Review

The changing landscape of atherosclerosis

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Emerging evidence has spurred a considerable evolution of concepts relating to atherosclerosis, and has called into question many previous notions. Here I review this evidence, and discuss its implications for understanding of atherosclerosis. The risk of developing atherosclerosis is no longer concentrated in Western countries, and it is instead involved in the majority of deaths worldwide. Atherosclerosis now affects younger people, and more women and individuals from a diverse range of ethnic backgrounds, than was formerly the case. The risk factor profile has shifted as levels of low-density lipoprotein (LDL) cholesterol, blood pressure and smoking have decreased. Recent research has challenged the protective effects of high-density lipoprotein, and now focuses on triglyceride-rich lipoproteins in addition to low-density lipoprotein as causal in atherosclerosis. Non-traditional drivers of atherosclerosis—such as disturbed sleep, physical inactivity, the microbiome, air pollution and environmental stress—have also gained attention. Inflammatory pathways and leukocytes link traditional and emerging risk factors alike to the altered behaviour of arterial wall cells. Probing the pathogenesis of atherosclerosis has highlighted the role of the bone marrow: somatic mutations in stem cells can cause clonal haematopoiesis, which represents a previously unrecognized but common and potent age-related contributor to the risk of developing cardiovascular disease. Characterizations of the mechanisms that underpin thrombotic complications of atherosclerosis have evolved beyond the 'vulnerable plaque' concept. These advances in our understanding of the biology of atherosclerosis have opened avenues to therapeutic interventions that promise to improve the prevention and treatment of now-ubiquitous atherosclerotic diseases.

Although atherosclerotic cardiovascular disease was previously considered a problem that was concentrated in the industrialized world, it now spans the globe. We have witnessed an 'epidemiological transition'[1,2]. Increased sanitation, vaccination and the treatment of acute infections have diminished the prevalence of communicable diseases in developing countries, and more individuals now survive to experience chronic diseases such as atherosclerosis (see ref. [3] for an introduction to the fundamental concepts of atherosclerosis). The adoption of less healthy dietary patterns may also have contributed to this trend. Many people now live longer only to suffer the consequences of atherosclerosis, including myocardial infarction, ischaemic cardiomyopathy (which is the commonest cause of heart failure), strokes (which often rob people of their independence, mobility, cognition or ability to communicate) and peripheral arterial disease, which limits activity and jeopardizes limbs. These conditions contribute to 'morbidity extension' in the developing world such that, although many individuals escape early death, they must bear the burden not only of chronic cardiovascular diseases but also of arthritis, depression and other long-term impediments to a healthy life. Today, the major pool of risk for developing cardiovascular disease occurs not in Western countries but in the more populous developing world. Atherosclerotic cardiovascular disease now accounts for the majority of mortality worldwide. This global spread creates an urgent need to understand the genesis of this malady, advance in its management and develop prospects for alleviating its burden. This Review addresses the evolving concepts of atherogenesis and the opportunities for preventing and treating atherosclerosis afforded by new insights into its pathogenesis.

The changing face of atherosclerosis

The classic candidate for heart attack was a middle-aged, white man with hypertension and hypercholesterolaemia, who smoked cigarettes. This picture has evolved considerably in recent decades. We now possess effective therapies for the treatment of high blood pressure and lipid disorders, and control of hypertension and hypercholesterolaemia has improved[4]. A reduction in smoking, accompanied by a decrease in second-hand smoke, has gained a foothold in many societies. We have further witnessed a vast change in people with cardiovascular risk and those who suffer from acute coronary syndromes. Although individuals in mid-life do not evade risk, coronary artery disease now affects an increased number of younger women, and—with the ageing of the population in many countries—the very old now account for an increasing proportion of patients with cardiac conditions[4–6].

An epidemic of obesity has swept across the world[7,8]. Excess adiposity (especially that accumulated in the abdomen) and a fatty liver drive insulin resistance, which sets the stage for diabetes, and shows links with hypertension. From a metabolic perspective, individuals of some ethnicities often tolerate the accumulation of visceral adipose tissue

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particularly poorly[9]. Asian and South Asian individuals, as well as people of some ethnicities in Central and South America, can develop dysmetabolism manifested as glucose intolerance at lower abdominal girths than white individuals. Given the large populations in Asia and Central and South America, increased prosperity—with attendant shifts from traditional dietary habits—and continuing tobacco use, as well as the growing burden of obesity and diabetes (often accompanied by hypertension) presents an enormous public health challenge and is a contributor to regional risks of atherosclerotic cardiovascular disease.

Rather than elevated low-density lipoprotein (LDL) cholesterol, an elevation in triglyceride-rich lipoproteins (TGRL) and low high-density lipoprotein (HDL) now comprise the major pattern of lipid abnormality in many patients who are treated for atherosclerotic cardiovascular disease[10]. Highly effective and now-inexpensive therapies for lowering LDL have contributed to an overall drop in LDL, whereas obesity, its attendant insulin resistance and a high-carbohydrate diet favour a rise in the prevalence of the cluster of conditions referred to as the 'metabolic syndrome', which is characterized in part by an elevation in TGRL. The prevalence of this cluster—which also includes increased waist circumference, low HDL cholesterol, high blood pressure and raised fasting blood glucose—rose by 35% from 1988–1994 to 2007–2012 in the USA[11]. Women, members of minoritized groups and populations in developing countries thus bear an increasing burden of atherosclerotic cardiovascular disease. Indeed, despite advances in controlling risk factors in many high-income countries, atherosclerotic cardiovascular disease now predominates in lower-income areas. The Global Burden of Disease study shows that world prevalence of ischaemic heart disease has increased from about 100 million in 1990 to over 180 million cases in 2019[8]. In some regions of the USA and UK, the decline in prevalence of ischaemic heart disease—attributed to controlling risk factor—has slowed or halted in the period 2014 to 2019[8]. Atherosclerotic cardiovascular disease has become a global concern, and we may be losing ground in prevention even in higher-income countries.

