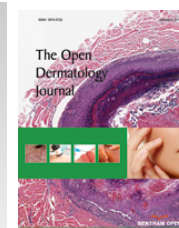




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REVIEW ARTICLE

The Psoriasis Pathogenesis and the Metabolic Risk

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Abstract:

Summary

Psoriasis is a multifactorial disease that can be related to genetic, environmental and immunological causes. Therefore, not only a single factor but different aspects contribute to the onset of the disease, varying from individual to individual. It would be characterized by an abnormal proliferation and differentiation of keratinocytes, mediated by a dysregulation in the auto-immune T cell response in which several cytokines participate, including Interleukin (IL)-17, IL-17A, IL-12, IL-22, IL-23. These cells and cytokines are responsible for the aggression on skin cells, inflammation and accelerated reproduction of the cells of the epidermis. Due to the chronic inflammation, psoriasis is frequently associated with other concomitant non-dermatological morbid conditions such as arthropathy which can be complicated by a disabling evolution. Psoriasis is also frequently associated with comorbidities such as Cardiovascular Diseases (CVD), hyperlipidemia, diabetes and obesity.

The knowledge of common inflammatory pathways and of the potential links between psoriasis and other diseases should encourage dermatologists to a multidisciplinary approach to psoriasis and to an optimal management also in the light of new therapeutic possibilities.

Keywords: Psoriasis, Comorbidities, Cardiovascular disease, IL-17, Metabolic risk, Systemic inflammation.

1. INTRODUCTION

Psoriasis is a chronic inflammatory disease of variable severity affecting 2-3% of the general population and is characterized by an abnormal proliferation and differentiation of keratinocytes, mediated by the dysregulation in the T cell response [1 - 3].

Psoriasis has long been considered the "disease of the healthy", but many evidences are increasingly contradicting this traditional concept. Today, it is identified as a pathology with systemic involvement and frequent associations with other concomitant non-dermatological morbid conditions [4, 5].

In about 10-30% of patients it coexists with a form of arthropathy with peripheral or axial articular involvement, responsible for joint pain and functional limitations of the joints, which can be complicated by a disabling evolution [6 - 10].

These aspects often have an impact on the quality of life, limiting the daily activities [11].

Psoriasis is also frequently associated with other metabolic diseases such as obesity, hyperlipidemia and diabetes. Accumulating data prove that this association predisposes psoriatic patients to an increased cardiovascular risk [12 - 15].

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2. PATHOGENESIS

The etiopathogenesis is immune-mediated and based on a polygenic and multifactorial genetic susceptibility where numerous triggering factors (infections, drugs, stress, trauma, *etc.*) are involved. The disease has a strong but complex genetic background, so that 60-80% of white psoriasis are carriers of HLA-Cw6 against 20% of the population of the same breed [16]. The genetic loci associated with the disease are called psoriasis susceptibility (PSORS). Among the loci associated with psoriasis we find PSORS1 on the short arm of chromosome 6. But it is also possible to mention: PSORS2 on the long arm of chromosome 17, PSORS4 on the long arm of chromosome 1, PSORS5 on the long arm of chromosome 3, PSORS6 on short arm of chromosome 19, PSORS7 on the short arm of chromosome 1, PSORS8 on the long arm of chromosome 16, PSORS9 on the long arm of chromosome 4 and PSORS10 on the short arm of chromosome 18.

They encode proteins expressed at the level of epidermis, such as corneodesmosina. It is known that in the immunopathogenesis of psoriasis there is a dysregulation of the immune system with an imbalance in favor of the T helper (Th)1-derived cytokine pattern. Many immunophenotypic studies have shown that the predominant cells in the inflammatory infiltrate of psoriatic skin are polarized towards a Th1 phenotype, are mature T lymphocytes (CD3+) showing signs of activation (CD25+, DR+) and belong to the subclass CD4+ at the level of the dermis and CD8+ in the epidermis.

The first step in the cell-mediated response is characterized by the interaction between the naïve T cell and the antigen-presenting cell (APC), which determines the activation and differentiation of the T lymphocyte. This initial interaction process involves the T cell receptor (TCR) and stimulates the interaction between a glycoprotein expressed in the APC called CD40 and its ligand, known as CD40L, expressed in the T lymphocyte. This binding results in a high release of proinflammatory cytokines from mature dendritic cells (DCs), including IL-12 [17].

