Role of cytokines in cardiovascular diseases: a focus on endothelial responses to inflammation

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ABSTRACT

Complex cellular and inflammatory interactions are involved in the progress of vascular diseases. Endothelial cells, upon exposure to cytokines, undergo profound alterations of function that involve gene expression and de novo protein synthesis. The functional reprogramming of endothelial cells by cytokines is of importance especially in patients with chronic vascular inflammation. The intercellular network of dendritic cells, T-lymphocytes, macrophages and smooth muscle cells generates a variety of stimulatory cytokines [e.g. TNF-α (tumour necrosis factor-α), IL (interleukin)-1, IL-6 and IFN-γ (interferon-γ)] and growth factors that promote the development of functional and structural vascular changes. High concentrations of proinflammatory cytokines increase oxidative stress, down-regulate eNOS (endothelial nitric oxide synthase) bioactivity and induce endothelial cell apoptosis. Chemoattractant cytokines [e.g. VEGF (vascular endothelial growth factor), TGF-β1 (transforming growth factor-β1) and IL-8] are important regulators of inflammation-induced angiogenesis and are directly modulated by nitric oxide. This review will focus on the vascular mechanisms orchestrated by cytokines and summarizes the current knowledge concerning the contribution of cytokines to cardiovascular diseases.

INTRODUCTION

Cytokines are small soluble proteins secreted by one cell that can alter the behaviour or properties of the cell itself or of another cell. Cytokines can be grouped into families by structure as follows: the interferons, the chemoattractant cytokines (chemokines), the members of the TNF (tumour necrosis factor) family, the haematopoietins [IL (interleukin)-2, IL-3, IL-4 etc.), the EGF (epidermal growth factor) family [EGF and TGF (transforming growth factor)-α], the β-trefoil family [FGFs (fibroblast growth factors)] and the cysteine knots (including TGF-β, VEGF (vascular endothelial growth factor) and PDGF (platelet-derived growth factor)]. Most cytokines are glycoproteins which are secreted by cells using classical secretory pathways. Many genes encoding cytokines can give rise to a variety of variant forms of cytokines by means of alternative splicing, yielding molecules with slightly different but biologically significant bioactivities. In many cases, the expression patterns of different forms of cytokines or of members of a cytokine family are only partially overlapping, suggesting a specific role for each factor [1–3].

Key words: cardiovascular disease, cytokine, endothelial response, inflammation.

Abbreviations: ACE, angiotensin-converting enzyme; ADMA, asymmetric dimethylarginine; AT1, angiotensin II type 1 receptor; CAD, coronary artery disease; CI, confidence interval; COX, cyclo-oxygenase; CRP, C-reactive protein; CSF, colony stimulating factor; DMARD, disease-modifying antirheumatic drug; EGF, epidermal growth factor; EC, endothelial cell; FGF, fibroblast growth factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; IL, interleukin; IL-1ra, IL-1 receptor antagonist; IFN-γ, interferon-γ; LD, low-density lipoprotein; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor κB; NO, nitric oxide; NOS, NO synthase; eNOS, endothelial NOS; NYHA, New York Heart Association; O2•−, superoxide anion; PDGF, platelet-derived growth factor; RA, rheumatoid arthritis; RR, risk ratio; SLE, systemic lupus erythematosus; TGF, transforming growth factor; Th1, T-helper 1; TNF, tumour necrosis factor; TNFR, TNF-receptor; VEGF, vascular endothelial growth factor.

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Cytokines affect their target cells by binding to specific receptors, triggering the receptor to deliver signals to the cell on which it is expressed. This causes protein kinases associated with the cytoplasmic domains of cytokine receptors to become active by phosphorylating each other [4]. The intracellular signal transduction pathways of cytokines ultimately activate transcription factors such as NF-κB (nuclear factor κB), Smad (sma- and mad-related proteins) and STAT (signal transduction and activators of transcription), and act as gene-regulatory proteins [1,3,5,6]. Recently, the negative-feedback regulation of these pathways has been identified [3].

