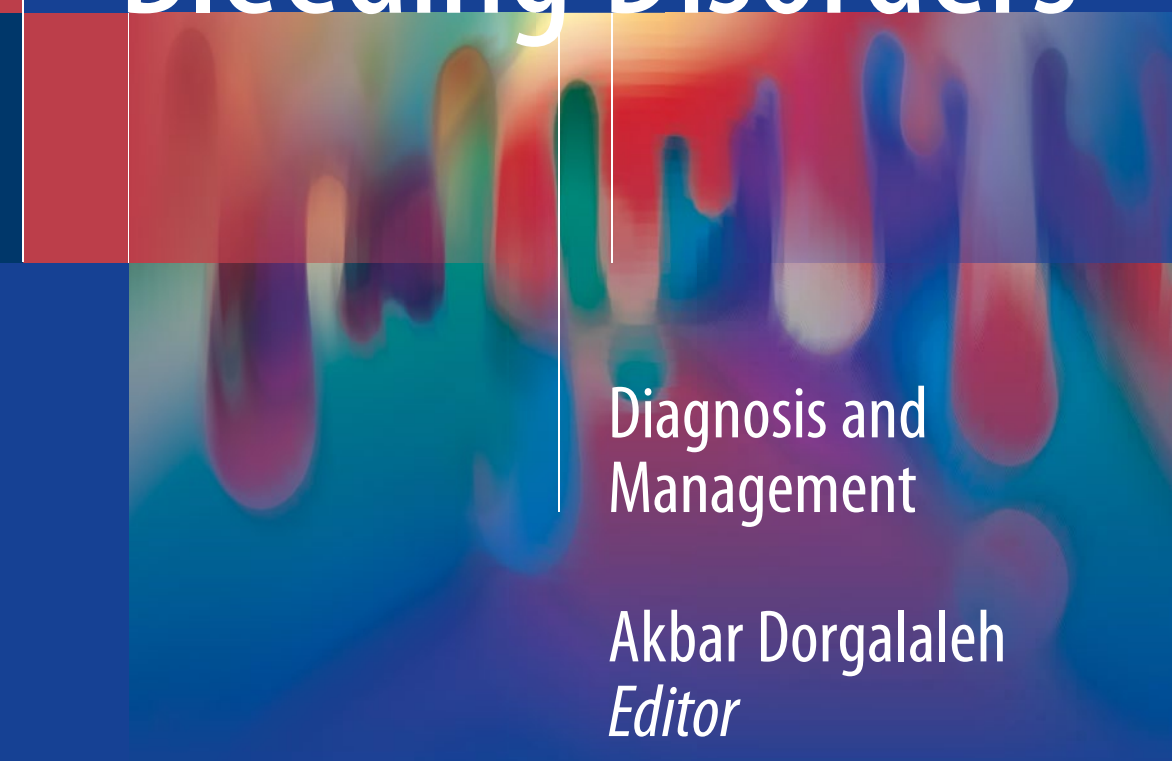
Congenital Bleeding Disorders



Diagnosis and Management

Akbar Dorgalaleh
Editor

Springer

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ISBN 978-3-319-76722-2 ISBN 978-3-319-76723-9 (eBook)
https://doi.org/10.1007/978-3-319-76723-9

Library of Congress Control Number: 2018947184

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

It is a privilege to be given the opportunity of preparing a brief foreword to this magisterial and comprehensive work by Dr. Dorgalaleh and his associates.

Indeed, it is not inappropriate for me to have been invited to provide these few words, as I have been a living witness, in the course of over half a century, of the astonishing evolution of the diagnosis and, most particularly, the care of patients suffering from inherited bleeding disorders, both in this country and the world.

Care has ranged, during this period, from the use of whole blood for the hemophilias in the 1950s to the current employment of recombinant products and the promise of a revolutionary bipolar monoclonal antibody in hemophilia A (HA), and the successful implementation of gene therapy in both HA and hemophilia B (HB).

Those among us who have lived through this astonishing clinical and scientific journey have witnessed a parade of phases in hemophilia care: the initial dearth of therapeutic options; the crippling effects of chronic joint bleeding; the scourge of blood-borne virus infection; and the affliction of inhibitors, which remains current, although a future resolution is within sight.

A few words about the early origins of these bleeding disorders are needed, in order to provide some historical context for this book.

The mutations giving rise to hemophilia are probably of great antiquity, because they occur in at least three orders of placental mammals: the Ungulata, the Carnivora, and the Primates. Hemophilia has been described in the horse, and nine breeds of dog, as well as in all races of man. The orders to which these groups belong may have been distinct from the end of the Cretaceous—say sixty five million years ago, and the mutations have probably recurred independently many times in all three, since they must be lethal in the wild state. The mutation rate has been estimated at about $1–4 \times 10^{-5}$.

The earliest references to what may have been human hemophilia are attributed to Jewish records of the second century A.D. A ruling of Rabbi Judah the Patriarch exempts a woman's third son from circumcision, if two older brothers had died of bleeding following the operation.

It is now well known that Queen Victoria herself (1819–1901) was a carrier of hemophilia B, affecting coagulation factor IX. No evidence of the disorder exists among her antecedents, so we must assume that the mutation occurred at spermatogenesis in her father, Edward, Duke of Kent. The disorder only manifested itself for the first time with the birth of her eighth child in 1853, when Leopold, Duke of

Albany, was born with hemophilia, which proved fatal when he died of a cerebral hemorrhage at the age of 31.

Leopold's sisters, Beatrice and Alice, were both carriers. Alice married the Grand Duke of Hesse, and two of her daughters, Irene and Alix, had hemophilic sons. Alix, better known as Alexandra (Queen Victoria's granddaughter), married Tsar Nicholas II of Russia, and their son, probably the most famous hemophiliac in the world, was Alexei, who was born in 1904. Alexei was also the most tragic example of the disorder, who created so much anguish in the Romanov family. It was through his successful treatment of Alexei's extreme pain by hypnosis, when he was 8 years old (probably due to a psoas muscle hemorrhage), that Rasputin, the charismatic monk, gained such a sinister influence upon the entire household of the Tsar.

The last known carrier of Queen Victoria's mutation was Princess Alice, wife of the Earl of Athlone, who represented the British Crown at the celebration in Tehran, of Crown Prince Mohammad Reza Pahlavi's marriage to Princess Fowziyeh, the sister of Malek Farouq, the king of Egypt, in 1941.

Until 1964, no one took any interest in the inherited bleeding disorders, such as the hemophilias, in Iran. These were truly clinical orphans, and those unfortunate children suffering from the severe form of hemophilia A, or B who had survived into adulthood, were already hopeless cripples. In addition, they had little recourse to treatment, as the sole available form of therapy was fresh whole blood, carrying infinitesimal quantities of the relevant coagulation factor.

At the newly established Tehran University Clinical Hematology Department at the 500-bed Pahlavi (now Emam Khomeini) Hospital, the small associated laboratory was only equipped to carry out blood counts and May-Grunwald staining and microscopy of patients' peripheral blood and bone marrow aspirates, at the time.

However, a personal grant of 18,000 pounds sterling from the Sir Henry Wellcome Trust enabled me to purchase all the equipment required to set up a modern clinical hematology laboratory.

