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Psoriasis and cardiovascular risk: Immune-mediated crosstalk between metabolic, vascular and autoimmune inflammation☆

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ABSTRACT

Introduction and background: In the last few years, a substantial body of evidence indicates that cutaneous psoriasis and psoriatic arthritis patients are at higher risk of developing cardiovascular disease. However, underlying mechanism remains not completely understood. In this review we discuss the role of the immune system in the development of atherosclerosis, focusing on available data implicating the role of an enhanced immune-mediated proinflammatory status in psoriasis and psoriatic arthritis diseases.
Methods: A systematic search was performed on Pubmed until November 2014, with preference to the sources published within the past 8 years, including epidemiological studies (prospective and retrospective); cross-sectional case–control studies and reviews. Articles were selected according critical associations using the following keywords: arthritis, immune-mediated inflammatory diseases, and psoriasis. These were combined with closely related keywords reflecting cardiovascular diseases: atherogenesis, endothelial dysfunction, intima media thickness, subclinical atherosclerosis, plaque, thrombosis, thrombus, fibrinolysis, coagulation, and reactive oxygen species. Both types of disease selected terms were separately combined with non-traditional (innate and adaptive pro and anti-inflammatory immune molecules and cells) and traditional (metabolic related conditions and molecules) cardiovascular risk factors.
Results and conclusions: Psoriasis and psoriatic arthritis diseases illustrate that immune-mediated activated crossroads of inflammation beyond enhanced cardiovascular risk factors are the result of an interplay between different proatherogenic mediators derived from metabolic, vascular and autoimmune joint and skin inflamed target tissue. Consistent with this point of view, psoriasis and psoriatic arthritis diseases offer an invaluable opportunity to reinforce our knowledge about atherosclerotic cardiovascular disease.

Contents

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1. Introduction

One hundred years ago, Nikolai N. Anichkov demonstrated that cholesterol alone by consumption of fat was able to produce lesions and atheromatous changes in the vascular wall [1]. He also described the presence of inflammatory cells in the lesion, but these findings remained forgotten for many decades. In 1995, Hansson and others established that atherosclerosis has many features of a chronic inflammatory process, giving rise to the immune-mediated hypothesis behind atherogenesis [2]. However, the interest among cardiologists and in preventive medicine at that time was limited. Nowadays, the importance of such discoveries can be critically valued in immune-mediated inflammatory disorders (IMID) in general but more critically in psoriasis (Ps) and psoriatic arthritis (PsA). It is known that both, adaptive and innate immunity, participate in every step of atherogenesis and associated cardiovascular risk (CVR) factors. In fact, these diseases seem to increase CVR using both traditional and non-traditional CVR factors [3], offering a comprehensive basis to explain the immune-mediated nature of atherogenesis beyond autoimmune condition, 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 the skin and joints. The prevalence of Ps varies between 2% and 3% [4] worldwide with a similar distribution among male and female. Epidemiological studies show a peak in incidence between the second and third decades in life [5]. It has been estimated that 7–42% of Ps patients develop an 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. Several suspected environmental triggers and poorly characterized factors (e.g. infections, drugs, physical and emotional stress) have been implicated in the initial course of these diseases, most likely against a genetically predisposed background [9]. Nowadays, Ps is considered an immune-mediated skin disease, and PsA regarded as a seronegative (rheumatoid factor negative) arthritis. In Ps and PsA, the inflammatory features/responses in skin and joints are very similar, including the composition of inflammatory infiltrates, and vascular changes [12]. Moreover, the cellular infiltrate is predominantly perivascular [13].

The contribution of B lymphocytes to the pathogenesis is poorly understood. However, none of the forms of Ps or PsA have been associated with serum auto-antibodies. In contrast, T lymphocytes are the most abundant in both skin and the synovial fluid of joints, where the dominant subpopulations include Tc1 (subpopulation of CD8+ cytotoxic T cells that secrete IFN and IL-4) as well as T-helper 1 lymphocyte subpopulation (Th1) and Th17 (IL17+ T-helper cells) which interact with dendritic cells, macrophages and target tissue cells. These cells are attracted among other molecules by elevated concentrations of MCP-1 as was found in synovial fluid [14] and skin biopsies obtained from Ps and PsA patients [15]. Their role in the pathogenesis will be discussed in more detail below.

3. Atherosclerosis

Atherosclerosis is a complex low inflammatory disease characterized by derangements in the metabolic and immune system homeostasis that lead to pathogenic chronic progressive vascular damage. Classical knowledge distinguishes between inflammatory and non-inflammatory diseases. However, this distinction is no longer appropriate because the identification of inflammatory mechanisms is associated with the traditionally called “non-inflammatory diseases”. Although atherogenesis belonged to this group during several decades, now it is well known 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. In addition the immune system is critically involved in the production of atherosclerosis plaque containing macrophages, lymphocytes and other immune cells [16].

Studies in hypercholesterolemia induced immune activation in mouse models of atherosclerosis highlight the critical balance between Th1 cells [17] and Treg [18]. Inflammation in the arterial intima seems to be related with protective and pathogenic immune responses against modified self-antigens in the atherosclerotic plaque.

