COAGULATION: BASIC PRINCIPLES

Peyman Eshghi
Prof. of Pediatric Hematology & Oncology
Haemostasis overview:

- **BV Injury**
- **Platelet Activation**
- **Platelet Aggregation**
- **Blood Vessel Constriction**
- **Coagulation Cascade**
- **Contact/Tissue Factor**
- **Primary hemostatic plug**
- **Reduced Blood flow**
- **Platelet Activation**
- **Fibrin formation**
- **Stable Hemostatic Plug**

Neural
Haemostasis:

- Vasoconstriction – N
- Platelet activation
- Haemostatic plug
- Coagulation
- Stable clot formation
- Clot dissolution
ENDOTHELIAL FUNCTIONS

- Vasomotor tone
- Barrier function
- Hemostatic balance
- Leukocyte trafficking
- Angiogenesis
- Cell survival/apoptosis
- Antigen presentation
- Innate immunity
ANTITHROMBOTIC COMPONENTS OF THE VESSEL WALL
Vascular Endothelium Function

Prostacyclin: COX-2-derived

Thromboxane A\(_2\): COX-1-derived

ELAMs, ICAMs

von Willebrand factor

Vasodilation, inhibition of platelet aggregation

From platelets, muscular arteries constrict

Cytokines induce synthesis to promote leukocyte adhesion

Promote platelet-collagen adhesion to exposed sub-endothelium
Vascular Endothelium Function

- **Tissue factor pathway inhibitor**
- **Thrombomodulin**
- **Tissue plasminogen activator**
- **Heparan sulfate proteoglycans**
- **Tissue factor**

**Anticoagulant**
- Inhibits coagulation extrinsic pathway
- Inhibits coagulation by activating protein C system
- Inhibits coagulation by activating fibrinolysis
- Inhibits coagulation by activating antithrombin

**Procoagulant**
- Inflammatory cytokines (IL-1, TNF) induce expression
• an endothelial cell from a liver capillary relies more on VWF, PAI-1, and TFPI to balance hemostasis, whereas an endothelial cell from a lung capillary expresses more thrombin receptor, tPA, and heparan.
Blood Platelets

• Platelets are formed from the cytoplasm of bone marrow megakaryocytes and are the smallest of the blood cells.

• Normal platelet count lies between 150-400 x 10⁹/L

• Platelet life span: 7 to 10 days before being cleared by the liver and spleen - being controlled, at least in part, by an antagonistic balance between the apoptotic proteins Bcl-xL and Bak-.
Blood Platelets (cont’d)

- Disc-shaped, anucleated cells with complex internal structure reflecting the specific hemostatic functions of the platelet.

- Platelets also contain two highly specialized membrane systems not found in other cells of the body:
  - the surface-connected open canalicular system (OCS);
    - increase surface area
    - Alpha granules fuse with membranes of the OCS and release their contents to the exterior of the cell.
  - the dense tubular system (DTS): reservoire of Ca
    - contain a 100-kd calcium adenosine triphosphatase (ATPase) known as SERCA2b34 that functions to sequester and store cytosolic calcium in resting cells
Blood Platelets (cont’d)

• Platelet size is undoubtedly regulated by numerous factors during their biogenesis, but both the 224-kd nonmuscle myosin heavy chain IIA (MYHIIA) and the cell surface glycoprotein Ib (GPIb) complex appear to play critical roles.

• The volume of a platelet (mean platelet volume) normally ranges from 6 to 10 fL.
Blood Platelets (cont’d)

• Two major types of intracellular granules:
  ▪ a-granules contain: coagulation factors (fibrinogen, von Willebrand Factor, and coagulation factors V and VIII); and platelet-derived growth factor (PDGF).
  ▪ dense granules (because of their appearance on EM) contain: ADP, ATP and serotonin.