While awaiting the delivery of all these myriad items of equipment from abroad, I became interested in the investigation of inherited bleeding disorders. Using the Thromboplastin Generation Test of Biggs and Douglas (1953), together with the classic Prothrombin Time test of Armand Quick, it became possible to distinguish hemophilia A from hemophilia B, then known as Christmas disease in the UK, and to carry out bioassays of these factors, using a broken 37° waterbath and hand-pulled Pasteur pipettes. Although it was exciting to have been able to actually demonstrate the hemostatic defect in the laboratory for the first time in Iran, this academic exercise was of little benefit to the wretched children affected by these bleeding disorders.

As a result of repeated acute hemarthroses, particularly affecting weight-bearing joints, such as knees and ankles, many of them were bedridden due to contractures and muscle wasting. Some had become drug addicted because of pain and despair. Mothers felt guilty for being carriers; sisters were in an agony of doubt as to whether or not they were carriers of the genetic disorder, and would pass it on to their sons. Indeed, in some cases, wives were ostracized and returned to their families, once the husband learned that his spouse was the cause of the disease. The education of

affected boys is disrupted, resulting in unemployment and a sense of inadequacy. The cost of these inherited bleeding diatheses to society is enormous, not only because of the premature death of potentially useful members of society but also because, if left untreated, patients end up hopelessly crippled, and a burden upon their families, and the health facilities of their country.

Dr. Judith Graham Pool's discovery of cryoprecipitate allowed for the preparation of a crude, home-made concentrate of factor VIII in the Hematology Department laboratories. Bottles of cell-free fresh plasma were snap-frozen in a mixture of dry ice and alcohol, and subsequently thawed slowly at 4° C. A precipitate at the bottom of the bottles contained most of the FVIII, Fibrinogen, and FXIII from the original crude plasma, and was stockpiled in deep freeze cabinets for future use. The cryo-supernatant plasma was also stored for use in hemophilia B, burns, and hypovolemia.

Major orthopedic surgery, mainly arthrodesis of knees, was successfully carried out in the late 1960s, in cases of severe hemophilia A by a few intrepid surgeons in Tehran, such as Dr. Sheikh ol-Eslamzadeh or Dr. Gorgi, using only cryoprecipitate to prevent bleeding, and circulating FVIII levels were assayed daily, before and after each infusion for at least ten days. Soft tissue surgery, such as pyloroplasty and vagotomy for repeated hematemesis, or pulmonary lobectomy for hydatid cyst causing life-threatening hemoptyses was also undertaken with success by Dr. Kazemi, with similar replacement therapy.

It must be emphasized that in the mid-1960s, commercial preparations were not easily available anywhere in the world, with the sole exception of Fraction 1-O, pioneered by Birger and Margaretha Blomback at the Karolinska Institute in Stockholm, which was later manufactured on an industrial scale by Kabi. The only alternatives were bovine and porcine FVIII, produced in the UK, which, although they were potent, were dangerously antigenic. Indeed, one of the cases I treated with bovine FVIII developed both thrombocytopenia and a protein-losing nephropathy, probably caused by an immunogenic reaction to this fraction.

Baruch Blumberg had recently reported what came to be known as "Australian Antigen" or hepatitis B surface antigen, and since hemophilic patients had been repeatedly exposed to plasma, even though there had been no history of overt jaundice, it was felt that they should all be screened for the antigen by the Ouchterlony gel-immunodiffusion technique—the only method available at the time. This was the first application of a test for hepatitis B in Iran, and it was found that this viral infection was common among blood donors.

Inevitably, seeking treatment for hemophilic patients drew attention to the appalling state of blood transfusion in Iran. Virtually without exception, blood for transfusion, whether in private hospital practice or in government and university hospitals, was procured through disreputable dealers. Professional blood sellers exploited the poorest sectors of society, who were prey to malnutrition, anemia, and hepatitis, as well as drug addiction. This was also true of the transfusion services of the Red Lion & Sun Society, the Iranian affiliate of the International Red Cross, currently renamed the Red Crescent Society. Even the military hospitals relied solely upon soldiers—never officers—who were ordered to volunteer, in return for 72 h leave, ostensibly

to allow for their recovery. In addition, modern advances in blood group serology and proper compatibility testing had made little impact upon the rudimentary, fragmented, and grossly commercialized blood services available at the time. Increasing population density and rapid advances in hospital surgery and medicine, together with the growing expectations of both the expanding middle classes and highly trained medical practitioners revealed the glaring inadequacies and dangers of the blood services, and set the scene for fundamental reforms in this vital sector of public health infrastructure.

The unsatisfactory state of blood transfusion services led to the conception of a plan, in 1972, for the establishment of a modern, centralized, national service for blood transfusion, based entirely upon the voluntary, unremunerated donation of blood by healthy members of the public. Implementation of such a program called for a veritable social revolution and a profound change in public attitudes, together with an extensive public education and recruitment campaign.

In 1974, the Iranian National Blood Transfusion Service achieved legal status, and within a relatively short time, a technically advanced service based entirely upon voluntary blood donation replaced the commercialism and inadequacies of the past.

In 1971, the World Federation of Hemophilia (WFH) agreed to hold their 7th international congress in Tehran—the first time such a meeting had been held outside of Europe or Canada. This was a groundbreaking meeting in other ways as well, in that the main thrust of the Congress emphasized the impossibility of providing adequate, comprehensive hemophilia care, without the close support of a safe, modern blood transfusion service, which formed an integral part of the national health services.

Even in the 1970s, it was clear that support for the hemophilic population could not remain confined to doctors and scientists alone. There had to be at least a minimal participation by parents of affected children, and the patients themselves. Early efforts to establish a viable Hemophilia Society remained unfulfilled for many years. It is a source of satisfaction that today a strong Iranian Hemophilia Society (IHS) has been established, which is devoted to the interests of patients and their families, which defends their rights as citizens, and acts as their advocate at both national and international levels. The IHS has not merely confined its efforts to the conventional range of activities typical of similar societies elsewhere in the world: social services, dormitory services for patients from the provinces, support for employment and education, counseling affected families, providing information booklets, etc.; it has gone much further by creating the first comprehensive, interdisciplinary hemophilia care center in Iran as well. The Iranian Comprehensive Hemophilia Care Center (ICHCC) in Tehran is officially affiliated to the World Federation of Hemophilia and was inaugurated in April 2001.

A network of hemophilia centers now exists throughout Iran, often affiliated to regional medical schools.

Registered patients suffering from inherited bleeding disorders are covered by a national insurance scheme under the aegis of the Ministry of Health, such that all

their laboratory investigation expenses as well as replacement therapy with either plasma-derived or recombinant concentrates are provided free of charge.

In sum, the authors of this definitive reference book concerning both common and rare inherited hemostatic disorders meticulously bring together the clinical signs, symptoms, complications, the phenotypic and genotypic diagnoses in the laboratory, together with all the latest forms of treatment currently available, including physiological background, and molecular studies.

This will be an invaluable source of all the relevant, up-to-date and exhaustively reviewed evidence for postgraduate students, scientists, and research workers in the field.

