Cellular immunity, low-density lipoprotein and atherosclerosis: Break of tolerance in the artery wall

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Abstract
Atherosclerosis is a chronic inflammatory disease. Atherosclerotic plaques contain abundant immune cells that can dictate and effect inflammatory responses. Among them, T cells are present during all stages of the disease suggesting that they are essential in the initiation as well as the progression of plaque. Experimental as well as clinical research has demonstrated different T cell subsets, i.e. CD4+ Th1, Th2, Th17, and Treg as well as CD8+ and NKT cells in the plaque. Moreover, candidate antigens inducing T cell responses have been identified.

Knowledge about the pathological role of these cells in atherogenesis may lead to development of new therapies. This review provides an overview of the research field of cellular immunity in atherosclerosis. It emphasises the events and findings involving antigen specific T cells, in particular low-density lipoprotein-specific T cells.

Keywords
Atherosclerosis, immunity, inflammation, lipoproteins

Introduction
Atherosclerosis is a chronic inflammatory disease characterised by the formation of a plaque or lesion (also called atheroma) in the intimal layer of the vessel wall. The atherosclerotic lesion is a very complex tissue composed of oxidised lipids and lipoproteins, inflammatory cell infiltrates, areas of cell death and fibrosis (1). Immune cells are commonly found in the plaque during all stages of the disease, with a predominance of macrophages and a prominent infiltrate of T cells.

T cells play a central role in adaptive immunity. Several different subsets of T cells exist in the plaque, each having a distinct function which influences a lesion’s fate, e.g. the development of an unstable versus a stable plaque phenotype (Fig. 1). Elucidation of the precise mechanisms that lead to the aggressive responses of T cells in the plaque is a central objective in cardiovascular research. This article briefly summarises the evidence pertaining to antigen specific T cells, in particular low-density lipoprotein (LDL)-specific T cells.

Basic concepts of cellular immunity
T cells are involved in a wide range of immune mechanisms, i.e. host defense against viral, bacterial, mycobacterial and fungal pathogens, and in autoimmune and inflammatory disorders. T cells are specialised lymphocytes which can mediate antigen-specific immune responses. T cells can be divided according to phenotype (e.g. surface protein composition) and functional characteristics, including the release of cytokines, involvement in B cell help, or delayed-type hypersensitivity (DTH) reactions (2, 3) (Table 1).

T cells are commonly categorised by the expression of antigen receptors that are either alpha/beta or gamma/delta T-cell receptors (TCRs), co-expression of either one of the mutually exclusive co-receptors CD4 or CD8, and the pan-T cell marker CD3. Together, these molecules form the TCR complex that enables T cells to respond specifically to a linear peptide presented to the T cell when it is bound to self major histocompatibility complex molecules (MHC; and human leukocyte antigen (HLA) in humans). CD4+ T cells (T helper cells, Th) and CD8+ T cells (cytotoxic or cytolytic T cells, CTLs), can recognise an epitope in association with MHC class II or MHC class I molecules on the antigen presenting cells (APC), respectively (2, 3). The signal provided by the binding of the TCR to the peptide-MHC complex, along with the proper co-stimulatory molecules on the surface of the APCs and the T cells, will lead to activation and a broad range of responses, i.e. proliferation, release of soluble mediators and cytokines, and expression of surface molecules.

Another type of T cells called natural killer T (NKT) cells recognise complex lipid antigens such as complex glycolipids presented in the context of CD1 rather than MHC molecules on the APC. Recognition occurs through a limited set of TCRs and results in cytokine secretion similar to that of classical MHC restricted T cells (2, 3).

