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Lymphocytes in atherosclerosis

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Abstract

It is well established that atherosclerosis is caused by an inflammatory process in the arterial intima. However, it is only in recent years that it has become clear that this inflammation is modulated by immune responses against plaque antigens. These antigens are primarily believed to be modified self-antigens such as oxidized LDL. The immune system is challenged to determine whether these antigens should be regarded self and tolerated or non-self and eliminated. The latter will result in plaque development while the first will be protective. T cells are key effectors of both types of responses. An activation of regulatory T cells inhibits auto-reactive T effector cells and is anti-inflammatory. In contrast, if Th1 cells become activated in the plaque this is associated with increased inflammation and disease progression. The role of B cells in atherosclerosis remains to be clarified but some species of athero-protective antibodies have been identified. The elucidation of role of immune system in atherosclerosis has revealed new targets for intervention and both vaccines and antibody-based therapies are presently in or due to enter clinical testing.

Highlights

♦ Atherosclerosis involves an inflammatory process in the arterial intima ♦ Immune responses against plaque antigens modulate plaque inflammation ♦ Regulatory T cells inhibits auto reactive T effector cells and inflammation ♦ Th1 cells are pro-inflammatory and promote plaque progression ♦ Novel therapies aim to mimic or selectively activate athero-protective immune responses
1. Introduction

The role of inflammation in the development of atherosclerosis has been a well-established fact for more than a century. Originally this inflammation was solely regarded as a result of accumulation of toxic lipids, but recent research has revealed that it is regulated by a complex pattern of immune responses. These immune responses may drive disease progression by activating pro-inflammatory Th1 and NKT cells against self-antigens in the plaque but can also be protective by inducing anti-inflammatory regulatory T cells. It is likely that the latter dominate in pre-stages of the disease and help to clear away damaged cells and lipoproteins from the vascular wall before causing further tissue injury. As the disease advances the immune responses (presumably against the same self-antigens) shift towards Th1 and exuberates inflammation. According to this view the interactions between antigen presenting cells (APC) and T cells that determine if immune responses against self-antigens in the plaque will be tolerogenic or pro-inflammatory play a key role in the disease process. Consequently, there has been an increasing focus on the role of T cells in atherosclerosis. Increased lymphocyte number is well documented as an independent risk factor for cardiovascular disease (1, 2). Interestingly, decreased lymphocyte numbers also confer increased risk (3), further underlining their complex role of the immune system in atherosclerosis. This review will summarize our current understanding of the role of different lymphocytes in atherosclerosis and briefly discuss the possibility of developing novel treatments for cardiovascular disease by targeting these cells. The role of the immune system is summarized in the figure.

2. CD4+ T cells

CD4+ T cells, also named T helper (Th) cells, are believed to play an important role in atherosclerosis. Initial evidence of their atherogenic potential came from studies with
hypercholesterolemic severe immune-deficient (SCID) mice that were injected with CD4\(^+\) T cells resulting in increased atherosclerosis (4). Moreover, Zhou and co-workers reported that CD4\(^+\) T cell-deficient Apoe\(^/-\) mice have reduced lesions in the aortic root (5). In contrast, Elhage and co-workers, found no difference in aortic root lesions but increased atherosclerosis in en face preparations of the total aorta in the same type mice (6) indicating that CD4\(^+\) T cells may have site-specific actions. CD4\(^+\) T cells are a heterogeneous group of cells that include both pro- and anti-inflammatory cells. IL-12 and IL-18 from antigen presenting cells promote naïve CD4\(^+\) T cells to express the Th1-specific transcription factor T-box expressed in T cells (Tbet) along with the signal transducer and activator of transcription 4 (STAT4) leading to Th1 cell differentiation. T-bet deficiency reduces atherosclerosis in Ldr\(^{-/-}\) mice indicating that Th1 cells are pro-atherogenic (7). Th1 cells produce pro-inflammatory cytokines such as IFN-\(\gamma\) and TNF-\(\alpha\). Hypercholesterolemic mice lacking IFN-\(\gamma\) or TNF-\(\alpha\) are characterized by reduced atherosclerosis providing further support of a pro-atherogenic role of Th1 cells (8, 9). Th2 cells represent a lineage of CD4\(^+\) T that primarily interact with B cells. The role of Th2 cells in atherosclerosis appears to be more complex than that of Th1 cells and both pro-and anti-atherogenic actions have been reported. Th2 cell differentiation is initiated by the Th2 cell signature cytokine IL-4. This cytokine prevents production of IFN-\(\gamma\) leading to inhibition of Th1 cell differentiation. The role of IL-4 and Th2 cells in experimental atherosclerosis remains to be fully elucidated and hypercholesterolemic mice deficient in IL-4 have been reported to have reduced as well as unaltered atherosclerosis (10, 11). Activated Th2 cells typically also produce the cytokines IL-5, IL-9, IL-13 and IL-25 (12-14). IL-5 has a protective effect on atherosclerosis in hypercholesterolemic mice, a phenomena that has been attributed to the ability of IL-5 to stimulate the synthesis of so called natural antibodies from B cells of the B1 type (15, 16). These antibodies are IgM that bind to phospholipid-epitopes in oxLDL and prevent scavenger
receptor-mediated uptake of oxLDL in macrophages (15). The roles of IL-9, IL-13 and IL-25 in atherosclerosis development are poorly studied and remain to be fully elucidated. IL-33 is another cytokine with the potential to induce Th2 responses and IL-33 treatment has been shown to reduce atherosclerosis development in Apoe−/− mice (17).

