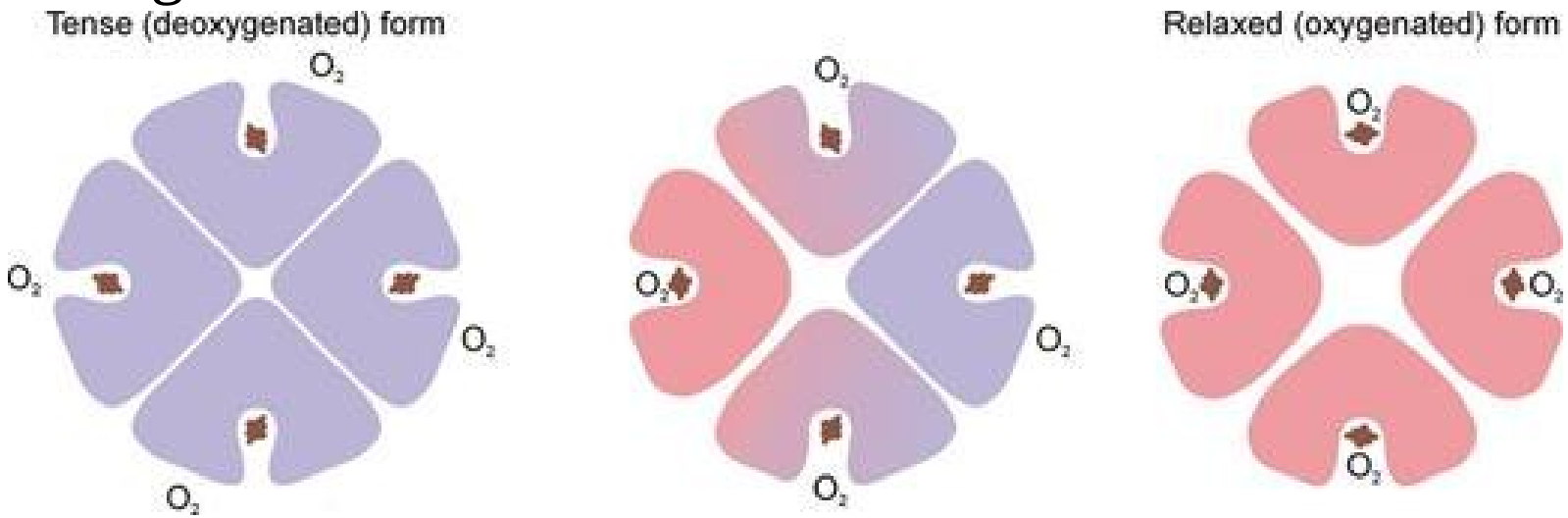
- The average normal hemoglobin content of blood is 16 g/dL in men and 14 g/dL in women,
- In the body of a 70-kg man, there are about 900 g of hemoglobin,
- About 0.3g of hemoglobin is destroyed and 0.3 g synthesized every hour
- The heme portion of the hemoglobin molecule is synthesized from glycine and succinyl-CoA

Hemoglobin

- Hb chains are alpha chains, beta chains, gamma chains, and delta chains
  - HA α 2 β 2
  - HA2 α 2 δ 2
  - HF α 2 γ 2
- Glycated hemoglobins, HbA1c
- Each hemoglobin molecule has 4 heme groups, binds 4 oxygen molecules
- Hemoglobin Oxygen binding is reversible
- The iron stays in the ferrous state, so that the reaction is oxygenation (not oxidation).