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T cells are present in the plaque

In the early 1970s, atherosclerosis was understood as a neoplastic process involving altered smooth muscle cells (SMCs), or alternatively a SMC hypertrophic lesion produced in response to injury, e.g. mechanical or chemical (4). However, the discovery that most lipid-laden foam cells in plaques were derived from macrophages challenged the established paradigm (5, 6). Since macrophages were already known as key players in the immune system, it seemed conceivable that other immunocompetent cells would also

Figure 1: Adaptive immunity and atherogenesis. Low-density lipoprotein (LDL) is trapped in the intima of the vessel wall and subjected to enzymatic/oxidative modifications. Modified LDL particles are taken up by macrophages that accumulate cholesterol and become foam cells. Modified LDL can additionally activate endothelial cells to over-express adhesion molecules, e.g. VCAM-1 and ICAM-1, and macrophages to release pro-inflammatory mediators, e.g. TNFα, IL-1β, MCP-1, LTB4, and proteolytic enzymes such as metalloproteinases, MMPs. Loaded with LDL and its constituent apolipoprotein ApoB100, macrophages and dendritic cells process and present ApoB100 peptides to CD4+ T helper cells via MHC class II molecules. Antigen presentation to CD4+ T cells triggers their activation, with ensuing release of a set of cytokines. Under such conditions, effector CD4+ T cells of the Th1 type release IFNγ and TNFα, two proinflammatory cytokines with known proatherogenic effects. Regulatory T cells (Treg) down-regulate inflammatory responses, at least partly by local release of TGFβ and IL-10. Antigen loaded DC (and also soluble antigens) transported in lymphatic vessels reach draining lymph nodes and/or spleen. There, naive T cells develop into effector T cells that can re-enter the bloodstream. When these cells reach the atherosclerotic lesion, they are recruited across endothelia expressing adhesion molecules, and re-activated by local APCs, which could amplify the lesion inflammatory response. In parallel, activated T cells may help B cells to mount antibody-specific responses. Soluble mediators released by activated T cells and macrophages can reduce the stability of plaque and induce expression of pro-thrombotic and pro-coagulant factors. This promotes plaque rupture and thrombosis.
be involved in the disease (7). The discovery of HLA in atherosclerotic plaques suggested a cellular immune response in the vessel wall (7); this notion was supported by the detection of T cells in human plaques (8, 9). Together, these findings put T cells at the centre of studies attempting to elucidate the immunopathogenesis of the atherosclerotic disease.

Within the T cell population of the human plaque, around 70% are CD4+, with the remaining being CD8+. Analysis of fatty streaks show that CD4+ T cells are frequent, both in clusters and as single cells. In advanced atherosclerotic plaques, CD4+ T cells are prominent in the fibrous cap and subendothelial space, whereas CD8+ T cells are sparse (10).

The majority of CD4+ T cells in the plaque express HLA-DR and interleukin-2 receptor (IL-2R; CD25), indicating an activated state of these cells (7, 11). Most of these CD4+ T cells are of the Th1 type (8), the major source of the pro-atherogenic cytokine interferon gamma (IFNγ) and also a major source of tumour necrosis factor (TNF), a cytokine with multiple pro-inflammatory and metabolic activities. Less common and incompletely understood, Th2 cells and/or their related cytokines have been identified in lesions (12–13). Existing as a minor population of T cells, Tregs can be found in plaques (14) and Th17 cells and their signature cytokine IL-17 are also present in these lesions (15, 16). Similarly, TCRγδ+ T cells occur in lesions throughout the development of atherosclerosis (17). Finally, NKT cells have been identified in lesions of experimental animals (18) and also in human atherosclerotic plaques (19–20).

### Role of different T cell subsets in atherosclerosis

Previous studies showed that absence of CD4+ T helper cells in mice leads to reduced atherosclerosis (21) and that transfer of purified CD4+ T cells from atherosclerotic mice to immunodeficient mice (Apoe−/−, scid/scid) accelerates lesion progression mirrored by increased levels of IFNγ (22). The importance of Th1 cells in atherosclerosis is demonstrated by the abrogation of T cell-specific transforming growth factor (TGF)β signalling. Apoe−/− mice with defective TGFβ receptor II display exacerbated Th1 responses that culminate in a dramatically increased atherosclerosis (23). Deletion of the Th1 transcription factor T-bet or deficiency in the Th1 signature cytokine IFNγ leads to reduction in plaque size and burden in hypercholesterolaemic mice (24, 25).

