4 Pathophysiology of Large-Artery Atherosclerosis

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Abstract

Large-artery atherosclerosis (LAA) is one of the major three causes of ischemic stroke, together with cardioembolism and small-vessel occlusion, accounting for approximately 20–30% of all cases, albeit by race and ethnicity. Pathophysiology of coronary atherosclerosis responsible for acute coronary syndrome is well established, and recent development of knowledge about atherosclerosis is mostly from studies on coronary diseases. Researches on cerebral atherosclerosis causing stroke has not been enough to fully elaborate its pathophysiology, but there are a lot of similarities and differences as compared to the pathophysiology of coronary atherosclerosis. In this chapter, I will describe mechanisms of LAA-related stroke in detail.

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4.1 Atherosclerosis: A General Concept

4.1.1 Formation of Atherosclerosis

Atherosclerosis is a chronic inflammatory disease in which an initial endothelial damage leads to deposition and denaturation of lipids in the vessel walls for several years, as shown in Fig. 4.1. The vascular endothelial cell dysfunction can be caused by various vascular risk factors, such as hypertension, diabetes, and smoking, resulting in increased permeability among the endothelial cells and invasion of monocytes, which plays a crucial role in the development of early-stage atherosclerosis. Meanwhile, low-density lipoprotein (LDL) cholesterols penetrate to the vascular walls and lodge in the internal extracellular matrix. If the risk factors are not properly corrected, LDL cholesterol particles continue to be accumulated due to sustained vascular stresses and begin to form a lipid mass inside the vessel walls. Then, the LDL cholesterols are transformed by modification such as oxidization, which is a very strong pro-inflammatory material, causing a further exacerbation of inflammation during the process of atherosclerosis.

The monocytes that penetrate into the subendothelial areas are subsequently differentiated into the macrophages by the macrophage colony-stimulating factor. The macrophages show two distinct subtypes that are markedly differentiated

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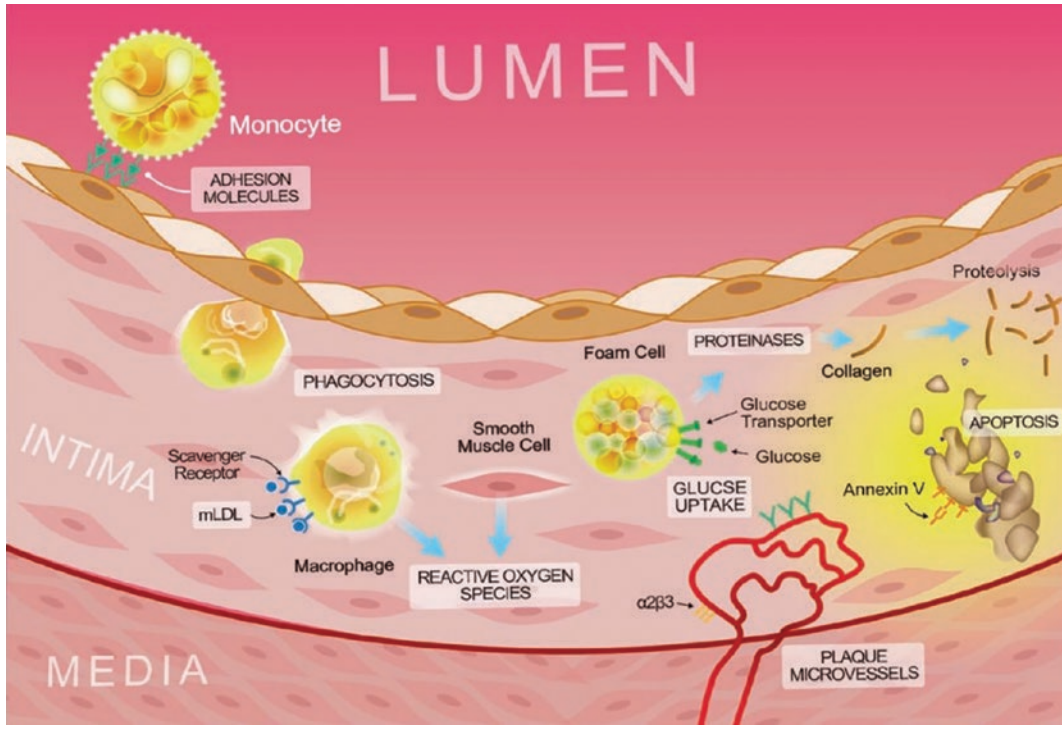


Fig. 4.1 Progression of atherosclerosis. LDL: low-density lipoprotein

by polarization in stages of atherosclerosis, M1 and M2 (Fig. 4.2): M1 macrophages generally have a pro-inflammatory function, but in contrast, M2 macrophages have an anti-inflammatory function [1]. In the early stage of atherosclerosis, macrophages are differentiated to M1, and by presenting surface pattern recognition receptors that recognize modified LDL, they are subsequently transformed into foam cells through uptake of lipids. The foam cells further aggravate inflammatory status by releasing pro-inflammatory cytokines and growth factors. In the meantime, the vascular smooth muscle cells (VSMCs) move from the media to the intima, producing extracellular matrix material that is important for the formation of fibrous caps. The foam cells may be removed in the form of apoptosis by M2 macrophages, which is called efferocytosis. If this process is active enough, overall inflammation process can be reduced. However, when the inflammation process is more severe than M2-related efferocytosis, the M2 macrophages ingest apoptotic cells too excessively, stress to the endoplasmic reticulum inside the M2 macrophages are increased, resulting in dysfunction of efferocytosis. Then, inflammatory factors, coagulation factors, and matrix metalloproteinases (MMPs) are released, which induce a structural instability of atheromatous plaques and ultimately, a rupture of the plaques. After the ruptures, von Willebrand factors (vWFs) and collagen from the lesions stimulate the platelets in the blood, which form a thrombus by adhesion and aggregation of the platelets, causing a thromboembolism to organs of the body such as brain. The plaque instability or vulnerability increases with fewer VSMCs and more undifferentiated new blood vessels (angiogenesis) in the necrotic plaque cores.

