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Review

Interleukin 8 and cardiovascular disease

Stavros Apostolakis, Konstantina Vogiatzi, Virginia Amanatidou, and Demetrios A. Spandidos*

Laboratory of Clinical Virology, Faculty of Medicine, University of Crete, 71409 Heraklion, Crete, Greece

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Since the establishment of the inflammatory basis of atherosclerosis, several pro- or anti-inflammatory agents have been examined as potential mediators of the biochemical pathways of lesion formation. Interleukin (IL)-8 was first characterized in 1987. Since then, knowledge regarding its role in leucocyte trafficking and activation has advanced rapidly, especially in the field of cardiovascular disease. In the scientific literature, there is sufficient evidence to support beyond any doubt the involvement of IL-8 in the establishment and preservation of the inflammatory micro-environment of the insulted vascular wall. However, how the information derived from *in vitro* studies and animal models can be applied in clinical practice has yet to be determined. In the present review, the available evidence regarding the role of IL-8 in cardiovascular disease is presented, and future perspectives are discussed.

1. Introduction

1.1 Chemokines

The concept of proteins dedicated to cell recruitment and activation in sites of inflammation has been recognized since the days of Metchnikoff. However, it was not until 1970 that the term 'cytokine' was introduced to refer to a large family of peptides involved in a broad range of cell signalling and activation.[1]

Chemokines are low molecular weight chemotactic cytokines. They consist of an expanding family of ~50 ligands and 20 receptors.[2] Chemokines are defined and classified by their functional and structural characteristics. As their name implies, their function is to induce the direct migration of cells to the site of inflammation. In terms of their structure, chemokines are small, with a molecular mass of 8–10 kDa.[2,3] They share ~20–50% gene and amino acid sequence homology, and possess conserved amino acids that are responsible for the creation of their three-dimensional or tertiary structure. Typically, the first two cysteines in a chemokine are situated close together near the N-terminal of the mature protein, with a third cysteine residing in the centre of the molecule and a fourth near the C-terminal.[2,4] Based on the number and structural arrangement of their amino-terminal polypeptide sequence, chemokines are divided into four subfamilies.[4] CXC chemokines have a single amino acid separating the two amino-terminal cysteine residues of the protein. CC chemokines do not have the intervening amino acid between the cysteines.[4] The CX3C subfamily has a single member, fractalkine (FKN), which possesses three amino acids separating the two amino-terminal cysteine residues.[5] The C subfamily comprises the recently discovered lymphotactine (XCL1) and single C motif chemokine 1 (SCM1 or XCL2). These are the only C family members identified to date and are characterized by a lack of two of the four conserved cysteines in the mature protein.[6,7] Most chemokines are produced as propeptides, beginning with a signal peptide of ~90 amino acids that gets cleaved to the bioactive molecule during the process of its secretion from the cell.[8] Chemokines exert their biological activity by binding to specific cell surface receptors. An unusual characteristic of most chemokine receptors is their high affinity for multiple ligands.[8]

1.2 The chemokine network in atherosclerosis

Atherosclerosis is considered to be a disease involving inflammatory cascades initiated by a diverse group of stimuli. The implication of chronic inflammation in the pathogenesis of atherosclerotic lesions was initially proposed by Virchow[9] in the mid-nineteenth century and evolved over the next century into the response-to-injury hypothesis described by Ross and Glomset.[10] One of the earliest events in the latter model of atherogenesis is leucocyte adhesion to the dysfunctional endothelium. A variety of cells have been identified in the time course of lesion development. Monocyte-derived macrophages comprise the majority of cellular components of the inflamed vascular tissue. However, the presence of lymphocytes and, to a lesser extent, mast, dendritic, and endothelial progenitor cells has been directly demonstrated in various experimental settings.[11] Although a variety of stimuli can trigger the inflammatory cascade, lipid accumulation is by far the most favourably substantiated factor in experimental

* Corresponding author. Tel: +30 2810394633; fax: +30 210 725 2922.
E-mail address: spandidos@spandidos.gr

atherosclerosis. Extracellular accumulation of lipids occurs early in response to increased plasma lipoprotein levels.[12] Low-density lipoprotein (LDL) is modified rapidly in the subendothelial space into minimally modified LDL, and subsequently into oxidized LDL (oxLDL).[12] Although direct chemotactic properties have been attributed to oxLDL,[13,14] the accumulation of oxLDL in the intima of the vessel promotes infiltration of the inflammatory cells mostly by inducing chemokine activity.[12,15] Each stage of atherogenesis is regulated by specific chemokine ligand/receptor interaction appropriately described by Zernecke *et al.*[16] as 'a framework of highly elaborated and specialized division of labour'.

In the initial stages of atherogenesis, oxLDL induces the expression of monocyte chemotactic protein (MCP)-1, FKN, and growth-related oncogene (GRO)-α by smooth muscle cells (SMCs) and endothelial cells (ECs).[17,18] Activated platelets can be an alternative chemokine source depositing regulated on activation normal T cell expressed and secreted (RANTES) and platelet factor 4 on ECs lining early atherosclerotic lesions.[17,18] The interaction of FKN, RANTES, and GRO-α with the receptors CX3CR1, CCR1, and CXCR2, respectively, is currently considered to be an early pathway leading to the firm adhesion of rolling monocytes to stimulated endothelium.[17–19] GRO-α immobilized on the surface of ECs via heparin proteoglycans induce the firm adhesion of rolling monocytes expressing CXCR2[17], whereas FKN as a structurally unique chemokine fused to a transmembrane mucin stalk acts as an efficient adhesion molecule through an integrin-independent mechanism.[20]

MCP-1 takes the process one step further. Soluble MCP-1, secreted by ECs and SMCs, induces structural changes in the cytoskeleton of CCR2-expressing adherent monocytes, potentiating transendothelial migration.[17–19] Concurrently, CXC chemokines induced by interferon (IFN)-γ, as well as IFN-inducible protein 10, monokine induced by IFN-γ, and IFN-inducible T cell α chemoattractant expressed on stimulated ECs interact with CXCR3-expressing T cells, inducing their rapid and shear-resistant arrest and increasing the vascular inflammatory response.[17–19,21] The peripheral blood homeostasis and homing of neutrophils and vascular progenitor cells with relevance to atherosclerosis is controlled by CXCR2 and CXCR4 and their ligands interleukin (IL)-8 and GRO-α.[16] IL-8 is highly expressed by lesion macrophages, as well as by ECs and SMCs. IL-8, although mainly a granulocyte chemoattractant, also induces the firm adhesion of CXCR2-expressing monocytes to endothelium under physiological flow conditions.[21] As in the case of RANTES, GRO-α, and FKN, IL-8 is involved in the firm adhesion of rolling monocytes in the early stages of atherogenesis.[16,17] However, a role is implied in the more advanced stages of atherosclerosis, probably by potentiating plaque angiogenesis.[22] Therefore, in the course of atherosclerosis, chemokines form a complicated network by promoting specific cellular interactions.