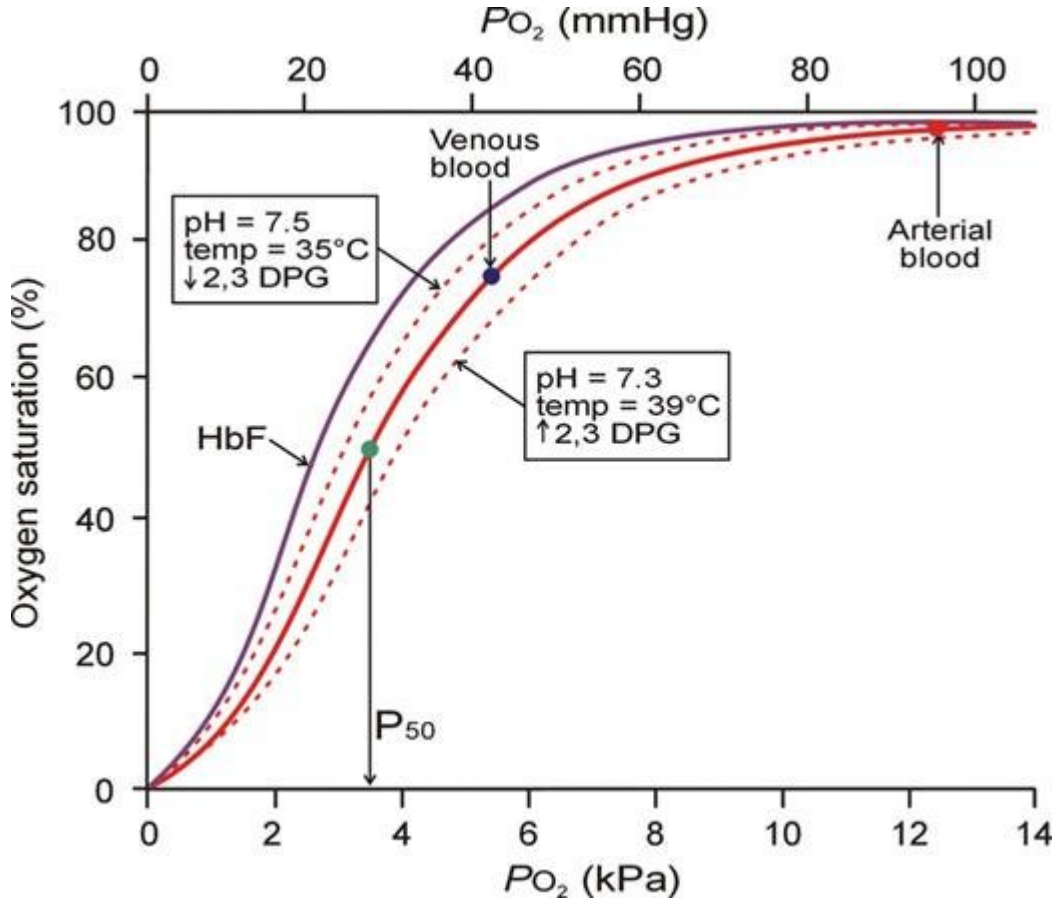


- The quaternary structure of hemoglobin determines its affinity for O2
  - Deoxyhemoglobin → tense (T)
  - Oxyhemoglobin → Relaxed (R)



Oxygen–hemoglobin dissociation curve

- Sigmoid shape due to the T–R interconversion
- Saturation unsaturation of Hgb is by changes in PO2
- Other factors affecting affinity
  - pH
  - Temperature
  - Concentration of 2,3-diphosphoglycerate
- Carbon monoxide markedly affect oxygen-carrying capacity of blood

