CHAPTER 1
Arterial thrombosis: a brief overview

Lina Badimon¹ and Valentin Fuster²
¹Cardiovascular Research Center, CSIC-ICCC, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
²Mount Sinai Medical Center, New York, NY, USA

Introduction

Arterial thrombosis comprises four basic pathways: platelet activation and aggregation, blood coagulation with fibrin formation, inflammation, and fibrinolysis. These pathways interact with each other and with the vessel wall in the special regulatory conditions set by the local blood flow to form a thrombus with a determined growth rate, mass, and stability on top of an atherosclerotic plaque [1,2]. Numerous pathologic and angiographic, and several angioscopic and intravascular ultrasound reports have documented the presence of intraluminal thrombi both in unstable angina and in acute myocardial infarction (MI). In contrast with the very high incidence of thrombi in acute MI, the incidence in unstable angina has varied significantly among different studies, related in part to the interval between the onset of symptoms and the angiographic study. Accordingly, when cardiac catheterization was delayed for weeks, the incidence of thrombi was low; on the other hand, angiography early after the onset of symptoms revealed the presence of thrombi in approximately two-thirds of cases. Presumably, the thrombus is occlusive at the time of anginal pain and later may become subocclusive and slowly lysed or digested. Local and systemic “thrombogenic risk factors” at the time of coronary plaque disruption may influence the degree and duration of thrombus deposition and hence the different pathologic and clinical syndromes [3,4].

The concept of vascular injury and local geometry as triggers and modulators of a thrombotic event is relevant to the pathogenesis of different cardiovascular disorders, including the initiation and progression of atherosclerosis, acute coronary syndromes (ACS), vein graft disease, and restenosis following coronary angioplasty. The unveiling of the molecular interactions prevalent in thrombosis will serve the development of more accurate strategies of pharmacologic intervention (Figure 1.1).

Pathogenesis of arterial thrombosis

The endothelium has a central role in the preservation of vascular homeostasis and hemostasis. The endothelium, the inner layer of blood vessels, is a dynamic autocrine and paracrine organ that regulates contractile, secretory, and mitogenic activities in the vessel wall and the hemostatic process within the vessel lumen by producing several locally active substances. Vascular hemostasis, defined as the ability of the vascular system to maintain blood fluidity and vascular integrity, is achieved by the interaction between the endothelium and blood cells. In physiologic conditions, the normal endothelium actively supports the fluid state of
flowing blood and prevents activation of circulating cells. In this context, of all the endothelial-borne agents, nitric oxide (NO) and prostacyclin (PGI₂) are the most efficacious platelet inhibitors. Endothelial dysfunction, as well as a breach of the endothelial integrity, triggers a series of biochemical and molecular reactions aimed at arresting blood flow and promoting vessel wall repair. Vasoconstriction, platelet adhesion, and fibrin formation at the site of injury achieve a hemostatic aggregate, and are the first steps in vessel wall repair and prevention of excessive loss of blood. A few scattered platelets may interact with a subtly injured, dysfunctional endothelium and contribute, through the release of growth factors, to very mild intimal hyperplasia. In contrast, with endothelial denudation and mild intimal injury, a monolayer to a few layers of platelets may deposit on the lesion, with or without mural thrombus formation. The release of platelet growth factors, as occurs in the coronary vein graft within the first postoperative year, may contribute significantly to an accelerated intimal hyperplasia. In severe injury with exposure of components of deeper layers of the vessel, as occurs in spontaneous plaque rupture or in angioplasty, marked platelet aggregation with mural thrombus formation follows. Vascular injury of this magnitude also stimulates thrombin formation through both

the intrinsic (surface-activated) and extrinsic (tissue-factor dependent) coagulation pathways, in which the platelet membrane facilitates interactions between clotting factors. This concept of vascular injury as a trigger of the thrombotic response is important in understanding the pathogenesis of various vascular diseases associated with atherosclerosis in contrast to venous thrombosis (Figure 1.2).
Growing thrombi may locally occlude the lumen, or embolize and be washed away by the blood flow to occlude distal vessels. However, thrombi may be physiologically and spontaneously lysed by mechanisms that block thrombus propagation. Thrombus size, location, and composition are regulated by hemodynamic forces (mechanical effects), thrombogenicity of exposed substrate (local molecular effects), thrombogenicity of the fluid phase and cellular blood components (local cellular effects), and the efficiency of the physiologic mechanisms of control of the system, mainly fibrinolysis [5]. The inflammatory pathways triggered both by the underlying atherosclerotic lesion and the evolving thrombus contribute to the general risk of the patient and the progression of the disease.