(Some sections of this piece have been published in a modified form in: Arch. Iranian Medicine (2016); 19(3): 229–232)

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Introduction

I did visit Iran at least twice before the Islamic Revolution. In 1971 the World Federation of Hemophilia held in Tehran its 7th World Congress and in September 1978 I organized in the same city a Hemophilia Workshop on behalf of the same international organization. During the two visits I was most impressed by the extraordinary and warm friendship that Iranian people expressed for foreign visitors, as well as by the high level of development in the country of blood transfusion services and the advanced degree of clinical and research knowledge in the field of bleeding disorders. The long, useless and bloody war with Iraq that lasted for a whole decade in the 1980s devastated Iran and made practically impossible for foreigners to visit the country. In addition many of the excellent scientists and clinicians left and went abroad. I returned to Tehran only in December 1995, prompted by the collaboration with Flora Peyvandi who, a native of Iran, had graduated in medicine at the University in Milan and then became a postgraduate hematology fellow with me. I noticed several changes in the lifestyle of Iranians compared with my previous experiences in the 1970s, but two positive aspects had remained unchanged: the spirit of friendship and collaboration with us foreigners and the high quality of medical services, including those dealing with inherited bleeding disorders. I remember distinctly that during my visit and clinical seminar at the Imam Khomeini hospital in Tehran my attention was drawn by a map of the whole country that identified with colored flags the patients with different inherited coagulation disorders. Together with my Italian colleague Alessandro Gringeri we were impressed to notice that the flags representing patients with hemophilia A and B were outnumbered by those identifying patients with recessively inherited coagulation disorders (RICD), with absolute numbers much higher than those that I knew for countries that like Italy and the United Kingdom had general populations not very different in size from that of the Islamic Republic of Iran. Cognizant that global knowledge about the molecular basis but also about the most prevailing symptoms of these disorders was rather limited, Flora, myself, and the whole staff of clinicians and scientists of the Angelo Bianchi Bonomi developed a strong collaboration program with Iranian clinicians and scientists with emphasis on RICD. This collaboration led to the publication of an array of manuscripts that contributed significantly to extend our general knowledge on these rare disorders. Needless to say these studies, which made Flora Peyvandi the main scientific authority in this field, were possible due to the enthusiastic collaboration of Iranian clinicians and scientists, of

whom the most active at that time were Manijeh Lak, Sharifian, and Sirous Zeinali, the latter at the Tehran Pasteur Institute. Not surprisingly, the publications on Iranian patients with RICD attracted the attention and interest of international experts other than those from Milan. For instance, Tuddenham, one of the authors of this book, visited Iran during a summer period, and with the help of Flora Peyvandi managed to publish a seminal study on the molecular basis of the combined deficiency of coagulation factors V and VIII.

The seeds of the international scientific collaboration that Flora and myself put on the fertile soil of Iranian hematologists and pediatricians produced subsequently several additional fruits, and this book is clearly witnessing the role that Iran currently plays in the competitive global arena of hemostasis and thrombosis. At a personal level, it was with great pride that owing to my contributions to the advancement of medical sciences I was honored to receive in Teheran in 2008 the Khwarizmi International Award, a most prestigious international initiative of the Iranian Research Organization for Science and Technology, named after a famous Persian mathematician of the seventh century. Flora and myself are continuing to collaborate with Iranian scientists, who for sake of an example were recently major contributors to the landmark SIPPET study published in 2006. All in all, this excellent book and its contents demonstrate clearly the role prominent achieved by clinicians and scientists of the Islamic Republic in an important field of hematology such as that of inherited bleeding disorders.

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Part I

An Overview of Hemostasis and Congenital Bleeding Disorders

An Overview of Hemostasis

1

Akbar Dorgalaleh, Maryam Daneshi, Jamal Rashidpanah, and Elaheh Roshani Yasaghi

1.1 Introduction

The term hemostasis is derived from Greek roots "heme," which means blood, and "stasis," which means halt, and therefore the word means the halt of blood. The hemostasis is a physiological and well-controlled process in the body in which the integrity of the circulatory system is maintained after vascular injury. Several cellular and noncellular components are involved in this process. These components include coagulation system, platelets, vascular system, fibrinolysis system, kinin system, complement system, and serine protease inhibitors. From the other view, hemostasis has three main components including vascular system, cellular components, and noncellular components (Fig. 1.1).

1. Vascular system: Endothelial cells, smooth muscle, and connective tissue
2. Cellular components: Platelets, granulocytes, monocytes, and lymphocytes
3. Noncellular components: Coagulation factors, fibrinolysis system, serine protease inhibitors, complement system, and kinin system

Following vascular damage, these components work together in close relationship to stop bleeding and then remove the formed clot from the bloodstream. These hemostatic components have also important role in other processes such as wound

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A. Dorgalaleh (ed.), *Congenital Bleeding Disorders*,
https://doi.org/10.1007/978-3-319-76723-9_1

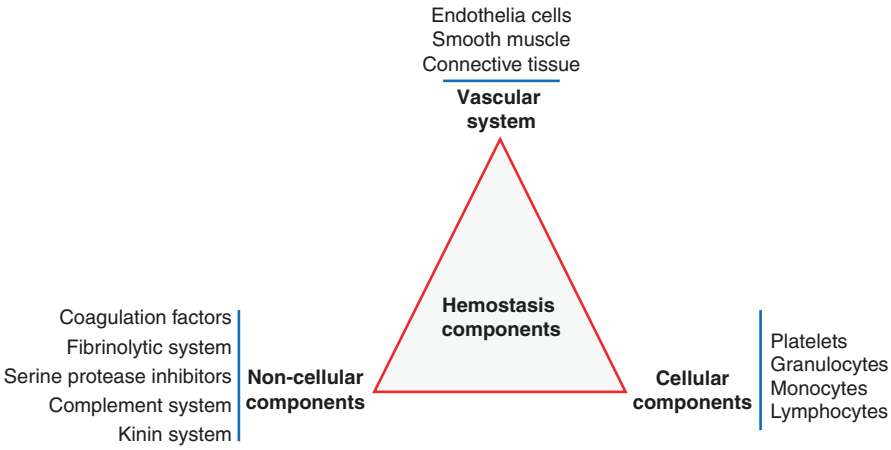

Fig. 1.1 Hemostasis has three main components including vascular system, cellular components, and noncellular components. These components closely work together to keep the hemostasis system in the best situation. Each of these three arms of hemostasis has several other components

healing and angiogenesis. The response of hemostasis system to vascular injury is prompt and well-controlled, and following vascular injury, three steps occur to stop the bleeding:

1. Vasoconstriction
2. Platelet plug formation
3. Blood coagulation [1–3]

Vasoconstriction occurs as the first response of vascular system injury. This process occurs almost promptly in the smooth muscle cells, via the sympathetic nervous system. This response occurred due to the direct damage in the smooth muscles as well as the release of endothelin-1 from the endothelial cells and platelets. This response leads to a decreased blood flow in the area of injury that reduces blood loss. In the second step, platelets adhere to the subendothelium of vasculature in the site of injury, a process known as adhesion. Platelet shape change occurs during the process, and platelet granules are released. This process leads to activation and recruitment of further platelets and induces platelet aggregation, resulting in platelet plug formation. In fact, with vascular injury, subendothelial elements, notably collagen I and III, laminin, and microfibrils, are exposed to the circulating blood. These elements cause platelet adhesion, activation, and secretion. Collagen is the main subendothelial element that allows platelet adhesion. Platelet adhesion to subendothelial collagen is performed by the two main platelet glycoproteins (GP), namely, GPIa/IIa (integrin α2β1, CD49b/CD29) and GPVI, which are the main platelet collagen receptors. GPVI is exclusively expressed on platelet/megakaryocyte lineage, while integrin α2β1 is not restricted to this lineage. Deficiency

