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16.13 Coronary heart disease CONTENTS 16.13.1 Biology and pathology of atherosclerosis 3596 Robin P. Choudhury, Joshua T. Chai, and Edward A. Fisher 16.13.2 Coronary heart disease: Epidemiology
and prevention 3603 Goodarz Danaei and Kazem Rahimi 16.13.3 Management of stable angina 3616 Adam D. Timmis 16.13.4 Management of acute coronary syndrome 3626 Rajesh K. Kharbanda and Keith A.A. Fox 16.13.5 Percutaneous interventional cardiac procedures 3655 Edward D. Folland 16.13.6 Coronary artery bypass and valve surgery 3666 Rana Sayeed and David Taggart 16.13.1 Biology and pathology of atherosclerosis Robin P. Choudhury, Joshua T. Chai, and Edward A. Fisher ESSENTIALS Formation of an atheromatous plaque—this is an inflammatory pro- cess that involves the contribution of endothelial cells, lymphocytes, monocytes, and smooth

muscle cells in conjunction with the de- position of atherogenic lipoproteins in the intimal layer of the vas- cular wall. The initial stage involves activation of the endothelium at regions of nonlaminar flow in vessels resulting in increased perme- ability to Apo B-containing lipoproteins. Inflammatory cells, in par- ticular monocytes, are recruited into the intimal layer of the vessel wall via the action of chemokines and adhesion molecules mobilized by activated endothelium. Progression of atheroma—ingestion of low-density lipoprotein by monocytes, predominantly via scavenger receptors, generates lipid-rich foam cells. Atheroma progression is promoted by the failure to clear macrophages and foam cells that, on dying, re- lease cholesterol-rich material promoting further inflammation. Leucocytes and endothelial cells also contribute through the release of growth factors that stimulate proliferation of vascular smooth muscle cells. These cells migrate from the medial layer to the intima where they undergo transformation to both a synthetic phenotype (contributing to extracellular matrix formation), and ‘macrophage- like’ vascular smooth muscle cells capable of phagocytosis of low- density lipoprotein. Further development of the atheromatous plaque—extracellular matrix formation by vascular smooth muscle cells is stimulated by cytokines (e.g. TGFβ and platelet-derived growth factor) released from T lymphocytes, platelets, and macrophages. The extracellular matrix confers structural integrity to the atheromatous plaque and the overlying collagen-rich fibrous cap and promotes retention of lipoprotein molecules. Neovascularization of atheroma via the ac- tion of vascular endothelial growth factor results in susceptibility to plaque haemorrhage. Calcification is common although its patho- genic significance is uncertain. The progression of the atheromatous plaque is not always linear. Regression of atheroma—previously observed in preclinical models, clinical regression of atheroma has also been demonstrated with increasing frequency as low-density lipoprotein-lowering has be- come more potent. In preclinical models, the mechanism appears to involve the resolution of the inflammatory state of plaque macro- phages, which remodels diseased artery towards a normal state in a process that is akin to wound healing. Clinical manifestations—although atherosclerosis develops within
the wall of the artery, eventual encroachment of the expanding plaque into the lumen may be sufficient to retard blood flow, causing stable angina. Progression may also occur in stepwise fashion due to minor plaque rupture or haemorrhage. Acute cor- onary syndromes arise from more profound, and usually abrupt, transformations of atheromatous plaques due to plaque haem- orrhage, erosion, and rupture that can precipitate the formation of occlusive luminal thrombus. Atheromatous lesions with a large lipid-rich core and thin fibrous cap are predisposed to plaque rup- ture, releasing lipid-containing prothrombotic material and giving rise to thrombosis. Thrombotic occlusion due to plaque erosion arises in areas denuded of endothelium and is more common in women smokers.