Different chemokines promote different pathways. However, the interaction of the same chemokine ligand with different receptors also results in a different outcome. Through the use of selective receptor antagonists, Weber *et al.* demonstrated that CCR1, but not CCR5, mediated RANTES-induced arrest of monocytes, and activated T and Th1 cells. CCR5 promoted spreading of the cells along the endothelium, whereas both CCR1 and CCR5 contributed to transendothelial chemotaxis of the cells triggered by RANTES.[23] Moreover, specific chemokine/ligand interactions lead not only to specific mononuclear subpopulations recruitment but also to the chemotaxis and activation of distinct monocyte subsets.[16] Thus, it is obvious that chemokine pathways most actively implicated in atherosclerosis, such as FKN/CX3CR1, MCP-1/CCR2, GRO-α/CXCR2, and IL-8/CXCR2, are recruited in specific stages of lesion formation in a highly specialized and collaborative manner.

In the present review, an effort is made to provide data related to the role of IL-8 in atherogenesis. Data derived from *in vitro* studies and animal models regarding the role of IL-8 in atherogenesis are limited, perhaps due to the initial role that has been attributed to IL-8, i.e. as a mainly neutrophil chemoattractant. However, IL-8 has been intensively studied as a potential marker of atherosclerosis. Serum IL-8 levels have been tested for their ability to identify the presence of subclinical atherosclerosis, as well as to predict the occurrence and outcome of acute coronary events.

1.3 IL-8: structural and functional characteristics

IL-8, or CXCL8 based on the latest nomenclature, represents the prototypical chemokine of the CXC subfamily.[24] IL-8 is actively secreted in the extracellular space as a result of a variety of cellular stimuli. It is a small protein; its mature, fully active form has only 72 amino acids. Transcription of the IL-8 gene encodes for a protein of 99 amino acids that is proteolytically cleaved to a biologically active peptide of either 77 amino acids in non-immune cells or 72 amino acids in monocytes and macrophages.[25]

A wide variety of cell types, including virtually all nucleated cells, are potential sources of IL-8.[24–26] However, the principal cellular sources of IL-8 are typically monocytes and macrophages. IL-8 bears the primary responsibility for the recruitment of monocytes and neutrophils, the signature cells of acute inflammatory response. Cellular recruitment occurs through the development of a chemotactic gradient, which causes the inflammatory cell to move towards an area of increased chemokine concentration.[27] *In vivo*, the chemotactic gradient may be generated by the binding of IL-8 to basement membrane proteins. This gradient aids in bringing cells towards the site of inflammation and also retains them once they have arrived.[27] In addition to recruitment, IL-8 serves to promote the activation of monocytes and neutrophils.[24–27]

The biological effects of IL-8 are mediated through the binding of IL-8 to two cell surface receptors, CXCR1 and CXCR2.[28,29] These G-protein-coupled receptors share considerable structural similarity and induce a nearly identical range of biological activities.[28,29] Signals are transmitted across the membrane through ligand-induced structural changes, exposing epitopes on the intracellular loops and carboxy-terminal tail of the receptor. These epitopes promote coupling to functional heterotrimeric G proteins.[30,31] The biological activity of IL-8 and other CXC chemokines is in part dependent on the ELR amino acid motif. The presence of these three specific amino acids is crucial for the binding of IL-8 to its receptor.[32]

IL-8 is resistant to temperature and proteolysis, and is relatively resistant to acidic environments. These

biochemical characteristics make it an ideal candidate molecule for sites of acute inflammation, where it must withstand harsh and hostile conditions.[32] Another unique functional characteristic of IL-8 is its relative longevity at sites of acute inflammation.[32] It is produced early in the inflammatory response, but remains active for a prolonged period of time, even days and weeks. This is in contrast to most other inflammatory cytokines, which are typically made and cleared *in vivo* in a matter of hours.[32] A third interesting aspect IL-8 involves the oxidant regulation of gene expression. IL-8 is highly sensitive to oxidants, and anti-oxidants substantially reduce IL-8 gene expression.[33] The role of oxidants in the regulation of IL-8 and other chemokines has relevance in the field of cardiovascular disease, where ischaemia-induced oxidative stress is both a marker of disease and a potential therapeutic target.

2. IL-8 and cardiovascular disease: the facts

2.1 Data derived from *in vitro* studies and animal models

IL-8 was first characterized in 1987. Since then, knowledge regarding its function in leucocyte trafficking and activation has advanced rapidly, especially regarding its role in atherosclerosis. Several studies have identified IL-8 in sites of vascular injury, whereas others have demonstrated that IL-8 potentially plays a role in various stages of atherosclerosis.

Rus *et al*. first reported high levels of IL-8 in the human arterial atherosclerotic wall, as cellular and extracellular deposit in the connective tissue matrix. Quantitative determination of IL-8 by enzyme-linked immunosorbent assay revealed that IL-8 levels were significantly increased in fibrous plaques compared with normal intima.[34] Apostolopoulos *et al*. took this one step further, identifying macrophages as the main source of IL-8 in atherosclerotic plaques. The authors demonstrated an enhanced capacity of macrophages to produce IL-8 compared with normal and patient blood monocytes, and concluded that macrophages are a major site of IL-8 mRNA production in atherosclerotic plaques.[35] Similarly, a year later, Liu *et al*. detected high levels of IL-8 in foam cells from human atherosclerotic tissue, compared with monocytes or monocyte-derived macrophages in culture. The authors further demonstrated that oxysterols stimulate IL-8 production by monocytes and monocyte-derived macrophages *in vitro* in time- and dose-dependent manners.[36]