Cytokines are important regulators of haematopoiesis, immune, inflammatory and vascular reactions. Both stimulatory and inhibitory cytokines play crucial roles in the function of ECs (endothelial cells), smooth muscle cells, dendritic cells, macrophages and T-cells. This review summarizes the current knowledge concerning the pivotal contribution of cytokines in the process of atherogenesis, angiogenesis and heart failure.

**CYTOKINES EXPRESSED BY VASCULAR CELLS**

The endothelium is the maestro of the circulation, a major determinant of vascular tone (blood flow), leucocyte and thrombocyte adhesion, and smooth muscle cell proliferation [7]. When the endothelium becomes diseased, the synthesis and bioactivity of vasodilators [such as NO (nitric oxide), prostacyclin and endothelium-derived hyperpolarizing factor] is reduced and the balance tips in favour of endothelium-derived vasoconstrictors, such as endothelin and thromboxane [7]. An alteration in the redox balance in ECs leads to increased \( \text{O}_2^{•−} \) (superoxide anion) production and oxidative stress. \( \text{O}_2^{•−} \) degrades NO to reduce its bioactivity. As a result of the impairment in endothelial function, there is a reduction in coronary blood flow, enhanced adhesion of inflammatory cells and smooth muscle cell proliferation [7]. All these alterations contribute to an acceleration of the atherosclerotic process.

ECs are not only targets but, responding to proper stimulation, contribute to cytokine secretion themselves [8–10]. Human endothelium is capable of expressing a broad spectrum of pro- and anti-inflammatory cytokines, including IL-1, IL-5, IL-6 and IL-8, MCP-1 (monocyte chemotactic protein-1), CSFs (colony-stimulating factors), GM-CSF (granulocyte/macrophage CSF), G-CSF (granulocyte CSF), M-CSF (macrophage CSF), PDGF, VEGF and FGF (Figure 1; for review, see [10]).

Endothelial activation, as an early step in vascular dysfunction, can be induced by several signal transduction

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**Figure 1  Potential sources and targets of cytokines in atherogenesis**

Antigen-presenting dendritic cells may initiate vascular inflammation by activating T-cells. Subsequently, activated endothelial cells can produce an extraordinary number of biologically relevant molecules that induce or inhibit replication and protein expression of smooth muscle cells, T-cells and macrophages. Macrophages importantly contribute to smouldering immune activation and atherogenesis by releasing a variety of growth modulators and chemokines, exerting profound effects on vascular ECs and smooth muscle cells. CC, chemotactic chemokine; IGF-1, insulin-like growth factor-1; INF, interferon; SMCs, smooth muscle cells.
mechanisms [9]. Endotoxin, TNF-α, IL-1β, viruses [such as CMV (cytomegalovirus)] and bacterial pathogens (such as Chlamydia pneumoniae and Helicobacter pylori) can activate NF-κB, which binds to specific sites on the promoter regions of target genes. This, in turn, modulates the endothelial synthesis of proinflammatory cytokines (IL-1, IL-6 and TNF-α) and chemokines [IL-8, MCP-1 and RANTES (regulated upon activation, normal T-cell expressed and secreted)] [2]. Importantly, conditions of high immune activation (e.g. chronic rejection after transplantation) may lead to cardiac cytokine release in vivo [11–13].

In addition to ECs, all vascular cells can act as producers of, or responders to, cytokines (see Figure 1). Dendritic cells (the major regulators of cellular immune response), macrophages and T-cells are commonly observed in early vascular lesions. Cytokines released by these vascular cells may activate new gene expression in ECs and smooth muscle cells that induce the capacity to perform new effector functions, such as leucocyte recruitment and activation or initiation of intravascular coagulation [2,9,10,14].

