EDITORIAL

CHOLESTEROL, CYTOKINES AND DISEASES

A. SAGGINI[1], A. ANOGEIANAKI[2], G. MACCAURO[3], S. TETÉ[4], V. SALINI[5], A. CARAFFA[6], F. CONTI[7], M. FULCHERI[8], R. GALZIO[9] and Y.B. SHAIK-DASTHAGIRISAHEB[10]

[1]Department of Dermatology, University of Rome Tor Vergata, Rome, Italy; [2]Physiology Department, School of Medicine, Aristotle University of Thessaloniki, Greece; [3]Department of Orthopaedics, Catholic University of Rome, Rome, Italy; [4]School of Dentistry, University of Chieti, Italy; [5]Orthopaedics Division, University of Chieti, Chieti, Italy; [6]Orthopaedics Division, University of Perugia, Perugia, Italy; [7]Department of Gyneacology, "Santo Spirito" Hospital, Pescara, Italy; [8]Department of Clinical Psychology, University of Chieti, Italy; [9]Department of Health Sciences, University of L'Aquila, Italy; [10]Department of Medicine, Boston University School of Medicine, Boston, MA, USA

Received June 10, 2011 – Accepted July 28, 2011

A high level of cholesterol is associated with obesity, cardiovascular diseases and atherosclerosis. Immune response in atherosclerosis is mediated by chemokines which attract monocytes, leading to the innate immune response characterised by the production of cytokines. The immunoregulatory cytokines are an important bridge between innate and adductive immunity. TH1 cytokines are involved as effector T cells in inflammatory response, while TH2 cytokines can be anti-inflammatory such as IL-10 and IL-4. It is well known that statins enhance the production of TH2 cytokines whereas the secretion of TH1 cytokines is suppressed. For this purpose, we studied the significance of anti-inflammatory effect and suppression of inflammation by statins. In this paper we revisited the role of cholesterol and cytokines IL-18, IL-10, IL-12, TNF-α, interferon-γ, and chemokines in inflammatory diseases.

Elevated cholesterol (lipids) is associated with obesity and an increased risk of heart attack. Cholesterol can be lowered by diet and/or medication in most patients. The main underlying pathology of cardiovascular disease, the formation of atherosclerotic lesions, can be described as a chronic inflammatory disease that proceeds in the context of enhanced plasma lipid levels (1-6). The inflammatory component of atherosclerosis can be divided into an innate immune response involving monocytes and macrophages that respond to the excessive uptake of (modified) lipoproteins, and an adaptive immune response that involves antigen-specific T cells. The innate immune response in atherosclerosis is initiated by the response of arterial endothelial cells to modified lipoproteins, which leads to their activation and the production of chemokines that attract monocytes to the site of injury where monocytes take up (modified) lipoproteins, and the subsequent foam cell formation leads to an innate immune response characterized by the production of chemokines and interleukins (ILs).

Key words: cholesterol, cytokines, inflammation, chemokines

Mailing address: Dr Y.B. Shaik-Dasthagirisaheb, Dept. of Medicine, Section of Infectious Diseases, Boston University School of Medicine, 650 Albany St., Room 63, Boston, MA, USA
Tel: ++1 617 414 5270 Fax: ++1 617 414 5280
e-mail: bashasy@bu.edu

0394-6320 (2011)

The local production of these mediators enhances the influx of new immune cells and promotes the progression of the atherosclerotic lesion.

The adaptive autoimmune response is a complex response of the entire body and is not restricted to the actual site of injury, the atherosclerotic lesion, but also involves the activation of B and T cells within the lymphoid organs that drain from the atherosclerotic lesions. The B and T cells respond to antigens presented by dendritic cells that have migrated from the lesion to the lymph nodes. This may lead to the production of antibodies specific for the aforementioned antigens by B cells under the control of T-helper (Th) cells (1-6).

Immune cells are the gate keepers that detect cellular damage and initiate a response allowing our body to defend against 'offending' insults.

Endogenous danger signals are from intracellular or secreted extracellular products; some are constitutive, whereas others are inducible and require either neosynthesis or modifications before they can activate the innate immune system. Atherosclerosis is characterized by a chronic inflammatory state in which interplay between metabolic factors and cytokines leads to stimulation of the innate immune system when these signals are detected as a danger.

Circulating leukocytes adhere poorly to the normal endothelium under normal conditions. When the endothelium becomes inflamed, however, it expresses adhesion molecules that bind cognate ligands on leukocytes. Selectins mediate a loose rolling interaction of leukocytes with the inflammatorily-activated endothelial cells. Integrins mediate firm attachment. Chemokines expressed within atheroma provide a chemotactic stimulus to the adherent leukocytes, directing their diapedesis and migration into the intima, where they take residence and divide.

The immunoregulatory cytokine that favours the development of an effector Th1 cell phenotype and IL-12 forms an important bridge between the innate and adaptive immunity. The Th1 cytokines involved in the effector T-cell response aggravate atherosclerosis, whereas Th2 cytokines, such as IL-10, are anti-atherosclerotic.

The rationale to develop additional therapies that aim to diminish the inflammatory response in atherosclerosis is the fact that more than a decade of cholesterol-lowering via statin therapy has successfully reduced the incidence of death from cardiovascular disease (CVD), but still a large percentage of individuals treated with statins suffer from cardiovascular complications.

Macrophages augment the expression of scavenger receptors in response to inflammatory mediators, transforming them into lipid-laden foam cells following the endocytosis of modified lipoprotein particles. Macrophage-derived foam cells drive lesion progression by secreting proinflammatory cytokines. T lymphocytes join macrophages in the intima and direct adaptive immune responses. These leukocytes, as well as endothelial cells, secrete additional cytokines and growth factors that promote the migration and proliferation of SMCs. In response to inflammatory stimulation, vascular SMCs express specialized enzymes that can degrade elastin and collagen, allowing their penetration into the expanding lesion. Endothelial cells (ECs) normally resist leukocyte adhesion.

Interleukin-18

Human preadipocytes of all differentiation stages spontaneously secrete IL-18, supporting the concept that adipocytes participate in innate immunity and that IL-18 mediates a fraction of the complications of obesity such as cardiovascular disease and type 2 diabetes (7). Importantly, IL-18 release from adipocytes of obese patients exceeds approximately 3-fold that from adipocytes of non-obese donors (7). Increased concentrations of IL-18 associate with a significantly increased risk of developing type 2 diabetes in middle-aged men and women after adjustment for classic risk factors such as age, body mass index, systolic blood pressure, and physical activity (8). In addition, IL-18 may predict development of the metabolic syndrome, with concentrations rising in parallel to increasing numbers of metabolic risk factors (9-13).

IL-18 is not currently considered a useful screening tool for the presence of subclinical atherosclerosis in the general population, on the basis of results from 2 large independent imaging studies (14-17). However, in the AtheroGene study, IL-18 serum concentration independently predicted cardiovascular death in patients with documented

coronary artery disease (18). In this patient population, those within the highest quartile of IL-18 had a 3.3-fold increase in hazard risk compared to those in the first quartile (18). In addition, data from the Prospective Epidemiological Study of Myocardial Infarction (PRIME) demonstrate an independent association between baseline plasma IL-18 concentration in healthy middle-aged men and future coronary events (19-21). This association remains after adjustment for classic cardiovascular risk factors. These studies suggest that IL-18 measurement may add prognostic information to lipid and inflammatory markers in patients with or without clinically established atherosclerotic disease.

Chemoattractant factors, which include monocyte chemoattractant protein-1 produced by vascular wall cells in response to modified lipoproteins, direct the migration and diapedesis of adherent monocytes (22-23). Monocytic cells directly interacting with human ECs increase monocyte matrix metalloproteinase 9 (MMP-9) production several fold, allowing for the subsequent infiltration of leukocytes through the endothelial layer and its associated basement membrane (24-26). Within the intima, monocytes mature into macrophages under the influence of macrophage colony-stimulating factor, which is overexpressed in the inflamed intima (27-30). Macrophage colony-stimulating factor stimulation also increases macrophage expression of scavenger receptors, members of the pattern-recognition receptor superfamily, which engulf modified lipoproteins through receptor-mediated endocytosis.