However, not only macrophages, but practically every cellular component of the vascular wall has been reported to be a potential source of IL-8. Dje N'Guessan *et al*.[37] showed that oxLDL induced IL-8 and MCP-1 secretion in cultured ECs, and further demonstrated that oxLDL-induced IL-8 and MCP-1 were reduced in cells treated with statins. Geisel *et al*.[38] reported that IL-8 expression by cultured ECs was enhanced in a dose-dependent manner by homocysteine—a well-recognized independent risk factor for atherosclerosis. Ryoo *et al*. reported that vascular SMCs are another potential source of IL-8, demonstrating that LDL-stimulated vascular SMCs induced IL-8 production in dose- and time-dependent manners at the transcription level. The authors further revealed that LDL intracellular signalling is conveyed via the generation of hydrogen peroxide (H_2O_2), the phosphorylation of p38 MAPK, the activation of AP-1, and the participation of NF-κB.[39] Similarly, Ito *et al*. reported that Ang II increased IL-8 production, whereas fluvastatin decreased basal and Ang II-induced IL-8 production in human SMCs. These findings indicated that Ang II may exacerbate atherosclerosis through the induction of IL-8 in vascular SMCs. The authors concluded that statins may exert therapeutic effects by modulating IL-8 synthesis in patients with atherosclerotic disease.[40]

Once the presence of IL-8 in atherosclerotic plaques was sufficiently substantiated, with macrophages, SMCs, and ECs identified as its main sources, many investigators sought to identify the pathways leading to IL-8 release in sites of atherogenesis. Notably, Gerszten *et al*. demonstrated that IL-8 can rapidly cause rolling monocytes to firmly adhere to monolayers expressing E-selectin, whereas related chemokines do not. These effects were not correlated with the induction of a calcium transient or with chemotaxis. The authors concluded that IL-8 is an important modulator of monocyte–endothelial interaction under flow conditions—a rather unexpected role for a chemokine that was previously considered a mere neutrophil chemoattractant.[41] Yue *et al*.[42] demonstrated that IL-8 is also a mitogenic and chemotactic for vascular SMCs, as it induced the concentration-dependent stimulation of DNA synthesis and cell proliferation in both human and rat aortic SMCs. Additionally, Moreau *et al*., by applying immunohistochemistry in human atherosclerotic plaques, revealed the expression of tissue inhibitor of metallopeptidase (TIMP)-1 in some but not all macrophage- and IL-8-rich areas. The authors further demonstrated that IL-8 inhibited TIMP-1 accumulation *in vitro* and concluded that IL-8 may play an atherogenic role by inhibiting local TIMP-1 expression, thereby leading to an imbalance between matrix metalloproteinases and TIMPs at focal sites in the atherosclerotic plaque.[43] Rydberg *et al*.[44] demonstrated that hypoxia enhanced 25-hydroxycholesterol (25-OH-chol)-induced IL-8 secretion in human monocyte-derived macrophages, and provided evidence indicating that both 25-OH-chol and hypoxia mediate increased IL-8 secretion by increasing the level of the intracellular signalling molecule, H_2O_2. Yang *et al*. demonstrated that tumour necrosis factor (TNF)-α stimulated IL-8 expression at the RNA and protein level in human umbilical vein ECs. The authors further demonstrated that aspirin significantly inhibited the release of TNF-stimulated MCP-1 and IL-8, proposing an additional therapeutic effect of aspirin in atherosclerosis.[45] Kim *et al*. evaluated the expression of IL-8 in cultured vascular SMCs obtained from the thoracic aorta of spontaneously hypertensive rats (SHRs) and normotensive Wistar–Kyoto rats (WKY), and demonstrated that IL-8 expression in thoracic aorta tissue and vascular SMCs was significantly higher in SHRs than in WKY mice. This suggests that IL-8 plays an important role in the pathogenesis of hypertension.[46] In an entirely novel experimental setting, Henrichot *et al*. showed that perivascular white adipose tissue (pWAT)—which is markedly increased by a high-fat diet—is in close proximity to the vascular walls and serves as a potential source of IL-8, particularly at sites that tend to develop atherosclerosis. The authors concluded that human pWAT has chemotactic properties due to its secretion of different chemokines, and proposed that it might contribute to the progression of obesity-associated atherosclerosis.[47]

Simonini *et al*. assessed whether IL-8 plays a role in mediating angiogenic activity in atherosclerosis. The authors demonstrated in a rat cornea micropocket assay that neutralizing IL-8 attenuated *in vivo* corneal neovascular response, and concluded that in human coronary atherosclerosis, IL-8 is an important mediator of angiogenesis that may contribute to plaque formation via its angiogenic properties.[22]

Additional supporting evidence that IL-8 plays a role in atherogenesis was provided by a brilliant animal model constructed by Boisvert *et al*. The authors used LDL receptor knockout mice that were irradiated and repopulated with bone marrow cells lacking the murine homologue of IL-8 receptor, CXCR2. They concluded that double knockout mice had less extensive lesions and fewer macrophages than those receiving bone marrow cells expressing the receptor.[48] However, since CXCR2 has multiple ligands (CXCL1 and CXCL8), the latter study is not definitive in substantiating a role for IL-8 in atherosclerosis. In fact, Weber *et al*.[49] provided evidence that macrophage migration inhibitory factor (MIF) might also be an alternative CXCR2 ligand. The authors further demonstrated that MIF possesses a pseudo-(E)LR motif that enables MIF to act as a non-canonical CXCR2 ligand, and concluded that this structural resemblance may be the background of pro-inflammatory MIF/CXCR2 interactions. Consequently, deletion of CXCL1 in $LDLr^{-/-}$ mice[16] reduces atherosclerosis to a lesser extent than bone marrow CXCR2 deficiency in $LDLr^{-/-}$ mice, with effects on macrophage accumulation in established rather than early lesions. Thus, MIF, as a CXCR2 alternative ligand, may partially compensate for a lack of CXCL1.[16] Nevertheless, Boyle *et al*.[50] evaluated the effect of direct IL-8 inhibition on the degree of myocardial injury encountered during reperfusion in New Zealand White rabbits, demonstrating that the neutralization of IL-8 significantly reduced the degree of necrosis in a rabbit model of myocardial ischaemia–reperfusion injury.

2.2 Data derived from case—control studies

The scientific literature is overflowing with evidence regarding the potential role of IL-8 in atherosclerosis, either as a marker or as a potential therapeutic target.