The role of Th2 cells in atherogenesis is unclear. Predicted to be protective against atherosclerosis, the effects of Th2 cells in atherogenesis are controversial and some studies in animal models suggest a pro-atherogenic role of these cells. Instead of increased lesions, deficiency in IL-4−/−, the prototypic Th2 cytokine, leads to less severe disease (26, 27). On the other hand, when the role of the Th2 cytokine IL-5 was evaluated in Ldlr−/− mice, a protective role for these cells was suggested (28). Of note, in vivo transfer of IL-10, a cytokine secreted by Th2 and Treg cells, into ApoE−/− mice shows anti-atherosclerotic effects (29, 30).

More recently, the role of the CD4+ T cell subtype Th17 has been evaluated in animal models of atherosclerosis. While deficiency in

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**Table 1: T cell subsets described in atherosclerosis.**

<table>
<thead>
<tr>
<th>T helper cells (CD4+) MHC class II restricted</th>
<th>Physiological role</th>
<th>Common markers</th>
<th>Characteristic cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th1</td>
<td>Immunity against intracellular pathogens</td>
<td>T-bet, IL-12, IL-18, and CCR3</td>
<td>IFNγ, TNFα, and LTα</td>
</tr>
<tr>
<td>Th2</td>
<td>Immunity against extracellular parasites</td>
<td>GATA3, DEC2, MAI-4r, IL-33r, CCR4, IL-17b, CTH2</td>
<td>IL-4, IL-5, IL-13, and IL-10</td>
</tr>
<tr>
<td>Th17</td>
<td>Immunity against different species of bacteria and fungus</td>
<td>RORγt, RORγt, CCR4, and CCR6</td>
<td>IL-17A, IL-17F, IL-21, IL-22, and CCL20</td>
</tr>
</tbody>
</table>

| Tregs (CD4+) MHC class II restricted          | Inducible Treg | Peripheral tolerance and immunoregulation | FOXP3, CD25, CTLA4, and GITR |
| Lymphocytic T cells (CD8+) MHC class I restricted | CTL | Immunity against viruses and cancer | CD8, EOMES, T-bet, and BLIMP1 |
| D4+CD28null T cells                          | No CD28, NK2G20, CX3CR1 | IFNγ and TNFα, perforin, and granzymes |
| γ6 T cells                                   | γ6 T cells | Mucosal immunity/barrier | γ6 TCR |
| Natural killer T cells                       | NKT | Peripheral tolerance, immunity against pathogens and cancer; Recognise lipid antigens | PZLF, NK1.1, CD56, CD1d restricted or not; Vσ14-Jcx18 (mouse); and Vσ24-Jcx18 (human) |

For more detailed information about the different T cell subsets involved in atherosclerosis read references: 1–3; 8; 10; 12–20; 22; 25–30; 36–39; 45; and 90.
IL-17A or its receptor, and also neutralisation of IL-17 by administration of an anti-IL-17 antibody all confer protection against atherosclerosis (31–34), administration of a recombinant IL-17 limited early lesion development in LDLR-deficient mice (35). Hence, these conflicting data suggest that further investigations are necessary to elucidate the role of the Th17 cell subset in atherosclerosis.

Analysis of T cell subsets in peripheral blood of coronary artery disease patients has revealed the expansion of an unusual subset of T cells, characterised by the lack of CD28 (a co-stimulatory molecule that binds CD80/86 on the surface of APCs) and therefore named CD4+CD28null T cells (36). Characterised by the production of high levels of IFNγ and TNFα, these cells have been suggested as important players in lesion progression and instability (37, 38). Furthermore, CD4+CD28null T cells have been shown to be expanded in patients with unstable angina and infrequent in patients with stable angina (36) suggesting these cells may play a direct role in the pathophysiology of plaque activation and atherosclerosis. Unfortunately, the absence of CD4+CD28null cells in mice limits research options.

