REVIEW

Helper T cells and atherosclerosis: the cytokine web

S G Baidya, Q-T Zeng

There is growing evidence regarding the importance of inflammation in the pathogenesis of atherosclerosis and its ultimate progression to the clinical syndromes. Recently there has been an increasing interest in the role of helper T (Th) cells in atherosclerosis. The Th cells act with the macrophages and the dendritic cells via the various cytokines in bringing about a variety of changes thus leading to the progression of atherosclerosis. Atherosclerotic lesions have been seen to have increased expression of type 1 helper T (TH1) cells together with increased levels of the Th1 related cytokines. It is mainly the cytokines involved with Th1 functioning that seem to show a prominent effect, with the whole process centred around interferon gamma, making it seem like every pathway and the cytokines involved lead to a final common pathway of interferon gamma secretion; the increase or decrease of which dictates the progression of atherosclerosis and its final manifestation as the clinical syndromes.

In this review we discuss ways in which the Th cells, in particular the type 1 subset of Th cells, interact in the process of atherogenesis and the web of cytokines involved around the functioning of these cells in the regulation of the immune response in atherosclerosis.

IMMUNOLOGICAL BACKGROUND: T HELPER CELLS AND THEIR SUPPORTERS

The immune response of the body to an antigen is a complicated process with the involvement of multiple cells and a whole range of adhesion molecules and cytokines. Antigen presenting cells (APCs), like the dendritic cells (DCs) and macrophages, process antigens and present them to specific immune system cells through major histocompatibility complex (MHC) expression on the cells surface. T cells are activated only if they could recognise the antigens presented by the APCs through MHC. The APCs also produce cytokines that help in their interaction with the T cells. Activation of T cells, in particular the Th cells, cause the production and release of cytokines and further leads to the activation of Th cells themselves to proliferate and differentiate into effector cells playing a part in the development of cellular or humoral immune responses.

Th cells have an important role in the regulation of the immune response. Th cells develop in the thymus gland together with cytotoxic T cells. T cells bearing the CD4 molecule as their specific surface antigens become Th cells. Those bearing the CD8 molecules become cytotoxic T cells. T cells in the immature stage when not exposed to antigens are known as naive T cells. These naive T cells recognise antigens presented by the APCs such as the DCs, macrophages, and the B cells. These APCs phagocytose antigens, process them, and then present them with the MHC class II molecule. Th cells then recognise the antigens in the context of MHC class II molecules. Th cells are classified functionally into Th1 and Th2 subtypes on the basis of difference in cytokine production. The Th1 subset shows specific production of interferon gamma, interleukin (IL) 2, and tumour necrosis factor (TNF) x and plays a greater part in the cellular immunity. Th2 cells, which mainly

The multifactorial causation of chronic diseases makes them a challenge for therapeutic interventions and atherosclerosis is no exception. Atherosclerosis as a process is today known to begin even during fetal development especially in fetuses of hypercholesterolaemic mothers. With both the genetic and environmental factors acting in concert, the disease process can have severe consequences. The world of science has come up with a whole list of factors regarded as risk factors for the start and the progression of atherosclerosis ending up in its clinical manifestations. Within the past few years there has been growing evidence regarding the importance of inflammatory mechanisms in the pathogenesis of atherosclerosis and its ultimate progression to atherosclerosis related diseases, particularly coronary artery diseases (CAD). Fatty streak, the earliest manifestation of atherosclerosis is an inflammatory lesion consisting of macrophages and T lymphocytes. Studies further suggested a role for CD4+ helper T (Th) cells in atherosclerosis. These Th cells are important regulators of the immune system, and when activated secrete multiple cytokines that modulate the immune response and control the secretion of cytokines from other cells, like the macrophages. Evidence further shows that among the CD4+ T cells it is the Th helper 1 (Th1) subtype that seems to be dominant in atherosclerosis.

