Obesity, inflammation, and atherosclerosis

Viviane Z. Rocha and Peter Libby

Abstract | Understanding of the pathophysiology of atherogenesis has evolved substantially during the last few decades. Atherosclerosis was once identified as a lipid-storage disease, but is now recognized as a subacute inflammatory condition of the vessel wall, characterized by infiltration of macrophages and T cells, which interact with one another and with cells of the arterial wall. The pathological mechanisms of obesity recapitulate many features of the inflammatory processes at work in atherosclerosis. Our current appreciation of the similarities between obesity and atherosclerosis has already fostered innovations for the diagnosis, prognosis, and prevention of these two conditions.

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Introduction

Atherosclerosis commonly causes coronary and cerebrovascular diseases, two major morbidities worldwide.[1] As life expectancy increases in low-income and middle-income countries, projections predict a substantial rise in deaths caused by cardiovascular diseases. In the US and Western Europe, however, reductions in risk-factors and improvements in the treatment of cardiovascular disease have yielded a decrease in the number of age-adjusted cardiovascular deaths, more so in men than in women.[1] Nevertheless, the dramatic increase in the prevalence of obesity that has occurred in the last decade[1] threatens to undermine the gains attributed to reductions in risk factors such as hypertension, hypercholesterolemia, and cigarette smoking. Furthermore, the growing problem of obesity among children could have devastating consequences, including a predicted decrease in life expectancy at birth in the US during the first half of the 21st century.[2]

The links between obesity and atherosclerosis extend beyond their overlapping incidence and association with cardiovascular risk. These conditions also share similar pathophysiological pathways. Once considered to be simple lipid-storage diseases, many researchers now view obesity and atherosclerosis as chronic inflammatory processes, characterized by activation of both innate and adaptive immunity.[3,4] In addition to lipid accumulation, other processes such as inflammatory cell infiltration, cytokine production, and cell death also contribute to both conditions, their interplay, and their complications. This Review summarizes some current concepts in the pathophysiology of atherosclerosis and obesity, with a particular focus on inflammation, which is an important feature of both diseases.

Competing interests
The authors declare no competing interests.

Common pathophysiologies

The role of lipids

Although atherosclerosis and obesity are distinct diseases, there are commonalities in the evolution of their pathophysiological concepts. Both were traditionally viewed as lipid-storage diseases, principally involving triglycerides in adipose tissue and cholesteryl ester in atheromata. The association between hyperlipidemia and atherosclerosis evolved over many decades and dominated our understanding of atherogenesis until the 1970s.[5] Despite contemporary evidence for the involvement of several other factors in the pathophysiology of atherosclerosis, a century's worth of data, from studies encompassing population analysis through to experimental research, support a major role for cholesterol in atherogenesis.[5–7] In rabbits, a diet rich in cholesterol promotes inflammation—measured by endothelial expression of vascular cell adhesion molecule 1—as early as 1 week after diet initiation.[8] While in the arterial intima, and in association with local proteoglycans, LDL particles can undergo oxidation (oxLDL), becoming a putative promoter of atherogenesis[9] (Figure 1). Once oxidized, LDL particles can induce endothelial and smooth muscle cell activation, secretion of inflammatory mediators, and expression of adhesion molecules,[9] a sequence of steps that culminates in leukocyte accumulation in the subendothelial space. Recruited inflammatory cells can enhance the oxidation of LDL particles, leading to a vicious local loop. Once in the intima, monocytes become tissue macrophages, which can avidly internalize local particles of oxLDL via scavenger receptors.[10] This process generates cells loaded with lipids (also known as foam cells), which are a prominent feature of atherosclerotic plaque (Figure 1). By capturing these lipid particles, intimal macrophages can follow different pathways, ranging from those that promote local vascular damage through various secreted mediators, to cell apoptosis that can contribute to atheroma progression by adding antigenic and thrombogenic debris to the lesion.

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Key points

- Although they are distinct conditions, atherosclerotic disease and obesity share common pathophysiological features
- Lipids contribute critically to atherosclerosis and obesity; oxidized LDL and free fatty acids can trigger inflammation and initiate disease
- Inflammation mediates all stages of atherogenesis—from early lesion development to atheroma complication—and is associated with obesity, insulin resistance, and type 2 diabetes
- Inflammation constitutes a mechanistic link between obesity and atherosclerosis: adipokines released by adipose tissue induce insulin resistance, endothelial dysfunction, hypercoagulability, and systemic inflammation, all of which can promote atherosclerosis
- The accumulation of heterogeneous macrophage populations, T-cell activation, cell death, and the effects of numerous cytokines and chemokines characterize both atherosclerosis and obesity
- Inflammatory biomarkers, such as high-sensitivity C-reactive protein, can predict cardiovascular events, guide therapy, and reflect the pathophysiological links between obesity and its associated metabolic disorders

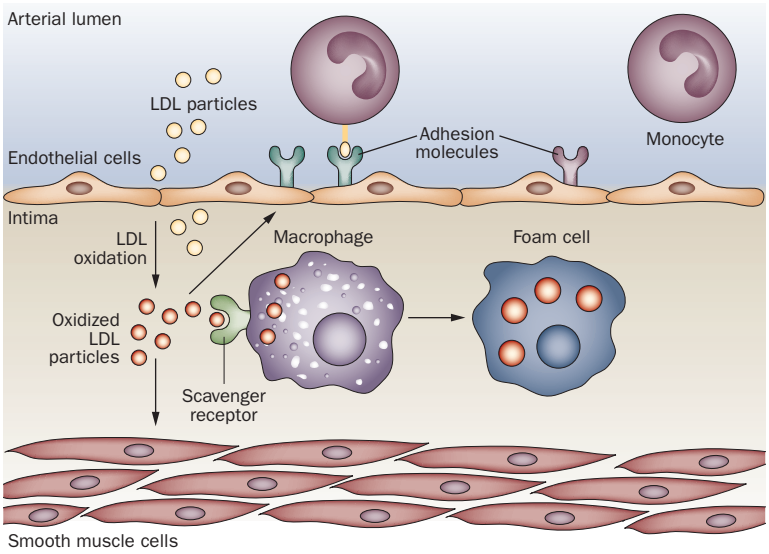

Figure 1 | Effects of LDL particles on the vessel wall. Circulating LDL particles invade the arterial wall and accumulate in the intima, where they undergo chemical modifications, such as oxidation. Modified LDL can induce endothelial cell activation and expression of adhesion molecules. Furthermore, intimal macrophages can internalize modified LDL particles through scavenger receptors and become foam cells—a key process in the development of atherosclerotic plaque. Oxidized lipids probably modulate smooth muscle cell functions, for example increasing their adhesion to macrophages and foam cells in the plaque.