• a- and dense granules contents released by platelet activation.
Diagrammatic Representation of the Platelet

- Glycogen
- Glycocalyx
- Electron dense granule: nucleotides (ADP), Ca^{2+}, serotonin
- Specific α-granule: growth factor, fibrinogen, factor V, VWF, fibronectin, β-thromboglobulin, heparin antagonist (PF 4), thrombospondin
- Mitochondria
- Dense tubular system
- Plasma membrane
- Platelet phospholipid
- Open canalicular system
- Submembranous filaments (platelet contractile protein)
Table 15-1: α-Granule Contents\textsuperscript{4,21,23–29}

<table>
<thead>
<tr>
<th>Category</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesion molecules</td>
<td>P-Selectin,\textsuperscript{a} von Willebrand factor,\textsuperscript{a} thrombospondin, fibrinogen,\textsuperscript{a} integrin αIIbβ3, integrin αvβ3, fibronectin</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Platelet basic protein\textsuperscript{b,c} [platelet factor 4 and its variant\textsuperscript{b} (CXCL4) and β-thromboglobulin\textsuperscript{b}], CCL3 (MIP-1α), CCL5 (RANTES), CCL7 (MCP-3), CCL17, CXCL1 (growth-regulated oncogene-α), CXCL5 (ENA-78), CXCL8 (IL-8)</td>
</tr>
<tr>
<td>Coagulation pathway</td>
<td>Factor V,\textsuperscript{a} multimerin,\textsuperscript{a} factor VIII</td>
</tr>
<tr>
<td>Fibrinolytic pathway</td>
<td>α\textsubscript{2}-Macroglobulin, plasminogen, plasminogen activator inhibitor 1</td>
</tr>
<tr>
<td>Growth and angiogenesis</td>
<td>Basic fibroblast growth factor, epidermal growth factor, hepatocyte growth factor, insulin-like growth factor 1, transforming growth factor β, vascular endothelial growth factor-A, vascular endothelial growth factor-C, platelet-derived growth factor</td>
</tr>
<tr>
<td>Immunologic molecules</td>
<td>β1H Globulin, factor D, cl inhibitor, IgG</td>
</tr>
<tr>
<td>Other proteins</td>
<td>Albumin, α\textsubscript{1}-antitrypsin, Gas6, histidine-rich glycoprotein, high molecular weight kininogen, osteonectin protease nexin-II (amyloid beta-protein precursor)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}These platelet selective proteins are synthesized or taken up by megakaryocytes-platelets and found in relatively few other cells.

\textsuperscript{b}These platelet specific proteins are unique to platelets.

\textsuperscript{c}Platelet basic protein undergoes proteolysis to yield platelet factor 4 and β-thromboglobulin-related proteins.

Note: Many other molecules have been identified in platelet releasate but their presence in granules has yet to be demonstrated.
Table 15-2: Dense Granule Contents$^{4,31,138,139}$

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ions</strong></td>
<td>Ca, Mg, P, pyrophosphate</td>
</tr>
<tr>
<td><strong>Nucleotides</strong></td>
<td>ATP, GTP, ADP, GDP</td>
</tr>
<tr>
<td><strong>Membrane proteins</strong></td>
<td>CD63 (granulophysin), LAMP 2</td>
</tr>
<tr>
<td><strong>Transmitters</strong></td>
<td>Serotonin</td>
</tr>
</tbody>
</table>
Platelet Function

- During primary hemostasis, platelets display 4 properties:
  - adhesion to a surface
  - shape change
  - release of granule content
  - aggregation

Tissue Injury

Platelet Adhesion

Platelet shape change

Platelet aggregation

Secretion

Primary hemostatic plug
Phases of Hemostasis

Primary

- Platelet-mediated
- Endothelial cell-mediated

Secondary

- Fibrin-formation mediated

- Results in clinicians obtaining a clinical history using a two-compartment classification system:
  - primary defects result in immediate bleeding;
  - secondary defects cause delayed bleeding.
Old model - Normal coagulation cascade

**Intrinsic Pathway**

- FXII → FXIIa
- FXI → FXIa
- FIX → FIXa
- FVIII → FVIIIa
- Ca²⁺-PL

**Extrinsic Pathway**

- FX, TF, FVII → FVIIa

**Common Pathway Leading to Clot**

- FXa → FII → FIIa (Thrombin)
- FVa → FV
- Fibrinogen → Fibrin → Fibrin Polymer
- FXIII

Blood coagulation

PL = Phospholipids

QUESTIONS NOT ADDRESSED BY THE WATERFALL MODEL:

• Why don’t patients with FXII-deficiency bleed?

