Psoriasis and Systemic Inflammatory Diseases: Potential Mechanistic Links between Skin Disease and Co-Morbid Conditions

Batya B. Davidovici[1], Naveed Sattar[2], Prinz C. Jörg[3], Luis Puig[4], Paul Emery[5], Jonathan N. Barker[6], Peter van de Kerkhof[7], Mona Ståhle[8], Frank O. Nestle[9], Giampiero Girolomoni[10] and James G. Krueger[1], for Psoriasis Education and Learning Syllabus (PEARLS)

Psoriasis is now classified as an immune-mediated inflammatory disease (IMID) of the skin. It is being recognized that patients with various IMIDs, including psoriasis, are at higher risk of developing "systemic" co-morbidities, e.g., cardiovascular disease (CVD), metabolic syndrome, and overt diabetes. In non-psoriatic individuals, the pathophysiology of obesity, aberrant adipocyte metabolism, diabetes, and CVDs involves immune-mediated or inflammatory pathways. IMIDs may impact these co-morbid conditions through shared genetic risks, common environmental factors, or common inflammatory pathways that are co-expressed in IMIDs and target organs. Given that pathogenic immune pathways in psoriasis are now well worked out and a large number of inflammatory mediators have been identified in skin lesions, in this review we will consider possible mechanistic links between skin inflammation and increased risks of (1) obesity or metabolic alterations and (2) CVD. In particular, we will discuss how well-established risk factors for CVD can originate from inflammation in other tissues.

Journal of Investigative Dermatology (2010) **130,** 1785–1796; doi:10.1038/jid.2010.103; published online 6 May 2010

[1]*Laboratory for Investigative Dermatology, The Rockefeller University, New York, New York, USA;* [2]*BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK;* [3]*Department of Dermatology, University of Munich, Munich, Germany;* [4]*Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain;* [5]*Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK;* [6]*St John's Institute of Dermatology (King's College), London, UK;* [7]*Department of Dermatology, Radboud University Medical Centre, Nijmegen, The Netherlands;* [8]*Department of Medicine, Karolinska Institutet, Stockholm, Sweden;* [9]*St John's Institute of Dermatology, King's College London and Guy's & St Thomas' Hospitals, London, UK and* [10]*Clinica Dermatologica, Università di Verona, Verona, Italy*

Correspondence: James G. Krueger, Laboratory for Investigative Dermatology, The Rockefeller University, 1230 York Avenue, Box 178, New York, New York 10065, USA. E-mail: kruegej@rockefeller.edu

Abbreviations: CVD, cardiovascular disease; IMID, immune-mediated inflammatory disease; KC, keratinocyte; RA, rheumatoid arthritis; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

Received 12 January 2010; revised 3 March 2010; accepted 6 March 2010; published online 6 May 2010

INTRODUCTION

Psoriasis vulgaris is a prototypical Th-1, Th-17, and Th-22 inflammatory disease. It is characterized by expansion and activation of Th-1, Th-17, and Th-22 T cells, with production of associated cytokines such as interferon-γ, tumor necrosis factor (TNF), IL-17, and IL-22 in the skin (Lowes *et al.*, 2008; Nograles *et al.*, 2009). In turn, T-cell activation is likely to be controlled by an extensive array of dendritic antigen-presenting cells that are also increased in the skin. Myeloid dendritic cells in psoriasis produce high levels of IL-23 and they strongly stimulate T-cell proliferation *in vitro*. One type of dendritic cell in psoriasis, the TNF-α/inducible nitric oxide synthase (i-NOS)-producing dendritic cells, produces high levels of TNF, IL-20, and other inflammatory molecules (Lowes *et al.*, 2007). As such, this cell could be a key driver of ''innate'' inflammation, inducing a much wider range of inflammatory molecules in keratinocytes (KCs) or other cell types through TNF- and IL-20-driven pathways. Hence, excess production of IL-1, IL-6, IL-8, vascular endothelial growth factor (VEGF), and numerous chemokines may originate from this pathway. The range of inflammatory molecules produced in psoriasis lesions is also strongly regulated by Th1 and Th17 T cells, as interferon-γ, IL-17, and IL-22 each induce a characteristic array of inflammatory products in KCs and other cell types present in psoriasis skin lesions (Nograles *et al.*, 2008). Overall, a vast range of inflammatory products (hundreds of individual gene products as identified on gene arrays) are produced in psoriasis skin lesions and many of these appear to be released into the systemic circulation as a function of severity and extent of skin lesions (Liu *et al.*, 2007). Furthermore, effective treatment of psoriasis reduces the levels of circulating cytokines such as TNF and IL-1, which, at higher sustained levels, are likely risk factors for cardiovascular disease (CVD) (Zaba *et al.*, 2007).

A central theme in CVD relates to inflammation as a risk factor for progressive development of atheroma and other vascular alterations. Fisman *et al.* (2003) put forward the concept of good, bad, and indifferent interleukins for cardiovascular risk, with the recognition that CVD has been linked to increased expression of specific interleukins by epidemiological and/or experimental studies. Figure 1 presents a modification of the Fisman model that has been updated to include a broader classification of inflammation-associated molecules that affect the cardiovascular risk, including cytokines that are not named as interleukins and

hormones (adipokines) that originate from adipose tissues. In our model, some cytokines have been re-classified as ''bad'' based on new experimental evidence or new risk data. Figure 1 is by no means a comprehensive listing of all mediators with cardiovascular or metabolic effects, but it serves as an organizing principle for the subsequent discussion. Although this model is useful to conceptualize a complex array of cardiovascular risk factors, it does not serve well to indicate the cellular and tissue beds that produce cytokines with altered levels in the systemic circulation. Hence, as shown in Figure 2, in this review we have classified risk-associated molecules that may be produced within different organs or tissues and discussed factors that regulate production.

During periods of active disease, systemic release of specific cytokines or exposure of leukocytes to skin-derived inflammation factors while circulating through the inflamed cutaneous vasculature could alter the properties of circulating leukocytes or affect endothelial cells at distant sites, e.g., by inducing expression of ICAM or other adhesion molecules (Figure 2). There are potential interactions of many inflammatory products synthesized in psoriasis skin lesions with adipose tissue and cardiovascular tissues that are discussed in the following sections. The skin (hypodermis) contains many of the adipocytes that are expanded in obese psoriasis patients and increased numbers of macrophages in psoriasis lesions extend (at least) to the dermal or adipose interface; hence, there may be direct interchange of inflammatory cells and molecules between skin compartments that drive obesity and alter normal metabolic functions as a consequence of psoriasis activity. This concept is presented in Figure 3 and specific ''at-risk'' molecules are discussed in the next section.

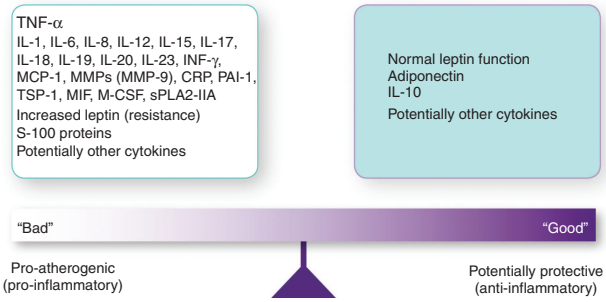

Figure 1. Potentially protective (anti-inflammatory) ''good'' and pro-atherogenic (proinflammatory) ''bad'' mediators of inflammation: modification of the Fisman model for cardiovascular risk (Fisman *et al.*, 2003). CRP, C-reactive protein; MCP-1, monocyte-chemoattractant protein 1; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; PAI-1, plasminogen activator inhibitor-1; sPLA2-IIA, secretory phospholipase A2 group IIA; TNF-α, tumor necrosis factor α.

INFLAMMATORY MOLECULES AND PATHWAYS IN OBESITY

Epidemiological studies indicate that obesity leads to a higher risk of developing psoriasis and a poorer long-term clinical outcome of psoriasis. Furthermore, losing weight may improve psoriasis (Higa-Sansone *et al.*, 2004; Naldi *et al.*, 2005; Wolters, 2005). In addition, several case studies have shown that weight loss from gastric bypass surgery results in remission of psoriasis (Moll *et al.*, 1974; de Menezes Ettinger *et al.*, 2006). Likewise, a recent controlled study showed that moderate weight loss (i.e. 5–10% of the body weight) increases the therapeutic response to a low dose of cyclosporine in obese patients with moderate-to-severe chronic plaque psoriasis, suggesting that lifestyle modifications, including a low-calorie diet, may supplement the pharmacological treatment administered to obese psoriasis patients (Gisondi *et al.*, 2008), further supporting