While overall T cell responses aggravate atherosclerosis, certain T cell subsets, i.e. Tregs, may limit inflammation and counterbalance plaque formation. Many studies have already shown that different subpopulations of Tregs, i.e. FOXP3+ natural Tregs (nTreg; generated through selection in the thymus) or inducible Tregs (iTreg; generated from the conversion of naïve T cells in peripheral lymphoid tissues), and Tr1 cells (IL-10 induced subset of CD4+ T cells) can exert immunoregulatory and suppressive functions through production of the anti-inflammatory cytokines TGFβ and IL-10 (reviewed in [39]). In the context of atherosclerosis, it has been shown that antibody depletion of Tregs significantly increases atherosclerotic plaque size in a process involving TGFβ signalling (40). In agreement, blockade of TGFβ, loss of TGFβ signalling in T cells, and also deficiency in IL-10 accelerates atherosclerosis (23, 41, 42). Induction of Tr1 cells in Apoe-/− mice leads to significant reduction in atherosclerotic lesion size (43) and mucosal immunisation with an ApoB100 peptide fused to CTB (cholera toxin B subunit), a natural adjuvant implicated in mucosal tolerance, triggers Tr1 type Tregs which can inhibit pro-atherogenic T cell responses in vivo and attenuate atherosclerosis (44). Yet another T cell type called TCRγδ+ CD4 CD8− (double negative, DN T cells) has gained more attention lately. DN T cells can strongly suppress proliferation and cytokine production of highly activated effector T cells (45). However, whether these cells play a role in atherogenesis needs to be clarified.

The role of CD8+ T cells or CTLs has been only incompletely addressed in the context of atherosclerosis. Deficiency of CD8+ T cells in hyperlipidaemic Apoe−/− mice showed no major influence on atherogenesis (46). However, the parallel increase in lesion size and CD8+ T cell recruitment into lesions after stimulation with a CD8+ T cell stimulatory CD137 agonist antibody (47) suggests that these cells play a pathogenic role in the disease.

Interestingly, T cells and other cells can reciprocally modulate each others’ functions. In addition to macrophages and dendritic cells, the vascular endothelial cell is particularly effective as a T cell regulator and can also present foreign antigen to CD4+ T cells (48). Recent work shows that platelets, through their expression of chemokines, also regulate T cell activity (49). This may obviously be important during plaque activation and atherothrombosis.

**Break of tolerance**

An uncontrolled response to self-antigens leads to the development of auto-immune disease. Known as central tolerance, elimination of self-reactive T cells in the thymus are suggested as a major mechanism by which auto-reactive T cells are deleted during their ontogeny. In addition, control against auto-reactivity could be achieved by peripheral tolerance mechanisms, e.g. immunosuppressive activity of Tregs and possibly other cells (3).

Despite evolutionary selection of such “control systems”, autoimmune diseases can still develop. Modifications of self antigens could break tolerance leading to deleterious immune responses (3). Since many T cells are activated in the plaque, modification of self-antigens leading to T cell activation was proposed as a mechanism leading to plaque inflammation. Such a mechanism would be in line with the oxidation hypothesis for atherosclerosis.

**The oxidation hypothesis**

Lipid-laden macrophage foam cells are the hallmark of atherosclerosis. They are present in the intima of the vessel wall during all stages of atherosclerosis.

In their seminal studies on receptor-mediated endocytosis of lipoproteins, Brown and Goldstein proposed a molecular mechanism behind foam cell formation. Using acetylated LDL that is internalised by scavenger receptors distinct from the LDL receptor, they were able to convert macrophages into foam cells (5). However, acetylated LDL is synthetically derived and does not occur in vivo. Indeed, Henriksen et al. two years later discovered that endothelial cells have the potential to modify LDL, into a particle that is rapidly taken up by macrophages through the same scavenger receptor responsible for uptake of acetylated LDL (50). Finally, Steinbrecher et al. showed that incubation of LDL with endothelial cells led to oxidative modifications (51). These findings rejuvenated the oxidation hypothesis in atherogenesis.

Subsequent work showing the presence of oxLDL and oxLDL-derived molecules in the atherosclerotic plaque (52, 53) and in plasma (54) using monoclonal antibodies, and the demonstration that different biologically active molecules are generated when LDL undergoes oxidation (55) implicated oxLDL as a key player in atherogenesis.
oXLDL and atherogenesis