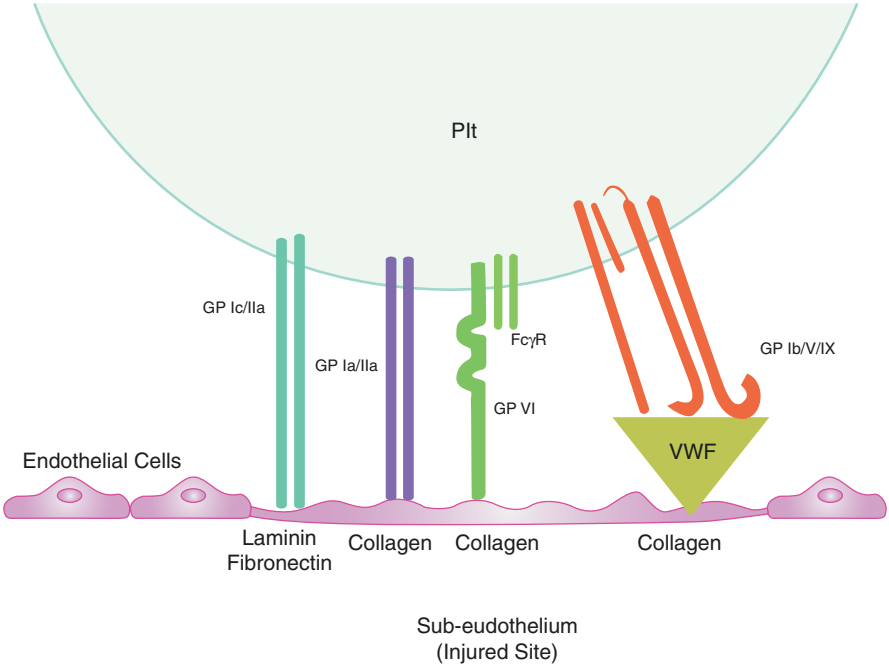

Fig. 1.2 Platelet adhesion, molecular mediations, and subendothelial factors. Glycoprotein (GP) Ic/IIa, GPIa/IIa, GPVI, and GPIb/V/IX are the most important GPs that mediate platelet adhesion. GPIc/IIa and GPIa/IIa directly bind to laminin/fibronectin and collagen, respectively, in the injured site. GPVI also binds to the subendothelial collagen directly, and FcγR has a main role in signal transduction. GPIb/V/IX is comprised of four chains: GPIbα, GPIbβ, GPV, and GPIX. Its binding to collagen is mediated by VWF. *Plt* platelet, *GP* glycoprotein, *VWF* von Willebrand factor

of both GPs leads to extremely rare and mild bleeding disorders. Primary platelet adhesion to the subendothelium at high shear is performed via binding of GPIb/V/IX (CD42a-c) to von Willebrand Factor (VWF) in the subendothelial matrix. This interaction helps in binding of other platelet surface GPs to collagen and other subendothelial elements, which results in firm adhesion of platelets to the injured site (Fig. 1.2) [4, 5].

Activated platelets have a considerable number of agonists that can activate other platelets. These components may be weak platelet stimuli, such as adenosine diphosphate (ADP) and epinephrine, or may be strong such as thrombin. These agonists lead to further activation and subsequent conformational changes of other platelets. Activation of integrin αIIbβ3 (GPIIb/IIIa) on activated platelets is one of the most important events in platelet response to vascular injury. Integrin αIIbβ3 as the most abundant platelet surface GP has a crucial role in platelet–platelet interaction and platelet plug formation at the site of injury. In this process, which is called aggregation, integrin αIIbβ3 and fibrinogen molecules have crucial role. In fact, fibrinogen is attached to integrin αIIbβ3 of neighboring platelets and mediates platelet–platelet interaction (Fig. 1.3) [6].

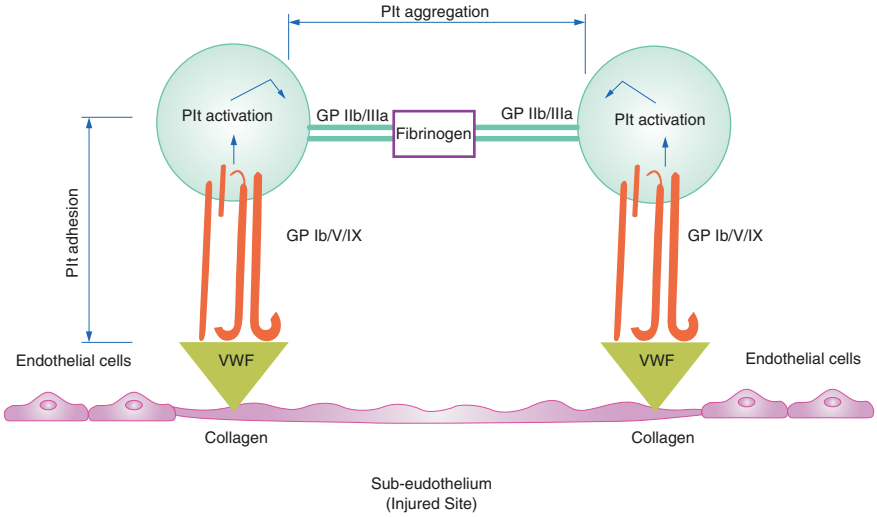

Fig. 1.3 Platelet activation and aggregation and their mediators. Glycoprotein (GP)Ib/V/IX and GPIIb/IIIa are the main GPs that mediate platelet adhesion and aggregation, respectively. Fibrinogen also has an important role in platelet aggregation. *Plt* platelet, *GP* glycoprotein, *VWF* von Willebrand factor

In fact, in addition to well-known role of most of these components in hemostasis, a considerable number of these components have vital roles in other body processes. The process of hemostasis is under precise regulation in the body. Any abnormality in this process can result in severe consequences. Bleeding and thrombotic complications are consequences of abnormalities in the process of hemostasis including missing or dysfunction of specific elements of hemostasis.

Hemostasis is categorized into two main categories, including primary and secondary hemostasis [7].

1.2 Platelets

Platelets are anucleated cells that, in addition to their well-known role in hemostasis, are involved in several other crucial processes in the body including inflammatory processes and tumor angiogenesis and have a role in defense against microbial infections. In normal circumstances, they don't have significant interaction with the vessel walls, but in vascular injury, they promptly interact with the subendothelial extracellular matrix at the injured site in order to stop bleeding. This adhesion leads to platelet activation and granule releases. Stable platelet adhesion at the site of injury occurs in a dynamic process, which includes platelet tethering, rolling, activation, and firm adhesion (Fig. 1.4) [8, 9].

Subendothelial extracellular matrix has several molecules; most of them are ligands for different platelet GPs. Among these adhesive macromolecules, collagen type I and III are the most important for platelet adhesion.