4.1.2 Classification of Atherosclerosis

Atherosclerosis has various morphological features, depending on the location of blood vessels, the degree of exposure to risk factors, and

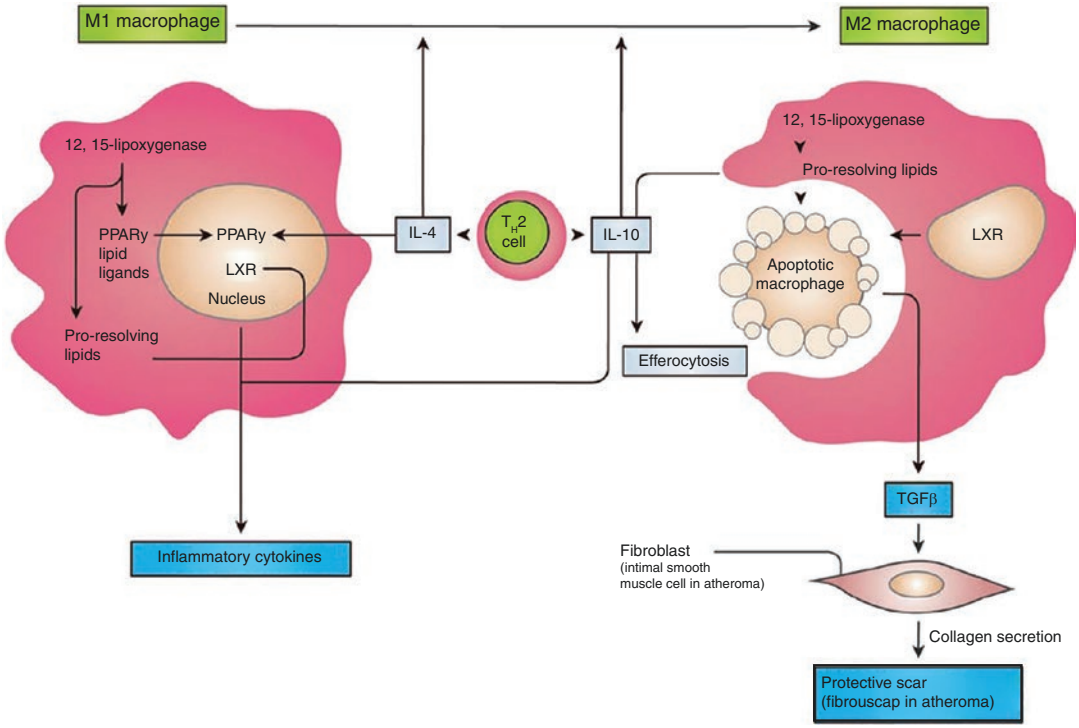


Fig. 4.2 The M1 and M2 subtypes of macrophage with differential functions according to atherosclerotic stage

the process stages. Therefore, classification of the lesions is indispensable to understand its pathophysiology. In 1958, WHO first classified arteriosclerosis into four categories: fatty streak, atheroma, fibrous plaque, and complicated lesion [2]. In the mid-1990s, the American Heart Association (AHA) recommended new classification criteria for atherosclerotic plaques, which was established after some minor modifications (Table 4.1, Fig. 4.3) [3–5]. However, there might be a caveat: this is a pathophysiological classification for the coronary arteries, and it is not clear whether it can be applied to all arteries in our bodies, including cerebral arteries. Because the nature of atherosclerosis is not considered to be significantly different between the cerebral arteries and coronary ones, application of this classification for understanding of stroke mechanism would be plausible. As described in this classification, atherosclerotic plaque lesions responsible for the thrombosis are plaque ruptures, an erosion of the plaque, and a calcified nodule (Figs. 4.4 and 4.5), and I will explain the thrombosis mechanisms from these lesions in this chapter [6].

4.1.2.1 Plaque Rupture

Plaque rupture is observed in the form of a rupture of the necrotic core and the fibrous cap, which are usually infiltrated with macrophages and T cells [3]. The extracellular matrix of the fibrous cap is mostly composed of collagen type I, biglycan and decorin, and VSMC is rarely found. Thrombus found on the ruptured lesion is mostly composed of platelets—so we called it as white thrombus by its color, which turns red-colored thrombus in the form of red blood cells embedded in fibrin layers (lines of Zahn) distal to the center of the thrombus. This is the evidence that platelets are activated early due to rupture of the plaque, and that clotting factors are activated subsequently after stagnation of blood. Rupture of the fibrous cap occurs in the shoulder area of the plaque, which is generally considered the weakest part of the plaque. Secretion of proteolytic enzymes from macrophages and the shear