The paradigm of atherosclerosis as an inflammatory disease is widely accepted, although little is known about its association with rheumatic diseases, particularly the underlying mechanisms. Chronic inflammatory systemic diseases could share common immune-mediated inflammatory pathways. Molecules and immune cells derived from both diseases may interact together in promoting a pathogenic effect. Despite differing initial events between the above-mentioned diseases that could exist, increasing evidence indicates that even in clinically heterogeneous diseases both of them could share common immunological pathways that may damage the CV system. The contribution of the chronic inflammatory state to the CVR, has mainly been investigated in the prototypical inflammatory disorder, i.e. rheumatoid arthritis (RA) [19–21].

Consistent with these studies, the chronic activation of innate and adaptive inflammatory pathways, which are described below, is believed to accelerate or trigger critical atherosclerosis events in Ps and PsA, including atherosclerotic plaque progression, destabilization, and ultimately rupture, with subsequent clinical sequelae like myocardial infarction (MI) or stroke.

Identifying critical inflammatory pathways involved in progression and destabilization of pre-existing atherosclerotic plaques may help to define novel therapeutic strategies to further reduce CVD burden, particularly in patients with chronic inflammatory disorders. Based on previous papers, a multidisciplinary expert committee was designated a few years ago in accordance with EULAR (European League against

Table 1
Representative summary of epidemiological studies (prospective and retrospective) linking *PsA* to associated cardiovascular risk and comorbidities (RCM), published between 2006 and 2014. AC: alcohol consumption; BMI: body mass index; CAD: coronary artery disease; CCF: controlled for confounding factors; CHF: congestive heart failure; GP: general 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.

Author/year	Number of patients & study profile	Findings
Han, 2006	3066 PsA patients vs clinically asymptomatic controls matched by age, sex, geographic region	Higher prevalence for CHF, PVD, IHD atherosclerosis, type II diabetes, HL, and HTN in PsA patients than controls
Sattar, 2007	127 patients with active Ps/PsA after at least first failure with DMARDS treatment, onset of disease after 16 years old, PsA of more than 6 month duration with active arthritis in 3 or 4 swollen joints. Double–blind placebo (n = 42) controlled study performed with two doses of Onercept 100 (n = 42) and 50 mg (n = 43) for 12 weeks.	Result compared against baseline before and after the end of treatment with Onercept. Results indicate higher CRP, that positively correlate with Lp(a); ICAM-1; IL6; homocysteine; same levels Apo-I, Apo-B & TG
Gonzalez-Juanatey, 2007	59 PsA patients vs. 59 control patients Without clinically evident CVD adjusted for age and ethnic.	Carotid artery IMT correlated with age, time of PsA diagnosis, disease duration, total cholesterol & LDL
Eder, 2008	40 PsA patients compared with 40 controls matched by age, sex, and CVR factors.	Higher IMT among PsA patients. Multivariate analysis demonstrated that PsA status, age & TG levels were associated with the presence of carotid plaque. TRF prevalence was higher among PsA patients.
Tam, 2008	102 PsA patients from Southern China.	Increased prevalence of DM and HTN was found in PsA group compared with age- and sex-matched controls, even after adjusting for the BMI.
Kimhi, 2009	Carotid artery IMT from 47 patients with PsA were compared with 43 healthy controls matched for age and sex.	The average IMT (mean/SD) in PsA patients was significantly compared to GP even after adjustment for age, GR, BMI, HTN&HL.
Gladman 2009	648 patients with Ps and PsA	CV risk. Severity of skin involvement is an independent CVR factor
Shang, 2011	94 PsA patients without clinical evidence of CVD and 63 healthy subjects.	PsA patients without established CVD & in the absence of TRF have a high prevalence of subclinical ED via echocardiography and imaging studies.
Eder, 2013	Cross-sectional study comparing 125 PsA with 114 Ps patients.	Study suggests that PsA patients suffer from more severe subclinical atherosclerosis compared with Ps patients, independent of *TRF* & correlates with inflammatory markers.
Ogdie, 2014	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 have a significantly risk of mortality.

Rheumatism) to analyze CVR evidence in rheumatic diseases and to make recommendations for the management of RA and other forms of inflammatory arthritis. Apart from the management of conventional risk factors, this committee suggests an aggressive inflammation suppressive therapy to further reduce CVR [22].

Emerging evidence supports the hypothesis that cardiovascular morbidity and mortality in Ps and PsA are increased in comparison to the general population being the leading causes of death in PsA [23]. On other hand, CVD is increasingly considered an extra-articular manifestation in Ps patients, with the chronic inflammatory state as a potential driving force behind the accelerated atherogenesis [24]. In this direction few papers have been published related to CVR factors [7,8,25] which are shown in Table 1. Some representative prospective and retrospective epidemiological surveys, published between 2006 and 2014 (Table 1) indicate that Ps and PsA patients, as compared to normal controls, exhibit an increased prevalence of MI, ischemic heart disease, hypertension, diabetes and dyslipidemia.