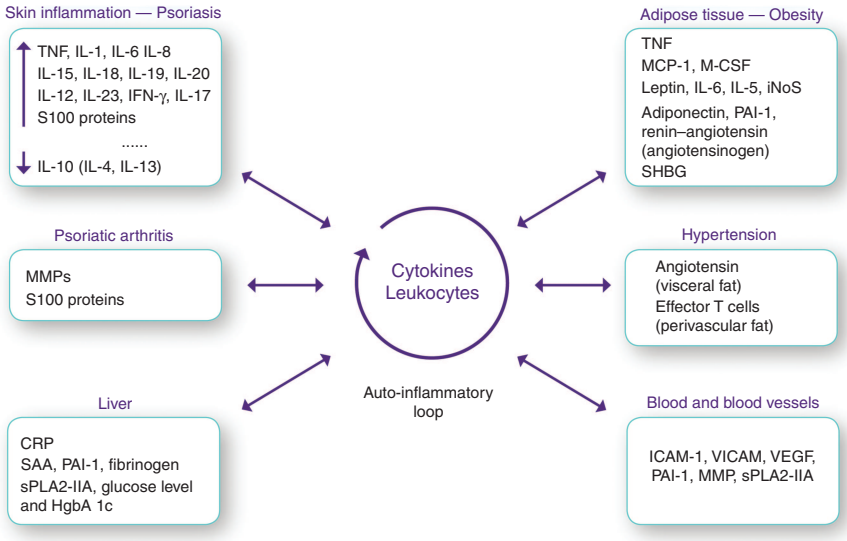

Figure 2. ''Vicious circle of inflammation'': mediators of inflammation produced in different organs or tissues are released into the systemic circulation and thus may contribute to the increased risk of inflammation in additional organs or tissues. CRP, C-reactive protein; HgbA 1c, hemoglobin A 1c; iNOS, inducible nitric oxide synthase; MCP-1, monocyte-chemoattractant protein 1; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; PAI-1, plasminogen activator inhibitor-1; SAA, serum amyloid A; sPLA2-IIA, secretory phospholipase A2 group IIA; TNF-α, tumor necrosis factor α; VEGF,vascular endothelial growth factor; VICAM, vascular intercellular adhesion molecule.

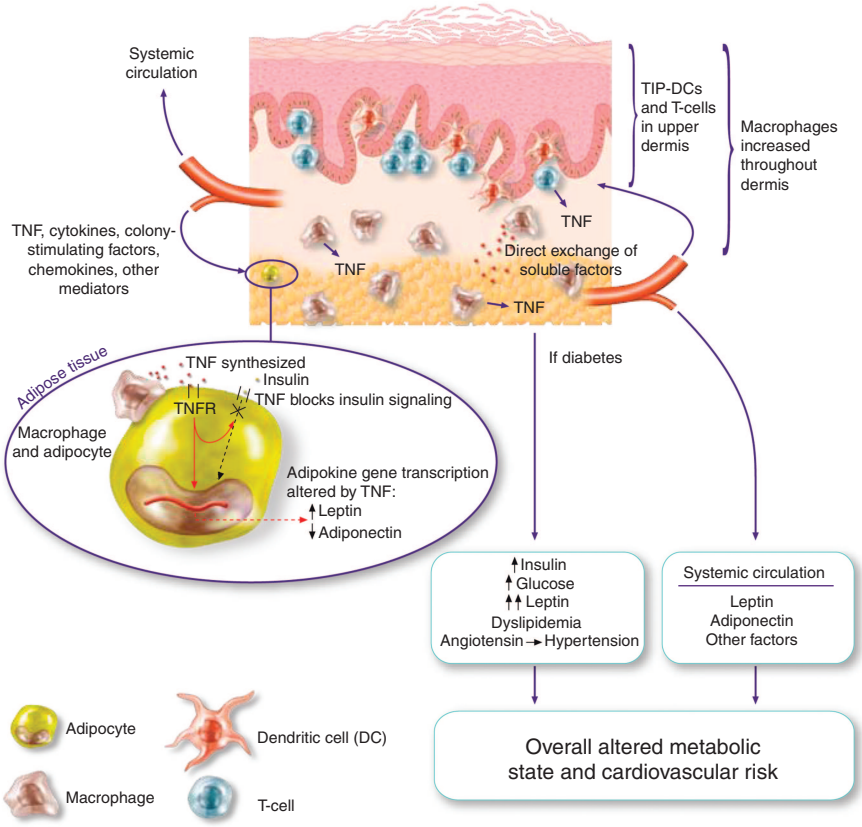

Figure 3. "Psoriasis and obesity": a two-compartment model of inflammation. This diagram depicts inflammation in the epidermis and dermis associated with psoriasis vulgaris and likely inflammatory molecules that would be produced in adipose tissue of obese individuals. The model proposes that soluble factors could enter the systemic circulation from either dermal or adipose tissue beds and, in addition, there could be direct exchange (diffusion) of factors between dermal and adipose sites. The steps involved in blockade of insulin signaling and alteration of the production of adipokines by tumor necrosis factor (TNF) are shown. DC, dendritic cell; TNFR, tumor necrosis factor receptor.

the relevance of obesity to psoriasis. Moreover, the ''obesity of psoriasis'' is thought to be a key link to excess diabetes risk and to the metabolic syndrome, as well as contributing to excess cardiovascular risk. What might be the interrelationships?

In addition to energy storage and lipid synthesis production, adipose tissue is an active endocrine organ with many secretory products, including adipocyte-derived hormones, adipokines, and a variety of proinflammatory cytokines, including IL-6 and TNF-α. Adipokines are proteins produced mainly by adipocytes. Although adipose tissue secretes a variety of factors, many of which are still to be fully characterized, we will focus only on leptin and adiponectin, which are primarily produced by adipocytes and for which most data exist.

Moreover, the adipose tissue is now recognized as a part of the innate immune system and adipocytokines have an important role in the pathogenesis of insulin resistance and are associated with metabolic complications such as dyslipidemia, hypertension, and premature heart disease (Rasouli and Kern, 2008).

Adipose tissue is composed of many cell types, but mainly of adipocytes and the stromo-vascular fraction, which includes macrophages. Although adipocytes and macrophages are derived from a common mesothelial origin, it is not clear whether preadipocytes can differentiate into macrophages. In fact, in mice it was shown that the macrophages in adipose tissue are bone marrow derived (Weisberg *et al.*, 2003). In obesity, leptin (an adipokine) and possibly other factors produced by adipocytes, macrophages, or both upregulate adhesion molecules on endothelial cells such as ICAM-1 and platelet–endothelial cell adhesion molecule 1. It is also possible that chemokines such as monocyte-chemoattractant protein 1, which is expressed by adipocytes and the levels of which correlate with adiposity, might contribute to monocyte recruitment and transmigration of bone marrow-derived monocytes, leading to an increase in white adipose tissue-resident macrophages, some of which fuse to generate giant multinucleated cells (Xu *et al.*, 2003). These cells have been found to be increased in number and shape in proportion to the body mass index, rising up to 60% of the total number of adipose tissue components. The proportional accumulation of macrophages could lead to an increase in expression of proinflammatory molecules and contribute to the inflammatory state in a significant way.

In addition, although lymphocytes are not a constituent of the adipose tissue, there is often a close physical proximity particularly in the lymph nodes, which are generally

surrounded by pericapsular adipose tissue. Data indicate the presence of intriguing two-way paracrine interactions between lymphocytes and adjacent adipocytes (Pond, 2003).

Leptin in obesity

Leptin is a 16-kDa adipocyte-derived hormone discovered in 1994. Leptin, the product of the *OB* (obese) gene, exerts biological actions through activation of its cognate receptors that belong to the type 1 cytokine receptor superfamily (Zhang *et al.*, 1994). Binding of leptin to its receptor induces activation of the Janus activated kinase signal transducers and activators of transcription signal pathway, activating signal transducer and activator of transcription-3 (Hegyi *et al.*, 2004).

Circulating-leptin levels directly correlate with adipose tissue mass and clinically can be used to reflect the percentage of fat mass. Control of appetite is the primary role of leptin. However, leptin is a key factor in regulating a wide range of biological responses, including energy homeostasis, hematopoiesis, neuroendocrine function, and immune responses (Auwerx and Staels, 1998; Fruhbeck *et al.*, 1998; Huang and Li, 2000; Otero *et al.*, 2005). Thus, in addition to being a hypothalamus modulator of food intake, body weight, and fat stores, leptin exerts an important role in acute and chronic inflammatory processes through regulation of cytokine expression that modulates the balance of helper T-cell types 1 and 2 (Juge-Aubry and Meier, 2002; Matarese *et al.*, 2005; Otero *et al.*, 2006). Its receptor is expressed in various tissues, including adipocytes, peripheral blood mononuclear cells, endothelial cell fibroblasts, and injured KCs (Tartaglia, 1997; Eckel *et al.*, 2005). The injured KCs show a behavior similar to that of psoriatic hyperproliferative KCs, wherein signal transducer and activator of transcription-3 activation has also been reported (Eckel *et al.*, 2005). Leptin protects T lymphocytes from apoptosis and modulates T-cell proliferation, increasing the proliferation of naive T cells but reducing the proliferation of memory T cells. Leptin modulates T-cell-derived cytokine production and increases expression of the activation markers CD25 and CD71 in $CD4^+$ and $CD8^+$ T cells. In monocytes, leptin increases the expression of various activation markers and upregulates phagocytosis and cytokine production. In endothelial cells, leptin upregulates the expression of adhesion molecules and induces oxidative stress. Hence, leptin has a dual role in inflammation: it activates monocytes and macrophages, potentiates production of the proinflammatory cytokines TNF-α, IL-6 and IL-9, and directs T-cell differentiation to a Th1 phenotype (Matarese *et al.*, 2002; La Cava *et al.*, 2004; Otero *et al.*, 2005). In addition, leptin has been shown to stimulate keratinocyte proliferation and angiogenesis (Bouloumie *et al.*, 1998; Frank *et al.*, 2000; Cao *et al.*, 2001; Stallmeyer *et al.*, 2001; Murad *et al.*, 2003; Bernotiene *et al.*, 2006).