T cells, representing the adaptive arm of the immune response, also play a critical role in atherogenesis, entering lesions in response to the chemokine-inducible protein-10, monokine induced by IFN-γ, and IFN-inducible T cell chemoattractant (31). The CD4+ subtype, which recognizes antigens presented as fragments bound to major histocompatibility complex class II molecules, predominates in the lesion. Interestingly, human lesions contain CD4+ T cells reactive to the disease-related antigens associated with oxidized LDL (32). The atherosclerotic lesion contains cytokines that promote a T-helper 1 response, inducing activated T cells to differentiate into T-helper 1 effector cells (33-35). These cells amplify the local inflammatory activity by producing proinflammatory cytokines such as IFN- and CD40 ligand (CD40L, CD154), which contribute importantly to plaque progression. Adiponectin also directly affects the function of endothelial cells, reducing VCAM-1 expression and macrophages, decreasing the expression of scavenger receptors and the production of TNF-α (36-40).

Foam cell accumulation characterizes fatty streaks, whereas deposition of fibrous tissue defines the more advanced atherosclerotic lesion. Smooth muscle cells (SMCs) synthesize the bulk of the extracellular matrix that characterizes this phase of plaque evolution (41). In response to platelet-derived growth factor released by activated macrophages and endothelial cells, and silent plaque disruptions that lead to clinically unapparent mural thrombi, SMCs migrate from the tunica media into the intima via degradation of the extracellular matrix mediated by MMP-9 and other proteinases (42-44). In the intima, SMCs proliferate under the influence of various growth factors and secrete extracellular matrix proteins, including interstitial collagen, especially in response to transforming growth factor-β and platelet-derived growth factor. This process causes the lesion to evolve from a lipid-rich plaque to a fibrotic and, ultimately, a calcified plaque that may create a stenosis.

Human atheromata express IL-18 and increased concentrations of its receptor subunits, IL-18R/β (45-48). IL-18 occurs predominantly as the mature 18-kD form and colocalizes with mononuclear phagocytes, while ECs, SMCs and macrophages all express IL-18R/β. Importantly, IL-18 signaling evokes essential effectors involved in atherogenesis, e.g., adhesion molecules (VCAM-1), chemokines (IL-8), cytokines (IL-6), and matrix metalloproteinases (MMP-1/-9/-13). In addition, IL-18, particularly in combination with IL-12, is a proximal inducer and regulator of the expression of IFN-γ, a major proinflammatory cytokine, during atherogenesis. Interestingly, IL-18 induces IFN-γ expression not only in T cells (49-53), but also in macrophages and, surprisingly, even in SMCs, thus activating in a paracrine mode several proinflammatory pathways operating during atherogenesis (54-57).

One study showed that a high-fat meal increases IL-18 concentrations and decreases adiponectin concentrations in both non-diabetic and diabetic subjects, and a high-carbohydrate high-fiber meal,

decreases IL-18. The high-carbohydrate low-fiber meal significantly decreases adiponectin concentrations in diabetic subjects, whereas IL-8 concentrations are not affected.

In another study, a 4-week consumption of 30 g/d of alcohol from red wine led to a significant decrease in serum concentrations of hsCRP (21%), as well as endothelial adhesion molecules (vascular cell adhesion molecule-1 [VCAM-1], ICAM-1) in healthy adult men. Also, most of the studies have reported effects on CRP, whereas few have focused on pro-inflammatory cytokines such as IL-1β, IL-6, or TNF-α. Future research needs to focus on the role of specific dietary factors on biomarkers of inflammation, because they may modulate inflammation through different mechanisms. Therapeutic lifestyle changes remain the cornerstone in modulating inflammation and cardiovascular disease and much further research is needed to define the anti-inflammatory or pro-inflammatory effects of specific dietary factors.

Immunization against endogenous proteins in atherosclerosis has been applied to cytokines. As outlined, Th1 cytokines such as TNF-α, IFN-γ and IL-12 play a pro-atherogenic role. More recent studies have, however, shown that a deficiency in TNF-α reduces atherosclerosis (58-61), whereas treatment with TNF blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis (RA) (62-65). TNF neutralization therapy is accompanied by increased HDL-cholesterol levels and decreased C-reactive protein and IL-6 levels after 2 weeks of treatment (66), but prolonged therapy affects lipoprotein profiles in a pro-atherogenic fashion (67-70).

TNF-α is a pivotal cytokine in the pathogenesis in RA and TNF-α blockade has been shown to be very effective in controlling disease activity. TNF-α antagonists, frequently in combination with methotrexate, appear to be the most effective anti-rheumatic drugs and the data available to date do not indicate major safety problems.

At present, three anti-TNFα blockers are available for clinical use. Infliximab is a chimeric mouse/human anti-TNFα monoclonal antibody and binds to soluble as well as membrane-bound TNFα. Infliximab is intravenously administered, and after the initial infusion it is given at two, six and then every 8 weeks. Etanercept consists of two human TNF-α receptors linked to each other and binds to circulating as well as cell-bound TNF-α molecules. Etanercept is given subcutaneously once or twice weekly. Adalimumab is a human immunoglobulin (Ig) G1 antibody and is administered subcutaneously once every two weeks.

There is an increasing number of reports regarding the effects of treatment with tumor necrosis factor (TNF) blocking agents on the lipid profile in RA patients with active disease. These investigations with TNF blocking agents reveal a transient increase of total cholesterol and HDL-C, mostly accompanied with improvement of the atherogenic index, during the first few months of the TNF blocking agents.

Immunization against IL-12 is accomplished by administering a complex of IL-12 with a T-cell epitope in combination with a water-soluble adjuvant. This immunization induces antibodies that functionally block IL-12, and specifically diminishes the induction of IFN-γ by IL-12 in vaccinated mice (71-75). The blockade of IL-12 by the vaccination of LDL receptor-deficient mice results in strongly reduced (70%) atherogenesis accompanied by a strong, beneficial reduction in circulating IFN-γ levels and expression in the lesion itself and an increase in plaque stability.

A recent study in which IFN-γ was blocked by the administration of a soluble interferon receptor also shows that interruption of the IFN-γ pathway inhibits the initiation and progression of atherosclerosis (76-79). The effect on plaque stability is explained by the observation that blockade of IL-12 may diminish the recruitment of T cells into the plaque (80-83).

Chemokine pathways

Annexin V and lamin A were potently decreased by homocysteine in HUVEC cells. Annexin V is an anti-thrombotic molecule. Mutations in nuclear lamin A result in perturbations of plasma lipids associated with hypertension. Genistein reversed the homocysteine-induced decrease of these anti-atherogenic proteins. Ox-LDL treatment increased ubiquitin conjugating enzyme 12, a protein involved in foam cell formation.

ET-1 is elevated in rats with genetically determined hypertension (84) and in hypertensive patients (85-88). Besides their vasoconstructive

properties, endothelins stimulate the production of cytokines, growth factors (including vascular endothelial growth factor, VEGF) and extracellular matrix proteins (89-92). Furthermore, endothelins enhance neutrophil adhesion and platelet aggregation, and are chemotactic for monocytes/macrophages.

A number of studies during the past year have implicated an important role of Tregs in atherosclerosis (93-95). Tregs can counteract effector T cells and activation of Tregs may form an attractive new immunotherapy for atherosclerosis.