Additionally, macrophages can present moieties derived from oxLDL particles as antigens to recruited T cells, an activity that supports the crucial role of lipids not only in the innate immune response in atherosclerosis, but also in its adaptive immunological aspects.

The pathophysiology of obesity predominantly involves fatty acids and triglycerides, rather than LDL cholesterol, as in atherosclerosis. The long-term nutrient excess and unbalanced energy expenditure that characterizes obesity leads to fatty acid accumulation in the liver, muscles, and adipose tissue. In turn, the higher level of fatty acids observed in obesity, compared with the lean state, is likely to contribute to insulin resistance. When taken up by hepatocytes or myocytes, free fatty acids can either undergo oxidation in the mitochondrial compartment or be stored as triglycerides. Excessive amounts of these lipids overload the oxidation and storage pathways, leading to accumulation of fatty acid intermediates, such as diacylglycerol and ceramide.[11,12] By activating various serine kinase pathways, including members of two of the most potent proinflammatory cascades—IκB kinase (IKK) and c-Jun *N*-terminal kinase (JNK)—diacylglycerol, ceramide, and other free fatty acid metabolites can inhibit insulin function[12] (Figure 2). Free fatty acids might also bind toll-like receptor 4,[13] present in adipocytes and macrophages, constituting an important trigger of innate immunity through recognition of pathogen-associated molecular patterns. After ligation, members of the toll-like receptor family activate mitogen-activated protein-kinase-activator protein 1 and nuclear factor κB (NFκB) signaling pathways, initiating a potent downstream inflammatory response[14] (Figure 2). Apolipoprotein CIII is a constituent of some triglyceride-rich lipoproteins that might accumulate, particularly in obese individuals, and is associated with increased cardiovascular risk. This apolipoprotein can also activate vascular and inflammatory cells through toll-like receptor 2.[15]

Mediators, macrophages, and innate immunity

The original cholesterol hypothesis of atherosclerosis has evolved toward a more contemporary view that acknowledges the role of inflammation.[6,7,16–18] The identification of abundant monocyte-derived macrophages in atherosclerotic plaques, and the gradual recognition of their importance in atherogenesis, provided the missing link between cholesterol and the biology of the disease. Following the observation that infiltrating monocytes can internalize lipids and become activated macrophages and foam cells in the nascent atheroma, studies involving chemokine-deficient and chemokine-receptor-deficient animals provided additional support for the role of mononuclear cells in atherosclerosis. The reduced atherosclerotic burden in animals deficient in CC-chemokine ligand 2 (also known as monocyte chemoattractant protein 1 [MCP-1]) and its receptor CC-receptor 2 (CCR2), supports the relevance of monocyte recruitment in atheroma development.[19,20] Antagonism or deficiency of other monocyte chemoattractant molecules, such as CC-chemokine ligand 5 (also known as RANTES), its receptor CC-receptor 5 (CCR5),[21,22] and CX_3-chemokine receptor 1 (CX_3CR1)[23] also reduces atherosclerosis, reinforcing the importance of monocyte trafficking in plaque progression, and the contribution of multiple chemokines to this phenomenon.

Several studies have highlighted the heterogeneity of inflammatory cells involved in atherogenesis. Monocytes seem to commit to distinct roles while in the blood, and exhibit different recruitment mechanisms and

functions in the plaque reflected by their surface structures[24,25] (Figure 3). Ly6C^{hi}CCR2^{+}CX$_3$CR1^{low} monocytes (or CD14^{hi}CD16^{-} in humans) more efficiently infiltrate sites of inflammation (inflammatory monocytes), while Ly6C^{low}CCR2^{-}CX$_3$CR1^{hi} monocytes (or CD14^{+}CD16^{+} in humans) have a major surveillance function in homeostasis (resident monocytes). The Ly6C^{hi} monocyte subset increases dramatically in hypercholesterolemic mice[24] and uses not only CCR2, but also CCR5 and CX$_3$CR1 to invade plaques.[25] Interestingly, Ly6C^{low} monocytes can also enter plaques, although they do so less frequently than Ly6C^{hi} monocytes, and seem to require CCR5 rather than CX$_3$CR1.[25] Although both Ly6C^{hi} and Ly6C^{low} monocyte subsets can differentiate into CD11c^{+} dendritic cells, Ly6C^{low} monocytes are more prone to becoming CD11c^{+} cells within lesions, indicating functional differences between these two monocyte populations[25] (Figure 3). The role of this dendritic-cell-like population in atherosclerotic plaques will require further study.

Interest in the inflammatory features of obesity has intensified over the past 15 years. Studies reporting increased expression of tumor necrosis factor (TNF) in obese compared with lean adipose tissue, and improved glucose tolerance after neutralization of TNF in obese rodents,[26,27] support the role of inflammation in obesity and regulation of its complications by inflammatory mediators. The discovery of TNF involvement in obesity prompted the study of a wide range of other inflammatory mediators (such as interleukin [IL] 6, IL-1β, and MCP-1) and hormones (such as adiponectin and leptin), which are all expressed differentially in obese adipose tissue.[28]

Despite the abundance of adipocytes, other cells can also produce inflammatory mediators in adipose tissue. Several research groups have investigated the source of these adipose-tissue-derived molecules, and implicated macrophages in the inflammatory aspects of obesity.[29,30] In both animal and human studies of genetic and diet-induced obesity, macrophages infiltrate adipose tissue, participate in the secretion of important inflammatory mediators and could, therefore, promote obesity-induced insulin resistance.[29,30]