3. CD4+ regulatory T cells

Regulatory T cells (Tregs) are a heterogeneous group of immune-inhibitory cells that suppress pathogenic immune responses primarily to self-antigens, but also against foreign antigens such as allergens and dietary antigens (18). Regulatory T cells are found in very low numbers in atherosclerotic plaques as compared to other chronically inflamed tissues (19, 20). This suggests that local tolerance is impaired in the plaques which could contribute to increased arterial inflammation. A protective role of regulatory T cells have been demonstrated in hypercholesterolemic mice deficient in co-stimulatory molecules important for regulatory T cell development as well as in mice which have been depleted of regulatory T cells through treatment with anti-CD25 antibody (22, 23). The athero-protective role of regulatory T cells is further substantiated by experiments in which regulatory T cells were eliminated in hypercholesterolemic mice through immunization with Foxp3-transfected dendritic cells, leading to regulatory T cell apoptosis and increased atherosclerosis (24). The anti-inflammatory cytokines IL-10, TGF-β and the more recently discovered IL-35 are mediators of regulatory T cell suppression. IL-10 and TGF-β have been shown to have anti-atherogenic effects in experimental atherosclerosis (25) (26) (27) (28). The translation of these experimental findings into clinical studies has been hampered by the difference in phenotypic definition of regulatory T cells in mice and humans. Whereas CD4+CD25+ T cells in mice almost exclusively are functional suppressor cells (29) this phenotype is not always associated with suppressor function in humans (30) complicating characterization of human Tregs.
Recently, Schuler et al. reported that the ATP converting enzyme CD39 was present on CD4^+CD25^+FoxP3^+ T cells with suppressor function distinguishing these from the CD4^+CD39^+CD25^FoxP3^- cells with no suppressor function (31). Since nearly all CD39^+CD25^ T cells were FoxP3^+, this constitutes a promising marker of functional suppressor cells in humans. Studies evaluating the clinical significance of Tregs in atherosclerosis are few and report conflicting results. Decreased levels of circulating Tregs have been reported in patients with acute coronary syndrome (32). However, a study by Ammirati et al showed that circulating Tregs were not correlated with carotid intima media thickness (33). Taken together these data show that more studies on human Tregs and atherosclerosis needs to be performed before it can be concluded whether Tregs can be used as a clinical marker of cardiovascular disease severity and/or risk.