In light of the above activities, leptin has been implicated in the pathogenesis of immune-mediated inflammatory diseases (IMIDs) such as type 1 diabetes, rheumatoid arthritis (RA), inflammatory bowel disease, and psoriasis (Trayhurn, 2005). Hamminga *et al.* (2006) hypothesized that high levels of leptin in obese patients may contribute to psoriasis by releasing proinflammatory mediators. Body weight loss has been reported to significantly decrease leptin levels and improve insulin sensitivity (Ballantyne *et al.*, 2005; Hamminga, 2006), thus reducing the likelihood of developing metabolic syndrome and adverse cardiovascular diseases.

Leptin, in addition to the adipocytokines, may act as a link between severe psoriasis and obesity by inducing or augmenting inflammation. Indeed, recently elevated circulating-leptin levels were reported to be associated with psoriasis (Wang *et al.*, 2008). Moreover, hyperleptinemia was found to be associated with psoriasis independent of female sex and other conventional cardiovascular risk factors such as obesity. Hyperleptinemia in psoriasis may contribute to metabolic syndrome (Chen *et al.*, 2008). In patients with severe psoriasis, leptin and leptin-receptor expression were found to be significantly higher than in patients with mild-to-moderate psoriasis and in controls. A positive correlation between leptin and leptin-receptor expression, serum leptin levels and the disease duration was also observed (Cerman *et al.*, 2008). This finding links the chronic inflammation status of psoriasis with metabolic disturbances. It seems that high circulating-leptin levels in psoriasis may derive not only from adipose tissue but also from an inflammatory process.

Adiponectin in obesity

Adiponectin is an adipocyte-specific secretory protein abundantly present in the circulation. Adiponectin is composed of a collagenous and a globular domain. Adiponectin monomers trimerize through tight interactions in the collagenous domain. Trimers can then oligomerize. Both trimers and oligomers are present in the circulation and might have different effects on insulin sensitivity. Leukocyte elastase released by activated immune cells cleaves the globular domain of adiponectin, which might have activities distinct from those of the full-length molecule.

Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist in monocytes and macrophages, while inhibiting the IL-6 level. A recent study indicates that adiponectin inhibits TNF-α production and TNF-α inhibits adiponectin production, thus antagonizing each other's function (Campfield *et al.*, 1995). Adiponectin also inhibits the biological activity of TNF-α. Inhibition of NF-κB by adiponectin might explain at least part of these effects (Wulster-Radcliffe *et al.*, 2004). In endothelial cells, adiponectin downregulates the expression of adhesion molecules, ICAM-1 and vascular cell adhesion molecule 1, thus contrasting the effect of TNF-α. Thus, adiponectin is considered to have overall beneficial effects (Figures 2 and 3). Plasma levels of adiponectin are decreased in obesity, insulin resistance, and type 2 diabetes. Low levels of adiponectin are a strong independent predictor of elevated diabetes risk in several populations (Spranger *et al.*, 2003; Snijder *et al.*, 2006; Wannamethee *et al.*, 2007), although its association with incident vascular risk remains unclear (Sattar *et al.*, 2006). Hypoadiponectinemia is assumed to be closely associated with the metabolic syndrome (Hulthe *et al.*, 2003). Plasma adiponectin levels in psoriasis are decreased compared with healthy controls. It is assumed that aberrant secretion of adipocytokines induces metabolic syndrome,

which is a strong predictor of cardiovascular diseases (Eckel *et al.*, 2005). As regards its interaction with inflammation, although earlier studies on anti-TNF-α therapy have suggested increased serum adiponectin level with the improvement of RA (Komai *et al.*, 2007), much larger controlled trials have not confirmed this (Popa *et al.*, 2009). This suggests that the links between adiponectin, inflammation, and CVD are perhaps much more complex than originally determined and more studies are required.

Other cytokines in obesity

In addition to leptin and adiponectin, adipocytes produce TNF-α, IL-6, MCP-1, and other factors. Adipose tissue macrophages produce TNF-α, IL-5, and MCP-1. Macrophage products driven by granulocyte colony-stimulating factor may even trigger adipocyte growth increase (Figure 3). Expression analysis of macrophage and non-macrophage cell populations isolated from adipose tissue demonstrates that adipose tissue macrophages are responsible for almost all TNF-α expression in the adipose tissue and significant amounts of inducible nitric oxide synthase and IL-6 expression. Moreover, macrophages present in the white adipose tissue of obese individuals produce higher levels of proinflammatory chemokines compared with those in lean persons. At the same time, adiponectin production by adipocytes is reduced, possibly through upregulated local TNF-α levels.

Although its ultimate source has not been identified, IL-1 receptor antagonist is markedly increased in the serum of obese subjects, as in IL-18, IL-8, and macrophage inflammatory protein 1(Esposito *et al.*, 2002; Juge-Aubry *et al.*, 2003). So far, only one published study has investigated the Th-17 response as a potential marker of the inflammatory syndrome in obesity (Sumarac-Dumanovic *et al.*, 2009). It showed that blood concentrations of the proinflammatory cytokines IL-17 and IL-23 are increased in obese women. This increase is independent of the production of the proinflammatory mediators leptin and macrophage migration inhibitory factor, and is not directly associated with the increase in adipose tissue mass or insulin resistance. Additional studies are required to explore whether the IL-23/IL-17 cytokine axis has a pathogenic role in the metabolic disturbances associated with obesity.

INFLAMMATORY MOLECULES AND PATHWAYS IN INSULIN RESISTANCE OR DIABETES MELLITUS

Insulin resistance is a condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle, and liver cells. Insulin resistance in fat cells results in elevated hydrolysis of stored triglycerides leading to elevated levels of free fatty acids in the blood. Insulin resistance in muscle cells reduces glucose uptake and local storage of glucose glycogen, whereas insulin resistance in liver cells causes impaired glycogen synthesis and a failure to suppress hepatic glucose production. Elevated blood fatty acid levels further reduce muscle glucose uptake and increase liver glucose production, thus contributing to elevated blood glucose levels. It appears that inflammatory mediators might be involved in the development of insulin resistance. Cytokines and adipocytokines including TNF-α, interleukin-6, leptin, and adiponectin (Fantuzzi, 2005; Wellen and Hotamisligil, 2005) are increasingly recognized as important regulators of both insulin sensitivity and inflammation, and a dysregulation of their levels and/or functions has been shown in both obesity and other inflammatory diseases, including psoriasis (Figures 1–3). Consistent with this, insulin resistance was found in non-obese adults with psoriasis (Ucak *et al.*, 2006). Moreover, insulin resistance was found to be significantly correlated with the psoriasis area and severity index score (Boehncke *et al.*, 2007).

TNF and insulin receptor signaling

TNF acts on adipocytes and muscle cells to induce insulin-signaling defects by several ways, such as by impairing insulin signaling through inhibition of the tyrosine kinase activity of the insulin receptor; by activating peroxisome proliferator-activated receptor-δ that promotes epidermal proliferation and modulates adipogenesis and glucose metabolism; and by suppressing adiponectin secretion from adipocytes, which is an important anti-inflammatory molecule that also functions in regulating insulin sensitivity (Gustafson *et al.*, 2007; Wakkee *et al.*, 2007; Romanowska *et al.*, 2008). Although the actions of TNF on adipocytes and monocytes are complex with respect to metabolic regulation, there is experimental evidence that TNF directly regulates insulin secretion and disrupts lipid synthesis, which are the central features of type 2 diabetes and obesity. This noted, there is inconclusive evidence for the effects of therapeutic TNF blockade on the insulin resistance of obesity.

IL-6 in diabetes

Recent studies suggest that IL-6 could be implicated in insulin resistance and its complications (Ihle *et al.*, 1995; Kroder *et al.*, 1996; Yudkin *et al.*, 2000; Bastard *et al.*, 2000, 2002). The IL-6 receptor belongs to the class I family of cytokine receptors, which uses Janus activated kinases as intracellular signaling pathways (Ihle *et al.*, 1995). Studies have shown an interaction between cytokines and insulin signaling pathways leading to decreased insulin signaling in the presence of cytokines. The mechanisms involved are not clear, but there is evidence suggesting the participation of protein kinases and tyrosine phosphatase activation (Kroder *et al.*, 1996) or suppressor of cytokine signaling interaction with the insulin receptor (Mooney *et al.*, 2001; Lagathu *et al.*, 2003; Rieusset *et al.*, 2004). Elevations of IL-6 plasma levels have been linked to risk for type 2 diabetes independently of obesity and insulin resistance (Wannamethee *et al.*, 2007) and also appear to predict an elevated risk of vascular events, at least as strongly as C-reactive protein (CRP) (Danesh *et al.*, 2008).