16.13.1 Biology and pathology of atherosclerosis 3597 Medical management—therapies to promote atheroma regres- sion target plasma lipoproteins (especially low-density lipoprotein cholesterol), plaque inflammation, and plaque remodelling. Dietary and pharmacological modification of plasma lipids are effective
secondary prevention measures that have been shown to pro- mote plaque regression, but their impact on clinical events appears to relate to complex mechanisms that modify inflammation, plaque stability, and thrombosis and are more difficult to assess using cur- rent techniques. Specific therapies targeting the inflammatory component of the atheromatous plaque (in particular monocyte re- cruitment, macrophage function and apoptosis) are attractive, and the first evidence of possible clinical effectiveness of this approach is emerging. Initiation of atheroma Atherosclerotic

plaques are not randomly distributed, but tend to form at the inner curvatures and branch points of arteries, where laminar flow is either disturbed or insufficient to sup- port the normal, quiescent state of the endothelium (the lining of endothelial cells that separates the circulating blood from the arterial wall). Mechanical transduction of laminar shear stress in- volves the activation of integrins with downstream inactivation of the Yes-associated protein (YAP)/transcriptional coactivator with a PDZ-binding domain (TAZ), the prime mediators of the Hippo pathway. Loss of laminar stress leads to activation of YAP and TAZ, which promotes the activation of several in- flammatory pathways including the atherosclerosis-promoting JNK-protein. Activation of the endothelium is associated with increased permeability to lipoproteins and an accumulation of extracellular matrix proteins that cause diffuse intimal thickening and the retention of the atherogenic apolipoprotein B (apoB)- containing lipoproteins. Endothelial activation also promotes the recruitment of cir- culating monocytes that originate from either the bone marrow or spleen. Monocyte entry into the arterial intima depends on endothelial cell up-regulation of molecules that mediate their arrest on the luminal surface of the endothelium. The recruited monocytes transmigrate across the endothelium, where they differentiate into macrophages, some of which encounter the retained apoB-lipoproteins. The subsequent uptake of the re- tained apoB-lipoproteins by these macrophages is one of the earliest pathogenic events in the nascent plaque and results in the development of macrophage foam cells. The mechanisms of foam cell formation have been intensely studied. Although macrophages can take up apoB-containing lipoproteins through the low-density lipoprotein (LDL) receptor, expression of this receptor is down-regulated early during foam cell formation by the increased cellular cholesterol levels. These observations led to the hypothesis that lipoproteins must become modified in the artery wall and be taken up by other mechanisms, notably by scavenger receptors. Multiple means of LDL modification that facilitate cholesterol loading of macrophages in vitro have been identified, including oxidation. The physiologically rele- vant in vivo pathways of foam cell formation are still debated, though it is widely accepted that the appearance of foam cells in arterial sites represents the initiation of an atherosclerotic plaque. Leucocyte recruitment Though many cell types contribute to the formation of atheroscler- otic plaques, including endothelial cells, monocytes, dendritic cells (DCs), lymphocytes, eosinophils, mast cells, and smooth muscle cells, macrophage foam cells are so central in the initi- ation and progression of atherosclerosis that emphasis has long been placed on understanding the mechanisms of monocyte re- cruitment into plaques. Circulating monocytes in mice have been considered in two major subsets, Ly6Chi and Ly6Clow, with the corresponding subsets in humans being CD14+CD16− and CD14lowCD16+. In mice, and presumably in humans, the more in- flammatory monocyte subsets (Ly6Chi and CD14+CD16−) make up the majority of cells recruited to progressing atherosclerotic plaques and are thought to be the source of the M1 (classically ac- tivated) macrophages found in both murine and human plaques that are responsible for maintaining a chronic inflammatory state. While these classifications, based on the expression of molecules on the cell membrane, have provided insights into the potential for differential function within a given cell population, more so- phisticated appreciation of function is emerging from quantitative transcriptomic, metabolomic, and proteomic analyses. Monocyte recruitment, as noted earlier, begins at the luminal surface of the endothelium. The capture and rolling phases of the recruitment cascade depend on the immobilization of chemokines, particularly CC-chemokine ligand 5 (CCL5) and CXC-chemokine ligand 1 (CXCL1), to endothelial cell glycosa- minoglycans, and on P-selectin, which is expressed on the lu- minal side of endothelial cells. Vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1), which bind to the integrins VLA4 and lymphocyte function-associated antigen 1 (LFA1), respectively, are important for the firm