The presence of mature DC in the dermis is important in the pathogenic psoriatic process for their ability to secrete a vast cytokine network such as Tumor Necrosis Factor (TNF)- α , interferon (IFN)- α , IL-12, IL-23, and IL-15, always considered indispensable in the formation of the plaque.

In psoriatic plaques myeloid DCs have mainly been found, both mature and immature, able to produce inducible Nitric Oxide Synthase (iNOS) and plasmacytoid DCs. The release of the iNOS in psoriatic patients has allowed us to hypothesize how these cells induce keratinocyte proliferation and vascular endothelial turnover directly [18 - 22].

The imbalance between the two subpopulations of Th1 and Th2, with a consequent deviation towards the pattern of Th1 is mediated by IL-10. This cytokine is able to promote the development of a Th2 pattern cytokine, through the inhibition of the production of INF- γ by of T lymphocytes, which is accomplished by blocking the production of IL-12 by the APC. In fact, IL-10 inhibits the release of pro-inflammatory cytokines by blocking directly the activity of the APC, such as monocytes/macrophages and DCs. These observations are confirmed by the studies of Asadullah *et al.*, who emphasized the role of IL-10 in the pathogenesis of psoriasis, showing that the deficit of expression of this cytokine in the skin can play a key role in causing the disease [23].

Recently another subset of Th17 producing IL-17, strongly implicated in the pathogenesis of psoriasis has been identified [24]. The function of Th17 cells in the skin has been studied in the models of psoriasis and it has been observed that these cells are responsible for stimulating proliferative processes, including acanthosis, hyperkeratosis and angiogenesis, for maintaining the inflammatory process, promoting the chemotaxis of monocytes and neutrophils, and further migration and activation of T cells. The cytokinetic profile deriving from Th17 comprises IL-17 A, IL-17 F, IL-20, IL-22, and IL-6. It has been shown that IL-20 and IL-22 induce keratinocyte proliferation in psoriatic skin with amplification of the inflammatory process and lymphocyte activation. The cytokines produced by Th17 also regulate the production of antimicrobial peptides, and this is in favor of the hypothesis that these cells create a connection between the innate and the acquired immunity [17].

The differentiation of naive CD4+ T lymphocytes into Th17 lymphocytes is stimulated by IL-23, which therefore plays a key role in the pathogenesis of psoriasis. A recent study showed that in psoriatic lesions there is an increased expression of IL-23 [25], thus confirming the importance of IL-23 in the pathogenesis of psoriasis, as a part of a complex cellular immune system [24 - 26].

3. LINKING BETWEEN PSORIASIS AND METABOLIC RISK

Inflammatory mechanisms that mediate the pathogenesis of the disease overlap between psoriasis and CVD. This

hypothesis is confirmed by recent studies, in which the role of IL-17A, involved in the activation and proliferation of keratinocytes, is widely emphasized [27, 28].

It has been highlighted that the blockade of IL-17A or its receptor significantly improves clinical, histological and molecular features of psoriasis [29]. In addition, drugs such as secukinumab and ixekizumab, which target selectively IL-17A, are effective in moderate to severe plaque psoriasis [30].

The presence of systemic inflammation in psoriasis has been demonstrated at the whole body level by the fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (PET/CT) [31]. In this case systemic inflammation was detected in focal areas of skin, vessels, joints and visceral tissues of patients with moderate to severe psoriasis [31].

Therefore the role of IL-17 is reaffirmed and overlapping mechanisms appear to support the inflammatory events responsible for the formation of atherosclerotic plaque and of the psoriatic plaque [32].

The hypothesis is further confirmed by the fact that patients with psoriasis have increased the number of Th17 and IL-17 in the circulation and in the psoriatic plaques. Similarly, patients with acute coronary syndrome have increased the number of circulating Th17 and associated cytokines, including IL-17A [33]. Furthermore, IL-17A induces hyperlipidemia and causes additional human aortic endothelial cell activation [34].

In particular, it has been observed that there is an axis between the two IL: IL-17 and IL-23, where the IL-17 has a proinflammatory and proatherogenic function, and therefore plays a key role in the production of atheroma. Atheroma is also produced in response to the stimulation of IL-23. In particular the IL-23 is in turn responsible for the production of thin fibrous filaments in the lesions, which are a prelude to the plaque instability with consequent easy breaking. Therefore it follows that the IL-23 has an indirect effect in the formation and maintenance of the atherogenic process [35].