As with the distinct subsets of macrophages in atheroma, mononuclear phagocytes in adipose tissue also exhibit heterogeneity (Figure 4). Here, infiltrative and resident macrophages coexist and seem to contribute to local homeostasis.[31,32] Whereas resident macrophages—the predominant type of macrophage in lean adipose tissue—usually express markers of alternative activation (M2) such as arginase, infiltrative macrophages (largely present in obese adipose tissue) have a classically activated phenotype (M1) and, therefore, have increased expression of IL-6, nitric oxide synthase 2, and CCR2[31,32] (Figure 4). The recruitment of macrophages by adipose tissue in the obese state resembles the chemotaxis of these cells in the atheroma. MCP-1-deficient and CCR2-deficient animals present reduced numbers of adipose tissue macrophages, less fat inflammation, and greater insulin sensitivity, which supports the importance of MCP-1 and CCR2 in

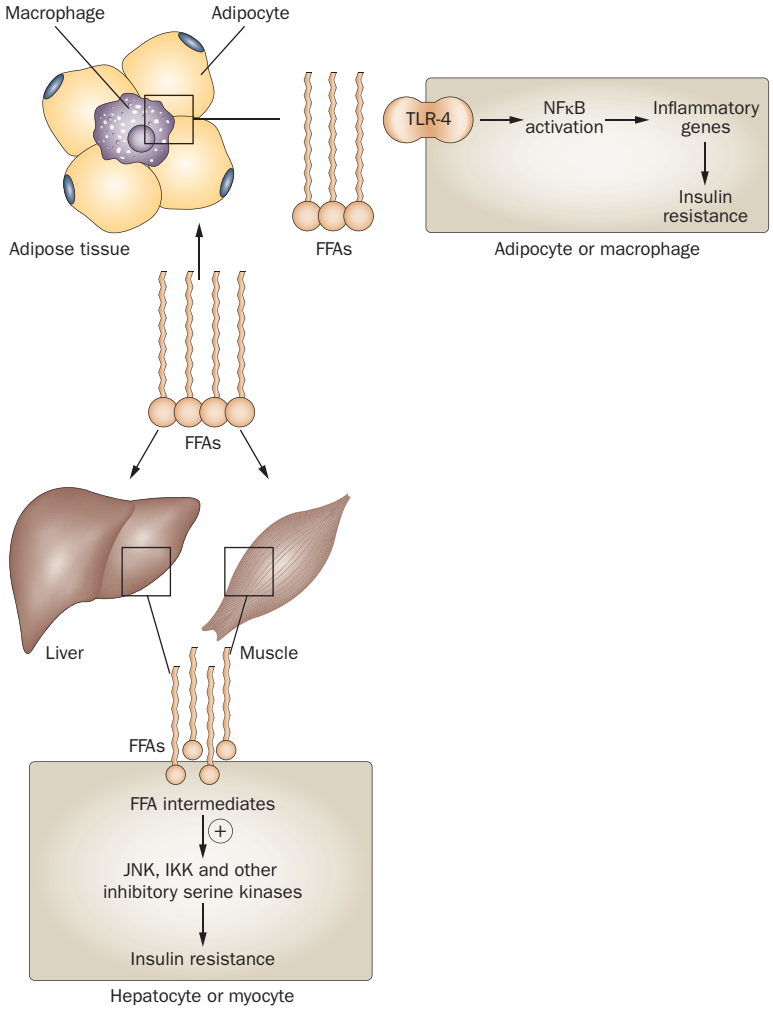

Figure 2 | Effects of free fatty acids on various organs. The increased levels of free fatty acids in obese individuals can induce insulin resistance in various cell types through different mechanisms. Excessive amounts of free fatty acids saturate the oxidative and storage capabilities of hepatocytes and myocytes, resulting in accumulation of fatty acid intermediates. By activating several inhibitory serine kinases, these metabolites can impair insulin signaling. Free fatty acids can also bind TLR-4, which is present in macrophages and adipocytes. Upon interaction with TLR-4, free fatty acids induce NFκB activation and expression of an array of inflammatory genes, some of which suppress insulin signaling. Abbreviations: FFA, free fatty acids; IKK, IκB kinase; JNK, Jun N-terminal kinase; NFκB, nuclear factor κB; TLR-4, toll-like receptor 4.

macrophage migration to obese adipose tissue, and the relevance of macrophages in the metabolic complications of obesity.[33,34] Furthermore, obese CCR2-deficient animals have significantly less expression of M1 markers than their wild-type counterparts, and have levels of M2 comparable to those of lean mice.[32] Therefore, although CCR2-deficient animals have a much less prominent population of infiltrative, proinflammatory macrophages, their resident macrophage subset remains preserved, indicating the local operation of different chemotactic systems. By contrast, other studies have found no influence of MCP-1 or CCR2 deficiency on adipose tissue macrophage infiltration or insulin sensitivity.[35,36] The