Abbreviations: Th, T helper; IFN, interferon; CAD, coronary artery disease; DC, dendritic cell; APC, antigen presenting cell; MHC, major histocompatibility complex; IL, interleukin; TLR, toll-like receptor; SMC, smooth muscle cell; LPL, lipoprotein lipase; LDL, low density lipoprotein; oxLDL, oxidised low density lipoprotein; ACAT, acyl coenzyme A cholesterol acyltransferase; CRP, C reactive protein; HSP, heat shock protein; ECM, extracellular matrix; TNF, tumour necrosis factor
produce IL4, IL5, and IL10, on the other hand promote humoral immunity. Two other important cell types and their cytokines are closely interwoven with Th cell functioning; the antigen presenting DCs and monocyte derived macrophages. DCs are potent regulators of the immune system that show their functional activity by processing and presenting antigens to other cells, mainly T cells. DC precursors (blood monocytes) undergo transendothelial migration and phagocytosis and with the help of coactivators like GM-CSF and IL4 form DCs. Distinct subsets of DCs are involved in the differential regulation of the Th1/Th2 balance. Type 1 DCs (DC1) originate from DC1 precursors. These myeloid-like DC1 stimulate Th1 cells, with expression of CD154 (CD40L). This gives an outlet for the cell mediated immune response. Lymphoid-like type 2 DCs (DC2) arise from DC2 precursors. It is the Th2 cells that are stimulated by the DC2, which further help B cells to produce antibodies. Macrophages are an essential part of the immune defences in a host and they act as the most important agents for host defences in primitive organisms. With evolution there has been a shift in importance from innate to adaptive immune response with the T lymphocytes taking increasing control of the immune system. Nevertheless, macrophages still are important players in the immune response, acting in concert with the other agents, especially the T lymphocytes, by producing various cytokines. The relation can be to such an extent that the macrophages have been seen to show varied responses (M1 or M2 type responses) that might be able to differentially influence Th1/Th2 or other types of immune responses. Apart from the other functions of macrophages it is the formation of foam cells in the atherosclerotic lesions that makes them a prominent cell type in atherosclerosis.

**IMPORTANCE OF THE INNATE IMMUNE SYSTEM**

Although the adaptive immune system forms a more specialised form of defence mechanism, the response to an antigen leading to clonal expansion of the lymphocytes takes at least a few days to result in the generation of effector cells. It is becoming more evident that the innate immune system, which acts through antimicrobial peptides, phagocytes, and the alternative pathway, has a much more important role than was thought before. In contrast with the adaptive immune system, the innate immune system starts its effector functions immediately after coming in contact with the antigens.

Innate immune system mainly acts via recognition of a range of molecular patterns (bacterial lipopolysaccharides, peptidoglycans, lipoteichoic acids, bacterial DNA, double stranded RNA, and the mannans) associated with the pathogens. The receptors in the innate immune system that recognise such molecular patterns are known as “pattern recognition receptors”. Such receptors are mainly present on the professional antigen presenting cells such as macrophages and DCs. A group of such receptors, the endocytic pattern recognition receptors, are found on the surface of macrophages and promote the attachment of microorganisms to phagocytes leading to their subsequent engulfment and destruction. The resulting peptides are then presented with the MHC on the surface of the macrophages. In recent years another group of receptors belonging to the toll family has been seen to play important parts in immune responses. Toll-like receptors (TLRs) are named for the homologues of the toll receptors in drosophila. TLRs induce the activation of NFKB pathway that further leads to the expression of a range of cytokines and costimulatory molecules important for the activation of the adaptive immune system, mainly to drive the naïve Th cells towards the IFN gamma producing Th1 subtype. Activated NFKB has been detected in the different cells in atherosclerotic lesions and experimental studies have shown the role of TLRs and NFKB in atherosclerosis, thus supporting the concept of the innate immune system also taking part in the immune mechanisms involved in atherogenesis.

**MAJOR INTERLEUKINS INVOLVED WITH THE T HELPER CELL RESPONSE**

A whole range of identified cytokines have been shown to play a part in atherogenesis, some with pro-atherogenic properties while others having antiatherogenic properties. Here we will discuss in brief only a few cytokines, the interleukins related to the Th cell response in atherosclerosis.