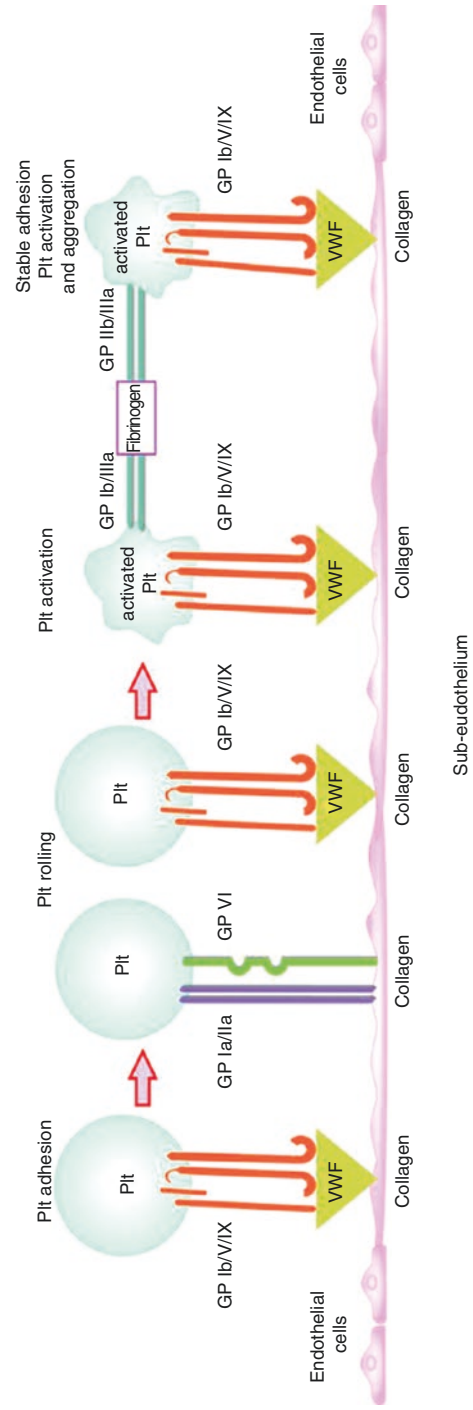

Fig. 1.4 Stable platelet adhesion at the site of injury occurs in a dynamic process that includes platelet tethering, rolling, activation, and firm adhesion. Firstly platelet adhesion is mediated by glycoprotein (GP)Ib/V/IX. This GP also has a role in platelet rolling accompanied with GPIa/IIa and GPVI. After platelet activation, firm adhesion has occurred. GPIIb/IIIa and fibrinogen are the main molecules in platelet aggregation. *Plt* platelet, *GP* glycoprotein, *VWF* von Willebrand factor

Although platelet adhesion is primarily mediated by interaction of GPIb/V/IX complex with VWF in subendothelial matrix, integrin α2β1 (GPIa/IIa) has a crucial role in adhesion process. Binding of integrin α2β1 to collagen leads to the promotion of intracellular process and subsequently platelet activation and firm adhesion to subendothelial.

Initially, integrin α2β1–collagen interaction results in inducing collagen and GPVI interaction. In addition, this interaction leads to the activation of integrin αIIbβ3. Although integrin αIIbβ3, in inactivated form, doesn't bind to fibrinogen, upon activation of platelets, conformational changes occur in this integrin, so the integrin gains the fibrinogen-binding ability. Therefore, integrin αIIbβ3 has a role in both adhesion and aggregation processes. The final stage of adhesion process is firm platelet adhesion to the extracellular matrix. This process requires activation of platelets and shifting integrin αIIbβ3 to its high affinity state. The mechanism of platelet adhesion is different in two conditions, that is, low (20–200 s^{-1}) and high shear (300–800 s^{-1}) conditions. In high shear, initial interaction of platelets GPIb/V/IX complex with VWF in the external subendothelial matrix is loose. This initial adhesion is firmed by integrin receptors and their ligands, including α5β1 (GPIc/IIa) and α2β1 (GPIa/IIa) integrins. In low shear, αIIbβ3 and α2β1 integrins interact with fibrinogen and collagen, respectively, directly initiating platelet adhesion. Following platelet adhesion and with the activation of integrin αIIbβ3 and platelet agonist release, platelet aggregation occurs and subsequently hemostatic plug is formed [10].

1.3 Platelet Surface Glycoproteins

1.3.1 Integrin $\alpha_{IIb}\beta_3$ (Glycoprotein IIb/IIIa) (CD41/CD61)

Out of 18 integrin α and 10 integrin β subunits, platelets express 4 members of β1 including α2β1, α5β1, α6β1, and α8β1 and both β3, αVβ3 and αIIbβ3 subfamilies. α2β1, α5β1, and α6β1 are collagen, fibronectin, and laminin receptors, respectively. Integrin αIIbβ3 is the receptor of several extracellular matrix elements such as collagen, VWF, fibronectin, and vitronectin. Although β1 family members have a crucial role in adhesion, they have a minor role in platelet aggregation, but they are unable to independently support this process (Table 1.1).

Integrin αIIbβ3 is the most abundant platelet integrin with 40,000 to 80,000 copies on unstimulated platelets plus exposable intracellular pool of this integrin. Integrin αIIbβ3 is the main platelet glycoprotein that is required for platelet aggregation and has an important role in the final step of adhesion, which is known as firm adhesion. Although platelet aggregation mainly is mediated by integrin αIIbβ3 and its ligands including VWF and fibrinogen, other molecules such as GPIb and VWF also have some roles.

Glanzmann thrombasthenia (GT) is a moderate to severe hemorrhagic disorder due to mutation in *ITGA2B* or *ITGB3* genes that leads to quantitative or qualitative defects

Table 1.1 Platelet glycoprotein properties

Glycoprotein	Alternative name	Number/ cell	Function	Ligand	Prevalence of related defect	Bleeding tendency
GPIa/IIa	1. Integrin α2β1 2. VLA-2 3. CD49b/CD29	2000–4000	Adhesion	1. Collagen 2. Laminin 3. Vitronectin 4. Tenascin 5. Decorin	Extremely rare	Mild
GPIc/IIa	1. Integrin α5β1 2. VLA-5		Adhesion	1. Fibronectin 2. Denatured collagen 3. Laminin	Extremely rare	Mild
GPIb/V/IX	CD42 a–d	~25,000[a]	1. Platelet adhesion 2. Platelet-endothelial cell adhesion 3. Platelet-leukocyte adhesion	1. VWF 2. Mac-1 3. P-selectin 4. α-Thrombin 5. HMWK 6. FXI 7. FXIIa	Rare	Mild–moderate
GPIIb/IIIa	1. Integrin αIIbβ3 2. CD41/CD61	40,000–80,000	1. Aggregation 2. Adhesion	1. Fibrinogen 2. VWF	Rare	Moderate–severe
GPIV	GP IIIb, CD36		1. Adhesion 2. Aggregation signaling	1. Collagen	Extremely rare	Mild
GPVI	–		1. Adhesion	1. Collagen 2. Collagen-related peptide (CRP) 3. Convulxin	Extremely rare	Mild
GPα6/IIa	1. Integrin α6β1 2. VLA-6		Adhesion	1. Laminin 2. Epiligrin	Extremely rare	Mild
–	α8β1 CD29/CD49h		Adhesion	1. Fibronectin 2. Vitronectin 3. Tenascin 4. Laminin	Extremely rare	Mild
VR (vitronectin receptor)	1. αVβ3 2. CD51/CD61	A few hundreds	1. Adhesion 2. Aggregation	1. Collagen 2. Osteopontin 3. Tenascin 4. VWF	Rare	Mild

[a]Approximately 25,000 copies of the first three peptides including GP Ibα, GP Ibβ, and GP IX reside in the platelet surface along with half as many copies of GPV

in integrin αIIbβ3 with defect in platelet aggregation. In heterozygotes of GT, about 50% amount of integrin αIIbβ3 is present, which is sufficient for normal aggregation.

