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Arterial and Venous

Thrombosis OVERVIEW OF THROMBOSIS ■ ■GENERAL OVERVIEW Thrombosis is hemostasis “at the wrong place and at the wrong time” (MacFarlane). The obstruction of blood flow due to the formation of thrombus may result in tissue anoxia and damage, and it is a major cause of morbidity and mortality in a wide range of arterial and venous diseases and patient populations. As reported in 2020, 655,000 Americans die from heart disease each year or about 1 in 4 deaths. In 2020, coronary disease killed 382,820 people and stroke killed 160,747 in the United States with approximately 805,000 suffering from heart attacks and 795,000 having strokes. It is estimated that as many as 600,000 people each year have a pulmonary embolism or deep-venous thrombotic event, and 60,000– 80,000 Americans die of these conditions annually. In the nondiseased state, physiologic hemostasis reflects a delicate interplay between fac tors that promote and inhibit blood clotting, favoring the former. This response is crucial as it prevents uncontrolled hemorrhage and exsan guination following injury. In specific settings, the same processes that regulate normal hemostasis can cause pathologic thrombosis, leading to arterial or venous occlusion. Importantly, many commonly used therapeutic interventions may also alter the thrombotic–hemostatic balance adversely. Hemostasis and thrombosis primarily involve the interplay among three factors: the vessel wall, coagulation and fibrinolytic proteins, and platelets. Many prevalent acute vascular diseases are due to thrombus formation within a vessel, including myocardial infarction, throm botic cerebrovascular events, and venous thrombosis. Although the end result is vessel occlusion and tissue ischemia, the pathophysiologic processes governing these pathologies have similarities as well as distinct differences. While many of the pathways regulating thrombus formation are similar to those that regulate hemo stasis, the processes triggering or per petuating thrombosis may be distinct and can vary in different clinical and genetic settings. In venous thrombosis, primary hypercoagulable states reflecting defects in the proteins governing coagulation and/or fibrinolysis or secondary hypercoagulable states involving abnormalities of blood vessels and blood flow or stasis lead to thrombosis. By contrast, arterial thrombo sis is highly dependent on the state of the vessel wall, the platelet, and factors related to blood flow. Endothelial cells Inactive platelets ARTERIAL THROMBOSIS ■ ■OVERVIEW OF ARTERIAL THROMBOSIS In arterial thrombosis, platelets and abnormalities of the vessel wall typically play a key role in vessel occlusion. Arterial thrombus forms via a series of sequential steps in which platelets adhere to the vessel wall, additional

platelets are recruited, and thrombin is activated (Fig. 122-1). The regulation of platelet adhesion, activation, FIGURE 122-1 Platelet activation and thrombosis. Platelets circulate in an inactive form in the vasculature. Damage to the endothelium and/or external stimuli activate platelets that adhere to the exposed subendothelial von Willebrand factor and collagen. This adhesion leads to activation of the platelet, shape change, and the synthesis and release of thromboxane (TxA2), serotonin (5-HT), and adenosine diphosphate (ADP). Platelet stimuli cause conformational change in the platelet integrin glycoprotein (GP) IIb/IIIa receptor, leading to the high-affinity binding of fibrinogen and the formation of a stable platelet thrombus.

aggregation, and recruitment will be described in detail below. In addi tion, while the primary function of platelets is regulation of hemostasis, our understanding of their role in other processes, such as immunity, metastasis, wound healing, and inflammation, continues to evolve.

■ ■ARTERIAL THROMBOSIS AND VASCULAR DISEASE Arterial thrombosis is a major cause of morbidity and mortality both in the United States and, increasingly, worldwide. Although the rates have declined in the United States, the overall burden remains high. Overall, in 2020, heart disease was estimated to cause about 1 of every 4 deaths in the United States. In addition to the 605,000 Americans who will have a new coronary event annually, an additional 200,000 myocardial infarctions occur in those with previous heart attacks. Although the rate of strokes has fallen, each year about 795,000 people experience a new or recurrent ischemic stroke. In 2018, about 1 in 6 deaths from cardiovascular disease were due to stroke in the United States. ■ ■THE PLATELET Many processes in platelets have parallels with other cell types, such as the presence of specific receptors and signaling pathways; however, unlike most cells, platelets lack a nucleus and are unable to adapt to changing biologic settings by altered gene transcription. Plate lets sustain limited protein synthetic capacity from megakaryocytederived and intracellularly transported messenger RNA (mRNA) and microRNA (miRNA). Most of the molecules needed to respond to various stimuli, however, are maintained in storage granules and mem brane compartments. CHAPTER 122 Platelets are disc-shaped, very small, anucleate cells (1–5 μm in diam eter) that circulate in the blood at concentrations of 200–400,000/μL,