Leptin in diabetes

Leptin improves insulin sensitivity through activation of adenosine monophosphate protein kinase, which controls cellular concentrations of malonyl-CoA, thereby inhibiting acetyl-CoA carboxylase (the enzyme involved in malonyl-CoA transformation; Minokoshi *et al.*, 2002). As a result, there is a decrease of intracellular malonyl-CoA and a decline of

lipogenesis associated with increased fatty-acid β-oxidation. Interestingly, in generalized lipodystrophy, wherein adipose tissue is nearly absent, leptin administration improves insulin sensitivity (Oral *et al.*, 2002). However, in common human obesity, there are high circulating-leptin levels, suggesting leptin resistance, and leptin administration has little or no effect on insulin resistance. In fact, the leptin-signaling pathway activates suppressor of cytokine signaling -3, which might inhibit insulin signaling (Howard and Flier, 2006). Therefore, while leptin deficiency very likely contributes to insulin resistance when adipose tissue is lacking, leptin resistance is a main feature of human obesity (Figure 3). Furthermore, a recent study found that the leptin:adiponectin ratio is a reliable measure of insulin resistance in non-diabetic white adults as the gold standard measure of insulin resistance (clamp insulin sensitivity index (*M/I*) value) or as currently used methods, such as fasting insulin or homeostasis model assessment for insulin sensitivity. Given that variations between fasting insulin and postprandial leptin and adiponectin levels tend to be small, leptin:adiponectin ratio might also have potential value in assessing insulin sensitivity in the non-fasted insulin state (Finucane *et al.*, 2009).

Adiponectin in diabetes

Adiponectin is underexpressed in obese patients with insulin resistance or type 2 diabetes, and in patients with coronary heart disease. Similar to leptin, adiponectin enhances insulin sensitivity through activation of adenosine monophosphate protein kinase (Yamauchi *et al.*, 2002). Adiponectin also affects hepatic glucose production by decreasing the mRNA expression of two essential gluconeogenesis enzymes: phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (Kadowaki and Yamauchi, 2005). It appears that high-molecular weight adiponectin may be the most insulin-sensitizing. Signal transduction pathways linking inflammation and insulin resistance through inhibition of phosphorylation of insulin signaling include NF-κB, c-Jun N-terminal kinase, and endothelial reticulum stress, such as obesity (Hotamisligil, 2003; Ozcan *et al.*, 2004; Arkan *et al.*, 2005; Cai *et al.*, 2005). Recent research shows that endoplasmic reticulum is the cellular structure in adipocytes that detects disrupted metabolic homeostasis, transmits the signal and activates inflammatory signal-transduction systems such as IκB kinase and c-Jun N-terminal kinase.

Other factors in diabetes

Chronic inflammation in psoriasis leads to increased IGF-II in the skin and blood of psoriasis patients (Yoo *et al.*, 2007). IGF-II promotes epidermal proliferation and is also implicated in promoting atherosclerosis, in modulating body fat mass and lipid metabolism in mice, and is linked to diabetes and hyperlipidemia in animal and human models (Zaina and Nilsson, 2003). Immunocytes and KCs in psoriatic skin produce angiogenic factors, such as VEGF, which promote angiogenesis and endothelial cell activation. VEGF levels are increased in plaques of psoriasis and serum concentration of VEGF correlates with clinical severity of disease (Griffiths and Barker, 2007). VEGF is also increased in hyperinsulinemic states such as the metabolic syndrome, in which adipocytes are its primary source (Cao, 2007). Therefore, hyperinsulinemic states such as obesity and the metabolic syndrome might promote susceptibility to psoriasis or exacerbate existing psoriasis not only through their aforementioned role in promoting and facilitating inflammation, but also through increased and sustained levels of circulating VEGF. Decades of chronic angiogenesis necessary to maintain the psoriasis phenotype could also theoretically be related to cardiovascular disorders through exhausting the pool of endothelial precursor cells in the bone marrow, which are believed to have a crucial role in maintenance of endothelial integrity, function, and repair (Shantsila *et al.*, 2007).

INFLAMMATORY MOLECULES AND PATHWAYS IN CVDs

The development of atherosclerotic vascular disease is a progressive process in which inflammation has also been implicated (Libby, 2000). Early intimal infiltration and activation of peripheral blood T cells followed by macrophage infiltration are important events in the immune-mediated pathogenesis of arteriosclerosis (Figure 4; Hansson and Libby, 2006). Transendothelial migration of T cells is a key early step in atherosclerosis that is mediated by cell adhesion molecules, such as ICAM-1 and vascular cell adhesion molecule-1, on the vascular endothelium. Thereafter, macrophages accumulate releasing cytokines and enzymes, including matrix metalloproteinases, which degrade the connective tissue matrix. The next step is the formation of a more advanced fibrous lesion that is characterized by the accumulation of lipid-rich necrotic debris and smooth muscle cells. These lesions normally have a fibrous cap composed of smooth muscle cells and an extracellular matrix that surrounds a lipid-rich necrotic core. The plaque, which is covered by a fibrous cap, then gradually develops into an advanced and complex lesion. Continuing inflammatory processes gradually result in thinning of the fibrous cap to create a potentially unstable plaque that can eventually rupture, with thrombosis and clinical evidence of vascular occlusion (Ribatti *et al.*, 2008). Thus, inflammation is not only instrumental in the development of human atheromatous plaques, but, significantly, also has a crucial role in the destabilization of internal carotid artery plaques, thus converting chronic atherosclerosis into an acute thromboembolic disorder (Figure 4).

Hepatocytes and arterial smooth muscle cells are thought to be primarily responsible for the production of secretory phospholipase A2 group IIA, an acute-phase reactant, in response to stimulation by cytokines (Hurt-Camejo *et al.*, 2001). Secretory phospholipase A2 group IIA is associated with depressed plasma-cholesterol levels, altered lipoprotein compositions, an enhanced ability to deliver cholesterol to cells, and increased lipid depositions in aortic walls. This mechanism is likely to contribute to the development of hypocholesterolemia observed in patients with inflammatory diseases. Secretory phospholipase A2 group IIA can also be detected in the intima, adventitia, and media of the atherosclerotic wall not only in developed lesions but also in very early stages of atherosclerosis. Thus, secretory phospholipase A2 group IIA appears to be an important link

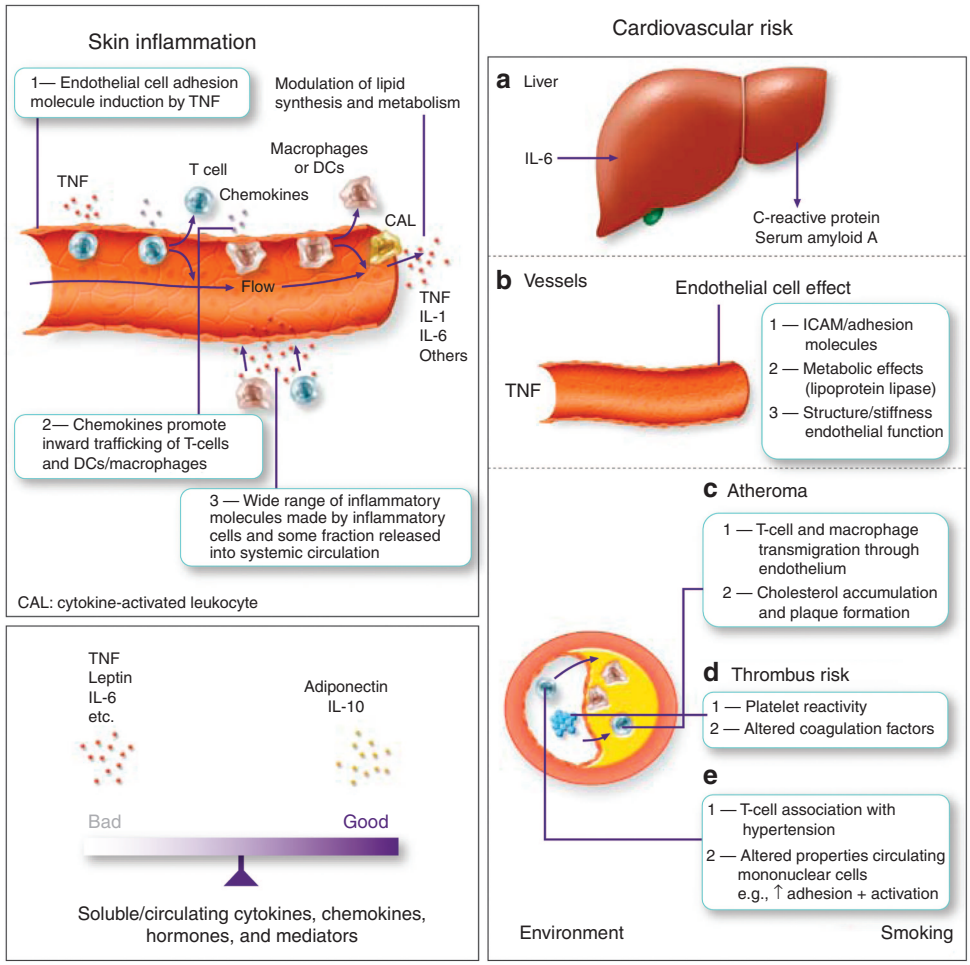

Figure 4. "Cardiovascular risk factors": some potential cellular and molecular inflammatory pathways that could be triggered in the skin (left) and that would then reach target tissues for cardiovascular risk (right). Cytokine (chemokine)-activated leukocytes (CAL) in cutaneous sites could either enter the skin tissue or circulate after rolling on inflamed endothelial cells in psoriasis lesions. These cells and cytokines released into the systemic circulation, e.g., tumor necrosis factor (TNF), IL-1, or IL-6, may alter the function of hepatocytes (**a**), vascular cells (**b**), atheroma (**c**), thrombus risk (**d**), or leukocyte physiology (**e**) to increase cardiovascular risk factors or overt pathological pathways, as detailed in the right side of this figure. DCs, dendritic cells.

between the lipid and the inflammation hypothesis of atherosclerosis. Furthermore, studies showing that therapies that reduce inflammation may improve cardiovascular outcome also support the role of inflammation (Ridker *et al.*, 2005).

