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Protective Autoimmunity in Atherosclerosis

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Abstract

Objective—Atherosclerosis is an inflammatory disease of the arterial wall. It is accompanied by an autoimmune response against ApoB100, the core protein of LDL, which manifests as CD4 T cell and antibody responses.

Approach and Results—To assess the role of the autoimmune response in atherosclerosis, the nature of the CD4 T cell response against ApoB100 was studied with and without vaccination with MHC-II restricted ApoB100 peptides. The immunological basis of autoimmunity in atherosclerosis is discussed in the framework of theories of adaptive immunity. Older vaccination approaches are also discussed. Vaccinating *Apoe*$^{-/-}$ mice with MHC-II restricted ApoB100 peptides reduces atheroma burden in the aorta by ~40%. The protective mechanism likely includes secretion of IL-10.

Conclusion—Protective autoimmunity limits atherosclerosis in mice and suggests potential for developing preventative and therapeutic vaccines for humans.

This article is based on the 2015 Russell Ross Memorial Lecturer in Vascular Biology, presented at the American Heart Association's Scientific Sessions Annual Conference, November 7-11, 2015, Orlando, FL. Atherosclerosis is an inflammatory disease of the arterial wall. This was first described by the Rudolf Virchow, the founder of cellular pathology, in 1858, who viewed atheroma as the result of chronic inflammatory disease of the arterial intima [1]. Electron microscopic evidence of monocyte association with atherosclerotic lesions was provided by Ross Gerrity [2-4]. Russell Ross, who originally had proposed the “response to injury model”, focused on endothelial cell damage and smooth muscle proliferation [5], later became a key proponent of the inflammatory nature of atherosclerosis [6, 7], and his work was instrumental in the widespread adoption of the inflammation hypothesis [8].

The role of low density lipoprotein (LDL)

The development of atherosclerosis requires levels of LDL cholesterol above those found in pre-agricultural societies[9], although the clinical definition of “elevated” LDL cholesterol has changed over the years. The blood level of LDL cholesterol is the best known biomarker for atherosclerosis and its adverse events [10]. LDL accumulates in lesions, can be oxidized

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(oxLDL) [11-13] and taken up by macrophages and dendritic cells [14, 15]. However, this uptake of LDL is not per se pro-inflammatory. When human blood monocyte-derived macrophages are exposed to oxLDL in vitro, they express a gene expression pattern that is more similar to that of dendritic cells than to that of MCSF-driven macrophages [15]. Indeed, dendritic cells in non-lymphoid tissues are mostly monocyte-derived whereas tissue macrophages are derived from embryonal precursor cells [16]. Most macrophages in the healthy mouse aorta can self-renew and are also embryonal-derived [17], but monocyte-derived cells enter the arterial wall under pro-atherogenic conditions. The macrophage populations in atherosclerosis are heterogeneous [18], and their origin [19] is actively being discussed [20]. When *Ldlr*$^{-/-}$ mice are challenged with a high fat diet, their peritoneal macrophages accumulate desmosterol and show an overall reduced level of inflammatory markers [21]. Although LDL and its modified forms are unlikely to drive inflammation directly, vascular inflammation is widely recognized as a major contributor to the atherosclerotic process [7, 8, 22-24]. Therefore, it becomes necessary to revisit the nature of the pro-inflammatory stimuli. Candidates include T cells [25], B cells [26] and direct activators of innate immune cells [27].

Immunological basis

An immune response is elicited when an antigen is recognized by T cells expressing a T cell receptor (TCR) that can bind the antigen with sufficient affinity. T cell-independent antigens, many of them carbohydrates or other non-peptide entities, will not be discussed here. A productive response requires co-stimulation by CD28 binding to CD80 or CD86 [28] and/or by certain TNF/TNF receptor superfamily members [29]. CD4 T cells recognize peptides presented by major histocompatibility complex (MHC)-II and CD8 T cells recognize peptides presented by MHC-I.