with an average life span of 7–10 days. Platelets are derived from megakaryocytes, polyploidal hematopoietic cells found in the bone marrow. The primary regulator of platelet formation is thrombopoietin (TPO). The precise mechanism by which megakaryocytes produce and release fully formed platelets is unclear, but the process likely involves formation of proplatelets, pseudopod-like structures generated by the Arterial and Venous Thrombosis Active platelets Fibrinogen GPIIb-IIIa TxA2 ADP 5-HT Active GPIIb-IIIa Collagen von Willebrand factor

evagination of the cytoplasm from which platelets bud. After release into the circulation, (young, large) platelets may continue to divide. Platelet granules are synthesized in megakaryocytes before thrombo poiesis and contain an array of prothrombotic, proinflammatory, and antimicrobial mediators. The two major types of platelet granules, alpha and dense, are distinguished by their size, abundance, and con tent. Alpha-granules contain soluble coagulation proteins, adhesion molecules, growth factors, integrins, cytokines, and inflammatory modulators. Platelet dense-granules are smaller than alpha-granules and less abundant. Whereas alpha-granules contain proteins that may be more important in the inflammatory response, dense-granules contain high concentrations of small molecules, including adenosine diphosphate (ADP) and serotonin, that

influence platelet aggregation and other related vascular processes, such as vasomotor tone.

Platelet Adhesion (See Fig. 122-1) The formation of a thrombus is initiated by the adherence of platelets to the damaged vessel wall. Damage exposes subendothelial components responsible for triggering platelet reactivity, including collagen, von Willebrand factor, fibronec tin, and other adhesive proteins, such as vitronectin and thrombos pondin. The hemostatic response may vary, depending on the extent of damage, the specific proteins exposed, and flow conditions. Certain proteins are expressed on the platelet surface that subsequently regulate collagen-induced platelet adhesion, particularly under flow conditions, and include glycoprotein (GP) IV, GPVI, and the integrin α2β1. The platelet GPIb-IX-V complex adhesive receptor is central both to platelet adhesion and to the initiation of platelet activation. Damage to the blood vessel wall exposes subendothelial von Willebrand factor and collagen to the circulating blood. The GPIb-IX-V complex binds to the exposed von Willebrand factor, causing platelets to adhere (Fig. 122-1). In addi tion, the engagement of the GPIb-IX-V complex with ligand induces signaling pathways that lead to platelet activation. von Willebrand fac tor–bound GPIb-IX-V promotes a calcium-dependent conformational change in the GPIIb/IIIa receptor, transforming it from an inactive lowaffinity state to an active high-affinity receptor for fibrinogen. PART 4 Oncology and Hematology Platelet Activation The activation of platelets is controlled by a variety of surface receptors that regulate various functions in the acti vation process. Platelet receptors control many distinct processes and are stimulated by a wide variety of agonists and adhesive proteins that result in variable degrees of activation. In general terms, the stimula tion of platelet receptors triggers two specific processes: (1) activation of internal signaling pathways that lead to further platelet activation and granule release, and (2) the capacity of the platelet to bind to other adhesive proteins/platelets. Both of these processes contribute to the formation of a thrombus. Stimulation of nonthrombotic receptors results in platelet adhesion or interaction with other vascular cells, including endothelial cells, neutrophils, and mononuclear cells. Many families and subfamilies of receptors are found on platelets that regulate a variety of platelet functions. These include the seven transmembrane receptor family, which is the main agonist-stimulated receptor family. Several seven transmembrane receptors are found on platelets, including the ADP receptors, prostaglandin receptors, lipid receptors, and chemokine receptors. Receptors for thrombin comprise the major seven transmembrane receptors found on platelets. Among this last group, the first identified was the protease activation receptor 1 (PAR1). The PAR class of receptors has a distinct mechanism of acti vation that involves specific cleavage of the N-terminus by thrombin, which, in turn, acts as a ligand for the receptor. Other PAR receptors are present on platelets, including PAR2 (not activated by thrombin) and PAR4. Adenosine receptors are responsible for transduction of ADPinduced signaling events, which are initiated by the binding of ADP to purinergic receptors on the platelet surface. There are several distinct ADP receptors, classified as P2X1, P2Y1, and P2Y12. The activation of both the P2Y12 and P2Y1 receptors is essential for ADP-induced platelet aggregation. The thienopyridine derivatives, clopidogrel and prasugrel, are clinically used inhibitors of ADP-induced platelet aggregation. Platelet Aggregation Activation of platelets results in a rapid series of signal transduction events, including tyrosine kinase, serine/