A reassessment of the lipid risk factors

LDL, a particle encircled by its signature apolipoprotein B component, causes atherosclerosis[12,13]. If the entire population maintained LDL concentrations akin to those of a neonate (or to those of adults of most other animal species), atherosclerosis might well be an orphan disease[14]. The duration and extent of exposure to above-ideal concentrations of LDL associate with atherosclerotic disease[13,15]. However, the treatment of children and adolescents with cholesterol-lowering drugs presents many challenges, and lifelong elevated concentrations of LDL cholesterol have already sown the seeds of atherosclerosis in millions of people, increasing their risk for cardiovascular disease. Despite effective interventions for the control of LDL, blood pressure and other traditional risk factors, a considerable residual risk remains for atherosclerotic cardiovascular disease[16]. For example, recent clinical trials of novel cardiovascular agents performed in subjects optimally treated with standard-of-care background therapy found that about 1 in 20 will have a recurrent ischaemic event in the year after an acute coronary syndrome[17,18]. One in ten individuals who survive an acute myocardial infarction in the USA will require readmission within one month, at considerable personal and societal cost[19]. Moreover, in addition to obesity and its associated insulin resistance, rises in air pollution, transitions from traditional diets towards those that may aggravate cardiovascular risk and other exposures under intense investigation (ranging from environmental noise to impaired sleep) may mitigate some of the advances that have been made in prevention[20–22]. Chief among readily remedied shifts towards unhealthy diets, the consumption of sugar-sweetened beverages, often high in fructose content, may contribute to obesity and its adverse metabolic consequences[23,24] Indeed, modifiable risk factors contribute enormously to the global burden of ischaemic heart disease[2].

Large-scale cohort investigations, such as the Framingham study, revealed risk factors for atherosclerosis that we now regard as 'traditional'[25]. However, long-term trends have modified risk factors such that these traditional factors no longer capture the contemporary reality of atherosclerosis. Genetic risk scores have undergone continuing refinement and incorporate increasingly expanded numbers of inherited variants that influence atherosclerotic events. As these genetic panels can predict risk from birth, they may inform the early targeted allocation of preventive measures in younger individuals who have an augmented genetic predilection to develop atherosclerotic disease[26]. Indeed, lifestyle measures appear to mitigate risk of cardiovascular events across the spectrum of estimated genetic risk. Yet, the ability of even the latest generation of genetic risk scores to improve prediction of atherosclerotic events over more traditional algorithms remains controversial[27,28].

Recent research has challenged and expanded on the traditional risk factors. With global trends towards a decrease in LDL and the introduction of highly effective therapies for lowering LDL, as well as inexpensive and efficacious antihypertensive therapies, these drivers of chronic risk contribute less today than in previous years. Most markedly and despite decades of belief that HDL protected from atherosclerosis, recent human genetic studies—and the failure of several independent pharmacological measures to raise HDL to reduce atherosclerotic events—have called into question the protective effect of HDL[29]. Mendelian randomization studies that have corrected for pleiotropy have, however, provided some support for the protective effect of HDL[30]. Moreover, functional attributes of HDL fractions that are not captured by steady-state measurements of total HDL cholesterol concentrations (such as the capacity to mediate cholesterol efflux or anti-inflammatory actions) may yet exert anti-atherosclerotic effects[31,32].

The risk of plasma triglyceride concentration (a biomarker of a class of lipoproteins that include the TGRL) was passed over for many years, as the belief in the protective effect of HDL rendered it logical to adjust triglycerides for HDL—a precaution that attenuated the risk attributed to TGRL[33]. Triglycerides and HDL tend to vary inversely, and a recent ranking[34,35] of the relevant risk factors demotes HDL as a protective factor and points to TGRL as a potent predictor of cardiovascular risk. Moreover, in contrast to the situation with HDL, contemporary and concordant human genetic studies strongly support a causal role for TGRL in atherosclerosis and its complications[36]. A variety of inherited sequence variations that affect lipoprotein lipase, or factors that modulate the activity of this enzyme, alter the rate of atherosclerotic events, and these findings furnish strong human genetic evidence for the causal role of TGRL in their pathogenesis. Apolipoprotein CIII, ANGPTL3 and ANGPTL4 inhibit the ability of lipoprotein lipase to hydrolyse triglycerides in TGRL, and thus cause accumulation of these particles. By contrast, apolipoprotein V augments the activity of lipoprotein lipase and enhances TGRL clearance[37,38]. The activity of lipoprotein lipase thus regulates plasma triglyceride concentrations. Gain- or loss-of-function variants in this pathway that raise TGRL track with increased numbers of atherosclerotic events, and those that lower TGRL correlate with improved outcomes. The triglyceride component of TGRL does not appear to account for their atherogenicity[10]. TGRL, as with LDL, bear apolipoprotein B; they also contain cholesterol, and can deliver it effectively to macrophages in the atheroma. TGRL provoke inflammation, in part owing to their apolipoprotein CIII content. TGRL concentrations correlate better with inflammatory status than does LDL itself[39,40]. This refocusing on TGRL as a causal risk factor, and lack of actionability of altering HDL thus far, has notable therapeutic implications.