**Platelets**

After plaque rupture, the exposed vessel structures induce platelet aggregation and thrombosis by mechanisms that in some instances are different from those prevalent in hemostatic plug formation. The ulcerated atherosclerotic plaque may contain a disrupted fibrous cap, a lipid-rich core, abundant extracellular matrix, and inflammatory cells. Such structures exhibit a potent activating effect on platelets and coagulation. Exposed matrix from the vessel wall and thrombin generated by the activation of the coagulation cascade as well as circulating epinephrine are powerful platelet agonists. Adenosine diphosphate (ADP) is a platelet agonist that may be released from hemolyzed red cells and other platelets in the area of vessel injury. Each agonist stimulates the discharge of calcium from the platelet-dense tubular system and promotes the contraction of the platelet, with the subsequent release of its granule contents. Arachidonate, which is released from the platelet membrane by the stimulatory effect of collagen, thrombin, ADP, and serotonin, is another platelet agonist. Arachidonate is converted to thromboxane A₂ by the sequential effects of cyclooxygenase (COX) and thromboxane synthetase. Thromboxane A₂ not only promotes further platelet aggregation, but is also a potent vasoconstrictor [2].

Signal transduction mechanisms initiated upon binding of agonists to membrane-spanning receptors on the platelet surface have been partially elucidated [2]. The initial recognition of a damaged vessel wall by platelets involves (a) adhesion and activation; (b) spreading of the platelet on the surface; and (c) aggregation of platelets to form a platelet plug or white thrombus (Figure 1.3). The efficiency of the platelet recruitment will depend on the underlying substrate and local geometry. A final step of recruitment of other blood cells also occurs; erythrocytes, neutrophils, and occasionally monocytes are found on the evolving mixed thrombus.

Platelet function depends on adhesive interactions and most of the glycoproteins on the platelet membrane surface are receptors for adhesive proteins. Many of these receptors have been identified, cloned, sequenced, and classified within large gene families that mediate a variety of cellular interactions. The most abundant is the integrin family, which includes glycoprotein (GP) IIb/IIIa, GP Ia/IIa, GP Ic/IIa, the fibronectin receptor, and the vitronectin receptor, in decreasing order of abundance. Another gene family encoding proteins present in the platelet membrane glycocalyx is the leucine-rich glycoprotein family, represented by the GP Ib–IX complex, the receptor for von Willebrand factor (vWF) on unstimulated platelets that mediates adhesion to subendothelium, and GP V. Other gene families are the selectins (such as GMP-140) and immunoglobulin domain proteins (HLA Class I antigen and platelet/endothelial cell adhesion molecule 1 [PECAM-1]). Unrelated to any other gene family is GP IV [6].

The GP Ib–IX complex consists of two disulfide-linked subunits (GP Ibα and GP Ibβ) tightly (not covalently) complexed with GP IX in a 1:1 heterodimer. GP Ibβ and GP IX are transmembrane glycoproteins and form the larger globular domain. The elongated, protruding part of the receptor corresponds to GP Ibα. The major role of GP Ib–IX is to bind immobilized vWF on the exposed vascular subendothelium and initiate adhesion of platelets. GP Ib does not bind soluble vWF in plasma; apparently it undergoes a conformational change upon binding to the extracellular matrix, and then exposes a recognition sequence for GP Ib–IX. The vWF-binding domain of GP Ib–IX has been narrowed...
Therapeutic Advances in Thrombosis

Adhesive proteins. On activated platelets, the GP IIb/IIIa is a receptor for fibrinogen, fibronectin, von Willebrand factor, vitronectin, and thrombospondin. The receptor recognition sequences are localized to small peptide sequences (RGD) in the adhesive proteins. Fibrinogen contains two RGD sequences in its α chain, one near the N-terminus (residues 95–97) and a second near the C-terminus (residues 572–574). Fibrinogen has a second site of recognition for GP IIb/IIIa, the 12-amino acid sequence located at the C-terminus of the γ chain of the molecule. This dodecapeptide is specific for fibrinogen and does not contain the RGD sequence, but competes with RGD-containing peptides for binding to GP IIb/IIIa [6,7].