IL2, mainly secreted by Th1 cells, is an autocrine stimulator of Th1 cell differentiation and proliferation resulting in a T cell shift towards Th1 phenotype. It was found to be expressed in atheroma and suggested to have a pro-atherogenic effect in experimental models. The serum concentrations of IL2 were found to be increased in patients of ischaemic heart diseases further suggesting its role in atherosclerosis related diseases. IL4, a Th2 cell interleukin, is considered to be potentially pro-inflammatory and pro-atherogenic while having some antiatherogenic effects as well. It thus shows pleiotropic effects giving rise to a complex function. Some examples of the pro-atherogenic effects are up regulation of p-selectin, 15- lipoxigenase, and VCAM-1. The antiatherogenic actions are the inhibition of smooth muscle cells proliferation and inhibition of macrophage adhesiveness. Uyemura et al however showed the expression of IL4 in atherosclerotic plaques to be limited, casting doubts over the pro-atherogenic roles in vivo.

IL10 is a prototype anti-inflammatory interleukin produced mainly by activated T cells, B cells, and macrophages. It was described in mice as a Th2 cytokine that selectively inhibited IFN gamma and GM-CSF production by the Th1 cells, while in humans IL10 was seen to affect the cytokine production from both Th1 and Th2 cells. IL10 also has been seen to down regulate the pro-inflammatory roles of macrophages. A potential modulatory role for IL10 in the progression of atherosclerosis was seen in murine models, and a possible protective role of IL10 against atherosclerosis was further seen. Significantly low concentrations of IL10 have been seen in patients with CAD. IL12 is a proinflammatory interleukin mainly produced by the macrophages, B cells, and DCs. It promotes Th1 cells functioning while causing suppression of Th2 cells functions. Apo-E deficient mice when given with IL12 showed progression of atherosclerosis with a change in the levels of oxidised LDL suggesting a pro-atherogenic role for IL12. IL12 further acts in synergy with IL18 for the production of IFN gamma by the T cells. Furthermore, cross regulatory roles for IL12 and IL10 have been shown suggesting antagonising action of each to the biological effects of the other. Increased serum concentrations of IL12 have been seen in patients with CAD. IL18, earlier also known as the IFN gamma inducing factor, is another pro-inflammatory interleukin with multiple biological functions. It is mainly produced by macrophages. IL18 by its actions on T cells, specifically the Th1 subtype, induces IFN gamma production. IL18 has further been seen to induce production of IFN gamma by the macrophages as well as the human vascular smooth muscle cells. It has been seen to be expressed in atherosclerotic plaques and studies suggest a pro-atherogenic role for it. The serum concentrations of IL18 are increased in patients of acute coronary syndromes and seem to correlate with the severity of myocardial dysfunction.
T HELPER TYPE 1 CELL DOMINANCE IN ATHEROSCLEROSIS

Most of the T lymphocytes present in the atherosclerotic plaques both in humans1 as well as in animal models2 were seen to be CD4+ T cells. These CD4 bearing Th cells have a central regulatory role in immune and autoimmune responses and are further classified mainly into Th1 subtype and Th2 subtype according to the cytokines they secrete. Studies in experimental models show a pro-atherogenic role for Th1 cells and an antiatherogenic role for Th2 cells.3 4 5 Th cells present in the atherosclerotic lesions showed properties of Th1 phenotype with increased levels of IFN gamma and IL2 whereas the Th2 cytokines IL4, IL5, and IL10 were found in only modest quantities.5 The cells in the lesion also produce the Th1 stimulatory cytokines IL12 and IL18.3 4 5 Both DCs and activated macrophages by means of the IL12 they produce interact with the Th1 cells leading to the production of IFN gamma and IL2. IL12 further acts in synergy with IL18 mainly produced by the activated macrophages, resulting in production of IFN gamma and thus cause a shift towards Th1 type cytokine production.3 4 5 The Th2 cytokines IL4 and especially IL10 are mainly of anti-inflammatory nature both of which can act to inhibit the production of IFN gamma by Th1 cells. IL10 and IL12 have cross regulatory roles whereby IL10 inhibits the functions of Th1 cells and IL12 inhibits Th2 cell functions.3 4 5 IL4 and IL10 were only detected in a minority of the atherosclerotic plaques studied compared with the finding of IFN gamma in all the atherosclerotic lesions suggesting the suppressed activity of Th2 cells.3 4 5 All these findings together with the increased levels of Th1 related cytokines such as IL12, IL18, and IFN gamma seen in patients of CAD and the decreased levels of Th2 related cytokine IL10 seen in the same groups as discussed earlier point towards a dominant role of Th1 cell activity in atherosclerosis and its progression. This summarises the role of cytokines involved in Th cell response leading to progression of atherosclerosis.

