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Chapter 6

Immune System Links Psoriasis-Mediated Inflammation to Cardiovascular Diseases via Traditional and Non-Traditional Cardiovascular Risk Factors

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Additional information is available at the end of the chapter

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Abstract

Background. Cutaneous psoriasis and psoriatic arthritis increase the risk of cardiovascular diseases though the reasons are not clear. Here we discuss the role of the immune system in atherosclerosis and of the proinflammatory status in psoriasis and psoriatic arthritis diseases.

Methods. We performed a Pubmed query covering publications within the last ten years including epidemiological studies, cross-sectional case-control studies, and reviews. Articles were selected according critical associations using arthritis, immune-mediated inflammatory diseases, and psoriasis as key fields. These were crossed and combined with atherogenesis, endothelial dysfunction, intima-media thickness, subclinical atherosclerosis, plaque, thrombosis, thrombus, fibrinolysis, coagulation, and reactive oxygen species, all closely related to cardiovascular diseases. Both types of disease selected terms were separately combined with cardiovascular risk factors both non-traditional (innate and adaptive pro- and anti-inflammatory immune molecules and cells), and traditional (metabolic conditions and related molecules).

Results and conclusions. Immune-activated crossroads came out as the main contributors to proatherogenic inflammation in psoriasis and psoriatic arthritis disease. Traditional and non-traditional cardiovascular risk factors′ interactions result from an active cross-talk between proatherogenic mediators derived from metabolic, vascular and autoimmune joint and skin inflammation in target tissues. Consistently, psoriasis and psoriatic arthritis diseases offer an invaluable scenario to deepen our knowledge on atherosclerotic cardiovascular disease.

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Keywords: psoriasis, psoriatic arthritis, inflammation, immune system, cardiovascular risk factors

1. Introduction

Traditional cardiovascular risk factors like smoking, diabetes mellitus, hypertension, and hypercholesterolemia can barely account for the high prevalence of cardiovascular disease.

At the beginning of the last century, Nikolai N. Anichkov demonstrated that cholesterol per se was able to produce atheromatous lesions in the vascular wall [1]. He also described the presence of inflammatory cells in the lesions, but these findings were dismissed for many decades. In 1995, Hansson and others established that atherosclerosis exhibited many features of a chronic inflammatory process, giving rise to the immune-mediated hypothesis behind atherogenesis [2]. At the time, however, preventive medicine was not a priority. Nowadays, such discoveries can be highly valuable in immune-mediated inflammatory disorders (IMID) in general, and in psoriasis (Ps) and psoriatic arthritis (PsA) in particular. It is known that adaptive and innate immunity participate in every step of atherogenesis. In fact, both traditional and non-traditional cardiovascular risk (CVR) factors increase in the course of these diseases [3]. This provides a comprehensive basis to explain the immune-mediated nature of atherogenesis beyond autoimmune condition while outlining the different crossroads of inflammation.

2. Psoriasis and psoriatic arthritis

Psoriasis (Ps) and psoriatic arthritis (PsA) belong to the family of IMID, affecting predominantly skin and joints. The prevalence of Ps varies between 2 and 3% worldwide with a similar distribution according to sex [4]. Epidemiological studies show peak incidence between the second and third decades in life [5]. It has been estimated that 7–42% of Ps patients develop inflammatory arthropathy, usually manifesting as a mono or asymmetrical oligo-arthritis [6]. Substantial body of evidence suggests that PsA patients are at higher risk of developing atherosclerotic cardiovascular disease (CVD) [7–9] and mortality [10, 11]. To date, the pathogenesis of Ps and PsA remains unknown. Autoantigens have not been identified and the specificity of infiltrating lymphocytes is still unknown [2]. Genetically predisposed background and several suspected environmental triggering factors (e.g., infections, drugs, physical, and emotional stress) have been implicated in the initial stages of these diseases [9]. PsA is considered a seronegative (rheumatoid factor negative) arthritis. In Ps and PsA, the inflammatory features/reactions in skin and joints are very similar regarding composition of inflammatory infiltrates and vascular changes as explained in **Figure 1** [12]. Moreover, the cellular infiltrate is predominantly perivascular and due to mononuclear cells [13].

The contribution of B lymphocytes to Ps and PsA pathogenesis is poorly understood. However, none of the forms of Ps or PsA have been associated with serum auto-antibodies [14]. In contrast, T lymphocytes are the most abundant in both skin and the synovial fluid of joints, with

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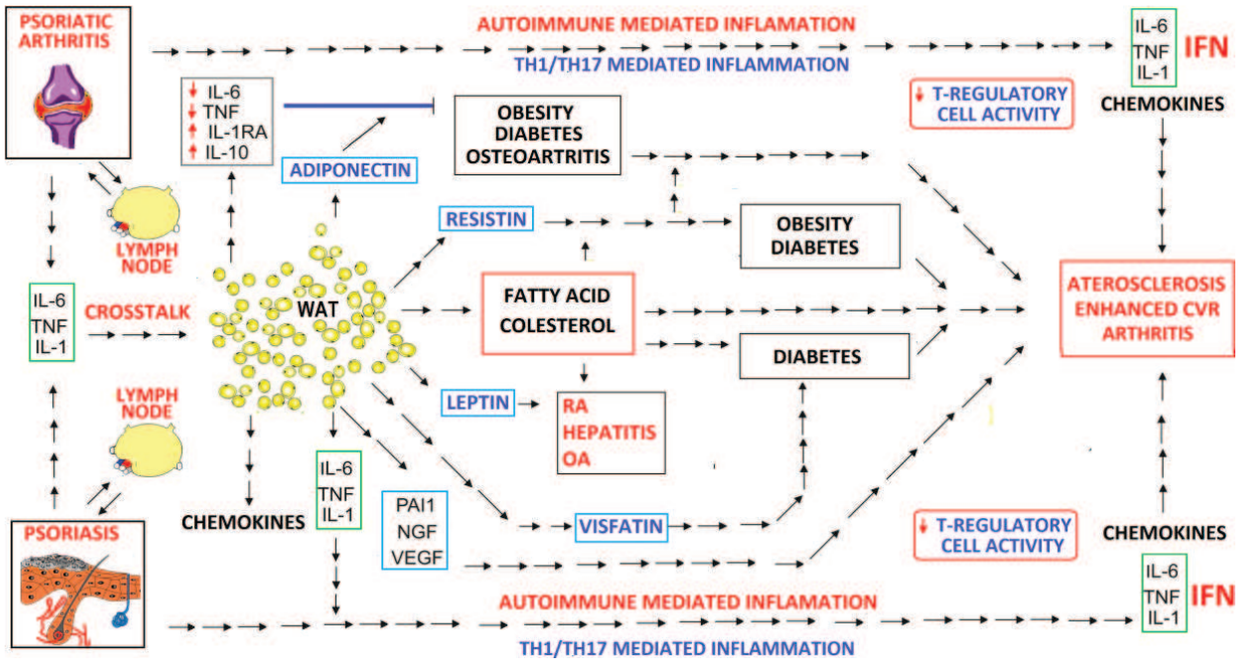