Observational epidemiological studies have long associated a special form of LDL, lipoprotein(a), with atherothrombotic risk[41]. Lipoprotein(a) consists of an LDL particle, the signature apolipoprotein (apolipoprotein B) of which has bound covalently to apolipoprotein(a). Lipoprotein(a) carries oxidized lipids and may inhibit fibrinolysis owing to a structural similarity with plasminogen. Concordant human genetic

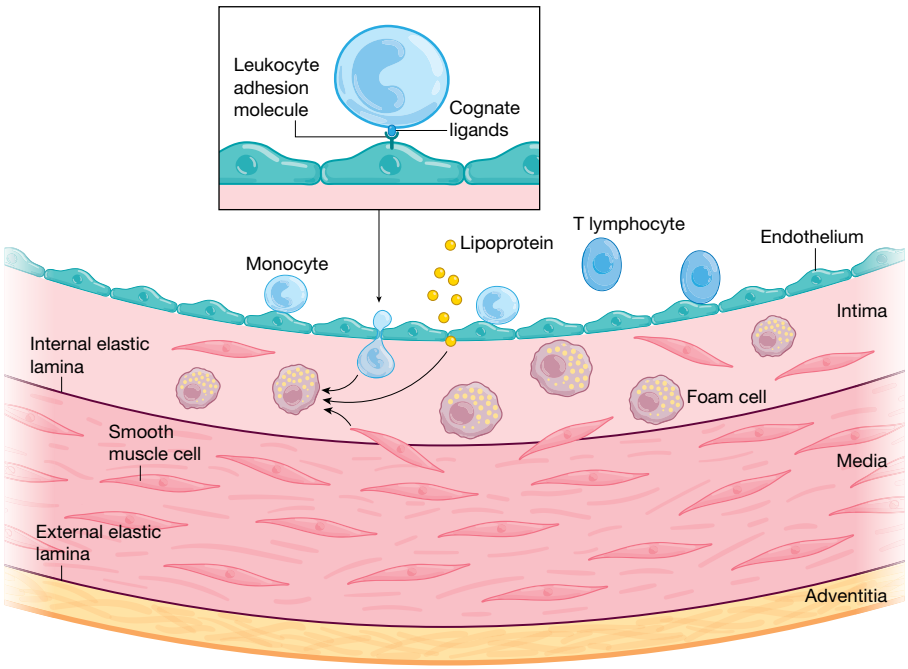

Fig. 1 | Initiation of atherosclerosis. The normal artery comprises three layers: the innermost intima (in close contact with the bloodstream), the tunica media, and the outer coat and adventitia. Under homeostatic conditions, the endothelial monolayer that lines the intima does not gather blood leukocytes. When activated by proinflammatory cytokines or other irritative stimuli related to cardiovascular risk factors, endothelial cells can express a leukocyte adhesion molecule (such as VCAM-1) that interacts with its cognate ligands (VLA4) to promote the rolling, and eventually adherence, of blood monocytes and lymphocytes to the endothelial layer. Chemoattractant cytokines can direct the migration of these bound leukocytes into the intima. Within the intima, foam cells form by uptake of lipids. Some of these lipid-laden foam cells arise from blood monocytes that have matured into macrophages. Recent evidence[146] in mice indicates that smooth muscle cells can undergo metaplasia, and give rise to foam cells that bear markers in common with those of macrophages. T lymphocytes—although fewer in number than the foam cells—produce mediators that orchestrate many functions of these innate immune cells. In humans (but not in many of the small animals that are often used experimentally), the intima contains resident smooth muscle cells. Other smooth muscle cells (that are usually located in the media) can penetrate into the intima, where they join resident smooth muscle cells to promote the accumulation of extracellular matrix that these cells synthesize within the expanding intima.

studies provide persuasive evidence for the causality of elevated lipoprotein(a) not only in atherosclerosis but also in calcific aortic valve disease[42–45].

Inflammation drives atherosclerosis

Beyond dyslipidaemia, a convincing body of experimental and clinical data now indicates that inflammation participates fundamentally in atherogenesis and in the pathophysiology of ischaemic events[46]. Inflammation does not supplant or demote lipid risk; rather, inflammatory responses provide a series of pathways that link lipids and other traditional risk factors to atherosclerosis. For example, concentrations of remnant lipoprotein show links with levels of C-reactive protein, a biomarker of inflammation[40]. A large body of evidence implicates inflammation in hypertension[47]. Experimental investigations have pinpointed the participation of innate and adaptive immunity in atherosclerosis (Figs. 1, 2). Human biomarker studies have shown that indicators of inflammation predict risk of cardiovascular disease in a broad swath of individuals with or without manifest cardiovascular disease, and independently of all traditional risk factors[48]. The acute phase reactant (C-reactive protein), which can be measured with a highly sensitive assay (known as hsCRP), is a validated and clinically useful gauge of the overall innate immune status of an individual in relation to atherosclerotic risk[49].

In addition to innate immunity (which depends largely on cytokines and macrophages), the adaptive arm of the immune response operates during atherogenesis. T lymphocytes primarily aggravate atherogenesis, but T-helper 2 and regulatory T cells can mute this process, at least in mice[46,50]. Candidate antigens include forms of LDL as discussed in 'Oxidized LDL and the initiation of lesions'. B lymphocytes also can exert a dual role in atherogenesis. Natural IgM antibodies encoded in the germline and produced by B1 cells mitigate experimental atherosclerosis[51,52]. B2 cells can produce antibodies that may drive this process. One candidate antigen, the mitochondrial enzyme ALDH4A1, emerged from analysis of B cells isolated from mouse atheromata[53].