Although the direct mechanisms of the association between metabolic disturbances and unfavorable cardiovascular events in psoriasis have yet to be elucidated, psoriasis and atherosclerosis also have similar histological characteristics involving T cells, macrophages, and monocytes. In particular, the extravasation of leukocytes through the endothelium is characteristic of both psoriatic and atherosclerotic plaques. Both unstable psoriatic and atherosclerotic plaques also have an increased percentage of activated T cells expressing a Th-1 pattern of cytokines, including local and systemic expression of adhesion molecules, and endothelins. Th-17 cells secreting IL-17 have an important role in the pathogenesis of psoriasis and broadly activate inflammation in a variety of organ systems (Arican *et al.*, 2005; Sabat *et al.*, 2007). IL-17 is also elevated in the sera of patients with unstable CVD (Hashmi and Zeng, 2006) and is also preferentially expressed in animal models of aged coronary arteries that are susceptible to ischemia (Csiszar *et al.*, 2003) Figure 4 shows some of the effects of cytokines associated with psoriasis lesions and cardiovascular biology. Effects of inflammation on coagulation and hypertension are also shown in this figure and are discussed below. Well-recognized CVD risk factors such as diabetes mellitus, hypertension, and obesity (Preis *et al.*, 2009) thus stem from triggers that could be located in inflamed skin, adipose tissue, or other inflamed site. In particular, elevated CRP most probably reflects hepatic synthesis in elevated levels of IL-6 in the circulation (Figures 2 and 4).

Recent genome-wide association studies have identified at least 21 distinct gene loci that contribute to CVD (Arking and Chakravarti, 2009). Interestingly, none of the identified genes overlap with psoriasis susceptibility loci. Hence, these data suggest that pathogenic links may be mediating more through systemic inflammation and/or metabolic dysregulation associated with inflammation.

INFLAMMATORY MOLECULES AND PATHWAYS IN HYPERCOAGULATION

Factors that control coagulation include circulating factors in blood (platelets and coagulation protein factors) and the endothelial surface in target organs. Psoriasis has the potential to affect both of these coagulation components.

Platelets

In psoriasis patients, evidence for an *in vivo* platelet activation, which could contribute to the development of thrombotic events, has been established (Kasperska-Zajac *et al.*, 2008). Spontaneous platelet hyperaggregability, mean platelet volume, plasma levels of β-thromboglobulin, and platelet factor 4, which are markers of platelet activation, were found to be significantly higher in psoriasis patients compared with that in controls. Interestingly, these markers, as well as platelet aggregability, were significantly reduced after psoriasis had cleared (Hayashi *et al.*, 1985). Moreover, platelet regeneration time, measured as malondialdehyde recovery after aspirin ingestion, was significantly shorter in psoriasis patients (Berrettini *et al.*, 1985; Tamagawa-Mineoka *et al.*, 2008). Finally, *P*-selectin expression by platelets was also increased in psoriasis patients, showing a direct correlation with disease severity (Ludwig *et al.*, 2004). Increased platelet aggregation could be partly accounted for by the increased release of arachidonic acid etherified in platelet plasma membrane, as a response to platelet activators, as well as by enhanced cyclooxygenase activity, which would result in more thromboxane A2 availability (Vila *et al.*, 1990, 1991).

On the other hand, activated platelets may exert a role in psoriasis pathogenesis by favoring leukocyte rolling in the skin microvasculature (Ludwig *et al.*, 2004) and platelet-derived 12-hydroxyeicosatetraenoic acid may increase KC-DNA synthesis (Kragballe and Fallon, 1986). These data suggest that the homeostatic balance is deranged toward a prothrombotic state in psoriasis patients, which might be sustained by platelet hyperactivity (Gisondi and Girolomoni, 2009).

In a recently published study, it was shown that platelet-derived microparticles, which are released only by activated platelets, were significantly increased in patients with psoriasis compared with healthy controls, indicating that blood platelets are in a state of activation in patients with psoriasis (Tamagawa-Mineoka *et al.*, 2009). Moreover, it was found that plasma platelet-derived microparticle levels were closely correlated with disease severity in psoriasis (psoriasis area and severity index); therefore, the authors suggested that platelet-derived microparticles may be a useful indicator of disease severity. It is thought that platelet-derived microparticles can increase leukocyte adhesion to the endothelium and promote leukocyte activation by modulating leukocyte–leukocyte and leukocyte–endothelial cell interactions (Wagner and Burger, 2003). Several kinds of chemokines that are secreted by platelets after activation (Wagner and Burger, 2003; von Hundelshausen and Weber, 2007) are also detected in psoriatic plaques (Nickoloff *et al.*, 2007). Taken together, these observations suggest that platelet-derived mediators may contribute to leukocyte recruitment to psoriatic skin lesions.

Coagulation protein factors

Inflammatory markers that are shed into the bloodstream in psoriatic and/or obese patients, such as TNF-α, IL-1, IL-6, can induce synthesis and release of acute-phase proteins, i.e. CRP and serum amyloid A, by the liver and increase the expression of cellular adhesion molecule on endothelial cells (e.g., ICAM-1, vascular cell adhesion molecule), which is required for the migration of leukocytes out of the circulation into the inflamed tissue, and potentially modulate prothrombic factors, thus increasing plasminogen activator inhibitor-1 and decreasing tissue plasminogen activator (Barton, 1996). In addition, adipokines also interface with thrombosis, as thrombospondin-1 is synthesized by adipocytes. Thrombospondin-1 activates transforming growth factor-β, which regulates plasminogen activator inhibitor-1 production also by adipocytes as well as hepatocytes and endothelial cells (Fain *et al.*, 2004). Thus, plasminogen activator inhibitor-1 levels are increased in obesity and in patients with metabolic syndrome; this prothrombotic state could contribute to thrombus formation and therefore to CAD (Figures 1 and 4). In addition, in cell culture, both CRP and serum amyloid A promote a number of proinflammatory cellular effects, including monocyte recruitment, activation of complement, and stimulation of cellular adhesion molecule and cytokine expression (Pasceri *et al.*, 2000; Woollard *et al.*, 2002; Han *et al.*, 2004). Serum amyloid A is also closely related to high-density lipoprotein and may displace apolipoprotein A-I from high-density lipoprotein to inhibit cholesterol efflux and reverse cholesterol transport (Banka *et al.*, 1995). However, these direct actions in cell culture have been questioned in recent years (Pepys and Hirschfield, 2003). A key idea in the cardiovascular risk is that even low-level systemic inflammation can serve as a permissive environment for thromboembolism and overt cardiovascular morbidity and mortality. The association between inflammation and thrombosis was recently reinforced by a new placebo control study. In apparently healthy persons, with normal low-density lipoprotein-cholesterol levels but elevated CRP, the occurrence of symptomatic venous thromboembolism was significantly reduced in the rosuvastatin-treated group as compared with the placebo group (Albert *et al.*, 2001). Rosuvastatin is known to have anti-inflammatory effects in addition to lipid-lowering effects (Glynn *et al.*, 2009). However, this study showed that rosuvastatin is able to prevent thromboembolism probably because of its anti-inflammatory effects and independent from its lipid-lowering effects.

INFLAMMATORY MOLECULES AND PATHWAYS IN HYPERTENSION

All components of the renin–angiotensin system are found in adipose tissue (Karlsson *et al.*, 1998; Gorzelniak *et al.*, 2002; Figures 1 and 3). In fact, adipose tissue is the major extrahepatic source of angiotensinogen, enabling the rise in its plasma concentration in obese individuals (Engeli *et al.*, 2005). Angiotensinogen is the precursor of angiotensin-I, which, after conversion to angiotensin-II, has a major role in blood pressure regulation. Angiotensin II increases thirst, promotes salt retention by the kidney, causes vasoconstriction, enhances

the release of catecholamines from nerves and the adrenal gland, and stimulates T-cell proliferation (Nataraj *et al.*, 1999; Jackson *et al.*, 2004). Angiotensin II was also found to enhance inflammation and the development of atherosclerosis (Kim and Iwao, 2000). Moreover, angiotensinogen mRNA expression is increased in visceral fat (Dusserre *et al.*, 2000; Van Harmelen *et al.*, 2000), which might partially explain the relationship between systemic hypertension and obesity in the metabolic syndrome and also provide insight into why weight loss commonly leads to blood pressure reduction (Moore *et al.*, 2005). However, it is still unclear whether angiotensin II secreted by adipose tissue has an important systemic hemodynamic (vasoconstriction) and/or non-hemodynamic (stimulation of expression of adhesion molecules, macrophage chemoattractant protein-1, and macrophage colony stimulating factor in endothelial cells) role (Tham *et al.*, 2002). Although angiotensinogen from adipose tissue has been shown to have a role in hypertension in rodent models, this has yet to be shown in humans. Moreover, it is clear that obesity is a major risk factor for hypertension and many relevant studies have now examined and confirmed this, as recently reviewed (Wild and Byrne, 2006; Figure 4).