• What is the role of FVII, TF, and Extrinsic pathway?
HEMOSTASIS TAKES PLACE ON CELL SURFACES.

- TF-expressing cell
- thrombin activated platelet
HEMOSTASIS

TF

TF-BEARING CELL

VIIa

ACTIVATED PLATELET

THROMBIN

FIBRIN HEMOSTATIC PLUG

INITIATION OF HEMOSTASIS

PROPAGATION OF HEMOSTASIS
New, Cell Based Coagulation Model
modified from Hoffman & Monroe, Thromb Haemost 2001; 85: 958-965
New, Cell Based Coagulation Model

Initiation

TF-Bearing Cell

TF

VIIa

TF

VIIa

X

Xa

VIIa
New, Cell Based Coagulation Model

Initiation

TF-Bearing Cell

TF

VIIa

X

Xa

Va

IIa

II

XIIa
New, Cell Based Coagulation Model

Initiation

TF-Bearing Cell

Amplification

Activated Platelet
New, Cell Based Coagulation Model

Initiation
TF-Bearing Cell
TF
VIIa
Xa
Va
II
X

Propagation
IX
IXa
VIIIa

Amplification
XI
XIa
Activated Platelet

Platelet
VIIIa
VIII / VWF

V
Va

New, Cell Based Coagulation Model

Amplification

Activated Platelet

Platelet
VIIIa
VIII / VWF

V
Va
New, Cell Based Coagulation Model

Initiation:
- TF-Bearing Cell
- Initiates coagulation cascade

Propagation:
- Xa, Va, IIa, VIIIa
- Amplification of coagulation

Amplification:
- Activated Platelet
- XI, XIa, IX, IXa

TF, VIIa, Xa, Va, IIa, VIIIa, V, Va
New, Cell Based Coagulation Model

**Initiation**
- TF-Bearing Cell
  - TF
  - VIIa
  - Xa
  - Va

**Propagation**
- IIa
- VIIIa
- Platelet
- Clot formation

**Amplification**
- IXa
- XIa
- IX
- X
- IIa
- Activated Platelet

**Factors Involved**
- II
- V
- VIII / VWF
- XI
- XIa
Normal Haemostasis

1. TF-bearing cell
2. VIII/vWF → VIIIa
3. V → Va
4. XI → Xla
5. activated platelet
6. platelet
THROMBIN

- Activates platelets
- Activates FVIII and FV
- Activates FXIII necessary for the formation of fully stabilized fibrin clots/plugs
- Activates FXI (feed-back loop leading to more thrombin formation via FIX)
- Activates TAFI (thrombin activatable fibrinolytic inhibitor)

NECESSARY FOR HEMOSTASIS
FIBRINOGEN → FIIa (THROMBIN) → FIBRIN (SOLUBLE FIBRIN MONOMERS) → FXIIIa → STABILIZED, CROSS-LINKED FIBRIN (HAEMOSTATIC PLUG)

FIBRINOLYSIS → TAFI
Activated FXIII (FXIIIa) is a transglutaminase:

FXIIIa covalently crosslinks:

- fibrin polymers: forms a fibrin network that is resistant to shear stress
- a2-plasmin inhibitor to fibrin: protects it from the fibrinolytic enzyme plasmin.

Fibrinogen is composed of six polypeptide chains (two Aa chains, two B~ chains, and two γ chains)
Fibrinogen

Thrombin

Factor XIIIa

Soluble Fibrin Polymer

Plasmin

D dimers
• Fragment X can be converted to fibrin by thrombin, like Fibrinogen

• The fragments Y, D, and E are all nonclottable and may in fact inhibit the spontaneous polymerization of fibrinogen
• fibrin has been extensively cross-linked by factor XIII, however, the resulting D fragments are cross-linked to an E domain fragment.