Table 4.1 The AHA classification of atherosclerotic lesions

Type of lesion	Subtype of lesion	Morphological description
Nonatherosclerotic intimal lesions	Intimal thickening	Natural accumulation of smooth muscle cells in the absence of lipid, macrophage foam cells, and thrombosis
	Intimal xanthoma	Superficial accumulation of foam cells without a necrotic core, fibrous cap, or thrombosis
Progressive atherosclerotic lesions	Pathological intimal thickening	Plaque rich in smooth muscle cells, with hyaluronan and proteoglycan matrix and focal accumulation of extracellular lipid. Absence of thrombosis
	Fibroatheroma	During early necrosis: Focal macrophage infiltration into areas of lipid pools with an overlying fibrous cap. During late necrosis: Loss of matrix and extensive cellular debris with an overlying fibrous cap. With or without calcification. Absence of thrombosis
	Intraplaque hemorrhage or plaque fissure	Large necrotic core (size >10% of plaque area) with hemorrhage, and plaque area shows the presence of angiogenesis. Necrotic core communicates with the lumen through a fissure. Minimal tear without obvious thrombus
	Thin-cap fibroatheroma	A thin, fibrous cap (<65 μm) infiltrated by macrophages and lymphocytes, with rare or no smooth muscle cells and relatively large underlying necrotic core (>10% of plaque area). Intraplaque hemorrhage and/or fibrin might be present. Absence of thrombosis
Lesions with acute thrombi	Plaque rupture	Thin-cap fibroatheroma with cap disruption. Thrombosis is present and might or might not be occlusive. The luminal thrombus communicates with the underlying necrotic core
	Plaque erosion	Can occur on pathological intimal thickening or on a fibroatheroma. Thrombosis is present and might or might not be occlusive. No communication of the thrombus with the necrotic core
	Calcified nodule	Eruptive (shedding) of calcified nodule with an underlying fibrocalcific plaque with minimal or no necrosis. Thrombosis is usually not occlusive
Healed lesions	Healed plaque rupture, erosion, or calcified nodule	Healed lesion composed of smooth muscle cells, proteoglycans, and collagen type III with or without underlying disrupted fibrous cap, necrotic core, or nodular calcification. Lesions can contain large areas of calcification with few inflammatory cells and have a small or no necrotic core. The fibrotic or fibrocalcific collagen-rich plaque is associated with significant luminal stenosis. Absence of thrombosis

An updated version of the modified AHA classification published in 2016, which was based on the original AHA classification published in the mid-1990s. *AHA* American Heart Association

stress and tension on the plaque may act as a basal mechanism for the rupture. In addition, dying macrophages or VSMC-derived microcalcifications (>5 μm) inside the fibrous caps may induce detachment from plaques under blood pressure, resulting in rupture of the plaques.

4.1.2.2 Plaque Erosion

Plaque erosion refers to atherosclerotic lesions that can cause blood clots without rupture, exposing the VSMCs and the proteoglycan matrix with a slight peeling of the endothelial lining. These lesions usually occur during the intimal thickening or early- or late-stage fibroatheroma, and they are less inflammatory than the ruptured plaques. The plaque rupture causes positive remodeling, whereas the plaque erosion causes negative remodeling. Usually, large calcifications are rarely observed in the plaque erosion, and only microcalcifications are observed at about 40% [7]. The tissue at the thrombosis-occurring site of the plaque erosion was identified as activated VSMCs embedded to a proteoglycan-rich substrate composed mainly of collagen type III, hyaluronan, and versican. This is in contrast to the fibrous caps mainly composed of collagen type I in the ruptured or stable plaques. Plaque erosion may cause more microembolization to

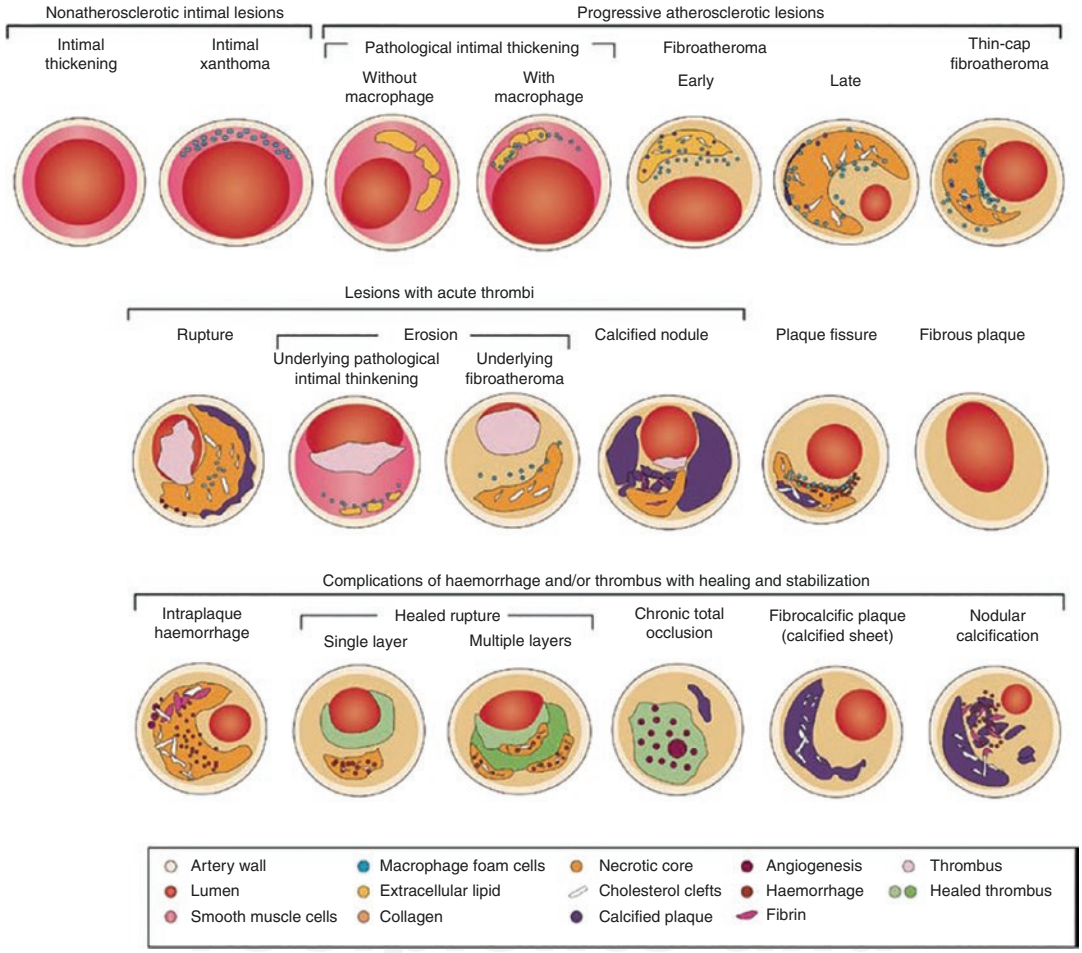
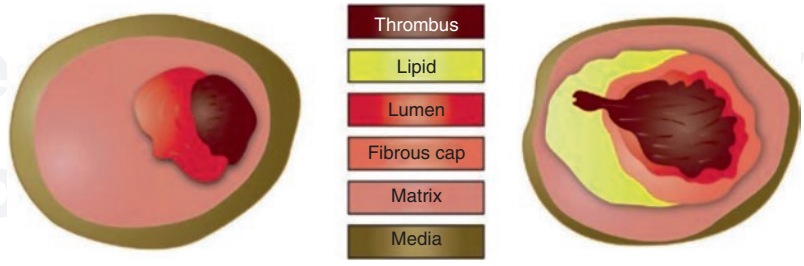