threonine kinase, and lipid kinase activation. In unstimulated platelets, the major platelet integrin GPIIb/IIIa is maintained in an inactive con formation and functions as a low-affinity adhesion receptor for fibrino gen. This integrin is unique as it is only expressed on platelets. After stimulation, the interaction between fibrinogen and GPIIb/IIIa forms intercellular connections

between platelets, leading to the formation of a platelet aggregate (Fig. 122-1). A calcium-sensitive conformational change in the extracellular domain of GPIIb/IIIa enables the highaffinity binding of soluble plasma fibrinogen as a result of a complex network of inside-out signaling events. The GPIIb/IIIa receptor serves as a bidirectional conduit with GPIIb/IIIa-mediated signaling (outsidein signaling) occurring immediately after the binding of fibrinogen. This binding interaction leads to additional intracellular signaling that further stabilizes the platelet aggregate and transforms platelet aggrega tion from a reversible to an irreversible process (inside-out signaling). ■ ■THE ROLE OF PLATELETS AND THROMBOSIS

IN INFLAMMATION Inflammation plays an important role during the acute thrombotic phase of acute coronary and other vascular occlusive syndromes. In the setting of acute upper respiratory infections, people are at higher risk of myocardial infarction and thrombotic stroke. Patients with acute coro nary syndromes have not only increased interactions between platelets (homotypic aggregates) but also increased interactions between plate lets and leukocytes (heterotypic aggregates) detectable in circulating blood. These latter aggregates form when platelets are activated, often directly by pathogens, and adhere to circulating leukocytes as part of their contribution to the immune process. Platelets bind via P-selectin (CD62P) expressed on the surface of activated platelets to the leukocyte receptor, P-selectin glycoprotein ligand 1 (PSGL-1). This association leads to increased expression of CD11b/CD18 (Mac-1) on leukocytes, which amplifies immunity but may also support further interactions with platelets partially via bivalent fibrinogen linking this integrin with its platelet surface counterpart, GPIIb/IIIa. Platelet surface P-selectin also induces the expression of tissue factor on monocytes, which pro motes fibrin formation. In addition to platelet–monocyte aggregates, the immunomodu lator, soluble CD40 ligand (CD40L or CD154), also reflects a link between thrombosis and inflammation. The CD40 ligand is a trimeric transmembrane protein of the tumor necrosis factor family and, with its receptor CD40, is an important contributor to the inflammatory process, leading both to thrombosis and atherosclerosis. While many immunologic and vascular cells have been found to express CD40 and/ or CD40 ligand, in platelets, CD40 ligand is rapidly translocated to the surface after stimulation and is upregulated in the newly formed thrombus. The surface-expressed CD40 ligand is cleaved from the platelet to generate a soluble fragment (soluble CD40 ligand). Links have also been established among platelets, infection, immu nity, and inflammation. Bacterial and viral infections are associated with a transient increase in the risk of acute thrombotic events, such as acute myocardial infarction and stroke. In addition, platelets con tribute significantly to the pathophysiology and high mortality rates of sepsis. The expression, functionality, and signaling pathways of Toll-like receptors (TLRs) have been established in platelets. Stimula tion of platelet TLR2, TLR3, and TLR4 directly and indirectly activates the platelet’s thrombotic and inflammatory responses, and live bacteria induce a proinflammatory response in platelets in a TLR2-dependent manner, suggesting a mechanism by which specific bacteria and bacte rial components can directly activate platelet-dependent thrombosis. Additionally, viruses, such as SARS-CoV-2, HIV, hepatitis C virus, and Dengue, are also known to elevate thrombosis; recently, platelets have been shown to regulate immune responses to viruses via receptors TLR7 and TLR8. Risk Factors for Arterial Thrombosis In addition to immune burden, various factors increase the risk of developing arterial thrombo sis. Classically, the cardiovascular-dependent risk factors implicated in thrombosis have been hypertension, high levels of low-density lipopro tein cholesterol, and smoking. However, diabetes, pregnancy, age, and chemotherapeutic agents may also contribute to arterial thrombosis.