A recent interesting study showed that peripheral blood T cells are activated to produce TNF-α, IFN-γ, and to express tissue-homing receptors upon angiotensin II infusion (Guzik *et al.*, 2007). Blockade of TNF-α by etanercept normalized the blood pressure and vascular $O_2^{\cdot-}$ production in angiotensin II-infused animals. Another important finding in that study was the localization of T cells to the perivascular fat. Thus, another potential explanation of the common coexistence of visceral obesity and hypertension is that the increase in visceral adipose tissue leads to accumulation of perivascular fat, which in turn serves as a reservoir for activated effector T cells, which promote vascular dysfunction and hypertension.

CONCLUSIONS AND FUTURE PROSPECTIVE FOR PREVENTION OF CO-MORBIDITIES

To conclude, psoriasis is a prototypical T-cell-mediated inflammatory disease. It is characterized by activation of antigen-presenting cells, and activation and expansion of Th-1 and Th-17 T cells. Th-1 and Th-17 inflammatory cytokines are elevated in the skin and blood of patients with psoriasis and are critical to recruiting T cells to the skin and joints, promoting angiogenesis, and epidermal hyperproliferation. At the same time, these inflammatory mediators have pleiotropic effects on diverse processes such as angiogenesis, insulin signaling, adipogenesis, lipid metabolism, and immune cell trafficking (Figure 4). Therefore, the metabolic aspects of chronic Th-1 and Th-17 inflammation in psoriasis have the potential to impact other conditions such as obesity, diabetes, thrombosis, and atherosclerosis. Conversely, inflammatory molecules and hormones produced in conditions such as obesity, diabetes, and atherosclerosis may influence the pathogenesis of psoriasis by promoting a proinflammatory state, which increases the susceptibility to the development of psoriasis or the severity of established psoriasis (Figure 2).

Psoriasis has widened its scope as an IMID showing a potential for systemic co-morbidity (Nestle *et al.*, 2009). In view of the chronic nature of inflammation in psoriasis and the lingering process of the development of its related co-morbidities, the most important question is whether long-term control of psoriasis could prevent, reverse, or attenuate these co-morbidities. Therefore, effective treatment modalities should aspire to benefit beyond direct disease target. In another chronic systemic inflammatory disease, RA, which is also associated with an increased risk for CVD, treatment with methotrexate has been linked to a reduction in CVD events and mortality (Krause *et al.*, 2000; Prodanovich *et al.*, 2005). Similarly, there is suggestive evidence of lower CVD risk with TNF blockade in patients with RA (Dixon *et al.*, 2007). Together with such observations, biomarkers of CVD risk (e.g., high CRP) that measure ''inflammation'' are clearly associated with increased cardiovascular risk. One recent study (JUPITER; Albert *et al.*, 2001) sought to determine whether low-grade inflammation in patients with elevated CRP values, but ''normal'' lipid levels, could be modulated by a statin and/or reduce the overall cardiovascular morbidity. The JUPITER study targeted apparently healthy men and women with low levels of low-density lipoprotein-cholesterol, but with elevated high-sensitivity CRP levels that were randomized to treatment with rosuvastatin versus placebo. Statins are proposed to have anti-inflammatory effects in addition to lipid-lowering effects (Albert *et al.*, 2001). The study was stopped early, as the group receiving rosuvastatin had a reduced incidence of major cardiovascular events (Ridker *et al.*, 2008). This study has been interpreted as showing a functional link between systemic inflammation and cardiovascular risk, but others had argued that the main effect of the JUPITER study could entirely be predicted on the basis of reduction in low-density lipoprotein-cholesterol level (Sattar and Hingorani, 2009). Resolution of this issue must thus be addressed by future trials in normal individuals, but the increased cardiovascular risk associated with frank inflammatory diseases stands as independent evidence of potential links between inflammation and cardiovascular risk.

A question for the future is whether long-term treatment of psoriasis will alter the pathophysiology of co-morbid conditions in primary sites, e.g., reduction in fat-cell metabolism, so clearly linked to inflammation and thus reduction of the overall risk through the integrated pathway discussed in this review. Biological treatments for psoriasis, e.g. anti-TNF-α (etanercept) or anti-p-40 (ustekinumab), have also been shown to reduce CRP in short-term trials (Sattar *et al.*, 2007) and might thus have an overall beneficial systemic effect. It is suggested that for effective management of psoriasis and its related co-morbidities, we need an integrated approach targeting both cutaneous and systemic inflammation. Potentially, effective treatment of co-morbidities, in particular obesity, may also decrease psoriasis disease activity and severity.

Careful studies are now needed to determine the impact of treating ''cutaneous'' disease in psoriasis on systemic co-morbidities. We must also determine whether direct targeting of co-morbid disease states, e.g. obesity, hyperlipidemia,

insulin resistance, or other factors, can improve skin and cardiovascular functions.

At present, there is no independent biomarker of increased cardiovascular risk in psoriasis patients. The N-terminal pro-brain natriuretic peptide (B-type natriuretic peptides) is a newly identified marker for incipient cardiac risk (Di Angelantonio *et al.*, 2009). There is some evidence for the N-terminal pro-brain natriuretic peptide to be higher in RA and to be reduced by anti-inflammatory therapy (Peters *et al.*, 2010); therefore, it would be interesting to investigate it in psoriasis patients. Clearly, good clinical management of metabolic and cardiovascular health is indicated for psoriasis patients. A recent consensus report provides some new guidance for management of CVD risk and advocates using more conservative thresholds of conventional biomarkers in starting treatment (Friedewald *et al.*, 2008). We think similar attention should be drawn to obesity, smoking, and other life-style-controllable factors, particularly as each of these elements is found to be higher in psoriatic patients (Naldi *et al.*, 2005).

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES

Albert MA, Danielson E, Rifai N *et al.* (2001) Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 286:64–70

Arican O, Aral M, Sasmaz S *et al.* (2005) Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm* 2005:273–9

Arkan MC, Hevener AL, Greten FR *et al.* (2005) IKK-beta links inflammation to obesity-induced insulin resistance. *Nat Med* 11:191–8

Arking DE, Chakravarti A (2009) Understanding cardiovascular disease through the lens of genome-wide association studies. *Trends Genet* 25:387–94

Auwerx J, Staels B (1998) Leptin. *Lancet* 351:737–42

Ballantyne GH, Gumbs A, Modlin IM (2005) Changes in insulin resistance following bariatric surgery and the adipoinsular axis: role of the adipocytokines, leptin, adiponectin and resistin. *Obes Surg* 15:692–9

Banka CL, Yuan T, de Beer MC *et al.* (1995) Serum amyloid A (SAA): influence on HDL-mediated cellular cholesterol efflux. *J Lipid Res* 36:1058–65

Barton BE (1996) The biological effects of interleukin 6. *Med Res Rev* 16:87–109

Bastard JP, Jardel C, Bruckert E *et al.* (2000) Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *J Clin Endocrinol Metab* 85:3338–42

Bastard JP, Maachi M, Van Nhieu JT *et al.* (2002) Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both *in vivo* and *in vitro*. *J Clin Endocrinol Metab* 87:2084–9

Bernotiene E, Palmer G, Gabay C (2006) The role of leptin in innate and adaptive immune responses. *Arthritis Res Ther* 8:217

Berrettini M, Parise P, Constantini V *et al.* (1985) Platelet activation in psoriasis. *Thromb Haemost* 53:195–7

Boehncke S, Thaci D, Beschmann H *et al.* (2007) Psoriasis patients show signs of insulin resistance. *Br J Dermatol* 157:1249–51

Bouloumie A, Drexler HC, Lafontan M *et al.* (1998) Leptin, the product of Ob gene, promotes angiogenesis. *Circ Res* 83:1059–66

Cai D, Yuan M, Frantz DF *et al.* (2005) Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med* 11:183–90

Campfield LA, Smith FJ, Guisez Y *et al.* (1995) Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 269:546–9

Cao R, Brakenhielm E, Wahlestedt C *et al.* (2001) Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF. *Proc Natl Acad Sci USA* 98:6390–5

Cao Y (2007) Angiogenesis modulates adipogenesis and obesity. *J Clin Invest* 117:2362–8

Cerman AA, Bozkurt S, Sav A *et al.* (2008) Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. *Br J Dermatol* 159:820–6

Chen YJ, Wu CY, Shen JL *et al.* (2008) Psoriasis independently associated with hyperleptinemia contributing to metabolic syndrome. *Arch Dermatol* 144:1571–5

Csiszar A, Ungvari Z, Koller A *et al.* (2003) Aging-induced proinflammatory shift in cytokine expression profile in coronary arteries. *FASEB J* 17:1183–5