The main subsets of Tregs are $CD4^+CD25^+Foxp3^+$ T cells (natural Tregs), type 1 Tregs and Th3 cells (adaptive Tregs) that may acquire Foxp3 expression in the periphery, and all these types of Tregs are essential for the maintenance of peripheral tolerance (93-96). Natural Tregs are thymus-derived, express the transcription factor forkhead box p3 (Foxp3) combined with the surface receptors cytotoxic lymphocyte-associated antigen 4 and the glucocorticoid-induced TNF receptor family-related gene (GITR), and mainly prevent autoimmunity. Type 1 Tregs regulate immune responses in transplantation, allergy and autoimmunity. The regulatory function of natural Tregs is mainly mediated by cell–cell contact via surface-bound transforming growth factor beta (TGF-β) and cytotoxic lymphocyte-associated antigen 4 (97), whereas type 1 Tregs and Th3 cells rely on soluble IL-10 and TGF-β, respectively, for their suppressive activity. The Treg subsets, type 1 Treg and Th3 cells, can be enhanced by nasal or oral tolerance induction, respectively.

A final class of immune cells that modulate atherosclerosis is NKT cells, which respond to lipid antigens. NKT cells express an invariant T-cell receptor composed of Vα14 and Jα18 subunits paired with a restricted set of Vβ chains. NKT cells recognize (glyco)lipid antigens presented by CD1d expressed on macrophages and dendritic cells (98-103). Upon recognition of a glycolipid antigen, invariant NKT cells rapidly produce a unique mixture of cytokines, including Th1 (IFN-g, IL-12 and TNF-α) and Th2 (IL-4, IL-5, IL-10 and IL-13) cytokines (104-106). NKT cells can be activated by the *in-vivo* administration of α-galactosylceramide, and mature NKT cells respond with an early burst of IL-4 followed by IFN-γ, which are both pro-atherogenic cytokines (107-109). Repeated activation of NKT cells induces an adaptive immune response polarized towards Th2 cytokines, which may be protective against experimental autoimmune diseases (110-113). NKT cells have so far been identified as pro-atherogenic: $apoE^{-/-}$ or $LDLr^{-/-}$ mice crossed with $CD1d^{-/-}$ mice (NKT cell deficient) exhibit a 25% reduction in lesion size and NKT cell activation by treatment with α-galactosylceramide or OCH (a sphingosine-truncated analogue of α-galactosylceramide) in $apoE^{-/-}$ mice results in an increased lesion size (114). NKT cells are found in the aortic arch of atherosclerosis-prone mice fed a western-type diet, and NKT cells have been identified in human lesions in the shoulder of the lipid core and in the fibrous cap (115), especially in close connection with dendritic cells. It was recently shown that the transfer of spleen-derived NKT cells from Vα14Jα18 T-cell receptor transgenic mice resulted in a 73% increase in lesion area (116) . Interestingly, VanderLaan et al. (117) also demonstrated that an endogenous serum lipid carried by lipoproteins activates the NKT cells, which may provide a possibility to intervene in the recognition or level of this lipid and to modulate atherosclerosis.

A cluster of hormonal, metabolic, and cytokine changes that promote inflammation and chronic disease, including diabetes and CVD, accompany the accumulation of excess adipose tissue, particularly with adiposity of the visceral compartment.

Patients consuming the Mediterranean-style diet had higher intake of fruits, vegetables, nuts, whole grains, and olive oil in comparison to the control group. These patients showed a concomitant decrease in serum concentrations of hsCRP and cytokines (IL-6, IL-7, and IL-18, $P<0.05$), and decreased insulin resistance compared with the control group.

Statins

Competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) act at a rate-limiting step in cholesterol synthesis by strongly blocking conversion of HMG-CoA to mevalonate. Inflammatory processes play a crucial role in the initiation and progression of atherosclerosis and coronary heart disease such as myocardial infarction. Endothelial dysfunction with vascular injury in response to cardiovascular

risk factors is initiated by the migration of leukocytes, including monocyte/macrophages and T lymphocytes. Adhesion molecules, proinflammatory cytokines, and chemokines mediate the extravasation of inflammatory cells.

Within atherosclerotic sites, endothelial cells and leukocytes both have increased their expression of numerous adhesion molecules and their receptors, including intracellular adhesion molecule-1, vascular cell adhesion molecule-1, β_1-integrin, β_2-integrin and P-selectin (118-121). *In vivo* studies (122-123) have shown that blocking these adhesion molecule interactions by the administration of antibodies or gene targeting attenuates the formation of atherosclerotic lesions, indicating a potential therapeutic role for inhibition of leukocyte adhesion and extravasation. *In vitro* studies demonstrate the beneficial effects of statins by decreasing adhesion molecules, such as monocyte CD11b and the leukocyte function antigen-1 (124).

Furthermore, statins suppress the secretion of proinflammatory cytokines including IL-1β and IL-6, but not TNF-α. These results support human studies suggesting that statins decrease the number of inflammatory cells in atherosclerotic plaque (125). Nitric oxide (NO) plays a crucial role in mediating this anti-inflammatory action.

The new statin, rosuvastatin, has significant anti-inflammatory effects via inhibition of P-selectin synthesis by endothelial cells. The protective action of the statin is mediated by vascular endothelial NO (126). Rosuvastatin has no effect on leukocyte–endothelium interactions in endothelial NOS nitric oxide synthase (eNOS)-deficient mice, emphasizing the important role of NO in anti-inflammation. Thus, increased NO production by statins could explain the modulation of these leukocyte–endothelium interactions. The suppression of inflammation by statin treatment reduces the production of high-sensitivity CRP, a clinical marker of inflammation produced by the liver in response to proinflammatory cytokines such as IL-6 (127). CRP expression is elevated in patients with coronary heart disease. Patients who clinically benefit from statin therapy also have abnormally elevated CRP concentrations (127). As statins decrease CRP concentrations in serum (127). Statin use would contribute to the prevention and remission of inflammatory diseases. Thus, statins have beneficial effects as immunosuppressors after cardiac transplantation (128). Multiple sclerosis is believed to develop when the body's immune cells, such as T-helper cells, attack myelin, the insulating, fatty sheath around nerve cells. This damages the myelin and the underlying neurons in both the brain and spinal cord, leading to impaired transmission of nerve impulses and progressive physical disability. Youssef et al (2002) found that atorvastatin inhibits the expression by brain cells of a pivotal regulatory protein CIITA, which regulates the expression of MHC-II molecule (129).

Statins up-regulate eNOS expression (130-133), stimulate endothelial NO production (134) and increase the supply of the NO substrate L-arginine (135), important in cardiac function. In an animal study using magnetic resonance imaging (MRI) post-myocardial infarction (MI) to assess remodelling, the effect of cerivastatin on attenuating hypertrophy after MI was completely abrogated by NOS inhibition (136-138). Statins are also known to inhibit mitogen-activated protein kinase (MAPK), and to interfere with cellular proliferation (139-141), the integrity of the actin cytoskeleton and the induction of matrix proteins (142-143), all important in the development of heart failure.

The antifibrotic effects of statins are likely to be very important in the beneficial effects on mortality post-MI. Connective tissue growth factor (CTGF; also known as CCN2) is a profibrotic inducer of matrix proteins activated by the profibrotic factors transforming growth factor-β (TGF-β) and AngII (144). This has been shown to be reduced with statins (145).

A major effect of statins on fibrosis is via its effect on the expression of the nuclear transcription factor NF-kB, a controller of gene encoding cytokines, chemokines, interferons, MHC proteins, growth factors, cell adhesion molecules and viruses, which is activated by hypoxia and hyperglycaemia. Lastly, the pro-angiogenic properties of statins and their effects on re-endothelialization following vessel injury are many, and statins have been shown (146) to induce new blood vessel growth in ischaemic limbs in a manner similar to vascular endothelial growth factor (VEGF), an important effect in cardiac disease post-ischaemia.