Figure 1. Schematic representation of the immune system-derived crosstalk between IMID and metabolic tissue, with events that worsen cardiovascular risk profile. Chronic inflammation of the skin and joints have many common immunopathological features, including genetic predisposition, composition of inflammatory infiltrates, vascular changes, early immune events, and proangiogenicity. Antigen is presented to naive CD4 T cells during immune synapse in the lymph node. Emerging lymphocytes migrate preferentially to skin and joints, where the above-mentioned infiltrating T lymphocytes (CD4 and CD8) interact with local APC (Langerhans cells, myeloid-DC, and plasmacytoid-DC) to produce chronic inflammatory conditions. Local re-activated T cells secrete chemokines and cytokines that amplify the inflammatory environment, resulting in the formation of psoriatic plaque, induction of cartilage degradation, and perhaps formation of atherosclerotic plaque. Since the suppressive activity of regulatory T cells is decreased in both tissue and blood, chronic production of proinflammatory cytokines (IFN-γ and TNF-α) crucially contributes to perpetuate the disease. In addition, deregulated adipose tissue (WAT) that secretes cytokines and chemokynes enhances systemic inflammatory burden leading to metabolic diseases (diabetes, metabolic syndrome, and dislipemia).

predominance of Tc1 (subpopulation of CD8+ cytotoxic T cells that secrete interferon (IFN) and IL-4), T-helper 1 lymphocyte subpopulation (Th1) and Th17 (IL-17+ T-helper cells) which interact with dendritic cells, macrophages, and target tissue cells [15]. Positive chemotaxis is observed between these cells and MCP-1 as found in synovial fluid [16] and skin biopsies obtained from Ps and PsA patients [17]. The role of lymphocytes in Ps and PsA pathogenesis is discussed later.

3. Atherosclerosis

Atherosclerosis is a complex inflammatory disease characterized by disturbances in the metabolic and immune system homeostasis that lead to pathogenic chronic progressive vascular damage and production of atherosclerosis plaque containing macrophages, lymphocytes, and other immune cells.

Classical knowledge distinguishes between inflammatory and non-inflammatory diseases. However, this distinction is no longer appropriate following the identification of inflammatory mechanisms associated with the traditionally called “non-inflammatory diseases.”

Although atherogenesis belonged to this group for several decades, now it is confirmed that the immune system acts on the endothelial wall and triggers an inflammatory cascade, leading to a progressive low-grade inflammatory process of the arterial vascular wall in response to accumulation and oxidation of lipoproteins. Yet, further considerations pinpoint a prominent and severely pathogenic role of the immune system in these diseases [18].

Studies in hypercholesterolemia-induced immune activation in mouse models of atherosclerosis highlight the critical balance between Th1 cells [19] and Treg [20]. Inflammation in the intima layer appears to be related with protective and pathogenic immune responses against modified self-antigens in the atherosclerotic plaque [21].

The paradigm of atherosclerosis as an inflammatory disease is widely accepted. Interestingly, systemic inflammatory rheumatic diseases might share several immune-mediated inflammatory pathways with atherosclerosis. In fact, molecules and cells from innate and adaptive immune system (described below) mediate chronic inflammatory pathways activation derived from both diseases interacting in a positive feedback pathogenic circuit.

Increasing evidence suggests that even in clinically heterogeneous diseases, both of them could share common immunological pathways that might damage the cardiovascular (CV) system (**Table 1**). The contribution of chronic inflammation to CVR has mainly been investigated in rheumatoid arthritis (RA), the prototypical inflammatory disorder [22–24]. Consistently,

Author, year	Number of patients and study profile	Findings
Han et al., 2006 [33]	3066 PsA patients vs. clinically asimptomatic controls matched by age, sex, and geographic region.	Higher prevalence for CHF, PVD, IHD atherosclerosis, type II diabetes, HL, and HTN in PsA patients than controls.
Sattar et al., 2007 [34]	127 patients with active Ps/PsA after at least first failure with DMARDS treatment, PsA- with 6 months duration or more with active arthritis in 3 or 4 swollen joints. Double-blind placebo (n = 42) controlled study performed with two doses of Onercept for 12 weeks.	Result compared against baseline before and after the end of treatment with Onercept. Results indicate higher CRP, that positively correlate with reduced Lp (a); higher ICAM-1; reduced IL6; reduced Homocysteine; same levels Apo-I¸ higher Apo-B, and higher TG.
Gonzalez-Juanatey et al., 2007 [35]	59 PsA patients vs. 59 control patients without clinically evident CVD adjusted for age and ethnia.	Carotid artery IMT correlated with age, time of PsA diagnosis, disease duration, total cholesterol, and LDL.
Eder et al., 2008 [36]	40 PsA patients compared with 40 controls matched by age, sex, and CVR factors.	Multivariate analysis indicates that PsA status, age, and TG levels were associated with IMT and carotid plaque.
Tam et al., 2008 [37]	102 PsA patients from Southern China.	Increased prevalence of DM and HTN was found in PsA group compared with age- and sex and BMI-matched controls.
Kimhi et al., 2007 [38]	Carotid artery IMT from 47 patients with PsA were compared with 43 healthy controls matched for age and sex.	The average IMT (mean/standard deviation) in PsA patients was significantly higher compared to CP even after adjustment for age, GR, BMI, HTN, and HL.