An increased number of links between inflammation, immunity and intermediary metabolism have recently emerged. Inflammatory activation of mononuclear phagocytes and endothelial cells tends to shift their metabolism towards glycolytic pathways[54–56]. Altered tryptophan metabolism has also garnered considerable interest in atherosclerosis. Cytokines induce indolamine dioxygenase (the rate-limiting step in tryptophan catabolism), which lowers intracellular tryptophan stores and augments the production of kynurenine and its metabolites; this latter pathway may have a counter-regulatory function by muting inflammation and the cellular immune response[57–59].

The applicability to humans of experimental evidence that implicated inflammation in atherosclerosis has engendered considerable controversy[60,61]. However, recent clinical trials have shown that targeting inflammation can reduce cardiovascular events even in individuals who have already been treated with a full panel of effective standard therapies. The 'Canakinumab Anti-inflammatory Thrombosis Outcomes Study' (CANTOS) allocated randomly an antibody that neutralizes the proinflammatory cytokine IL-1β to patients with stable coronary artery disease at least one month after a qualifying myocardial infarction[62]. The enrolled population had signs of inflammation despite standard-of-care medical therapy, as mandated by prevailing

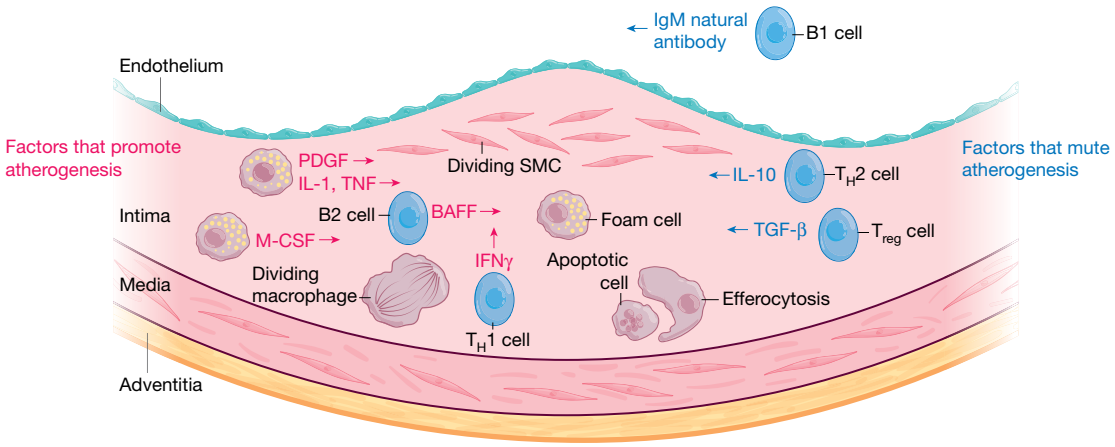

Fig. 2 | The progression of atherosclerosis reflects and interplay between factors that promote or mitigate atherogenesis. This diagram summarizes results from experimental studies in mice, and observations on human atherosclerotic plaques. Pathways thought to promote lesion formation (factors in red) are shown on the left, and mechanisms that may moderate atherogenesis (factors in blue) are on the right. Smooth muscle cells and macrophages can proliferate as the intimal lesion grows. PDGF promotes the migration and replication of smooth muscle cells, and then production of extracellular matrix. All cells in the atheromatous plaque can secrete cytokines, examples of which include IL-1, TNF and M-CSF (also known as CSF1). Activated T-helper 1 (T_H1) lymphocytes produce IFNγ, which can stimulate mononuclear phagocytes and aggravate atherosclerosis. Other types of cell produce countervailing mediators. B1 lymphocytes can secrete IgM natural antibody; T-helper 2 (T_H2) lymphocytes produce the anti-inflammatory cytokine IL-10; and regulatory T (T_{reg}) cells can secrete TGFβ. These mediators can antagonize cellular proliferation, promote extracellular matrix synthesis and quell inflammation. Mononuclear phagocytes can engulf dying or dead cells that arise through apoptosis, through a process known as efferocytosis. Inefficient efferocytosis favours the accumulation of debris from dead or dying cells, and promotes formation of the central lipid core of the atherosclerotic plaque. B2 lymphocytes secrete mediators (such as BAFF, a member of the TNF family) that can aggravate atherogenesis. This diagram shows only a subset of the mediators that have been implicated in promoting or antagonizing aspects of atherogenesis. Current research suggests an ongoing struggle between proliferation and death, involving proinflammatory, anti-inflammatory and proresolving mediators—generally through a prolonged course of many years in the evolution of the human atherosclerotic plaque.

guidelines (gauged by an hsCRP above 2 mg l^{-1}). The participants had a baseline LDL of approximately 2 mM (81 mg dl^{-1}). The anti-inflammatory therapy yielded a 15% relative reduction in risk for recurrent myocardial infarction, stroke or cardiac death. In an on-treatment analysis, individuals who responded to the IL-1β neutralization by achieving a greater-than-median reduction in hsCRP had a 26% reduction in the primary end point, and a decrease in all-cause mortality. As IL-1β participates in host defences, it was not surprising that CANTOS showed a small but statistically significant increase in infections (including fatal infections) in patients randomized to canakinumab. A highly significant reduction in incident and fatal lung cancer noted in exploratory analyses counterbalanced this risk of infection[63].