Statins effectively repress the induced MHC-II

protein and gene expression by IFN-γ and, thus, act as direct repressors of MHC-II-mediated T-cell activation, whereas statins do not affect constitutive expression of MHC-II in APC, such as dendritic cells (DCs) and B lymphocytes.

It has also been shown that statins selectively block the β-2 integrin, leukocyte function antigen-1 (LFA-1) (147). Leukocyte function antigen-1 is constitutively expressed in an inactive state on the surface of leukocytes. In response to several stimuli, including the T-cell receptor cross-linking with MHC-II complex, LFA-1 binds to intercellular adhesion molecule-1 (ICAM-1) and provides a potent costimulatory signal for activated T cells. The inhibitory effect of statins on LFA-1 is unrelated to the inhibition of HMG-CoA reductase, but occurs via the binding to a novel allosteric site within LFA-1 (148). Thus, statin-induced immunosuppression can also be related to the inhibition of LFA-1/ICAM-1 interaction.

Non-lipid related functions of statins might implicate a regulation of many different inflammatory molecules. Beneficial effect of statins could also be due to the type of immune response they induce. In a murine model of autoimmune encephalomyelitis, atorvastatin induced secretion of T_H2 cytokines (IL-4, -5, and -10) and transforming growth factor β (TGF-β), whereas secretion of T_H1 cytokines (IL-2, IL-12, IFN-γ, and TNF-α) was suppressed (129). It has been shown that lovastatin induced a reduction in T-cell proliferation and a decrease in IFN-γ production, whereas it had no effect on T_H2 cytokine production. In a patient with no known cardiovascular disease, pravastatin reduced proinflammatory cytokine production (148); furthermore, in a recent study, it has been observed that, whereas it has no effect on T_H2 cell functions, atorvastatin can reduce T_H1 development in patients with acute myocardial infarction, suggesting that reduction of T_H1 bias may be one of the mechanisms through which atorvastatin improves heart function after acute myocardial infarction. Taken together, these animal and human findings suggest that statins regulate T_H1/T_H2 imbalance both *in vitro* and *in vivo*. Thus, all these observations could explain the beneficial effect of statins in atherosclerosis because it has been shown that the T_H2 cytokines have anti-atherogenic properties, and their overexpression protects against atherosclerosis.

Statin-induced shift to a T_H2 immune response

Statins enhance secretion of T_H2 cytokines such as IL-4, IL-5, IL-10, and TGF-β, whereas secretion of T_H1 cytokines IL-2, IL-6, IL-12, IFN-γ, and TNF-α is suppressed by statins. Increasing evidence suggests a central role for the CD40–CD40L signaling pathway in the pathogenesis of atherosclerosis (149), and it has been shown that blocking CD40–CD40L interactions significantly prevents the development of atherosclerotic plaques and reduces pre-established lesions (150). Moreover, CD40 signaling has been implicated in other chronic disorders such as rheumatoid arthritis, multiple sclerosis, and allograft rejection after organ transplantation (151). CD40 acts as costimulatory molecule to enhance T-cell activation by DCs. Dendritic cells are APCs with a unique ability to initiate a primary immune response. The activation of T cells by DCs requires the maturation of DCs with the upregulation of costimulatory molecules, such as CD40, and MHC-II molecules. A recent study that demonstrates the colocalization of DC and T cells, as well as the expression of MHC-II and costimulatory molecules on DCs in atherosclerotic plaques, suggests that DCs initiate an antigen-specific immune response, contributing to the progression of atherosclerosis (152). Yilmaz et al. (2004) recently showed that, in contrast to non-treated DCs, statin-pretreated DCs exhibited an immature phenotype and a significantly lower expression of the maturation-associated markers, CD40 and MHC-II molecules. The authors also showed that statins significantly reduced the ability of cytokine-stimulated DC to induce T-cell proliferation (153).

REFERENCES

1. Robertson AL, Hansson GK. T cells in atherogenesis: for better or for worse? Arterioscler Thromb Vasc Biol 2006; 26:2421-32.
2. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev 2006; 86:515-81.
3. Palinski W, Miller E, Witztum JI. Immunization of low density lipoprotein (LDL) receptor-deficient

rabbits with homologous malondialdehyde-modified LDL reduces atherogenesis. Proc Natl Acad Sci USA 1995; 92:821-25.

4. Richardson VJ. Divergent and synergistic regulation of matrix metalloprotease production by cytokines in combination with C-C chemokines. Int J Immunopathol Pharmacol 2010; 23:715-26.
5. Li Q, Kobayashi M, Inagaki H, et al. A day trip to a forest park increases human natural killer activity and the expression of anti-cancer proteins in male subjects. J Biol Regul Homeost Agents 2010; 24: 157-65.
6. Symeonidou I, Kourelis A, Frydas I, Karagouni E, Anogeianaki A, Hatzistilianou M, Frydas S. Modulation of NF-KB signalling pathways by parasites. J Biol Regul Homeost Agents 2010; 24: 471-79
7. Skurk T, Kolb H, Muller-Scholze S, Rohrig K, Hauner H, Herder C. The proatherogenic cytokine interleukin-18 is secreted by human adipocytes. Eur J Endocrinol 2005; 152:863-68.
8. Thorand B, Kolb H, Baumert J, Koenig W, Chambless L, Meisinger C, et al. Elevated levels of interleukin-18 predict the development of type 2 diabetes: results from the MONICA/KORA Augsburg Study, 1984–2002. Diabetes 2005; 54:2932-38.
9. Hung J, McQuillan BM, Chapman CM, Thompson PL, Beilby JP. Elevated interleukin-18 levels are associated with the metabolic syndrome independent of obesity and insulin resistance. Arterioscler Thromb Vasc Biol 2005; 25:1268-73.
10. Profumo E, Buttari B, Alessandri C, Conti F, Capoano R, Valesini G, Salvati B, Riganò R. Beta2-glycoprotein I is a target of T cell reactivity in patients with advanced carotid atherosclerotic plaques. Int J Immunopathol Pharmacol 2010; 23: 73-80.
11. Zicari AM, Tancredi G, Rugiano A, Zappalà D, Midulla F, Indinnimeo L, De Castro G, Celani C, Duse M. An infant with diaphragmatic eventration and respiratory distress. J Biol Regul Homeost Agents 2010; 24:481-84.
12. Angelini A, Di Ilio C, Castellani ML, Conti P, Cuccurullo F. Modulation of multidrug resistant P-glycoprotein activity by flavonoids and honokiol in human doxorubicin-resistant sarcoma cells (MES-SA/Dx-5): implications for natural sedatives as chemosensitizing agents in cancer therapy. J Biol Regul Homeost Agents 2010; 24:197-205.
13. Hossein-Nezhad A, Mirzaei K, Birami Jamal F, Mirfakhraei R, Sedighi N. Variation in the COX-2 gene may modify the effect of alendronate on vertebral fracture prevention. Eur J Inflamm 2010; 8: 143-49.
14. Chapman CM, McQuillan BM, Beilby JP, Thompson PL, Hung J. Interleukin-18 levels are not associated with subclinical carotid atherosclerosis in a community population: the Perth Carotid Ultrasound Disease Assessment Study (CUDAS). Atherosclerosis 2006; 189:414-19.
15. Zirlik A, Abdullah SM, Gerdes N, Macfarlane L, Schonbeck U, Khera A, et al. Interleukin-18, the metabolic syndrome, and subclinical atherosclerosis: results from the Dallas Heart Study. Arterioscler Thromb Vasc Biol 2007.
16. Corsaro A, Anselmi C, Polano M, Aceto A, Florio T, De Nobili M. The interaction of humic substances with the human prion protein fragment 90-231 affects its protease K resistance and cell internalization. J Biol Regul Homeost Agents 2010; 24:27-39.
17. Preetha SP, Devaraj H. Role of sulphated polysaccharides from *Sargassum wightii* in the control of diet-induced hyperlipidemia and associated inflammatory complications in rats. Eur J Inflamm 2010; 8:23-30.
18. Blankenberg S, Tiret L, Bickel C, Peetz D, Cambien F, Meyer J, et al. Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina. Circulation 2002; 106:24-30.
19. Blankenberg S, Luc G, Ducimetiere P, Arveiler D, Ferrieres J, Amouyel P, et al. Interleukin-18 and the risk of coronary heart disease in European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Circulation 2003; 108:2453-59.
20. Sharma JN. Activation of the bradykinin system by angiotensin-converting enzyme inhibitors. Eur J Inflamm 2010; 8:55-61
21. Malerba M, Radaeli A, Mancuso S, Polosa R. The potential therapeutic role of potassium channel modulators in asthma and chronic obstructive pulmonary disease. J Biol Regul Homeost Agents

2010; 24:123-30.

