

# Environmental risk factors and epigenetic alternations in psoriasis

Marek Roszkiewicz<sup>1,B-E</sup>, Klaudia Dopytalska<sup>1,B-E</sup>, Elżbieta Szymańska<sup>1,E-F</sup>, Artur Jakimiuk<sup>2,E-F</sup>, Irena Walecka<sup>1,A,E-F</sup>

<sup>1</sup> Dermatology Department of Centre of Postgraduate Medical Education, Warsaw, Poland

<sup>2</sup> Center of Reproductive Health, Institute of Mother and Child, Warsaw, Poland Department of Obstetrics and Gynecology CSKMSWiA, Warsaw, Poland

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

Roszkiewicz M, Dopytalska K, Szymańska E, Jakimiuk A, Walecka I. Environmental risk factors and epigenetic alternations in psoriasis. *Ann Agric Environ Med*. doi: 10.26444/aaem/112107

## Abstract

**Introduction and objective.** Psoriasis is a quite common, chronic and immune-mediated skin disorder. The prevalence of psoriasis differs in various countries, but it is said to affect 2% of the world's population in general. Psoriasis has many different clinical features but all lesions have the same characteristic: erythema, thickening and scale, although other clinical features are also connected, such as psoriatic arthritis, obesity and metabolic syndrome. All of these may lead to conditions impairing the quality of life. This review is an attempt to summarize recent data regarding environmental factors, together with epigenetic markers and processes playing an important role in psoriasis.

**State of knowledge.** Many different environmental factors play a role in genetically predisposed patients. This causes epigenetic alternations which may be a linking part in the whole process. Many studies have indicated a connection between psoriasis and various genes and antigens. The presence of HLA-Cw6 is common as well a strong link between its presence and the onset of psoriasis being observed. The main alternations are DNA methylation, histone's modifications and the role of microRNA. Excessive reaction is usually not present without a triggering factor. Environmental factors are mostly rated, such as drugs, life style and habits (smoking, alcohol), diet, physical trauma (skin injury provoking Koebner phenomenon), stress, microorganism and infections.

**Conclusions.** The correlation between pathogenesis of psoriasis and environmental risk factors, together with epigenetic alternations still require more investigation. Education about diet habits, nutrition, weight loss and healthy lifestyle seems to be important during the treatment of psoriasis.

## Key words

psoriasis, habits, environmental factors, epigenetic alternations

## INTRODUCTION AND OBJECTIVE

Psoriasis is a quite common, chronic and immune-mediated skin disorder [1, 2]. However, environmental factors also play an important role in genetically predisposed patients during the course of the disease. Psoriasis also has many different clinical features and locations, e.g. plaque, guttate, erythrodermic, palmoplantar, nail, and scalp psoriasis [1]. It occurs as sharply demarcated and erythematous papulosquamous lesions. Simultaneously, different manifestations may be seen, but the lesions have the same characteristics: erythema, thickening and scaling. Skin changes are accompanied by intensive itching. Together with psoriasis, other clinical features can also be manifested, such as psoriatic arthritis (PA), obesity and metabolic syndrome, which may lead to impairment of the quality of life (*arthritis deformans*, ischemic heart disease, heart failure, and stroke) [3, 4, 5].

The prevalence of psoriasis is higher in well-developed countries compared to those with a low income. It is reported to be even as high as 4.6% in Canada and the USA, and only 0.4% – 0.7% in African and Asian regions. The prevalence

is said to be 2% of the world's population in general [6]. Psoriasis may occur at any age, although two peaks of onset are observed: the first in the second decade of life, and the other in the fifth decade. Almost 75% of cases begin before the age of 40. PA is shown to affect 20%-30% of psoriatic patients [3, 7].

This review is an attempt to summarize the knowledge on how environmental factors (such as microbiota and infections, diet and obesity, drugs and medications, psychological factors), together with epigenetic markers and processes play an important role in psoriasis development.