The natural product colchicine has served as an anti-inflammatory therapy for many years, and its use has become standard-of-care in the treatment of pericarditis. Two recent large-scale outcome trials have indicated efficacy in reducing recurrent cardiovascular events after the development of acute coronary syndromes. The 'Colchicine Cardiovascular Outcomes Trial' (COLCOT) showed a 23% reduction in the composite primary end point, driven primarily by fewer revascularizations in patients treated in the early phase after developing an acute coronary syndrome (4–30 days)[64]. The incidence of pneumonia more than doubled in the group who were treated with colchicine. The 'Low Dose Colchicine 2' (LoDoCo2) study administered colchicine (5 mg d^{-1}) to individuals with stable coronary artery disease, and reported a reduction in recurrent events similar to that seen in the COLCOT[65].

These recent large-scale clinical outcome trials have bolstered the clinical applicability of decades of fundamental research into inflammatory pathways in the pathogenesis of atherosclerosis. The increase in infections noted with canakinumab and colchicine indicate an opportunity for the refinement of anti-inflammatory therapy for atherosclerosis that retains efficacy in limiting adverse outcomes, while interfering less with host defence. But not all anti-inflammatory interventions have yielded clinical benefit[66]. For example, a trial with low-dose weekly methotrexate did not improve cardiovascular outcomes nor did it exert an anti-inflammatory effect in the population studied[67].

Obesity and its attendant dysmetabolism, often manifested by insulin resistance and diabetes, now drives an increasing proportion of cardiovascular disease risk worldwide. Adipose tissue abounds with inflammatory cells, produces proinflammatory mediators and inflammation contributes mechanistically to the link between obesity, insulin resistance and atherosclerotic risk[68]. Moreover, environmental factors, such as air pollution, noise, disturbed sleep and other stressors have gained increasing recognition as contributors to the risk of atherosclerotic events in part thorough the activation of inflammatory pathways[20,21].

An additional aspect of risk allied with inflammation has recently emerged. With age, we accumulate somatic mutations in haematopoietic stem cells in the bone marrow in genes that drive the development of acute leukaemia[69,70]. Investigators seeking the origins of leukaemia found that individuals who are apparently well and do not have haematological malignancies can generate clones of leukocytes that circulate in peripheral blood and that bear mutations in a handful of the known driver genes for leukaemia. The prevalence of this condition in individuals aged 70 exceeds 10%, and this burden increases with further ageing. As the population ages, the number of individuals who bear these clones will increase. As expected, those who have this condition—known as clonal haematopoiesis of indeterminate potential (CHIP)—have a risk of developing acute leukaemia of more than tenfold that of unaffected individuals. However, the increase in total mortality in individuals with CHIP by far exceeds that attributable to transformation to acute leukaemia.

Cardiovascular disease accounts for this gap in mortality[71]. Fully adjusted for all traditional risk factors, CHIP confers a risk for

myocardial infarction and stroke equal to or greater than previously recognized contributors to cardiovascular risk, save for age itself. The qualification 'indeterminant potential' reflects the lack of symptoms or consistent laboratory findings in bearers of these mutant clones of peripheral leukocytes and our current inability to predict which individuals with CHIP will develop leukaemia or cardiovascular disease. Indeed, many carriers of CHIP will never know that they have this condition[72,73].

The connection between CHIP and inflammation arises from experimental work that demonstrated that mice engineered to simulate CHIP with mutations in *Dnmt3a* or *Tet2* have accelerated atherosclerosis, and demonstrate increased activity of the NLRP inflammasome IL-1β–IL-6 proinflammatory pathway[71,74]. Mice with myeloid cells that bear *Jak2*^{V617F} (another mutation associated with CHIP) show activation of the AIM2 inflammasome[75]. Concentrations of the marker of inflammation hsCRP do not rise consistently in individuals with CHIP. This observation indicates the existence of aspects of inflammation that mark augmented cardiovascular risk but that are not captured by measurements of hsCRP.

In sum, we have witnessed a considerable change in the ranking of risk factors for atherosclerosis: some factors have receded in importance and relevance given current therapies, and others have rapidly expanded, in part owing to socioeconomic and behavioural factors[2] (Table 1).

Revised concepts of atherogenesis

Oxidized LDL and the initiation of lesions

Most reviews of the mechanisms of atherosclerosis posit a pivotal role for oxidized LDL as the prime mover of this disease (Fig. 1). Although LDL participates causally in atherogenesis, despite a large body of animal research, scant evidence actually supports the causal role of oxidized LDL in humans. A variety of clinical intervention trials with antioxidant vitamins or one of a highly effective lipophilic antioxidant drug have not reduced atherosclerotic events. Native, rather than oxidized, LDL appears to drive the adaptive immune response in mice[76]. LDL per se appears to be a relatively weak stimulus to innate immune activation. Recent work supports the participation of cavelolin-1-dependent LDL transcytosis through the endothelium in experimental atherosclerosis[77]. ALK1 and SRB1 can also participate in LDL transcytosis[78,79]. Although these results emphasize the causality of LDL in atherogenesis, they do not invoke the participation of oxidized LDL in this process. How LDL causes atherosclerosis is not understood completely, and we should seek explanations beyond the oxidation hypothesis. When oxidized lipid binds to plasminogen, they can activate fibrinolysis[80]. Thus, oxidized lipids may promote atherogenesis but boost thrombolysis—an opposing effect that could contribute to the net lack of benefit in trials of anti-oxidant strategies[81]. LDL that aggregates in the intima in association with proteoglycan, or adaptive immune responses to native LDL, provide alternative mechanisms through which this lipoprotein promotes atherogenesis. Macrophages in plaques take up aggregated LDL[82], and the LDL receptor-related protein can mediate the update of aggregated LDL by intimal smooth muscle cells[83].