Stillbirth and loss of multiple pregnancies may increase the risk of isch emic stroke and myocardial infarction, as does hormonal replacement therapy. Systemic lupus erythematosus and rheumatoid arthritis are now well-recognized risks for thrombosis, and the former, in particu lar, may contribute in the pediatric population. The antiphospholipid syndrome is also another widely recognized autoimmune prothrom botic risk for arterial (and venous) thrombosis. ■ ■GENETICS OF ARTERIAL THROMBOSIS Some studies have associated arterial thrombosis with genetic variants (Table 122-1A); however, the associations have been weak and not consistently confirmed in larger series. Platelet count and mean platelet volume have been studied by genome-wide association studies (GWAS), and this approach identified signals located to noncoding regions. Of 15 quantitative trait loci associated with mean platelet volume and platelet count, one located at 12q24 is also a risk locus for coronary artery disease. In the area of genetic variability and platelet function, studies have primarily dealt with pharmacogenetics, the field of pharmacology dealing with the interindividual variability in drug response based on genetic determinants (Table 122-2). This focus has been driven by the wide variability among individuals in terms of response to anti thrombotic drugs and the lack of a common explanation for this vari ance. The best described is the issue of “aspirin resistance,” although heterogeneity for other antithrombotics (e.g., clopidogrel) has also TABLE 122-1 Heritable Causes of Arterial and Venous Thrombosis A. Arterial Thrombosis Platelet Receptors β3 and α2 integrins Pl A2 polymorphism Fc(gamma)RIIA GPIV T13254C polymorphism GPIb Thrombin receptor PAR1-5061 → D Redox Enzymes Plasma glutathione peroxidase, GPx3, promoter haplotype H2 H2 promoter haplotype Endothelial nitric oxide synthase –786T/C, –922A/G, –1468T/A Paraoxonase –107T allele, 192R allele Homocysteine Cystathionine β-synthase 833T → C 5,10-Methylene tetrahydrofolate reductase (MTHFR) 677C → T B. Venous Thrombosis Procoagulant Proteins Fibrinogen –455G/A, –854G/A Prothrombin (20210G → A) Protein C Anticoagulant Pathway Factor V Leiden: 1691G → A (Arg506Gln) Thrombomodulin 1481C →T (Ala455Val) Fibrinolytic Proteins with Known Polymorphisms Tissue plasminogen activator (tPA) 7351C/T, 20 099T/C in exon 6, 27 445T/A in intron 10 Plasminogen activator inhibitor (PAI-1) 4G/5G insertion/deletion polymorphism at position –675 Homocysteine Cystathionine β-synthase 833T → C 5,10-MTHFR 677C → T