Although multiple CVR factors are associated with Ps, key components of the metabolic syndrome are more strongly connected with more severe PsC [26] Recent studies [27] also indicate an increase in inflammatory burden in PsA compared to Ps (Table 1). In contrast the risk of developing a CV outcome (MI, ischemic stroke and transient ischemic attack), was not elevated in early Ps patients in a matched follow-up study case–control analysis [28,29].

4. Inflammatory and classical cardiovascular risk factors

4.1. Inflammatory risk factors

Accelerated atherogenesis in Ps and PsA may involve multiple inflammation-related and non-inflammatory factors. Since a substantial amount of data accumulate in the past of this issue we provide a brief insight into the most common mechanisms involved.

As previously mentioned, Ps and atherosclerosis have a similar immune innate and adaptive pathogenic profile. Both share a similar histological hallmark involving activated lymphocytes (Th1/Th17cells), proinflammatory cytokines and inflammatory cells, including skin, joint-tissue and endothelial wall macrophages [30] (See Figs. 1 and 2 for more details).

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, which are involved in atherosclerosis [31], Ps and other pathologies [32]. TLR expression is positively correlated with plasma tumor necrosis alpha (TNF-α) levels [33]. 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, CRP, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) release [34].

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 PsA and atherosclerosis may be related to other factors by the high number of overlapping molecules, including cytokines [interleukins (IL-2, IL-6, IL-15, IL-17, IL-18, IL-20, IL-23)], interferon alpha (IFN-α), Oncostatin M, (TNF-α), chemokines (Fractalkine, growth-regulated