Inflammation may promote thrombosis further by acting both locally and systemically. Local mechanisms include the cytokine-stimulated expression of tissue factor by ECs and macrophages. Indirectly, inflammation may act locally to induce thrombosis by weakening the fibrous cap of the atheromatous plaque, leading to plaque rupture. Moreover, inflammation can affect systemic haemostatic activity by IL-6-mediated stimulation of hepatocytes to produce acute-phase reactants [15]. These include certain coagulation factors, such as increased levels of fibrinogen and plasminogen activator inhibitor, which induce a prothrombotic state. An enhanced CD40 ligand–CD40 interaction also promotes thrombosis by enhancing tissue factor expression in macrophages and through the direct regulation of endothelium procoagulant activity [16]. Intravascular fibrinolysis induced by tissue-type plasminogen activator may contribute to atherosclerosis by inducing P-selectin and platelet-activating factor, as well as to plaque rupture by activating metalloproteinases [15].

In this way, both circulating and resident cells can participate in cell-mediated immune reactions as donors and recipients of cytokine signals.

**ECs AS TARGETS OF CYTOKINE ACTIVITY: IMPACT ON VASOMOTOR DYSFUNCTION**

Aoki et al. [17] first reported that TNF-α selectively diminished the ability of arterial rings to relax to the endothelium-dependent vasodilator acetylcholine, indicating that cytokine activity may be associated with endothelial vasodilator dysfunction. Iversen et al. [18] have performed a detailed analysis of the potential human cytokines modulating arterial vascular tone. They found that the cytokine stem cell factor G-CSF and erythropoietin relaxed, whereas TNF-α, IL-6 and IL-10 induced contraction of, human arterial segments [18]. Cytokine-induced relaxation or constriction were inhibited by blockers of endothelial-derived NO and endothelin respectively [18].

Reports in patients with congestive heart failure have shown a correlation between plasma levels of IL-6 and TNF-α and impaired endothelium-dependent vasodilation of the brachial artery and vein [19,20].

Bhagat and Vallance [21] demonstrated that the proinflammatory cytokines TNF-α and IL-1β (but not IL-6) induced transient and reversible endothelial dysfunction in humans. We have shown [12] that cytokines might be released from the transplanted heart and that coronary endothelial dysfunction is associated with specific cytokine patterns. Whereas high transcardiac levels of soluble TNF-αR1 (TNF-α-receptor pp55) seem to be protective of endothelial function (probably by inactivating circulating TNF-α), high IL-6 and soluble IL-2R (IL-2-receptor) levels were associated with impaired microvascular function [12].

Several TNF-α-mediated mechanisms may cause endothelial dysfunction [22,23]. Importantly, TNF-α activates NF-κB with subsequent expression of endothelial adhesion molecules [24–26]. Adhesion and transmigration of different leucocyte subsets are stimulated after TNF treatment of ECs (for review, see [27]). In this regard, TNF-α enhances endothelial adhesion and vascular invasion of dendritic cells [28], the most potent antigen-presenting cell type. Subsequently, dendritic cells may activate T-cells and monocytes/macrophages which aggravate vascular inflammation and cytokine production. High concentrations of TNF-α have been demonstrated to directly decrease levels of eNOS (constitutive NOS (NO synthase)) mRNA in human ECs [29] and are able to promote the production of oxygen-derived free radicals by neutrophils, vascular smooth muscle cells and ECs [23]. TNF-α is a potent stimulus of iNOS (inducible NOS) in ECs in combination with IFN-γ [(interferon-γ) from activated Th1 (T-helper 1) cells]. Moreover, TNF-α has been shown to reduce degradation of ADMA (asymmetric dimethylarginine; the endogenous inhibitor of NOS) by down-regulating the enzyme dimethylarginine dimethylamionohydrolase which degrades ADMA [30]. Therefore TNF-α might decrease endothelial NO bioactivity by several pathways. Importantly, ECs transfected with eNOS (endothelial NOS) reduce monocyte–endothelial binding after TNF-α stimulation [31]. Finally, TNF-α-mediated oxidative stress may directly cause apoptotic cell death of the endothelium and up-regulates the death signalling protein, Fas/apo-1/CD95, a cell-surface-borne protein belonging to the TNFR (TNF-receptor) superfamily [23]. Recently, Napoli et al. [32] provided the first evidence that mildly oxidized LDL
(low-density lipoprotein)-induced apoptosis of human coronary ECs involves TNFRs.