In 1961, Burnet proposed that T cells distinguish between self and non-self [30]. However, this is not plausible for CD4 T cell responses because of the way positive and negative selection operate: If no peptide from self at the time of T cell development (childhood) is presented in the thymus, the corresponding T cell will simply not mature (dies by neglect). Many thymic-derived regulatory T cells (Tregs) recognize peptide antigens from the host-associated microbiome, suggesting that microbiome-derived antigens may also be involved in T cell development [31]. Therefore, all T cells must recognize self (or microbiome-derived) peptides to develop. Negative selection eliminates T cells that bind the self-peptide/MHC complex with high affinity [32, 33]. However, negative selection is not completely efficient [34, 35], and the natural repertoire, i.e. the number of antigen-specific T cells present without vaccination or infection, is only slightly lower for peptides similar to self peptides than for foreign peptides [36]. The limited effectiveness of negative selection necessitates that self-tolerance is instead maintained by Tregs, whose TCRs bind self antigens presented by MHC-II with low to intermediate affinity [37]. This view is strongly supported by the observation that interfering with antigen presentation in knockout mice does not result in immunodeficiency as expected, but instead results in rampant autoimmunity in mice in which dendritic cells are eliminated by diphtheria toxin expressed under the CD11c promoter [38]. This means that dendritic cells (DCs) and other antigen-presenting cells are busy presenting self antigens to make Tregs to prevent autoimmunity. In fact, Tregs for organ-specific antigens are found in

the draining lymph node of each organ [39]. This concept is important for understanding how protective autoimmunity and vaccination against atherosclerosis work.

In 1989, the concept of self/non-self discrimination was modified because of findings that macrophages recognize non-self pathogen-associated molecular patterns (PAMPs) [40]. According to this view, a productive immune response requires engagement of such patterns by Toll-like receptors (TLRs) and other PAMP-recognizing receptors [41]. To be effective, vaccines require PAMP receptor stimulation, which is achieved by vaccinating with dead or attenuated infectious organisms that contain PAMPs, or by adding alum as an adjuvant, which stimulates inflammasome assembly and IL-1 production [42]. Related to the PAMP model, the "danger" model [43] was proposed, which suggests that an immune response will be made against an antigen only when this antigen is seen in the context of danger. Indeed, vaccinating with an MHC-binding peptide alone, without adjuvant or other help, does not result in an effective immune response.

A more current concept is that of sequential immune responses[44], recognizing that the primitive immune responses by parenchymal cells and by macrophages [45] were not superseded by the adaptive immune system, but are still very much active in all animals including humans. Some of the first animals, amoebas, are basically free-living macrophages [44-46]. When multicellular animals evolved, cellular functions became compartmentalized and macrophages became specialized [47]. Macrophages developed the ability to recruit and activate other newly appearing innate killer cells, such as neutrophils and innate lymphoid cells [48, 49]. The adaptive immune system did not appear until fish species evolved 450-500 mya [46].

Various helper CD4 T cells

Depending on the costimulatory molecules, PAMP recognition, and cytokine environment, naïve CD4 T helper (Th) cells become polarized. Th1 develop in response to IL-12 and IFN-γ, express the defining transcription factor T-bet (*Tbx21*) and secrete the signature cytokine IFN-γ. Th2 develop in response to IL-4, IL-5 and IL-13, express the defining transcription factor GATA-3 (*Gata3*) and secrete the signature cytokines IL-4, IL-5 and IL-13. Regulatory T cells (Tregs) develop in response to TGF-β, express the defining transcription factor FOXP3 (*Foxp3*) and secrete the signature cytokine IL-10; natural Tregs develop in the thymus and induced Tregs develop in the periphery. Tr1 cells do not express FoxP3, but produce IL-10. Th17 cells develop in response to IL-6, TGF-β and IL-1, express the defining transcription factor ROR-γt (*Rorc*) and secrete the signature cytokines IL-17A, IL-17F and IL-21. Follicular helper T cells (TFH) develop in response to CD40 and ICOS ligand, express the defining transcription factor BCL6 (*Bcl6*) and secrete the signature cytokine IL-21. Undoubtedly, more T-helper subsets remain to be discovered.

In mouse experiments, it was established that it is the macrophage and dendritic cell M1/M2 polarization that shapes the immune response (Th1/Th2), not the other way around [45, 47]. There is emerging evidence that "tolerogenic" DCs promote the differentiation of T cells to Tregs[50] or, in the absence of retinoic acid, to Th17. A regulatory macrophage subset (Mregs)

have formally been proposed based on in vitro experiments [51], supported by in vivo data in mice [52, 53]. The antigen-presenting cell promoting TFH may be a germinal center B cells [54].