Several reports suggest that components of LDL particles can trigger vascular inflammation (56). LDL is a complex particle composed of a high-molecular-weight protein, apolipoprotein B-100 (ApoB100), neutral and polar lipids, and lipophilic antioxidants, e.g. vitamin E and β-carotene. When trapped in the intima of the vessel wall, LDL particles become susceptible to oxidative modification, caused by enzymes such as myeloperoxidase and lipoxigenases, and also by non-enzymatic oxidative reactions (57). Oxidation causes the cleavage of double bonds of fatty acid residues in phospholipids, cholesterol esters, and triglycerides generating reactive aldehydes and truncated lipids (55). Among the latter, modified phospholipids, such as lysophosphatidylcholine, oxidised 1-palmitoyl-2-araachidonyl-sn-glycero-3-phosphocholine (ox-PAPC) and trimethylamine N-oxide (TMAO), can initiate several innate immune responses such as activation of endothelial cells, macrophages, and NK T cells, and secretion of natural antibodies (28, 58–60). Such antibodies are mostly of the IgM isotype and produced by the B1 subtype of B cells. Natural antibodies are encoded in the germline genome and not dependent on immunoglobulin gene rearrangement. They have broad specificities, including both microbial and altered self antigens, but display low affinities and do not depend on T cell stimulation of the antibody producing B cell.

ApoB100 is also susceptible to oxidative modification, whereby, for example, malondialdehyde (MDA) adducts, 4-hydroxynonenal, and other molecular species form on lysyl residues of ApoB100 (61, 62). Some modification products could also mediate degradation of ApoB100 (61) and the release of bioactive peptides of ApoB100 that are capable of increasing vascular permeability (63).

oXLDL as candidate T cell antigen in atherosclerosis

Antibodies are formed against MDA-lysine (64) and other oxidatively generated epitopes of LDL particles (65). Such antibodies circulate in peripheral blood and are found in atherosclerotic lesions (53, 65–67). In contrast to the B1 cell-produced natural antibodies against oxidised phospholipids, antibodies to native and MDA-modified ApoB100 are mostly IgG molecules (68), implying activation of antigen specific T cells that promote isotype switching in the B cell. Previous research showed that TCR usage is highly restricted and strongly skewed, both in human plaques and those of Apoe/-/- mice (69, 70). These results indicate that an oligo-clonal expansion of T cells takes place in the plaque and suggests the presence of antigen-driven T cell proliferation in atherosclerosis.

In the early 1990s the first evidence suggesting apolipoprotein-derived antigens, in particular from oXLDL, emerged. Frostegård et al. showed in 1992 that exposure of peripheral blood mononuclear cells to oXLDL activates T cells, reflected in increased DNA synthesis and an increased expression of HLA-DR (71). Definitive evidence for LDL-reactive T cells from Stemme et al. showing in 1995 that T cells isolated from fresh human plaques could respond to oXLDL in vitro (72). Experimental data corroborated these studies, implicating oXLDL as the prototype antigen recognised by T cells in atherosclerosis (73–75).

T cells recognise native LDL instead of oXLDL

Despite the rapid advance in the identification of components derived from LDL and oXLDL which could induce innate and humoral immune responses, the lipoprotein-derived epitopes triggering T cell responses in atherosclerosis (peptide sequences) remained unknown.

In order to identify the possible oXLDL-derived epitopes, we generated T cell hybridomas from mice that were immunised with human oXLDL. Surprisingly, none of the hybridomas responded to oxidised LDL. Instead, the clones reacted to native LDL and purified ApoB100, and an inverse correlation was observed between the degree of oxidation and activation. Further characterisation of hybridomas showed that ApoB100 responding CD4+ T cells expressed a single TCR variable (V) β chain, TRBV31, with different Vα chains. Further, we showed that in vivo blocking of native ApoB100 reactive T cells significantly reduced atherosclerosis and plaque burden (76).

Several factors contributed to our lack of knowledge about LDL-specific epitopes driving T cell responses in atherosclerosis. For instance, ApoB100 is a large protein (> 500 kDa) with many hydrophobic parts that are difficult to prepare for cellular immunology studies; and oxidative changes induced to LDL in vivo may differ from those obtained in vitro. However, our recent data suggest that the role of oxidation as an inducer of T cell epitopes was overestimated. Re-evaluating previously published data, it can be noticed that T cell reactivity to non-modified LDL was registered for T cell clones from plaque as well as peripheral blood (71, 72). Indeed, native, unmodified ApoB100 epitopes could be triggers of pro- and anti-atherogenic T cell responses. Hence, Fredrikson et al. showed a large number of epitopes from ApoB100 that can induce an immune response in humans (77).