A popular field of investigation is the determination of whether IL-8 is a predictor of short- or long-term outcome in patients with coronary artery disease (CAD). Most recently, Inoue *et al*. evaluated the serum levels of 10 cytokines as potential markers of long-term outcome in angiographically identified stable CAD. The authors concluded that IL-8 was the only cytokine to predict cardiovascular events, doing so independently of the other nine cytokines and high sensitivity C-reactive protein.[51] Elmas *et al*.[52] demonstrated higher TIMP-1 and IL-8 serum levels in patients with ventricular fibrillation (VF) complicating myocardial infarction, suggesting that patients prone to VF during myocardial infarction are in an increased pro-inflammatory state compared with those without VF. Panichi *et al*. evaluated the impact of serum IL-8 on the outcome of end-stage renal disease (ESRD) patients. The authors demonstrated that IL-8 is a powerful independent predictive factor for cardiovascular and overall mortality in ESRD patients.[53] Finally, in the largest case–control study assessing the predictive value of IL-8 in patients with CAD, Herder *et al*. demonstrated that baseline concentrations of IL-8 were significantly higher in CAD than in non-CAD patients. However, adjustment for further cardiovascular and immunological risk factors attenuated the observed association, and the authors concluded that systemic levels of IL-8 precede CAD, but do not represent an independent risk factor.[54]

In the field of interventional cardiology, Dominguez-Rodriguez *et al*. evaluated IL-8 levels after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI). The authors concluded that increased serum levels of IL-8 after PCI are probably a predictor of the development of heart failure in patients with AMI.[55] Vogiatzi *et al*. investigated the potential influence of two common polymorphisms of the IL-8 gene, −251A/T, and 781C/T, on susceptibility to CAD. The authors reported that the frequency of the 251AA genotype was lower in CAD patients with a history of acute coronary syndromes than in asymptomatic subjects or patients with stable CAD, and suggested that the genetic diversity of the IL-8 gene influences the clinical manifestation of CAD.[56] The same authors later assessed the impact of the −251A/T and 781C/T polymorphisms on the outcome of PCI, reporting an association between the T251T781 haplotype and in-stent restenosis (ISR) and suggesting that IL-8-mediated pathways are implicated in the process of ISR.[57]

IL-8 has also been thoroughly investigated in terms of its impact on the outcome of cardiopulmonary bypass (CPB) and cardiac transplantation (CT) surgeries. Kawamura *et al*.[58] assessed serum IL-8 levels in patients subjected to coronary artery bypass grafting (CABG), ascertaining that the levels increased significantly and remained elevated for 180 min after the declamping of the aorta. Hummel *et al*. evaluated IL-8 levels in patients with cardiogenic shock or end-stage heart disease treated with assist device implantation as a bridge to heart transplantation. Reduced levels of IL-8 were correlated with uncomplicated course of disease, and the authors concluded that monitoring IL-8 values during ventricular assist device support allows for the early identification of high-risk patients and may aid in the optimization of antimicrobial therapy and the selection of the appropriate time for transplantation.[59] Kawamura *et al*. reported increased serum levels of IL-8 in patients 1 h after CABG surgery. Patients pre-treated with methylprednisolone had lower serum concentrations of IL-8 compared with non-treated patients.[60] Oz *et al*. reported increased serum levels of IL-8 in patients subjected to CT compared with those who underwent elective cardiac surgery (non-CT). This observation was attributed to the longer ischaemic times of CT patients compared with those of non-CT patients, and the authors suggested that IL-8 may contribute to myocyte injury after prolonged hypothermic cardiac ischaemia, as occurs during human CT.[61] Burns *et al*. evaluated the expression levels of IL-8 in myocardial and skeletal muscle tissue in patients subjected to CPB with or without hypothermic arrest. The authors concluded that during CPB, the production of IL-8 mRNA in myocardial and skeletal muscle occurs in most patients. This may result in increased local IL-8 concentrations, contributing to tissue injury after CPB.[62] Nandate *et al*. measured IL-8 levels in paired arterial and jugular bulb samples obtained before, during, and after CPB, and observed an increase in juguloarterial IL-8 gradients 1 h post-CPB up to 6 h post-CPB. The authors concluded that these data imply

specific and significant IL-8 production in the cerebrovascular bed during CPB.[63] Wu *et al*.[64] assessed the impact of IL-8 serum levels post-CABG on the incidence of post-operative atrial fibrillation (AF) in CABG patients and reported higher concentrations of serum IL-8 in CABG patients with post-operative AF, suggesting that inflammation is implicated in the pathogenesis of post-operative AF following open heart surgery.

Many investigators have assessed IL-8 as a potential marker of unstable CAD, with remarkably equivalent results. Kanda *et al*.[65] evaluated serum levels of IL-8 related to the clinical presentation of CAD and concluded that elevated serum IL-8 is a useful marker for the detection of unstable angina, as well as an earlier marker of AMI than changes in serum myoglobin, leucocytes, creatine kinase, or creatine kinase-MB. Similarly, Zhou *et al*.[66] demonstrated that serum levels of IL-8 were significantly higher in patients with unstable angina or AMI than in healthy control subjects, suggesting that IL-8 is involved in the process of ischaemic heart disease. Subsequently, Romuk *et al*. evaluated serum IL-8 in patients with stable and unstable CAD. Higher levels of IL-8 were observed in patients with unstable CAD, leading the authors to conclude that IL-8 may be a useful clinical predictor of unstable CAD.[67] The same hypothesis was tested more recently by Hashmi and Zeng. The authors assessed serum IL-8 levels in patients with different clinical presentations of CAD. In accordance with previous results, the increased activity of IL-8 was observed in patients with unstable angina and AMI compared with those with stable CAD.[68] Abe *et al*.[69] reported that serum IL-8 concentrations showed a transient rise during the very early phases of AMI, indicating the importance of IL-8-mediated pathways in the development of myocardial injury in AMI. Schömig *et al*. investigated the relationship of circulating progenitor cells and IL-8 in AMI, demonstrating an association of IL-8 and circulating CD133+ CD45-progenitor cells in AMI and concluding that in AMI, IL-8 is associated with circulating progenitor cells. The above pathway, in addition to the pro-angiogenic functions of IL-8, may contribute to new vessel generation and may thereby improve myocardial function.[70] Riesenberg *et al*. reported increased levels of IL-8 in the sera of patients with AMI, with significantly higher levels in those with complicated myocardial infarction. The highest levels of IL-8 were detected at the time of admission to the coronary care unit, and thereafter decreased significantly. This indicated that IL-8 contributes to neutrophil-mediated tissue injury.[71] Finally, de Winter *et al*.[72] reported that IL-8 released in plasma after AMI subsequently binds to red blood cells, resulting in only a transient rise of plasma IL-8 and a more prolonged increase in erythrocyte-bound IL-8. In accordance with the latter observation, Tziakas *et al*. later reported that erythrocyte membrane-bound IL-8 is elevated in patients with acute coronary syndromes compared with those with chronic stable angina. The authors suggested that these findings underscore the role of erythrocytes in the development of unstable atherosclerotic plaque.[73]