Integrin αIIbβ3 is present on platelets in both inactivated and activated conformations, but to prevent spontaneous aggregation, it is constrained to inactivated conformation on circulating platelets. Upon vascular injury, nearly immediate activation of integrin αIIbβ3 occurs via stimulation of platelet agonists such as thrombin and ADP [11, 12].

1.3.2 Glycoprotein Ib/V/IX (CD42 a–d)

GPIb/V/IX (CD42 a–d) is the major platelet adhesion GP that initiates platelet adhesion to the subendothelial matrix in high shear stress. In fact, adhesion process at high shear is initiated by interaction between GPIb/V/IX and VWF in extracellular matrix at the site of vascular injury. This initial interaction enables platelet arrests at high shear, inducing signal transduction and finally integrin-mediated platelet adhesion. α2β1 (GPIa/IIa), α5β1 (GPIc/IIa), and αIIbβ3 (GPIIb/IIIa) integrins are involved in firm platelet adhesion.

Following this adhesion, signal transduction leads to platelet shape change and activation, granule secretion, and inside-out integrin activation that promote platelet adhesion and aggregation. During this phase, platelet agonists such as ADP and thrombin are released. These agonists cause platelet activation and additional platelet recruitment at the site of injury. Signal transduction via GPIb/V/IX leads to activation of integrin αIIbβ3 on platelets, which is required for firm platelet adhesion and aggregation. GPIb/V/IX complex consists of several separated subunits, GPIbα (CD42bα), GPIbβ (CD42bβ/CD42c), GPIX (CD42a), and GPV (CD42d), in a ratio of 2:2:2:1, all of them are members of the leucine-rich repeat (LRR) family. GPIbα and GPIbβ are linked with each other with disulfide bond(s) while noncovalently associated with GPIX and GPV subunits.

The N-terminal of GPIbα has binding sites for VWF, Mac-1 (CD11b/CD18), P-selectin, α-thrombin, high-molecular-weight kininogen (HMWK), and coagulation factors including factor (F) XI and FXIIa. α-Thrombin binding to N-terminal of GPIbα leads to platelet activation by thrombin via protease-activated receptor-1 (PAR-1).

GPIbα can mediate platelet–endothelial and platelet–leukocyte adhesion by binding to P-selectin or leukocyte integrin, Mac-1. Platelet–endothelial adhesion also can be mediated by integrin αIIbβ3 on activated platelets and integrin αVβ3 on activated endothelial cells via adhesive molecules such as fibrinogen. Qualitative and quantitative defects in GPIbα, GPIbβ, and GPIX lead to the occurrence of Bernard–Soulier syndrome (BSS) [13, 14].

1.3.3 Integrin α2β1 (Glycoprotein Ia/IIa) (CD49b/CD29)

Integrin α2β1 is one of the main platelet surface collagen receptors that are expressed in different cell types. In fact, platelets have two receptors with

definitive role in platelet–collagen interaction; integrin α2β1 is expressed on the platelet surface on low affinity state for collagen, but upon platelet activation, inside-out signaling leads to occurrence of conformational changes in this integrin and increasing its affinity. Initial adhesion of platelets by GPVI causes platelet activation, and inside-out signaling results in conformational change in integrin α2β1, increasing its affinity, that is, from low to high, which leads to stable platelet adhesion.

Integrin α2β1 and collagen binding has several consequences, including promoting GPVI and collagen interaction and activating integrin αIIbβ3. Integrin α2β1 deficiency is an extremely rare disorder with mild bleeding tendency [15].

1.3.4 Glycoprotein VI

GPVI is a member of immunoglobulin superfamily that initiates platelet activation and promotes integrin αIIbβ3 activation, which is required for platelet aggregation at the site of injury. GPVI is present on platelet surface in complex with Fc receptor (FcR) γ-chain. Extracellular region of GPVI has no affinity for collagen but in dimeric form (GPVI-FcR) has this affinity. This shows that dimeric structure of GPVI is necessary for the affinity of this receptor to collagen. Similar to GPIb/V/IX (CD42 a–d), GPVI is critical for the initial interaction of platelets with extracellular matrix at the site of vascular injury under high shear condition. GPVI deficiency is an extremely rare hemorrhagic disorder with mild bleeding tendency. One of the most important laboratory findings in these patients is lack of platelet aggregation in response to collagen with normal response to other agonists in aggregometry studies. Some patients have very low response to collagen, which is attributed to presence of other collagen receptors on the platelet surface including integrin α2β1 [16, 17].

1.3.5 Integrin α5β1 (Glycoprotein Ic/IIa)

Integrin α5β1 (GPIc/IIa) as the major platelet receptor of fibronectin has a supplemental role in platelet adhesion at the site of vascular injury.

1.3.6 Integrin αVβ3 (CD51/CD61)

Only a few hundreds of integrin αVβ3 (CD51/CD61) are presented on the platelet surface. The expression of this integrin is not restricted to megakaryocyte lineage. Similar to other integrins, αVβ3 (CD51/CD61) is presented in low affinity state on unstimulated platelet surface, while in other cells this integrin is presented in high affinity state. In fact, integrin αVβ3 (CD51/CD61) is presented in low affinity default state in circulating platelets, while in tissue cells, it is presented in high affinity default state [18–20].

1.4 Platelet Granules and Secretion

Platelet adhesion is accompanied with their activation and release of procoagulatory mediators such as ADP, thrombin, and prostaglandins. This process leads to thrombus formation that in addition to platelets, incorporates red blood cells (RBC) and leukocytes. In addition to lysosomes, platelets have two main types of secretory granules including α-granules and dense granules. These small, anucleated cells have more than 300 distinct molecules that have been detected in their releasates. α-granules and dense granules are lysosome-related organelles that are restricted to the platelets. α-granules with a frequency of 50–80 per platelet are the most frequent, while only 0–3 lysosome can be found in each platelet. This number is 3–8 per platelet for dense granules. The diameters of α-granules, dense granules, and lysosomes are 200–500, 200–300, and 200–250 nm, respectively. Platelet granules participate in a variety of body functions including the well-known process of hemostasis, inflammation, wound healing, and angiogenesis as well as malignancies and antimicrobial host defense. Most of these functions including thrombosis and hemostasis, inflammation, angiogenesis, wound healing, and antimicrobial host defense are related to α-granules. The majority of platelet α-granules constitutes are synthesized in megakaryocytes, while the minority including fibrinogen, FV, albumin, and immunoglobulins are captured and endocytosed by circulating platelets and transported to α-granules. Platelets serve as circulating reservoirs of these components and can rapidly release them at local sites after activation (Table 1.2) [21, 22].

α-granules are immediately exocytosed after platelet activation and enhance hemostasis and inflammation processes. α-granules express large amount of P-selectin that after platelet activation are moved to the surface of these cells for interaction with neutrophils, monocytes, endothelial cells, and other platelets.

This interaction between P-selectin and P-selectin glycoprotein ligand-1 (PSGL-1) leads to tethering of platelets, and rolling of them at the site of vascular injury allows firm platelet adhesion.

In addition to the relatively well-known role of platelets on trapping of pathogens, they have a crucial role in directly killing of some pathogens. After *Plasmodium falciparum* infection, activated platelets are attached to infected RBCs and released platelet factor 4 (PF4) from their α-granules. This chemokine inhibits the growth of pathogen and kills it. β-defensins are other platelet constitutes that have direct antimicrobial effects on *Staphylococcus aureus*. PF4 is also able to recruit cells to the inflamed site. Defensins are not located in the mentioned granules and are either cytosolic molecules or contents of other unidentified granules.