## STATE OF KNOWLEDGE

**Genes and epigenetics.** The genetic predisposition to psoriasis was established many years ago [8], and to-date 424 genes loci with single nucleotide polymorphism have been proven to be associated with psoriasis [9]. However, many studies have shown that these are not the sole critical factors in the pathogenesis of the disease: the role of epigenetic modifications has been emphasized along with environmental factors and lifestyle habits [2, 10]. According to the widely-known concept of Lalonde published in 1971, the genetic input in a healthy subject is up to 20%. Almost equal, also up to 20%, are environmental factors, but the majority are

Address for correspondence: Marek Roszkiewicz, Dermatology Department of Centre of Postgraduate Medical Education, Warsaw, Poland  
E-mail: marek.roszkiewicz@cskmswia.pl

Received: 06.02.2019; accepted: 03.09.2019; first published: 12.11.2019

lifestyle habits that amount to 50% of psoriasis occurrences. Between those external factors (70%) and internal ones (20%), there is a link of epigenetic modifications.

Previous studies have shown a connection between psoriasis and various genes and antigens. Histocompatibility antigens (HLA), situated on the surface of cells and connected with the chromosomal region, the so-called major histocompatibility complex (MHC) also plays an important role. The presence of HLA-Cw6 has been observed at the onset of psoriasis and is seen in 90% of patients with early-onset and 50% with late onset. In a control population, HLA-Cw6 was present in barely 7% [11, 12]. Another HLA compound connected to psoriasis, and specifically to reactive arthritis or sacroiliitis – HLA-B27 – is also seen in other diseases, especially rheumatic [13, 14].

Furthermore, there are at least 15 chromosomal regions suspected of being associated with psoriasis, called *PSORS1–15*, among which HLA-Cw6 is contained [9, 15]. In 2012, Tsoi et al. identified 15 new psoriasis susceptibility *loci* by employing meta-analysis of three genome-wide association studies (GWAS) and two other datasets [16]. Establishing those new correlations increased the number of psoriasis associated genes to 36 (Tab. 1), most of which are connected to innate and adaptive immunity and their mutual relations; only a few encode skin-specific proteins. There is a main gene link to interferon (INF), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) signalling, interleukin (IL) 4 and IL-23/17 axis [17, 18, 19].

**Table 1.** Psoriasis susceptibility genes [16–19]

PSORIASIS SUSCEPTIBILITY GENES	
Character	Pathways and genes
Innate immunity	NF- $\kappa$ B signaling: <i>CARD14, CARM1, FBXL19, NFKBIA, REL, TNFAIP3, TNIP1, UBE2L3</i>
	IFN signaling: <i>DDX58, ELMOI, IFIHI, IL-28RA, RNF114</i>
	Inflammation: <i>NOS2</i>
Adaptive immunity	IL-23/17 axis and IL-17: <i>IL-23R, IRF4, STAT3</i>
	T cell: <i>RUNX3, TNFRSF9, TAGAP</i>
	IL-4/13 signaling: <i>IL-4/13</i>
	TGF-beta signaling: <i>ZMIZ1</i>
Mutual (innate and adaptive) immunity	INF signaling: <i>SOC1</i>
	IL-23/17 axis: <i>IL-12B, IL-23A, TRAF31P3, TYK2</i> MHC antigen presentation: <i>ERAPI, HLA-C</i>
Skin specific	Skin barrier: <i>LCE3B/3C/3D, KLF4</i>
	Other: <i>ETS1</i>
Other	Redox signaling: <i>PRDX5</i>
	Carbohydrate metabolism: <i>B3GNT2</i> Other: <i>MBD2, ZC3H12C</i>

Since the last decade, the importance of epigenetic alternations has been studied worldwide to shed more light on understanding the pathological pathway in psoriasis. The main alternations are DNA methylation, histone modifications and the role of microRNA [20]. The influence of epigenetic modifications on the gene expression may be twofold: DNA hypermethylation of the region plays an important role in silencing gene transcription, while hypomethylation in its activation [21, 22].

In 2008, Chen et al. indicated a potential role of the *p16* gene alternation in psoriasis. They report methylation of *p16INK4a* gene promoter in the epidermis of 30% of psoriatic patients and correlation with higher Psoriasis Area and Severity Index (PASI) scores [23]. Protein p16INK4a negatively regulates CDK4 and CDK6 proteins, which promotes progression from G1 to S phase in the cell growth cycle [24]. Also, the down regulation of p16INK4a due to methylation leads to higher levels of CDK4 and CDK6, which has been identified in different hyperproliferative skin diseases and skin malignancies (e.g. squamous cell carcinoma) [25]. Furthermore, Zhang et al. report decreased levels of programmed cell death 5 protein (PDCD5) and tissue inhibitor of metalloproteinases 2 (TIMP2) in the psoriatic lesions [26]. Methylation of both proteins is associated with keratinocytes proliferation as well as in tumour formation [27, 28].

