EPIGENETIC ASPECTS IN PSORIASIS

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Summary

Our study, based on data from the literature in recent years, looks at a number of aspects of the epigenetic changes encountered in psoriasis. DNA methylation, histone alterations (methylation, acetylation) and microRNA changes were considered.

The selection criterion was the frequency of certain types of epigenetic changes encountered in psoriasis and their association with known elements in the patogeny of psoriasis. The epigenetic changes presented interfere with the main pathogenic processes in psoriasis: the proliferation of keratinocytes and the immunological changes in the level of T lymphocytes, with the alteration of the cutaneous immune response. The main changes in DNA methylation, acetylation and histone methylation and changes in various types of microRNAs are presented.

Our study focused on explaining the epigenetic mechanisms and the impact that these changes have on the pathogenesis of psoriasis. Where possible, the impact of these epigenetic changes on the clinical course of psoriasis and on the response to therapy has also been presented.

At present, epigenetics opens a new field of research in the pathogenesis, clinical evolution and therapy of psoriasis.

Keywords: *psoriasis, DNA methylation, histone alteration, microRNA.*

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Protein synthesis in eukaryotic cells is a complex process in which genetic information from nuclear DNA is transmitted to ribosomes via messenger RNA (mRNA). This complex process can be synthesized in three phases: transcription, translation and protein synthesis, the latter taking place in ribosomes.

During transcription, nuclear DNA receives a signal that „identifies" the portion of DNA to be copied by RNA polymerase, which forms mRNA. Finally, the RNA polymerase receives a stop signal (codon stop) and the transcription ends. The result of transcription is the formation of mRNA containing the genetic information copied from the nucleus, from a fragment of DNA (gene) by RNA polymerase and is removed from the nucleus [1].

Translation involves the transport of mRNA through the cytoplasm to the ribosomes. Ribosomes are made up of ribosomal proteins and ribosomal RNA. In ribosomes, mRNA binds to transfer RNA, which „translates" the message from the nucleotide sequences in the mRNA into amino acid sequences, which subsequently bind together to form protein structures [1,2,3].

Both transcription and translation are modulated by numerous feedback or checkpoint mechanisms. A number of molecules and bacterial products that act after transcription have been identified and can modulate the

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transcription of a gene to the point of inhibition. The importance of these molecules and processes in cell protein biosynthesis and the disturbances that occur at this level, with the clinical implications that occur, have made this new field a special field of genetics called „epigenetics" (epi-out). The processes and molecules included in the field of epigenetics do not refer to the nucleotide sequence in DNA and may or may not be inherited to other cells or at the individual level. Diet and pollutants can frequently alter the processes included in the field of epigenetics. [2,4]

The most important changes included in the field of epigenetics are: DNA methylation, changes in histones and alteration of the action of non-coding RNA fragments (ncRNA). These changes are found in many pathogenic processes, the most important being: tumor development, inflammation, autoimmunity [5, 6, 7].

Psoriasis is a chronic inflammatory condition in which there is an abnormal proliferation and differentiation of keratinocytes, in which there is an abnormal activation of T lymphocytes, possibly by autoimmune mechanisms, environmental factors (stress) infections, interacting with genetic changes contribute to the appearance and severity of the disease [8,9,10]. The main epigenetic changes, namely DNA methylation, changes in histones and alteration of the action of non-coding RNA fragments are also found in psoriasis [11].

DNA methilation

Broadly speaking, methylation involves the attachment of a methyl group (-CH3) or a group of atoms that also contains the methyl group.

In the case of DNA, the methyl group attaches to a cytosine pyrimidine base group that precedes a guanine molecule. The cytosine/guanine pair is found everywhere in the DNA structure but the highest density is at the level of the promoter of several genes. The addition of a methyl group to the promoter of a gene (methylation) via a methyl transferase inhibits the expression of this gene [11]. In normal cells, cytosine/guanine groups (islands) are not methylated but may be methylated and may be found sporadically in the DNA structure [11]. It is now accepted that DNA hypermethylation, especially in the promoter area of one or other of the DNA regions, inhibits the transcription of that gene, while hypomethylation induces the expression of that gene. Hypomethylation facilitates the attachment of a transcription factor to the promoter area (the area where transcription begins), with the actual onset of transcription [12,13].