• An assay of cross-linked D-dimer fragments is used clinically to identify **disseminated intravascular coagulation** like states associated with excessive plasmin-mediated fibrinolysis.
Molecular biology, biochemistry of coagulation Prs

• **Zymogens**
  – Vit K dependent zymogens (II, VII, IX, X, PrC)
  – Contact Factors

• **Cofactor**
  – Soluble cofactors (prS, V, VIII, vWF, PrZ, HK)
  – Cell-associated cofactors (Tissue factor-Thrombodulin)

• **Fibrinogen**

• **Plasma coagulation protease inhibitor** [Serpins] (ATIII, TFPI)
<table>
<thead>
<tr>
<th>Protein</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKDF</td>
<td>Liver</td>
</tr>
<tr>
<td>FV</td>
<td>Mainly Liver; minimally megakaryocytes</td>
</tr>
<tr>
<td>FVIII</td>
<td>Liver and Spleen</td>
</tr>
<tr>
<td>VWF</td>
<td>Endothelial cells and megakaryocytes</td>
</tr>
<tr>
<td>AT</td>
<td></td>
</tr>
<tr>
<td>TFPI</td>
<td>Mainly Endothelial cells; minimally megakaryocytes</td>
</tr>
<tr>
<td>FXIII</td>
<td>A subunits in BM (50% in MK); B subunits in liver</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Liver</td>
</tr>
</tbody>
</table>
- Vit K1 (Phyloquinone): leafy green vegetables
- Vit K2 (Menaquinone): synthesized in gut by Gr-bacteria
- Vit K3 (Menadiones): no intrinsic activity until in vivo modification
<table>
<thead>
<tr>
<th>ENZYME: SERINE PROTEASE (VKDF)</th>
<th>CO-FACTORS</th>
<th>COMPLEX name</th>
<th>Substrate/product</th>
<th>Location of activity: Membrane surface of an exposed or activated cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prothrombinase</td>
<td>II/II a</td>
<td>platelet</td>
</tr>
<tr>
<td>Xa</td>
<td>Va</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IX a</td>
<td>VIII a</td>
<td>Intrinsic Xase</td>
<td>X/Xa</td>
<td>platelet</td>
</tr>
<tr>
<td>VII a</td>
<td>TF</td>
<td>Extrinsic Xase</td>
<td>X &amp; IX/Xa</td>
<td>many cells</td>
</tr>
<tr>
<td>II a</td>
<td>TM</td>
<td>PCase</td>
<td>PC/APC</td>
<td>endothelium</td>
</tr>
<tr>
<td>APC</td>
<td>PS</td>
<td></td>
<td>VIII a &amp; V a</td>
<td>endothelium</td>
</tr>
</tbody>
</table>
Extrinsic factor Xase

Intrinsic factor Xase

Prothrombinase

Protein Case
<table>
<thead>
<tr>
<th>CONDITIONS</th>
<th>RELATIVE RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>XaCa²⁺</td>
<td>1</td>
</tr>
<tr>
<td>XaCa²⁺/platelet⁹</td>
<td>150⁹</td>
</tr>
<tr>
<td>XaCa²⁺/VIIIa</td>
<td>250³</td>
</tr>
<tr>
<td>XaCa²⁺/platelet⁹/VIIIa</td>
<td>9,000,000⁹</td>
</tr>
</tbody>
</table>
TF & FVII

• In the absence of injury or stimulation, active TF is not ordinarily expressed.
• Monocytic cells and monocytes also express TF when stimulated by bacterial endotoxin or other proinflammatory agents.
• TF can bind either factor VII or factor Vlla to form a high-affinity 1:1 complex. Once bound to TF, the zymogen factor VII may be converted to factor Vlla via limited proteolysis.
SUMMARY

• Each complex catalyst is orders of magnitude $10^3$- to $10^6$-fold more efficient than the individual serine protease acting on its substrate in solution.

• The factor IXa-factorVIIIa complex is $10^6$-fold more active as a factor X activator and 50 times more efficient than the factor VIIa-TF complex.