Recent studies by Chandra et al. and Zhao et al. report epigenome-wide DNA methylation as one of the features playing a key role in psoriasis [21, 29]. The study by Chandra revealed a significant difference in the enrichment of methylated CpGs in PSORS regions, where it shows an inverse correlation with higher gene expression [29]. A link between histopathological findings (such as Munro's microabscess, parakeratosis, and neutrophil accumulation) has also been established [29]. Zhao reports that global DNA methylation is significantly increased in peripheral blood mononuclear cells and skin lesions of psoriatic patients compared to healthy controls [21]. Moreover, different pathways of hematopoietic cells and psoriatic lesions have also been indicated, e.g. SHP-1 promoter 2 methylation, although for clear understanding of those compound, further studies are required [22, 30].

In the study by Gervin et al., 66% of the co-occurrence of psoriasis in monozygotic (MZ) twins did not show a significant difference in DNA methylation in CD4+ and CD8+ cells of MZ twins [31]. Analysis of the data showed no difference in methylated or expressed genes between twins when analyzed separately. However, combined analysis of DNA methylation and gene expression identified genes where the differences in DNA methylation between unaffected and affected twins were correlated with differences in gene expression (IL-13, *ALOX5AP*, *PTHLH* and *TNFSF11*) [31, 32, 33, 34, 35].

The significance of epigenetic alternations in psoriasis has also been shown in histone (H) modifications. Ovejero-Benito et al. report a significant difference in psoriatic patients, presenting reduced levels of acetylated H3 and H4, and increased levels of methylated H3K4. Moreover, after introducing biological treatment there were no significant changes in histone modification. Nevertheless, a significant difference in H3K27 alternations was found between responders and non-responders to the biological agent after three months of treatment [36].

Another candidate for playing a significant role in the course of psoriasis may be microRNA (miRNA), and recent studies have provided new insight regarding miRNA importance in the disease. Some studies reported an over-expression of many types of miRNA play a triggering or exaggerating role (e.g. miRNA-21, -31, -146), but on the other hand, others revealed downregulation of miRNA (e.g. miRNA-145-5p, -197) in patients with active psoriasis [37, 38, 39]. A recent study by Wu et al. showed new miRNA in psoriasis, which happens to be one of the most investigated

miRNA's to-date – miRNA-210 [40]. The study compared the expression of miRNA-210 in psoriatic patients and mice models (imiquimod or interleukin (IL) 23 induced psoriatic-like lesions). Wu reports significantly increased levels of miRNA-210 in CD4+ T cells in both psoriasis patients and mice models in the dermis as well as the epidermis. Moreover, miRNA-210 promotes Th1 and Th17 activation increasing IL-17 levels while lowering IL-4. This leads to an imbalance in T cell population (Th1/Th2 and Th17/Treg) [41]. Th2 cell differentiation was also inhibited by repressing the signal transducer and the activator of transcription 6 (STAT6) and tyrosine-protein kinase Lyn (LYN) genes expression. Mice models were also transfected with oligonucleotides that induce miRNA overexpression or silencing [42]. A further study shows that TGF-beta and IL-23 enhance overexpression of miRNA-210 by histone H3 acetylation in the miRNA-210 region. Finally, inducing psoriasis-like lesions in mice models was blocked when the miRNA-210 region was deleted or inhibited [40]. As indicated above, new compound targeting miRNA-210 may play an important role in future therapeutic investigations in psoriasis.

All these factors, genetic predisposition merged with epigenetic modification caused by strong environmental factors, influenced results in immune system activation [10]. Antigen-presenting cells and different T cell's populations (e.g. Th17 helper cells) and their relation to HLA play a key role in the psoriasis pathogenic pathway by recruiting other CD8+T-cells CD8+ as well as natural killers (NK) [43]. Activated cells produce a vast number of pro-inflammatory cyto- and chemokines (such as interleukins, interferons – INF, etc.). The connection between psoriasis and at least IL-4, 17, 23 has been established [44, 45, 46]. Those are also a grip point for modern, biological treatment options, which inhibit the exaggerated immune reaction which is usually not present without a triggering factor. Such factors are mostly environmental and are related, among others, to drugs, lifestyle habits (smoking, alcohol), diet, physical trauma (skin injury provoking Koebner phenomenon), stress, microorganisms and infections [10, 47, 48].