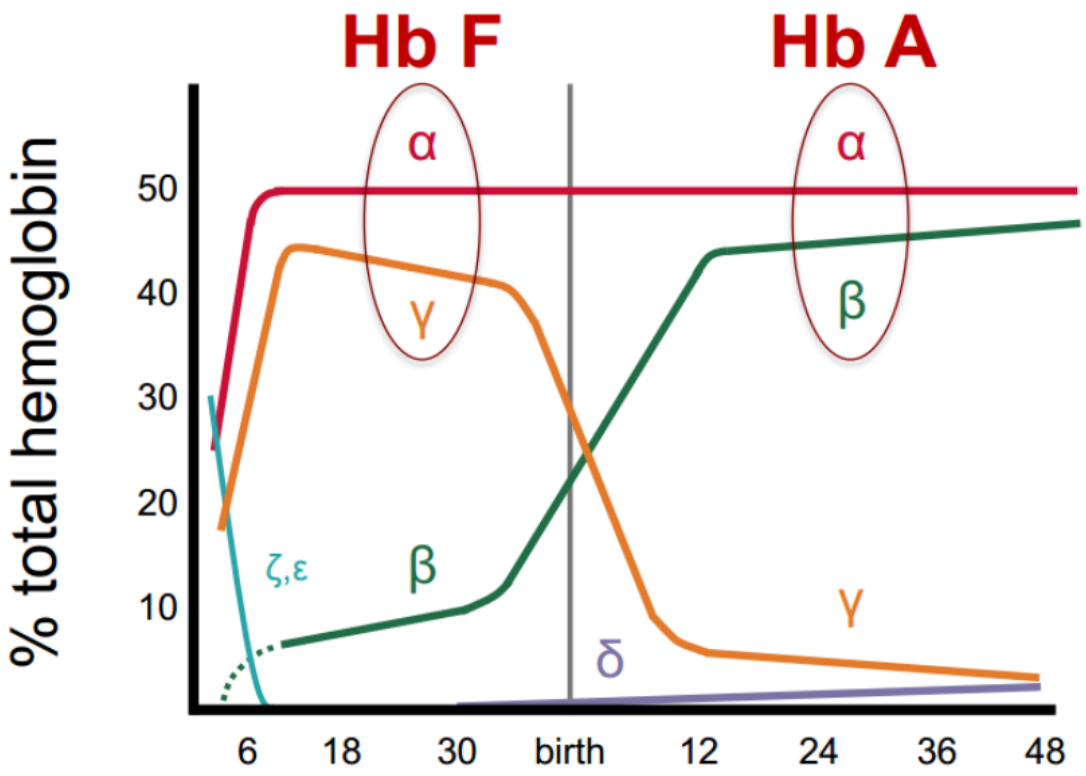


Methemoglobin

- Ferrous iron (Fe^{2+}) is converted to ferric iron (Fe^{3+})
- May occur normally, (NADH) methemoglobin reductase system converts it back to hemoglobin
- Drugs and other oxidizing agents
- Congenital absence of methemoglobin reductase system results in hereditary methemoglobinemia
- Dark-colored, poor oxygen carrying, causes dusky discoloration of the skin

HEMOGLOBIN IN THE FETUS

- In young embryos Gower 1 hemoglobin (ζ2ε2) and Gower 2 hemoglobin (α2ε2)
- Later in intrauterine life hemoglobin F (α2γ2) predominate
- Hemoglobin F to hemoglobin A transformation completes during first months of life reaching adult value at 12 months.



Life-Span of RBC's

- Cytoplasmic enzymes metabolize glucose and produce ATP to keep RBC's viable
  - Maintains integrity of cell membrane (pliability and transport of ions)
  - Keeps iron in the ferrous
  - Prevents oxidation of cell proteins

- With aging membrane becomes fragile and RBC's lyse while passing through tight spots of the circulation

- Hemoglobin is phagocytized by macrophages mainly in liver Kupffer cells, spleen & marrow

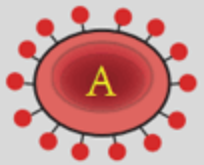
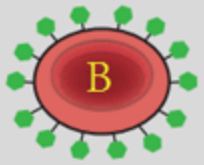
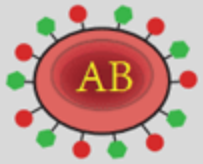
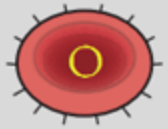
- Macrophages release the iron which is either
  - carried by transferrin for further production of Hgb in marrow erythroblasts OR
  - Stored as ferritin liver and other organs

- Porphyrin is converted to biliverdin which is converted to bilirubin, which is secreted by liver into bile

BLOOD TYPES

- Typing depends on blood group antigens called agglutinogens.
- The most important are the A and B antigens,
- H antigen is usually present in individuals of all blood types
- Type A individual has a terminal N-acetylgalactosamine on the H antigen,
- Type B individual has a terminal galactose on the H antigen
- Type AB individual has both, Type O has neither

Agglutinins

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in red blood cell	 A antigen	 B antigen	 A & B antigens	None

Transfusion reaction

- Dangerous hemolytic reactions from incompatible transfusion
- The plasma in the transfusion doesn't agglutinate recipient's RBCs
- The recipient's plasma has agglutinins against the donor's red cells, the cells agglutinate and hemolyze
- The severity of the resulting transfusion reaction can vary
- Blood should always be cross-matched before transfusion
- Autologous transfusion

INHERITANCE OF A & B ANTIGENS

- The A and B antigens are inherited as mendelian allelomorphs, A and B being dominants,
- Individual with type B blood may have inherited a B antigen from each parent or a B antigen from one parent and an O from the other
- ABO typing can prove that a man cannot be the father

Blood group	Antigen(s) present on the red blood cells	Antibodies present in the serum	Genotype(s)
A	A antigen	Anti-B	AA or AO
B	B antigen	Anti-A	BB or BO
AB	A antigen and B antigen	None	AB
O	None	Anti-A and Anti-B	OO