• Most (>90%) of factor Xa is ultimately produced by the factor VIIIa-factor IXa complex.
• The sum of inhibitory functions is far in excess of the potential coagulant response:
  – TFPI
  – Thrombomodulin-dependent activation of protein C
  – AT
  – Actively non thrombogenic and nonadhesive surface of the vascular endothelium.
<table>
<thead>
<tr>
<th>ANTI COAGULANT</th>
<th>TARGET</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>SERINE PROTEASE*&lt;br&gt;II,Xa,IXa,VIIa-TF*,Xla,XIIa,Kallikrein</td>
</tr>
<tr>
<td>TFPI</td>
<td>VIIa-TF</td>
</tr>
<tr>
<td>APC</td>
<td>VIII a; V a</td>
</tr>
</tbody>
</table>

*FVIIa unlike other serine proteases is not readily inhibited by AT-HEP unless bound to TF. Otherwise coagulation cascade could not be started.
TFPI

- TFPI is the principal stoichiometric inhibitor of the extrinsic pathway.
- 90% in endothelium; 10% in platelets.
- The inhibitory activity of TFPI is enhanced by heparin. (2 to 10 folds)
- Synergistic regulatory effect when combined with the stoichiometric inhibitor AT: inducing high kinetic "thresholds" for initiating TF stimulus.
Once the extrinsic tenase complex activates factor X to factor Xa, TFPI can form a quaternary complex (factor VIIa- Tffactor Xa- TFPI) with no enzymatic activity facilitates the inhibition of factor VIIa
• When AT is complexed with heparin, its rate of binding to thrombin increases 1000-fold.

• After complex formation with antithrombin, the complex rapidly dissociates from the heparan.
The endothelial cell protein C receptor (EPCR) provides cell-specific binding sites for both protein C and APC.
• Approximately 40% of protein S circulates in the free form: cofactor for APC

• the remaining 60% circulates as a 1:1 complex with C4b-binding protein (C4bBP), a regulatory protein of the complement system: may inhibit factor X activation as well
Fibrinolytic Proteins

- **PROTEASES:**
  - Plasminogen
  - tPA
  - uPA
  - Accessory Plasminogen Activators: kallikrein, factor Xla, and factor XIIa (no more than 15% of the total plasmin-generating activity)

- **FIBRINOLYTIC INHIBITORS**
  - **MAJOR SERPIN (SERINE PROTEASE) INHIBITORS**
    - alpha2AP
    - PAI-1
    - PAI-2
  - **NONSERPIN INHIBITORS**
    - TAFI
    - a2-MG
zymogen plasminogen (Pig) is converted to the active serine protease plasmin (PN) through the action of tissue plasminogen activator (tPA) or urokinase (uPA).

- tPA, plasminogen, and fibrin form a ternary complex that accelerates the catalytic efficiency of plasmin generation by approximately 500-fold.
• Urokinase is also an efficient plasminogen activator (uPA), but its action is only minimally enhanced by fibrin
• Both tPA and uPA can be inhibited by plasminogen activator inhibitor I (PAI-1), which is released by endothelial cells and activated platelets.
• PAI-2, on the other hand, neutralizes uPA more efficiently than it does tPA.
• On the surface of a fibrin-containing thrombus, tPA and plasmin are protected from their major circulating inhibitors (PAI-I) and a2-Antiplasmin (a2-AP), respectively.

• Bound plasmin degrades cross-linked fibrin, which gives rise to soluble fibrin degradation products (FDPs).
• Plasmin(ogen) and tPA interact directly with fibrin, which acts as a cofactor in PLG activation stimulating fibrin degradation. In solution a2AP can bind plasmin(ogen) thereby occluding binding to fibrin.

• a2AP can also cross-link to fibrin that both prevents plasmin from binding to fibrin and neutralizes the activity of the enzyme.
• **TAFI** (thrombin-activated fibrinolysis inhibitor a) is an antifibrinolytic enzyme that is converted from a proenzyme by thrombin bound to thrombomodulin. It can also be activated by plasmin.

• Conversion of TAFI (the procarboxypeptidase) to TAFia (the active carboxypeptidase) requires a high concentration of thrombin.

• TAFia is a carboxypeptidase that cleaves lysine residues exposed by plasmin proteolysis, reducing the cofactor effect of fibrin on tPA-induced plasminogen activation, thereby inhibiting further proteolysis by plasmin.