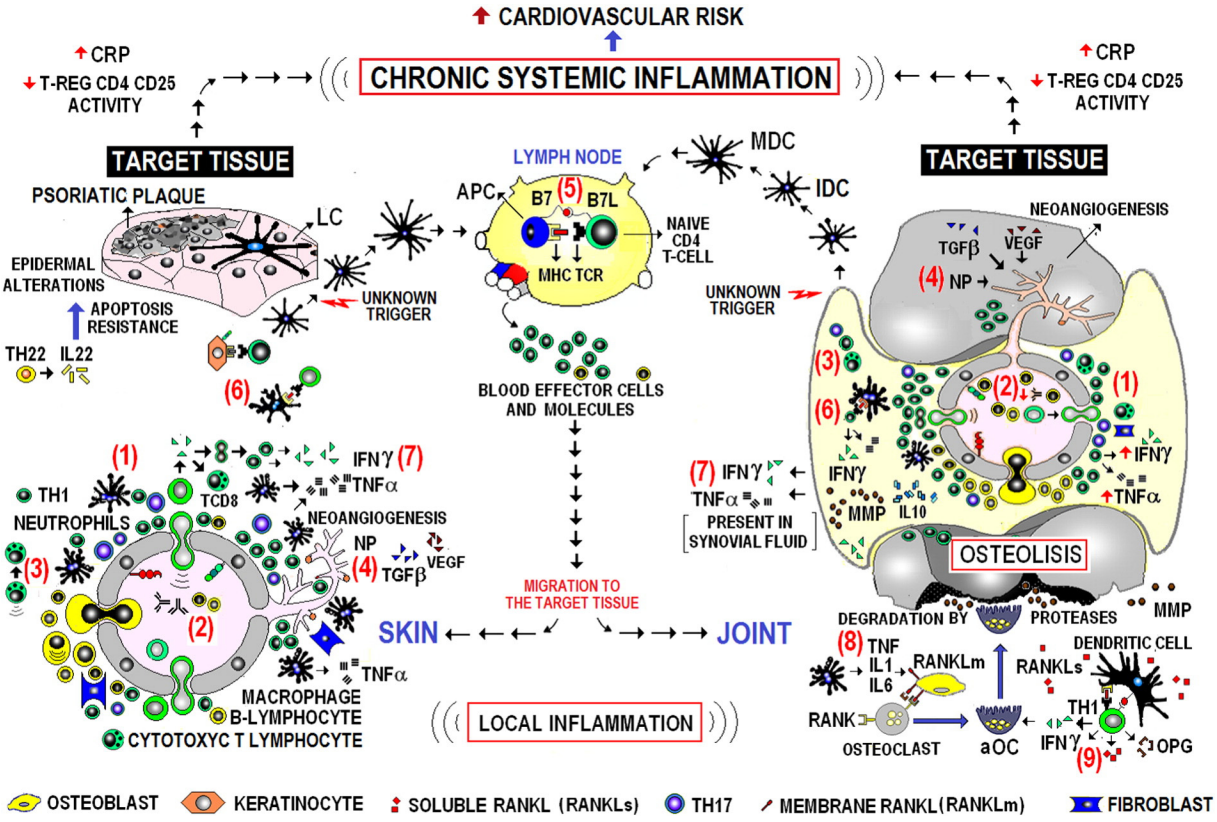

Fig. 1. Immunopathogenesis of Ps & PsA associated events that worsen the cardiovascular risk profile. Chronic inflammation of the skin and joints have many common immunopathological features, including genetic predisposition, composition of inflammatory infiltrates, vascular changes, early immune events and proangiogenic similarities. The cellular infiltrate is predominantly perivascular (1). B lymphocytes are abundant but the contribution of B cells to the pathogenesis is unlikely (2). T lymphocytes are the most abundant in both skin and joints, where the dominant types are cytotoxic T lymphocyte CTL, Th1 and Th17 (3). Neuropeptides (NP) are also involved in proinflammatory pathways (4). Antigen is presented to naive CD4 Th cells during immune synapse (5) in the lymph node. Emerging lymphocytes migrate preferentially to skin and joints, where the above-mentioned infiltrating T lymphocytes (CD4, CD8) interact with local APC (Langerhans cells, myeloid-DC and plasmacytoid-DC) to produce chronic inflammatory conditions. Local re-activated T cells (6) secrete chemokines and cytokines that amplify the inflammatory environment, resulting in the formation of psoriatic plaque, induction of degradation of cartilage and perhaps atherosclerotic plaque. Since the suppressive activity of regulatory cells is decreased in both tissue and blood, lymphocytes show high replicative power. The chronic production of proinflammatory cytokines (IFNγ, TNFα) crucially contributes to the perpetuation of the disease (7). TNFα is critically involved in induction of inflammatory degradation of cartilage and bone (8). The osteolytic activity (9) is the result of the activation of osteoclasts by the action of IFNγ. APC: antigen-presenting cell; aOC: activated osteoclast; DC: dendritic cells; MDC: mature DC; IDC: immature DC; CRP: C reactive protein; OPG: osteoprotegerin; MHC: major histocompatibility complex; MMP: metalloproteinases; RANKL: receptor activator of Nuclear Factor-Kappa B Ligand; VEGF: vascular endothelial growth factor; B7L: family of structurally related ligands, which bind to APC counter-receptor (B7).

oncogene (GRO) alpha), interferon-gamma inducible protein-10 kDa (IP-10), IL-8, MCP-1, monokine induced by interferon gamma (MIG/CXCL9), adipokines (Resistin, Leptin, PAI-1), adhesion molecules (ICAM /LFA-1 (leukocyte function-associated antigen-1),/CD154 (OX40L)/CD134 (OX40), co-stimulatory molecules (CD80, CD28, CD40/CD40L), lymphocyte profile (Th1 /Th17 up-regulation, Treg down-regulation, CTL effector activity), NK cells, Natural killer T (NKT) cells, myeloid dendritic cells, plasmacytoid dendritic cells, monocytes/macrophages, mast cells and neutrophils), complement activation [35], TLR-mediated inflammation (TLR-2, TLR-4, TLR-9) [28–30], and other important factors (CRP, endothelin-1, inducible nitric oxide synthase (iNOS), heat shock protein (HSP60, HSP65, HSP70), matrix metalloproteinases (MMP-2, MMP-9), and oxidized low density lipoprotein (LDL)) [36–38]. Some molecules listed before and other PsA-related serum cytokine patterns have been demonstrated by multiplex cytokine array systems in Norwegian PsA patients [39]. In the same study cytokine serum profile in PsA patients indicates that IL-10, IL-13, IFN-α, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), CCL-3 (MIP-1α), CCL-4 (MIP-1α), CCL-11 (Eotaxin) and GCSF are increased. Few of these cytokines previously mentioned [40,41] and their pathogenic contribution at different stages in the pathobiology of atherothrombosis and PsA are not clear yet [34]. NK cells possess both inhibitory and activating killer immunoglobulin-like receptors (KIRs). Activated KIRs (KIR2DS-1 and KIR2DS-2) increase the susceptibility to PsA [42]. In addition, NK cells are found in 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 the predominant CD56−/CD16+ Lo NK cell population and body mass index. Therefore, adipose immune cell phenotype and function, may provide greater insight into cardio-metabolic pathophysiology in psoriasis [43].

One of the natural killer group 2 member D (NKG2D) ligands in human is the MHC class-I chain-related molecule A (MICA). MICA is usually absent on normal cells, but its expression rises upon cellular stress on target cells such as endothelial cells. Xia et al. reported that immune activation resulting from NKG2D–ligand interaction promotes atherosclerosis [44].

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 [45]. Controlling the activation state of NKT cells may represent a potential new therapy for atherosclerosis [46].

Our knowledge of biologically active serum molecules and cells involved in the pathogenesis of both PsA and atherosclerosis is still not