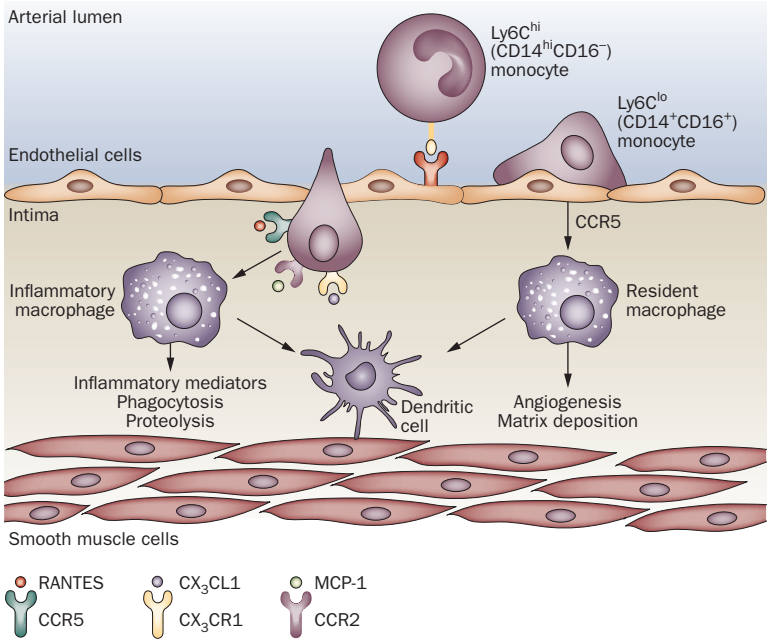

Figure 3 | Monocyte subsets in atherosclerosis. Studies indicate that several distinct monocyte subsets participate in the composition and evolution of the atheroma. In mice, Ly6C^{hi} monocytes (or CD14^{hi}CD16^{-} in humans) can infiltrate atherosclerotic plaques most efficiently and use CCR2, CX_3CR1, and CCR5 in this chemotactic activity. Ly6C^{low} monocytes (or CD14^{+}CD16^{+} in humans) enter plaques less frequently using predominantly CCR5. The exact role of these different populations of monocytes in atherosclerosis is still not clear, but studies of these cells in other inflammatory conditions indicate that Ly6C^{hi} monocytes are likely to be involved in inflammatory amplification, while Ly6C^{low} monocytes promote inflammation resolution through angiogenesis and matrix deposition. Both Ly6C^{hi} and Ly6C^{low} monocyte subsets can differentiate into CD11c^{+} dendritic cells, but Ly6C^{low} monocytes are more predisposed to becoming CD11c^{+} cells within lesions, suggesting functional differences between these two cell populations. Abbreviations: CCR2, CC-receptor 2; CCR5, CC-receptor 5; CX_3CL1, CX_3-chemokine ligand 1; CX_3CR1, CX_3-chemokine receptor 1; MCP-1, monocyte chemoattractant protein 1.

degree to which MCP-1 and its receptor contribute to inflammation in obesity remains unclear.

Two studies, published in the last two years,[37,38] have helped elucidate the role of alternatively activated macrophages in adipose tissue. The macrophage-selective deficiency of peroxisome proliferator-activated receptor γ (PPARγ)—a nuclear receptor required for maturation of alternatively activated macrophages—increases the susceptibility of mice to obesity and insulin resistance, indicating that these cells have a protective function in metabolic homeostasis.[37] Additionally, PPARδ, whose absence in myeloid cells increases the susceptibility of mice to insulin resistance and hepatosteatosis, also regulates adipose tissue macrophage polarization toward alternative activation.[38] Interestingly, the same study identified the type 2 T-helper (T_H2) cytokines IL-4 and IL-13, which are critical stimuli to the alternative polarization of macrophages, as important inducers of macrophage PPARδ.[38] This finding also supports the link between immunity and metabolism, and suggests a role for adaptive immunity in obesity.

T cells and adaptive immunity

The discovery of T cells in atherosclerotic plaques came after the detection of macrophages, probably because of the lower numbers of T cells in these lesions. Despite their relative paucity, T cells powerfully modulate the immune response in atherogenesis.[39] T cells probably migrate to the plaque after initial contact with atherosclerosis-related antigens through dendritic cells in local lymph nodes.[39] Entry into the plaque occurs through various chemoattractants, including RANTES and an important chemokine trio—CXC-chemokine ligand (CXCL) 9 (also known as MIG), CXCL10 (or IP-10), and CXCL11 (or ITAC), and their common receptor CXCR3[21,40–42] (Figure 5). While in the plaque, T cells interact with macrophages through antigen presentation and assume distinct programs of activation, with type 1 T-helper (T_H1) and T_H2 cells differently influencing plaque evolution[39,43] (Figure 5). The preponderance of T_H1 over T_H2 cytokines in human and mouse atheromata supports the hypothesis that the T_H1 arm of adaptive immunity, which is characterized by proinflammatory mediators and local tissue damage, is predominant in atherogenesis.[39,43,44] Indeed, interferon-γ (IFN-γ),—a signature T_H1 cytokine—induces the classic activation of macrophages and, therefore, the secretion of proteases, vasoactive mediators such as nitric oxide, and proinflammatory cytokines such as TNF, which can perpetuate local inflammation[45] (Figure 5). IFN-γ also potently inhibits endothelial cell and smooth muscle cell proliferation as well as collagen production,[46–48] all of which might contribute to plaque fragility. These and other properties of IFN-γ, together with the finding of reduced plaque burden in IFN-γ-deficient and IFN-γ-receptor-deficient animals,[49,50] support IFN-γ as a potent proatherogenic mediator.

The T_H2 cytokines, IL-4 and IL-13, induce alternative activation in macrophages and can mitigate inflammation[45] (Figure 5). By sharing a common receptor chain (IL-4 receptor α), these two cytokines can antagonize the many effects of IFN-γ, attenuating the macrophage respiratory burst and other proinflammatory actions. Despite their roles in the resolution of inflammation, IL-4 and IL-13 seem to be less consistently anti-inflammatory than IL-10 or transforming growth factor β, and the exact role of IL-4 and IL-13 in atherogenesis remains unclear. Whereas some studies have found a protective role for IL-4, others demonstrated decreased atherosclerotic burden in the absence of this cytokine.[51,52]

The nature of the relationship between macrophages and T cells depends greatly on the antigen recognized by the T cell bound to class II major histocompatibility molecules on the surface of the antigen-presenting cell. The precise contribution of various putative plaque antigens to atherogenesis warrants further study. Studies of T-cell clones from atherosclerotic plaques reveal that T cells recognize oxLDL[53] and heat shock protein (HSP) 60, which is a member of the HSP family of stress-related chaperones.[54] Interestingly, microorganisms, such as *Chlamydia pneumoniae*, resident in atherosclerotic plaques can also

be a source of highly conserved HSP60,[54] and antibodies generated in response to infection with HSP60-expressing microorganisms can, therefore, react to human HSP60. The link between atherogenesis and infectious agents remains clinically unproven, and antibiotics have failed to reduce cardiovascular events in several trials.[55,56]