adhe- sion of monocytes to the luminal surface of the endothelium. The next phase is the transmigration of monocytes across the endothelium into the intimal (subendothelial) space. This is mediated by chemokines secreted by endothelial cells, in- timal macrophages, and smooth muscle cells. Although several chemokines have been implicated in atherosclerosis, the three major chemokine receptor–chemokine pairs involved in mono- cyte transmigration are CCR2–CCL2, CX3CR1–CX3CRL1, and CCR5-CCL5. In addition to these chemokines, CD31 (also known von Willebrand factor; an endothelial cell surface immunoglobulin-like adhesion molecule) and VCAM1 may also have a role in monocyte transmigration into atherosclerotic plaques. See Fig. 16.13.1.1. Although most studies of monocyte recruitment have been conducted in mice, the key players just described all have human homologues thought to function in similar ways.

section 16 Cardiovascular disorders 3598 Progression of atheroma Beyond plaque initiation (see ‘Initiation of atheroma’ earlier), two factors conspire to promote the progression of atheroma. These are the ongoing entry and subsequent retention of the apoB-containing lipoproteins, and the continued expansion of the plaque cellular component due to both recruitment of monocytes, and to the local proliferation of macrophages. Recruitment of monocytes to a site of inflammation is not ab- normal; rather, it is the failure to remove macrophages and re- solve the inflammation that leads to pathology. In part this is due to macrophage chemostasis (cellular paralysis) that is not typical in other settings (such as in pneumonia or wound healing) and which might reflect the expression of retention molecules that render the macrophages and foam cells relatively unresponsive to chemokines, as shown in mice. Macrophages are key cellular components of atherosclerotic plaque and produce interleukin-1β (IL-1β), which is also pro- moted by activation of NLRP3 inflammasomes by the formation of crystals as cellular cholesterol accumulates. Interleukin-1β and interleukin-1α exert pro-inflammatory effects that are inhibited by the endogenous antagonist interleukin-1 receptor antagonist (IL- 1RA). Atherosclerosis-prone mice that are deficient for IL-1β de- velop smaller lesions, and administration of IL-1RA reduces early atherogenesis in mice, while IL-1RA deficient mice have shown in- creased atherosclerosis and vascular inflammation, associated with destruction of elastic tissues. The key role of IL-1β as a mediator of innate immunity and the effects of interleukin inhibition in ex- perimental atherosclerosis have led to interventions to reduce in- flammation through IL-1β being in clinical trials for the treatment atherosclerosis and its complications. Atherosclerotic plaques contain cells with markers of senescence, with stress response marked by growth arrest along with secretion of a variety of biologically active molecules, collectively termed the senescence-associated secretory phenotype. Senescent intimal foam cells increase the expression of pro-inflammatory cytokines and chemokines in early atherosclerosis and promote degradation of connective tissue elements in advanced plaques. There is at least one other contributing factor; as in other tissues, a fraction of the macrophage population in plaques undergoes apop- tosis, and is normally phagocytosed by healthy macrophages in a pro- cess called ‘efferocytosis’. Even in an early plaque, in which the local environment is not fully toxic, clearance by efferocytosis cannot keep up with the influx of newly recruited monocytes, leading to plaque growth. As the disease advances, the plaque accumulates more in- flammatory and injurious factors that can signal macrophages and other immune cells through Toll-like receptors (TLRs). Among other adverse effects, this reduces macrophage capacity to perform Vulnerable plaque • Fibrous cap weakens by proteolytic enzymes • Intraplaque haemorrhage may occur secondary to neovascularisation • Eventually may lead to rupture and thrombosis Intraplaque haemorrhage Neovascularisation ApoB-containing lipoproteins Circulating monocytes Adhesion molecules e.g. VCAM1, ICAM1 Monocyte recruitment and