IFN GAMMA AND ATHEROSCLEROSIS

There seems to be a complex interwoven relation between a multitude of cytokines arising from DCs, macrophages, and Th cells that includes both the type 1 as well as the type 2 cells (fig 1). Centred within this complex web seems to be IFN gamma, secreted mainly by Th1 cells as well as by macrophages and smooth muscle cells (SMCs).3 4 5 Cytokines like IL12 and IL18 secreted by macrophages and DCs mainly in combination induce the production of IFN gamma. IFN gamma in turn activates macrophages, which produce proinflammatory cytokines, oxygen radicals, and metalloproteinases. IFN gamma directly inhibits Th2 cells proliferation and creates a positive feedback loop by up regulating the production of IL12 receptors.3 4 In recent years IFN gamma has been postulated to have a significant role in atherogenesis as well as its complications. Proliferation of the vascular SMC is one of the hallmarks of atherogenesis and IFN gamma has been seen to be important regulator of SMC proliferation.4 5 IFN gamma has been reported to increase vascular cell adhesion molecule-1 on endothelial cells4 5 and MHC class II antigens on macrophages and smooth muscle cells4 5 thus implicating its role in the immune response. One of the most important effects of IFN gamma in atherogenesis is related to cholesterol metabolism and foam cells formation. IFN gamma may play a part by affecting lipid accumulation in atherosclerotic lesion by inhibiting macrophage lipoprotein lipase (LPL) at least in part via a reduction of LPL synthesis.4 5 The enzyme cholesterol 27-hydroxylase, which promotes the removal of cholesterol from the arterial walls and acts as a defence against atherogenesis, has been seen to be down-regulated by IFN gamma.4 5 IFN gamma further inhibits cholesterol efflux in the macrophages mediated by down-regulation of ATP binding cassette transporter 1 (ABC1)4 5 and the stimulation of acyl coenzyme A: cholesterol acyl-transferase (ACAT),4 5 shifting the balance towards lipid accumulation and formation of foam cells, ultimately thus the progression of atherosclerosis. A further role of IFN gamma in the formation of foam cells was seen through its ability to up regulate the CXCL16/SR-PSOX,4 5 a scavenger receptor for phosphatidylserine and oxidised LDL (SR-PSOX), seen to be expressed in atherosclerotic lesions that mediate internalisation of oxidised low density lipoproteins (oxLDL) and phosphatidylserine coated particles such as apoptotic bodies.4 5 A direct relation between IFN gamma
and atherosclerosis has been shown in animal models where enhancement of the disease process in apolipoprotein E-/-mice occurred on administration of IFN gamma.53

An atherosclerotic plaque becomes vulnerable when the fibrous cap gets thinned out with a large lipid core, decrease in the SMC content, and extensive inflammatory cells (mainly macrophages) accumulation occurs within the plaque together with endothelial denudation or dysfunction.54 IFN gamma can lead to the plaques being vulnerable via its effects on extracellular matrix synthesis.55 Furthermore, it is a potent regulator of cathepsin S, a serine protease, expressed in vascular smooth muscle cells,56 and cathepsin S has been seen to play a part in the breakdown of extracellular matrix in atherosclerosis.57 Possible effects of IFN gamma in the induction of inducible Ca2+/calmodulin independent NOS (iNOS)58 further suggests its role in endothelial dysfunction. Plaque instability, regarded as a gateway to the consequences of atherosclerosis, has an important contribution from the accelerated apoptosis of the macrophages.59 IFN gamma has also been seen to induce the apoptosis of THP1 macrophages.59 The possible proatherogenic effects of IFN gamma discussed in this review are summarised in the box.