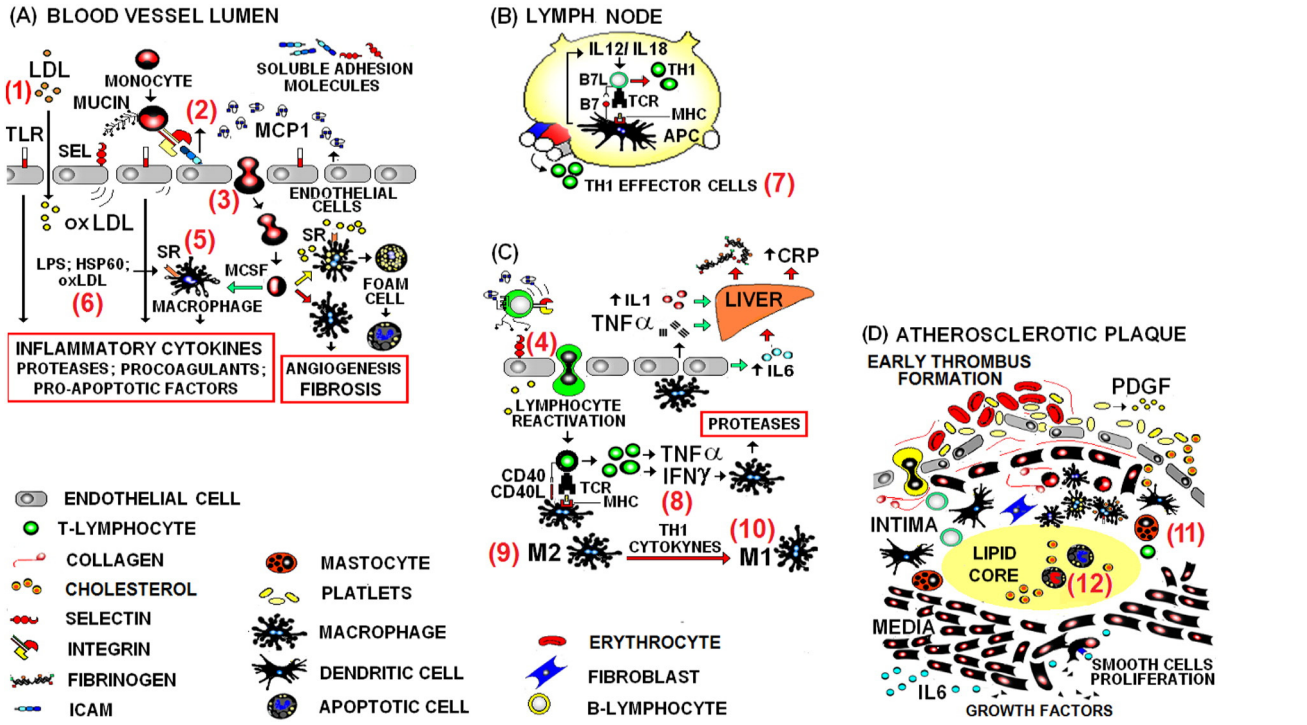

Fig. 2. Schematic of early and late immune-mediated events implicated in atherosclerosis. (A) LDL from blood is modified by enzymes and oxygen radicals to form oxidized LDL (oxLDL) (1). Biologically active lipids induce endothelial cells (EC) to express leukocyte adhesion molecules (2), leading to early monocytes (3) and later T cells (4) entrance into inflamed tissue. Monocytes differentiate into macrophages (5) in response to local macrophage colony-stimulating factor (M-CSF) and others stimuli. Expression of many pattern-recognition receptors increases, including scavenger receptors (SR) and Toll-like receptors (TLRs). Macrophage, active ingest oxLDL particles without a regulated pattern, leading to intracellular cholesterol accumulation and the formation of foam cells. TLRs bind oxLDL (6), which in turn triggers the production of many proinflammatory molecules by macrophages. (B) Antigen presentation and Th-cell activation and differentiation occur in regional lymph nodes. Antigen involved in immune synapsis presentation is unknown, but the specificity of effector cells recognizes oxLDL and HSP60. (7) Lymph node emerging Th1 effector cells could migrate to endothelial wall and undergo "re-activation" after interacting with antigen-presenting cells (APCs), such as macrophages or dendritic cells, both of which process and present local antigens including oxLDL. Th1 produce inflammatory cytokines including IFNγ and TNFα (8) and express CD40 ligand (CD40L). (C) Locally (in plaques) macrophages and smooth muscle cells (SMC) produce IL12 and IL18 and they can indirectly affect the development of plaques by promoting Th1-cell differentiation. IFNγ activates macrophages, thereby releasing proinflammatory cytokines, CRP, pro-thrombotic and vasoactive mediators. In addition, IFNγ inhibits EC proliferation, induces vascular SMC proliferation and collagen production. During early steps of atherogenesis, when innate immune response is prevalent, the M2 (9) macrophage phenotype predominates. (10) The transition to a M1 phenotype might depend upon the type of the adaptive immune response. Th1 lymphocytes promote the M1 phenotype. (D) Atherosclerotic plaques have a complex organization from cellular (11) and molecular point of view, consisting of two main structures: a lipid core (12) and debris from dead cells and a surrounding fibrous cap consisting of SMC, collagen fibers and immune cells. Decreasing collagen content of the fibrous cap might reduce the stability of the plaque and produce eventually its rupture. ChRc: chemokine receptor. SEL: selectin.

clear. 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 [39], and suggests that the measurement of inflammatory-related markers may enhance CV risk evaluation. Current evidence suggests that the pathway of inflammation in atherosclerosis culminates in altered concentrations of various markers in peripheral blood, including oxidative stress molecules [48,49] and markers of vascular inflammation like CRP [49], IL-6, ICAM-1 and MCP-1 [50].