Regardless of the initial trigger or triggers, experimental and human observations agree that the recruitment of blood leukocytes mediated by activation of endothelial cells that line the arterial lumen occurs early in lesion formation (Fig. 1). The resting endothelium resists attachment of blood leukocytes. In an atherogenic environment, endothelial cells can express leukocyte adhesion molecules that mediate the rolling and firm attachment of white blood cells to the intimal surface (Fig. 1). Chemokines direct the migration of the adherent leukocytes into the arterial intima. Mononuclear phagocytes can proliferate within the intimal layer (the site of lesion initiation)[84]. These cells engulf lipids and become foam cells, the hallmark of atherosclerotic lesions. T lymphocytes, which drive the adaptive immune response, interact with innate immune cells within the intima[85,86]. A proinflammatory subset of monocytes gives rise to lesional macrophages[87,88]. Recent lineage-tracking experiments support a smooth muscle origin of many foam cells in mouse atheromata[89]. The cooperation between these cellular constituents of innate and adaptive immunity stimulate the production of proinflammatory cytokines that sustain and amplify the local inflammatory response.

Inexorability of atheroma progression

Many have considered atherosclerosis an inevitable 'degenerative' process that progresses continuously over time (Fig. 2), but current evidence supports a much more dynamic and discontinuous evolution of atheromata[90–92]. Episodes of systemic inflammation or regional inflammation that is remote from the atherosclerotic plaque itself can provoke 'crises' in the evolution of the plaque, and stimulate a round of inflammatory activation that can promote cell migration, proliferation, lesion progression and complication (Fig. 2). The concept of 'trained immunity' raises the possibility that successive encounters with irritative stimuli elicit exaggerated responses[93,94]. Arterial smooth muscle cells—which normally reside quiescent in the middle layer of the artery (the tunica media)—enter the intimal layer, where they can proliferate and may undergo metaplasia to become macrophage-like cells[89]. The application of advanced cell-sorting techniques and of single-cell RNA sequencing has disclosed a high degree of heterogeneity in the cellular contributors to atherosclerosis[95–97]. Sorting out the functional consequences of the newly identified cell types that participate in atherogenesis will require considerable work, and holds promise for advancing the identification of new therapeutic targets.

Atherosclerosis may not proceed continuously, but rather in phases of relative quiescence punctuated by periods of rapid growth. Emerging evidence points to haematopoiesis as a key contributor to lesion evolution and as a link between regional inflammation, environmental stimuli and atherogenesis[98]. Mental stress, sleep disturbance and remote injury or infection can stimulate haematopoiesis in the bone marrow, furnishing leukocytes that can populate the plaque[98,99]. Extramedullary haematopoiesis, as well as the mobilization of preformed pools of leukocytes in the spleen, furnish further leukocytes that can home in on atheromata under stress situations. Indeed, the work that identified CHIP as a risk factor for atherosclerosis underscores the link between atherosclerosis and haematopoiesis. These observations have opened a window onto the pathogenesis of atherosclerosis, and provide a link between oncogenesis and atherogenesis that was unsuspected only a few years ago. The death of mononuclear phagocytes in the lesion, and their ineffective clearance (defective efferocytosis), promote the formation of the lipid or necrotic core of the atherosclerotic lesion[100]. Lesion progression can occur silently over many decades. Indeed, many young or middle-aged individuals contain asymptomatic and subclinical atherosclerotic lesions, as shown by autopsy and imaging studies[101–103].

'Vulnerable plaques'

The acute events such as myocardial infarctions and ischaemic strokes that complicate atherosclerosis arise from thrombosis or formation of blood clots (Fig. 3), a physical disruption of atherosclerotic plaques provokes most acute thromboses. The so-called 'vulnerable plaque' has received considerable attention[104,105]. A fracture of the fibrous cap of the plaque (which overlies the necrotic core) exposes blood and its coagulation proteins to thrombogenic substances (such as tissue factor) within the plaque, triggering acute thrombosis[106] (Fig. 3a). The fibrous cap owes its tensile strength largely to interstitial collagen. The thinning of the fibrous cap arises from an inflammation-related decrease in collagen synthesis and augmented degradation owing to overexpression of collagenases by inflammatory cells[107]. Autopsy studies[104] have implicated rupture of the fibrous cap as the cause of the majority of fatal acute coronary syndromes, stimulating focus on the thin-capped fibroatheroma as a possible culprit. Yet, post-mortem