In psoriasis, studies have been performed on methylation of the entire genome as well as punctiform, for one or more genes. Biopsies performed in psoriasis patients with healthy individuals were compared. Patients with psoriasis had hypermethylated areas but also hypomethylated areas at the nuclear level that did not show in normal individuals, suggesting the involvement of abnormal methylation in the pathogenesis of psoriasis. Abnormal methylation has been observed especially in the DNA of keratinocytes but also of cells with immune functions [14].

Keratinocyte methylation in psoriasis lesions has been shown to correlate with disease progression and severity (PASI) but is poorly correlated with DNA methylation in peripheral blood mononuclear cells [15]. Monoclonal antibodies (anti-TNF) tend to reduce methylation to healthy skin [16]. It has been observed that DNA methylation has different degrees on various areas of the body: extremities, abdomen, back [17].

A number of studies have attempted to highlight the methylation of genes known to be important in the pathology of psoriasis. Thus, p16ink4a gene promoter methylation was found in 30% of psoriasis patients with elevated PASI values [18]. Other genes investigated were the genes from the PSORS region, respectively S100A9, SECENBP1, CARD14, KAZN and PTPN22. An inverse correlation could be established between the degree of methylation and the expression of these genes. Moreover, it has been established that methylation also involved the control of disease progression as well as the appearance of classic histopathological lesions in psoriasis [21,22].

Other studies have shown that the methylation of the PDCD5 and TIMP2 genes involved in keratinocyte proliferation must be correlated

with mRNA expression and whole DNA methylation [19].

Hypomethylation has been identified in several genes such as the p15, p16, p21 gene promoter. Hypomethylation of these genes has also been identified in hematopoietic stem cells in patients with psoriasis. The p15, p16, and p21 genes are genes that control the cell cycle and cell proliferation [20]. Also, hypomethylation of the OAS2, S100A7 genes. S100A12 has been shown to increase the severity of psoriasis [14,15].

A number of DNA methyltransferase disruptions have been found that transfer the methyl group to the cytosine / guanine dinucleotide. There is a family of DNA transferases that are also found in keratinocytes. The most important is DNMT1, which opposes keratinocyte differentiation. Inhibition of DNMT1 expression has a strong antiproliferative effect by suppressing the wnt / beta catenin pathway [24.25].

In addition to keratinocytes, methylation changes have also been reported in single peripheral mononuclear cells (PMBCs). It has been observed that there is a difference between global methylation in psoriasis patients compared to healthy ones, and an increase in DNMT1 in psoriasis patients [26]. CD4 + lymphocytes from patients with psoriasis had a different methylation profile than healthy subjects [14,26]. In the case of Treg lymphocytes, the FOXP3 genes had a higher level of methylation compared to healthy individuals, which implies a decrease in the activity of T reg cells [27].

Histone alterations

Histones are alkaline proteins that are found in the nucleus of eukaryotic cells, participating in the formation of nucleosomes, being the main components of nucleosomes. Their role is to keep the DNA stranded and to avoid altering the double helix structure. They contain large amounts of arginine and lysine and depending on the content of these amino acids are divided into several classes: H1 / H5, H2, H3, H4. Through the action of various enzymes, histones can undergo several chemical changes that can influence the transcription of genes. The most important changes at this level are methylation and acetylation. Methylation is accomplished by binding one or more methyl groups to the lysine or arginine in the histone molecule and acetylation is done by adding the acetyl group to the lysine. These changes alter the histone / DNA or histone / histone interaction by altering the activity of transcription factors and ultimately the entire transcription process [28, 29].