transmigration Foam cell formation Activation of endothelium • ↑ Permeability to lipoproteins • ↑ Expression of adhesion molecules • Activation of integrin-YAP/TAZ-JNK cascade Scavenger receptor Efferocytosis Intact/thick fibrous cap M1 M2 Pro-inflammatory Anti-inflammatory/ tissue repair VSMC phenotypic “switch” Macrophage-like Synthesize collagen Progression of atherosclerosis • ↑ Recruitment of leukocytes • ↑ Foam-cell formation and pro- inflammatory phenotype of recruited macrophage/foam cell • Activation of NLRP3 inflammasome Established atheroma • Large lipid-rich necrotic core with cholesterol crystals and foam cells • Efferocytosis of dead cells inhibited • VSMCs secrete collagen that forms fibrous cap but can also adopt a macrophage-like phenotype • ↑ Proliferation and chemostasis of inflammatory cells with ongoing inflammatory stimuli (e.g., continued entry of LDL) Thinning of fibrous cap eventually leads to plaque rupture / thrombosis Proteolytic enzymes e.g. MMPs Vasa vasorum Plaque rupture Macrophage Lipid-laden foam cell Macrophage/foam cell which has undergone necrosis or apoptosis Collagen Weakened collagen Vascular smooth muscle cells (VSMC) Lipid-rich necrotic core YAP/TAZ Loss of lamina flow Activation of inflammatory pathways NLRP3 inflammasome Crystal Local Proliferation Integrin
Fig. 16.13.1.1 Stages of atherosclerosis progression from activated endothelium, to leukocyte recruitment, established atheroma, to eventual development of vulnerable plaque features.

16.13.1 Biology and pathology of atherosclerosis 3599 efferocytosis. This results in the disintegration of the dying macro- phages, with the release into the extracellular plaque environment of inflammatory material, thrombotic factors, and the cholesterol-rich gruel found in the necrotic core. Efferocytosis of apoptotic cells (the process by which they are removed by phagocytic cells) has recently been recognized as an activator of a certain type of macrophage that resolves inflammation and favourably remodels tissues, hence its failure likely contributes to disease progression by sustaining the in- flammatory milieu. In parallel with the macrophage ‘itinerary’ just described, as the atheroma advances, other immune cells—both innate (dendritic cells) and acquired (T and B lymphocytes)—also enter the plaque and modulate its inflammatory state. For example, T lymphocytes, depending on their stimuli, can either exacerbate macrophage ac- tivation by the secretion of Th1 cytokines (e.g. IL-1, IL-6, TNFα) or ameliorate it by secreting Th2 cytokines (e.g. IL-4, IL-10). Furthermore, B cells can elaborate antibodies to substances gener- ated from the oxidation of LDL that resemble antigens derived from microorganisms, in an attempt to neutralize the harmful effects of these products, with levels of such antibodies considered by some as a marker of disease burden. Smooth muscle cells In normal arteries, vascular smooth muscle cells (VSMC) are con- fined to the medial layer, which is delimited from the intimal space, where plaques form and grow, and from the outer arterial wall by internal and external elastic laminae, respectively. The cells are in the ‘contractile’ state, meaning that they serve mainly to set the vas- cular tone in response to a variety of stimuli by either contracting or relaxing. Activated endothelial cells in coronary arteries not only upregulate their leukocyte recruitment factors, they also down- regulate their production of nitric oxide, increasing arterial tone and adversely affecting blood flow to the myocardium. The loss of vasorelaxation is not the only change in VSMC in the progressing plaque. Both activated leucocytes and endothelium secrete growth factors that stimulate the proliferation of VSMC, which then migrate out of the medial layer into the intima. The migration of synthetic VSMC to the subendothelium and their elaboration of collagen forms the fibrous cap. The historical view has been that the VSMC phenotype switches from ‘contractile’ to ‘synthetic’, in recognition of increased produc- tion of extracellular matrix (ECM) by these cells (see ‘Extracellular matrix’). However, it is now appreciated that the phenotypic spec- trum of VSMC in atheroma is more complex than originally real- ized. For example, VSMC can gain properties of