ABO genotype in the offspring		ABO alleles inherited from the mother		
		A	B	O
ABO alleles inherited from the father	A	A	AB	A
	B	AB	B	B
	O	A	B	O

Rhesus system

- A system composed primarily of the C, D, E, c, d, and e antigens
- It is not detected in tissues other than red cells
- D is the most antigenic component
- Rh positivity corresponds to the presence of agglutinogen D
- Anti-D antibodies only develop after exposure to D-positive red cells
- Anti-D antibodies may persist for years after exposure
- Anti-Rh antibodies are IgG
- Rh negativity varies in different racial groups

Hemolytic disease of newborn

- Arises when an Rh-negative mother carries an Rh-positive fetus
- Maternal sensitization may happen
  - Fetal–maternal hemorrhage during pregnancy
  - During labor
  - During abortion
  - After previous Rh+ve transfusion
- Anti-Rh agglutinins cross the placenta to an Rh-positive fetus causing hemolysis (erythroblastosis fetalis).

- Hydrops fetalis: severe hemolysis and anemia, severe jaundice, and edema may lead to intrauterine fetal death
- Kernicterus: deposition of unconjugated bilirubin in the basal ganglia, infants have immature
  - Blood brain barrier
  - Bilirubin Conjugating system
- The first Rh +ve child born to Rh -ve mother is usually normal
- Prevention of maternal sensitization by administering single dose of Rh immunoglobulin during the postpartum period.

PLASMA

- The fluid portion of the blood,
- A solution containing large number of ions, inorganic molecules, and organic molecules.
- Volume is about 5% of body weight, or roughly 3500 mL in a 70-kg man
- Plasma can clots unless an anticoagulant is added
- If whole blood is allowed to clot and the clot is removed, the remaining fluid is called serum.
- Serum has the same composition of plasma after removing fibrinogen, factor II, V, VIII and variable amounts of other factors

PLASMA PROTEINS

- Albumin, globulin, and fibrinogen fractions
- Circulating immunoglobulins are manufactured by lymphocytes. Most of the other plasma proteins are synthesized in the liver
- Oncotic pressure pulls water into the blood
- The plasma proteins contribute to the buffering capacity of the blood
- Many have specific functions

- Synthesis of albumin plays an important role in the maintenance of its normal levels.
- Plasma albumin level is 3.5–5.0 g/ dL, 38–45% of it is intravascular
- Between 6 and 10% are degraded daily, then replaced by hepatic synthesis of 200–400 mg/kg/d
- Albumin is decreased during fasting and in nephrosis in which there is excessive albumin loss

HYPOPROTEINEMIA

- Caused by
  - Prolonged starvation
  - Malabsorptionsyndromesdue to intestinal diseases
  - Liver disease
  - Nephrosis
  - Congenital synthetic defect (rare)
- Oedema tends to happen because of low oncotic pressure