Despite the prominence of proinflammatory cytokines in atherogenesis, atheromata often also contain cytokines with anti-inflammatory and atheroprotective functions. Deficiency or inhibition of IL-10 and transforming growth factor β—the most representative members of this group of cytokines—enhances atherosclerotic disease in mice.[57,58] Although various cell types can produce these potent anti-inflammatory mediators, the T-regulatory (T_{REG}) cells are their primary source. T_{REG} cells comprise $CD4^+CD25^+$FoxP3-expressing cells that can suppress the function of T-helper effector cells and counteract inflammation and atherosclerosis. Transfer of T_{REG} cells to atherosclerosis-susceptible mice reduces plaque burden, whereas depletion of these cells results in increased disease.[59]

Although the data implicating T lymphocytes in atherosclerosis are abundant, the importance of these cells in obesity came to light only within the last 2 years.[60–62] Several studies have demonstrated that adipose tissue from obese mice contains significantly more T cells than lean adipose tissue.[60–62] Interestingly, T cell accumulation in adipose tissue from mice with diet-induced obesity occurs as early as 5 weeks after high-fat diet initiation, precedes adipose tissue macrophage infiltration, and is associated with impaired glucose metabolism in these animals.[62] The mechanisms of lymphocyte accumulation in adipose tissue remain unknown, but increased expression of RANTES and its receptor CCR5 in obese adipose tissue of mice and humans alludes to the importance of this duo in local T-cell migration.[60]

The proatherogenic molecule IFN-γ also seems to be important in obesity inflammation (Figure 6). Deficiency in IFN-γ or the IFN-γ receptor markedly reduces the expression of inflammatory genes in obese adipose tissue and improves metabolic parameters in obese animals.[61] Additionally, a positive correlation between $CD3^+$ and IFN-γ mRNA expression and waist circumference in a cohort of patients with type 2 diabetes mellitus suggests that the T_H1 arm of adaptive immunity is involved in obesity–metabolic disorders.[62]

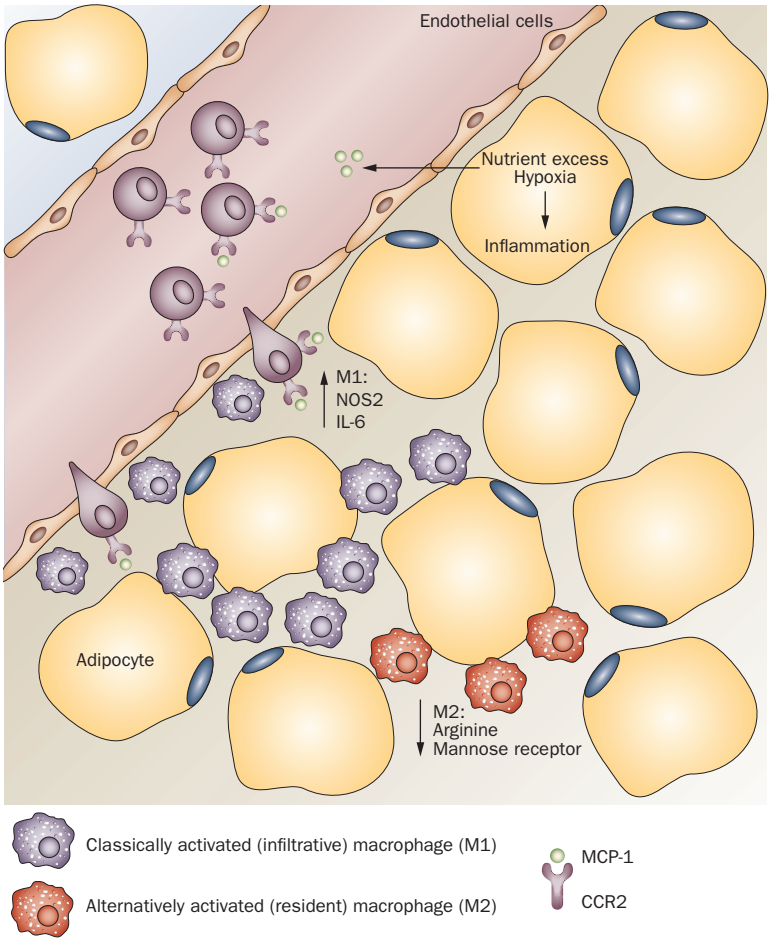

Figure 4 | Monocyte subsets in adipose tissue inflammation. The nutrient overload and hypoxia of adipocytes that occur with weight gain and obesity can ultimately trigger the expression of several inflammatory genes. Among them, MCP-1 stands out as an important monocyte chemoattractant in adipose tissue when interacting with its receptor CCR2. In obesity, $CCR2^+$ monocytes preferentially accumulate in adipose tissue, and give rise to classically activated macrophages (M1), which are characterized by the production of nitric oxide synthase 2 and interleukin 6. Alternatively activated macrophages (M2), however, are recognized by their production of arginase and populate lean adipose tissue to a greater extent than obese adipose tissue, indicating that these cells are involved in local homeostasis. Abbreviations: CCR2, CC-receptor 2; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein 1; NOS2, nitric oxide synthase 2.

Cell death in atheromata and adipose tissue

Apoptosis of smooth muscle cells in atheromata might favor fibrous cap thinning and forms procoagulant cell debris, contributing to plaque weakening and thrombotic potential.[63,64] Nevertheless, the role of apoptotic macrophages in necrotic core expansion, increased inflammation, and progression of atherosclerosis remains uncertain.[65] In adipose tissue, the number of necrotic adipocytes is increased dramatically in obese individuals compared with nonobese individuals. Cinti *et al.* reported the clustering of macrophages around necrotic fat cells, suggesting that adipocyte death mediates macrophage infiltration and activation in obesity.[66]

Insulin resistance and plaque rupture

Inflammatory molecular insights

Inflammation characterizes all stages of plaque development, and also seems to contribute to complications such as arterial stenosis and thrombosis. Thrombosis caused by plaque rupture, which leads to the majority of fatal myocardial infarctions, depends greatly on the balance between the biochemical strength of the plaque's fibrous cap and local enzymatic destruction—both of which are regulated by inflammatory factors. By activating macrophages, proinflammatory IFN-γ induces downstream