inflammatory cells presumably because their TLRs become stimulated as they do in macrophages (see previous section). Another way in which the VSMC phenotype can be altered is by accumulating lipids. Relative to macrophages, whose transition to foam cells is enabled by their expression of scavenger receptors that take up large amounts of lipoprotein-derived lipids well after their LDL receptors are down- regulated, VSMC appear to become engorged more through a phagocytic process. Once it occurs to a significant degree, however, the cells in vitro and in vivo assume a macrophage foam cell-like state, both morphologically and phenotypically (in terms of cell- specific marker expression). In advanced plaques in patients, it has been estimated that as much as 40% of cells that would be tradition- ally classified as macrophage foam cells are actually of VSMC origin. Unlike the subendothelial VSMC that retain the synthetic pheno- type, it is likely that the 'macrophage-like' VSMC have negative ef- fects on plaque inflammation and stability. Extracellular matrix The ECM is made up of a mixture of macromolecules including col- lagen, elastin, glycoproteins, and proteoglycans, that confer tensile strength and viscoelasticity to the arterial wall. However, the ECM components function beyond furnishing a scaffold for the arterial wall and developing atherosclerotic plaque. Some constituents (not- ably proteoglycans) bind apoB-lipoproteins (described earlier), prolonging their residence in the intima. Retention of lipoprotein particles occurs due to steric hindrance and ionic interactions be- tween positively charged amino acids in apoB-containing lipopro- teins and negatively charged residues in the glycosaminoglycan chains. As a result, extravasated LDL are liable to retention and sus- ceptible to the oxidative modification (and glycation) that drives atherogenesis. In addition to lipoprotein retention, as atherosclerotic plaques de- velop, the ECM participates in other processes that are important in the context of atherosclerosis and its complications, including cell migration and proliferation, and thrombosis. Furthermore, the distribution of fibrous elements relative to other components, such as the lipid-rich necrotic core, can influence plaque behaviour. Elements of ECM can be found diffusely in a reticular distribution through the plaque but may also be found in a dense 'fibrous cap' overlying the lipid-rich necrotic core. Indeed, when considering pathogenicity, the deposition of ECM, comprised of fibrous and cellular components, confers structure and stability. Disruption of the fibrous cap (discussed later) is a precipitant of acute vascular syndromes. The matrix also contains growth factors, and cleaving certain components such as laminin releases sequestered mediators that promote cellular migration. Cytokines such as TGFβ and platelet- derived growth factor from T cells, platelets, macrophages, and monocytes stimulate smooth muscle cells to produce ECM. Atherosclerotic plaques Cell death in atherosclerotic plaques As noted earlier, intimal macrophages can undergo apoptosis, a type of programmed death that usually prevents necrosis. This process occurs throughout atherosclerotic lesion development, and in ad- vanced atherosclerotic lesions, apoptotic macrophages necrose and coalesce to contribute to a lipid-rich necrotic core that harbours the tissue factor that contributes to the formation of the intraluminal clot after plaque rupture. One mechanism underlying postapoptotic macrophage necrosis is the defective phagocytic clearance, or efferocytosis, of apoptotic cells. Studies in mouse models of ad- vanced atherosclerosis have provided evidence that several mol- ecules known to be involved in efferocytosis, including TG2, MFG-E8, complement C1q, Mertk, lysoPC, and Fas, play important

 roles in the clearance of apoptotic cells in advanced plaques. Another mechanism related to postapoptotic macrophage necrosis that is emerging is a regulated process dubbed 'necroptosis', with several reports confirming its existence in preclinical models and beginning to identify the regulatory factors and their hierarchy. Neovascularization in atherosclerotic plaques Human arteries possess a microvasculature in their adventitial layers