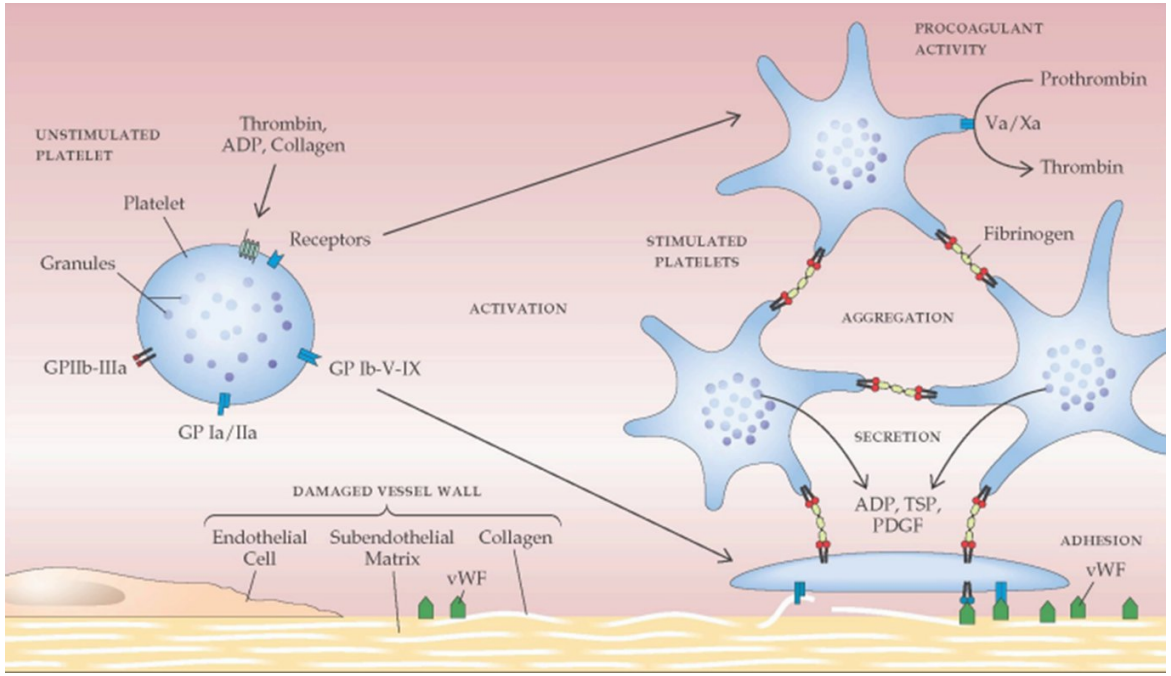
Hemostasis

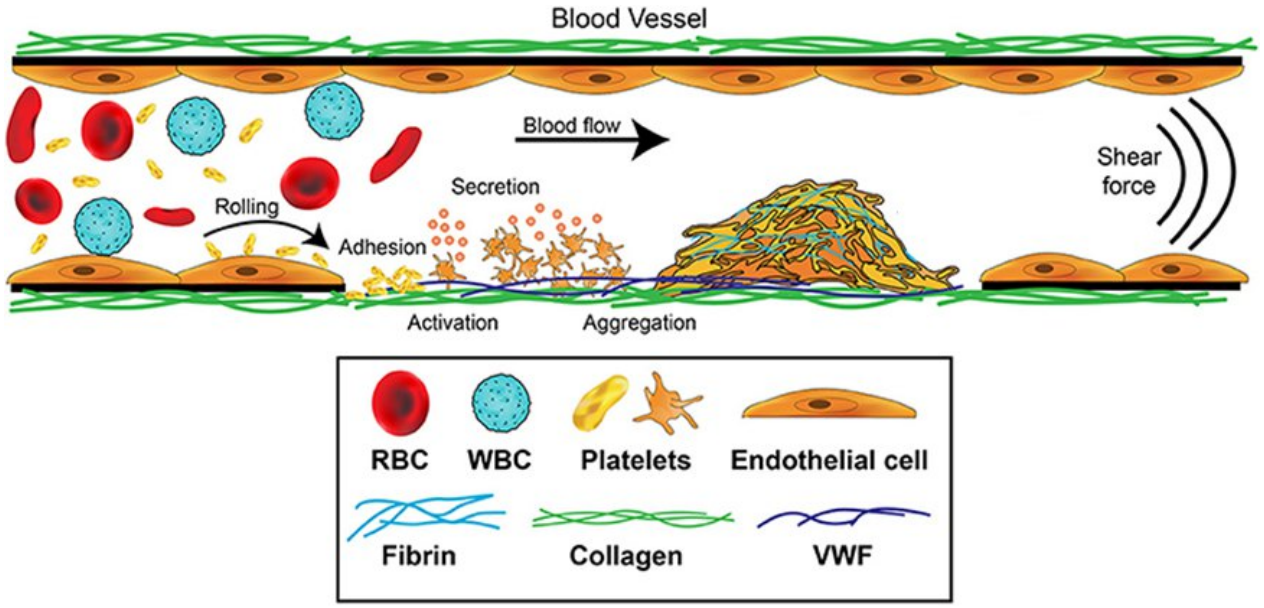
- Hemostasis is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system.
  - Vascular constriction
  - Formation of a platelet plug (primary hemostasis)
  - Formation of a blood clot as a result of blood coagulation (secondary hemostasis)
  - Eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently

VASCULAR CONSTRICTION

- Trauma to the vessel wall causes smooth muscle in the wall to contract reducing the flow of blood from the ruptured vessel.
  - Local myogenic spasm
  - Local factors from the traumatized tissues and blood platelets
  - Nervous reflexes
  - In small vessels, thromboxane A2 from PLTs
- The more severely a vessel is traumatized, the greater the degree of vascular spasm.