Fig. 4.3 Schematic figures showing composition and morphology of atherosclerotic lesion according to the classification suggested by the American Heart Association

Fig. 4.4 The characteristics of plaque erosion and plaque rupture



Plaque erosion
Lipid poor
Proteoglycan and glycosaminoglycan rich
Non-fibrillar collagen breakdown
Few inflammatory cells
Endothelial cell apoptosis
Secondary neutrophil involvement
Female predominance
High triglycerides

Plaque rupture
Lipid rich
Collagen poor, thin fibrous cap
Interstitial collagen breakdown
Abundant inflammation
Smooth muscle cell apoptosis
Macrophage predominance
Male predominance
High LDL

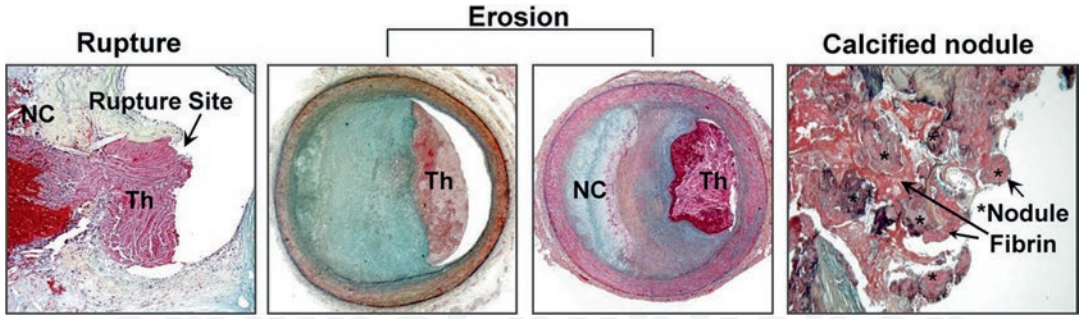


Fig. 4.5 Pathology of the coronary plaques of three different morphologies (rupture, erosion, and calcified nodule). Ruptured plaques have thin fibrous cap which is critical site of rupture. In case of rupture, the luminal thrombus (Th) has communication with the lipid-rich necrotic core (NC). Surface erosions usually occur in area lacking surface endothelium. In rare cases of erosion with necrotic core, the necrotic core does not communicate with the luminal thrombus. Calcified nodules are fibrocalcific plaques protruding into lumen with disruption. Adapted with permission from Heart, Lung and Circulation, Copyright Elsevier [6].

the distal regions than that the plaque ruptures (artery-to-artery embolism). It was reported that tobacco smoking rather than blood lipid levels are correlated with the incidence of plaque erosion, but it needs to be more verified [7].

4.1.2.3 Calcified Nodule

Among thrombosis-related atherosclerotic lesions, calcified nodules are the least common form: only 5% of thrombosis in coronary arteries are caused by these lesions—even so with advanced calcifications [8]. Because cerebral arteries show lower incidence of arterial calcification than coronary arteries, the attributable fraction of calcified nodules for cerebral infarction is likely to be much lower. The mechanism by which thrombosis develops on the calcified nodules is uncertain, and it was hypothesized as follows: when calcified tissue membranes break down due to blood pressure, fibrin accumulates around the destroyed lesions, and eventually erupt up to the luminal surface [9]. Fibrin is relatively common even in non-erupted calcified nodules but not communicated to the lumen, which may come from the surrounding damaged capillaries. Eruptive calcified nodules are common in asymmetrically shaped lesions, and these eruptions may stimulate platelet activation. Calcified nodules are more observed in older people. These lesions should not be confused with the nodular calcification: the nodular calcification can destroy the structure of the media, but not invade to the adventitia, and is not associated with thrombosis.

4.2 Large Artery Atherosclerosis: Intracranial Versus Extracranial

LAA causing ischemic stroke can be divided into two types: atherosclerosis in intracranial arteries and those in extracranial arteries. Intracranial arteries mean all cerebral large arteries in the intracranial space, and extracranial arteries mean large arteries in the extracranial area, but relevant to ischemic stroke: parts of aorta (ascending and arch), common carotid artery, internal carotid artery, and vertebral artery. Internal carotid artery and vertebral artery run through both extracranial and intracranial space, so these arteries belong to both categories according to their locations. Extracranial artery and intracranial artery not only differ in embryological origin but also in histologic findings. Due to their structural differences, clinical features of atherosclerosis and thromboembolism is a little different from those of coronary artery. This will be explained in detail below.