Thrombin plays an important role in the pathogenesis of arterial thrombosis. It is one of the most

Figure 1.3 Platelet adhesion and aggregation. The diagram shows the principal receptors and signaling pathways involved in platelet adhesion and aggregation. 5-HT, 5-hydroxytryptophan; AA, arachidonic acid; GP, glycoprotein; PAR, protease activated receptor; Rc, receptor; TP, thromboxane receptor; TXA₂, thromboxane A₂; vWF, von Willebrand factor.

to amino acids 251–279 on GP Iβα. The GP Iβα-binding domain of vWF resides in a tryptic fragment extending from residue 449 to 728 of the subunit that does not contain an RGD (Arg–Gly–Asp) sequence. The cytoplasmic domain of GP Iβ–IX has a major function in linking the plasma membrane to the intracellular actin filaments of the cytoskeleton, and functions to stabilize the membrane and to maintain the platelet shape.

Randomly distributed on the surface of resting platelets are about 50,000 molecules of GP IIb/IIIa. The complex is composed of one molecule of GP IIb (disulfide-linked large and light chains) and one of GP IIIa (single polypeptide chain). It is a Ca²⁺-dependent heterodimer, noncovalently associated on the platelet membrane. Calcium is required for maintenance of the complex and for binding of adhesive proteins. On activated platelets, the GP IIb/IIIa is a receptor for fibrinogen, fibronectin, vWF, vitronectin, and thrombospondin. The receptor recognition sequences are localized to small peptide sequences (RGD) in the adhesive proteins. Fibrinogen contains two RGD sequences in its α chain, one near the N-terminus (residues 95–97) and a second near the C-terminus (residues 572–574). Fibrinogen has a second site of recognition for GP IIb/IIIa, the 12-amino acid sequence located at the C-terminus of the γ chain of the molecule. This dodecapeptide is specific for fibrinogen and does not contain the RGD sequence, but competes with RGD-containing peptides for binding to GP IIb/IIIa [6,7].

Thrombin plays an important role in the pathogenesis of arterial thrombosis. It is one of the most
potent known agonists for platelet activation and recruitment. The thrombin receptor has 425 amino acids with seven transmembrane domains and a large N-terminal extracellular extension that is cleaved by thrombin to produce a “tethered” ligand that activates the receptor to initiate signal transduction [8]. Thrombin is a critical enzyme in early thrombus formation, cleaving fibrinopeptides A and B from fibrinogen to yield insoluble fibrin, which effectively anchors the evolving thrombus. Both free and fibrin-bound thrombin are able to convert fibrinogen to fibrin, allowing propagation of thrombus at the site of injury.

Therefore, platelet activation triggers intracellular signaling and expression of platelet membrane receptors for adhesion and initiation of cell contractile processes that induce shape change and secretion of the granular contents. The expression of the integrin IIb/IIIa (\(\alpha_{IIb}\beta_3\)) receptors for adhesive glycoprotein ligands (mainly fibrinogen and vWF) in the circulation initiates platelet-to-platelet interaction. The process is perpetuated by the arrival of platelets brought by the circulation (see Figure 1.3). Most of the glycoproteins in the platelet membrane surface are receptors for adhesive proteins or mediate cellular interactions. Ligand binding to the different membrane receptors triggers platelet activation with different relative potencies. The platelet ADP receptors (P2Y\(_{AC}\), P2y1R, P2X\(_{1R}\)) have recently attracted much interest because of the availability of pharmacologic inhibitors, and there is new research in relation to protease activated receptors (PARs).