Taken together, the current view of adaptive immunity [44] suggests that antigens will elicit an immune response based on the context of macrophage and dendritic cell polarization in which they "see" the antigen. It follows that it should be possible to elicit a Treg or other anti-inflammatory T cell response (Tr1, mixed) by vaccination. The challenge is to determine the correct conditions for the desired response. One of the benefits of vaccination is that the resulting Tregs, just like other T cells, are antigen-specific and will secrete their immunosuppressive cytokines like TGF-β and IL-10 in response to TCR ligation. Unlike blocking inflammatory molecules or cytokines, vaccination for atherosclerosis is therefore unlikely to impair host defense.

Autoimmunity in Atherosclerosis

Both the innate [55-59] and the adaptive immune systems [25, 56, 60-63] play important roles in atherosclerosis. Early experiments in severe combined immunodeficiency (SCID) or recombinase activating gene (Rag) deficient mice indicated a role of the adaptive immune system[62, 64-66]. However, in these mice, B cells, CD4, CD8 and γδ T cells are all absent, making these results difficult to interpret because each of these lineages can have pro- and anti-atherosclerotic effects. Much stronger evidence for a role of T cells comes from various adoptive transfer experiments [67, 68], reviewed in [63, 69, 70].

Autoimmune diseases are characterized by antibodies and T cells recognizing self antigens. In most autoimmune diseases, this is believed to be associated with increased pathology. By contrast, clinical epidemiology suggests that autoantibodies are NEGATIVELY correlated with atherosclerotic disease burden and clinical events. This is best documented for autoantibodies to (modified) low density lipoprotein (LDL) [71, 727336]. In humans, IgM (and in some studies IgG) antibodies to oxidized (ox) LDL [73] negatively correlate with lesion burden [72, 74], reviewed in [25]. Some studies suggest that much of the protective antibody activity resides in the IgM compartment [75]. Statin treatment increases levels of oxidized phospholipids and IgM antibodies against these in patients with atherosclerosis. These IgMs are thought to be beneficial [76]. Statins are thought to promote mobilization and clearance of oxidized phospholipids [77].However, opposite data (positive correlation between atherosclerosis and autoantibodies to modified LDL) was also reported [78]. One report suggested that autoantibodies against a peptide found in ApoB100 are inversely related to atherosclerosis [79]. Other studies found weak positive correlations between autoantibodies to modified LDL and cardiovascular disease [80] that were perhaps indirect [81]. Many, but not all [26], studies suggest that antibodies to (modified) LDL can be protective in mice [78, 82-84]. It is important to note that a positive correlation of antibodies and atherosclerosis does not necessarily mean the antibodies are proatherogenic. Recombinant antibodies to modified LDL were shown to induce regression of atherosclerosis in mouse models [85, 86], but interpretation of these data is limited by the fact that human, not mouse antibodies were infused. Adoptive transfer of IgM antibodies against phosphorylcholine reduced neointima formation in a vein graft model in mice [87], but effects on atherosclerosis were not reported. In a multicenter, randomized, double blind, placebo-controlled phase II study finished in

July of 2012, the safety, tolerability, and activity of intravenous MLDL1278A, a monoclonal antibody to oxLDL, was evaluated using FDG-PET/CT imaging to assess vascular inflammation (ClinicalTrials.gov Identifier: NCT01258907). No study results were posted, and no further trials are listed. The contradictory nature of these findings illustrates that the field of vascular immunology is very much in flux.

Witztum and his group hypothesized that autoantibodies to oxLDL work by reducing the uptake of modified LDL into macrophages [8889], and this has been proposed as an atheroprotective mechanism. Manipulations of B cells, which differentiate into antibody-secreting plasma cells, have shown both atheroprotective and pro-atherogenic roles of B cells. Splenectomy removes many B cells and exacerbates atherosclerosis [90], and mice lacking IL-5 show exacerbated atherosclerosis [90]. Conversely, depleting B cells with an antibody to CD20 was atheroprotective [26].