• **TAFI** is a FXIIla substrate and is covalently bound to fibrin.
• NL fibrinolysis pathway
  • Degradation of clot
  • Inhibitor of clot formation in nontraumatized areas

Endothelial Cell

A2-antiplasmin
  ↓
Va, VIIIa
  ↓
Vi, VIIIi
  ↓
XIIIa

Plasminogen
  ↓
Plasmin
  ↓
FDP

Fibrinogen
  ↓
Fibrin

t-PA
  ↓
PAI-1
  ↓
u-PA

XIIa
Figure 110-01

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The potentially antifibrinolytic effect of thrombin appears to be mediated through its ability to activate TAFI in the presence of thrombomodulin.
Developmental Hemostasis

• In the newborn, plasma concentrations of the vitamin K-dependent coagulation factors (II, VII, IX, X), contact factors (XI, XII, prekallikreine and high molecular weight kininogen) are approximately 50% of adult values, potentially increasing bleeding risk.

• Adult values for coagulation proteins are achieved in most components by 6 months of age.
Developmental Hemostasis

• In general, the hemostatic system in neonates is a balanced physiologic system:
  – low concentrations of plasma coagulation proteins with prolonged thromboplastin time and partial thromboplastin time,
  – physiologically decreased levels of natural coagulation inhibitors.

• Children are protected from thrombosis: VTE secondary to acquired risk factors occur considerably less frequently in children compared to adults.
Developmental Hemostasis

• protein S in neonatal plasma, :
  – reduced total protein S antigen
  – a relatively high level of active protein S was found due to nearly undetectable levels of C4b-binding protein,
  – thereby minimizing the risk of vascular accidents

• Antithrombin, heparin cofactor II and protein C are reduced to approximately 50% of that of adults,

• Hypofibrinolytic state in neonates:
  – Increased concentrations of tissue type plasminogen activator (t-PA),
  – the decreased plasma levels and activity of plasminogen and
  – the increased concentration of tissue type plasminogen activator inhibitors (PAI)
  – alpha-2 macroglobulin are increased over adult values at birth reaching twice adult values by six months of age
VWF

• VWF is expressed by endothelial cells and megakaryocytes and is stored in Weibel-Palade bodies in endothelial cells and in alpha granules in platelets.

• Endothelial cells secrete VWF multimers that are larger than those found circulating in plasma. The function of these large multimeric forms of VWF is to bind to and agglutinate blood platelets under high shear rates.
VON WILLEBRAND FACTOR (VWF)

VWF gene in Chromosome 12
VWF characteristics

• VWF is synthesized as a protein of 2813 amino acids that includes:
  – a signal peptide of 22 amino acids,
  – a prepropeptide of 741 amino acids [residues 23-763]
  – and a mature protein of 2050 amino acids [residues 764-2800].

• In the acidic compartment of the Golgi apparatus the pre-propeptide of VWF is separated from the mature VWF protein generating the VWF Propeptide [VWFpp] and the mature protein.

• The VWFpp has a concentration in plasma of 1 µg/ml and a T½ of 2-3 hours whereas the mature VWF protein has a concentration in plasma of 10 µg/ml and a T½ of 8-12 hours.
MULTIMERIZATION OF VWF

Endoplasmic reticulum:
Dimerization e glycosylation

Golgi Apparatus:
Multimerization e glycosilation

Weibel-Palade bodies:
Cleavage of propeptide
Normal Subject

Cleaved unusually large multimers of von Willebrand factor

ADAMTS 13

Binding site

Endothelial cell

Secretion of multimers from Weibel-Palade body

Moake et al. 2002
SHEAR STRESS FORCES OF THE BLOOD

Globular VWF  Extended VWF

Siedlecki et al Blood
VWF FUNCTIONS

1) In vascular high-shear stress conditions VWF promotes:

- Platelet adhesion to the exposed sub-endothelium via collagen binding and platelet GP Ibα receptor

- platelet-platelet interactions (GP IIb/IIIa)

2) As a carrier protein of FVIII, VWF protects FVIII from rapid proteolysis
Mechanisms of Platelet Adhesion

- GP Ibα
- αIIbβ3
- Nonactivated
- Activated

- Arrest
- Activation
- Collagen Fibrils
- Shear Rate

- Tethering
- Translocation
- Adhesion

- A1
- RGDS
- A3
BASIC MECHANISMS OF VWF FUNCTION IN NORMAL SUBJECTS

von Willebrand Factor

Activated Collagen Reception

Nonactivated GP Ib\(\alpha\)\(\alpha_{l\beta} \beta_{3}\)