FORMATION OF THE PLATELET PLUG





FORMATION OF THE PLATELET PLUG

- Platelets get activated, begin to swell and assume irregular forms with numerous pseudopods
- Adhesion, contractile proteins cause degranulation of multiple active factors, strengthening adherence to collagen and to a protein called von Willebrand factor via GP Ib IX
- Aggregation, active PLTs secrete large quantities of ADP and thromboxane A2 activating more PLTs and these get linked together by fibrinogen that binds GP IIb IIIa receptor.
- The platelet-plugging mechanism is extremely important for closing minute ruptures in very small blood vessels

THE CLOTTING MECHANISM/ COAGULATION

- The loose platelets aggregate solidification by fibrin.
- The fundamental reaction is conversion of fibrinogen by thrombin
- Thrombin is formed from prothrombin by the action of activated factor X in the presence of factor V (prothrombin activator).
- The rate limiting factor in causing blood coagulation is usually the formation of prothrombin activator

Formation of prothrombin activator

- Prothrombin activator is generally considered to be formed in two ways
  - Extrinsic pathway
  - Intrinsic pathway that begins in the blood

- Both pathways Involve a cascade of enzymatic reactions and a series of numbered clotting factors (coagulation factors).

Extrinsic Pathway for Initiating Clotting

1. Release of tissue factor
2. Activation of Factor X—role of Factor VII and tissue factor.
3. Effect of Xa to form prothrombin activator—role of Factor V.

Intrinsic Pathway for Initiating Clotting

1. Blood trauma causes activation of Factor XII and release of platelet phospholipids
2. Activation of Factor XI
3. Activation of Factor IX by activated Factor XI
4. Activation of Factor X—role of Factor VIII
5. Action of activated Factor X to form prothrombin activator—

CONVERSION OF PROTHROMBIN TO THROMBIN CONVERSION OF FIBRINOGEN TO FIBRIN FORMATION OF THE CLOT

- Prothrombin activator, in the presence of sufficient amounts of ionic calcium (Ca++), causes conversion of prothrombin to thrombin
- Thrombin is a protein enzyme with weak proteolytic capabilities that converts fibrinogen to fibrin monomers that polymerize to form fibrin fibers.

- Calcium ions are required in blood-clotting reactions
- Calcium ion concentration seldom falls low enough to significantly affect the kinetics of blood clotting
- When blood is removed from a person, it can be prevented from clotting

FIBRIN CLOT STABILIZATION

- Initially, the polymerized fibrin monomers are held together by weak bonds
- Fibrin stabilizing factor (F XIII) present in the plasma and released from PLTs in the clot, it is activated by thrombin.
- Activated factor XIII causes covalent bonds between more and more of the fibrin monomer molecules, as well as multiple cross-linkages between adjacent fibrin fibers adding more strength to the fibrin meshwork

Clot Retraction and Expression of Serum

- Begins few minutes after the clot is formed expressing most of the fluid in the clot (serum)
- Platelets are necessary for clot retraction
- Platelets in blood clots are attached to the fibrin fibers in such a way that they actually bond different fibers together.
- Contractile Proteins in the platelets thrombosthenin, actin, and myosin, cause strong contraction of the platelet spicules attached to the fibrin
- As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to hemostasis

ANTICLOTTING MECHANISMS

- The tendency of blood to clot is balanced in vivo by a) factors that prevent clotting inside the blood vessels, b) factors that break down any clots that do form, or c) both
- **Antithrombin III (AT III)** is a circulating protease inhibitor that inactivate thrombin remained after fibrin adsorbed most of it.
- AT III when combined to heparin, become many hundred time more efficient in removing thrombin
- **Thrombomodulin** All endothelial cells except those in the cerebral microcirculation produce thrombomodulin, a thrombin-binding protein, on their surfaces

- Thrombin is a procoagulant at the site of injury but when it binds to thrombomodulin, it becomes an anticoagulant in that thrombomodulin–thrombin complex activates protein C
- Activated protein C (APC), along with its cofactor protein S, inactivates factors V and VIII and inactivates an inhibitor of tissue plasminogen activator, increasing the formation of plasmin.

FIBRINOLYSIS

- Tissue-type plasminogen activator (t-PA) forms plasmin from its inactive precursor, plasminogen
- Plasmin lyses fibrin and fibrinogen, with the production of fibrinogen degradation products (FDP) that inhibit thrombin
- Plasminogen receptors are located on the surfaces of many different types of cells and are plentiful on endothelial cells.
- When plasminogen binds to its receptors, it becomes activated, so intact blood vessel walls are provided with a mechanism that discourages clot formation.

Thank you