Protective autoimmunity

The concept of protective autoimmunity was first proposed in 1981, when vaccination with attenuated encephalitogenic T cell clones showed protection from experimental autoimmune encephalitis (EAE), a rodent model of multiple sclerosis (MS) [91]. Vaccination with peptides derived from the oligoclonal TCR sequences of encephalitogenic T cells was shown to deplete these T cells and curb EAE [92]. A similar approach was later used in a mouse model of atherosclerosis [93]. The term “protective autoimmunity” was coined by Michal Schwartz in 1999 [94]. Based on findings in models of traumatic brain injury [95-97], Schwartz proposed that vaccination with “safe” autologous peptide antigens would be protective under these conditions. Vaccinating mice with a homogenate of whole retinal proteins, interphotoreceptor retinoid-binding protein (IRBP) or S-antigen (retinal arrestin) was protective in a model of intraocular injection of aggregated β-amyloid or glutamate [98]. For this protective autoimmunity to be effective, a Th1-like response must be induced and a Treg response is counterproductive [99]. Neurodegeneration was augmented when Tregs were depleted and exacerbated when Tregs were injected into mice [98]. This surprising insight has led to efforts to develop a vaccine for glaucoma [100]. Encouraging results have been reported in rat models, but it not clear whether translational efforts were ever completed [101]. One hypothesis is that activated T cells provide useful growth factors and cytokines for neuronal repair [102]. So far, translational efforts have not been successful [103, 104]. The concept of protective autoimmunity has not been explored in tissues and organs other than the central nervous system.

Vaccination against atherosclerosis

Many vaccination schemes against atherosclerosis have been proposed [105]. Immunization of mice with modified LDL was shown to be protective, but the protection did not correlate with antibody titers, suggesting a possible T cell mechanism [106]. Witztum's approach was to immunize rabbits with malondialdehyde (MDA)-LDL, which represents an LDL particle that contains MDA adducts of the apoB100 protein. LDL eluted from arteries of rabbits and humans contains LDL modified with MDA (and other) adducts. The modified LDL is taken up by macrophages via scavenger receptors [107]. As mentioned above, autoantibodies to

oxLDL were also found in plasma of people and animals with atherosclerosis [11-13]. Vaccination with MDA-LDL resulted in reduced atherosclerosis [108]. The mechanism was proposed to be antibody-based inhibition of uptake of modified LDL by macrophages [25, 738889], but this was never rigorously tested. The various vaccination approaches are reviewed in [109, 11070, 111].

Nilsson's group identified peptides from ApoB100 that were recognized by autoantibodies in human plasma [112], and immunization with these peptides conjugated to bovine serum albumin (BSA) reduced atherosclerosis in *Apoe*$^{-/-}$ mice [113]. An intranasal vaccine was later developed based on one of these peptides known as p210 [114]. Animal experiments with intranasal and oral vaccines targeted to oxLDL [115, 116] or heat shock protein-60 [117118] have also been reported, but have not been developed clinically. The atheroprotection seen in these studies remains unexplained: First, p210 was conjugated to BSA, an allo-antigen, and the response to BSA alone was not tested. Second, because p210 does not bind I-A^{b} [63] and thus cannot elicit a p210-specific CD4 T cell response, its mechanism of action remains obscure.

By analyzing T cells from human atherosclerotic plaque, Hansson's group discovered that the immune response to oxLDL was (largely) MHC-II restricted [119]. They later immunized human ApoB100 transgenic *Ldlr*$^{-/-}$ mice with human oxLDL and showed that all derived T cell clones recognized sequences found in native ApoB100 [93], challenging the LDL oxidation hypothesis. The T cell clones were oligoclonal, and most expressed a single TCR β variable chain, TRBV31. Hansson hypothesized that the protective effect may be due to Tregs [120]. Tregs were elevated in mice immunized with the p210 peptide of ApoB100 [121], but antigen specificity of these Tregs was not tested. The hypothesis that Tregs are atheroprotective is indirectly supported by a recent study from Tabas' group, who showed that the net effect of inhibiting Toll-like receptor (TLR) signaling in dendritic cells (DCs) was pro-atherogenic, presumably by preventing the formation of Tregs [122]. In the natural course of atherosclerosis, the number of Tregs decreases [123] and that of effector T cells (Teff) increases over time [124]. Statins, the most widely used class of drugs to prevent atherosclerosis, have been reported to increase Tregs [125-127]. Some CD4 T cells in atherosclerotic plaques are known to express FoxP3, the defining transcription factor of regulatory T cells (Tregs) [128]. Since Tregs have been shown to be atheroprotective [67, 121, 129, 130], it is reasonable to suspect that vaccines may work by increased Tregs in atherosclerotic lesions or other locations. However, no such effects have been reported to date.