These data suggest that ECs are the major targets of cytokine signals derived from different vascular cells. Cytokine exposure to the endothelium modulates vascular inflammation by inducing endothelial activation. Long-term exposure of ECs to proinflammatory cytokines accelerates oxidative stress and apoptosis, and promotes leucocyte extravasation and thrombosis. Accelerated inflammation, vascular dysfunction and plaque growth interact and stimulate each other. Finally, the activity of this cellular network determines the course of the underlying vascular disease (Figure 2).

**ROLE OF CYTOKINES IN CARDIOVASCULAR DISEASES**

Growing evidence supports the role of local and systemic inflammation as a common pathophysiological mechanism in different cardiovascular diseases, including congestive heart failure or CAD (coronary artery disease). Indeed, it is well established that atherosclerosis is an inflammatory disease [33].

A variety of plasma markers have been shown to predict future cardiovascular risk. Of these markers, the acute-phase reactant CRP (C-reactive protein) has been the most extensively studied, and there is now robust evidence from primary prevention cohorts and among patients presenting with acute coronary syndromes that elevated CRP levels predict future cardiovascular events [34]. IL-6 is the main hepatic stimulus for CRP. Elevated plasma levels of IL-6 and TNF-α were detected consistently in patients with stable or unstable angina and myocardial infarction [11,35–37]. A direct relationship exists between the number of circulating and local inflammatory cells and the severity of the coronary syndrome. In the atherosclerotic plaque, cytokines are released from macrophages, dendritic cells, T-cells, ECs and smooth muscle cells (IL-1β, TNF-α, IL-6, IL-8 and MCP-1). The unstable plaque is characterized by infiltrating Th1 cells, producing IFN-γ, IL-2, IL-6 and TNF-α [38]. However, it should be noted that cytokines such as IFN-γ can induce arteriosclerotic changes in the absence of detectable immunocytes by acting on vascular smooth muscle cells to potentiate growth factor-induced mitogenesis [39]. Whatever the source, the proinflammatory cytokines aggravate plaque instability by inhibiting extracellular matrix synthesis and promoting smooth muscle cell apoptosis. IL-8, a CXC chemokine produced by neutrophils, smooth muscle cells and ECs, induces the migration and proliferation of ECs and smooth muscle cells. Elevated levels are found in atherosclerotic plaques, suggesting that it may be an important mediator of angiogenesis in this tissue, contributing to plaque formation. In agreement, VEGF enhances atherosclerotic plaque progression [40] and PGF (placental growth factor), a member of the VEGF family, has been shown to be an independent biomarker of adverse outcome in patients with suspected chest pain [41].

In patients with unstable CAD, circulating IL-6 is a strong independent marker of increased mortality and identifies patients who benefit most from a strategy of early invasive management [36]. Recently, serum IL-18 levels were identified as a strong independent predictor of death from cardiovascular causes in patients with CAD regardless of the clinical status at admission [42]. Moreover, elevation of soluble CD40 ligand levels indicates an increased risk of cardiovascular events and identifies a subgroup of patients at high risk who are likely to benefit from antiplatelet treatment with glycoprotein IIb/IIIa antagonists [43]. Intriguingly, a proinflammatory shift in the profile of vascular cytokine expression may contribute to the aging-induced phenotypic changes in coronary arteries, promoting the development of ischaemic heart disease in the elderly [44]. In aged vessels, expression of TNF-α, IL-1β, IL-6, IL-6Ra (IL-6-receptor α) and IL-17 genes was significantly increased compared with young vessels [44].

Anti-inflammatory cytokines exerting inhibitory effects on vascular cells include TGF-β, IL-10 and IL-1ra (IL-1-receptor antagonist) [45]. In this regard, elevated serum levels of IL-10 are associated with a more favourable prognosis in patients with acute coronary syndromes [46]. Recently, activin A, a member of the TGF-β superfamily, has been shown to have anti-inflammatory potential in angina patients [47].