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 mediates several effects, including increased CV risk. Studies in animal models and humans provide compelling evidence identifying TNF-α as one of several regulators of vascular homoeostasis [32]. Among its proatherogenic effects, TNF-α may induce lipid abnormalities, including high LDL-cholesterol and low HDL-cholesterol [51]. TNF-α may also promote 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 [52]. The majority of epidermal T cells in Ps vulgaris lesions can produce type 1 cytokines (IFN-γ, IL-2, and TNF-α). CTL and Th1 effector lymphocyte populations are also measured in circulating blood in psoriatic patients [53]. TNF-α also induces endothelial dysfunction including low nitric oxide availability and up-regulation of endothelial adhesion molecules such as VCAM-1 [54,55], a critical early step in atherogenesis.

On 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. 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 [56]. 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 [57]. 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 both atherosclerotic plaque development and destabilization [58]. Increased and sustained

IL-6 levels in turn stimulate the hepatic release of acute-phase reactants including CRP levels, a widely accepted CVR factor [59]. 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 [60]. 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 the pathophysiology of metabolic syndrome and insulin resistance [61].

IL-6-gene polymorphisms were found to correlate with the severity of coronary artery disease and the risk of MI [62], but not with carotid atherosclerosis, which seems to be independent [63,64]. Large-scale human genetic studies are consistent with a causal association between IL-6 R-related pathways and coronary heart disease [65]. These findings clearly suggest a strong association between IL-6 levels and atherosclerosis, MI risk and cardiovascular mortality [66]. 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. With regards to SMC, some authors have described a shift from STAT3-dependent anti-inflammatory signaling pathway to STAT-1 proinflammatory signaling pathway when IFN-γ and TLR-4 signaling pathways are activated [67].

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. In particular, IL-6 has a pivotal role in synovitis, bone erosion and in the systemic features of inflammation [68].

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 [69].

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 [70].

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. In addition, IL-6 combined with transforming growth factor beta (TGF-β) promotes the differentiation of IL-17-secreting Th17-cells [71], potentiating the immune effector mechanism. In both pathologies, 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, fibrosis and has mitogenic potential for SMC [72]. 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 [73]. Synovial tissue and serum of patients with PsA all show strongly enhanced ET-1 receptor expression [74].

4.1.1.4. C-reactive protein. A considerable amount of evidence implicates CRP as a predictive marker for future CV events and mortality in different settings, particularly under metabolic syndrome conditions in the general population [75,76]; CRP has also been implicated as a direct partaker [77,7,78]. CRP stimulation of the production of plaque-destabilizing MMPs and MCP-1, a decrease in the activity of endothelial nitric oxide synthase (eNOS) and an impairment in endothelium-dependent vasodilation can be mentioned among the most prominent findings [79]. In vitro studies provide evidence for direct proatherogenic effects of CRP, including increased endothelial dysfunction [80]. 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 [81].

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 immunity and links inflammation, metabolic dysfunction and cardiovascular disease [82].

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 [83,84]. MMP-1 serum levels and gene expression are elevated in PsA [85].

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 [57], and are elevated in circulating blood [53]. In contrast, the T regulatory activity is reduced.

4.1.2.1. Cellular immune response. Myeloid dendritic cells (mDCs) 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. 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. Adhesion molecules are therefore particularly implicated 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, 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 [86] 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 [87] and a growing body of evidence suggests that IL-17A might also be involved in atherosclerosis [88].

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. IFN-γ and IL-17 serum levels are increased in patients with coronary artery disease but are undetectable in healthy volunteers. Coronary syndrome correlates with increased IL-17 levels as well as high-sensitivity CRP and IL-6, both of which predict MI risk [89]. In addition, TNF-α and IL-17 synergistically up-regulate further cytokine transcription in both diseases, Ps and atherogenesis [90].

These observations make IL-17A an interesting therapeutic target to modulate both PsA/Ps disease activity as well atherosclerosis/cardiovascular risk. Obesity may play an important role by amplifying the inflammation of arthritis through the Th1/Th17 response [91].

Limited evidence from Ps patients indicates that induction therapy with infliximab, with moderate to severe plaque Ps, led to decreases in clinical disease scores and circulating levels of Th17, Th1 cells and associated TNF-α release [92].

T cell activation is under control from T-regulatory immune cell (Treg) activity via IL-10 and TGF-β [93,94]. Treg lymphocytes are characterized by expression of TGF-β, a T cell suppressive cytokine [95]. Reduced numbers and/or activity of Treg cells may produce hyperactivity of Th1 /Th17 subsets in both pathologies [96–98]. Ps and coronary artery disease patients show impaired inhibitory function of Treg [99,100]. Serum and epidermal levels [93,94] of TGF-β in Ps patients are associated with Ps disease severity [101,102] and are diminished in low Ps [5]. In atherosclerosis, high serum levels of TGF-β and IL-10 may inhibit plaque formation [103,104]. In addition, TGF-β promotes plaque stabilization. Taken together protective effect of TGF-β is due to its inhibition of T cells. Of note, substance P (SP), the prototype tachykinin peptide, displays Nuclear Factor-Kappa β (Nf-κβ)-dependent proinflammatory effects, which are silenced by IL-10 and TGF-β in T lymphocytes and macrophages, respectively [105].