22. Boring L, Gosling J, Cleary M, Charo IF. Decreased lesion formation in CCR2-/- mice reveals a role for chemokines in the initiation of atherosclerosis. Nature (Lond) 1998;394:894-97.
23. Gu L, Okada Y, Clinton SK, Gerard C, Sukhova GK, Libby P, et al. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. Mol Cell 1998; 2:275-81.
24. Amorino GP, Hoover RL. Interactions of monocytic cells with human endothelial cells stimulate monocytic metalloproteinase production. Am J Pathol 1998; 152:199-207.
25. Zhang QL, Niu Q, Niu PY, Ji XL, Zhang C, Wang L. Novel interventions targeting on apoptosis and necrosis induced by aluminum chloride in neuroblastoma cells. J Biol Regul Homeost Agents 2010; 24:137-48.
26. Shaik-Dasthagirisaheb YB, Castellani ML, Tripodi D, et al. PGD2, IL-1-family members and mast cells. Eur J Inflamm 2010; 8:137-42.
27. Rajavashisth TB, Andalibi A, Territo MC, et al. Induction of endothelial cell expression of granulocyte and macrophage colony-stimulating factors by modified low-density lipoproteins. Nature (Lond) 1990; 344:254-57.
28. Clinton SK, Underwood R, Hayes L, Sherman ML, Kufe DW, Libby P. Macrophage colony-stimulating factor gene expression in vascular cells and in experimental and human atherosclerosis. Am J Pathol 1992; 140:301-16.
29. Mazzoccoli G, De Cata A, Greco A, Carughi S, Giuliani F, Tarquini R. Circadian rhythmicity of lymphocyte subpopulations and relationship with neuro-endocrine system. J Biol Regul Homeost Agents 2010; 24:341-50.
30. Shekhawat N, Vijayvergia R. Investigation of anti-inflammatory, analgesic and antipyretic properties of *Madhuca indica* Gmel. Eur J Inflamm 2010; 8:165-71.
31. Mach F, Sauty A, Iarossi AS, Sukhova GK, Neote K, Libby P, et al. Differential expression of three T lymphocyte-activating CXC chemokines by human atheroma-associated cells. J Clin Invest 1999; 104: 1041-50.
32. Stemme S, Faber B, Holm J, Wiklund O, Witztum JL, Hansson GK. T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. Proc Natl Acad Sci USA 1995; 92:3893-97.
33. Robertson AK, Hansson GK. T cells in atherogenesis: for better or for worse? Arterioscler Thromb Vasc Biol 2006; 26:2421-32.
34. Magni P, Ruscica M, Dozio E, Passafaro L, Stefani L, Morelli P, Banfi G, Corsi MM. Plasma adiponectin and leptin concentrations in professional rugby players. J Biol Regul Homeost Agents 2010; 24:87-91.
35. Castellani ML, Anogeianaki A, Felaco P, Toniato E, De Lutiis MA, Shaik B, Fulcheri M, Vecchiet J, Tetè S, Salini V, Theoharides TC, Caraffa A, Antinolfi P, Frydas S, Conti P, Cuccurullo C, Ciampoli C, Cerulli G. IL-34 a newly discovered cytokine. Eur J Inflamm 2010; 8:63-66
36. Okamoto Y, Kihara S, Funahashi T, Matsuzawa Y, Libby P. Adiponectin: a key adipocytokine in metabolic syndrome. Clin Sci (Lond) 2006; 110: 267-78.
37. Fantuzzi G, Mazzone T. Adipose tissue and atherosclerosis: exploring the connection. Arterioscler Thromb Vasc Biol 2007; 27:996-1003.
38. Borrelli I, Loffredo S, Staiano RI, Frattini A, Bergamaschi A, Marone G, Triggiani M. Benzene metabolites inhibit the release of proinflammatory mediators and cytokines from human basophils. Int J Immunopathol Pharmacol 2010; 23:737-44.
39. Garzaro M, Pecorari G, Nadalin J, Raimondo L, Palmo A, Baccega M, Giordano C. Objective and subjective assessment of digestion after ingestion of an iced dessert in healthy volunteers. J Biol Regul Homeost Agents 2010; 24:215-20.
40. Amanti A, Potalivo G, Pelosi F, Rende R, Cerulli G. Randomized prospective study on the use of Eufiss in the prevention of infections in patients treated with external fixation. Eur J Inflamm 2010; 8:189-92.
41 Raines EW, Ferri N. Thematic review series: the immune system and atherogenesis, cytokines affecting endothelial and smooth muscle cells in vascular disease. J Lipid Res 2005; 46:1081-92.
42 Mason DP, Kenagy RD, Hasenstab D, et al. Matrix

metalloproteinase-9 overexpression enhances vascular smooth muscle cell migration and alters remodeling in the injured rat carotid artery. Circ Res 1999; 85:1179-85.