Proinflammatory cytokines (IL-1, IL-6 and TNF-α) can exert negative inotropic effects and, therefore, directly modulate cardiac contractility [48]. In fact, elevated circulating and/or myocardial levels of IL-6, TNF-α and
The inflammatory system may modify the risk of coronary disease and environmental factors. Future trials are needed to provide some evidence that alterations in the genetics of pleiotropy, variations with age, selection due to the high lethality of the disease and interactions with other genes and environmental factors. However, the degree of natural variability in circulating cytokine levels in patients with heart failure underlines the need for prospective clinical trials [52].

Obesity also leads to a proinflammatory and prothrombotic state that potentiates atherosclerosis. Pathways leading directly from adiposity to the genesis of dyslipidaemia and hypertension have been elucidated. Recent findings imply a role for fat-derived ‘adipokines’, including TNF-α, IL-1β, IL-6, IL-8, IL-10, TGF-β and adiponectin, as pathogenic contributors or protective factors [53,54]. Importantly, the release of IL-6 (a major inducer of CRP) from isolated human adipocytes can be stimulated by IL-1β [55]. Peripheral actions of leptin, expressed by adipocytes, include EC and T-cell activation, with subsequent stimulation of proinflammatory cytokines [56]. It is, however, unclear to what extent adipose tissue contributes quantitatively to the elevated circulating levels of cytokines in obesity and whether there is a generalized or local state of inflammation [54].

POLYMORPHISMS IN CYTOKINE AND ADHESION MOLECULE GENES IN CAD

Epidemiological studies have investigated the association between CAD and polymorphisms of TNF-α and TNF-β, TGF-β1 and TGF-β2, and IL-1 and IL-1ra genes [57]. The majority of studies conducted showed no significant association between genetic polymorphisms in cytokines and coronary atherosclerosis, but the data currently available are somewhat controversial [57]. The associations between candidate gene polymorphisms and atherosclerosis are complex as a consequence of pleiotropy, variations with age, selection due to the high lethality of the disease and interactions with other genes and environmental factors. Future trials are needed to provide some evidence that alterations in the genetics of the inflammatory system may modify the risk of coronary atherosclerosis.

AUTOIMMUNE DISEASES: CYTOKINE ACTIVATION AS A LINK TO ATHEROSCLEROSIS?

Patients with RA (rheumatoid arthritis), who, by definition, manifest persistent high levels of inflammation, are at greater risk of developing cardiovascular disease [58,59]. The systemic inflammatory response in RA is critical to accelerated atherogenesis operating via accenetuation of established and novel risk factor pathways [59]. Considerable indirect evidence supports systemic endothelial activation in RA [59]. By implication, long-term suppression of the systemic inflammatory response in RA should be effective in reducing the risk of coronary heart disease. Indeed, DMARDs (disease-modifying antirheumatic drugs) may offer patients protection against acute myocardial infarction, according to findings presented at the European Congress of Rheumatology in 2004 [60]. The investigators identified 41885 individuals who had been diagnosed with RA and who were given prescriptions for methotrexate, leflunomide and TNF-α. The patients treated with a DMARD had a RR (risk ratio) of 0.6 [95 % CI (confidence interval), 0.4–1.0] of acute myocardial infarction compared with those not currently using such medication at the time of the event. For patients being treated with a COX (cyclo-oxygenase)-2 inhibitor, the RR was 1.7 (95 % CI, 1.1–2.6). For conventional NSAIDs (non-steroidal anti-inflammatory drugs) and glucocorticoids, the RRs were 1.2 (95 % CI, 0.8–1.0) and 1.0 (95 % CI, 0.7–1.5) respectively. However, this observational data could be subject to bias or confounding (confer discordance between the results of observational versus randomized studies of hormone replacement therapy or antioxidant vitamins and coronary disease).

SLE (systemic lupus erythematosus) is a chronic inflammatory disease characterized by circulating autoantibodies, activated T-cells, immune complexes and proinflammatory cytokines. The reason that premature coronary atherosclerosis develops in patients with SLE is unknown [61–63]. The leading theory is that immune complex deposition causes the initial intimal damage, which is followed by accelerated development of atherosclerosis in patients with traditional risk factors [61,63]. In mice with lupus-like disease, vascular lesions are caused by antigen–antibody complexes. Humans with SLE have also been shown to have immune deposits in the walls of blood vessels [61]. Chronic vascular inflammation, a hallmark of SLE, may contribute further to the development of vascular stiffness.