4.1.2.2. Humoral immune response. Not all immune responses that mounted during the course of atherosclerosis are pathogenic. 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]. Although the underlying mediating mechanism of this effect remains poorly understood, most evidence so far indicates that athero-protection is due to a T cell dependent B-cell-mediated mechanism, probably involving antibody dependent clearance of LDL and T cell-mediated inhibition of vascular inflammation or humoral dependent regulation [15]. This atheroprotective response must be confirmed in humans.

4.2. Non-inflammatory risk factors

Ps, PsA and atherosclerosis share derangements 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. Ps/PsA derangements mentioned above may act due 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 [52].

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. The majority of these papers establish a relationship between the severity of Ps and the risk of hypertension [106–108]. Other authors have not observed a significant association between Ps and hypertension [109].

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. In a case-control study from Israel, the risk of diabetes was significantly higher in individuals with Ps [110]. Similarly, PsA patients have a higher prevalence of IDDM, even after adjusting for the BMI [111]. TNFα antagonist therapy in patients with Ps seems to improve insulin sensitivity in limited preliminary data [112]. Finally, a few isolated cases of Ps patients with diabetes develop unpredictable hyperglycemia after starting treatment with TNF-α inhibitors [113].

4.2.3. Obesity

Recent studies have shown that obesity may precede the onset of Ps as a risk factor [114], whereas a higher BMI is associated with more severe skin disease activity [26]. 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 [52]. Some studies have shown that the use of anti-TNF-α drugs is associated with significant weight gain and BMI increase in Ps and PsA patients [124].

4.2.4. Smoking

Heavy and long-term smoking [125] have been associated with increased Ps risk in both men and women [126], particularly pustular Ps [116,117,118]. Smoking increases oxidative damage, promotes inflammatory changes and enhances Ps-associated gene expression [119] and CVR [50,120].

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 [121].

Several cross-sectional studies using varying populations and analytic approaches have found an association between Ps and an increased risk of hyperlipidemia [122,123]. Studies regarding the effects of TNF antagonists on blood lipids have shown mixed and unclear results.

4.2.6. Metabolic syndrome

The metabolic syndrome consists of a constellation of clinical features involving abdominal obesity (waist circumference > 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. 2008 reported that, among Ps patients without systemic medication, forty-year-old and older people have a higher prevalence of metabolic syndrome. This association is independent from the severity of Ps but directly related to its duration [124].

Recently, Raychaudhuri et al. observed an increased prevalence of metabolic syndrome in patients with PsA; among these patients, 24.6% had coronary artery disease and 39.3% DM type 2 [52]. Patients with metabolic syndrome and PsA have an increased risk for CVD and mortality [125–129].

On the other hand, serum uric acid exerts its influence by conditioning the association of Ps with metabolic syndrome [130]. High serum uric acid levels correlate with an increased risk of carotid IMT or with the presence of carotid plaques. The study of a fifty-three -PsA-patient cohort, without CVR factors or clinically evident CVD, has shown a significant correlation between carotid IMT and serum uric acid concentration. Taken together, asymptomatic hyperuricemic PsA patients have been associated with subclinical atherosclerosis [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 and growth factors have been shown to be significantly elevated in Ps patients compared to

healthy controls [132]. Upon activation, keratinocytes release other angiogenesis-inducing factors, including VEGF, hypoxia-induced factor-1 (HIF-1), TGF-β, TNF-α, IL-8 and IL-17.

Some recent reports [133] have demonstrated that VEGF overexpression in serum and skin biopsies of Ps patients has a key role in the pathogenesis of Ps. VEGF exerts an early and late cardiovascular effect. In fact, it primes endothelial cells to overexpress E-selectin, an adhesion molecule necessary for transepithelial migration of leukocytes [134, 135], leading to the enrichment of immune cells into the intima at various stages of atherogenesis.

6. Oxidative mechanisms common to atherosclerosis and Ps

Cellular dysregulation and damage [47] 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) [136], lipoxygenases [137], NADPH oxidases [138] and myeloperoxidases [139]. Exogenous sources that trigger ROS production include UV radiation and heavy metals [47]. 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 [47,140, 141].

The antioxidant activity of vitamin D is well known/widely characterized. The knowledge of nonclassical functions emerges from studies that indicate a close association between a low vitamin D status and increased risk of IMID and CVD [142].

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 [143].

Immunomodulatory role of vitamin D in human health implicates appropriate signaling for both innate immune responses (antimicrobial activity and antigen presentation) and adaptive immune responses (T and B lymphocyte function) [144, 145,146].