4.2.1 Epidemiology of Intracranial Atherosclerosis

First, we need to look at the burden of intracranial atherosclerosis in the general population. A European population study indicated that by age 65, 80–97% had pathological evidence of intracranial atherosclerosis [10]. In addition, according to the Rotterdam Scan Study, calcification of intracranial internal carotid arteries confirmed by CT scan was found in 82% [11]. A clinicoradiologic study in patients with ischemic stroke, 45–62% of patients were identified to have intracranial plaques or stenoses [12]. The prevalence of symptomatic intracranial stenosis has been reported to be 20–53%, depending on the subjects, methods, and races [13]. In particular, intracranial atherosclerosis is much more prevalent in Asian (Korea, Japan, China and etc.) and African-American individuals than in Caucasian whites [14]. According to the Northern Manhattan Study, intracranial atherosclerosis was found only in 9% for white individuals as compared with 17% for African-American, and 15% for Hispanic [15]. East Asia studies have shown that the prevalence is up to 30–40% [16, 17].

4.2.2 Histologic Comparisons of Normal Arteries

Extracranial arteries belong to elastic arteries, because elastin is profuse in tunica media. In contrast, intracranial arteries are classified as muscular arteries, because they have little elastic fibers [18]. In terms of internal carotid arteries, a transition from elastic artery to muscular artery occurs in carotid bifurcation due to differences in embryological development. Compared to extracranial arteries, intracranial arteries are characterized by a thin tunica media and adventitia, no external elastic lamina, but an intense internal elastic lamina. External elastic lamina exists to the petrous portion of the internal carotid artery but disappears at the cavernous portion, which may be associated with frequent occurrence of atherosclerotic stenosis at this site.

In extracranial arteries, vasa vasorum plays an important role in the survival of vascular cells, but intracranial arteries do not have vasa vasorum from 1.5 cm after dural penetration: the function of vasa vasorum, delivery of oxygen and nutrients, is replaced by luminal diffusion from the cerebrospinal fluid [18]. Due to the thin media and adventitia, and the absence of external elastic lamina, the intracranial artery can carry out this process. Given that the vasa vasorum may play an important role in atherogenesis, a later onset of intracranial atherosclerosis is likely related to the absence of vasa vasorum.

4.2.3 Pathologic Comparisons of Atherosclerosis

Aging in the intracranial arteries gradually reduces the elastic fibers and muscle components and replaces them with collagen tissue. Initially, intimal thickening, reduplication, and splitting of the thick internal elastic lamina occur, together with fibrosis and hyalinization of the media and adventitia [18]. At this time, there was little lipid in the vessel wall. Intracranial atherosclerosis is predominantly found as fibrous plaques, with less frequent fatty streaks or complicated lesions. Plaque ruptures or calcified nodules, representative complicated atheromatous lesions causing thrombosis, are found at internal carotid arteries, basilar artery, and proximal segments of vertebral arteries, but rarely in old age. In the proximal segment of distal internal carotid arteries or middle cerebral arteries, fibrous plaques rather than calcification and plaque rupture are predominant [19]. However, uncontrolled exposure to risk factors can result in complicated plaques with high-lipid content, intraplaque necrosis or hemorrhage, neovascularization, macrophage and T lymphocyte infiltration, which can lead to thrombosis-related stroke.

The progression of atherosclerosis differs in occurrence timing and rate of intracranial arteries from those of extracranial arteries. Aortic atherogenesis increases linearly, whereas intracranial atherogenesis occurs very late, but dete-

riorates very rapidly in the 1950s and 1960s, and then slowly in the 1970s and 1980s. This is quite contrast to the coronary atherogenesis, which is rapidly deteriorating in the 1930s and relieving from the 1940s to the 1970s [18]. The sites of atherosclerosis development in the intracranial arteries are mainly anterior circulation: internal carotid arteries are the most common, followed by middle cerebral arteries, basilar artery, vertebral arteries, posterior cerebral arteries, and anterior cerebral arteries. In Asian countries, middle cerebral arteries are known to be the most common site, with ICA being the next most frequent.

4.3 Thrombus Formation in Large Artery Atherosclerosis

Thrombus or blood clot is the final product of the coagulation process and consists of two components: (1) a plug agglomerated with platelets and (2) a fibrin-derived meshwork structure to secure the platelet plug firmly. Thrombosis is basically a result of a defense mechanism against bleeding, but when it occurs inside the lumen of blood vessels without bleeding, we generally call it thrombosis. It may occur that a thrombus suddenly obliterates cerebral blood vessels leading to cerebral infarction, but it can be originated from an atherosclerotic lesion or from the heart with dysfunctions such as atrial fibrillation.

In general, the conditions for development of thrombi are firstly illustrated as "Virchow's triad": (1) damage to vascular endothelial cells: trauma or arteriosclerosis, (2) abnormal blood flow: loss of laminar flow due to stagnation of blood flow in veins or turbulence in arteries, and (3) hypercoagulability. The thrombi can be classified into white thrombi, which are mainly composed of aggregated platelets, and red thrombi, which are mainly composed of red blood cells and fibrin, depending on its composition (Fig. 4.6) [20]. Both types of thrombi can result in ischemic stroke, but the type of thrombus may influence the patient's early course, effect on acute treatment, and prognosis and secondary prevention. Therefore, in order to properly diagnose and treat ischemic strokes, it