In contrast, inflammatory bowel diseases (such as ulcerative colitis and Crohn’s disease), which represent a dysregulated inappropriate response of the intestinal mucosal immune system, have not been associated with enhanced atherosclerosis. Thus, in inflammatory bowel disease, immune activation is more restricted to the intestinal mucosal system and is not usually directed towards the coronary endothelium.

IMPACT OF CYTOKINES IN ANGIOGENESIS

Angiogenesis (i.e. the generation of new capillary blood vessels from pre-existing vasculature) is potentiated by VEGF, FGF, PDGF and TGF-β and via the chemokines...
MCP-1 and MIP (macrophage inflammatory protein) [2,64–67]. VEGF stimulates EC proliferation and increases vascular permeability [68]. Importantly, VEGF may be transcriptionally up-regulated in response to NO and, in a cyclic fashion, VEGF also drives NOS in ECs [68]. ECs as a primary target of this angiogenic factor express high-affinity receptors for VEGF, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1) [65,68]. Besides VEGF, FGFs transduce signals via four protein tyrosine kinase receptors to mediate key events involved in angiogenesis [64]. FGFs recruit ECs and also direct their proliferation, differentiation and plasminogen activator synthesis. The cellular events underlying neovascularization are clearly a multifactorial process and are also affected directly by TGF-β1, EGF, IL-8, ET-1 (endothelin-1) and leptin and, indirectly, by TNF-α and IL-1β [66,67]. Of necessity, angiogenesis is a tightly controlled process. Among the endogenous inhibitors of revascularization identified are TSP-1 (thrombospondin), IFN-γ, IL-10, IL-12, IL-4 and TIMPs (tissue inhibitors of metalloproteinases) [64], in addition to the recently recognized activities of angiotatin and endostatin [65,67,69].

**THERAPEUTIC STRATEGIES TO MODULATE CYTOKINE ACTIVITY IN VASCULAR TISSUE**

ECs are major targets of immune-mediated injury. Consequently, increasing resistance of endothelium to immune effector mechanisms may protect tissues from damage. Known vasculoprotective therapies include ACE (angiotensin-convertingenzyme)-inhibitors and AT1 (angiotensin II type 1 receptor) blockade. β1-Receptor blocker, aspirin and statins (HMG-CoA reductase inhibitors) have been shown to decrease systemic cytokine concentrations in patients [70–76]. High-dose enalapril therapy was associated with a significant decrease in IL-6 activity in patients with chronic congestive heart failure [70], whereas metoprolol treatment induced a significant, but temporary, decrease in sIL-2R levels [71]. ACE inhibition and AT1 blockade reduced serum MMP-9 (matrix metalloproteinase-9) protein/activity to a similar extent, whereas only AT1 blockade reduced hsCRP (highly sensitive CRP) and IL-6 in patients with CAD [76].

Treatment with aspirin reduced plasma levels of M-CSF, IL-6 and CRP in patients with documented CAD [72]. Intriguingly, aspirin prevented endothelial dysfunction induced by inflammation, effects partially mediated by IL-1 down-regulation [77].

Patients recovering from an acute coronary syndrome had lower levels of CRP and IL-6 at 1 month and lower CRP levels at 3 months when treated with rofecoxib, a COX-2 inhibitor, plus aspirin [78].

The statin simvastatin decreased systemic IL-6, IL-8 and MCP-1 concentrations and down-regulated the expression of the cytokines in peripheral blood mononuclear cells in hypercholesterolaemic patients [75]. In heart transplant patients (with accelerated CAD) treated with simvastatin over 12 months, the reduced cardiac cytokine activity (IL-6 and TNF-α) was associated with an improved coronary endothelial function and increased coronary lumen area [74]. The potential of statins to reverse endothelial dysfunction in non-transplant patients is controversial; a fact that might be attributed to lower systemic inflammation in non-transplant compared with transplant patients.