Author, year	Number of patients and study profile	Findings
Gladman et al., 2009 [39]	648 patients with Ps and PsA.	Enhanced CV risk. Severity of skin involvement is an independent CVR factor.
Shang et al., 2011 [40]	94 PsA patients without clinical evidence of CVD and 63 healthy subjects.	PsA patients without established CVD and in the absence of TRF have a high prevalence of subclinical ED via imaging studies.
Eder et al., 2013 [29]	Cross-sectional study comparing 125 PsA with 114 Ps patients.	PsA patients suffer from more severe subclinical atherosclerosis compared with Ps patients.This difference is independent of CVR factors.
Ogdie et al., 2014 [27]	Longitudinal cohort study comparing 8706 PsA, 41,752 RA, 138,424 Ps and 82,258 controls.	Patients with RA and Ps have increased mortality compared with the GP but patients with PsA do not.
Svedbom et al., 2015 [41]	The study compared the risk of death in 39,074 patients with mild and severe psoriasis vs. 154,775 sex-, age-matched referents.	Cardiovascular disease was the main driver of excess mortality patients with mild and severe psoriasis.
Cea-Calvo et al., 2016 [42]	PSO-RISK was a cross-sectional, multicenter, single-visit study of 368 patients (≥18) with Ps on systemic therapy.	CVR factors were detected in 27.5% (n = 101) of patients with previously unknown cardiovascular risk factors.
Tejón et al., 2016 [43]	The study compared age- and sex-matched case-control study PsA patients who developed CV events during the study (2010–2014) vs. control group CV events.	Traditional CV risk factors as well non-inflammatory CV risk factors of the disease were the main predictors of CV complications in this PsA population.

AC: Alcohol consumption; BMI: Body mass index; CAD: Coronary artery disease; CCF: Controlled for confounding factors; CHF: Congestive heart failure; CP: Control population; CVD: Cardiovascular disease; DM: Diabetes mellitus; DMARDS: Disease-modifying antirheumatic drugs; ED: Endothelial dysfunction; GR: Gender: GP: General population; HDL: High-density lipoprotein; HL: Hyperlipidemia; HTN: Hypertension; ICAM-1: Intercellular adhesion molecule 1; IHD: Ischemic heart disease; IL6: Interleukin 6; LDL: Low-density lipoprotein; Lp (a): Lipoprotein A; MI: Myocardial infarction; OB: Obesity; PVD: Peripheral vascular disease; TC: Total cholesterol; TG: Triglycerides; TRF: Traditional risk factors; VLDL: Very low-density lipoprotein.

Table 1. Representative summary of epidemiological studies (prospective and retrospective) linking Ps to associated Cardiovascular Risk and Comorbidities (RCM), published between 2006 and 2016.

chronic activation of immune-mediated pathways is believed to accelerate or trigger critical atherosclerosis events in Ps and PsA.

A multidisciplinary expert committee was designated a few years ago in accordance with European League against Rheumatism (EULAR) suggests apart from the management of conventional risk factors, an aggressive inflammation suppressive therapy to further reduce [3] death in PsA patients [25]. Chronic inflammatory state seems to be the potential driving force behind the accelerated atherogenesis [26]. In this regard, few papers have been published related to CVR factors (**Table 1**) [7, 8, 27]. Some representative prospective and

retrospective epidemiological surveys, published between 2006 and 2015 (**Table 1**), indicate that Ps and PsA patients exhibit higher prevalence of myocardial infarction (MI), ischemic heart disease, hypertension, diabetes, and dyslipidemia compared with normal controls. Although multiple CVR factors are associated with Ps, key components of the metabolic syndrome are more strongly connected with more severe Cutaneous psoriasis (PsC) [28]. Recent studies [29] suggest an increased inflammatory burden in PsA compared with Ps (**Table 1**). In contrast, the risk of developing a CV event (MI, ischemic stroke, and transient ischemic attack) was not elevated in early Ps patients in a matched follow-up study, case-control analysis [30, 31].

4. Inflammatory and classical cardiovascular risk factors

4.1. Inflammatory risk factors

Since a substantial amount of data accumulates in the past of this issue, we provide a brief insight into the most common inflammation-related and non-inflammatory factors involved in accelerated atherogenesis in Ps and PsA. As previously mentioned, Ps and atherosclerosis have a similar immune innate and adaptive pathogenic hallmark and an active crosstalk between "traditional" or "non-traditional" (**Figure 1**) [32].

4.1.1. Innate immunity

Toll-like receptor 2 (TLR-2) and toll-like receptor 4 (TLR-4) trigger receptor-mediated events, including cytokine-mediated inflammation, are involved in atherosclerosis [44], Ps, and other pathologies [34]. TLR expression is positively correlated with plasma tumor necrosis factor-alpha (TNF-α) levels [45]. Cytokine-triggered TLRs activation is known to modulate major pathological processes, including inflammation, angiogenesis, tissue remodeling, and fibrosis. Although joints are the most obvious inflammation sites in PsA, proinflammatory cytokines, most likely TNF-α and interleukin 6 (IL-6), are released in blood circulation and act on distant organs (immune system, adipose tissue, liver, hematopoietic tissue, skeletal muscle, glands, and endothelium). These effects are linked to systemic inflammation and lead to a proatherogenic profile. Cytokines orchestrate endothelial adhesiveness, matrix metalloproteinases (MMPs) activation, reactive oxygen species (ROS) production, C-reactive protein (CRP), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) release [46].