Danesh J, Kaptoge S, Mann AG *et al.* (2008) Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. *PLoS Med* 5:e78

de Menezes Ettinger JE, Azaro E, de Souza CA *et al.* (2006) Remission of psoriasis after open gastric bypass. *Obes Surg* 16:94–7

Di Angelantonio E, Chowdhury R, Sarwar N *et al.* (2009) B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. *Circulation* 120:2177–87

Dixon WG, Watson KD, Lunt M *et al.* (2007) Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 56:2905–12

Dusserre E, Moulin P, Vidal H (2000) Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. *Biochim Biophys Acta* 1500:88–96

Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. *Lancet* 365:1415–28

Engeli S, Bohnke J, Gorzelniak K *et al.* (2005) Weight loss and the renin-angiotensin-aldosterone system. *Hypertension* 45:356–62

Esposito K, Pontillo A, Ciotola M *et al.* (2002) Weight loss reduces interleukin-18 levels in obese women. *J Clin Endocrinol Metab* 87:3864–6

Fain JN, Madan AK, Hiler ML *et al.* (2004) Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology* 145:2273–82

Fantuzzi G (2005) Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 115:911–9

Finucane FM, Luan J, Wareham NJ *et al.* (2009) Correlation of the leptin:adiponectin ratio with measures of insulin resistance in non-diabetic individuals. *Diabetologia* 52:2345–9

Fisman EZ, Motro M, Tenenbaum A (2003) Cardiovascular diabetology in the core of a novel interleukins classification: the bad, the good and the aloof. *Cardiovasc Diabetol* 2:11

Frank S, Stallmeyer B, Kampfer H *et al.* (2000) Leptin enhances wound re-epithelialization and constitutes a direct function of leptin in skin repair. *J Clin Invest* 106:501–9

Friedewald VE, Cather JC, Gelfand JM *et al.* (2008) AJC editor's consensus: psoriasis and coronary artery disease. *Am J Cardiol* 102:1631–43

Fruhbeck G, Jebb SA, Prentice AM (1998) Leptin: physiology and pathophysiology. *Clin Physiol* 18:399–419

Gisondi P, Del Giglio M, Di Francesco V *et al.* (2008) Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. *Am J Clin Nutr* 88:1242–7

Gisondi P, Girolomoni G (2009) Psoriasis and atherothrombotic diseases: disease-specific and non-disease-specific risk factors. *Semin Thromb Hemost* 35:313–24

Glynn RJ, Danielson E, Fonseca FA *et al.* (2009) A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med* 360:1851–61

Gorzelniak K, Engeli S, Janke J *et al.* (2002) Hormonal regulation of the human adipose-tissue renin-angiotensin system: relationship to obesity and hypertension. *J Hypertens* 20:965–73

Griffiths CE, Barker JN (2007) Pathogenesis and clinical features of psoriasis. *Lancet* 370:263–71

Gustafson B, Hammarstedt A, Andersson CX *et al.* (2007) Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. *Arterioscler Thromb Vasc Biol* 27:2276–83

Guzik TJ, Hoch NE, Brown KA *et al.* (2007) Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 204:2449–60

Hamminga EA, van der Lely AJ, Neumann HA *et al.* (2006) Chronic inflammation in psoriasis and obesity: implications for therapy. *Med Hypotheses* 67:768–73

Han KH, Hong KH, Park JH *et al.* (2004) C-reactive protein promotes monocyte chemoattractant protein-1-mediated chemotaxis through upregulating C chemokine receptor 2 expression in human monocytes. *Circulation* 109:2566–71

Hansson GK, Libby P (2006) The immune response in atherosclerosis: a double-edged sword. *Nat Rev Immunol* 6:508–19

Hashmi S, Zeng QT (2006) Role of interleukin-17 and interleukin-17-induced cytokines interleukin-6 and interleukin-8 in unstable coronary artery disease. *Coron Artery Dis* 17:699–706

Hayashi S, Shimizu I, Miyauchi H *et al.* (1985) Increased platelet aggregation in psoriasis. *Acta Derm Venereol* 65:258–62

Hegyi K, Fulop K, Kovacs K *et al.* (2004) Leptin-induced signal transduction pathways. *Cell Biol Int* 28:159–69

Higa-Sansone G, Szomstein S, Soto F *et al.* (2004) Psoriasis remission after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Obes Surg* 14:1132–4

Hotamisligil GS (2003) Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord* 27(Suppl 3):S53–5

Howard JK, Flier JS (2006) Attenuation of leptin and insulin signaling by SOCS proteins. *Trends Endocrinol Metab* 17:365–71

Huang L, Li C (2000) Leptin: a multifunctional hormone. *Cell Res* 10:81–92

Hulthe J, Hulten LM, Fagerberg B (2003) Low adipocyte-derived plasma protein adiponectin concentrations are associated with the metabolic syndrome and small dense low-density lipoprotein particles: atherosclerosis and insulin resistance study. *Metabolism* 52:1612–4

Hurt-Camejo E, Camejo G, Peilot H *et al.* (2001) Phospholipase A(2) in vascular disease. *Circ Res* 89:298–304

Ihle JN, Witthuhn BA, Quelle FW *et al.* (1995) Signaling through the hematopoietic cytokine receptors. *Annu Rev Immunol* 13:369–98

Jackson SH, Devadas S, Kwon J *et al.* (2004) T cells express a phagocyte-type NADPH oxidase that is activated after T cell receptor stimulation. *Nat Immunol* 5:818–27

Juge-Aubry CE, Meier CA (2002) Immunomodulatory actions of leptin. *Mol Cell Endocrinol* 194:1–7

Juge-Aubry CE, Somm E, Giusti V *et al.* (2003) Adipose tissue is a major source of interleukin-1 receptor antagonist: upregulation in obesity and inflammation. *Diabetes* 52:1104–10

Kadowaki T, Yamauchi T (2005) Adiponectin and adiponectin receptors. *Endocr Rev* 26:439–51

Karlsson C, Lindell K, Ottosson M *et al.* (1998) Human adipose tissue expresses angiotensinogen and enzymes required for its conversion to angiotensin II. *J Clin Endocrinol Metab* 83:3925–9

Kasperska-Zajac A, Brzoza Z, Rogala B (2008) Platelet function in cutaneous diseases. *Platelets* 19:317–21

Kim S, Iwao H (2000) Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. *Pharmacol Rev* 52:11–34

Komai N, Morita Y, Sakuta T *et al.* (2007) Anti-tumor necrosis factor therapy increases serum adiponectin levels with the improvement of endothelial dysfunction in patients with rheumatoid arthritis. *Mod Rheumatol* 17:385–90

Kragballe K, Fallon JD (1986) Increased aggregation and arachidonic acid transformation by psoriatic platelets: evidence that platelet-derived 12-hydroxy-eicosatetraenoic acid increases keratinocyte DNA synthesis *in vitro*. *Arch Dermatol Res* 278:449–53

Krause D, Schleusser B, Herborn G *et al.* (2000) Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. *Arthritis Rheum* 43:14–21

Kroder G, Bossenmaier B, Kellerer M *et al.* (1996) Tumor necrosis factor-alpha- and hyperglycemia-induced insulin resistance. Evidence for different mechanisms and different effects on insulin signaling. *J Clin Invest* 97:1471–7

La Cava A, Alviggi C, Matarese G (2004) Unraveling the multiple roles of leptin in inflammation and autoimmunity. *J Mol Med* 82:4–11

Lagathu C, Bastard JP, Auclair M *et al.* (2003) Chronic interleukin-6 (IL-6) treatment increased IL-6 secretion and induced insulin resistance in adipocyte: prevention by rosiglitazone. *Biochem Biophys Res Commun* 311:372–9

Libby P (2000) Changing concepts of atherogenesis. *J Intern Med* 247:349–58

Liu Y, Krueger JG, Bowcock AM (2007) Psoriasis: genetic associations and immune system changes. *Genes Immun* 8:1–12

Lowes MA, Bowcock AM, Krueger JG (2007) Pathogenesis and therapy of psoriasis. *Nature* 445:866–73

Lowes MA, Kikuchi T, Fuentes-Duculan J *et al.* (2008) Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol* 128:1207–11

Ludwig RJ, Schultz JE, Boehncke WH *et al.* (2004) Activated, not resting, platelets increase leukocyte rolling in murine skin utilizing a distinct set of adhesion molecules. *J Invest Dermatol* 122:830–6

Matarese G, La Cava A, Sanna V *et al.* (2002) Balancing susceptibility to infection and autoimmunity: a role for leptin? *Trends Immunol* 23:182–7

Matarese G, Moschos S, Mantzoros CS (2005) Leptin in immunology. *J Immunol* 174:3137–42

Minokoshi Y, Kim YB, Peroni OD *et al.* (2002) Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* 415:339–43

Moll JM, Haslock I, Macrae IF *et al.* (1974) Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore)* 53:343–64

Mooney RA, Senn J, Cameron S *et al.* (2001) Suppressors of cytokine signaling-1 and -6 associate with and inhibit the insulin receptor. A potential mechanism for cytokine-mediated insulin resistance. *J Biol Chem* 276:25889–93