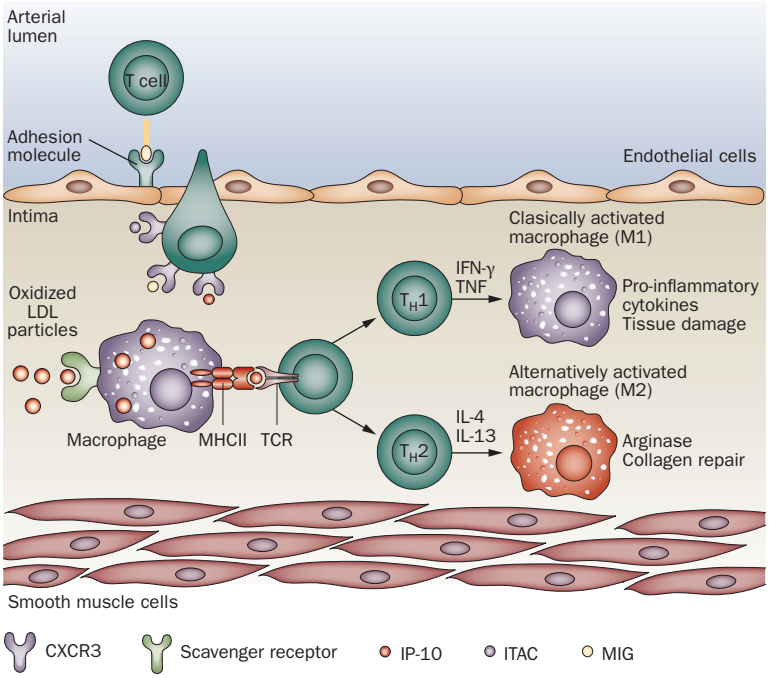

Figure 5 | T cells in atherosclerosis. T cells enter atheromata by interacting with adhesion molecules on the surface of endothelial cells in response to chemoattractants. The chemokines CXC-chemokine ligand (CXCL) 9 (also known as MIG), CXCL10 (also known as IP-10), and CXCL11 (also known as ITAC) bind specifically to their CXCR3 receptor on lymphocytes, promoting T-cell accumulation in the plaque. Once in the vessel wall, lymphocytes can use the T-cell receptor to recognize different antigens, possibly including those associated with modified LDL, presented by the major histocompatibility complex class II on macrophages or other antigen presenting cells. T cells then assume different programs of activation, typically becoming type 1 T-helper (T_H1) and type 2 T-helper (T_H2) cells. Cytokines from both groups differently influence plaque progression, meaning that T cells are important orchestrators in atherogenesis. While the T_H1 cytokine, interferon-γ, classically activates macrophages, the T_H2 cytokines, interleukin 4 and interleukin 13, promote alternative macrophage activation. Abbreviations: CXCR3, CXC-chemokine receptor 3; IFN-γ, interferon-γ; IL-4, interleukin 4; IL-13, interleukin 13; IP-10, interferon-γ-inducible protein 10; ITAC, interferon-γ-inducible T cell α chemoattractant; MHCII, major histocompatibility complex class II; MIG, monokine inducible by interferon-γ; TCR, T cell receptor; T_H1, type 1 T-helper cell; T_H2, type 2 T-helper cell; TNF, tumor necrosis factor.

mediators, such as CD40 ligand, which boost the production of various proteases that can degrade collagen and weaken the fibrous cap.[39,43] Additionally, this T_H1 cytokine inhibits the proliferation of smooth muscle cells[47] and their collagen-synthesizing capacity,[48] thus contributing to plaque instability. The interaction between the cell-surface molecules CD40 ligand and CD40 provides other important clues to the relationship between inflammation and plaque disruption.[67] Besides stimulating the production of various matrix-degrading proteases, CD40 ligand and CD40 can also elicit the expression of tissue factor, triggering of coagulation cascades, and thrombus formation.[67]

While arterial thrombosis can complicate atherosclerosis, insulin resistance—a process that is also subject to regulation by inflammation—often accompanies obesity. Indeed, inflammatory mediators, such as TNF, can inhibit insulin signaling. Interaction between insulin and its receptor promotes tyrosine phosphorylation of insulin receptor substrate proteins, an essential process in insulin signaling. In the presence of obesity-derived inflammatory stimuli such as TNF (and other stressors, such as lipids), however, insulin receptor substrate 1 is phosphorylated at serine rather than tyrosine residues, which impairs its capacity to interact with insulin receptors and promote insulin function.[12] Growing evidence supports the involvement of serine kinases, such as JNK and IKK, in insulin receptor substrate 1 serine phosphorylation.[12] These kinases also promote expression of inflammatory genes, thus contributing to a potential local positive feedback loop. Moreover, genetic deficiencies in JNK-1 or IKK-β and pharmacologic suppression of these pathways protect mice from insulin resistance,[68–70] confirming the inflammatory basis of this metabolic disturbance.

Although insulin resistance represents a central element in the association between obesity and atherosclerosis, the various adipokines secreted by obese adipose tissue can lead to other undesirable effects, such as endothelial vasomotor dysfunction, hypercoagulability, dyslipidemia, and an inflammatory state, all of which are potential promoters of atherosclerotic events.[71]