THE OTHER CYTKINES IN LINE AND CRP

One important multifunctional cytokine worth mentioning is TNFα, which is mainly produced by the macrophages although also seen to be produced by the Th1 cells. This cytokine, which is one of the most potent proinflammatory cytokines, has also been suggested to have a role in atherosclerosis and its progression.60 The Th1 cells together with the action of IFN gamma on the macrophages causes secretion of IL1. IL1 in itself is a key mediator of inflammation. Increased IL1 concentrations have been seen in human atherosclerotic plaques.61 It promotes the inflammatory response in atherosclerosis through a range of effects.62 IL1 can also cause the release of IL6, a secondary proinflammatory cytokine, from the SMCs.63 IL6 is also secreted by other cells like lymphocytes and macrophages64 and is an IL found in atherosclerotic plaques.65 It has an important role in the stimulation of CRP synthesis by the liver.66 CRP has also been seen to be synthesised locally within the atherosclerotic plaques.67 Previously believed to be an innocent by product of immune activation in atherogenesis, it is now known to have a role in stimulatory effects on many cells in the plaque,68 increased expression of chemotactic factors,69 and increased expression of MMP1,70 which have recently led to the possibility of CRP of being a proinflammatory factor in atherosclerosis and its progression. It thus seems that CRP too, in many ways participates in the web formed by the many cytokines in the process of atherosclerosis. Figure 1 shows the pathways by which the cytokines and CRP act to increase atherogenesis.

ROLE OF ANTIGENS AND IMMUNE RESPONSE IN Atherosclerosis

Evidences for activation of both the innate and the adaptive immune systems in atherosclerosis have lead to the search for the possible antigens involved in the initiation of these responses. Multiple antigens have been studied and proposed as the culprits, including oxLDL, heat shock proteins (HSP), and exogenous pathogens. oxLDL is a modified form of lipoprotein that has been seen to be present in both animals and humans.71 Studies have shown evidence regarding oxLDL as being an important antigen in the immune response in atherosclerosis.72 Further evidence showed that oxLDL can have an important role in cellular immune responses in atherosclerosis driving the activation of IFN gamma secreting Th1 cells73 and that it might play a part in antigen driven T cell response leading to plaque instability.73 One other possible autoantigen having a role in atherosclerosis is the HSP. These are proteins produced in large amounts by injured cells and act to limit denaturation of other cellular proteins. These proteins also act to start the autoimmune processes in many inflammatory disorders. In animal models HSP-65 has been seen to have a role in the process of atherogenesis.74 It is possible that these proteins have a role in innate immunity via activation of TLR4.75 Studies in human subjects show a possible role of HSP in early atherosclerotic disease.76 The presence of HSP60 antibodies was further seen to be associated with disease severity in CAD.77 Several studies have given evidence that show a link between atherosclerosis and the presence of some pathogens. One such pathogen, Chlamydia pneumoniae, has been detected in atherosclerotic lesions78 79 and that the presence of this pathogen can lead to the activation of T cells within the atherosclerotic lesions.80 There are certain groups of viruses that have been postulated to play a part in atherosclerosis. Among them the herpes simplex virus and cytomegalovirus have been found in the atherosclerotic lesions.81 Further studies are needed to establish the direct cause-effect relation between atherosclerosis and the pathogens.