Recent data indicate that vitamin D analog calcipotriol interferes with the Th17 cytokine-induced proinflammatory antimicrobial peptides (psoriasin and koebnerisin), which are released from keratinocytes present in psoriatic skin and act as chemoattractant and “danger signals” to amplify inflammation in Ps [147]. In addition, in vitro studies indicate that distinct DC subsets are differentially programmed by vitamin D, promoting the development of different types of Treg cells [148].

7. 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 [149]. 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. 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 [143]. Immunomodulatory or immunosuppressive therapies, such as cyclosporine and colchicine, may have benefits in coronary artery disease. 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 [150].

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 [151], 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 CV risk factors.

Other drugs with potential benefits may include the thiazolidinedione (TZD) family, which produces positive effects on both CVR factors and Ps.

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 [22].

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 nonclassical 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 [76,77]. 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 [152]. This autoimmune response to oxidized LDL is a driving force for T cell activation in the human atherosclerotic plaque [153]. 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 driven 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 [57]. In addition, reduced levels of circulating anti-inflammatory mediators and Treg, may increase CV risk in both diseases [154]. According to its common inflammatory cytokine profile, TNF-α levels are elevated in patients with Ps, PsA and CVD and exerts its powerful proinflammatory pathogenic influence in multiple ways, including activation of endothelial and immune cells status [155] inducing up-regulation of adhesion molecules [156] and promoting a more procoagulant [157] and vasoconstrictor phenotype [158]. This cytokine might be therapeutically antagonized with anti-TNF (Etanercept) leading to a chronic Th2 cytokine profile that could be beneficial for the attenuation of Ps development and atherogenesis. 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. [159]. Further evidence that accounts for the prevailing immune-mediated mechanism in inflammation status derives from the fact that 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. Proinflammatory TLR-2 and TLR-4 worsen atherosclerosis [160] in general population, in Ps and PsA 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, emerges usually from the concept that adipose tissue is 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, including IL-6, TNF-α, leptin, adiponectin, resistin and PAI-1. In addition, a consistent association was described between increasing obesity and lower serum 25-hydroxy vitamin D (25D) concentrations [161]. Because the immunomodulatory action of vitamin D is required for appropriate immune function, the balance of Th17 and Treg activity can be altered [149].

Pathogenic immune cells profile and proinflammatory circulating factors common to Ps/PsA and atherosclerosis, like deleterious immune cell types, proatherogenic cytokine and chemokine levels, enhanced acute-phase proteins, up-regulated vascular adhesion molecule expression, increased proteases, augmented ROS release, adipokines, activated innate receptors, increased vasoactive molecules, obesity-associated vitamin D depletion, altered thrombosis factor balance and increased proangiogenic factors should be critical in the pathological outcome of atherosclerosis.

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. Therefore, it makes sense for the Framingham risk score (FRS), which only takes into account traditional CV risk factors for estimating the 10-year risk of CV events, to consider factors related to Ps-comorbidities like metabolic syndrome and diabetes, but may underestimate CVR related to underlying inflammatory factors associated with this disease, also known as non-traditional risk factors. CRP has been shown to enhance the predictive value of FRS for MI and CV death in normal populations, although there is no way so far to perform a valid quantification of additional CV risk in PsA through CRP.

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 article strongly support the hypothesis that the inflammatory immune-mediated could be involved in the pathogenesis of 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 factor immune-modulation.

Although administration of non-selective immunosuppressive drugs will probably not be useful for treatment of idiopathic atherosclerosis, it must be evaluated in the context of an aggressive clinical presentation of Ps since the balance between potential toxicities and benefits is not the same in the two groups. Evidence so far suggests that patients with PsA 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. Taking into account that Ps and PsA activate the proatherogenic immune-mediated inflammatory response associated with both "traditional" and "non-traditional" CVR factors, it seems possible that future drug development in atherosclerosis in Ps/PsA-related therapy should change from the currently dominating biologic agents to more specific molecular immune mediators implicated in immunopathogenesis. This much more selective therapy requires long-term studies until it is available and accurate enough.

Conflict of interest statement

The authors have no competing interests, nor financial, political, personal, religious, ideological, academic, intellectual, commercial or any other to declare in relation to this manuscript.

List of Abbreviations[1]

(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
(IFNγ) 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

[1] They were defined in the text at first use.

(MCP-1) monocyte chemotactic protein-1
(MIG) monokine induced by interferon-c
(MI) myocardial infarction
(NK) natural killer
(NFkB) Nuclear Factor-Kappa B
(Ps) psoriasis
(PsA) psoriatic arthritis
(ROS) reactive oxygen species
(T-regs) regulatory T cell
(RA) rheumatoid arthritis
(PAI-1) plasminogen activator inhibitor type 1
(PRR) pattern-recognition receptors
(STAT) signal transducer and activator of transcription
(SLE) systemic lupus erythematosus
(Th) T-helper cells
(Th17) T-helper 17 subset
(TLR) Toll-like receptor
(Treg) T regulatory lymphocyte
(TGFβ) transforming growth factor-β
(TNFα) tumor necrosis alpha
(VCAM1) vascular cell-adhesion molecule 1
(VEGF) vascular endothelial growth factor
(VLA-4) very late antigen-4
(VD) vitamin D

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