4. CD8^+ T cells

The impact of CD8^+ T cells on atherosclerosis development is less well characterized than that of CD4^+ T cells. Whereas MHC class I deficient C57Bl/6 mice on high-fat diet develop increased atherosclerosis (34), CD8^+ T cell-deficient Apoe^−/− mice have similar lesion size as CD8-competent Apoe^−/− mice (6). A prerequisite for specific involvement in the disease process is that the CD8^+ T cells are present in atherosclerotic lesions. Indeed, CD8^+ T cells are found together with CD4^+ T cells in lesions of both mice (35) and humans (36). In advanced human lesions they even appear to be the predominating T cell type (36). A possible pathological mechanism of CD8^+ T cells is CTL killing of vascular cells which in turn would exacerbates inflammation. Evidence for involvement of this mechanism was reported by Ludewig et al. in a mouse model expressing beta-galactosidase specifically in vascular smooth muscle cells. Upon injection of beta-galactosidase specific DCs the mice developed arteritis and atherosclerosis mediated by CD8^+ T cells (37). More recently Escalante et al.
showed that vascular cells can attenuate CD8$^+$ effector functions (38). Human vascular ECs were shown to up-regulate CD155 in response to IFN-γ stimulation which in turn inhibited cytotoxic effects of activated CD8$^+$ T cells. However, such a regulatory mechanism may not withstand a strong cytotoxic response directed towards plaque specific antigens. We recently reported activation of CD8$^+$ T cells in response to diet-induced hypercholesterolemia in Apoe$^{-/-}$ mice and that in lymph nodes draining atherosclerotic lesions this activation precedes that of CD4$^+$ T cells (39). Accordingly, CD8$^+$ T cells that specifically recognize lesion antigens could be an important mediator of tissue destruction and chronic inflammation. Candidate antigens for CD8$^+$ T cell recognition are mimicry proteins of viral or bacterial origin. Jonasson et al. reported that patients with coronary artery disease had an expansion of CD8$^+$ T cells associated to cytomegalovirus infection (40). This notion is supported by observations that antibodies against cytomegalovirus cross-react with Heat shock protein 60 (HSP-60) and associate with atherosclerosis (41). Moreover, both CD8$^+$ and CD4$^+$ T cells isolated from human atherosclerotic plaque react with HSP60 and/or Chlamydia pneumoniae (42, 43) (44), implicating immune responses against these microorganisms in atherosclerosis.

5. CD8$^+$ regulatory T cells

Several cell markers have been proposed to define CD8$^+$ suppressor subsets. CD8$^+$ Treg markers largely corresponds to those for CD4$^+$ T cells and include FoxP3, CTLA-4, IL-10, GITR, IL-16, CD11c, TGF-beta, CD103, CD122 and PD-1 (45). One mechanism of T effector cell suppression by regulatory T cells is capture of IL-2 by a high expression of IL-2 receptors. Accordingly, IL-2R beta (CD25) has been proposed to characterize suppressor function also of CD8$^+$ T cells in mice (46) and humans (47). Interestingly, also the IL-2R alpha (CD122) is representative of a regulatory CD8$^+$ T cells. These cells have recently being reported to suppress colitis in mice (48) and to have a human counterpart in CD8$^+$CXCR3$^+$ T
cells (49). However, CD8⁺CD122⁺ T cells contain both regulatory and memory T cell populations. Dai et al. (50) proposed that programmed death-1 (PD-1) defines the suppressor function of CD8⁺CD122⁺ T cells, acting via IL-10 production. Interestingly, Gotsman et al. (51) found that PD-L1/L2/LDLR-deficient mice develop increased atherosclerosis characterized by an enhanced lesion infiltration of CD4⁺ and CD8⁺ T cells. Since the PD-ligands on APCs interact with PD-1, regulatory CD8⁺ T cells may have a protective role in atherosclerosis. Evidence supporting this possibility was recently reported by Zhao et al. who showed that adoptively transferred CD8⁺ T cells mediated the athero-protective effects of peptide immunization in Apoe⁻/⁻ mice (52).