TABLE 122-2 Genetic Variation and Pharmacogenetic Responses to Platelet Inhibitors POTENTIAL GENE ALTERED TARGET THERAPEUTIC CLASS SPECIFIC DRUG P2Y1 and P2Y12 CYP2C19, CYP3A4, CYP3A5 ADP receptor inhibitors Clopidogrel, prasugrel COX1, COX2 Cyclooxygenase inhibitors Aspirin PlA1/A2 Receptor inhibitors Abciximab, eptifibatide, tirofiban INTB3, GPIbA Glycoprotein IIb-IIIa receptor inhibitors been extensively examined. Primarily, platelet-dependent genetic determinants have been defined at the level of (1) drug effect, (2) drug compliance, and (3) drug metabolism. Many candidate platelet genes have been studied for their interaction with antiplatelet and antithrom botic agents. Many patients have an inadequate response to the inhibitory effects of aspirin. Heritable factors contribute to the variability; however, ex vivo tests of residual platelet responsiveness after aspirin administra tion have not provided firm evidence for a pharmacogenetic interac tion between aspirin and COX1 or other relevant platelet receptors. As such, currently there is no clinical indication for genotyping to opti mize aspirin’s antiplatelet efficiency. For the platelet P2Y12 receptor inhibitor clopidogrel, additional data suggest that genetics may affect the drug’s responsiveness and utility. The responsible genetic variant appears not to be the expected P2Y12 receptor but an enzyme respon sible for drug metabolism. Clopidogrel is a prodrug, and liver metabo lism by specific cytochrome P450 enzymes is required for activation. The genes encoding the CYP-dependent oxidative steps are polymor phic, and

carriers of specific alleles of the CYP2C19 and CYP3A4 loci have increased platelet aggregability. Increased platelet activity has also been specifically associated with the CYP2C19*2 allele, which causes loss of platelet function in select patients. Because these are common genetic variants, this observation has been shown to be clinically relevant in large studies. In summary, although the loss-of-function polymorphisms in CYP2C19 is the strongest individual variable affect ing pharmacokinetics and antiplatelet response to clopidogrel, it only accounts for 5–12% of the variability in ADP-induced platelet aggre gation by clopidogrel. In addition, genetic variables do not appear to contribute significantly to the clinical outcomes of patients treated with the P2Y12 receptor antagonists prasugrel or ticagrelor. CHAPTER 122 Arterial and Venous Thrombosis VENOUS THROMBOSIS ■ ■OVERVIEW OF VENOUS THROMBOSIS Coagulation is the process by which thrombin is activated and soluble plasma fibrinogen is converted into insoluble fibrin. These steps account for both normal hemostasis and the pathophysiologic processes influencing the development of venous thrombosis. The primary forms of venous thrombosis are deep-vein thrombosis (DVT) in the extremities and the subsequent embolization to the lungs (pul monary embolism), referred to together as venous thromboembolic disease (VTE). Although the majority of venous thromboembolic events occur as pulmonary embolism or DVT of the lower extremities, up to 10% of events may occur in other vascular locations. Venous thrombosis has both heritable causes (Table 122-1B) and acquired causes (Table 122-3). ■ ■DEEP-VENOUS THROMBOSIS AND

PULMONARY EMBOLISM It is estimated that DVT or pulmonary embolism (PE) occurs in ~1–2 individuals per 1000 each year, resulting in 300,000–600,000 new cases of venous thromboembolism each year in the United States. Approxi mately, 60,000–80,000 deaths are attributed to DVT or PE annually. Of new cases, up to 30% of patients die within 30 days and one-fifth suffer

TABLE 122-3 Acquired Causes of Venous Thrombosis Surgery Neurosurgery Major abdominal surgery Other Trauma Antiphospholipid syndrome Pregnancy Long-distance travel Obesity Oral contraceptives/hormone replacement Myeloproliferative disorders Polycythemia vera sudden death due to PE; 30% go on to develop recurrent VTE within 10 years. Data from the Atherosclerosis Risk in Communities (ARIC) study reported a 9% 28-day fatality rate from DVT and a 15% fatality rate from PE. PE in the setting of cancer has a 25% fatality rate. The mean incidence of first DVT in the general population is 5 per 10,000 person-years; the incidence is similar in males and females when adjusting for factors related to reproduction and birth control and increases dramatically with age from 2–3 per 10,000 person-years at 30–49 years of age to 20 per 10,000 person-years at 70–79 years of age. PART 4 Oncology and Hematology ■ ■OVERVIEW OF THE COAGULATION CASCADE AND ITS ROLE IN VENOUS THROMBOSIS Coagulation is defined as the formation of fibrin by a series of linked enzymatic reactions in which each reaction product converts the sub sequent inactive zymogen into an active serine protease (Fig. 122-2). This coordinated sequence is called the coagulation cascade and is a key mechanism for regulating hemostasis. Central to the function of the coagulation cascade is the principle of amplification: owing to a series of linked enzymatic reactions, a small stimulus can lead to much greater quantities of fibrin, the end product that prevents hemorrhage at the site of vascular injury. In addition to the known risk factors rel evant to hypercoagulopathy, stasis, and vascular dysfunction, newer areas of research have identi fied contributions from procoagulant micropar ticles, inflammatory cells, microvesicles, and fibrin structure. VII VIIa The coagulation cascade is primarily initiated by vascular injury exposing tissue factor to blood components (Fig. 122-2). Tissue factor may also be found in bloodborne cell-derived