Indeed, atherogenic lipid alterations, oxidative stress abnormalities, vascular injury repair failure, arterial stiffness, insulin resistance induction, endothelial dysfunction, hypercoagulable state, homocysteine elevation, and pathogenic T cell up-regulation could all be attributed in part to the proinflammatory actions of cytokines. Common inflammatory mechanisms in Ps and atherosclerosis may be related to other factors by the high number of overlapping molecules, including cytokines [interleukins (IFN-α, IL-2, IL-6, IL-10, IL-13, IL-15, IL-17, IL-18, IL-20, and IL-23)], interferon alpha (IFN-α), Oncostatin M, (TNF-α), chemokines [Fractalkine, growth-regulated oncogene (GRO) alpha], CCL-3(MIP-1α), CCL-4 (MIP-1α), CCL-11 (Eotaxin), IL-8, MCP-1, monokine induced by interferon gamma (MIG/CXCL9), adipokines

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(Resistin, Leptin, and PAI-1), adhesion molecules (ICAM/LFA-1(leukocyte function-associated antigen-1), CD154 (OX40L)/CD134 (OX40), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), and GCSF, co-stimulatory molecules (CD80, CD28, and CD40/CD40L), lymphocyte profile Th1/Th17 up-regulation, Treg down-regulation, CTL effect or activity, NK cells, natural killer T (NKT) cells, myeloid dendritic cells, plasmacytoid dendritic cells, monocytes/macrophages, mast cells and neutrophils, complement activation [47], TLR-mediated inflammation (TLR-2, TLR-4, and TLR-9) [27–29], and other important factors, such as CRP, endothelin-1, inducible nitric oxide synthase (iNOS), heat shock protein (HSP60, HSP65, and HSP70), matrix metalloproteinases (MMP-2 and MMP-9), and oxidized low-density lipoprotein (LDL) [45, 48, 49]. Some molecules listed before and other PsA-related serum cytokine patterns have been demonstrated by multiplex cytokine array systems in Norwegian PsA patients [50, 51]. Few of these cytokines previously mentioned [52, 53] and their pathogenic contribution at different stages in the pathobiology of atherothrombosis and PsA are not clear yet [36].

NK cells increase the susceptibility to PsA [51] and the inflammatory infiltrate in psoriatic skin lesions. Although more studies must be done, emerging evidence supports a role for NK cells in Ps. Inverse correlation exists between NK cell population and body mass index (BMI). Therefore, adipose immune cell phenotype and function may provide greater insight into cardio-metabolic pathophysiology in psoriasis [54, 55].

NKT cells are a heterogeneous subset of T cell lineage lymphocytes that bear NK cell molecules and T cell receptors, which recognize microbial glycolipids and their own endogenous mammalian lipids presented by the MHC I-like molecule (CD1d) and have been implicated in the pathogenesis of various autoimmune diseases including Ps. Due to the numerous functions of NKT cells that link innate and adaptive immunity, their role in Ps is complex and still elusive. ApoE and LDL receptors have been involved in antigen uptake for presentation to NKT cells [56] NKT cells may represent a potential new therapy for atherosclerosis [57].

Our knowledge of biologically active serum molecules and cells involved in the pathogenesis of both PsA and atherosclerosis is still not clear enough. Taken together, cytokines seem to play a pivotal role as the major link between PsA and atherosclerosis. Compiled data show that untreated PsA inflammation could produce damage to the CV system even before it affects the joints [50]. Current evidence suggests that the pathway of inflammation in atherosclerosis culminates in altered concentrations of various markers in peripheral blood, including oxidative stress molecules [58–60] and markers of vascular inflammation like CRP [59], IL-6, ICAM-1, and MCP-1 [61].

4.1.1.1. Tumor necrosis factor-α

The pleiotropic cytokine TNF-α is among the most potent mediators of inflammation. Circulating T lymphocytes and monocyte-derived macrophages isolated from PsA patients produce increased amounts of TNF-α in comparison with macrophages isolated from healthy controls [8]. Furthermore, levels of TNF-α in PsA patients are elevated in the synovial tissue and skin lesions and correlate with disease activity. TNF-α is a key regulator of vascular homoeostasis [34], leading to proatherogenic effects, lipid abnormalities, including high LDL cholesterol

and low HDL cholesterol [62], hypercoagulable state via induction of cell surface expression of tissue factor (TF) on the endothelial wall and suppress anticoagulant activity via the thrombomodulin-activated protein C system [63]. The majority of epidermal CTL and Th1 effector lymphocyte populations and molecules are elevated in Ps vulgaris lesions and in circulating blood in psoriatic patients [64]. TNF-α also induces endothelial dysfunction including low nitric oxide availability and up-regulation of endothelial adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) [65, 66], a critical early step in atherogenesis. On the other hand, TNF-α blockade leads to a significant decrease in the levels of lipoprotein a (Lpa) homocysteine and an increase in apolipoprotein A-I (Apo A-I), triglyceride, and Apo-B concentration [62]. Long-term use of TNF-α blocking agents interferes with TNF-α function reducing the high incidence of cardiovascular events and associated vascular complications in CV diseases [67]. Taken together, the above-mentioned studies confirm a critical role for TNF-α in altering a number of well-studied putative vascular, thrombotic, and metabolic risk parameters (lipids and lipoproteins).

4.1.1.2. Interleukin 6

As an inflammatory cytokine, IL-6 regulates chemokine-directed leukocyte trafficking and directs transition from innate to adaptive immunity through the regulation of leukocyte activation, differentiation, and proliferation [68]. During acute and chronic inflammatory response, macrophages release TNF-α in the presence of a great variety of stimuli, including atherogenic and poorly characterized arthritogenic factors. TNF-α action on macrophages triggers the release of more TNF-α and IL1-β, which stimulate endothelial cells to produce IL-6 and IL-8. IL-6 and their signaling events contribute to hepatic release of acute-phase reactants including CRP levels, atherosclerotic plaque development and destabilization [69, 70]. IL-6 may also contribute to atherosclerosis and arterial thrombosis by activating the production of tissue factor, fibrinogen and factor VIII; increasing endothelial cell adhesiveness and stimulating platelet production and aggregation [71]. In addition, IL-6 is produced by smooth muscle cells (SMC) of many blood vessels and by adipocytes and, together with CRP and TNF-α, is involved in metabolic syndrome pathophysiology, insulin resistance [72] and coronary artery disease and the risk of MI [73–76], and cardiovascular mortality [77]. In addition, IL-6 locally produced in the endothelium and in SMC is an important autocrine and paracrine regulator of SMC proliferation and migration. IL-6 decreases cardiac contractility via a nitric oxide (NO)-dependent pathway activating STAT3-dependent anti-inflammatory signal transduction [78].

Numerous studies show a strong association between IL-6 and joint immune-mediated diseases. In the joint, macrophages and mast cells trigger a proinflammatory cascade in the presence of unknown stimuli, releasing great amounts of TNF-α, which induce the expression of IL-1 and IL-6. Mice deficient in mast cells are comparatively resistant in experimentally induced arthritis. In addition, it is a major promoter of bone resorption in pathological conditions [79]. In particular, IL-6 has a pivotal role in synovitis, bone erosion, and in the systemic features of inflammation [80].