There is very strong evidence that T-helper 1 CD4 T cells (Th1) are pro-atherogenic. This was shown by loss of function experiments: knockout mice lacking interferon-γ [131] or the Th1 transcription factor T-bet [132] or the co-stimulatory molecules CD80 and CD86 [133]. Adoptive transfer of Th1 cells exacerbated atherosclerosis Conversely, knocking out the co-inhibitory molecules PDL1 and PDL2 exacerbated atherosclerosis, and PDL1 and 2-deficient dendritic cells were more effective at promoting T cell proliferation in vitro [134]. Similarly, ICOS-deficient mice had more atherosclerosis, suggesting that ICOS is needed for the expansion of Tregs[128]. Taken together, these data point to T cell-dependent pro- and anti-atherogenic mechanisms.

Vaccination with MHC-II-restricted ApoB100 peptides

Multiphoton imaging experiments showed that polyclonal CD62L^{lo} CD44^{hi} antigen-experienced CD4 T cells isolated from *Apoe*$^{-/-}$ mice interacted with antigen-presenting cells in the aortic wall identified by CD11c-YFP. In fact, the frequency and duration of these interactions was comparable to the frequency and duration of contacts between monoclonal CD4 T cells from TCR transgenic mice when antigenic peptide was added [135] (figure 1). This was specific, because the interaction was not seen when CD4 T cells were isolated from wild-type mice, or when naïve CD4 T cells from *Apoe*$^{-/-}$ mice were used. Remarkably, it was not necessary to add antigen. These experiments showed that the autoantigen and antigen-experience CD4 T cells were present in atherosclerotic mice. Since ApoB is a known autoantigen in atherosclerosis [111, 136], we next tested the ability of peptides from mouse Apo B in complete (1×) and incomplete (4×) Freund's adjuvant to prevent atherosclerosis in *Apoe*$^{-/-}$ mice, a widely used model of atherosclerosis. The peptides were selected for binding to mouse MHC-II (I-A^{b}, binding affinities ~10 nM). Vaccination with each of the peptides, but not irrelevant control peptides, reduced aortic en face lesion size by 35-60% [137]. We saw no change in the number of FoxP3+CD25+ Tregs in lymph nodes or spleens, but significantly increased expression of IL-10 mRNA induced in aortas of immunized mice. The number of CD11c+CD103+RALDH+ dendritic cells (DCs), a phenotype that is consistent with DCs inducing peripheral tolerance, was expanded in aortas of immunized mice. We conclude that vaccination with MHC-II restricted peptides can protect from atherosclerosis in a relevant mouse model. The mechanism may involve IL-10, but the type and location of immune cells producing IL-10 remain to be discovered. It is also possible that other cytokines may contribute. As expected, the antibodies induced by vaccination recognize the antigenic peptide with perfect specificity. However, these antibodies do not recognize native LDL or modified LDL [137], suggesting that the antigenic peptides are not accessible to antibodies on the intact lipoprotein. This makes it unlikely that autoantibodies play a role in atheroprotection after peptide-based vaccination, but this has not been formally investigated yet. These efforts have encouraged studies to translate this mouse work aimed at developing an MHC-II-restricted peptide-based atheroprotective vaccine for humans.

Conclusion

The view of the role of the immune system in atherosclerosis has evolved over the last few decades. In immunocompetent animals and patients, a complex autoimmune response always accompanies the development of atherosclerosis. This response is fundamentally T cell-driven and can be pro- or anti-atherogenic. Circulating antibodies to LDL and other atherosclerosis antigens may be potential biomarkers, but evidence for the causal involvement of antibodies in atherosclerosis is scant. The field of vascular immunology is currently in flux and many of the classical paradigms of immunology and vascular biology are being challenged by new findings. Evolving new concepts may form an improved basis for the development of vaccination approaches aimed at curbing atherosclerosis.