Both methylation and acetylation of histones have been reported in psoriasis. In the case of methylation, it has been observed that methylation of histone H3K9me2 in psoriasis lesion can alter IL-23 expression in keratinocytes. Decreased H3K9 demethylation in the IL-23 gene promoter increases IL-23 expression in keratinocytes in the psoriasis lesion [30]. In peripheral blood cells, histone H3K4 is elevated in patients with psoriasis compared to healthy ones. Patients treated with various biologic therapies who did not respond to treatment after three/six months have different levels of methylation of these histones [31]. Methyl transferase EZH2, which produces a trimethylation in the H3K27 component, is overexpressed in the lesional skin increasing keratinocyte proliferation [32]. On the other hand, demethylation of H3K7 by increasing the level of demethylase jmjd3 leads to the differentiation of Th17 cells [33]. It is observed that histone methylation/demethylation is involved in two key processes in the pathogenesis of psoriasis. Acetylation is performed by transferring the acetyl group to the lysine of their component, by means of an enzyme (histone acetyl transferase). There is also the reverse process, deacetylation, performed by enzymes such as deacetylases. The addition of an acetyl group or the loss of this group by histones alters their relationship to cellular DNA, favoring or inhibiting the expression of several genes.

In psoriasis, in the lesional skin, but in PBMC, deacetylation of HDAC-1 is overexpressed, without being different between various clinical forms of psoriasis. Another deacetylase, SIRTUIN-1, with anti-inflammatory and antiproliferative effect, is low in psoriasis [34]. There is an opposition between HDAC-1 and SIRTUIN-1 in psoriasis. Thus, HDAC-1 suppresses the expression of genes with inflammatory and proliferative action, SIRTUIN-1 induces anti-

inflammatory effects in keratinocytes and apoptosis can also act on the p53 gene [14, 34].

HDAC-1 also has an effect on the immune system. Thus, inhibition of HDAC-1 increases Foxp-3 gene expression with overproduction and exacerbation of regulatory T functions [35].

As with methylation, the ratio of acetylation/deacetylation of histones is very important for gene expression. The variation of this ratio is subject to internal cellular factors and a cellular microenvironment in which the constellation of ciotokines and growth factors play an important role.

Non-coding RNA

Non-coding RNA (RNA) is a non-RNA molecule that does not contain genetic information that can lead to the formation of proteins. There are a large number of these RNA molecules that are not directly involved in the transmission of genetic information to ribosomes and that do not directly contribute to protein synthesis. The role of these RNA molecules is in the post-transcriptional regulation of gene expression, intervening in the process of transmitting genetic information from the nucleus to ribosomes.

Three classes of RNA molecules of this type (ncRNA) are currently known, differentiated by the number of nucleotides that make up their composition:

1. long ncRNA with over 200 nucleotides (ribosomal RNA proper RNA)
2. short ncRNA, containing between 40 and 200 nucleotides (transfer RNA, sncRNA),
3. ncRNA shorter than 40 nucleotides (microRNA, RNApi).

A special category of long RNA is circular RNA, which has a tissue specificity and appears under certain specific physiological conditions [36,37].

These four forms of ncRNA show different expressions in various pathological processes in the body (inflammation, tumor processes, etc.), which is reflected in the transcription activity of various genes. There is a tendency to identify a number of changes in these ncRNA molecules that could suggest a number of changes at the clinical level for various conditions. On the other hand, there are many ncRNA molecules without a clearly defined function at present [37,38].

In psoriasis, dysfunctions have been identified at the level of microRNAs (mRNAs) and ncRNAs of clinical importance [39].

MICRO RNA (miRNA). Represents a small fragment of RNA that does not contain genetic information, having about 22 nucleotides. It has the ability to regulate post-transcriptional expression of numerous genes by coupling with complementary bases in the messenger RNA structure. Coupling results in the destruction of messenger RNA by blocking the transmission of genetic information from the gene to the ribosomes. This suppresses the activity of a gene after the gene has been transcribed. At the same time, miRNA may contribute to gene methylation or histone modification [1,2,40].