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In Ps, most available evidence indicates that the pathogenic action of IL-6 is important. In fact, IL-6 co-localizes with CD45+ perivascular cells within lesional tissue and reverses the suppressive function of human T-regulatory cells [81].

The successful treatment of certain autoimmune conditions with the humanized antibody anti-IL-6 receptor (IL-6R) (Tocilizumb) has emphasized the clinical importance of cytokines that signal through the β-receptor subunit glycoprotein 130 [82].

IL-6 may, in both cardiovascular and joint-diseases involving Th1/Th17 mechanisms, alter the balance between the effector and regulatory arms of the immune system and drive a proinflammatory phenotype reinforcing innate and adaptive immune-mediated positive feedback [83], potentiating the immune effector mechanism. In both arterial disease and Ps/PsA, IL-6 seems to be a critical mediator of long-term chronic inflammation and to have deleterious effect in the arterial wall and in the joint.

4.1.1.3. Endothelin-1

The family of endothelins (ET) includes three 21-aminoacid isoforms endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin-3 (ET-3), which have endogenous pressor activity and are secreted by different tissues and cells. In addition, ET-1 is a vasoactive peptide that induces vasoconstriction, inflammation, and fibrosis and has mitogenic potential for SMC [84]. In the skin, ET-1 participates in keratinocyte proliferation, neoangiogenesis, and chemotaxis. Its levels are elevated in psoriatic lesions and serum of patients with Ps [85]. Synovial tissue and serum of patients with PsA all show strongly enhanced ET-1 receptor expression [86].

4.1.1.4. C-reactive protein

A considerable amount of evidence implicates C-reactive protein (CRP) as a predictive marker for future CV events and mortality in different settings, particularly under metabolic syndrome conditions in the general population [87, 88]; CRP has also been implicated as a direct partaker [7, 89, 90]. In addition, CRP stimulates the production of plaque destabilizing MMPs and MCP-1, a decrease in the activity of endothelial nitric oxide synthase (eNOS) and impairment in endothelium dependent vasodilation [91]. In vitro, studies provide evidence for direct proatherogenic effects of CRP, including increased endothelial dysfunction [92]. Baseline CRP levels were elevated in patients with Ps with and without psoriatic arthritis and Etanercept, a biologic TNF antagonist, treatment may reduce CRP levels in both groups [93].

4.1.1.5. Adipokines

Interestingly, in metabolic disorders associated with Ps/PsA, inflamed adipose tissue may enhance inflammatory proatherogenic status via adipokine production (leptin, adiponectin, and resistin) and cytokine (TNF-α and IL-6) secretion. Adipose tissue influences both natural and adaptive immunities and links inflammation, metabolic dysfunction, and cardiovascular disease [94].

4.1.1.6. Matrix metalloproteinases (MMPs)

MMPs are endoproteases with collagenase and/or gelatinase activity which exert deleterious effects on the endothelium integrity and collagen fibers, promoting atherosclerotic plaque destabilization and accelerating the process of atherothrombosis [95]. MMP-1 serum levels and gene expression are elevated in PsA [96].

4.1.2. Adaptive immunity

As previously mentioned, Ps/PsA and atherosclerosis share certain common underlying pathogenic inflammatory mechanisms. Specifically, both are associated with Th1 and CTL (cytotoxic T lymphocyte) effector cell-mediated events in vivo [68], and are elevated in circulating blood [63]. In contrast, the T-regulatory activity is reduced.

4.1.2.1. Cellular immune response

Myeloid dendritic cells can stimulate both memory and naive T cells, and are the most potent of all the antigen-presenting cells in normal and various pathophysiological conditions [97]. In turn, activated T cells undergo firm adhesion and transendothelial migration to inflammatory focus. Extravasation is orchestrated by the combined action of cellular adhesion receptors and chemotactic factors in a wide variety of cardiovascular and autoimmune disorders that involve inflammation.

The development and maintenance of psoriatic plaque are dependent on the participation of infiltrating T lymphocytes (CD4 and CD8) and local antigen-presenting cells (APCs) (Langerhans cells, myeloid, and plasmacytoid-DC). DCs are increased in psoriatic lesions and are critically involved in the induction of Th1 and Th17 cell proliferation, which, in turn, release IFN-γ and IL-17, respectively. Activated mDCs produce IL-23 [98, 99] and TNF-α. IL-23 stimulates the secretion of IL-22 by Th17 cells, which may be involved in epidermal hyperplasia [5]. The effects of IL-17A-producing T-helper 17 (Th17) cells include suppressive effects of T-regulatory (Treg) subsets, which have also been implicated in both pathologies. The association of IL-17A with Ps and PsA has been extensively described [98, 99] and a growing body of evidence suggests that IL-17A might also be involved in atherosclerosis [100]. IL-17 seems to have a modulatory role in atherosclerosis, but studies available show contrasting results, which could be attributed to different approaches and models. Coronary syndrome correlates with increased IL-17 levels [101]. In addition, TNF-α and IL-17 synergistically up-regulate further cytokine transcription in both diseases, Ps and atherogenesis [102]. These observations make IL-17A an interesting therapeutic target to modulate both PsA/Ps disease activity and atherosclerosis/cardiovascular risk. Obesity may play an important role by amplifying the inflammation of arthritis through the Th1/Th17 response [103]. Limited evidence from Ps patients indicates that induction therapy with infliximab, with moderate to severe plaque Ps, led to decrease in clinical disease scores and circulating levels of Th17, Th1 cells, and associated TNF-α release [104].

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T cell activation is under control from T-regulatory immune cell (Treg) activity via IL-10 and TGF-β [105–107]. Reduced numbers and/or activity of Treg cells may produce hyperactivity of Th1/Th17 subsets in both pathologies [21, 108, 109]. Ps and coronary artery disease patients show impaired inhibitory function of Treg [110, 111]. Serum and epidermal levels [105, 106] of TGF-β in Ps patients are associated with Ps disease severity [112, 113] and are diminished in low Ps [5]. In atherosclerosis, high serum levels of TGF-β and IL-10 may inhibit plaque formation [114, 115] and plaque stabilization exerting protective effect due its inhibition of T cells [116].