Dense granules, dense bodies, or δ-granules contain adenine nucleotides such as adenosine triphosphate (ATP) and ADP and serotonin that are involved in different platelet functions including vasoconstriction, pro-inflammatory cytokine production, inflammation, and platelet aggregation (Table 1.3) [23].

Lysosomes are less frequent than α-granules and dense granules, and contain several enzymes involved in the degradation of carbohydrates, proteins, and lipids. These include glycosidases, proteases, and cationic proteins such as β-glucuronidase,

Table 1.2 Contents of α-granules

	Contents
Hemostatic factors	1. Factor V 2. von Willebrand factor (VWF) 3. Fibrinogen 4. Factor XIII 5. Factor IX 6. Protein S 7. Tissue factor pathway inhibitor (TAFI) 8. Antithrombin 9. Plasminogen 10. Plasminogen activator inhibitor-1(PAI-1)
Growth factors	1. Platelet-derived growth factor (PDGF) 2. Vascular endothelial growth factor (VEGF) 3. Basic fibroblast growth factor (bFGF) 4. Epidermal growth factor (EGF) 5. Transforming growth factor-β (TGF-β) 6. Stromal cell-derived factor-1 α (SDF-1 α)
Proteases	1. Matrix metalloproteinase-2 (MMP-2) 2. Matrix metalloproteinase-9 (MMP-9)
Angiogenic factors	1. Angiogenin 2. Vascular endothelial growth factor (VEGF)
Anti-angiogenic factors	1. Angiostatin 2. Platelet factor-4 (PF-4)
Necrotic factors	1. Tumor necrosis factor-α (TNF-α) 2. Tumor necrosis factor-β (TNF-β)
Chemokines	1. Chemokine (C-X-C motif) ligand-1 (CXCL-1) 2. Chemokine (C-X-C motif) ligand-4 (CXCL-4) 3. Chemokine (C-X-C motif) ligand-5 (CXCL-5) 4. Chemokine (C-X-C motif) ligand-7 (CXCL-7) 5. Chemokine (C-X-C motif) ligand-8 (CXCL-8) 6. Chemokine (C-X-C motif) ligand-12 (CXCL-12) 7. Chemokine (C-C motif) ligand-2 (CCL-2) 8. Chemokine (C-C motif) ligand-3 (CCL-3) 9. Chemokine (C-C motif) ligand-5 (CCL-5)
Granule membrane-specific proteins	1. P-selectin 2. CD63 3. Platelet alpha-granule membrane protein (GMP-33)

Table 1.3 Contents of dense granules

	Contents
Nucleotides	1. Adenosine triphosphate (ATP) 2. Adenosine diphosphate (ADP) 3. Guanosine 5′-triphosphate (GTP) 4. Guanosine diphosphate (GDP)
Amines	1. Serotonin or 5-hydroxytryptamine (5-HT) 2. Histamine
Bivalent cations	1. Calcium 2. Magnesium

Table 1.4 Contents of the lysosomes

	Contents
Acid proteases	1. Carboxypeptidase A 2. Carboxypeptidase B 3. Cathepsin D 4. Cathepsin E 5. Acid phosphatase 6. Collagenase
Glycohydrolases	1. Heparinase 2. β-*N*-Acetyl-glucosaminidase 3. β-Glycerophosphatase 4. β-Glucuronidase 5. β-Galactosidase 6. α-D-Glucosidase 7. α-L-Fucosidase 8. β-D-Fucosidase

elastase, and collagenase with bactericidal activity. These enzymes can help in pathogen and platelet thrombi clearance, extracellular matrix degradation, and heparin inactivation (Table 1.4) [24].

When platelets become activated, anionic lipids such as phosphatidylserine are exposed on platelet surface. Then FV of platelet α-granules is released and bound to these anionic lipids. This FV is activated by initial, small amount of thrombin that is generated from the initial interaction between tissue factor (TF) and FVII at the site of vascular injury. Activated FV (FVa) accompanied with FXa, calcium, and anionic lipids form the prothrombinase complex. This complex cleaves prothrombin and changes it to thrombin (FIIa). FXa bounded to FV is relatively protected from inhibition by plasma inhibitors such as antithrombin. The main consequence of these events is the dramatic increase of thrombin generation on activated platelet surface, and this process is restricted to the site of vascular injury. In fact, platelets localize coagulation process to thrombus and protect coagulation enzymes from inhibition by plasma and platelet inhibitors, therefore preventing the occurrence of disseminated intravascular coagulation (DIC). In Scott syndrome, as an inherited platelet function disorder (IPFD) with mutated *TMEM16F* gene, this procoagulant activity of platelets is impaired. These issues show close relationship between activated platelets and coagulation factors [25].

1.5 Endothelium

The endothelium has been described as a barrier between circulatory blood and surrounding tissues. It is a dynamic organ that can regulate its environment and response to external stresses. Although the endothelium is less than 0.2 μm thick, it includes 6×10^3 endothelial cells that weigh about 1 kg in an average person and

covers 4000–7000 m^2. The endothelium acts as a blood-compatible surface that maintains blood flow and regulates blood coagulation system [26].

Endothelial cells have several functions include vascular tone regulation, cellular adhesion, smooth muscle cell proliferation, and vascular inflammation. Endothelial cells have numerous functions that are specific to different vascular beds. The main function of the endothelium is to regulate systemic blood flow via change in vascular diameter. Furthermore, the endothelium acts as a barrier that controls fluid, ion, and macromolecule movement between the circulating blood and surrounding tissues selectively. Endothelium regulates recruitment and extravasation of procoagulation leukocytes in response to tissue injury and inflammation. Endothelial cells play a crucial role in the healing process after injury or inflammation. They also act as angiogenesis vector, which is necessary for tissue repair and obstructive fibrin clot recanalization. Endothelial cells accompanied with smooth muscle cells also regulate local blood pressure, because these cells are responsive to vasoactive agents. These cells can response to inflammatory cytokines and other stresses like hypoxia and metabolic stresses. Altogether, the endothelium expresses many molecules that regulate platelets and activate coagulation cascade that results in the prevention of post-vascular injury thrombosis development [27, 28].

Endothelial cells cover the arteries, veins, and microvessels. Shear stress, blood oxygenation, and smooth muscle cell density are different between these vessels, so endothelial cells differently response to procoagulation signals in different vascular beds. For instance, vasodilation regulation in the arteries is faster than in the veins. These cells adapt their phenotype according to the nature of the surrounding tissues and have abundant phenotypic heterogeneity.

Endothelial cells have an important role in clot development due to their position and are closely related to coagulation cascade. Intact endothelial cells express inhibitors to prevent thrombin synthesis and activation. When these cells are activated, they play a role in the initiation and development of thrombin production via procoagulation factor expression [29, 30].

Coagulation cascade can be activated via two pathways, intrinsic and extrinsic. Extrinsic and intrinsic pathways are initiated by converting FVII to FVIIa and FXII to FXIIa, respectively. Activated endothelial cells contribute to extrinsic pathway, expressing TF in response to vascular injury and inflammation. TF/FVIIa complex activates protease-activated receptor-2 (PAR-2) that induces a pro-inflammatory response. The endothelium regulates clot formation by PAR activation. Acute release of endothelial products is mostly mediated by PAR-1. PAR-1 plays an important role in response to procoagulation stimuli. It induces Weibel–Palade body (WPB) activation, and therefore VWF and tissue-type plasminogen activator (t-PA) are released. It also mediates nitric oxide (NO) and prostacyclin production, which reduces platelet activation. Finally, thrombin-mediated PAR-1 activation is related to surface TF exposure [31, 32].