**Microbiota and infections.** Recently, great attention has been paid to the role of microbiota in different diseases, especially in autoimmune or immune-mediated conditions. Among a vast number of such diseases, the most eminent is inflammatory bowel disease (IBD) – Crohn's disease (CD) [49, 50, 51]. The CD patient is at a higher risk of developing psoriasis than that of the general population. *Vice versa*, a psoriatic patient is more likely to suffer from CD [52]. In a healthy human subject, there is a mutual coexistence of different microorganisms (viruses, bacteria, and fungi) within the skin, mucous membranes (intestines, upper airways, urogenital tract), which constitutes an immunological balance with immune system cells [53]. Any disruption of this micro-environment may occur or provoke either infection by the domination of one kind of microorganism, or activation of the immune system. Many of the microorganisms' molecules can be a triggering antigen for immune reaction. Due to the similarity of different proteins and other compounds of the bacterial wall to human substances, a reaction may occur leading to an auto-aggressive process [54, 55]. Such reactions run through two kinds of pathways: innate and adaptive immune system response. The innate pathway is usually quick whereas the other takes time to develop, but creates a

**Table 2.** Microbiota and psoriasis [10, 51, 64]

MICROBIOTA	
Localization	Species
Tonsils	<i>Streptococcus spp.</i>
Skin	<i>Streptococcus spp.</i>
	<i>Staphylococcus spp.</i>
	<i>Candida spp.</i>
	<i>Malassezia spp.</i> <i>Propionibacterium acnes*</i>
Gut	<i>Bacteroides fragilis</i>
	<i>Clostridium spp.</i>

\* rarely present on skin of psoriatic patients

kind of immune memory using a special subtype of T cells. In psoriatic patients, the adaptive immune response plays a vital role because of the high sensitization of T cells (especially Th17 cells) due to exposure to microorganism antigens [19].

It has been shown that during the life span of the human, the microbiome is relatively stable [56]. An unhealthy lifestyle (e.g. tobacco, alcohol intake or diet) as well as stress affects this homeostatic microenvironment [57]. Especially diet and the quality of food play an important role. Due to the usage of hormones and antibiotics in animal breeding, but also due to the industrialization of agriculture, in general, diet can be an additional risk factor disturbing proper relations in such a micro-ecosystem [58]. It has been indicated that the skin of a psoriatic patient has different microbiome than a control group. *Staphylococcus* and *Streptococcus* are most commonly seen, even in all layers of the skin [10, 59]. Moreover *Malassezia* and *Candida* species are also connected to psoriasis [10]. On the contrary, *Propionibacterium acnes* is usually present on a healthy individual's skin rather than the psoriatic [59]. Because of this, as mentioned above, such a disturbance in microbiota's relations provokes immune reaction, conducted especially by IL-22 producing T cells which play a critical role in the aggravation of skin inflammation [10, 60].

Furthermore, the role of gastrointestinal microbiota has not been finally established. Multiple studies indicated an intestinal inflammation during the course of PA [61, 62, 63]. An evident relation is between psoriasis and IBD [52], for example, *Bacteroides fragilis* or *Clostridium species* promote Treg cells differentiation [64]. Another infectious factor is *Spreprococcus* in the tonsils. It is commonly known, that many upper airway tract infections may intensify psoriatic lesions [65, 66, 67].

Recently, a hypothesis of the gut-brain-skin axis is being developed [68]. It has been proved that various skin disorders (urticarial, atopic dermatitis, psoriasis) have a strong correlation with the emotional status of the patient [69, 70, 71, 72]. It has been shown that there is a negative influence on the immune system causing a greater risk of infections in patients subjected to mild to severe chronic stress [72]. Impairing work of the immune system occurs as an imbalance between the mutual microenvironment of microbiota and immune cells, which allows pathogens to extend and lead to infection [73]. On the other hand, this stimulates the immune system's reaction and usually occurs as an exacerbation, or even provokes the onset of psoriasis [65, 66, 67].