4.1.2.2. Humoral immune response

Humoral response seems to protect rather than harm the host. Several lines of evidence support the hypothesis that humoral immunity protects patients against atherosclerosis. First, the injection of immunoglobulin preparations inhibits atherosclerosis. Second, spleen removal (a B-cell rich lymphoid organ) seems to deteriorate vascular disease condition. Third, oxidized LDL plus adjuvant immunization promote atheroprotection [2]. Evidence so far indicates that atheroprotection is due to a T cell dependent B-cell-mediated mechanism, probably involving antibody dependent clearance of LDL and humoral dependent regulation of pathogenic T cell [17]. This atheroprotective response must be confirmed in humans.

4.1.3. Genes related to the innate and adaptive immune system associated with psoriasis and atherogenesis

At least 10 chromosomal locus associated with psoriasis have been identified as PSORS (PSORS, psoriasis susceptibility) [117]. Additionally, certain human leucocyte antigen (HLAs) are more common in psoriatic arthritis. HLA alleles that are specific for psoriatic arthritis are HLA-B27 and possibly HLA-B7, HLA-B38, and HLA-B39.

There is a strong association of psoriasis with the HLA-Cw6 allele, which increases 10–20 times the risk of psoriasis and is present in 90% of the patients with early onset psoriasis and in 50% of those with late onset psoriasis [118].

Some molecules of the innate immune system have an important influence on the pathophysiology of psoriasis, such as TLR2 and TLR4 play a key role in the pathogenesis of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, psoriasis, multiple sclerosis, and autoimmune diabetes [119].

Additionally, the expression of TLR2 and TLR4 correlates with the degree and severity of coronary disease [120, 121] oxidized phospholipids stimulate the TLR signaling pathway to induce inflammatory cytokine secretion by macrophages and endothelial cells [122].

Anti-CD14 and anti-TLR antibodies significantly inhibit the binding of fluorescein-labeled LDL to monocytes and interfering with cytokine release [123]. TNF-binding proteins are encoded by genes unrelated to PSORS, conferring susceptibility to psoriasis. Tumor necrosis factor, alpha-induced protein 3 (TNFAIP3) and tumor necrosis factor interacting protein 1 (TNIP1) are related to the inflammatory signal NF-κB, which regulates the release of TNF-α [124, 125].

TNFAIP3 promotes the survival of T-CD4 lymphocytes [126]. Certain cytokine genes have been implicated with psoriasis, including IL-12, IL-23, IL-4/IL-13 [127] conferring an increased risk of psoriatic arthritis [128].

These genes strengthened the assertion that psoriasis is an immune disorder, as these genes are linked to both the innate and adaptive immune response [129–131]. In summary, defects in these genes could amplify an inflammatory response by interfering with normal negative feedback of the NF-kB signal and therefore would link to psoriasis with other IMID and coronary pathology.

4.2. Non-inflammatory risk factors

Ps, PsA, and atherosclerosis share disturbances in different metabolic pathways involving insulin-dependent diabetes mellitus (IDDM), dyslipidemia, hypertension, obesity, and mostly metabolic syndrome, which may be related to an increase in the prevalence of CVD to their capability of inducing inflammation on the endothelial lining to initiate the process of atherosclerosis. So far, no pathophysiological mechanism for this association has been identified [63].

4.2.1. Hypertension

Several studies have found an increase in the prevalence of hypertension in Ps patients, although the definition of hypertension is very heterogeneous among these studies [117–121, 132]. Other authors have not observed a significant association between Ps and hypertension [122].

4.2.2. Diabetes mellitus

IDDM is responsible for metabolic alterations, accompanied by chronic inflammation and endothelium dysfunction. Observational studies show that the risk of IDDM is higher in patients with Ps compared with a healthy control group. This risk increases with the duration and severity of Ps and it is not related to a high body mass index (BMI) alone [133]. In a case-control study from Israel, the risk of diabetes was significantly higher in individuals with Ps [124]. Similarly, PsA patients have a higher prevalence of IDDM, even after adjusting for the BMI [125]. TNF-α antagonist therapy in patients with Ps seems to improve insulin sensitivity in limited preliminary data [126]. Finally, a few isolated cases of Ps patients with diabetes develop unpredictable hyperglycemia after starting treatment with TNF-α inhibitors [127].

4.2.3. Obesity

Recent studies have shown that obesity may precede the onset of Ps as a risk factor [120], whereas a higher BMI is associated with more severe skin disease activity [3]. The influence of obesity on psoriatic diseases is the result of complex interactions of inflammatory and metabolic factors. The proinflammatory cytokines stimulate adipocytes to synthesize neuropeptides and more cytokines, which are critical in the pathogenesis of the psoriatic and CVD [69].

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4.2.4. Smoking

Heavy and long-term smoking [128] have been associated with increased Ps risk in both men and women [129], particularly pustular Ps [116, 117, 120]. Smoking increases oxidative damage, promotes inflammatory changes, and enhances Ps-associated gene expression [121] and CVR [50, 122].

4.2.5. Dyslipidemia

Ps patients have a higher prevalence of dyslipidemia and triglycerides and lower prevalence of HDL levels. However, associations with total cholesterol and LDL have not been found statistically significant in a multivariate analysis study [116–118].

4.2.6. Metabolic syndrome

The metabolic syndrome consists of a constellation of clinical features involving abdominal obesity (waist circumference from >94 cm in men and >80 cm in women), and two or more of the following clinical situations:

HDL ≤ 40 mg/dl in men and 50 mg/dl in women, TG > 150 mg/dl, fasting blood glucose > 100 mg/dl, blood pressure > 130/85 mm Hg or treatment for hypertension. The metabolic syndrome is characterized by increases in the immunological activity of Th1, which suggests it may be associated with Ps because of shared inflammatory pathways.

Gisondi et al. [134] reported that, among Ps patients without systemic medication, 40-year-old and older people have a higher prevalence of metabolic syndrome [124].

Recently, Raychaudhuri et al. observed an increased prevalence of metabolic syndrome in patients with PsA; DM type 2 [58] and increased risk for CVD and mortality [125–129]. Ps with metabolic syndrome [130] associates with high serum uric acid levels that correlate with an increased risk of carotid intima-media thickness (IMT) or with the presence of carotid plaques [131].