Studies on human and animals with ischemic-reperfusion injury of the myocardium, unstable angina, acute myocardial infarction and atrial fibrillation support this pathogenetic model. Plasma IL-17A levels elevated in unstable angina or acute myocardial infarction or atrial fibrillation are directly correlated with the degree of platelet aggregation, suggesting that IL-17A may favor platelet aggregation in patients with acute coronary syndrome. IL-17A promotes vascular remodeling by recruiting neutrophils and triggering apoptosis of cardiomyocytes in animal models [36 - 38]. IL-17A inhibition improves ischemic damage and reduces proapoptotic marker levels from ischemic injury, suppresses inflammation, decreases the incidence and duration of atrial fibrillation episodes and reduces the probability of development of atrial fibrillation [39]. IL-17A overexpression increases systolic pressure, produces left ventricular hypertrophy and increases mortality [40].

In addition, there are recent studies on a heterodimeric glycoprotein implicated in a great variety of physiological and pathophysiological processes called clusterin that confirm the existence of common pathogenic aspects between psoriasis and the metabolic syndrome [41], confirming definitively that a greater predisposition to cardiovascular adverse events, in the course of metabolic syndrome, is mediated by the action of numerous pro-inflammatory cytokines (visfatin, cardiotropin-1), produced by the adipose tissue.

These inflammatory mediators, which play the role of link between obesity, insulin resistance and related inflammatory disorders, are involved in the pathogenesis of psoriasis and represent the possible link between the immune and the metabolic system [42].

4. PSORIASIS AND METABOLIC IMPLICATIONS

From a clinical point of view psoriasis is a chronic inflammatory disease that affects not only the skin but is also associated with various comorbidities and an increased risk of developing serious vascular events such as myocardial infarction and stroke. Hypertension, diabetes mellitus, dyslipidemia, obesity and metabolic syndrome (MetS) all contribute to the obvious repercussions on life expectancy in these patients compared to the general population [43].

In particular, various studies have shown that patients with psoriasis have a higher prevalence of MetS compared to the general population [44]. Langan *et al.* [45] found that psoriasis is associated with MetS with a probability of developing MetS directly proportional to the severity of psoriasis.

4.1. Serious Cardiovascular Events

The risk of major cardiovascular adverse events (including myocardial infarction, stroke and cardiovascular mortality) has been well documented in patients with psoriasis [46]. Epidemiological studies in the United States, Canada and Taiwan [47] have also shown that patients with psoriasis have a higher risk of developing myocardial infarction, especially those with severe psoriasis [48 - 51]. In addition, the life expectancy of patients with severe psoriasis is reduced by approximately 6 years, mainly due to cardiovascular mortality [52].

4.2. Atherosclerosis

Atherosclerosis and the subsequent chronic vascular inflammation can be considered among the main factors that can cause myocardial infarction and stroke in these patients. The use of the PET/CT has confirmed the association between the severity of psoriasis and the degree of vascular inflammation [53]. According to some studies there is a link between the Psoriasis Area Severity Index (PASI) and the thickness values of the intima-media thickness of the carotid artery [54].

4.3. Insulin Resistance and Diabetes Mellitus

Insulin resistance is a condition that precedes type 2 diabetes mellitus. It appears that inflammation mediators involved in insulin resistance (TNF- α , IL-6, leptin, adiponectin) are comparable to those of psoriasis [55 - 57]. Several studies have found an increased risk of diabetes in patients with psoriasis [58, 59]. Therefore, it appears that the risk of diabetes in psoriasis is linked to insulin resistance [60].

4.4. Hypertension

A recent meta-analysis showed an increased prevalence of hypertension among psoriasis patients [61]. It has been recently demonstrated that patients with psoriasis have an alteration of the Renin-Angiotensin-Aldosterone System (RAAS), with high plasma renin activity and elevated enzymatic conversion activity of angiotensin [62, 63].

Adipose tissue is a major source of angiotensinogen, the precursor of angiotensin, which plays an important role in controlling blood pressure. In addition to angiotensinogen, the secretion of resistin and leptin from adipose tissue have also been implicated in hypertension by MetS [64]. All these tests provide also an explanation of the relationship between hypertension and obesity in the case of MetS.

