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hemostasis

- steps
  - Primary hemostasis
    - Arteriolar vasoconstriction
      - occurs immediately and markedly reduces blood flow to the injured area.
      - it is mediated by reflex neurogenic mechanisms.
      - it is augmented by endothelin, a potent endothelium-derived vasoconstrictor.
      - this effect is transient, however, bleeding would resume if not followed by activation of platelets and coagulation factors.
    - platelet activation
      - Platelet adhesion:
        - is mediated via interactions with vwf, which acts as a bridge between the platelet surface receptor glycoprotein ib (gpib) and exposed collagen.
      - platelet activation.
        - changes in shape from smooth discs to spiky “sea urchins” with greatly increased surface area.
          - alterations in glycoprotein iib/iiia that increase its affinity for fibrinogen
          - the translocation of negatively charged phospholipids to the platelet surface
        - Secretion of granule contents,
          - Thrombin: activates platelets
          - ADP: create an additional rounds of platelet activation.
          - thromboxane A2 (TXA2): a potent inducer of platelet aggregation.
      - Platelet aggregation follows their activation.
        - The conformational change in glycoprotein iib/iiia allows binding of fibrinogen that forms bridges between adjacent platelets, leading to their aggregation
        - cytoskeleton cause contraction of the plug
  - Secondary hemostasis
    - deposition of fibrin.
    - Vascular injury exposes tissue factor at the site of injury.
    - Tissue factor binds and activates factor VII, setting in motion a cascade of reactions that culiminates in thrombin generation.
  - Clot stabilization and resorption
    - Polymerized fibrin and platelet aggregates undergo contraction to form a solid, permanent plug that prevents further hemorrhage.
    - Entrapped red cells and leukocytes are also found in hemostatic plugs, in part due to adherence of leukocytes to P-selectin expressed on activated platelet
    - At this stage, counterregulatory mechanisms (e.g., tissue plasminogen activator, t-PA made by endothelial cells) are set into motion that limit clotting to the site of injury , and eventually lead to clot resorption and tissue repair.
- Coagulation Cascade
  - pathways
    - intrinsic
      - components are assembled on a negatively charged phospholipid surface, which is provided by activated platelets
      - activates XII to XIIa which activates XI to XIa which activates IX to form IXa-VIIIa
      - IXa-VIIIa activates X to Xa-Va which activates prothrombin to thrombin
    - extrinsic
      - tissue factor TF binds VII to form VIIa-TF
      - VIIa-TF activates X to Xa-Va which activates prothrombin to thrombin
  - tests
    - The prothrombin time (PT
      - assesses the function of the proteins in the extrinsic pathway (factors VII, X, V, II (prothrombin), and fibrinogen).
    - The partial thromboplastin time (PTT)
      - screens the function of the proteins in the intrinsic pathway (factors XII, XI, IX, VIII, X, V, II, and fibrinogen.

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- **hemostasis**
  - **platelets**
    - play a critical role in hemostasis by forming the primary plug that initially seals vascular defects and by providing a surface that binds and concentrates activated coagulation factors.
    - Their function depends on several factors including:
      - Glycoprotein receptors.
      - A contractile cytoskeleton
      - two types of cytoplasmic granules.
        - α-granules have the adhesion molecule p-selectin, and contain proteins involved in coagulation.
        - dense (or δ) granules contain ADP and ATP , ionized calcium, serotonin, and epinephrine.
  - **endothelium**
    - Platelet inhibitory effects:
      - serve as a barrier that shields platelets from subendothelial vWF and collagen.
      - releases a number of factors that inhibit platelet activation and aggregation. Among the most important are prostacyclin (PGI2), nitric oxide (NO).
      - endothelial cells bind and alter the activity of thrombin, which is one of the most potent activators of platelets.
    - Anticoagulant effects
      - Normal endothelium shields coagulation factors from tissue factor in vessel walls
      - and expresses multiple factors that actively oppose coagulation
        - most notably thrombomodulin, endothelial protein C receptor, heparin-like molecules, and tissue factor pathway inhibitor
  - **Factors That Limit Coagulation.**
    - simple dilution:
      - blood flowing at the site of injury washes out activated coagulation factors, which are rapidly removed by the liver.
    - requirement for negatively charged phospholipids
    - fibrinolytic cascade:
      - plasminogen activators activate plasminogen to plasmin which breaks down fibrin and interferes with its polymerization.
  - **thrombin functions**
    - Conversion of fibrinogen into crosslinked fibrin.
      - Thrombin directly converts soluble fibrinogen into fibrin monomers that polymerize into an insoluble fibril.
    - .Platelet activation.
    - Anti-coagulant effects.
      - encountering normal endothelium, thrombin changes from a procoagulant to an anticoagulant.