IL-8 has also been assessed as a marker of outcome in patients resuscitated following cardiopulmonary arrest. Most recently, Oda *et al*.[74] evaluated cerebrospinal fluid and serum IL-8 and IL-6 levels in such patients, demonstrating a significant correlation between Glasgow Outcome Scale score evaluated 6 months after resuscitation with levels of cerebrospinal fluid, IL-8, and IL-6. These results are in agreement with the findings of Mussack *et al*., who compared S-100B and IL-8 serum levels at the time of admission and levels 12 h after admission with neurological long-term outcome 12 months after cardiac arrest following the return of spontaneous circulation, as well as after severe traumatic brain injury. The authors concluded that significantly elevated S-100B and IL-8 serum levels 12 h after cardiac arrest suggest that primary brain damage and systemic inflammatory response are comparably serious with the damage involved in traumatic brain injury.[75]

Finally, IL-8 has been evaluated as a marker of atherosclerosis in patients at high risk without direct evidence of CAD. In this area, Kim *et al*. demonstrated that circulating levels of MCP-1 and IL-8 are associated with obesity-related parameters such as body mass index, waist circumference, C-reactive protein, IL-6, HOMA, and high-density lipoprotein. These findings suggest that circulating MCP-1 and/or IL-8 may be a potential marker, linking obesity with obesity-related metabolic complications such as atherosclerosis and diabetes.[76] Similarly, in primary prevention, Trøseid *et al*. reported that physical exercise significantly reduced MCP-1 and IL-8 levels, demonstrating a reduction in serum IL-8 in patients with metabolic syndrome subjected to a physical exercise programme compared with baseline levels and with the levels of a non-exercise control group. The authors concluded that the protective effect of physical exercise might be due in part to the suppression of the inflammatory process.[77] Besides physical exercise, statins seem capable of affecting atherosclerosis-related increases in IL-8 production. In this respect, Rezaie-Majd *et al*. demonstrated that simvastatin exerts anti-inflammatory properties by down-regulating IL-8 production by the endothelium and leucocytes. These effects, which were substantiated *in vivo* and *in vitro*, may explain some of the clinical benefits of these drugs in the treatment of atherosclerosis.[78]

3. IL-8 and cardiovascular disease: perspectives or utopia

Inflammation is a hallmark of atherosclerosis and takes place as a consequence of endogenous or exogenous insult of the vessel wall. The progression of this inflammatory response is primarily regulated by specific patterns of cytokine expression. The balance of pro- and anti-inflammatory cytokines is of great importance in vascular inflammation and is underscored by the fact that the *in vivo* down-regulation of pro-inflammatory cytokines reduces atherogenesis.

Since the establishment of the inflammatory basis of atherosclerosis, several pro- or anti-inflammatory agents have been examined as potential mediators of the biochemical pathways of lesion formation. Almost every one of the 33 currently known ILs has been implicated, in a more or less disease-specific way, in aspects of cardiovascular disease, in particular atherosclerosis.

3.1 IL-8 as a marker of cardiovascular disease

There is sufficient evidence in the scientific literature to support beyond any doubt the involvement of IL-8 in the establishment and preservation of the inflammatory microenvironment of the insulted vascular wall. However, how

the information derived from *in vitro* studies and animal models can be applied in a clinical setting remains to be determined. The management of atherosclerotic cardiovascular disease consists of primary prevention, secondary prevention, and treatment of acute complications of atherosclerosis. Primary prevention requires overall cardiovascular risk estimation and risk factor modification. In cardiovascular risk estimation, several reports have indicated that increased serum levels of IL-8 are correlated with an increased risk of cardiovascular disease or acute cardiovascular events. However, these data are primarily the results of single-centre small-scale observational studies. There is limited data available derived from large-scale clinical trials illustrating the additive value of IL-8 on traditional risk factors as prognostic markers of short- or long-term outcome after acute cardiovascular events or in a primary prevention setting. Of note, the largest available cohort, including 381 CAD patients and 1977 controls, revealed that elevated systemic levels of IL-8 do not represent independent risk factors for coronary events. Another issue is whether additional markers for CAD are required in either a primary or a secondary setting. Inflammatory markers have to demonstrate high specificity and sensitivity and increase predictive value positively or negatively, especially if we take into account cost-efficiency parameters and the fact that most traditional risk factors are highly modifiable.

Regarding the therapeutic potential of IL-8, only limited data are available. As in any immune-modulating therapeutic approach, there are several drawbacks that need to be considered. First of all, atherosclerosis is a chronic condition; thus, long-term therapy must be applied. This raises tolerability and safety issues for a potential therapeutic agent that blocks a non-specific chemotactic pathway. Secondly, IL-8 is an important mediator of several aspects of immune response. Therefore, the complete blockade of IL-8 signalling pathways may not be desirable. Thus, techniques need to be applied to ensure that IL-8 signal blocking takes place in specific areas and tissues. An appealing area of investigation for immune-suppressive therapies is restenosis after PCI, in which IL-signalling blockers may be tested as potential agents for stent eluting. This latter approach insures better targeting and probably less side effects than systemic treatment. In human coronary atherosclerosis, IL-8 has been shown to be a mediator of angiogenesis and may contribute to plaque formation via its angiogenic properties.[22] Blocking angiogenesis has proven to be effective in reducing in-stent plaque progression.[79] No data are available to indicate that blocking IL-8 activity reduces neovascularization in the area of in-stent plaque formation. However, a specific IL-8 gene haplotype has been associated with reduced risk for ISR, providing indirect evidence that the IL-8-mediated pathways are involved in the process of ISR.[57] Thus, targeting IL-8 pathways in an effort to reduce the rate of ISR could be a challenging field of investigation.