5. Common angiogenic factors for Ps and atherosclerosis

Angiogenesis appears to be pathological in some chronic inflammatory diseases, like Ps and RA. It is possible for reactive homeostatic or pathological angiogenesis to play an important role in atherosclerosis. Serum levels of proangiogenic cytokines (TGF-β, TNF-α, IL-8, and IL-17), growth factors, including VEGF, and hypoxia-induced factor-1 have been shown to be significantly elevated in Ps patients compared to healthy controls [132, 133].

6. Oxidative mechanisms common to atherosclerosis and Ps

Cellular deregulation and damage [51] could be the result of overproduction or insufficient removal of ROS. In the skin, ROS can be generated either endogenous or exogenously.

Endogenously, ROS are produced through the electron transport chain and enzymes, such as cyclooxygenases (COX) [33], lipoxygenases [38], NADPH oxidases [135], and myeloperoxidases [39]. Exogenous sources that trigger ROS production include UV radiation and heavy metals [51]. In Ps, antioxidant defense mechanisms seem to be impaired, including superoxide dismutases (SODs), glutathione peroxidases, glutathione reductase, catalase, thioredoxin/thioredoxin reductase system, and metallothioneins. Augmented ROS production in the skin leads to downstream molecular events that promote atherosclerosis [51, 136, 137].

The antioxidant activity of vitamin D is well known/widely characterized. The knowledge of non-classical functions emerges from studies that indicate a close association between a low vitamin D status and increased risk of IMID and CVD [138]. It is also known that vitamin D insufficiency induces metabolic, procoagulant, and inflammatory perturbations. Recent studies indicate that it also increases the risk of MI by promoting established CVR factor-mediated mechanisms that predispose to atherothrombosis [139].

Immunomodulatory role of vitamin D in human health implicates appropriate signaling for both innate and adaptive immune responses (T and B lymphocyte function) [140–142] that amplify inflammation in Ps [143] and promote the development of different types of Treg cells [144].

7. Some lessons from CVD and rheumatic-associated therapies

Whether antirheumatic therapies increase or decrease CV risk is controversial. Glucocorticoids (GCs) are known to cause hypercholesterolemia, hypertriglyceridemia, weight gain, hypertension, and glucose intolerance, all factors promoting CVD. However, GCs are not ever conflicting. In RA patients with a known history of CVD, steroid therapy surprisingly attenuated the risk of CV death [145]. The mechanism of this apparent discrepancy with GC exposure is still unknown, but it seems to be related with dose, duration, and intensity of the exposure.

Although coronary artery disease and acute myocardial infarction are inflammatory disorders, the only drugs with anti-inflammatory effect so far widely used in ischemic heart disease are aspirin and statins (e.g., atorvastatin and simvastatin).

The contribution of coxibs and most nonsteroidal anti-inflammatory drugs (NSAIDs) to lowering CVR is not well established and the evidence available so far is controversial. Multiple studies provide evidence that methotrexate is protective against CV events and CV mortality, although the protective benefit is under discussion [146]. Immunomodulatory or immunosuppressive therapies, such as cyclosporine and colchicine, may have benefits in coronary artery disease [147]. Other studies have found that glucocorticoids plus cytotoxic immunosuppressive agents (azathioprine, cyclosporine, and leflunomide) are associated with an increased amount of CV events when compared with methotrexate alone [148].

The new targeted biological therapies, such as the suppression of systemic inflammation by anti-TNF therapies, seem to be associated with concomitant reduction in the risk of CV events

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[149], although the effect of TNF-α antagonists in lowering proatherogenic status needs further investigation. In addition, cardiovascular therapy drugs could change the proinflammatory status of PsA patients under treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), angiotensin converting-enzyme (ACE) inhibitors, and/or angiotensin II receptor antagonists (AT-II blockers). Hence, their prescription should be managed cautiously, especially for patients with a documented CV disease or in the presence of CVR factors.

Other drugs with potential benefits may include the thiazolidinedione (TZD) family, which produces positive effects on both CVR factors and Ps [14]. Targeted therapeutic interventions along with an effective control of the inflammation may have more beneficial CV effects than direct CV toxicity. There is a need for more studies addressing the role of current biological therapies on patients with a CV risk profile [3].

8. The central role of the immune system

Atherosclerosis is a complex disease but, as specific knowledge increases, the immune system can be clearly recognized to be involved in all steps of vascular pathology. Both classical and non-classical CVR factors are closely interconnected in the production of chronic inflammation through loss of immune homeostasis; indeed, either molecules or cells involved in atherogenesis present altered regulatory and/or effector immune functions, attenuating and promoting atherogenesis.

Some authors have proposed an autoimmune origin in atherosclerosis [82, 83]. Immune system homeostasis alterations against the patient's own antigens and the increasing prevalence of atherosclerosis in immune-mediated diseases, such as diabetes, periodontal disease, systemic sclerosis, antiphospholipid syndrome, RA, SLE, ankylosing spondylitis (AS), and PsA strongly reinforce the involvement of autoimmune mediators and the key role of inflammation in atherosclerosis [150]. This autoimmune response to oxidized LDL is a driving force for cell activation in the human atherosclerotic plaque [151]. The fact that low and high grade chronic inflammatory disorders present an accelerated progression of atherosclerosis constitutes indirect but critical evidence that strengthens the above-mentioned immune-mediated inflammation. The Ps/PsA proatherosclerotic profile seems to be related to chronic inflammation through classical and non-classical factors. Important insights reviewed in this article indicate that most, if not all inflammatory factors, are the result of immune activation and cytokine-driven inflammation.

For example, Th1, CTL, and Th17 effector cells are the dominant types in the pathogenesis of the psoriatic and cardiovascular diseases and are the most abundant T lymphocytes in skin, joints, and human atherosclerotic plaque [63]. In addition, reduced levels of circulating anti-inflammatory mediators and Treg may increase CV risk in both diseases [146, 152] inducing up-regulation of adhesion molecules [153] and promoting a more procoagulant [154] and vasoconstrictor phenotype [155]. Although anti-atherogenic humoral response could be verified, its anti-atherogenic action must be confirmed [2].