CLINICAL SIGNIFICANCE

Cytokines as inflammatory markers

With increasing evidence for the role of inflammation in atherosclerosis and its progression to the clinical syndromes, clinicians are looking towards possible biomarkers for risk stratification of the atherosclerotic CADs. Multiple cytokines and acute phase reactants have been studied having possible parts to predict cardiovascular events in healthy men as well
as for risk stratification in established cases of CAD. Most widely studied is the acute phase reactant, CRP. Studies have shown the significance of CRP in risk prediction for cardiovascular events in healthy people \(^5\) \(^6\) \(^7\) and also in established CAD.\(^8\) \(^9\) The secondary proinflammatory cytokine, IL6, is another such marker that has been seen to be of value in prediction of adverse events in patients with established CAD.\(^10\) \(^11\) With the Th cells having a central regulatory role in the immune processes and thus also in the inflammatory response in atherosclerosis, the cytokines related to the functioning of these cells can become possible candidate biomarkers. The concentration of IL10, a Th2 cytokine having anti-inflammatory properties, has been seen to be decreased in the acute coronary syndromes than that in stable CAD. Furthermore, lower concentration of IL10 in unstable CAD was associated with increased risk for cardiovascular events.\(^12\) One cytokine recently described as an important proatherogenic factor is seen to be a potential candidate biomarker for risk prediction in CAD is IL18. Blankenberg et al showed its value in prediction of cardiovascular events in healthy people\(^13\) \(^14\) and in established CAD.\(^15\) With continued introduction of new drugs and the availability of a range of therapeutic modalities for ischaemic cardiovascular events in healthy people and in established CAD.\(^16\)\(^17\) \(^18\) Inhibition of atherogenesis in murine models has been achieved with interleukin binding protein IL18bp, thus suggesting that inhibition of IL18 can lead to increased plaque stability.\(^19\) Direct blocking of IFN gamma functioning by targeted disruption of the IFN gamma receptors led to an inhibition of atherosclerosis by 60% in apoE-knockout mice.\(^20\) It has further been seen that induction of a regulatory T cell type 1 (Tr1) response that inhibits Th1 responses by inducing a bystander immune suppression limited the development of atherosclerosis in apolipoprotein E-knockout mice.\(^21\) Despite the strong potential of the cytokines maintaining the Th cell balance as a therapeutic target in atherosclerosis, it must not be forgotten that they also have wide ranging functions within the immune system in general. As an example, IL2, IL12, and IL18 involved mainly with the Th1 response have been implicated as potent antitumour agents and their inhibition may increase the risk of neoplasia. The Th2 cytokines on the other hand have a role in the pathogenesis of autoimmune diseases and prolonged up-regulation of the Th2 cytokines might lead to the development of a variety of autoimmune disorders. Difficulties in therapeutic interventions targeting the various cytokines involved are thus attributable to the pleiotropic effects of the cytokines in the immune system as a whole. The aim thus if any regarding the therapeutic intervention should be short term one or a localised use at the atherosclerotic lesion.

CONCLUSION

With recent developments in the field of immunology, there has been a great progress in the study of Th cell differentiation. Furthermore, with increasing evidence regarding the role of inflammation in atherosclerosis and further progression to CAD, the cytokines surrounding the Th cells have been seen to play an important part in orchestrating the inflammatory response. An increase in the proinflammatory cytokine series and a compromise in the production of antiinflammatory cytokines give evidence for the shift in the Th1/Th2 balance with increased role for Th1 dominance in atherosclerosis as well as the acute coronary syndromes. Among the Th1 cytokines themselves, IFN gamma seems to lie at the epicentre sharing a cause-effect relation with the progression of atherosclerosis. Further studies need to be conducted to confirm the causal relation between the various cytokines surrounding the Th cells and the occurrence of ACS together with the severity of the disease process, and to develop the related cytokines as inflammatory markers and therapeutic targets.

Therapeutic implications

With increasing evidence for the significant role of inflammation and the cytokines involved together with the Th1/Th2 imbalance in atherosclerosis and its progression to CADs, the cytokines can become potential therapeutic targets. IL10 has been tried in experimental models and has been seen to have a protective role against atherosclerosis.\(^22\) Furthermore, IL10 gene transfer in apolipoprotein E- knockout mice resulted in a reduction in atherosclerotic area and macrophage infiltrated area, and a decrease in plasma IFN gamma level.\(^23\) Inhibition of atherogenesis in murine models has been achieved with interleukin binding protein IL18bp, thus suggesting that inhibition of IL18 can lead to increased plaque stability.\(^24\) Direct blocking of IFN gamma functioning by targeted disruption of the IFN gamma receptors led to an inhibition of atherosclerosis by 60% in apoE-knockout mice.\(^25\) It has further been seen that induction of a regulatory T cell type 1 (Tr1) response that inhibits Th1 responses by inducing a bystander immune suppression limited the development of atherosclerosis in apolipoprotein E-knockout mice.\(^26\) Despite the strong potential of the cytokines maintaining the Th cell balance as a therapeutic target in atherosclerosis, it must not be forgotten that they also have wide ranging functions within the immune system in general. As an example, IL2, IL12, and IL18 involved mainly with the Th1 response have been implicated as potent antitumour agents and their inhibition may increase the risk of neoplasia. The Th2 cytokines on the other hand have a role in the pathogenesis of autoimmune diseases and prolonged up-regulation of the Th2 cytokines might lead to the development of a variety of autoimmune disorders. Difficulties in therapeutic interventions targeting the various cytokines involved are thus attributable to the pleiotropic effects of the cytokines in the immune system as a whole. The aim thus if any regarding the therapeutic intervention should be short term one or a localised use at the atherosclerotic lesion.

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