Clinical perspectives

Inflammation as a risk predictor

The substantial body of evidence that links inflammation, atherosclerosis, and obesity provides the rationale for inclusion of inflammatory biomarkers in risk-stratification and the use of anti-inflammatory drugs in the treatment of these conditions and their complications. High-sensitivity C-reactive protein (hsCRP) is a circulating, mainly liver-derived pentraxin, which provides a readily measured biomarker of inflammation that independently predicts cardiovascular events in apparently healthy individuals and those with manifest atherosclerotic disease.[72] Several large-scale prospective trials have demonstrated that baseline hsCRP levels independently correlate with future incidence of myocardial infarction and other vascular diseases, such as stroke and peripheral arterial disease.[73,74] Some of these studies also concluded that hsCRP predicted cardiovascular risk independently of traditional risk factors.[75–82] When classified in strata (<1 mg/l, 1–3 mg/l, and >3 mg/l), baseline blood levels of hsCRP provide additive prognostic information across the whole spectrum of LDL cholesterol levels and Framingham risk scores.[76] This accumulating evidence and the technical advantages (for example, stability, assay precision, accuracy, and availability) of hsCRP as an analyte over other biomarkers of inflammation suggest that use of hsCRP could improve risk assessment in primary prevention, particularly in patients at intermediate risk (10–20% risk of coronary heart disease over 10 years).[83] Indeed, incorporating hsCRP, together with family history, into traditional risk prediction models has been shown to substantially improve global cardiovascular risk prediction in men and women.[84,85]

hsCRP also correlates with BMI and, therefore, overweight and obese individuals have higher levels of this marker compared with normal-weight counterparts.[86] The distribution of body fat also constitutes a determinant of hsCRP, independent of BMI; the waist-to-hip ratio, which is used clinically to evaluate abdominal visceral adiposity, positively associates with hsCRP even after adjustment for BMI.[86] These findings support the hypothesis that increased adiposity, particularly visceral, is associated with a state of low-grade systemic inflammation. Interestingly, baseline levels of hsCRP also correlate with risk of incident type 2 diabetes mellitus, independently of obesity and other determinants of diabetes.[87] This finding suggests that, although CRP production by the liver strongly correlates with measures of obesity and with IL-6 secretion by adipose tissue,[88] other environmental factors on inflammatory processes might contribute to CRP blood levels.

Evidence is growing that other plasma biomarkers differentially expressed in obesity might also prove useful in the diagnosis and prognosis of cardiovascular disease. TNF, IL-6, plasminogen activator inhibitor 1, and angiotensinogen, which are already known to be important mediators of atherogenesis, are now included in the extensive list of adipose-tissue-derived bioactive substances known as adipocytokines.[28,89,90] Soluble products of adipocytes primarily involved in metabolic regulation, such as leptin and adiponectin, might also modulate vascular function and participate in the development of cardiovascular diseases. The adipocyte-derived protein adiponectin consists of three domains—a globular domain, a signal sequence, and a collagen-like domain.[91] Adiponectin molecules combine through its collagen-like motifs, producing at least two complexes in the blood—a hexamer of relatively low-molecular weight, and a high-molecular-weight adiponectin.[91] High-molecular-weight complexes are likely to constitute the most active form of adiponectin and, therefore, levels of high-molecular-weight adiponectin could be a more relevant marker of insulin sensitivity than total circulating adiponectin.[92] Unlike most adipocytokines, adiponectin paradoxically declines in obese individuals. Plasma adiponectin levels also correlate inversely with cardiovascular events and development of insulin resistance and type 2 diabetes mellitus.[93] This adipocytokine has anti-inflammatory, antiatherogenic, and antidiabetic properties, providing a novel link between inflammation, atherosclerosis, and obesity. Although the US Centers for Disease Control and Prevention and the AHA have defined a place for hsCRP in clinical risk stratification, most of the other biomarkers, including adiponectin, remain investigational, despite their correlation with disease.

Immunomodulation in obesity and atherosclerosis

Not only has the inflammatory hypothesis led to changes in the diagnosis and prognosis of atherosclerosis and obesity complications, it has also begun to influence therapeutic approaches for these two morbid conditions.

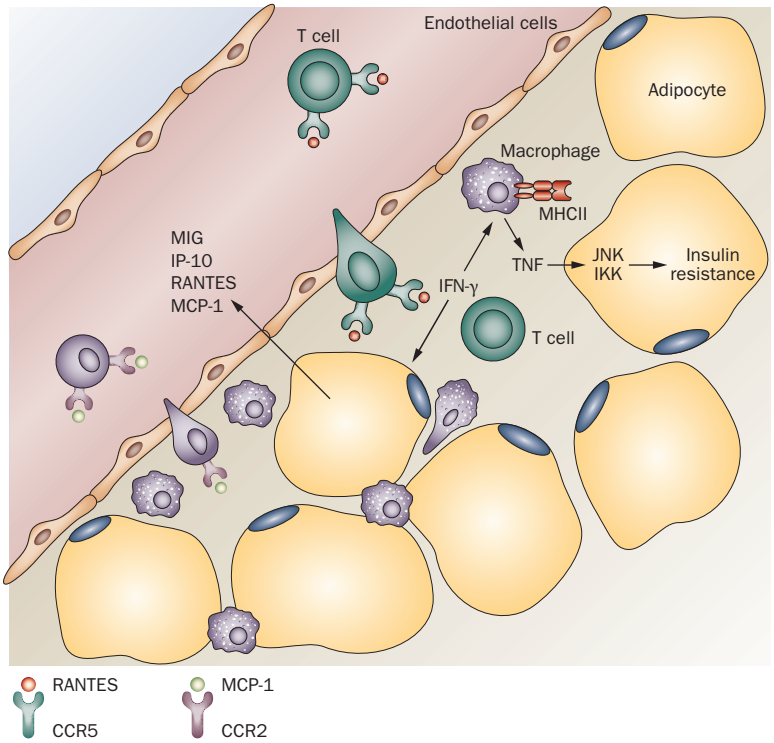

Figure 6 | T cells in the inflammatory network of obesity. By secreting the T_H1 cytokine, IFN-γ, T cells can modulate macrophage and adipocyte functions within adipose tissue. IFN-γ induces production of several chemokines from adipocytes, such as MCP-1, RANTES, IP-10 and MIG, which probably facilitate T-cell migration to the adipose tissue. As a consequence of IFN-γ stimulation, macrophages increase their expression of major histocompatibility molecules class II and secrete more TNF, which can in turn mediate local insulin resistance. Abbreviations: CCR2, CC-receptor 2; CCR5, CC-receptor 5; IFN-γ, interferon-γ; IKK, IκB kinase; IP-10, interferon-γ-inducible protein 10; JNK, Jun N-terminal kinase; MCP-1, monocyte chemoattractant protein 1; MHCII, major histocompatibility complex class II; MIG, monokine inducible by interferon-γ; T_H1, type 1 T-helper cell; TNF, tumor necrosis factor.