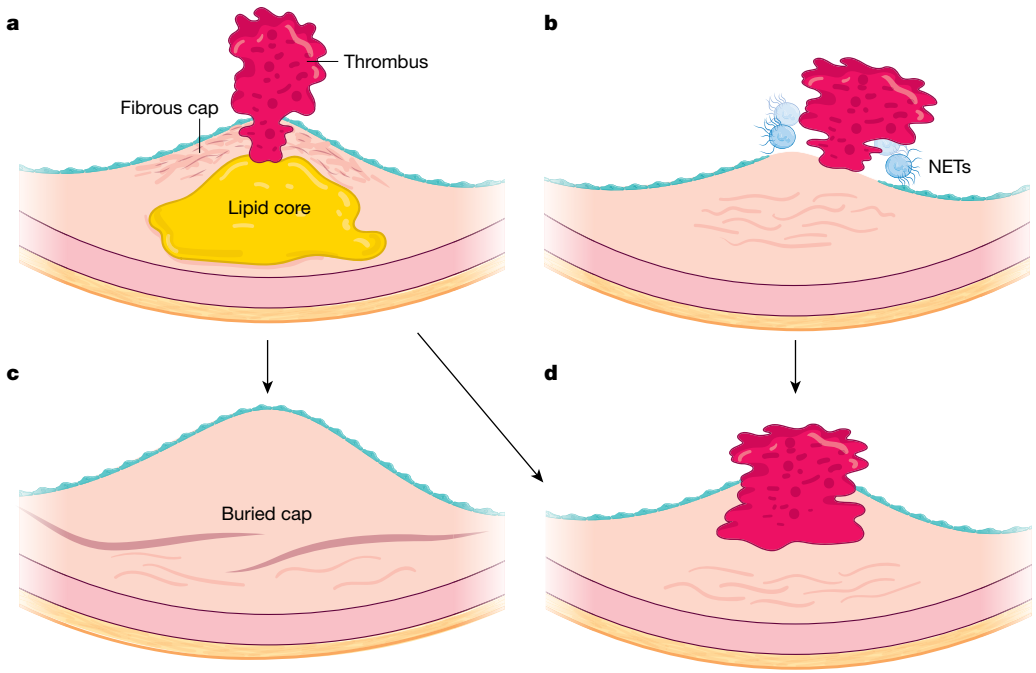

Fig. 3 | Thrombotic complications of atherosclerosis and evolution of the atherosclerotic plaque. a, Plaque rupture. This involves a fracture or fissure of the fibrous cap that overlies the lipid core of the plaque. This physical disruption permits contact of blood coagulation factors with thrombogenic material (principally the potent procoagulant tissue factor) within the plaque. The ensuing thrombosis can obstruct blood flow and lead to cardiac ischaemia. This mechanism accounts for about two-thirds of acute myocardial infarction, but appears to be waning; current preventive therapies lead to a reduction in accumulation of lipid within plaques and to the reinforcement of the fibrous cap. **b**, Superficial erosion. This cause of coronary artery clot formation involves a sloughing or desquamation of the endothelial monolayer. Granulocytes trapped in the plaque or adherent to the intimal basement membrane can form neutrophil extracellular traps (NETs). NETs are strands of nuclear DNA that have unwound, present various neutrophil granular proteins and bear other proteins that they bind from the blood, forming a solid-state reactor on the intimal surface. NETs can propagate inflammation and thrombosis. **c**, **d**, Plaques can heal, which augments the bulk of the plaque and promotes the formation of flow-limiting stenosis in previously disrupted arteries. During thrombosis, platelets release PDGF and TGFβ, which promote the synthesis of extracellular matrix proteins that contribute to fibrosis and plaque growth. **c**, Ruptured plaques that have healed often show morphologic evidence of the rupture underneath a layer of more recently deposited extracellular matrix (a 'buried' fibrous cap). **d**, Plaques can also grow through incorporation of a thrombus. Lesions can also calcify (not shown), in part owing to cell-derived microvesicles that can nucleate this process. Regions of spotty calcification imaged by computed tomography correlate with an increased risk of a thrombotic event. In contrast to smaller deposits of calcium, macroscopic plates of calcium may stabilize plaques from mechanical disruption (rather than create inhomogeneity in stresses that promotes thrombotic complications due to plaque disruption).

studies such as these lack a denominator for how many lesions with the characteristics attributed to vulnerability do not cause acute thrombotic complications. Recent in vivo imaging studies in humans have furnished this missing information, and have shown that plaques that thin-capped plaques seldom cause clinical events[108–110]. Thus, current evidence shows that 'vulnerable plaque' is a misnomer[111,112].

In an era of intense lipid lowering, plaques of the classical vulnerable morphology are on the wane[113]. Another mechanism of plaque disruption (known as superficial erosion) currently appears to be on the rise and probably has a distinct pathophysiology[114–116] (Fig. 3b). This trigger to coronary artery stenosis does not involve fissure or rupture of the fibrous cap of the plaque, but rather a discontinuity in the intimal endothelial lining. The application of an intravascular imaging modality known as optical coherence tomography enables identification of plaque rupture, and has led to the development of criteria for the diagnosis of probable or definite erosion in individuals with acute coronary syndromes[117]. The mechanisms of erosion involve endothelial injury, the participation of polymorphonuclear leukocytes and neutrophil extracellular traps as a local contributor to thrombus formation and propagation[114,118,119].

Clinical implications

From a therapeutic perspective, we have reason for optimism in addressing the growing burden of atherosclerotic risk. First, we face an imperative to encourage healthy lifestyle choices and a public environment that supports them by encouraging physical activity, discouraging sugar-sweetened beverages that contribute to the obesity epidemic and continuing to abate tobacco use. Indeed, a healthy lifestyle can mitigate—in part—genetic risk for atherosclerotic events[120]. Such public health measures include promoting pedestrian zones, bicycle paths and playgrounds, and providing healthy foods in schools. Second, the drug therapy for atherosclerosis has advanced not only in the availability of agents that address an expanded array of causal targets, but also by harnessing biomarkers and genetic information to deploy therapy more precisely[62,121]. The application of evidence-based interventions that address the established risk factors provides a firm foundation for future advances.