Nonetheless, it is necessary to take into account that all therapeutic approaches to cardiovascular disease have been evaluated in large-scale clinical trials with specific endpoints. Therefore, despite its promising *in vivo* and *in vitro* indications, any IL-8 modulating therapy must be proven to exhibit the ability to reduce cardiovascular morbidity and mortality. To the best of our knowledge, no large-scale clinical trials are currently evaluating the effectiveness of IL-8-based treatments in cardiovascular disease. It will be therefore a long wait before IL-8-based therapeutic approaches find their way into clinical practice.

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References

1. Mantovani A. The chemokine system: redundancy for robust outputs. *Immunol Today* 1999;**20**:254–257.
2. Luster AD. Chemokines—chemotactic cytokines that mediate inflammation. *N Engl J Med* 1998;**338**:436–445.
3. Chemokine/chemokine receptor nomenclature. *Cytokine* 2003;**21**:48–49.
4. Fernandez E, Lolis E. Structure, function, and inhibition of chemokines. *Annu Rev Pharmacol Toxicol* 2002;**42**:469–499.
5. Imai T, Hieshima K, Haskell C, Baba M, Nagira M, Nishimura M *et al*. Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. *Cell* 1997;**91**:521–530.
6. Curnock AP, Logan MK, Ward SG. Chemokine signalling: pivoting around multiple phosphoinositide 3-kinases. *Immunology* 2002;**105**:125–136.
7. Puneet P, Moochhala S, Bhatia M. Chemokines in acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol* 2005;**288**:L3–L15.
8. Apostolakis S, Papadakis GE, Krambovitis E, Spandidos DA. Chemokines in vascular pathology. *Int J Mol Med* 2006;**17**:691–701.
9. Virchow R. Phlogose und thrombose in gefassystem. In: *Gesammelte Abhandlungen zur Wissenschaftlichen Medicin*. Frankfurt, Germany: Staatsdruckerei, 1856. p458–468.
10. Ross R, Glomset JA. Atherosclerosis and the arterial smooth muscle cell. *Science* 1973;**180**:1332–1336.
11. Weber C. Chemokines in atherosclerosis, thrombosis, and vascular biology. *Arterioscler Thromb Vasc Biol* 2008;**28**:1896.
12. Cushing SD, Berliner JA, Valente AJ, Territo MC, Navab M, Parhami F *et al*. Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. *Proc Natl Acad Sci USA* 1990;**87**:5134–5138.
13. Quinn MT, Parthasarathy S, Fong LG, Steinberg D. Oxidatively modified low density lipoproteins: a potential role in recruitment and retention of monocyte/macrophages during atherogenesis. *Proc Natl Acad Sci USA* 1987;**84**:2995–2998.
14. McMurray HF, Parthasarathy S, Steinberg D. Oxidatively modified low density lipoprotein is a chemoattractant for human T lymphocytes. *J Clin Invest* 1993;**92**:1004–1008.
15. Rajavashisth TB, Andalibi A, Territo MC, Berliner JA, Navab M, Fogelman AM *et al*. Induction of endothelial cell expression of granulocyte and macrophage colony-stimulating factors by modified low-density lipoproteins. *Nature* 1990;**344**:254–257.
16. Zernecke A, Shagdarsuren E, Weber C. Chemokines in atherosclerosis: an update. *Arterioscler Thromb Vasc Biol* 2008;**28**:1897–1908.
17. Weber C, Schober A, Zernecke A. Chemokines: key regulators of mononuclear cell recruitment in atherosclerotic vascular disease. *Arterioscler Thromb Vasc Biol* 2004;**24**:1997–2008.
18. Barlic J, Murphy PM. Chemokine regulation of atherosclerosis. *J Leukoc Biol* 2007;**82**:226–236.
19. Weber KS, von Hundelshausen P, Clark-Lewis I, Weber PC, Weber C. Differential immobilization and hierarchical involvement of chemokines in monocyte arrest and transmigration on inflamed endothelium in shear flow. *Eur J Immunol* 1999;**29**:700–712.
20. Bazan JF, Bacon KB, Hardiman G, Wang W, Soo K, Rossi D *et al*. A new class of membrane-bound chemokine with a CX3C motif. *Nature* 1997;**385**:640–644.
21. Mehra VC, Ramgolam VS, Bender JR. Cytokines and cardiovascular disease. *J Leukoc Biol* 2005;**78**:805–818.
22. Simonini A, Moscucci M, Muller DW, Bates ER, Pagani FD, Burdick MD *et al*. IL-8 is an angiogenic factor in human coronary atherectomy tissue. *Circulation* 2000;**101**:1519–1526.