called the vasa vasorum. For the coronary arteries, normal vasa vasorum originate from branch points at regular intervals and run longitudinally along the vessel wall. A primary function of these ves- sels is to provide nutrients to the cells of the arterial wall. As plaques enlarge, angiogenic factors drive the formation of new blood vessels. For instance, oxidized phospholipids within the plaque can stimu- late the production of vascular endothelial growth factor isoforms in both monocytes and endothelial cells. New endothelial cell sprouts can form immature, leaky microvessels within the plaque. These ‘neo-vessels’ also provide a site for entry of inflammatory mono- cytes that perpetuate the atherosclerotic process. Microvessels also present a potential site for intraplaque haemorrhage, which is asso- ciated with plaque progression. Plaque calcification Electron microscopy has shown that calcification can occur initially as microdeposits through mineralization of organelles in cells as- sociated with the lipid-rich necrotic core. In some plaques, calcifi- cation progresses and can become diffuse and, particularly in older individuals, can become extensive. The presence of calcification has been targeted for quantification using CT techniques. Electron beam CT sensitively detects arterial calcification and its level can enhance prediction of risk of vascular complications over and above that associated with conventional risk factors. Furthermore, the process of calcification can be identified using positron emission tomography for 18F-sodium fluoride. In cor- onary arteries, tracer uptake can be demonstrated in ‘culprit’ plaques after acute coronary syndrome (ACS; see later), and in symptom- atic carotid arteries uptake was associated with histological evidence of active calcification, macrophage infiltration, apoptosis, and ne- crosis. Yet to be determined, however, is the pathogenic significance of calcification. Although calcification may indicate the presence of atherosclerosis, it may at least in part reflect reparative processes. While the level of calcification has found some acceptance as a stratifying factor for risk of cardiovascular disease, it does not seem well suited as a parameter to reflect treatment efficacy. Indeed, treat- ment with statins, which reduces the risk of complications of athero- sclerosis, does not appear to alter plaque calcification. Positive remodelling of the arterial wall Atherosclerosis develops within the vessel wall and, as the lesion en- larges, its growth is often accommodated by positive remodelling of the artery. In other words, outward expansion of the artery can enable lesion growth without encroachment on the vessel lumen, at least initially. In the original description of this phenomenon in the left main stem coronary artery, the lumen area did not decrease in relation to the percentage of stenosis (i.e. the percentage of the vessel cross-sectional area occupied by the plaque) for values up to 40%, but did diminish markedly and in close relation to the percentage of stenosis for values beyond that. So, human coronary arteries can enlarge in response to plaque growth to maintain their patency, but eventually this protective mechanism reaches a limit, and if the plaque continues to expand, stenosis ensues. Importantly, the com- pensatory outward expansion of the artery’s external elastic lamina can accommodate plaques with large lipid cores that do not appear on conventional X-ray arteriography but which may nonetheless rupture suddenly, causing thrombus formation and ACS. Positive remodelling has important implications for identifica- tion of atheromatous lesions using arteriographic imaging tech- niques that, like angiography, focus on the lumen rather than the vessel wall. Intravascular ultrasound studies have shown that larger areas of plaque burden may exist in regions of the arteries with little or no luminal stenosis. Appreciation of this limitation has led to the emergence of imaging techniques (e.g. dual source computed tom- ography, magnetic resonance imaging [multicontrast and mapping techniques] and intravascular ultrasound) that focus on quantifica- tion and characterization of lesions directly. Patterns of disease progression The course of pathological events associated with atheroma that are described earlier may suggest an ordered and formulaic progression of atherosclerosis. While atheroma may advance through gradual progression of these

physical and cellular processes, the develop- ment of individual lesions can also be punctuated by abrupt events, for example intraplaque haemorrhage, plaque erosion, and cap rup- ture. These events may occur relatively frequently, with a majority remaining subclinical. The healing phase that follows may involve smooth muscle cell proliferation and matrix deposition, which may stabilize but also enlarge the plaque and promote stenosis by con- strictive remodelling. Acute coronary syndromes An atherosclerotic plaque may develop over a period of several years and remain silent or subclinical throughout that time. Alternatively, encroachment of an enlarging but quiescent lesion may lead to symptoms of stable angina. Acute arterial syndromes typically occur due to the rupture or erosion of an atheromatous plaque. This ex- poses the contents of that plaque, including cellular debris, collagen, and tissue factor, to the elements of circulating blood that can ini- tiate blood coagulation, leading to partial or total thrombotic occlu- sion of the artery involved. Plaque rupture and erosion Post-mortem studies of human coronary artery have identified features that are associated with atherosclerotic plaque rupture. Atheromatous lesions with a large lipid-rich necrotic core and a thin fibrous cap with macrophage accumulation in the ‘shoulder’ regions seem to be susceptible to rupture. Propensity to rupture is further increased by the activity of proteolytic enzymes (matrix metalloproteinases) that digest and weaken elements of the fibrous cap. Plaque rupture exposes thrombogenic components of the plaque (including tissue factor and collagen) to the blood, leading to the generation of luminal thrombus, which may cause partial or total occlusion of the artery. As emphasized earlier, it is important to recognize that even lesions that do not cause a high degree of lu- minal stenosis can still behave in this way.