The introduction of statins (agents that are highly effective in lowering LDL and that also quell inflammation independently of effects on lipids) has revolutionized the prevention and treatment of atherosclerosis, a topic that has been well-reviewed in previous publications[122]. The availability of an inhibitor of intestinal absorption of cholesterol that targets the Niemann Pick C 1-like protein 1 yields further reductions in LDL and a further decrement in cardiovascular events[123]. The identification of mutations in *PCSK9* as a cause of autosomal dominant hypercholesterolaemia led rapidly to the development of therapeutic agents that can improve further cardiovascular outcomes in patients who were already treated with statins[17,18,124]. PCSK9 conducts the LDL

receptor to the lysosome, where it undergoes proteolytic degradation. Inhibition of PCSK9 favours the recycling of undegraded LDL receptors to the cell surface, where they can capture and internalize LDL, and thus lowers the plasma concentration of this highly atherogenic lipoprotein[124]. The introduction and recent approval in the USA of bempedoic acid (an inhibitor of ATP citrate lyase, which acts upstream of hydroxymethyglutaryl co-enzyme A (the target of statins)) adds to the range of non-statin agents that lower LDL[125,126]. The availability of inclisiran (a small interfering RNA that limits the production of PCSK9) provides a notably long duration of action, and could be administered twice a year or even annually[127]. Large-scale clinical trials in progress will evaluate the ability of these newer LDL-lowering treatments to improve cardiovascular outcomes. An antisense RNA agent has entered clinical investigation that targets lipoprotein(a), the highly atherogenic cousin of LDL[128]. Treatment of elevated lipoprotein(a) (which is often familial) has proven an enduring problem in preventive cardiology[129].

Beyond LDL, a cardiovascular end-point study is evaluating a selective PPARα agonist in individuals with high triglycerides and low HDL[130]. The 'Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial' revealed that prescription-grade eicosapentaenoic acid can reduce events substantially in individuals with hypertriglyceridaemia[131,132]. Part of this benefit (but probably not all of it) results from a lowering of blood triglycerides; some of the benefit may accrue from an anti-inflammatory action[133].

Recent studies targeting IL-1β (CANTOS) and trials with colchicine (COLCOT and LoDoCO2) have demonstrated the ability of anti-inflammatory therapies that do not lower atherogenic lipids to reduce cardiovascular events in patients who are already receiving a full standard-of-care regimen, including high-dose statins[62]. Beyond affirming the inflammation hypothesis of atherosclerosis, these studies identify colchicine as a readily actionable anti-inflammatory therapeutic agent for atherosclerosis.

There is currently a revolution at the conjunction of diabetes and cardiovascular disease. A 'glucocentric' view of diabetic complications has long prevailed[134]. Although microvascular complications (such as retinopathy, nephropathy and neuropathy) do respond to glucose lowering, the heightened atherosclerotic risk in people with diabetes had—until recently—proven intractable to traditional hypoglycaemic interventions. Recent studies with SGLT2 inhibitors and GLP1 receptor agonists indicate that the macrovascular complications of diabetes involve mechanisms beyond glucose lowering[135–141]. These late-generation agents promise to make inroads in the prevention of cardiovascular complications of diabetes (including myocardial infarction, stroke, heart failure, renal disease and premature death). The success of these drugs in forestalling cardiovascular events emphasizes protective mechanisms beyond those of glucose lowering; the investigation of these mechanisms promises to open avenues in the understanding and treatment of atherosclerosis and heart failure, a common complication of coronary artery disease.

Atherosclerosis is a moving target

A conjunction of fundamental research and clinical investigations has markedly altered traditional concepts of atherosclerosis, and has informed improvements in our ability to manage atherosclerotic risk (Table 1). At the same time, the clinical profile of patients with atherosclerosis has evolved considerably from that of classical cohort studies that have long furnished the basis of our thinking about this disease. Research advances have arisen from improvements in human genetics studies enabled by next-generation sequencing and other technological innovations (including bulk and single-cell RNA sequencing), and the ever-evolving toolkit for genetic manipulation of mice including gene-editing and induced pluripotential stem cell methodology[142,143]. Beyond DNA and mRNA analyses, understanding the functions of non-coding RNAs in atherosclerosis has improved. MicroRNAs and long non-coding RNAs alter the transcription of genes implicated in atherosclerosis[144,145]. These advances will doubtless lead to therapies to address the unacceptable burden of risk that persists in spite of current interventions.

Table 1 | Changing views on atherosclerosis

Past	Present
Atherosclerosis predominantly affects developed countries	Developing countries now bear the greatest burden of atherosclerosis
Coronary thrombosis affects primarily middle-aged white men	Women, younger individuals, individuals from a range of ethnic backgrounds and the very old suffer increasingly from acute coronary syndromes
Atherosclerosis is a lipid storage disease	Inflammation links dyslipidaemia and other risk factors to atherogenesis
Oxidized LDL drives atherosclerosis	Native or aggregated LDL drives atherogenesis
HDL cholesterol protects against atherosclerosis	TGRL participate causally in atherosclerosis
Thin-capped fibroatheromata are vulnerable plaques	The 'vulnerable plaque' is a misnomer; superficial erosion is an increasing cause of arterial thrombosis
Atherosclerosis is an inevitable, steady and degenerative accompaniment to ageing	Atherosclerosis evolves episodically, can regress, and lifestyle and medical measures can modulate the process

Transforming these scientific advances in therapies has required large-scale clinical investigations, which—because of the success of standard-of-care therapies—have required increasing ingenuity and investment. Placebo-controlled, randomized clinical trials remain the most reliable tool for validating the application to humans of therapies derived from laboratory discoveries. However, we also need to embrace targeting segments of the larger population of patients to enrich those enrolled in clinical trials for enhanced risk and responsiveness to specific interventions. This approach has revolutionized the management of cancer, but has barely begun in the cardiovascular arena. The application of polygenic risk scores may identify young people who may benefit particularly from early preventive treatments.

On the one hand, we are witnessing a globalization of cardiovascular disease risk that has increased the overall burden of atherosclerotic disease. On the other hand, progress in laboratory and clinical investigation promises to provide us with tools to confront this global epidemic. Ultimately, making inroads in the control of atherosclerosis will require a multidisciplinary partnership of public health measures, applied behavioural psychology, risk factor control, consistent application of existing therapies, and the development and validation of new therapeutic approaches.

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