Indirect evidence indicating that immune-mediated inflammation is a key regulator in the crossroad of pathogenesis between Ps/PsA and atherogenesis derives from the role of certain therapies. Some drugs used in the treatment of CV disease, such as statins and ACE inhibitors, have anti-inflammatory activity. In addition, systemic treatments for Ps that decrease inflammation also reduce CV risk [156]. TLRs are the best candidates to explain what triggers and sustains the natural and adaptive immune response, maintaining proinflammatory cytokine gene expression in chronic inflammation, worsening atherosclerosis [145] in general population and in Ps patients.

Finally, the role of obesity, metabolic syndrome (possible via hypertriglyceridemia and associated abdominal adiposity in Ps/PsA patients), and probably DM, in this scenario of severe Ps and accelerated CVR. Adipose tissue is not just an "endocrine organ." Now, we know adipocytes express TLRs, which are involved in the innate immune response reacting to exogenous and endogenous stimuli by releasing inflammatory cytokines, adipokines, and other key mediators of Ps and atherogenesis. In addition, a consistent association was described between increasing obesity and lower serum 25-hydroxy vitamin D (25D) concentrations [147, 157].

In summary, chronic immune-mediated inflammation plays a key role in the pathogenesis of atherosclerosis in Ps, acting independently and/or synergistically with the conventional risk factors.

Framingham risk score (FRS), which only takes into account traditional CV risk factors for estimating the 10-year risk of CV events like metabolic syndrome and diabetes, may underestimate CVR related to underlying inflammatory factors associated with this disease, also known as non-traditional risk factors. Improvement by inflammatory suppression argues strongly for immune-mediated inflammation as the central risk factor for CVD in PsA. However, many of the studies investigating mechanisms of PsA associated with atherogenesis are not definitive or conclusive enough. Larger, more systematic, and controlled studies are needed to confirm many of the findings previously reviewed.

9. Conclusions

Most evidence reviewed in this chapter strongly supports the hypothesis that the inflammatory immune-mediated pathogenesis is probably the mayor force beyond the atherogenesis, from its initiation to plaque formation, rupture, and associated thrombotic complications. Taken together, evidence so far strongly suggests immune-mediated inflammation is the central actor in atherogenesis beyond all risk factors, regardless of whether they are "traditional" or "non-traditional." Although certain crossroads between immune-mediated inflammation pathways are activated in general population under cardiovascular risk conditions, it seems to be potentiated in psoriasis patients and other IMID. This is in agreement with accumulated evidence so far that indicates an enhanced CVR associated with Ps via both traditional and non-traditional factors immune-modulation.

Evidence so far suggests that patients with PsA and aggressive clinical presentation of Ps should be treated more aggressively for CVR prevention and modification. Therefore, selective long-term anti-atherosclerotic immunomodulation-oriented therapy might improve atherogenesis in both general population and Ps patients.

The existence of proatherogenic immunological pathways in CID that could damage the CV system reveals potential targets for more efficient therapies. This much more selective therapy requires long-term studies until it is available and accurate enough (**Figure 2**).

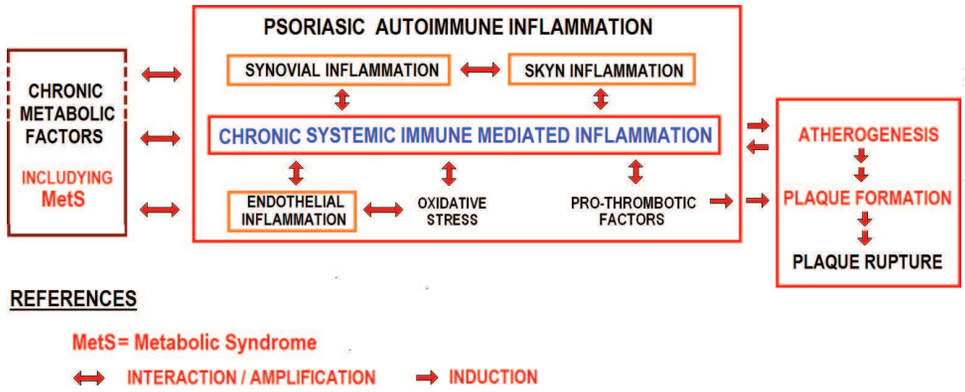


Figure 2. Interactions between autoreactive, metabolic, and endothelial inflammation. Adipose tissue releases numerous inflammatory cytokines (TNF, IL6, resistin, leptin, and vistatin) that contribute to elevate systemic inflammatory burden. The inflammatory load is also increased by the contribution of inflammatory cytokines derived from the affected tissues derived autoimmune diseases. The total inflammatory load is increased only in these patients. These molecules perpetuate and potentiate the inflammatory process, exerting a relevant proatherogenic effect. Increased uncontrolled inflammation also leads to increased oxidative stress and prothrombotic risk. Then, burden psoriatic disease is likely to be aggravated by the concurrence of augmented inflammatory burden along with disregulated activity.

Abbreviations

CV	Cardiovascular
CVD	Cardiovascular disease
CVR	Cardiovascular risk
CID	Chronic inflammatory disease
CRP	C-reactive protein
CLA	Cutaneous lymphocyte-associated antigen
EGF	Epidermal growth factor
eNOS	Endothelial nitric oxide synthase
ET	Endothelins
FGF	Fibroblast growth factors
GCs	Glucocorticoids
GCSF	Granulocyte colony-stimulating factor
GMCSF	Granulocyte macrophage colony-stimulating factor
CXCL-1 GRO-a	Growth-regulated oncogene-a

HSP	Heat shock protein
HDL	High-density lipoprotein
HIF-1	Hypoxia-induced factor-1
ICAM	Intercellular adhesion molecule
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IFN-γ	Interferon gamma
IP-10	Interferon-inducible protein 10
ICAM1	Intercellular cell-adhesion molecule 1
IMT	Intima-media thickness
LDL	Low-density lipoprotein
LFA	Lymphocyte function-associated antigen-1
MMPs	Matrix metalloproteinases
MAPK	Mitogen-activated protein kinases
MCP-1	Monocyte chemoattractant protein 1

Conflict of interest statement

The authors have no competing interests or financial, political, personal, religious, ideological, academic, intellectual, commercial, or any other issues to declare in relation to this manuscript.

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