Statins were originally developed as regulators of cholesterol metabolism, but many studies have revealed their additional immunomodulatory effects.[94,95] As well as having anti-inflammatory properties *in vitro*, statins reduced hsCRP levels in several clinical trials,[95–97] an effect that was associated with improved outcomes apparently beyond the reductions in plasma cholesterol levels.[95–97] Biomarkers of inflammation could also help guide therapy with statins, which is a possibility that was tested in JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin).[97] This study showed reduced cardiovascular events in apparently healthy individuals with LDL-cholesterol levels less than 130 mg/dl, but hsCRP levels greater than 2 mg/l, who were treated with rosuvastatin 20 mg per day.[97] Nevertheless, JUPITER has some potential limitations that require consideration. The study did not include a group of individuals with low levels of hsCRP, a decision that was made on the basis of the very low number of cardiovascular events and the lack of evidence of statin benefit among nonhyperlipidemic

individuals with low levels of hsCRP in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[95] Additionally, the early interruption of JUPITER limits the interpretation of longer-term effects of rosuvastatin in the treated population.

Members of the insulin-sensitizing class of thiazolidinediones also possess substantial anti-inflammatory effects. By activating PPARγ, thiazolidinediones regulate genes related to adipocyte differentiation, lipid metabolism, and glucose uptake, each of which can contribute to their beneficial metabolic effects.[98] PPARγ agonists also suppress inflammation.[99] In humans, thiazolidinediones reduce hsCRP plasma levels to an even greater extent than do statins, a finding that supports their anti-inflammatory effects.[100,101] Various PPARγ agonists have been shown to decrease atherosclerosis in mouse studies.[102,103] The PPARγ-mediated effects on inflammation, oxidative stress, advanced glycation, and the renin–angiotensin system present potential mechanisms of the anti-atherosclerotic actions of thiazolidinediones in animals. In humans, however, the net effect of thiazolidinediones on cardiovascular events has proven controversial. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) demonstrated that pioglitazone was associated with a significant reduction in the secondary end point, which included all-cause mortality, non-fatal myocardial infarction, and stroke.[104] Nevertheless, a meta-analysis that evaluated several thiazolidinedione trials suggested that treatment with rosiglitazone is associated with an increased risk of myocardial infarction and cardiovascular death.[105] The adverse effect profile of thiazolidinediones, which includes fluid retention and consequent cardiac stress, could explain some of the negative results of these trials and might counteract the possible beneficial actions of these drugs, rendering their therapeutic use questionable in some individuals.[98,106]

Salicylates (for example, aspirin) are anti-inflammatory drugs that have been in use for more than a century, and were once a mainstay for treatment of rheumatologic diseases. Initial studies of salicylates revealed that they have important hypoglycemic properties, but their antithrombotic and antiplatelet aggregation effects are associated with gastrointestinal irritation and carry a very high bleeding risk, which has limited their use. Interestingly, nonacetylated members of this drug group—particularly salsalates—do not prolong bleeding times, justifying clinical trials to test their efficacy in patients with hyperglycemic conditions. By inhibiting IKK-β, salsalates could provide an effective method of suppressing the chronic inflammation that underlies obesity-related dysmetabolism.[70] Some small trials of salsalates have already demonstrated improved glucose and inflammatory parameters in obese nondiabetic individuals,[107,108] but more extensive studies are yet to be performed.

The crucial and diversified role of inflammation in the pathophysiology of atherosclerosis and of obesity-associated disorders opens up several other therapeutic possibilities now under investigation. Current lines of investigation range from vaccination and immunomodulation, to chemokine–chemokine receptor antagonism.[109,110] Experimental interference with chemokine action has yielded positive results in various chronic conditions, including atherosclerosis and obesity. The relevance of MCP-1 and its receptor CCR2 in monocyte accumulation in the atherosclerotic plaque and in obese adipose tissue has motivated several studies involving the blockade of this chemoattractant system.[111–113] In atherosclerotic mice, the transfection of a dominant-negative inhibitor for CCR2 significantly reduced or stabilized atherosclerotic lesions.[111,112] Furthermore, the administration of an anti-inflammatory compound that targets CCR2, propagermanium, to genetically obese mice decreased adipose tissue inflammation and improved insulin resistance and hepatic steatosis,[113] which raises the possibility of MCP-1/CCR2 blockade as a therapeutic strategy in both atherosclerosis and obesity complications. Antagonism of RANTES could offer another approach in the treatment of those inflammatory disorders. Blockade of the interaction between RANTES and its receptors,[21] or inhibition of RANTES oligomerization, significantly decreased atherosclerosis in mice.[114] Moreover, because the interaction between CX_3CL1 and its receptor CX_3CR1 mediates the entry of $Ly6C^{hi}$ rather than $Ly6C^{low}$ monocytes into the atheroma,[25] and the genetic deletion of CX_3CR1 significantly reduces atherosclerosis,[23,115] targeting this system through selective antagonists could be another therapeutic option. Despite encouraging results in animal studies, several obstacles, such as redundancy of the chemotactic systems and impairment of host defenses against infection or malignancy, could limit the clinical application of these experimental approaches.

Conclusions

Atherosclerosis and obesity have long been linked in observational studies and in the public perception. By contrast, the similarities in the pathophysiology of these two conditions have emerged only in the last decade. Crucially, both involve inflammatory regulation of their development and complications. Experimental studies demonstrate an essential role for macrophages, T cells, and numerous inflammatory mediators and pathways in the progression of atherosclerosis and obesity-related metabolic disorders. The understanding of these diseases as inflammatory processes has now begun to influence clinical practice, from diagnosis and risk-stratification to therapeutic interventions.

Review criteria

We systematically searched the PubMed database for full-text articles published in the English language between 1990 and 2009, using terms such as "atherosclerosis", "obesity", "inflammation", "macrophage", "T cell", "chemokine", "adipose tissue", "adipocyte", "C-reactive protein", "adiponectin", "adipocytokine", "thiazolidinedione"and "salsalate". We also considered selected important publications published before 1990.

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