microparticles and, under pathophysiologic conditions, in leuko cytes or platelets. Plasma factor VII (FVII) is the ligand for and is activated (FVIIa) by binding to tis sue factor exposed at the site of vessel damage. The binding of FVII/VIIa to tissue factor activates the downstream conversion of factor X (FX) to active FX (FXa). In an alternative reaction, the FVII/ FVIIa–tissue factor complex initially converts FIX to FIXa, which then activates FX in conjunction with its cofactor factor VIII (FVIIIa). Thrombin can also activate factor XI (FXI) to active FXI (FXIa), which, in turn, can also activate FIX. FXa with its cofactor FVa converts prothrombin to thrombin, which then converts soluble plasma fibrinogen to insoluble fibrin, leading to clot or thrombus formation. Thrombin also activates FXIII to FXIIIa, a transglutaminase that covalently cross-links and stabilizes the fibrin clot. Formation of thrombi is affected by mechanisms governing fibrin structure and stability, including specific X Xa Thrombin Prothrombin FIGURE 122-2 Summary of the coagulation pathways. Specific coagulation factors (“a” indicates activated form) are responsible for the conversion of soluble plasma fibrinogen into insoluble fibrin. This process occurs via a series of linked reactions in which the enzymatically active product subsequently converts the downstream inactive protein into an active serine protease. In addition, the activation of thrombin leads to stimulation of platelets. HK, high-molecular-weight kininogen; PK, prekallikrein; TF, tissue factor.

fibrinogen variants and how they alter fibrin formation, strength, and structure. Several antithrombotic factors also regulate coagulation; these include antithrombin, tissue factor pathway inhibitor (TFPI), heparin cofactor II, and protein C/protein S. Under normal conditions, these factors limit the production of thrombin to prevent the perpetuation of coagulation and thrombus formation. Typically, after the clot has caused occlusion at the damage site and begins to expand toward adja cent uninjured vessel segments, the anticoagulant reactions governed by the normal endothelium become pivotal in limiting the extent of this hemostatically protective clot. ■ ■RISK FACTORS FOR VENOUS THROMBOSIS An array of different factors contributes to the risk of VTE; it is notable that women and men of all ages, races, and ethnicities are at risk for VTE. The risk factors for venous thrombosis are primarily related to hypercoagulability, which can be genetic (Table 122-1) or acquired, or due to immobilization and venous stasis. Independent predictors for recurrence include increasing age, obesity, malignant neoplasm, and acute extremity paresis. It is estimated that 5–8% of the U.S. population has a genetic risk factor known to predispose to venous thrombosis. Often, multiple risk factors are present in a single individual. Sig nificant risk is incurred by major orthopedic, abdominal, or neurologic surgeries. Cancer patients have an approximately fourfold increased risk of VTE as compared with the general population, and cancer patients with VTE have reduced survival. Hospitalized patients have a greatly increased risk of venous thrombosis with risk factors (increased age, male, ethnicity) and comorbid conditions, including infection, renal disease, and weight loss. Community- or hospital-acquired infec tion is also associated with increased risk of VTE. Supportive of this risk, nearly 20% of hospitalized COVID-19 patients were noted to have coagulation abnormalities as well as increased PE, DVT, and peripheral thrombotic risk. Moderate risk is promoted by prolonged bedrest; certain types of cancer; pregnancy; hormone replacement therapy or oral contraceptive use; and other sedentary conditions, such as longdistance plane travel. It has been reported that the risk of developing a VTE event doubles after air travel lasting 4 h, although the absolute XII PK XI HK TF XIa IX Ca2+ XIa VIIa/TF IXa PL/Ca2+ Activated platelets VIII VIIIa PL/Ca2+ Va V Fibrinogen Fibrin

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