6. Th17 cells

A population of IL-17 producing T cells (Th 17 cells) constituting a non-Th1/Th2 lineage has recently been described (53). Th17 cells are protective against fungal and bacterial infections, (54) but have also been implicated in atherosclerosis. However, their role in the disease process remains controversial because both pro-atherogenic (55-58) and protective effects (59) have been reported. Th17 cells have been shown to target collagen V exacerbating atherosclerosis (60) and Xie et al. suggested that an imbalance between Th17 and regulatory T cells may result in the progression of atherosclerosis (61). However, de Boer et al. did not observe Th17 cells in human plaques (62). Instead, the pro-inflammatory IL-17A/F was expressed by plaque neutrophils while SMCs, ECs and B cells produced the anti-inflammatory IL-17E. A correlation between IL-17 and neutrophils was also observed in patients with coronary artery disease (CAD) (63). The plasma level of IL-17 has been reported to correlate with that of IFN-γ in CAD patients (64). The same cytokine expression pattern was found in coronary artery-infiltrating T cells, indicating that these cytokines act synergistically to exacerbate atherosclerosis (64). Comparing the Th17/Th1 cell subsets in
peripheral blood of patients with acute coronary syndrome (ACS) Zhao et al found that patients had an increase in IL-17⁺/IFN-γ⁺ T cells, but not IL-17⁺/IFN-γ⁻ T cells, indicating that a subset of pro-inflammatory Th17 cells are activated in ACS (65). A recent report by von Vietinghoff et al. demonstrated that the athero-protective effects of the immunosuppressant mycophenolate mofetil (MMF) in Apoe⁻/⁻ mice is associated with a decrease in plasma and aortic IL-17, aortic T cell proliferation and IL-17A dependent accumulation of inflammatory peritoneal macrophages (66). Although the mechanism of Th17 suppression was not clarified, this study provides an interesting concept of specific IL-17 inhibition.

7. B cells

Th2 cell responses are typically associated with B cell activation, plasma cell differentiation and production of antigen-specific antibodies. B cells are present in atherosclerotic lesions, although they are less frequent than T cells (67). Early studies using splenectomised mice suggested that B cells have a protective role in atherosclerosis. The spleen is a major B cell reservoir and splenectomy leads to increased atherosclerosis which can be reversed by B cell replacement (68). It has also been shown that hypercholesterolemic mice deficient in B cells (through depletion of the gene encoding the μ-chain of the BCR, μMT) have more atherosclerosis (69). However, the role of B cells in atherosclerosis is now debated since recent data from two independent groups show that blocking B cells by treatment with an antibody against CD20 decreases atherosclerosis development in mice (70, 71). The concept of an athero-protective role of B cells is also based on the observations that some IgM and IgG species protect against atherosclerosis. Anti-oxLDL IgM antibodies have athero-protective effects (72), possibly through their capacity to bind oxLDL and thereby inhibit oxLDL uptake by macrophages and prevent foam cell formation (73). The role of oxLDL-specific IgG remains a matter of controversy because epidemiological studies have reported both positive and inverse associations with cardiovascular disease (74). One possible
explanation to these inconsistent results may be technical difficulties to standardize the antigens used in the ELISAs. In contrast, experimental studies more uniformly point to a protective role of antibodies. Intravenous administration of polyclonal IgG antibodies reduces plaque formation in hypercholesterolemic mice (75, 76), possibly through activation of inhibitory FcγIIb receptors (77). Antibodies against an aldehyde-modified peptide sequence in apolipoprotein B-100 have been produced by recombinant technique and been shown to inhibit the development of atherosclerosis as well as to induce regression of existing lesions in mice (78, 79). The ability of these antibodies to reduce atherosclerosis also in humans is presently being studied in a randomized clinical trial. Further support for the notion that latter type of antibodies are protective have come from clinical studies demonstrating an association between high levels of IgG autoantibodies to certain peptide sequences in apolipoprotein B-100 peptides and less atherosclerosis as well as lower risk for development of acute myocardial infarction (80, 81).

8. Antigen presenting cells in atherosclerosis

Dendritic cells (DCs) are antigen presenting cells (APCs) that present various types of antigens to T cells leading to initiation and maintenance of immune responses as well as inhibition of activation of T cells. Whether a DC will activate or inhibit T cells depends on its pattern of cytokine release and expression of cell surface co-stimulatory molecules. In general terms it can be said that activation of innate immune receptors, such as the Toll-like receptors (TLR), turns DCs into APCs that activate T effector cells, while antigen presentation that occurs in absence of TLR activation induces immunological tolerance. DCs are therefore a crucial link between innate and adaptive immune responses. Mouse DCs are characterized by expression of CD11c and are present in healthy mouse aortas, primarily in the adventitia (82). In atherosclerotic-prone parts of the aortic arch, mRNA expression of CD11c is elevated.
compared to the atherosclerosis-resistant parts. In contrast to healthy vessels the majority of the DCs in atherosclerotic aortas are found in the intima (83). Advanced human plaques have increased number of DCs compared to early plaques. Experimental models of atherosclerosis show that monocyte-derived DCs have an impaired potential to emigrate from advanced plaques compared to plaques from early stages of the disease (84). It has been reported that dyslipidemia impairs the ability of DCs to migrate into lymph nodes (85). The functional role of DCs in atherosclerosis is not fully understood but they potentially play an important role as APCs in T cell activation presenting plaque-derived antigens (86). It has recently been shown that the DC-derived chemokine CCL17 is present in both human and mouse atherosclerotic plaques and that CCL17 deficiency in hypercholesterolemic mice reduces disease development possibly through increased activation of Tregs (87). Modulation of the plaque DC phenotype represents a potential therapeutic target to decrease vascular inflammation and atherosclerosis development.