Autoreactive T cells should be kept in check by mechanisms of self-tolerance. As mentioned, it has been hypothesised that the risk for autoimmune to native LDL would be eliminated by clonal deletion of LDL reactive T cells in the thymus, i.e. by central tolerance. Hence, T cell autoreactivity to LDL would exclusively take place against neoepitopes generated by oxidation, i.e. oxidation-induced adducts on ApoB100 protein. However, our data demonstrate that T cells reactive to native LDL protein exist in lymph nodes and spleen of adult animals. Therefore, control must be exerted at the level of peripheral tolerance, with autoreactive, anti-ApoB100-specific T cells inhibited by immunosuppressive signals. Interestingly, recent studies of other autoantigens support the notion that “forbidden”, autoreactive T cell clones exist to a variety of endogenous protein antigens but are maintained in a non-reactive state by inhibitory signals such as those generated by regulatory T

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cells. This type of control appears to be particularly efficient for proteins secreted from the liver, the site of production of ApoB100 and LDL (78). The reasons for controlling autoreactivity peripherally rather than by clonal deletion are not fully understood but may reflect a need to maintain a broad enough T cell repertoire for host defense against all possible pathogens, even at the expense of potential autoreactivity.

The finding that native rather than oxidised LDL is an autantigen has already had implications for experimental therapy. Intravenous injection of tolerogenic dendritic cells (DCs) loaded with native LDL particle was found to significantly reduce atherosclerosis (79). In this experiment, DCs were made tolerogenic by treatment with the immunosuppressive cytokine, IL-10, loaded with purified ApoB100, and injected once into hypercholesterolaemic huB100/Ldlr−/− mice (mice transgenic for human ApoB100 and deficient for the LDL receptor). This treatment induced antigen-specific TRegs and dampened Th1 and Th2 immunity to ApoB100. A significant (70%) reduction of atherosclerotic lesions in the aorta occurred after one single injection of such DC, concomitantly with decreased CD4+ T cell infiltration in the plaque and signs of reduced systemic inflammation.

In line with previous work, circulating antibodies that recognise a large number of peptide sequences in ApoB100 have been identified (77, 80). Additionally, subcutaneous immunisation, as well as mucosal administration of native peptides from ApoB100, induce specific B cell and T cell responses which lead to protection against atherosclerosis (44, 81). More speculative, the recent data on native LDL and ApoB100 may partially explain why for the most part, clinical trials have failed to demonstrate a beneficial effect of antioxidant supplements on cardiovascular disease (CVD) morbidity and mortality (82).

Other T cell candidate antigens in atherosclerosis

Not only lipoprotein antigens but also other antigens found in the plaque were suggested to be able to activate T cells, e.g. beta-2 glycoprotein I (β2GPI), and as also heat shock proteins such as autologous and chlamydial HSP60 and mycobacterial HSP65 (reviewed in [83]). Among them, HSP65 is known to affect the development of atherosclerosis in hypercholesterolaemic animals, with reports of protective as well as pro-atherosclerotic effects (84–87). However, their importance and relative contribution to T cell responses during atherogenesis remain unclear.

Conclusions

Improvement in primary and secondary prevention has decreased CVD mortality rates (88). However, largely caused by atherosclerosis, CVD is still the main cause of death and one of the major causes of disability worldwide (89).

T cells can critically modulate atherosclerosis, by promoting macrophage activation and inflammation, inducing high-affinity antibody production, and modulating vascular tissue responses. Targeting T cells is attractive because of the antigen-specific, clonal nature of these cells. Thus, one could envisage designing a therapy that selectively targets T cell clones specific for a certain epitope, such as a peptide from ApoB100, without affecting any other part of the immune repertoire. “Global” blockade of T effector pathways and also activation of immunosuppressive regulatory T cell pathways have shown remarkable success in experimental approaches. It will now be important to refine these strategies and move forward to testing them in humanised models and eventually in clinical trials (90).

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Conflict of interest

None declared.
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