The discontinuity of the endothelial surface is not a prerequisite for functionally relevant interactions of platelets with vascular endothelial cells. For instance, platelets are activated by local flow disturbances in the vicinity of the atherosclerotic plaques. Indeed, high blood shear stress induces the exposure of platelet receptors and triggers the aggregation cascade [9]. Research results are describing new unknown mechanisms of platelet activation. For instances, GRP78, an endoplasmic reticulum (ER) chaperon, is exposed in the resting platelet membrane and is translocated to the cytosol after shear-induced platelet activation [10]. In addition, the chronic exposure to risk factors also induces platelet interaction with the intact but activated endothelial layer.

A proinflammatory milieu may also contribute to platelet activation and deposition on vascular substrates [11]. As such, C-reactive protein (CRP) has been shown to induce platelet adhesion to endothelial cells under high shear conditions [12]. In this regard, we have recently demonstrated that the monomeric form of CRP exerts a significant effect on platelet adhesion [13]. While circulating pentameric CRP does not affect platelet deposition, monomeric CRP displays a prothrombotic effect, enhancing not only platelet deposition but also thrombus growth under arterial flow conditions [14]. In addition, Eisenhardt et al. [13] have reported the capability of activated platelets to dissociate the native pentameric CRP into monomeric CRP, which may then be deposited in the atherosclerotic plaques.

**Coagulation system**

During plaque rupture, in addition to platelet deposition in the injured area, the clotting mechanism is activated by the exposure of the de-endothelialized vascular surface. Tissue factor (TF) may be exposed upon vessel injury and directly contributes to triggering thrombosis. The activation of the coagulation cascade leads to the generation of thrombin, which, as mentioned above, is a powerful platelet agonist that contributes to platelet recruitment in addition to catalyzing the formation and polymerization of fibrin. Fibrin is essential in the stabilization of the platelet thrombus, and allows it to withstand removal by the forces of flow, shear, and high intravascular pressure. These basic concepts have clinical relevance in the context of the ACS, where plaque rupture exposes vessel wall matrix and plaque core materials, which by activating platelets and the coagulation system results in the formation of a fixed and occlusive platelet–fibrin thrombus. The efficacy of fibrinolytic agents is pointedly demonstrated by the importance of fibrin-related material in the thrombosis associated with MI. The proteins that compose the clotting enzymes do not collide and interact on a random basis in the plasma, but interact in complexes in a highly efficient manner on platelet and endothelial
surfaces. The major regulatory events in coagulation (activation, inhibition, generation of anticoagulant proteins) occur on membrane surfaces.

The blood coagulation system involves a sequence of reactions integrating zymogens (proteins susceptible to being activated to enzymes via limited proteolysis) and cofactors (nonproteolytic enzyme activators) in three groups: (a) the contact activation (generation of factor Xla via the Hageman factor); (b) the conversion of factor X to factor Xa in a complex reaction requiring the participation of factors IX and VIII; and (c) the conversion of prothrombin to thrombin and fibrin formation [15].

The TF pathway, through the TF–factor VIIa complex in the presence of Ca²⁺, induces the formation of factor Xa. A second TF-dependent reaction catalyzes the transformation of factor IX into factor IXa. TF is an integral membrane protein that serves to initiate the activation of factors IX and X and to localize the reaction to cells on which TF is expressed. Other cofactors include factor VIIIa, which binds to platelets and forms the binding site for IXa, thereby forming the machinery for the activation of factor X and factor Va, which binds to platelets and provides a binding site for factor Xa. The human genes for these cofactors have been cloned and sequenced. In physiologic conditions, no cells in contact with blood contain active TF, although cells such as monocytes and polymorphonuclear leukocytes can be induced to synthesize and express TF [15].

Activated factor Xa converts prothrombin into thrombin. The complex which catalyzes the formation of thrombin consists of factors Xa and Va in a 1:1 complex. The activation results in the cleavage of fragment 1.2 and formation of thrombin from fragment 2. The interaction of the four components of the “prothrombinase complex” (Xa, Va, phospholipid, and Ca²⁺) yields a more efficient reaction.