9. Potential atherosclerosis antigens

When present in atherosclerotic plaques, DCs take up and present plaque-specific antigens. Activated DCs will migrate to adjacent lymph nodes where they activate T cells specific for these antigens. They may also accumulate in the plaque and activate T cells inside the plaque. Modified LDL particles, including minimally modified (mm) LDL, oxidized (ox) LDL and peptides sequences derived from ApoB100 are considered to be important autoantigens in atherosclerosis. When DCs take up LDL-derived antigens in a normal artery wall this will occur in absence of TLR activation. As discussed above such DCs will become tolerogenic and do not induce the activation of antigen-specific Th1 cells. In contrast, if DCs take up such antigens in the inflamed environment of an atherosclerotic plaque increased expression of co-stimulatory factors will favor activation of antigen-specific Th1 cells. As many as 10% of all
T cells cloned from human atherosclerotic plaques react by secreting IFN-γ when stimulated with oxLDL indicating that oxLDL-specific T cells induce a Th1 response in the plaque (88). Taken together, these observations suggest that atherosclerosis is aggravated by an autoimmune Th1 response against oxidized LDL. Interestingly, the first studies to test this hypothesis by immunizing of hypercholesterolemic animals with oxLDL or ApoB100 derived peptide fragments unexpectedly resulted in reduced development of atherosclerosis demonstrating that protective immune responses also exists (89-91). This apparent contradiction has subsequently been resolved and it is now clear that Th1 responses against oxLDL indeed are pro-atherogenic and that immunization can shift these immune responses towards tolerance and generation of athero-protective antibodies (92, 93). An atherosclerosis vaccine based on ApoB100 derived peptide has been developed for human use and is expected to enter in to clinical studies relatively soon (93). Another potential approach for immune-modulation to prevent and treat atherosclerosis is so called DC vaccination. This means that autologous DCs are isolated and exposed to a specific antigen ex vivo under conditions that either favors subsequent Th1/ Th2 or Treg activation. Accordingly, vaccination of hypercholesterolemic mice with DCs that have been treated with IL-10 (to become tolerogenic) and pulsed with ApoB100 have been shown to decrease atherosclerosis development and increases Treg generation (94). In contrast, non-tolerogenic DCs pulsed with malondialdehyde modified LDL increased atherosclerosis development in Apoe−/− mice (95) further demonstrating that similar antigens can give rise to both protective and atherogenic immune responses depending on how they are presented. Heat shock proteins (HSPs) represent another family of autoantigens that have been implicated in atherosclerosis. HSPs are highly conserved proteins produced by cells in response to stress factors. Serum levels of HSP60 have been shown to be elevated in subjects with atherosclerosis and to correlate with carotid intima media thickness (96). Immunization of hypercholesterolemic
mice with HSP65 have yielded inconsistent results as early atherosclerosis was increased in one report (97) and decreased in another one (98). A possible explanation to the divergent results may be difference in the adjuvants used. Infectious agents such as *Chlamydia pneumoniae* have also been suggested to play a role in atherosclerosis. *C. pneumoniae* is a small, intracellular bacterium causing pneumonia that has been shown to infiltrate arteries through peripheral mononuclear cells infecting endothelial cells, vascular smooth muscle cells or monocytes/macrophages. Viable bacteria (99) and non-replicating aberrant bodies (100) has been identified in human atherosclerotic plaques. As T cells isolated from human atheroma respond to Chlamydia antigens (101) and pneumococcal vaccination decreases murine plaque formation (102) a molecular mimicry association between bacterial antigens and self-antigens such as ox LDL and HSPs has been discussed as a possible disease mechanism in atherosclerosis. However, the specific impact of *C. pneumoniae* infections on atherosclerosis progression in the long-term perspective still remains to be thoroughly characterized.