43. Palumbo P, Melchiorre E, La Torre C, et al. Effects of phosphatidylcholine and sodium deoxycholate on human primary adipocytes and fresh human adipose tissue. Int J Immunopathol Pharmacol 2010; 23:481-89.
44. Cianci R, Pagliari D, Pietroni V, Landolfi R, Pandolfi F. Tissue infiltrating lymphocytes: the role of cytokines in their growth and differentiation. J Biol Regul Homeost Agents 2010; 24:239-29.
45 Gerdes N, Sukhova GK, Libby P, Reynolds RS, Young JL, Schonbeck U. Expression of interleukin (IL)-18 and functional IL-18 receptor on human vascular endothelial cells, smooth muscle cells, and macrophages: implications for atherogenesis. J Exp Med 2002; 195:45-257.
46. Migliore A, Padalino C, Massafra U, et al. Intra-articular injections of infliximab in the treatment of inflammatory rheumatic diseases: case reports and review of literature. Eur J Inflamm 2010; 8:49-54.
47. Genovese T, Melani A, Esposito E, et al. Selective adenosine A2A receptor agonists reduce the apoptosis in an experimental model of spinal cord trauma. J Biol Regul Homeost Agents 2010; 24:73-86.
48. Yanagitani N, Shimizu Y, Kazama T, Dobashi K, Ishizuka T, Mori M. Eosinophilic bronchiolitis indicating eosinophilic airway disease with overexpression of carcinoembryonic antigen in sinus and bronchiole: case report. J Biol Regul Homeost Agents 2010; 24:99-102.
49. Okamura H, Tsutsi H, Komatsu T, et al. Cloning of a new cytokine that induces IFN-gamma production by T cells. Nature (Lond) 1995; 378:88-91.
50. Riccioni G, D'Orazio N, Speranza L, et al. Carotenoids and asymptomatic carotid atherosclerosis. J Biol Regul Homeost Agents 2010; 24:447-52.
51. Giuca MR, Giuggioli E, Metelli MR, Pasini M, Iezzi G, D'Ercole S, Tripodi D. Effects of cigarette smoke on salivary superoxide dismutase and glutathione peroxidase activity. J Biol Regul Homeost Agents 2010; 24:359-66.
52. Sirotkin AV, Chrenek P, Pivko J, Balazi A, Makarevich AV. Phosphodiesterase inhibitor 3-isobutyl-1-methyl-xanthine affects ovarian morphology and stimulates reproduction in rabbits. Eur J Inflamm 2010; 8:173-79.
53. Calabrò P, Riegler L, Limongelli G, et al. Production of serum amyloid A in response to inflammatory cytokines by human adipocytes. Eur J Inflamm 2010; 8:99-105.
54. Lucchese A, Serpico R, Guida A, Crincoli V, Scully C, Kanduc D. Interkeratin peptide-protein interactions that promote HPV16 E7 gene expression. Int J Immunopathol Pharmacol 2010; 23:857-64.
55. Fernandez TD, Torres MJ, Lopez S, Antunez C, Gomez E, Del Prado MF, Canto G, Blanca M, Mayorga C. Role of effector cells (CCR7-CD27-) and effector-memory cells (CCR7-CD27+) in drug-induced maculopapular exanthema. Int J Immunopathol Pharmacol 2010; 23:437-47.
56. Pollice R, Bianchini V, Conti CM, Mazza M, Roncone R, Casacchia M. Cognitive impairment and perceived stress in schizophrenic inpatients with post-traumatic stress disorder. Eur J Inflamm 2010; 8:211-19.
57. Ursini F, Succurro E, Grembiale A, Rudi S, Grembiale RD, Arturi F. Sudden progression from impaired glucose tolerance to type 2 diabetes after discontinuation of administration of anti-tumor necrosis factor-alpha antibody infliximab. Int J Immunopathol Pharmacol 2010; 23:961-63.
58. Libby P, Aikawa M. Stabilization of atherosclerotic plaques: new mechanisms and clinical targets. Nat Med 2002; 8:1257-62.
59. Chiavaroli A, Brunetti L, Orlando G, Recinella L, Ferrante C, Leone S, Di Michele P, Di Nisio C, Vacca M. Resveratrol inhibits isoprostane production in young and aged rat brain. J Biol Regul Homeost Agents 2010; 24:441-46
60. Sancini A, Caciari T, Andreozzi G, et al. Respiratory parameters in traffic policemen exposed to urban pollution.. Eur J Inflamm 2010; 8:157-63.
61. Galliera E, Locati M, Mantovani A, Corsi MM. Chemokine system: new inflammatory markers on the horizon. Eur J Inflamm 2010; 8:1-6.
62. Skalen K, Gustafsson M, Rydberg EK, Hulten LM, Wiklund O, Innerarity TL, et al. Subendothelial retention of atherogenic lipoproteins in early

atherosclerosis. Nature (Lond) 2002; 417:750-54.

63. Marchese E, Vignati A, Albanese A, Nucci CG, Sabatino G, Tirpakova B, Lofrese G, Zelano G, Maira G. Comparative evaluation of genome-wide gene expression profiles in ruptured and unruptured human intracranial aneurysms. J Biol Regul Homeost Agents 2010; 24:185-95.
64. Guerranti R, Bertocci E, Fioravanti A, Papakostas P, Montella A, Guidelli GM, Cortelazzo A, Nuti R, Giordano N. Serum proteome of patients with systemic sclerosis: molecular analysis of expression and prevalence of haptoglobin alpha chain isoforms. Int J Immunopathol Pharmacol 2010; 23:901-9.
65. Mazzoccoli G, Pazienza V, Piepoli A, Muscarella LA, Inglese M, De Cata A, Giuliani F, Tarquini R. Hypothalamus-hypophysis-thyroid axis function in healthy aging. J Biol Regul Homeost Agents 2010; 24:433-39.
66 Kruth HS. Sequestration of aggregated low-density lipoproteins by macrophages. Curr Opin Lipidol 2002; 13:483-88.
67 Williams KJ, Tabas I. The response-to-retention hypothesis of atherogenesis reinforced. Curr Opin Lipidol 1998; 9:471-74.
68. Tarozzi A, Merlicco A, Morroni F, Bolondi C, Di Iorio P, Ciccarelli R, Romano S, Giuliani P, Hrelia P. Guanosine protects human neuroblastoma cells from oxidative stress and toxicity induced by amyloid-β peptide oligomers. J Biol Regul Homeost Agents 2010; 24:297-306.
69. Marotta F, Naito Y, Bishier MP, Jain S, Yadav H, Minelli E, Kumari A, Solimene U, Sollano J. Subclinical candiduria in patients with gastrointestinal malignancies: a preliminary study on the protective effect of a natural phytocompound. J Biol Regul Homeost Agents 2010; 24:317-24.
70. Neri G, Citraro L, Martinotti S, Toniato E, Castriotta A, De Rosa M, Filograna Pignatelli G. The role of atypical microorganisms in chronic oropharyngeal phlogosis. Eur J Inflamm 2010; 8:201-10.
71. Miller YI, Chang MK, Binder CJ, Shaw PX, Witztum JL. Oxidized low density lipoprotein and innate immune receptors. Curr Opin Lipidol 2003;14:437-45.
72. Tatone C, Carbone MC, Campanella G, Festuccia C, Artini PG, Talesa V, Focarelli R, Amicarelli F. Female reproductive dysfunction during ageing: role of methylglyoxal in the formation of advanced glycation end-products in ovaries of reproductively-aged mice. J Biol Regul Homeost Agents 2010; 24: 63-72.
73. Riccioni G, Bucciarelli V, Scotti L, Aceto A, D'Orazio N, Di Ilio E, Bucciarelli T. Relationship between asymmetric dimethylarginine and asymptomatic carotid atherosclerosis. J Biol Regul Homeost Agents 2010; 24:351-58.
74. Hossein-Nezhad A, Khoshniat Nikoo M, Mirzaei K, Mokhtarei F, Aghaei Meybodi HR. Comparison of the bone turn-over markers in patients with multiple sclerosis and healthy control subjects. Eur J Inflamm 2010; 8:67-73.
75. Sadeghi Koupaei MT, Ahangari G, Samanguiei Sh. Inflammatory mediator serotonin receptor gene (5-HTR3A) expression changes on human peripheral blood lymphocytes in rheumatoid arthritis. Eur J Inflamm 2010; 8:83-88.
76. Cybulsky MI, Gimbrone MA, Jr. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. Science (Wash DC) 1991; 251:788-91.
77. Ciprandi G, De Amici M, Tosca M, Marseglia G. Allergen-specific Ig classes in non-allergic individuals. J Biol Regul Homeost Agents 2010; 24: 335-340.
78. Schiavoni G, Di Pietro M, Ronco C, de Cal M, Cazzavillan S, Rassu M, Nicoletti M, del Piano M, Sessa R. *Chlamydia pneumoniae* infection as a risk factor for accelerated atherosclerosis in hemodialysis patients. J Biol Regul Homeost Agents 2010; 24: 367-75.
79. Garzaro M, Raimondo L, Nadalin J, Pecorari G, Giordano C. Subjective assessment of palatability, digestibility and emotions in healthy volunteers after ingestion of an iced dessert: preliminary report. J Biol Regul Homeost Agents 2010; 24:391-395
80. Li H, Cybulsky MI, Gimbrone MA, Jr, Libby P. An atherogenic diet rapidly induces VCAM-1, a cytokine-regulatable mononuclear leukocyte adhesion molecule, in rabbit aortic endothelium. Arterioscler Thromb 1993;13:197-204.
81. Bocchino M, Matarese A, Bellofiore B, Giacomelli P, Russo A, Signoriello G, Galati D, Sanduzzi A.

Usefulness of IFN-gamma release assays in clinical management of difficult TB cases:evidence from clinical practice. Eur J Inflamm 2010; 8:43-47.