**Diet and obesity.** Among the environmental risk factors for psoriasis, body weight and nutritional habits are considered

to be very crucial in the pathogenesis of the disease, and can trigger or exacerbate the symptoms. It is known that obesity, increased body mass index (BMI) and waist circumference are significant risk factors for the development of psoriasis [10, 74, 75, 76, 77]. Furthermore, the prevalence of obesity and metabolic syndrome is higher in psoriatic patients than in the general population – it is estimated, that around 50% of psoriatic patients are overweight or obese. This may lead to increased cardiovascular risks. Moreover, the severity of psoriasis (evaluated by the Psoriasis Area and Severity Index – PASI) is higher in obese or overweight patients [78, 79, 80].

Obesity is known as a low-grade chronic inflammatory process with elevated levels of C-reactive protein, IL-6, TNF- $\alpha$  and leptin. According to recent studies, a pathogenetic link between obesity and psoriasis could be an inflammatory-type involving macrophages, pro-inflammatory adipokines, and cytokines. The role of adipokines in psoriasis has been the aim of many recent studies [75, 81, 82]. Leptin is an adipokine, the main function of which is to regulate food intake. Besides, leptin has an immunomodulatory effect by stimulating macrophages to produce pro-inflammatory cytokines (TNF- $\alpha$ , IL-6) and may induce the proliferation of Th1 cells [83, 84]. Recent data has shown that psoriatic patients have elevated serum leptin levels, compared to the healthy population. Psoriasis is also considered to be a risk factor of hyperleptinaemia [85, 86]. Furthermore, in psoriasis, the serum level of adiponectin (anti-inflammatory adipocine) is decreased and inversely correlates with the extent of psoriasis symptoms. Not only adipokine is linked between psoriasis and obesity, but also TNF- $\alpha$ . It has been shown that excessive production of the tumour necrosis factor plays an important role in the pathogenesis of psoriasis and leads to a rapid proliferation of skin cells. There is evidence, that TNF- $\alpha$  may also influence the severity of psoriatic lesions in obese patients because of the overexpression of the TNF- $\alpha$  in adipose tissue [75, 87].

Obesity also influences the treatment of psoriasis by affecting both the drug's pharmacokinetics and pharmacodynamics. Obese patients with psoriasis often have a decreased response to systemic and biological therapy. This is observed especially with drugs that are administered in fixed doses rather than in those where the dose is adjusted to the patient's weight. Treatment with biological drugs in which the dose is not weight-adjusted (e.g. adalimumab, etanercept) may have worse efficiency, whereas the cost of therapy with weight-adjusted biological drugs (e.g. ustekinumab, infliximab) is higher. Also, obesity is often associated with metabolic or hepatic disorders, which raise the risk of adverse effects to conventional systemic therapy [75, 81, 88]. Recent data have shown that in obese patients during biological treatment with an eight week low-calorie diet (under 1,000 kcal/day), the weight reduction was associated with increased efficacy of the biologic drug [89].

Other reports underline cases of patients who had undergo gastric bypass surgery for other indications, had an improvement in the course of psoriasis [90]. Changing the lifestyle, especially losing weight, may due to the reduction of the obesity-related inflammation, improved effectiveness of therapy and decrease in the side-effects of conventional therapy.

The benefits of reduction in body weight in psoriasis are significant in both the severity of disease and the response to treatment. Diet and nutritional supplements may also have

benefits in psoriatic patients; evidence has been provided that diets rich in omega-3 polyunsaturated fatty acids (omega-3 PUFA) from fish oil have been associated with the improvement of psoriasis in clinical trials, mostly by exhibiting an anti-inflammatory effect [91, 92]. In some patients, particularly those with gluten intolerance, a gluten-free diet might be beneficial. Epidemiological and clinical data suggest that there could be a correlation between psoriasis, celiac disease and celiac disease markers, but further research into this matter is necessary [93].

There is some evidence that supplementation with selenium and vitamin B12 might have a positive influence on psoriasis symptoms [94]. It is also believed, that other vitamins (A, E, C) and microelements (iron, manganese, zinc) decrease oxidative stress and the production of reactive oxygen species, which play a role in inflammation [94]. Research has proved that in the patients with psoriasis and coexisting vitamin D insufficiency, oral vitamin D supplementation may have its benefits [92].

The traditional Mediterranean diet, composed of vegetables, fruits, nuts, cereals and fish, is considered a healthy eating pattern associated with reduced risk for metabolic, cardiovascular, neoplastic and chronic inflammatory diseases [75, 95, 96, 97]. High contents of antioxidants and polyphenols in the Mediterranean diet have anti-inflammatory and antioxidant properties, which are considered to be protective against chronic inflammatory diseases and may also provide benefits for psoriatic patients [75].