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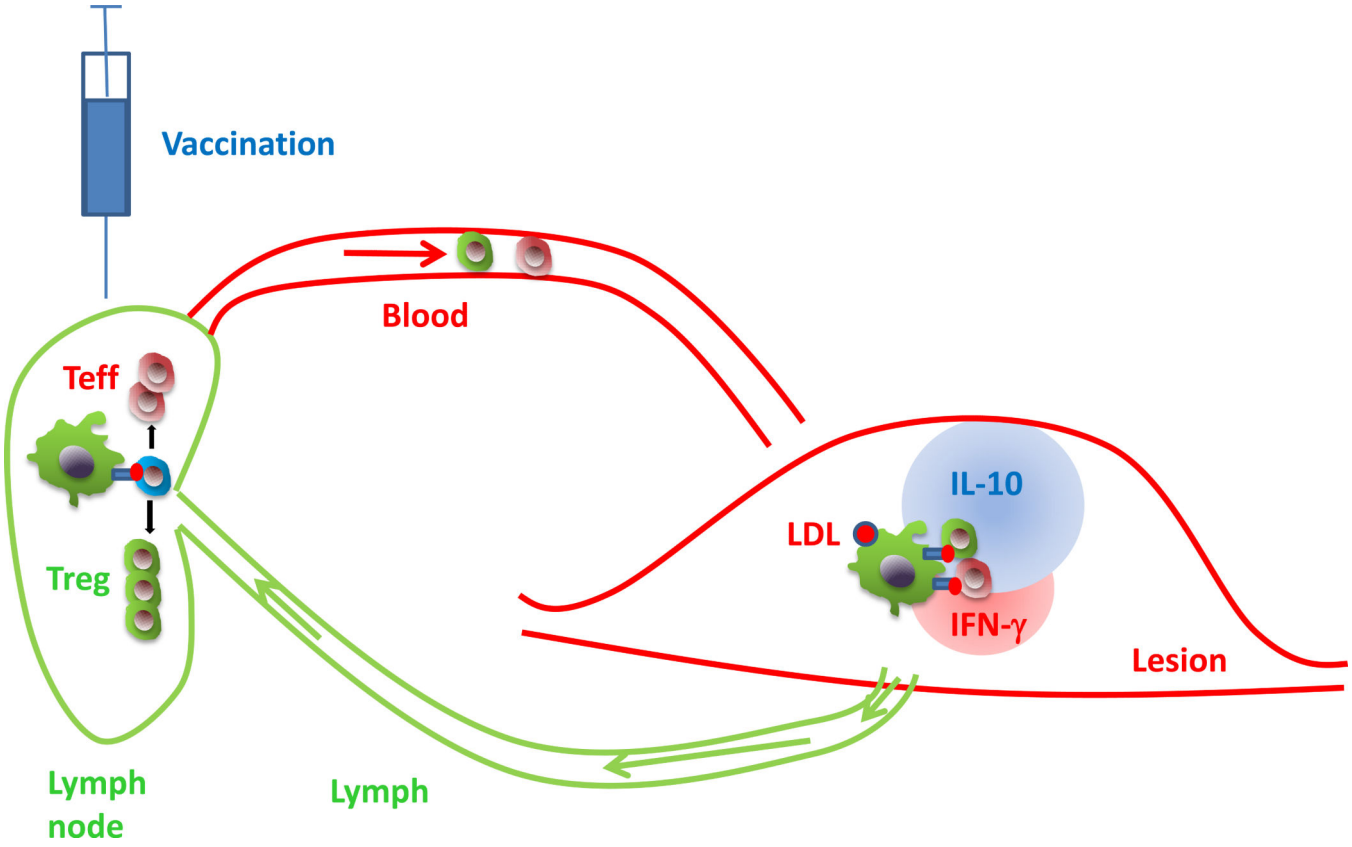

Figure. Protective autoimmunity in atherosclerosis

Antigen-containing LDL (red ball) is taken up by DCs (green) in the atherosclerotic lesion, and ApoB100 peptides (red) are presented on MHC-II (blue). Antigen-laden DCs leave the vessel wall via lymphatics (green) and enter the draining lymph node, where they encounter naïve CD4 T cells (blue). If their TCR recognizes the MHC-II-bound ApoB100 peptide, the CD4 T cells expand, acquire homing receptors and become antigen-experienced effector T cells (red) and Tregs (green). This expansion can be boosted by vaccination (syringe). The antigen-experienced CD4 T cells home back to the atherosclerotic vessel wall and encounter the ApoB100 peptide bound to MHC-II again (recall response). This triggers secretion of anti-inflammatory cytokines like IL-10 (blue) and pro-inflammatory cytokines like IFN-γ (red).