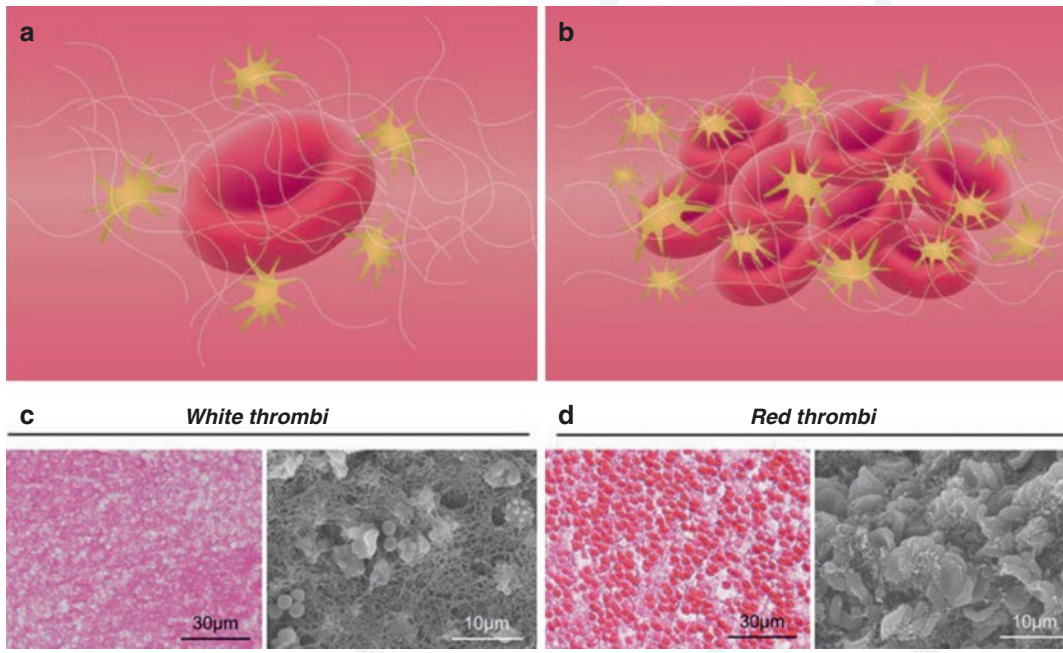


Fig. 4.6 Schematic figures and scanning electron microscopy images of white thrombi (**a**, **c**) and red thrombi (**b**, **d**). Adapted with permission from Stroke, Copyright Wolters Kluwer Health [20].

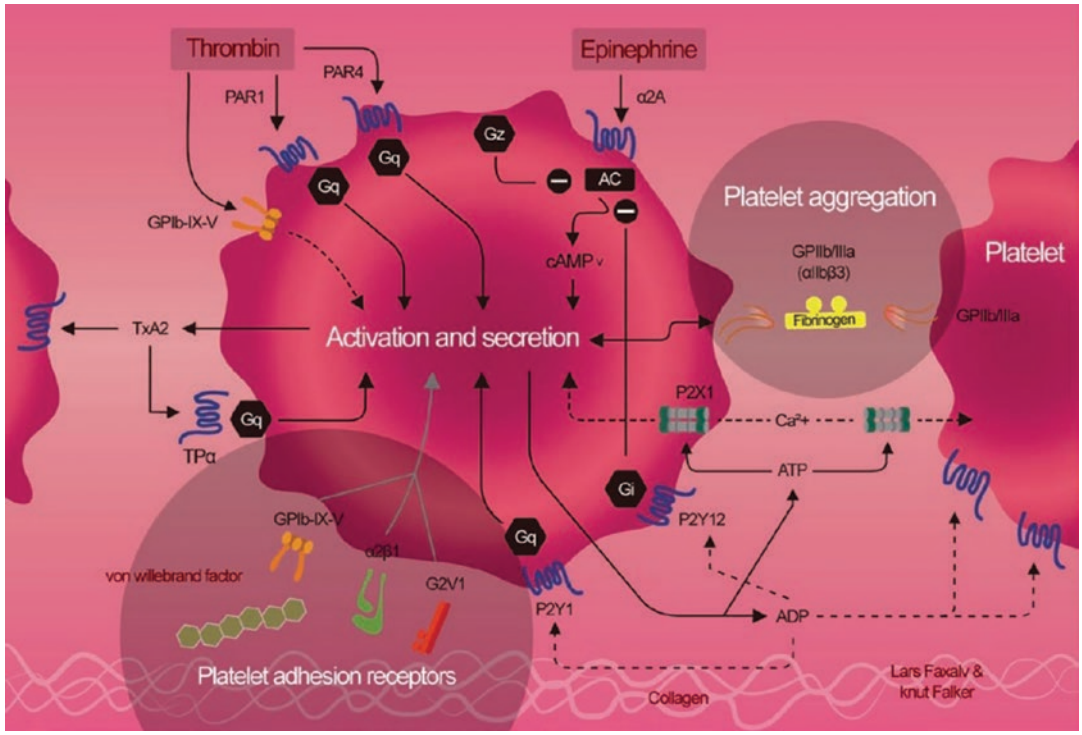


Fig. 4.7 Mechanism of platelet activation

is of note to understand the mechanisms, components, and related factors of thrombus development [21].

4.3.1 The Formation of Platelet Thrombus

Endothelial cells, collagen in subendothelial layer, and tissue factor (TF) are important for the maintenance and homeostasis of the vascular system. In particular, endothelial cells form the inner lining of blood vessels and produce three thromboregulators (nitric oxide, prostacyclin, and ectonucleotidase CD39) that inhibit blood clot formation.

4.3.1.1 Two Independent Pathways for Platelet Activation

There are two well-known substances that cause platelet activation: collagen and TF. When rupture of vessel walls causes bleeding to the surrounding tissue, collagen and TF are exposed to the blood and begin to form blood clots to stop the further bleeding (Fig. 4.7). Collagen promotes platelet aggregation and activation, while TF initiates thrombin formation, leading to further activation of platelets and conversion from fibrinogen to fibrin. The two pathways can be activated predominantly in either situation, with the same result—platelet activation.