It is observed that microvascular endothelial cells induce angiogenesis by releasing TF-rich microparticles.

Although activated endothelial cells are typically related to extrinsic pathway, they also may play a role in intrinsic pathway. The mechanism of endothelial cell function in intrinsic pathway is unclear, but there is a supposition that these cells prevent the inhibition of intrinsic pathway factors; for instance, FXIIa can be protected from C1 inhibition activity by the endothelial cells [33]. Investigations also have shown that these cells are the primary source of FVIII. Therefore, endothelial cells are probably the necessary component of both intrinsic and extrinsic coagulation pathways.

In addition to coagulation, endothelial cells have a main role in primary hemostasis. The interaction between platelets and endothelium is important for platelet activation and regulation. An intact endothelium prevents platelets from adhesion, while activated endothelial cells express molecules and receptors that enhance platelet adhesion to the injured site. WPB stores VWF, P-selectin, angiopoitin-2, t-PA, and endothelin-1 in endothelial cells which mediate platelet adhesion, leukocyte recruitment, inflammation regulation, fibrinolysis, and vasoconstriction, respectively.

VWF has two main roles in hemostasis: first, it is necessary for collagen to have platelet adhesion to GPIb/V/IX in the injured vascular sites and, second, it stabilizes plasma coagulation FVIII [34, 35].

Furthermore, an intact endothelium actively prevents thrombosis formation by suppressing platelet activation and adhesion. It expresses multiple anticoagulants such as tissue factor pathway inhibitor (TFPI), thrombomodulin, endothelial protein C receptor (EPCR), and heparin-like proteoglycans. There is an ectonucleotidase (CD39) on the endothelial cell surface that converts platelet stimulator ADP into adenosine. TFPI is one of the most important inhibitors of coagulation cascade. It inhibits coagulation cascade by direct inhibition of FXa and TF/FVIIa/FXa complex. Patients with less than 10% of the normal level of TFPI have increased risk of venous thrombosis and coronary heart disease. Thrombomodulin and EPCR catalyze thrombin-mediated protein C pathway activation. Activated protein C inactivates FVa and FVIIIa that results in reduced thrombin formation. Platelet activation is inhibited by prostacyclin and prostaglandin E2 (PGE2) which are released from the activated endothelium by vasoactive agents. NO enhances prostacyclin effect [36–38].

Endothelial cells are important components that contribute to clot destruction. In wound healing process, endothelial cells release proteofibrinolytic molecules, such as t-PA and urokinase-type plasminogen activator (u-PA), and metalloproteases for clot destruction. These cells also release ADAMTS13 and ADAMTS18 that mediate platelet aggregate dissolution [27, 39, 40]. The endothelial cells are one of the main parts of the blood vessels and can induce angiogenesis after stimulation. For instance, protein C can stimulate angiogenesis in the brain endothelium [41].

Endothelial disorders are responsible for inflammation and inappropriate clot formation and can be related to cardiovascular diseases.

1.6 Coagulation Factors

All coagulation factors are synthesized by the liver except for FVIII, which is produced by the endothelial cells. VWF is also synthesized in megakaryocytes, in addition to endothelial cells.

Initiation of blood coagulation is triggered by vascular injury and exposure of TF to bloodstream that leads to generation of small amount of thrombin. This thrombin is sufficient to activate platelets, FV, FVIII, and FXI and triggers consolidation pathway that leads to sufficient generation of thrombin. This thrombin is sufficient to convert fibrinogen to fibrin. Thrombin is the key coagulation enzyme that has two major functions in hemostasis including fibrinogen to fibrin conversion and activation of platelets.

From the initial theory of coagulation cascade by Macfarlane, Davie, and Ratnoff in 1964, which involved a series of enzymatic reactions by which initial small amount of stimulus was amplified and results in burst generation of thrombin that is sufficient for fibrinogen to fibrin conversion, extensive revision was made. Two alternative pathways, namely, intrinsic and extrinsic, have been introduced for the initiation of coagulation cascade (Table 1.5).

Coagulation cascade is a precise mechanism that leads to clot formation and blood loss prevention. In physiological status, this cascade is counterbalanced by anticoagulant system mechanisms. This exact regulation leads to prevent aberrant clot formation. In pathological status, due to hereditary or acquired defects, normal controlling mechanisms of coagulation system may be disrupted, which can result in pathological conditions such as thrombosis [42].

The Extrinsic Pathway Unlike intrinsic pathway, an external component of pathway, TF is present in this pathway. This pathway is initiated by a complex formation between plasma FVIIa with TF from the extravascular tissue. Although TF is not present in the bloodstream at high concentration, upon tissue injury, it's exposed to FVIIa. TF, as a cofactor of FVII, induces activation of FVII. This complex cleaves trace amount of FIX and FX to FIXa and FXa, respectively. FXa in combination with FVa, as a cofactor for FVa, forms the prothrombinase complex. This complex converts prothrombin (FII) into thrombin (FIIa), and thrombin converts fibrinogen into fibrin monomers. These fibrin monomers are unstable and cross-linked by FXIIIa to be stable.

The Intrinsic or Contact Activation Pathway This pathway is named intrinsic because all components are present in the blood, and this pathway is initiated by exposure of the blood to negatively charged surfaces. This pathway consists of several proteins including FXII that is activated by negatively charged surfaces. FXIIa converts prekallikrein into activated form, kallikrein. Kallikrein itself converts more

Table 1.5 Characteristics of blood coagulation factors

Coagulation factor	Alternative name	Structure	Function in coagulation cascade	Other functions	Plasma half–life	Hemostatic level	Normal range
Factor I	Fibrinogen	Heterotrimer	Clot formation	Platelet adhesion	72–120 h	20–30%	1.5–4.0 g/l
Factor II	Prothrombin	Monomer	Serine protease	Anticoagulant activity	60–70 h	20–40%	75–115 u/dl
Factor III	1. Tissue factor 2. Tissue thromboplastin 3. Tissue phospholipid 4. CD142	Extracellular, transmembrane, and intracellular zones	Cofactor	Arterial and vein thrombosis Myocardium infarction Angiogenesis	–	5–19 pM	–
Factor IV	Calcium	Ion	Cofactor	Role in proper muscle, nerve, and heart function	–	–	9–10.5 mg/dl
Factor V	1. Labile factor 2. Proaccelerin 3. Owern	Single-chain protein consists of six domains	Cofactor	Anticoagulant activity	36 h	10%	63–115 u/dl
Factor VII	Stable factor Proconvertin	FVII: single chain FVIIa: double chain	Serine protease	–	FVII: 4–6 h FVIIa: 2 h	10–15%	70–125 u/dl
Factor VIII	Antihemophilic factor	Non-covalent heterodimer	Cofactor	1. Essential blood-clotting protein 2. Association of factor VIIIa with factor IXa to form the intrinsic factor Xase complex 3. Increase the catalytic efficiency for factor Xa generation	17 h	30–60%	55–150 u/dl
Factor IX	Christmas	Monomer	Serine protease	Coagulation FX activator	24 h	20–30%	70–165 u/dl