4.5. Dyslipidemia

It has been found that patients with psoriasis have dyslipidemia and hypercholesterolemia, with a lowering of the level of High-Density Lipoprotein (HDL) and an increase in the level of Low-Density Lipoprotein (LDL) [65 - 67]. Serum triglyceride levels in patients with psoriasis are also increased if compared to healthy controls [68]. Moreover, it has been shown that in psoriatic patients there are alterations of proteins that bind Fatty Acids (FA) and that, in turn, the metabolism of FA plays a key role in the function of Th17 cells and in the pathogenesis of psoriasis [69]. FA are not only the source of energy and the substrate for forming cell membranes, but also act as signalling molecules in the metabolic pathways involved in the pathogenesis of inflammatory dermatosis such as atopic dermatitis or psoriasis [69]. Myśliwiec *et al.* have demonstrated the association of circulating FA levels with the metabolic phenotype of psoriatic patients and the positive correlation between the percentage of Polyunsaturated Fatty Acids (PUFA) and PASI in non-obese psoriatic patients [70]. In a study assessing correlations between serum adipocyte Fatty Acid-Binding Proteins (FABP4) and the severity of the disease in psoriatic patients, serum levels of FABP4 were proven to differ from controls [71]. Furthermore, according to Kralisch *et al.* high levels of FABP4 are closely linked to the development of obesity, insulin resistance, MetS, hypertension, coronary artery disease and atherosclerosis [72]. In a 5-year prospective study it has been stated that FABP4 is an independent predictive marker for the development of MetS [73]. A further link between FABP4 and psoriasis may be a correlation with the TNF- α , which is one of the cytokines involved in the pathogenesis of this dermatosis. FABP4 has been linked to angiogenesis and VEGF, that are also highly disturbed in psoriasis [74].

4.6. Obesity

Psoriasis is associated with obesity, which is strictly correlated with the severity of the disease [42, 75]. Furthermore, a dose-response relationship between the degree of obesity and the risk of developing psoriasis has also been found [76].

The molecular mechanisms underlying the association between psoriasis and obesity are still being studied. It has

been reported that the disordered production of adipokine from adipose tissue in obese patients with psoriasis can activate macrophages and stimulate adipocytes to secrete adipocytokine, such as TNF- α , IL-6, leptin and visfatin [77 - 79]. The circulating levels of leptin are correlated with fat mass; leptin exerts important roles in the inflammation and stimulates the proliferation of keratinocytes and angiogenesis [80]. Adiponectin has anti-inflammatory and anti-atherogenic properties and patients with psoriasis have decreased levels of adiponectin [81]. In contrast, Vascular Endothelial Growth Factor (VEGF) which promotes angiogenesis and activation of endothelial cells is increased in psoriatic skin and is correlated with the disease severity [82]. Baran *et al.* have shown that the measurement of adipokines can be useful to assess the severity of psoriasis and its relationship to other comorbidities. In fact, there would be a significant correlation between BMI and adiponectin levels [83]. In particular, the authors found that serum adiponectin levels increase with the severity of psoriasis defined as the PASI score, while the mean concentration of serum leptin in patients with psoriasis was significantly lower than in the controls [83]. In the light of these results, it is clear that the measurement of leptin in serum could be useful to evaluate the relationship between leptin, obesity and psoriasis.

CONCLUSION

The new acquisitions that highlight the importance of multiple inflammatory factors in the determination of dysmetabolism and the increased atherosclerotic risk in patients with psoriasis would find full comfort in the light of our data. In fact, patients with psoriasis have a high incidence of CVD, often correlated with the presence of known risk factors including hypertension, obesity, diabetes and hyperlipemia. In light of these data, it would be advisable to sensitize dermatologists for a multidisciplinary screening of psoriasis.

Furthermore, the awareness of the immune-mediated pathogenetic mechanisms and of the potential links between psoriasis and CVD can suggest the efficacy of new suitable therapies to modify or block the evolution of dermatological lesions and correlated comorbidities.

LIST OF ABBREVIATIONS

FABP4	=	Adipocyte Fatty Acid-Binding Protein
APC	=	Antigen-Presenting Cell
CVD	=	Cardio Vascular Disease
DCs	=	Dendritic Cells
FA	=	Fatty Acid
iNOS	=	inducible Nitric Oxide Synthase
HDL	=	High Density Lipoproteins
IFN	=	Interferon
IL	=	Interleukin
LDL	=	Low Density Lipoproteins
MetS	=	Metabolic Syndrome
PUFA	=	Polyunsaturated Fatty Acids
PET/ CT	=	Positron Emission Tomography-Computed Tomography
PASI	=	Psoriasis Area Severity Index
PSORS	=	Psoriasis Susceptibility
RAAS	=	Renin-Angiotensin-Aldosterone System
TCR	=	T cell receptor
Th	=	T helper
TNF	=	Tumor Necrosis Factor
VEGF	=	Vascular Endothelial Growth Factor

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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