Activated platelets provide a procoagulant surface for the assembly and expression of both intrinsic factor Xase and prothrombinase enzymatic complexes. These complexes catalyze the activation of factor X to factor Xa and prothrombin to thrombin, respectively. The expression of activity is associated with the binding of both the proteases, factors IXa and Xa, and the cofactors, factors VIIIa and Va, to procoagulant surfaces. The binding of factors IXa and Xa is promoted by factors VIIIa and Va, respectively, such that factor Va and likely factor VIIIa provide the equivalent of receptors for the proteolytic enzymes. The surface of the platelet expresses the procoagulant phospholipids that bind coagulation factors and contribute to the procoagulant activity of the cell.

Blood clotting is blocked at the level of the prothrombinase complex by the physiologic anticoagulant activated protein C, and oral anticoagulants. Oral anticoagulants prevent the post-translational synthesis of γ-carboxyglutamic acid groups on the vitamin K-dependent clotting factors, preventing binding of prothrombin and factor Xa to the membrane surface. Activated protein C cleaves factor Va to render it functionally inactive. Loss of factor Va decreases the role of thrombin formation to negligible levels [16].

Thrombin acts on multiple substrates, including fibrinogen, factors XIII, V, and VIII, and protein C, in addition to its effects on platelets. It plays a central role in hemostasis and thrombosis. The catalytic transformation of fibrinogen into fibrin is essential in the formation of the hemostatic plug and arterial thrombi. It binds to the fibrinogen central domain and cleaves fibrinopeptides A and B, resulting in fibrin monomer and polymer formation [17]. The fibrin mesh holds the platelets together and contributes to the attachment of the thrombus to the vessel wall.

The control of the coagulation reactions occurs by diverse mechanisms, such as hemodilution and flow effects, proteolytic feedback by thrombin, inhibition by plasma proteins (such as antithrombin III [ATIII]) and endothelial cell-localized activation of an inhibitory enzyme (protein C), and fibrinolysis. Although ATIII readily inactivates thrombin in solution, its catalytic site is inaccessible while bound to fibrin, but it may still cleave fibrinopeptides even in the presence of heparin. Thrombin has a specific receptor on endothelial cell surfaces, thrombomodulin, that triggers a physiologic anticoagulant system. The thrombin–thrombomodulin complex serves as a receptor for the vitamin K-dependent protein C, which is activated and released from the endothelial cell surface. Activated protein C blocks
the effects of factors V and VIII and limits thrombin effects. Endogenous fibrinolysis represents a repair mechanism, such as endothelial cell regrowth and vessel recanalization. Fibrinolysis involves the catalytic activation of zymogens, positive and negative feedback control, and inhibitor blockade [18].

**Effects of the severity of vessel wall damage and local geometry on the thrombotic response to atherosclerosis**

The dynamics of platelet deposition and thrombus formation following vascular damage are modulated by the type of injury and the local geometry at the site damage (degree of stenosis) [19,20]. Overall, it is likely that, when injury to the vessel wall is mild, the thrombogenic stimulus is relatively limited, and the resulting thrombotic occlusion is transient, as occurs in unstable angina. On the other hand, deep vessel injury secondary to plaque rupture or ulceration results in exposure of collagen, TF, and other elements of the vessel matrix, leading to relatively persistent thrombotic occlusion and MI [3,4].

It is likely that the nature of the substrate exposed after spontaneous or angioplasty-induced plaque rupture is one factor determining whether an unstable plaque proceeds rapidly to an occlusive thrombus or persists as nonocclusive mural thrombus. The analysis of the relative contribution of different components of human atherosclerotic plaques (fatty streaks, sclerotic plaques, fibrolipid plaques, atheromatous plaques, hyperplastic cellular plaque, and normal intima) to acute thrombus formation showed that the atheromatous core was up to six-fold more active than the other substrates in triggering thrombosis [21]. Therefore, plaques with a large atheromatous core content are at high risk of leading to ACS after spontaneous or mechanically-induced rupture due to the increased thrombogenicity of their contents [22]. As proof of concept, we showed that local tissue blockade of TF, by treatment with TF pathway inhibitor (TFPI), significantly reduces thrombosis [23]. The use of active site-inhibited recombinant FVIIa (TF–rFVIIa) has been shown to significantly reduce thrombus growth on damaged vessels devoided of TF, indicating that blockage of blood-borne TF at the site of a growing thrombus has therapeutic implications [24].