23. Weber C, Weber KSC, Klier C, Gu H, Horuk R, Wank R *et al*. Specialized roles of the chemokine receptors CCR1 and CCR5 in recruitment of monocytes and Th1-like/CD45RO+T cells. *Blood* 2001;**97**:1144–1146.
24. Remick GD. Interleukin-8. *Crit Care Med* 2005;**33**:s646–s647.
25. Waugh JJD, Wilson C. The interleukin-8 pathway in cancer. *Clin Cancer Res* 2008;**14**:6735–6741.
26. Standiford TJ, Kunkel SL, Basha MA, Chensue SW, Lynch JP 3rd, Toews GB *et al*. Interleukin-8 gene expression by a pulmonary epithelial cell line. A model for cytokine networks in the lung. *J Clin Invest* 1990;**86**: 1945–1953.
27. Gimbrone MA Jr, Obin MS, Brock AF, Luis EA, Hass PE, Hébert CA *et al*. Endothelial interleukin-8: a novel inhibitor of leukocyte-endothelial interactions. *Science* 1989;**246**:1601–1603.
28. Holmes WE, Lee J, Kuang WJ, Rice GC, Wood WI. Structure and functional expression of a human interleukin-8 receptor. *Science* 1991;**253**: 1278–1280.
29. Murphy PM, Tiffany HL. Cloning of a complimentary DNA encoding a functional human interleukin-8 receptor. *Science* 1991;**253**:1280–1283.
30. Moser B, Loetscher P. Lymphocyte traffic control by chemokines. *Nat Immunol* 2002;**2**:123–128.
31. Schraufstatter IU, Chung J, Burger M. IL-8 activates endothelial CXCR1and CXCR2 through Rho and Rac signaling pathways. *Am J Physiol Lung Cell Mol Physiol* 2001;**280**:L1094–L1103.
32. DeForge LE, Fantone JC, Kenney JS, Remick DG. Oxygen radical scavengers selectively inhibit interleukin 8 production in human whole blood. *J Clin Invest* 1992;**90**:2123–2129.
33. DeForge LE, Preston AM, Takeuchi E, Kenney J, Boxer LA, Remick DG. Regulation of interleukin 8 gene expression by oxidant stress. *J Biol Chem* 1993;**268**:25568–25576.
34. Rus HG, Vlaicu R, Niculescu F. Interleukin-6 and interleukin-8 protein and gene expression in human arterial atherosclerotic wall. *Atherosclerosis* 1996;**127**:263–271.
35. Apostolopoulos J, Davenport P, Tipping PG. Interleukin-8 production by macrophages from atheromatous plaques. *Arterioscler Thromb Vasc Biol* 1996;**16**:1007–1012.
36. Liu Y, Hultén LM, Wiklund O. Macrophages isolated from human atherosclerotic plaques produce IL-8, and oxysterols may have a regulatory function for IL-8 production. *Arterioscler Thromb Vasc Biol* 1997;**17**: 317–323.
37. Dje N'Guessan P, Riediger F, Vardarova K, Scharf S, Eitel J, Opitz BS *et al*. Statins control oxidized LDL-mediated histone modifications and gene expression in cultured human endothelial cells. *Arterioscler Thromb Vasc Biol* 2009;**29**:380–386.
38. Geisel J, Jödden V, Obeid R, Knapp JP, Bodis M, Herrmann W. Stimulatory effect of homocysteine on interleukin-8 expression in human endothelial cells. *Clin Chem Lab Med* 2003;**41**:1045–1048.
39. Ryoo SW, Kim DU, Won M, Chung KS, Jang YJ, Oh GT *et al*. Native LDL induces interleukin-8 expression via H_2O_2, p38 kinase, and activator protein-1 in human aortic smooth muscle cells. *Cardiovasc Res* 2004; **62**:185–193.
40. Ito T, Ikeda U, Yamamoto K, Shimada K. Regulation of interleukin-8 expression by HMG-CoA reductase inhibitors in human vascular smooth muscle cells. *Atherosclerosis* 2002;**165**:51–55.
41. Gerszten RE, Garcia-Zepeda EA, Lim YC, Yoshida M, Ding HA, Gimbrone MA Jr *et al*. MCP-1 and IL-8 trigger firm adhesion of monocytes to vascular endothelium under flow conditions. *Nature* 1999;**398**: 718–723.
42. Yue TL, Wang X, Sung CP, Olson B, McKenna PJ, Gu JL *et al*. IL-8. A mitogen and chemoattractant for smooth muscle cells. *Circ Res* 1994; **75**:1–7.
43. Moreau M, Brocheriou I, Petit L, Ninio E, Chapman MJ, Rouis M. Interleukin-8 mediates downregulation of tissue inhibitor of metalloproteinase-1 expression in cholesterol-loaded human macrophages: relevance to stability of atherosclerotic plaque. *Circulation* 1999;**99**:420–426.
44. Rydberg EK, Salomonsson L, Hultén LM, Norén K, Bondjers G, Wiklund O *et al*. Hypoxia increases 25-hydroxycholesterol-induced interleukin-8 protein secretion in human macrophages. *Atherosclerosis* 2003;**170**: 245–252.
45. Yang YY, Hu CJ, Chang SM, Tai TY, Leu SJ. Aspirin inhibits monocyte chemoattractant protein-1 and interleukin-8 expression in TNF-alpha stimulated human umbilical vein endothelial cells. *Atherosclerosis* 2004;**174**: 207–213.
46. Kim HY, Kang YJ, Song IH, Choi HC, Kim HS. Upregulation of interleukin-8/CXCL8 in vascular smooth muscle cells from spontaneously hypertensive rats. *Hypertens Res* 2008;**31**:515–523.
47. Henrichot E, Juge-Aubry CE, Pernin A, Pache JC, Velebit V, Dayer JM *et al*. Production of chemokines by perivascular adipose tissue: a role in the pathogenesis of atherosclerosis? *Arterioscler Thromb Vasc Biol* 2005;**25**: 2594–2599.
48. Boisvert WA, Santiago R, Curtiss LK, Terkeltaub RA. A leukocyte homologue of the IL-8 receptor CXCR-2 mediates the accumulation of macrophages in atherosclerotic lesions of LDL receptor-deficient mice. *J Clin Invest* 1998;**101**:353–363.
49. Weber C, Kraemer S, Drechsler M, Lue H, Koenen RR, Kapurniotu A *et al*. Structural determinants of MIF functions in CXCR2-mediated inflammatory and atherogenic leukocyte recruitment. *Proc Natl Acad Sci USA* 2008;**105**:16278–16283.
50. Boyle EM Jr, Kovacich JC, Hèbert CA, Canty TG Jr, Chi E, Morgan EN *et al*. Inhibition of interleukin-8 blocks myocardial ischemia-reperfusion injury. *J Thorac Cardiovasc Surg* 1998;**116**:114–121.
51. Inoue T, Komoda H, Nonaka M, Kameda M, Uchida T, Node K. Interleukin-8 as an independent predictor of long-term clinical outcome in patients with coronary artery disease. *Int J Cardiol* 2008;**124**:319–325.
52. Elmas E, Lang S, Dempfle CE, Kälsch T, Hannak D, Sueselbeck T *et al*. High plasma levels of tissue inhibitor of metalloproteinase-1 (TIMP-1) and interleukin-8 (IL-8) characterize patients prone to ventricular fibrillation complicating myocardial infarction. *Clin Chem Lab Med* 2007;**45**: 1360–1365.
53. Panichi V, Taccola D, Rizza GM, Consani C, Ghiadoni L, Filippi C *et al*. Interleukin-8 is a powerful prognostic predictor of all-cause and cardiovascular mortality in dialytic patients. *Nephron Clin Pract* 2006;**102**: 51–58.
54. Herder C, Baumert J, Thorand B, Martin S, Löwel H, Kolb H *et al*. Chemokines and incident coronary heart disease: results from the MONICA/KORA Augsburg case-cohort study, 1984–2002. *Arterioscler Thromb Vasc Biol* 2006;**26**:2147–2152.
55. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez M, Ferrer J. Prognostic value of interleukin-8 as a predictor of heart failure in patients with myocardial infarction and percutaneous intervention. *Int J Cardiol* 2006;**111**:158–160.
56. Vogiatzi K, Apostolakis S, Voudris V, Thomopoulou S, Kochiadakis GE, Spandidos DA. Interleukin 8 and susceptibility to coronary artery disease: a population genetics perspective. *J Clin Immunol* 2008;**28**: 329–335.
57. Vogiatzi K, Apostolakis S, Voudris V, Thomopoulou S, Kochiadakis GE, Spandidos DA. Interleukin 8 gene polymorphisms and susceptibility to restenosis after percutaneous coronary intervention. *J Thromb Thrombolysis* 2009. Published online ahead of print April 2009, doi:10.1007/s11239-009-0338-y.
58. Kawamura T, Wakusawa R, Okada K, Inada S. Elevation of cytokines during open heart surgery with cardiopulmonary bypass: participation of interleukin 8 and 6 in reperfusion injury. *Can J Anaesth* 1993;**40**: 1016–1021.
59. Hummel M, Czerlinski S, Friedel N, Liebenthal C, Hasper D, von Baehr R *et al*. Interleukin-6 and interleukin-8 concentrations as predictors of outcome in ventricular assist device patients before heart transplantation. *Crit Care Med* 1994;**22**:448–454.
60. Kawamura T, Inada K, Okada H, Okada K, Wakusawa R. Methylprednisolone inhibits increase of interleukin 8 and 6 during open heart surgery. *Can J Anaesth* 1995;**42**:399–403.
61. Oz MC, Liao H, Naka Y, Seldomridge A, Becker DN, Michler RE. Ischemia-induced interleukin-8 release after human heart transplantation. A potential role for endothelial cells. *Circulation* 1995;**92**: II428–II432.
62. Burns SA, Newburger JW, Xiao M, Mayer JE Jr, Walsh AZ, Neufeld EJ. Induction of interleukin-8 messenger RNA in heart and skeletal muscle during pediatric cardiopulmonary bypass. *Circulation* 1995;**92**: II315–II321.
63. Nandate K, Vuylsteke A, Crosbie AE, Messahel S, Oduro-Dominah A, Menon DK. Cerebrovascular cytokine responses during coronary artery bypass surgery: specific production of interleukin-8 and its attenuation by hypothermic cardiopulmonary bypass. *Anesth Analg* 1999;**89**:823–828.
64. Wu ZK, Laurikka J, Vikman S, Nieminen R, Moilanen E, Tarkka MR. High postoperative interleukin-8 levels related to atrial fibrillation in patients undergoing coronary artery bypass surgery. *World J Surg* 2008;**32**: 2643–2649.
65. Kanda T, Hirao Y, Oshima S, Yuasa K, Taniguchi K, Nagai R *et al*. Interleukin-8 as a sensitive marker of unstable coronary artery disease. *Am J Cardiol* 1996;**77**:304–307.