82. Castellani ML, Anogeianaki A, Toniato E, et al. Inter-relationship between chemokines and mast cells. Eur J Inflamm 2010; 8:7-14.
83. Miraglia Del Giudice M, Pedullà M, Brunese FP, Capristo AF, Capristo C, Tosca MA, Ciprandi G. Neutrophilic cells in sputum of allergic asthmatic children. Eur J Inflamm 2010; 8:151-56.
84 Kohno M, Yasunari K, Murakawa K, Yokokawa K, Horio T, Fukui T, Takeda T. Plasma immunoreactive endothelin in essential hypertension. Am J Med 1990; 88:614-18.
85 Ferri C, Bellini C, Desideri G, Mazzocchi C, De Siati L, Santucci A. Elevated plasma and urinary endothelin-I levels in human salt-sensitive hypertension. Clin Sci (Lond) 1997; 93:35-41.
86. Gasbarrini G, Zaccone V, Covino M, Gallo A. Effectiveness of a "cold dessert", with or without the addition of a mixture of digestive herbs, in subjects with "functional dyspepsia". J Biol Regul Homeost Agents 2010; 24:93-98.
87. Niedworok E, Muc-Wierzgoń M, Nowakowska-Zajdel E. Influence of magnesium on fatty acids and their esters in isolated rat hepatocytes. J Biol Regul Homeost Agents 2010; 24:377-80.
88. Antonucci A, Di Giampaolo L, Zhang QL, Siciliano E, Cipolla D'Abruzzo C, Niu Q, Boscolo P. Safety in construction yards: perception of occupational risk by Italian building workers. Eur J Inflamm 2010; 8: 107-15.
89 Pedram A, Razandi M, Hu RM, Levin ER. Vasoactive peptides modulate vascular endothelial cell growth factor production and endothelial cell proliferation and invasion, J Biol Chem 1997; 272:17097-103.
90. Vogel T, Wolters HH, Hölzen J, Schmidt HH, August C, Dahrenmöller C, Senninger N, Brockmann JG. Rituximab rescue therapy for refractory early acute rejection after liver transplantation. Eur J Inflamm 2010; 8:125-29.
91. Castellani ML, De Lutiis MA, Toniato E, et al. Impact of RANTES, MCP-1 and IL-8 in mast cells. J Biol Regul Homeost Agents 2010; 24:1-6.
92. Saggini R, Cavezza T, Di Pancrazio L, Pisciella V, Saladino G, Zuccaro MC, Bellomo RG. Treatment of lesions of the rotator cuff. J Biol Regul Homeost Agents 2010; 24:453-59
93. Goronzy JJ, Weyand CM. Immunosuppression in atherosclerosis: mobilizing the opposition within. Circulation 2006; 114:1901-4.
94. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 2006; 6:508-19.
95. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev 2006; 86:515-81.
96. Mallat Z, Ait-Oufella H, Tedgui A. Regulatory T cell responses: potential role in the control of atherosclerosis. Curr Opin Lipidol 2005; 16:518-24.
97. Albert ML, Pearce SF, Francisco LM, et al. Immature dendritic cells phagocytose apoptotic cells via alphavbeta5 and CD36, and cross-present antigens to cytotoxic T lymphocytes. J Exp Med 1998; 188: 1359-68.
98. Weiner HL. Oral tolerance: immune mechanisms and the generation of Th3-type TGF-beta-secreting regulatory cells. Microbes Infect 2001; 3:947-54.
99. Green EA, Gorelik L, McGregor CM, et al. CD4+CD25+ T regulatory cells control anti-islet CD8+ T cells through TGF-beta-TGF-beta receptor interactions in type 1 diabetes. Proc Natl Acad Sci USA 2003; 100:10878-83.
100. Chen ML, Pittet MJ, Gorelik L, et al. Regulatory T cells suppress tumor-specific CD8 T cell cytotoxicity through TGF-beta signals in vivo. Proc Natl Acad Sci USA 2005; 102:419-24.
101. Stachowicz M, Mazurek U, Nowakowska-Zajdel E, Niedworok E, Fatyga E, Muc-Wierzgoń M. Leptin and its receptors in obese patients with colorectal cancer. J Biol Regul Homeost Agents 2010; 24:287-95.
102. Mullol J, Callejas FB, Méndez-Arancibia E, Fuentes M, Alobid I, Martínez-Antón A, Valero A, Picado C, Roca-Ferrer J. Montelukast reduces eosinophilic inflammation by inhibiting both epithelial cell cytokine secretion (GM-CSF, IL-6, IL-8) and eosinophil survival. J Biol Regul Homeost Agents 2010; 24:403-11.
103. Ciprandi G, De Amici M, Tosca MA, Marseglia G. Immunoglobulin production pattern in allergic and non-allergic subjects. Eur J Inflamm 2010; 8:193-

99.

104. Belghith M, Bluestone JA, Barriot S, et al. TGF-beta-dependent mechanisms mediate restoration of self-tolerance induced by antibodies to CD3 in overt autoimmune diabetes. Nat Med 2003; 9:1202-8.
105. Randelli P, Randelli F, Cabitza P, Vaienti L. The effects of COX-2 anti-inflammatory drugs on soft tissue healing: a review of the literature. J Biol Regul Homeost Agents 2010; 24:107-14.
106. Singh SS, Yadav SK, Haldar C. Effect of glucocorticoid and melatonin on immune function of an Indian tropical bird, *Perdicula Asiatica:* an *in vivo* and *in vitro* study. Eur J Inflamm 2010; 8:89-97.
107. Bogdan C, Vodovotz Y, Nathan C. Macrophage deactivation by interleukin-10. J Exp Med 1991; 174: 1549-55.
108. Tedgui A, Mallat Z. Anti-inflammatory mechanisms in the vascular wall. Circ Res 2001; 88:877-87.
109. Grunig G, Corry DB, Leach MW, et al. Interleukin-10 is a natural suppressor of cytokine production and inflammation in a murine model of allergic bronchopulmonary aspergillosis. J Exp Med 1997; 185:1089-99
110. Miyamoto K, Miyake S, Yamamura T. A synthetic glycolipid prevents autoimmune encephalomyelitis by inducing TH2 bias of natural killer T cells. Nature 2001; 413:531-34.
111. Minella D, Biancolella M, Testa B, Prosperini G, Zenobi R, Novelli G, Giganti MG. Androgen- and insulin-related gene signature using a specific low density oligoarray „AndroChip 2" in peripheral blood mononuclear cells in agonists, recreational athletes and sedentary subjects. J Biol Regul Homeost Agents 2010; 24:413-23.
112. Chmielewska J, Szczepankiewicz D, Skrzypski M, Kregielska D, Strowski MZ Nowak KW. Ghrelin but not obestatin regulates insulin secretion from INS1 beta cell line via UCP2-dependent mechanism. J Biol Regul Homeost Agents 2010; 24:397-402.
113. Gelardi M, Cassano M, Cassano P, et al. Survival time of nasal mucous membrane ciliated cells: a preliminary study of cytological examination by phase-contrast microscopy. Eur J Inflamm 2010; 8: 37-41.
114 Hong S, Wilson MT, Serizawa I, et al. The natural killer T-cell ligand alpha-galactosylceramide prevents autoimmune diabetes in nonobese diabetic mice. Nat Med 2001; 7:1052-56.
115. Nakai Y, Iwabuchi K, Fujii S, et al. Natural killer T cells accelerate atherogenesis in mice. Blood 2004; 104:2051-59.
116. Aslanian AM, Chapman HA, Charo IF. Transient role for CD1d-restricted natural killer T cells in the formation of atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2005; 25:628-32.
117. VanderLaan P, Reardon CA, Sagiv Y, et al. Characterization of the natural killer T-cell response in an adoptive transfer model of atherosclerosis. Am J Pathol 2007; 170:1100-07.
118. Nakashima Y, Raines EW, Plump AS, Breslow JL, Ross R. Upregulation of VCAM-1 and ICAM-1 at atherosclerosis-prone sites on the endothelium in the ApoE-deficient mouse. Arterioscler Thromb Vasc Biol 1998; 18:842-51.
119. Su C, Picard P, Rathbone MP, Jiang S. Guanosine-induced decrease in side population of lung cancer cells: lack of correlation with ABCG2 expression. J Biol Regul Homeost Agents 2010; 24:19-25.
120. Zhang G-H, Liu Y-F, Hu H-Y. Preparation and cytotoxicity effect of anti-hepatocellular carcinoma SCFV immunoliposome on hepatocarcinoma cell *in vitro*. Eur J Inflamm 2010; 8:75-82.
121. Sancini A, Tomei F, Schifano MP, et al. Stress characteristics in different work conditions: is it possible to identify specificity of risk factors by the questionnaire method? Eur J Inflamm 2010; 8:117-23.
122. Nie Q, Fan J, Haraoka S, Shimokama T, Watanabe T. Inhibition of mononuclear cell recruitment in aortic intima by treatment with anti-ICAM-1 and anti-LFA-1 monoclonal antibodies in hypercholesterolemic rats: implications of the ICAM-1 and LFA-1 pathway in atherogenesis. Lab Invest 1997; 77: 469-82.
123. Shih PT, Brennan ML, Vora DK, et al. Blocking very late antigen-4 integrin decreases leukocyte entry and fatty streak formation in mice fed an atherogenic diet. Circ Res 1999; 84:345-51.
124. Weber C, Erl W, Weber KS, Weber PC. HMG-CoA reductase inhibitors decrease CD11b expression and CD11b-dependent adhesion of monocytes to endothelium and reduce increased adhesiveness of monocytes isolated from patients with