10. Challenges in transferring mouse data to humans

As has been outlined above there is convincing experimental evidence that the immune system plays a key role in modulating the atherosclerotic disease process. However, it should be kept in mind that the support for this concept rests almost entirely on studies performed in different mouse models. Also these experiments have been carried out on animals kept in sterile environment in which the general immunological challenge is unnaturally low as compared to humans. Although the immune systems of mice and humans share homology there are also some important differences. Mouse blood has a comparably high lymphocyte fraction whereas human blood is neutrophil-rich. In addition, humans have a more pronounced CD4+/CD8+ T cell ratio, while the Th1-Th2 differentiation is less clear (103).
Moreover, gender differences in lymphocyte numbers and sampling site should be thoroughly controlled to avoid introduction of misleading bias (104). As characterization of lymphocyte populations differ, cell surface markers coupled to a functional mechanism apparent in mice may not be functional in humans. Thus, translation of data from mice to man has to be performed with cautiousness in order to minimize misinterpretation.

11. Lymphocytes in development and quantification of atherosclerotic plaques – disparities in mice and humans

Experimental mouse models of atherosclerosis research are commonly based on gene defects and diets which generate several-fold higher plasma cholesterol level than in humans. This difference may cause a more rapid cholesterol accumulation and lesion development which is different from the slow build-up of human lesions that proceeds during decades in man (105). Differences in lipid metabolism may also affect immune responses differently in mouse and humans. Potentially, cell populations that respond to an immediate imbalance may dominate in mouse models of atherosclerosis, while the gradual development of human lesions involves different immune response. To overcome these problems mouse diets that only moderately increase cholesterol could be used but a likely downside of this approach is that only minimal atherosclerosis will develop. Additionally, genetically modified humanized mouse models could be used to better mimic the human immune response.

The location of plaque development represents another possible important limitation in the use of mouse models for atherosclerosis. Mouse lesions are usually studied at the aortic root where they first develop in mice whereas lesions rarely develop at this location in humans. Accordingly, lesion specific response to an intervention in mice may not be representative the human situation.
12. Concluding remarks and perspectives

The identification and characterization of the important role of the immune system in atherosclerosis has significantly increased our understanding of the disease process and also helped to identify novel targets for prevention and treatment of cardiovascular disease. There is large clinical need for such treatments because it appears difficult to achieve risk-reductions greater than 30-40% using the present risk factor intervention strategy. Novel treatments need to directly target the actual disease in the arterial wall and it is likely that modulation of plaque-specific immune responses represent a particularly promising approach to achieve this. Experimental animal studies have demonstrated the presence of both protective and atherogenic immune responses and evaluated candidate therapeutic strategies to specifically activate or mimic the protective immune responses. It has been clearly shown that the T cells are important effectors of both types of immune responses. The challenge for the future is to translate the knowledge obtained in experimental models into the clinic. The difficulties facing this process should not be underestimated. However, it should be kept in mind that the concept of atherosclerosis as a disease with partial autoimmune etiology is relatively new as compared to diseases such as type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis and that there is much to be learned from attempts to develop immune-based therapies for these diseases.

Disclosures

Jan Nilsson is signed as co-inventor on several patents on immune-modulatory therapies for atherosclerosis.
Figure legend

**Role of T cells in atherosclerosis.** T cells entering into an atherosclerotic plaque will be exposed to antigens presented by a dendritic cell (DC) or by a macrophage. If the antigen presentation is done by an activated DC CD4⁺ T cells will differentiate into Th1 cell secreting pro-inflammatory cytokines such as INF-γ and TNF-α, while presentation by a tolerogenic DC will result in formation of a suppressive regulatory T cell (Treg) secreting anti-inflammatory cytokines such as IL-10 and TGF-β. Activated CD8⁺ and Th17 T cells are also present in atherosclerotic plaques but their functional roles remains to be fully elucidated. Monocytes exposed to pro-inflammatory cytokines in the plaque will become activated and contribute to both plaque progression and plaque de-stabilization. Monocytes also differentiate into macrophages that take up oxidized (ox) LDL and develop into foam cells. Lipids and cellular debris released from dead foam cells contribute to the development of a necrotic core.
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