Zeuke et al. [79] have shown recently that cerivastatin reduced basal and LPS (lipopolysaccharide)-induced expression of IL-6 from human coronary ECs in vitro. Recent subgroup analysis from the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) Study demonstrated that high-dose atorvastatin (80 mg/day) potentiated the decline in inflammation in patients with acute coronary syndromes [80]. It is important to note that most of the described anti-inflammatory effects of statins operate independently of specific lipid-lowering actions. High-dose statins directly suppress basal and IL-1β-induced CRP gene expression in human hepatocytes [81]. The beneficial effects of statins on vascular inflammation may be attributed to their functional influences on small G-proteins such as Ras and Rho, resulting in an increase of endogenous NO. Indeed, NO has been shown to decrease cytokine-induced endothelial activation [82].

Finally, anti-TNF-α therapy with a recombinant TNFR profoundly improved systemic endothelial vasodilator capacity in patients with advanced heart failure [83]. In apoE (apolipoprotein E) knockout mice treated with recombinant soluble TNFR-1-releasing pellets, a significant reduction in relative atherosclerotic lesion size after 25 weeks has been demonstrated [84].

Over the past decade, a large number of studies have demonstrated that TNF-α plays an important role in the development of heart failure. Indeed, attenuation of the biological activity of TNF-α abrogates the development of heart failure in animal models. These preclinical studies suggested that anti-cytokine therapy could prove beneficial in the treatment of patients with heart failure. Although early studies supported this hypothesis, anti-TNF strategies have not demonstrated salutary benefits in larger multicentre randomized and placebo-controlled clinical trials in patients with symptomatic heart failure. In this regard, the ATTACH (Anti-TNF Therapy Against Congestive Heart Failure) trial, a small-sized, multicentre, randomized, double-blind, placebo-controlled dose-ranging ‘add-on’ study of infliximab in heart failure, has been published recently [85]. The investigation enrolled patients who were in NYHA class III–IV with an ejection fraction of ≤35 %. Short-term TNF-α antagonism with infliximab did not improve and high doses (10 mg/kg of body weight) adversely affected...
the clinical condition of patients with moderate-to-severe chronic heart failure [85].

These findings raise unresolved questions about the role of TNF-α in heart failure and important concerns about the safety of using TNF-α antagonists (especially at high doses) for the treatment of non-cardiac disorders in patients who also have moderate-to-severe heart failure. Whether infliximab can be used safely in patients with asymptomatic left ventricular dysfunction or mild symptoms of heart failure (NYH class I/II) remains to be determined [86].

FUTURE DIRECTIONS OF CYTOKINES IN CARDIOLOGY

The association of proinflammatory cytokines with endothelial dysfunction, atherosclerosis and heart failure is apparent, although further studies are necessary to establish specific causal relationships. The effects of established therapies directed towards conventional cardiovascular risk factors on proinflammatory cytokines should be evaluated further in outcome trials. Thereby it could be established if a reduction in these inflammatory markers corresponds to a reduction in cardiovascular events. Moreover, therapies directed specifically against proinflammatory cytokines have to be tested in appropriate prospective clinical trials to investigate their potential in heart failure and CAD management. Strategies to diminish proinflammatory cytokine signals should target the mechanisms of immune activation, the intracellular pathways regulating cytokine production and/or the fate of cytokines once they have been released into the circulation.

Pathways to selectively up-regulate anti-inflammatory cytokines such as TGF-β, activin A, IL-10 and IL-1ra in the target tissue (e.g. ECs and smooth muscle cells), as well as immunization with different autoantigens [e.g. oxidized-LDL and HSP (heat shock protein) 65/60], might improve future cardiovascular therapies.

Modulation of critical proximal signal transduction proteins for cytokine signalling [e.g. JAK (Janus kinase)-related cascades] and the differential expression of specific SOCS (suppressors of cytokine signalling) are on the horizon as newly targeted pathways in vascular medicine and transplantation [87,88].

Last, but not least, the central role of known and novel (membrane-bound) cytokines in mobilization and recruitment of endothelial and haematopoietic stem cells and their progenitors is currently under intensive examination [89–93].

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