16.13.1 Biology and pathology of atherosclerosis 3601 Plaque erosion, in which a patch of endothelium becomes de- nuded, thereby exposing the intima to the circulating blood, also causes acute thrombosis. Endothelial loss may occur due to apop- tosis of endothelial cells or shedding of cells from the basement membrane due to the action of proteases such as gelatinases on type IV collagen, or other components of the basement membrane upon which endothelial cells rest. Sites of plaque erosion may not exhibit prominent macrophage or lymphocyte accumulation. The underlying plaque in erosions consists of a thickened intima or fi- brous cap atheroma, and lesions may be eccentric or calcified. Fatal thrombosis due to plaque erosion is associated with smoking, espe- cially in women. Compared with fibrous cap rupture, death due to plaque erosion occurs more often in younger individuals and may affect less severely narrowed arteries. Vulnerable plaque and the vulnerable patient While it is possible to identify individual lesions as the proximate cause of acute vascular events, these do not develop or behave in iso- lation. Numerous strands of evidence implicate systemic processes, especially in relation to inflammation, as drivers for atherosclerosis and or potential importance in affecting plaque behaviours acutely. Specifically, systemic inflammatory disease, such as rheumatoid arthritis, promotes atherosclerosis and its complications. In an ex- perimental model, acute myocardial infarction itself led to increased atherosclerotic plaque macrophage content and atherosclerosis pro- gression. However, remote drivers of inflammation may include fac- tors originating from the liver, adipose tissue, and gut microbiota. Appreciation of the role of systemic factors in the pathogenesis of atherosclerosis has implications for diagnosis, risk prediction, and treatments and is an emerging area of great clinical interest with sev- eral relevant patient intervention trials in progress and planned. Atherosclerosis regression While delayed progression of atherosclerosis is a worthy clinical goal, the disease process starts early in life and by the time most patients begin risk factor treatments, they have considerable plaque burden, making regression a more desirable goal. Indeed, in multiple studies a number of interventions, including dietary ap- proaches, genetic manipulations, infusion therapies,