RGDS

A1

A3

von Willebrand Factor

Collagen Reception

Ruggeri ZM, JTH 2003 modified
BASIC MECHANISMS OF VWF FUNCTION

von Willebrand Factor

RGDS

A1 A3

A1

GP Ibα

Nonactivated

α1b β3

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BASIC MECHANISMS OF VWF FUNCTION

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Activated

Ruggeri ZM, JTH 2003 modified
BASIC MECHANISMS OF VWF FUNCTION

von Willebrand Factor

RGDS

A1

A3

GP Ib\(\alpha\)

Nonactivated
\(\alpha_{Ib} \beta_3\)

Activated

Collagen Reception

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

Activated Collagen Reception

Nonactivated GP Ibα

RGDS

A1

A3

von Willebrand Factor

Nonactivated αIib β3

Activated

Collagen Reception

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

Activated Collagen Reception

Nonactivated GP Ibα

RGDS

A1

A3

von Willebrand Factor

Nonactivated αIIb β3

Activated

Collagen Reception

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

Activated Collagen Reception

Nonactivated GP Ibα

A1

RGDS

A3

Collagen Reception

von Willebrand Factor

Modified

Ruggeri ZM, JTH 2003
von Willebrand Factor

Activated Collagen Reception

Nonactivated

RGDS

A1

A3

von Willebrand Factor

GP Ibα

Nonactivated

αIIb β3

Activated

Collagen Reception

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

Activated Collagen Reception

Nonactivated GP Ibα

Activated αIIb β3

RGDS

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

Activated Collagen Reception

Nonactivated GP Ibα

RGDS

A1

A3

von Willebrand Factor

Activated GP Ibα αIibβ3

Collagen Reception

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

RGDS

A1

A3

gp Iba

Nonactivated

Activated

Collagen Reception

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor
Activated
Collagen
Reception
Nonactivated
GP Ibα
αIIb β3
RGDS
A1 A3
von Willebrand Factor

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

Activated Collagen Reception

Nonactivated GP Ib\(\alpha\)\(\beta_\text{III}\)

RGDS

A1
A3

von Willebrand Factor

Collagen Reception

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

Activated Collagen Reception

Nonactivated

GP Ibα

αIIb β3

Activated

Collagen Reception

Ruggeri ZM, JTH 2003 modified
von Willebrand Factor

Activated Collagen Reception

Nonactivated GP Ibα

RGDS A1 A3

von Willebrand Factor

Collagen Reception

Nonactivated α<sub>IIb</sub> β<sub>3</sub>

Activated

Ruggeri ZM, JTH 2003 modified
A. Intact vessel wall

- Collagen fibrils
- Endothelial cell
- Plasma
- VWF
- GpIbα
- Non activated αIIbβ3
- Extracellular matrix

B. Damaged vessel wall

- Torque
- Initial platelet tethering
- Platelet rolling
- Platelet activation and adhesion
- Activated αIIbβ3
- GpIbα
- VWF
- Non activated αIIbβ3

C. Platelet plug formation

- Collagen fibrils
- Endothelial cell
- Plasma
- VWF
- GpIbα
- Activated αIIbβ3
- Extracellular matrix
CIRCULATING LEVELS OF VWF IN NORMAL INDIVIDUALS

Plasma VWF = 5 -15 ug/ml (50-150 U/dL)

90% from Endothelial Cells
- 80% = constitutive
- 10% = induced secretion by Weibel-Palade bodies

10% from the MK & Platelets (α-granules)
Under high shear stress conditions, a process of platelet cohesion (aggregation) appears to link platelets even before stable adhesion is established. Hypothesis: aggregation independent of activation.
At shear rates <5,000-10,000
Initial adhesion to a reactive surface and subsequent aggregation follow the paradigm of progressive accrual of single platelets.

At shear rates >10,000-20,000
Activation-independent platelet aggregation mediated by VWF multimers facilitates adhesion and precedes stable aggregation.
A key function of VWF is to initiate platelet aggregation independently of activation under elevated shear stress conditions.

This form of aggregation precedes and is necessary for stable adhesion to thrombogenic surfaces.