Platelet deposition is directly related to the degree of stenosis in the presence of the same degree of injury, indicating a shear-induced platelet activation [19,20]. In addition, analysis of the axial distribution of platelet deposition indicates that the apex, and not the flow recirculation zone distal to the apex, is the segment of greatest platelet accumulation. These data suggest that the severity of the acute platelet response to plaque disruption depends in part on the sudden changes in geometry following rupture [1].

Spontaneous lysis of thrombus does occur, not only in unstable angina, but also in acute MI. In these patients, as well as in those undergoing thrombolysis for acute infarction, the presence of a residual mural thrombus predisposes to recurrent thrombotic vessel occlusion [25,26]. Two main contributing factors for the development of rethrombosis have been identified. First, a residual mural thrombus may encroach into the vessel lumen, resulting in increased shear rate, which facilitates the activation and deposition of platelets on the lesion. Second, the presence of a fragmented thrombus appears to be one of the most powerful thrombogenic surfaces. As an example, rHirudin, a recombinant molecule that blocks both the catalytic site and the anion-exosite of the thrombin molecule, significantly inhibited the secondary growth. Thus, following lysis, thrombin becomes exposed to the circulating blood, leading to activation of the platelets and coagulation, further enhancing thrombosis.

Thrombin generated at the site of injury binds to thrombomodulin, an endothelial surface membrane protein, initiating activation of protein C, which in turn (in the presence of protein S) inactivates factors Va and VIIIa. Thrombin stimulates the subsequent release of both tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) from endothelial cells, thus initiating endogenous lysis through plasmin generation from plasminogen by t-PA with subsequent modulation through PAI-1. Thrombin therefore plays a pivotal role in maintaining the complex
balance of initial prothrombotic reparative events and subsequent endogenous anticoagulant and thrombolytic pathways [27].

**Inflammation in arterial thrombosis**
Atherothrombosis, the leading cause of mortality in the Western world, is a systemic disease involving the intima of large- and medium-sized arteries, including the aorta, carotids, coronaries, and peripheral arteries, that is characterized by intimal thickening due to cellular and lipid accumulation. Endothelial dysfunction and inflammation are the major facilitators of atherothrombotic disease. When fatty streaks progress to fibroatheroma, they develop a cap of smooth muscle cells (SMCs) and collagen, and when this plaque is disrupted, the subsequent thrombus formation brings about the onset of the ACS and strokes. Importantly, the culprit lesions leading to ACS are usually mildly stenotic and therefore barely detected by angiography [28]. The composition of the plaque, rather than the percent stenosis, appears to be the main determinant of risk of plaque rupture and ensuing thrombogenicity. High-risk rupture-prone lesions usually have a large lipid core, a thin fibrous cap, high density of inflammatory cells (particularly at the shoulder region, where disruptions most often occur), and high TF content [22]. Inflammatory processes also contribute decisively to atherosclerosis and its acute thrombotic complications, as is shown by the fact that many inflammatory mediators can augment TF gene expression by endothelial cells, thus triggering the coagulation cascade [29]. Due to the baffling heterogeneity in the composition of atherothrombotic plaques even within the same individual, a reliable, noninvasive imaging tool able to detect early atherosclerotic disease and characterize lesion composition would be clinically advantageous. Indeed, it would improve our understanding of the pathophysiologic mechanisms of atherothrombosis and help in patient risk stratification [30]. Atherothrombosis is also triggered by hyperthrombogenicity due to systemic factors, the so-called “high-risk blood,” with inflammatory mediators. As such, platelets have emerged as a source of inflammatory mediators. For example, they can both produce and respond to chemoattractant cytokines [31], or express CD154 (CD40 ligand), the molecule that regulates TF gene expression in the macrophage and SMCs [32]. Similarly, P-selectin, a transmembrane protein present in the alpha granules of platelets, can quickly move to the platelet surface after activation. It interacts with the P-selectin glycoprotein ligand-1 on leukocytes, forming aggregates and upregulating TF formation. Endothelial cells and platelets can also bind to one another via this interaction, which exposes P-selectin on endothelial cells, and this binds to platelet P-selectin glycoprotein ligand-1 (PSGL-1) receptors. P-selectin strengthens platelet aggregates through interaction with platelet sulfatides. This might explain why P-selectin expression in platelets has been linked to arterial thrombosis and coronary artery disease [33]. P-selectin is also present on activated endothelial cells, where it helps in the recruitment of leukocytes [34]. Activated platelets can also deposit chemokines (e.g., RANTES, PF4) onto endothelial cells during transient interactions, thereby promoting further monocyte recruitment and arrest.