Moore LL, Visioni AJ, Qureshi MM *et al.* (2005) Weight loss in overweight adults and the long-term risk of hypertension: the Framingham study. *Arch Intern Med* 165:1298–303

Murad A, Nath AK, Cha ST *et al.* (2003) Leptin is an autocrine/paracrine regulator of wound healing. *FASEB J* 17:1895–7

Naldi L, Chatenoud L, Linder D *et al.* (2005) Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. *J Invest Dermatol* 125:61–7

Nataraj C, Oliverio MI, Mannon RB *et al.* (1999) Angiotensin II regulates cellular immune responses through a calcineurin-dependent pathway. *J Clin Invest* 104:1693–701

Nestle FO, Kaplan DH, Barker J (2009) Psoriasis. *N Engl J Med* 361: 496–509

Nickoloff BJ, Xin H, Nestle FO *et al.* (2007) The cytokine and chemokine network in psoriasis. *Clin Dermatol* 25:568–73

Nograles KE, Zaba LC, Guttman-Yassky E *et al.* (2008) Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol* 159:1092–102

Nograles KE, Zaba LC, Shemer A *et al.* (2009) IL-22-producing ''T22'' T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol* 123:1244–52

Oral EA, Simha V, Ruiz E *et al.* (2002) Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 346:570–8

Otero M, Lago R, Gomez R *et al.* (2006) Towards a pro-inflammatory and immunomodulatory emerging role of leptin. *Rheumatology (Oxford)* 45:944–50

Otero M, Lago R, Lago F *et al.* (2005) Leptin, from fat to inflammation: old questions and new insights. *FEBS Lett* 579:295–301

Ozcan U, Cao Q, Yilmaz E *et al.* (2004) Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* 306:457–61

Pasceri V, Willerson JT, Yeh ET (2000) Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 102:2165–8

Pepys MB, Hirschfield GM (2003) C-reactive protein: a critical update. *J Clin Invest* 111:1805–12

Peters MJ, Welsh P, McInnes IB *et al.* (2010) Tumour necrosis factor {alpha} blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: results from a prospective cohort study. *Ann Rheum Dis*; e-pub ahead of print 7 April 2010

Pond CM (2003) Paracrine interactions of mammalian adipose tissue. *J Exp Zoolog A Comp Exp Biol* 295:99–110

Popa C, Netea MG, de Graaf J *et al.* (2009) Circulating leptin and adiponectin concentrations during tumor necrosis factor blockade in patients with active rheumatoid arthritis. *J Rheumatol* 36:724–30

Preis SR, Pencina MJ, Hwang SJ *et al.* (2009) Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. *Circulation* 120:212–20

Prodanovich S, Ma F, Taylor JR *et al.* (2005) Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 52:262–7

Rasouli N, Kern PA (2008) Adipocytokines and the metabolic complications of obesity. *J Clin Endocrinol Metab* 93:S64–73

Ribatti D, Levi-Schaffer F, Kovanen PT (2008) Inflammatory angiogenesis in atherogenesis–a double-edged sword. *Ann Med* 40:606–21

Ridker PM, Cannon CP, Morrow D *et al.* (2005) C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 352:20–8

Ridker PM, Danielson E, Fonseca FA *et al.* (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 359:2195–207

Rieusset J, Bouzakri K, Chevillotte E *et al.* (2004) Suppressor of cytokine signaling 3 expression and insulin resistance in skeletal muscle of obese and type 2 diabetic patients. *Diabetes* 53:2232–41

Romanowska M, al Yacoub N, Seidel H *et al.* (2008) PPARdelta enhances keratinocyte proliferation in psoriasis and induces heparin-binding EGF-like growth factor. *J Invest Dermatol* 128:110–24

Sabat R, Philipp S, Hoflich C *et al.* (2007) Immunopathogenesis of psoriasis. *Exp Dermatol* 16:779–98

Sattar N, Crompton P, Cherry L *et al.* (2007) Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum* 56:831–9

Sattar N, Hingorani AD (2009) C-reactive protein and prognosis in diabetes: getting to the heart of the matter. *Diabetes* 58:798–9

Sattar N, Wannamethee G, Sarwar N *et al.* (2006) Adiponectin and coronary heart disease: a prospective study and meta-analysis. *Circulation* 114:623–9

Shantsila E, Watson T, Lip GY (2007) Endothelial progenitor cells in cardiovascular disorders. *J Am Coll Cardiol* 49:741–52

Snijder MB, Heine RJ, Seidell JC *et al.* (2006) Associations of adiponectin levels with incident impaired glucose metabolism and type 2 diabetes in older men and women: the Hoorn study. *Diabetes Care* 29:2498–503

Spranger J, Kroke A, Mohlig M *et al.* (2003) Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 361:226–8

Stallmeyer B, Kampfer H, Podda M *et al.* (2001) A novel keratinocyte mitogen: regulation of leptin and its functional receptor in skin repair. *J Invest Dermatol* 117:98–105

Sumarac-Dumanovic M, Stevanovic D, Ljubic A *et al.* (2009) Increased activity of interleukin-23/interleukin-17 proinflammatory axis in obese women. *Int J Obes (Lond)* 33:151–6

Tamagawa-Mineoka R, Katoh N, Kishimoto S (2009) Platelet activation in patients with psoriasis: increased plasma levels of platelet-derived microparticles and soluble P-selectin. *J Am Acad Dermatol* 62:621–6

Tamagawa-Mineoka R, Katoh N, Ueda E *et al.* (2008) Elevated platelet activation in patients with atopic dermatitis and psoriasis: increased plasma levels of beta-thromboglobulin and platelet factor 4. *Allergol Int* 57:391–6

Tartaglia LA (1997) The leptin receptor. *J Biol Chem* 272:6093–6

Tham DM, Martin-McNulty B, Wang YX *et al.* (2002) Angiotensin II is associated with activation of NF-kappaB-mediated genes and down-regulation of PPARs. *Physiol Genomics* 11:21–30

Trayhurn P (2005) The biology of obesity. *Proc Nutr Soc* 64:31–8

Ucak S, Ekmekci TR, Basat O *et al.* (2006) Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. *J Eur Acad Dermatol Venereol* 20:517–22

Van Harmelen V, Ariapart P, Hoffstedt J *et al.* (2000) Increased adipose angiotensinogen gene expression in human obesity. *Obes Res* 8:337–41

Vila L, Cullare C, Sola J *et al.* (1991) Cyclooxygenase activity is increased in platelets from psoriatic patients. *J Invest Dermatol* 97:922–6

Vila L, Sola J, Puig L *et al.* (1990) Exogenous arachidonic acid metabolism in platelets from psoriatic patients. *Acta Derm Venereol* 70:110–4

von Hundelshausen P, Weber C (2007) Platelets as immune cells: bridging inflammation and cardiovascular disease. *Circ Res* 100:27–40

Wagner DD, Burger PC (2003) Platelets in inflammation and thrombosis. *Arterioscler Thromb Vasc Biol* 23:2131–7

Wakkee M, Thio HB, Prens EP *et al.* (2007) Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. *Atherosclerosis* 190:1–9

Wang Y, Chen J, Zhao Y *et al.* (2008) Psoriasis is associated with increased levels of serum leptin. *Br J Dermatol* 158:1134–5

Wannamethee SG, Lowe GD, Rumley A *et al.* (2007) Adipokines and risk of type 2 diabetes in older men. *Diabetes Care* 30:1200–5

Weisberg SP, McCann D, Desai M *et al.* (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 112:1796–808

Wellen KE, Hotamisligil GS (2005) Inflammation, stress, and diabetes. *J Clin Invest* 115:1111–9

Wild SH, Byrne CD (2006) ABC of obesity. Risk factors for diabetes and coronary heart disease. *BMJ* 333:1009–11

Wolters M (2005) Diet and psoriasis: experimental data and clinical evidence. *Br J Dermatol* 153:706–14

Woollard KJ, Phillips DC, Griffiths HR (2002) Direct modulatory effect of C-reactive protein on primary human monocyte adhesion to human endothelial cells. *Clin Exp Immunol* 130:256–62

Wulster-Radcliffe MC, Ajuwon KM, Wang J *et al.* (2004) Adiponectin differentially regulates cytokines in porcine macrophages. *Biochem Biophys Res Commun* 316:924–9

Xu H, Barnes GT, Yang Q *et al.* (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 112:1821–30

Yamauchi T, Kamon J, Minokoshi Y *et al.* (2002) Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 8:1288–95

Yoo H, Kim SJ, Kim Y *et al.* (2007) Insulin-like growth factor-II regulates the 12-lipoxygenase gene expression and promotes cell proliferation in human keratinocytes via the extracellular regulatory kinase and phosphatidylinositol 3-kinase pathways. *Int J Biochem Cell Biol* 39:1248–59

Yudkin JS, Kumari M, Humphries SE *et al.* (2000) Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 148:209–14

Zaba LC, Cardinale I, Gilleaudeau P *et al.* (2007) Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. *J Exp Med* 204:3183–94

Zaina S, Nilsson J (2003) Insulin-like growth factor II and its receptors in atherosclerosis and in conditions predisposing to atherosclerosis. *Curr Opin Lipidol* 14:483–9

Zhang Y, Proenca R, Maffei M *et al.* (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425–32