**Smoking and alcohol intake.** Most data have shown that smoking and exposure to second hand smoke are independent risk factors in psoriasis. Smoking is also often associated with an increased risk of cardiovascular diseases. Moreover, in the group of patients with psoriasis, an increased prevalence of smoking has been observed. They also continue to smoke more cigarettes than patients without psoriasis [74, 98].

Many pathophysiological mechanisms link smoking to psoriasis [99]. Smoking leads to oxidative stress, reduces the number of antioxidants and may increase vascular endothelial dysfunction and plasma viscosity [98, 100]. Increased exposure to free radicals, which are components of cigarette smoke, may trigger a cascade of systemic disorders, including developments of psoriasis [83]. Nicotine, through nicotine-activating pathways, can increase the secretion of cytokines, such as IL-12, IL-2, TNF, INF- $\alpha$ , and the granulocyte monocyte colony-stimulating factor [101]. Cigarette smoking may cause dysregulation of vascular endothelial growth factor and the processes of angiogenesis. This pathomechanism may partly explain the correlation between smoking, psoriasis, and atherosclerosis [98, 101]. Furthermore, according to a study on the relationship between smoking and the severity of psoriasis, higher PASI scores were observed in patients with psoriasis who were smokers, compared to non-smoking patients [102]. Additionally, research by Hojgaard et. al. showed, that heavy smoking could decrease the effectiveness of treatment with TNF- $\alpha$  inhibitors [103].

The correlation between alcohol consumption and risk of psoriasis is still unclear and many studies have drawn conflicting conclusions. It is known that alcohol intake may increase the production of pro-inflammatory cytokines, promoting lymphocytes proliferation, which can trigger chronic systemic inflammation. Studies have shown, that alcohol and acetone can stimulate keratinocyte proliferation,

raise the mRNA levels of genes characteristic of proliferating keratinocytes ( $\alpha 5$  integrin, cyclin D1, keratinocytes growth factor receptor) [98, 104].

The correlations between smoking or alcohol intake and psoriasis still require further investigation and understanding the pathomechanism, as well as their influence on the severity of symptoms in psoriasis and impact on treatment.

**UV in psoriasis.** The spectrum of ultraviolet radiation is divided due to the wavelengths into: the short band UVC (100–290 nm) – which is mostly absorbed by the ozone layer in the atmosphere, the medium band UVB (290–320), and the long band UVA (320–400 nm). The improvement of psoriatic skin lesions after exposure to sunlight or artificial UV sources has been observed for a long time. Psoralen-UVA (PUVA – combined therapy of taking oral Psoralen with exposure to UVA) and narrowband UVB (311 nm  $\pm$  2) – are widely used in the treatment of psoriasis [105].

Phototherapy is also considered to be an effective and relatively safe therapeutic option. The positive impact of phototherapy in the management of psoriasis is related to a few mechanisms. UVB stimulates the synthesis of vitamin D (25[OH]D), which has been proven to play a role in the treatment of psoriasis due to the regulation of dendritic cells. Moreover, the benefits of UVB include its pro-apoptotic effect and induction of pro- and anti-inflammatory cytokines production. It has been observed that UV suppresses the differentiation of Th17 and downregulates IL-23/IL-17 expression and psoriasis-related antimicrobial peptides (AMPs). Furthermore, phototherapy leads to a decrease in the immune cells migration to the skin, which results in a reduction of the inflammatory processes in psoriasis [106, 107].

Although UV exposure is most often beneficial in psoriasis, in some cases, however, the aggravation of psoriasis has been observed. The pathomechanisms of the worsening of the symptoms of psoriasis after UV exposure is not fully understood – the reason for this phenomenon include Koebner reaction after sunburn (as skin trauma) or coexistence of other photosensitivity disorders. Furthermore, there is a subset of patients with psoriasis in whom UV exposure can trigger the disease and induce *plaques de novo*. This has been described as severely photosensitive psoriasis (PP) with the tendency to seasonal exacerbations of the disease [108]. PP has similar features to polymorphic light eruption (PLE), and in approximately 40% of cases it can be associated with PLE [107, 109].