Collagen exposed to blood due to vascular damage causes platelets to adhere to the endothelial cells (platelet adhesion) through interactions between collagen and glycoprotein VI of platelets or between vWFs attached to collagen and glycoprotein Ib-V-IX of platelets. Glycoprotein VI acts as the most important promoter for early platelet activation and platelet granule secretion. Platelet activation here is not due to thrombin.

TF activates the TF pathway, the second most important pathway for early platelet activation. Platelet activation here is closely related to thrombin, but not to vascular endothelial rupture, vWFs, and glycoprotein VI. Originally, TF is present as two forms, either in an inactive form on the vessel wall or in an activated form inside the vessel wall. The inactivated TF form is

activated by protein disulfide isomerase, and forms a complex with factor VIIa, which in turn activates factor IX, producing thrombin along the proteolytic pathway. Thrombin activates platelets by breaking down protease-activated receptor 4 (Par 4 in mice, Par 1 in humans) on the platelet surface. As a result, activated platelets secrete adenosine diphosphate (ADP), serotonin and thromboxane A2, which in turn amplify the signal for thrombin formation, activating other platelets.

4.3.1.2 Thrombus Propagation

Platelet integrin αIIbβ3 (also known as glycoprotein IIb/IIIa) is activated and serves to platelet–platelet interaction and to draw platelets into thrombi. Integrin αIIbβ3 requires protein disulfide isomerase to be activated [22]. Platelets adhering to damaged endothelial cells promote structural changes in αIIbβ3, resulting in increased affinity with fibrinogen or vWFs as ligands of αIIbβ3. In addition, activated platelets secrete alpha granules and dense granules, which are critical for the formation of thrombi. Alpha granules contain a variety of proteins for thrombus formation, while dense granules contain ADP and calcium ions. As a result, the secreted ADP attaches to the P2Y1 and P2Y12 receptors on the platelets to further promote platelet activation.

4.3.2 Blood Coagulation

The coagulation pathway in blood plasma consists of the following three pathways that are sequentially activated (Fig. 4.8).

4.3.2.1 Contact Activation Pathway (Intrinsic Pathway)

The contact activation pathway begins with the formation of an initial complex after high-molecular-weight kininogen (HMWK), prekalli-

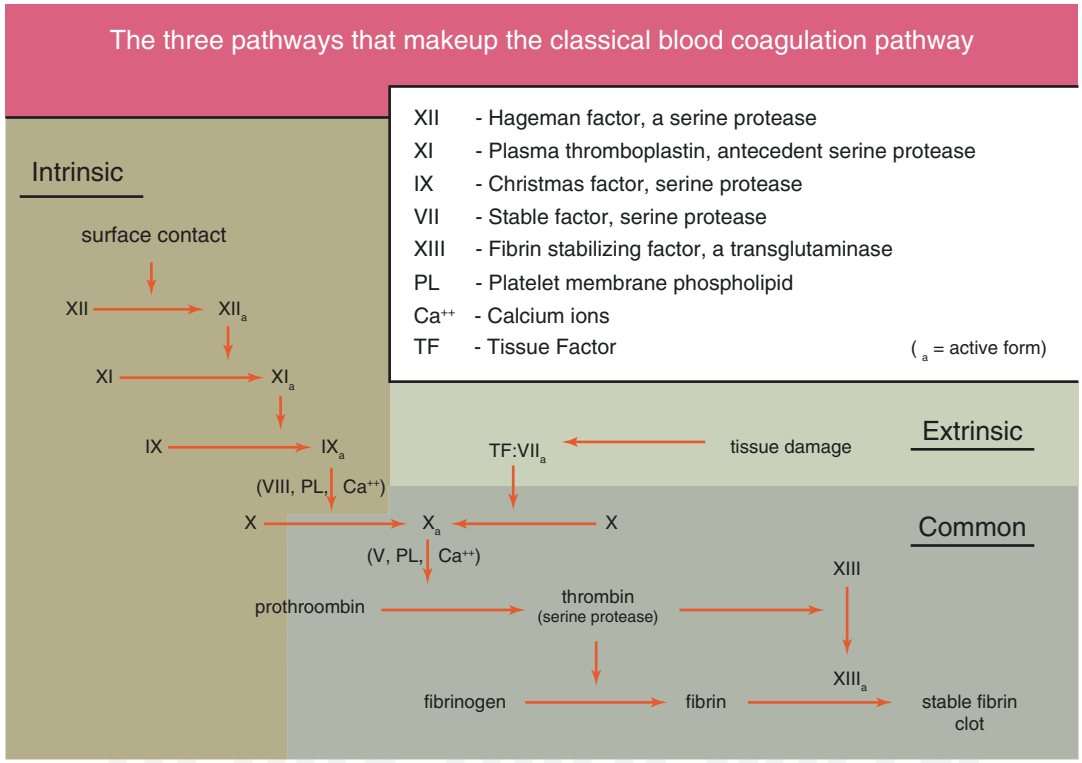


Fig. 4.8 Cascades of clotting factor activation: contact activation pathway, tissue factor pathway, and common pathway

krein, and factor XII (Hageman factor) encounter collagen. As prekallikrein changes to kallikrein, factor XII is activated by XIIa. Factor XIIa converts factor XI to XIa, and in turn, factor XIa converts factor IX to IXa. Factor IXa forms a tenase complex with a cofactor, factor VIIIa, which activates factor X to Xa. The contact activation pathways are very powerful for coagulation in laboratory environments, but are not necessary in vivo for initiation of blood coagulation. Activation of Factor XII is important as the starting point of the contact pathway, whose deficiency is identified by a prolonged partial-thromboplastin time (PTT). However, this does not necessarily mean that patients lacking factor XII have hemorrhagic disease, so the importance of factor XII and XI is to be more clarified.