Indeed, selectins are specialized in lymphocyte homing and involved in inflammation processes. In case of plaque rupture, endothelial cells, vascular SMCs, and especially foam cells also express TF [22], the latter two through the CD40 ligand [35], whereas the first are also notably affected by soluble ligands such as interleukin (IL)-1 and tumor necrosis factor [36]. The importance of TF is underscored by the fact that high levels are found in the circulation of those coronary artery disease patients who are most prone to thrombotic complications, such as diabetic or dyslipidemic subjects, and smokers. This blood-borne TF is a key determinant of thrombus formation by incorporating platelets into the growing thrombus [24].

TF synthesis is a rapid consequence of endotoxin infusion, which is a strong inflammatory stimulus, and this is followed by TF expression on inflammatory cells and on microparticles, inducing thrombin and fibrin generation [37]. Atherosclerosis is a chronic (or recurrent) inflammatory condition and the recurrent inflammatory drive leads to recurrent induction of TF (with intermediate phases of hyporesponsiveness to stimulation) and assembly
Arterial thrombosis: a brief overview

EPC homing to sites of injury by secreting epithelial-derived neutrophil-activating protein-78 (ENA-78 or CXCL5) and platelet basic protein/neutrophil activating peptide (PBP/NAP-2 or CXC7) [45]. Additionally, it has been demonstrated that the functional relevance of interactions between platelets or platelet-derived factors is not restricted to the recruitment of circulating stem/progenitor cells; they may also influence important progenitor cell functions such as migration or differentiation [46].

Summary

Arterial thrombus formation is a key factor in the conversion of chronic atherosclerosis to acute ischemic events after plaque rupture, in the progression of coronary disease, and in the acute phase of revascularization interventions. Disruption of a vulnerable or unstable plaque (Type IV and Va lesions of the American Heart Association [AHA] classification) with a subsequent change in plaque geometry and thrombosis usually resulting in an ACS. The high-risk plaques tend to be relatively small, but soft or vulnerable to “passive” disruption because of their high lipid content. Inflammatory processes are important components of all stages of atherosclerotic development, including plaque initiation and disruption. The knowledge gained of the mechanisms of platelet activation, signal transduction, receptor binding, zymogen activation and function, substrate recognition, and adhesive events has helped to design promising approaches for intervention. Receptors originally thought to be involved only in anchoring functions are also important factors in the transduction of information from the extracellular compartment to the inner cell, and they are involved in governing cell function, shape, proliferation, and differentiation. Inflammatory mediators and inflammatory triggers directed to or originating in the platelet and in the coagulation pathway are being identified and their prognostic value analyzed. It is being unveiled that platelets are also involved in functions beyond thrombosis and hemostasis. These studies together with those to find the most prevalent agonist and...
substrate to trigger and perpetuate a thrombotic event in every clinical situation will help to establish strategies to prevent clinical events and reduce their associated morbidity and mortality.

Acknowledgements

The authors are indebted to many investigators whose work in basic biochemistry and cell biology has served to advance our understanding of thrombosis. Because of space limitations it has been impossible to cite all these authors in the references.

References


23. Badimon JJ, Lettino M, Toschi V, et al. Local inhibition of tissue factor reduces the thrombogenicity of dis-