and pharma- cological treatments in multiple animal species (rabbits, pigs, mice), including nonhuman primates, have demonstrated favour- able effects on established atherosclerotic plaques. Most of these interventions have been ‘lipid/lipoprotein centric’ and involved ei- ther lowering plasma levels of the apoB-containing lipoproteins to reduce the formation and ongoing engorgement of the foam cells, or raising levels of cholesterol-efflux agents (e.g. high-density lipo- proteins, HDL) to unload cholesterol from these cells and return it to the liver for elimination through the bile as part of the process dubbed ‘reverse cholesterol transport’. See Fig. 16.13.1.2. A general finding has been that during atherosclerosis regres- sion, the plaque content of foam cells decreases. From recent studies in mouse models, evidence has accumulated to identify kinetic contributions to this decrease to include changes in mono- cyte recruitment, macrophage emigration, macrophage apoptosis and efferocytosis, and local macrophage proliferation. Knowledge of the critical role that the chronic inflammatory state of the plaque plays in the clinical disease process, especially the erosion and eventual rupture of a vulnerable plaque, has focused atten- tion on therapies that would dampen or even resolve the inflam- matory state in plaques. Preclinical findings have given cause for optimism that this approach will join the lipid-centric approaches to realize plaque regression. For example, in mouse models it has been shown that the inflammatory state of the plaque foam cells is dynamic. Most are in the M1 activated state (which encour- ages inflammation) during disease progression, but under experi- mental regression conditions, there is enrichment of cells in the M2 state, which are sometimes referred to as anti-inflammatory or tissue repair macrophages. It has been recently demonstrated that this change is instrumental in the resolution of the inflamma- tion and remodelling of the plaque to one with more stable features (i.e. fewer macrophages, thicker fibrous cap) in mouse models of atherosclerosis. This shift from M1 to M2 macrophages may be advantageous not only in atherosclerosis regression, as supported by recent preclin- ical studies in which the administration of agents that are strong polarizers of macrophages in vitro to the M2 state (such as IL-13) has consistently led to delayed progression of atherosclerosis. One challenge for anti-inflammatory therapies, of course, is targeting agents to the plaque for those having adverse systemic effects, but improvements in nanoparticle-based therapies to achieve such spe- cificity are rapidly advancing. Clinical studies of plaque regression There are limited clinical studies that have also shown that sig- nificantly lowering plasma apoB-containing lipoprotein levels or increasing the levels of functional HDL particles resulted in plaque regression, as judged by quantitative angiography or intravas- cular ultrasound. Patients in most of these trials had evidence of ACS, and the imaging techniques used were not only invasive (and therefore not appropriate in primary prevention studies), but also primarily sensitive to changes in plaque size, rather than compos- ition or inflammatory state. Such ‘qualitative’ changes are likely to be exceedingly important clinically as they are key components of plaque regression in preclinical models. Evidence of plaque regres- sion in the much larger primary prevention group is limited and largely restricted to noninvasive measurement of carotid intima- media thickness. Improved noninvasive techniques that assess plaque composition and activity are under development to assess the ability of current and future candidate therapies to favourably affect plaque characteristics. The first large clinical trial of an agent targeting the inflamma- tory component of the atheromatous plaque was reported in 2017. The CANTOS trial randomized 10 061 patients with previous myo- cardial infarction and elevated high sensitivity C-reactive protein levels (suggesting presence of an inflammatory state) to receive canakinumab (an antibody against the potent inflammatory cyto- kine IL-1β) or placebo. The middle (of three) dose of canakinumab was associated with a significantly lower rate of recurrent cardio- vascular events than placebo, although overall the agent was asso- ciated with no significant difference in

cardiovascular or all-cause mortality. Many other agents that might cause plaque regression (or less ideally stop their progression) are in clinical trials, or contem- plated for such testing. These include very aggressive LDL-lowering

section 16 Cardiovascular disorders 3602 using antibodies to PCSK9, infusions of HDL or artificial choles- terol acceptors (e.g. apoA1 Milano), and various anti-inflammatory treatments. Finally, therapeutics can be envisioned that will manipu- late the content of plaque macrophages by regulating monocyte recruitment or macrophage emigration, macrophage apop- tosis and efferocytosis, and the proliferation of macrophages in plaques. Advances in genetic, immunological, and nanoparticle therapies will further enhance the likelihood of successful im- plementation of these and other, yet to be discovered, promising approaches. FURTHER READING Allahverdian S, et al. (2014). Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. Circulation, 129, 1551–9. Bosurgi L, et al. (2017). Macrophage function in tissue repair and remodeling requires IL-4 or IL-13 with apoptotic cells. Science, 356, 1072–6. Burke AP, et al. (1997). Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med, 336, 1276–82. Cardilo- Reis L, et al. (2012). Interleukin-13 protects from atheroscler- osis and modulates plaque composition by skewing the macrophage phenotype. EMBO Mol Med, 4, 1072–86. Childs BG, et al. (2016). Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science, 354, 472–7. Detrano R, et al. (2008). Coronary calcium as a predictor of cor- onary events in four racial or ethnic groups. N Engl J Med, 358, 1336–45. Duewell P, et al. (2010). NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature, 464, 1357–61. Dutta P, et al. (2012). Myocardial infarction accelerates atherosclerosis. Nature, 487, 325–9. Galis ZS, et al. (1994). Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human ath- erosclerotic plaques. J Clin Invest, 94, 2493–503. Glagov S, et al. (1987). Compensatory enlargement of human athero- sclerotic coronary arteries. N Engl J Med, 316, 1371–5. Fig. 16.13.1.2 Mechanisms involved in atherosclerosis regression in experimental models.

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