**Medications.** There is evidence that some drugs may initiate psoriasis *de novo*, exacerbate pre-existing psoriasis lesions, and induce a treatment-resistant form of psoriasis. In the optimal management of psoriasis, it is essential to identify these medications, but in everyday clinical practice this it could be particularly difficult. The manifestations of drug-related psoriasis are varied, from plaque-type psoriasis to severe erythroderma. There are a few mechanisms of drug-related psoriasis. First, drugs exacerbate pre-existing skin lesions. In drug-induced psoriasis, improvement of the disease is observed after discontinuation of the suspected drug. On the other hand, in drug-aggravated psoriasis, the induced psoriatic skin lesions could last even after withdrawal of the drug. Second, drugs may lead to the onset of new psoriasis in patients with or without a

personal or family history of the disease [110]. Traditionally, drugs that are proven to be associated with the induction or exacerbation of psoriasis include beta-blockers, antivirals and antidepressants, lithium, synthetic antimalarials (chloroquine and hydroxychloroquine), non-steroidal anti-inflammatory drugs (NSAIDs), interferons and terbinafine [111, 112]. Moreover, quick discontinuation of systemic corticosteroids or high-potency topical corticosteroids can cause a rebound effect and induce the worsening of psoriasis [113].

Recently, new drugs have been reported to induce or exacerbate symptoms of psoriasis, and include monoclonal antibody- and small-molecule-based targeted therapies used for oncological and immunological indications, (TNF- $\alpha$ ) antagonists, nivolumab and pembrolizumab (anti-programmed cell death protein 1 immune checkpoint inhibitors), bupropion (nicotine receptor antagonist), vascular endothelial growth factor (VEGF) antagonists and rituximab (anti-CD20) [105]. One hypothesis suggests an interaction between TNF- $\alpha$  and INF- $\alpha$  (cytokine, which controls natural immunity), where TNF- $\alpha$  inhibits INF- $\alpha$  production. Anti-TNF biologic therapy may boost INF- $\alpha$  production and promote psoriasis [114].

**Psychological factors.** Psoriasis has a significant influence on the quality of life. The appearance of skin lesions in psoriasis may lead to mental disorders: which most often include sleep disorders, sexual dysfunction, personality disorders, anxiety disorders, adjustment and depressive disorders. The prevalence of depression in psoriatic patients is estimated to range from 10 – 62%, depending on different studies. On the other hand, stress and depression may have a role in the development and aggravation of the symptoms in psoriasis. This leads to a vicious circle, which worsens both diseases – psoriasis and depression [115, 116, 117]. Psychological stress is related to changes in the regulation of the immune system and the activation of abnormal T cells, which influence psoriasis [116]. Furthermore, psoriatic patients have a higher risk of manifesting psychopathological symptoms during childhood and adolescence. The disease could be also associated with personality alterations [118]. Data has shown that in psoriatic patients complying, self-motivation and self-drive are low, and they can be dependent, submissive, and often lack initiative or do not have opinions of their own. Overall, psoriasis is related to a lower satisfaction with life [119, 120].

## CONCLUSIONS

Correlation between environmental risk factors, epigenetic alternations, gene expression, and psoriasis has been investigated in many studies. Most data have shown that obesity and nutritional habits have significant roles in the pathogenesis of the disease, can trigger or exacerbate the symptoms of psoriasis, and have an impact on the effectiveness of the therapy. Also, some medications (beta-blockers, lithium, synthetic antimalarials, non-steroidal anti-inflammatory drugs) may be triggering factors in psoriasis. Psychological disorders, such as depression, could also aggravate skin lesions. It is also worth noting that changes in microflora and prolonged infections are considered to be risk factors in the development of psoriasis.

Moreover, maintaining regular, healthy microbiota on the skin or within the gastric tract is very dependent on a healthy diet and lifestyle habits. As shown by reported data, gene predisposition with environmental factors are intermediated by epigenetic alternations. Those three domains together play an important part in the formation of the disease; however, environmental factors (using Lalonde's concept) are mostly responsible for the occurrence of diseases such as psoriasis. The correlation between the pathogenesis of psoriasis and environmental risk factors, as well as the influence on gene expression by epigenetic modifications, require further investigation. Education about proper diet habits, nutrition, weight loss, and a healthy lifestyle, as well as an emphasis on the crucial role of those factors in the pathogenesis of the disease, cannot be overestimated during the treatment as they influence the occurrence, severity, and progression of psoriasis.

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