4.3.2.2 TF Pathway (Extrinsic Pathway)

The most important role of the tissue factor pathway is the "explosive increase in thrombin" by including feedback mechanisms, the most important component of the entire coagulation pathway. TF, as mentioned earlier, is a membrane protein with various roles. TF is consistently expressed in fibroblasts, pericytes in outer layers of vessels, and smooth muscle cells of vascular walls, and part expressed in cells which are not related to blood vessels as well. TF interacts with some nano- or microparticles (<1000 nm) in blood. During the thrombus formation, platelets attach to endothelial walls and become activated, expressing an adhesion molecule called P-selectin. P-selectin binds to microparticles expressing a receptor called P-selectin glycoprotein ligand 1 (PSGL-1), allowing microparticles expressing TF derived from monocytes to be caught to thrombi. As such, TF derived from blood plays an important role in the expansion of fibrin in thrombi.

Because only activated TF is associated with blood clotting activity, it is necessary for the inactivated TF (latent or encrypted form) present in the endothelial cells to become active in order to participate in blood coagulation. Although molecular mechanisms of TF activation have not been clearly identified, it is believed that TF activation needs release of disulfide bonds in the cysteine group of TF protein. This bond is separated by protein disulfide isomerase, which is released from activated endothelial cells or platelets. In other words, protein disulfide isomerase is involved in both fibrin production and platelet activation for thrombus formation.

Of the various coagulation factors, factor VIIa is higher in the amount than other coagulation factors. Factor VII is activated by thrombin, XIa, XII and Xa. When blood vessels are damaged, factor VIIa enters fibroblasts or monocytes containing TF and binds to TF to form complexes. This complex activates factors IX and X. Activation of X by the complex can be inhibited immediately by tissue factor pathway inhibitors (TFPI). Factor Xa and the cofactor factor Va form a prothrombinase complex, which converts prothrombin to thrombin. Thrombin affects various coagulation factors, such as factor V and factor VIII. Activated factor VIIIa, as mentioned above, acts as a cofactor for factor IXa, creating a tenase complex. Collectively, this process amplifies thrombin formation.

4.3.2.3 Common Pathway

Basically, thrombin exists from the initial aggregation of platelets and performs a lot of functions besides simply converting fibrinogen into fibrin, as the most important coagulation factor. Thrombin activates factors VIII and V and also activates protein C under the presence of thrombomodulin. Activated protein C inhibits VIII and V to compromise blood clotting. Thrombin also activates factor XIII to crosslink fibrin monomers into polymers. The common pathway acts to maintain coagulation tendency with sustained activation of factors VIII and IX until suppressed by anticoagulation mechanisms.

4.3.2.4 Cofactors and Modulators

Cofactors include calcium, phospholipids and vitamin K. Calcium and phospholipids as components of platelet cell membranes act as cofactors in the functions of the tenase complex and the prothrombinase complex. Calcium is also reported to play a role in the activation of other coagulation factors. Vitamin K is an essential component of the hepatic gamma-glutamyl carboxylase, which

attaches carboxyl groups to the glutamic acid residues of factors II, VII, IX, X and proteins C, S, and Z. In this process, vitamin K itself is oxidized. An enzyme called Vitamin K epoxide reductase (VKORC) returns vitamin K back to active state. VKORC is a pharmacologically important enzyme because it is a target of warfarin. Warfarin blocks VKORC, causing vitamin K deficiency and preventing clotting factors from being activated.

Modulators include protein C, antithrombin, TFPI, plasmin and prostacyclin (PGI2). First, as a major anticoagulant, protein C is activated by thrombin bound with cell surface protein thrombomodulin. Activated protein C inactivates factor Va and VIIIa along with cofactors S and phospholipids. Decreased levels of protein C or S cause various thrombosis, including ischemic stroke. Antithrombin is a serine protease inhibitor (serpin) that breaks down the serine proteases such as thrombin, factors IXa, Xa, XIa, and XIIa. It is always activated in the body, and the effect is enhanced when heparan sulfate is present or when heparin is injected from the outside. Its quantitative deficiency may also lead to various thrombosis, including ischemic stroke. Second, TFPI limits the action of TF. Third, in the liver, plasmin is produced by the decomposition of plasminogen. This process is catalyzed by tissue plasminogen activator (t-PA), which is synthesized and secreted from vascular endothelial cells. Plasmin decomposes fibrin into fibrin degradation product (FDP), which acts to inhibit the formation of excess fibrin. For the initial treatment of ischemic stroke, the method of injecting recombinant t-PA for thrombolysis has been widely used worldwide. Finally, prostacyclin (PGI2) is secreted from endothelial cells to activate the platelet Gs protein-linked receptor. This in turn activates adenylyl cyclase and increases cyclic adenosine monophosphate (cAMP) synthesis. cAMP lowers intracellular calcium levels, inhibits platelet activation, and inhibits the secretion of granules that induce secondary platelet/coagulant activation.

4.4 Conclusions

In this chapter, I carefully looked into the pathophysiology of LAA, one of the three major causes of ischemic stroke. Atherosclerosis results from chronic inflammatory processes due to innate immunity inside the vascular walls of large arteries, and monocytes and LDL cholesterol play a critical role in the pathogenesis. Atherosclerotic lesions responsible for thrombosis are plaque rupture, plaque erosion, and calcified nodule according to the AHA's morphological classifications: the plaque rupture is the most common lesion for acute coronary syndrome, but in terms of ischemic stroke, the attributable risk need to be clarified. Platelet activation is the main mechanism of LAA-derived thrombi, whose propagation is dependent on the coagulation factor cascades in the plasma [3]. This knowledge of pathophysiology on the LAA-related thrombosis is the key to prevent future stroke or coronary disease in patients with atherosclerosis.

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