66. Zhou RH, Shi Q, Gao HQ, Shen BJ. Changes in serum interleukin-8 and interleukin-12 levels in patients with ischemic heart disease in a Chinese population. *J Atheroscler Thromb* 2001;**8**:30–32.
67. Romuk E, Skrzep-Poloczek B, Wojciechowska C, Tomasik A, Birkner E, Wodniecki J *et al*. Selectin-P and interleukin-8 plasma levels in coronary heart disease patients. *Eur J Clin Invest* 2002;**32**:657–661.
68. Hashmi S, Zeng QT. Role of interleukin-17 and interleukin-17-induced cytokines interleukin-6 and interleukin-8 in unstable coronary artery disease. *Coron Artery Dis* 2006;**17**:699–706.
69. Abe Y, Kawakami M, Kuroki M, Yamamoto T, Fujii M, Kobayashi H *et al*. Transient rise in serum interleukin-8 concentration during acute myocardial infarction. *Br Heart J* 1993;**70**:132–134.
70. Schömig K, Busch G, Steppich B, Sepp D, Kaufmann J, Stein A *et al*. Interleukin-8 is associated with circulating CD133+ progenitor cells in acute myocardial infarction. *Eur Heart J* 2006;**27**:1032–1037.
71. Riesenberg K, Levy R, Katz A, Galkop S, Schlaeffer F. Neutrophil superoxide release and interleukin 8 in acute myocardial infarction: distinction between complicated and uncomplicated states. *Eur J Clin Invest* 1997; **27**:398–404.
72. de Winter RJ, Manten A, de Jong YP, Adams R, van Deventer SJ, Lie KI. Interleukin 8 released after acute myocardial infarction is mainly bound to erythrocytes. *Heart* 1997;**78**:598–602.
73. Tziakas DN, Chalikias GK, Tentes IK, Stakos D, Chatzikyriakou SV, Mitrousi K *et al*. Interleukin-8 is increased in the membrane of circulating erythrocytes in patients with acute coronary syndrome. *Eur Heart J* 2008; **29**:2713–2722.
74. Oda Y, Tsuruta R, Kasaoka S, Inoue T, Maekawa T. The cutoff values of intrathecal interleukin 8 and 6 for predicting the neurological outcome in cardiac arrest victims. *Resuscitation* 2009;**80**:189–193.
75. Mussack T, Briegel J, Schelling G, Biberthaler P, Jochum M. Effect of stress doses of hydrocortisone on S-100B vs. interleukin-8 and polymorphonuclear elastase levels in human septic shock. *Clin Chem Lab Med* 2005;**43**:259–268.
76. Kim CS, Park HS, Kawada T, Kim JH, Lim D, Hubbard NE *et al*. Circulating levels of MCP-1 and IL-8 are elevated in human obese subjects and associated with obesity-related parameters. *Int J Obes (Lond)* 2006;**30**: 1347–1355.
77. Trøseid M, Lappegård KT, Claudi T, Damås JK, Mørkrid L, Brendberg R *et al*. Exercise reduces plasma levels of the chemokines MCP-1 and IL-8 in subjects with the metabolic syndrome. *Eur Heart J* 2004;**25**:349–355.
78. Rezaie-Majd A, Maca T, Bucek RA, Valent P, Müller MR, Husslein P *et al*. Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. *Arterioscler Thromb Vasc Biol* 2002;**22**: 1194–1199.
79. Ganaha F, Kao EY, Wong H, Elkins CJ, Lee J, Modanlou S *et al*. Stent-based controlled release of intravascular angiostatin to limit plaque progression and in-stent restenosis. *J Vasc Interv Radiol* 2004;**15**:601–608.