hypercholesterolemia. J Am Coll Cardiol 1997; 30: 1212-17.

125. Vaughan CJ, Gotto AM Jr, Basson CT. The evolving role of statins in the management of atherosclerosis. J Am Coll Cardiol 2000; 35:1-10.
126. Stalker TJ, Lefer AM, Scalia R. A new HMG-CoA reductase inhibitor, rosuvastatin, exerts anti-inflammatory effects on the microvascular endothelium: the role of mevalonic acid. Br J Pharmacol 2001; 133:406-12.
127. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001; 344:1959-65.
128. Wenke K, Meiser B, Thiery J et al. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. Circulation 1997; 96:1398-402.
129. Youssef S, Stuve O, Patarroyo JC et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature 2002; 420:78-84.
130. Kureishi Y, Luo Z, Shoijima I, et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. Nat Med 2000; 6: 1004-10
131. Petruzzi M, Grassi FR, Nardi GM, Martinelli D, Serpico R, Luglie PF, Baldoni E. Sodium iodide associated to salicylic acid topical management of chronic oral candidiasis: a randomized trial. J Biol Regul Homeost Agents 2010; 24:381-84.
132. Gigante A, Cappella M, Manzotti S, Cecconi S, Greco F, Di Primio R, Mattioli-Belmonte M. Osteoinduction properties of different growth factors on cells from non-union patients: *in vitro* study for clinical application. J Biol Regul Homeost Agents 2010; 24:51-62.
133. Trikaliotis C, Soulountsi V, Tsorlini H, Katsifa H, Chatzidimitriou D, Trikaliotis K, Kalaitzopoulou P, Bitziani M, Chatzopouloy F, Arvanitidou M. Epidemiological study and classification of ICU infections, using the carrier state criterion. Eur J Inflamm 2010; 8:181-88.
134. Feron O, Dessy C, Desager J, Balligand J. Hydroxy-methylglutarylcoenzyme A reductase inhibition promotes endothelial nitric oxide synthase activation through a decrease in caveolin abundance. Circulation 2001; 103:113-18.
135. Vergnani L, Hatrik S, Ricci F, Passaro A, Manzoli N, Zuliani G. Effect of native and oxidized low-density lipoprotein on endothelial nitric oxide and superoxide production: key role of l arginine availability. Circulation 2000; 101:1261-66.
136. Nahrendorf M, Hu K, Hiller K-H, et al. Impact of hydroxymethylglutaryl conenzyme A reductase inhibition on left ventricular remodeling after myocardial infarction. J Am Coll Cardiol 2002; 40: 1695-700.
137. Vatrella A, Montagnani S, Calabrese C, Parrella R, Pelaia G, Biscione GL, Corcione N, Marsico SA, Guerra G. Neuropeptide expression in the airways of COPD patients and smokers with normal lung function. J Biol Regul Homeost Agents 2010; 24: 425-32.
138. Papakonstantinou P, Tziris N, Kapoukranidou D, Gotzamani-Psarrakou A, Tsonidis CHR, Patsikas MN, Papazoglou G. The effect of porcine Orexin A on glucose-dependent insulinotropic polypeptide plasma concentrations in pigs. Eur J Inflamm 2010; 8:15-21.
139. Vrtovsnik F, Couette S, Prie D, Lallemand D, Friedlander G. Lovastatin-induced inhibition of renal epithelial tubular cell proliferation involves a p21ras activated, AP-1-dependent pathway. Kidney Int 1997; 52:1016-27.
140. Raffaelli L, Scaramuzzo L, Rossi Iommetti P, Graci C, Maccauro G, Manicone PF. Jaw osteonecrosis related to bisphosphonate for bone metastasis. J Biol Regul Homeost Agents 2010; 24:115-21.
141. Ciprandi G, Fenoglio D, Ferrera F, De Amici M, Marseglia G. ELISPOT and ELISA assessment of interferon-gamma after sublingual immunotherapy. Eur J Inflamm 2010; 8:31-35.
142. Reissen R, Axel D, Fenchel M, Herzog U, Rossmann H, Karsch K. Effect of HMG-CoA reductase inhibitors on extracellular matrix expression in human vascular smooth muscle cells. Basic Res Cardiol 1999; 94:322-32.
143. Esposito G, Rossi F, Puca A, Albanese A, Sabatino G, Matteini P, Lofrese G, Maira G, Pini R. An experimental study on minimally occlusive laser-

assisted vascular anastomosis in bypass surgery: the importance of temperature monitoring during laser welding procedures. J Biol Regul Homeost Agents 2010; 24:307-15.

144. Ruperez M, Lorenzo O, Blanco-Colio L, Esteban V, Egido J, Ruiz-Ortega M. Connective tissue growth factor is a mediator of angiotensin II-induced fibrosis. Circulation 2003; 108:1499-505.
145. Martin J, Denver R, Bailey M, Krum H. *In vitro* inhibitory effects of atorvastatin on cardiac fibroblasts: implications for ventricular remodelling. Clin Exp Pharmacol Physiol 2005; 32:697-701.
146. Kureishi Y, Luo Z, Shoijima I et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. Nat Med 2000; 6: 1004-10.
147. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med 2001; 7:687-92.
148. Rosenson RS, Tangney CC, Casey LC. Inhibition of proinflammatory cytokine production by pravastatin, Lancet 1999; 353:983-84.
149. Schonbeck U, Libby P. The CD40/CD154 receptor/ligand dyad. Cell Mol Life Sci 2001; 58:4-43.
150. Lutgens E, Gorelik L, Daemen MJ, et al. Requirement for CD154 in the progression of atherosclerosis. Nat Med 1999; 5:1313-16.
151. Foy TM, Aruffo A, Bajorath J, et al. Immune regulation by CD40 and its ligand GP39. Annu Rev Immunol 1996; 14:591-617.
152. Bobryshev YV, Lord RS. Mapping of vascular dendritic cells in atherosclerotic arteries suggests their involvement in local immune-inflammatory reactions. Cardiovasc Res 1998; 37:799-810.
153. Yilmaz A, Reiss C, Tantawi O, et al. HMG-CoA reductase inhibitors suppress maturation of human dendritic cells: new implications for atherosclerosis. Atherosclerosis 2004; 172:85-93.