To date, about 250 types of miRNAs have been identified that are of greater or lesser importance in the pathogenesis of psoriasis. The investigation of these types of miRNAs was performed mainly in keratinocytes from psoriasis lesions compared to the healthy skin of the same patient. The results were compared with healthy individuals. The methods of investigation were of the PCR type [12,41]. Obviously, correlations were made between the increased or decreased expression of a certain type of miRNA, with disturbances in the transcription of a certain gene and the clinical and evolutionary aspects of the disease. Some of these miRNA disruptions may be important links in the pathogenesis of psoriasis.

miRNA-203. It is a type of miRNA with high specificity for the skin. MiRNA203 expression is increased in lesional keratinocytes in psoriasis [41] miRNA -203 to activate cytokine-induced signals by activating transcription factors for this molecule. [42]

miRNA -125. It has the ability to suppress keratinocyte proliferation and is low in psoriasis lesions. At the same time, it can regulate the expression of the EGF receptor (EGFR2) by exacerbating keratinocyte differentiation [43].

miRNA-210. It is another type of miRNA that is massively increased in psoriasis lesions as well as in CD4 + lymphocytes. In animal models of psoriasis lesions induced by imiquimod, the psoriasis lesions were significantly ameliorated.

The improvement being cholerized by the decrease in miRNA in the lesion as well as in the T lymphocytes [39]. At the same time, miRNA-210 inhibits Th2 lymphocyte differentiation, decreases the level of mRNA for IL-17, interferon, producing important immunological imbalances in Th1, Th2, Th17 lymphocytes [39, 47].

miRNA-200. There are elevated values in both plasma and psoriasis lesions. Elevated plasma values in patients with psoriasis are positively correlated with disease severity and cardiovascular risk [46,47].

miRNA-135b. It is a type of RNA well correlated with the evolution of psoriasis during biological therapy. A study of patients with psoriasis, with PASI over 10, which looked at the expression of many types of miRNAs after biological treatment (anti TNF, anti IL-17), showed that only miRNA-135b returned to baseline in lesional area. The decrease in miRNA-135b level was correlated with the decrease in PASI [45].

miRNA-146a. Keratinocytes from the psoriasis lesion, PBMC as well as components from the lesion dermis, express elevated levels of miRNA-146a [47]. At the same time, miRNA-146a is positively correlated with IL-17 expression, being a negative regulator of autoimmunity and inflammation [48]. It negatively regulates the transcription factor NF-κB in B cells and is involved in the production of proinflammatory cytokines [47,48,49].

On the other hand, miRNA-146a can suppress IL-17-mediated inflammation, this role being related to the polymorphism of a single nucleotide in the gene encoding the miRNA-146a gene promoter [49]. Decreased IL-17 activity has also been observed in animal models with miRNA -340, which reduces the expression of this cytokine [50].

miRNA-21. Elevated values of miRNA-21 were found in keratinocytes and inflammatory infiltrate in psoriasis lesions. These elevated values were correlated with increased TNF-alpha miRNA expression [51,52]. miRNA -21 has a strong immunological action promoting inflammation, suppressing T cell apoptosis and altering the functions of regulatory T cells. Decreased miRNA expression in regulatory T cells is associated with reduced normal function of these cells. MiRNA-21 also decreases IL-17 and IL-10 expression. In some cases, it has been shown that miRNA-21 can act on opposite functions of regulatory T cells [53].

miRNA-31. At the legislative level, an over-expression of miRNA-31 was highlighted. Suppression of miRNA-31 inhibits the signals produced by the transcription factor NF-κB, decreasing the production of IL-1 beta and several cytokines. miRNA-31 acts on genes encoding serine threonine kinase enzymes, producing keratinocyte proliferation and has a regulatory role in their migration. Overall, over-expression of miRNA-31 massively promotes inflammation in the lesional skin, regulating the production of cytokines and chemokines. At the same time, miRNA-31 is involved in proliferation, differentiation, cell migration as in apoptosis [54,55]. Other types of miRNAs, such as miRNA-155, have elevated levels in psoriasis, directly influencing the expression of mediators in psoriasis lesions [56].

Long non-coding RNA (lncRNA) is a type of RNA that does not transmit genetic information, which are composed of more than 200 nucleotides. Several thousand lncRNAs are known without a good understanding of the functions of each type [57].

It is seen that lncRNA intervenes post-transcriptionally in histone methylation, regulates transcription factors and protein translation [58]. At the same time, lncRNA, by blocking several genes, controls the cell cycle and apoptosis.

There is a positive correlation between increased lncRNA values and a number of processes in which keratinocytes are involved: wound healing, psoriasis, skin cancers [59,60]. In psoriasis, more than 1000 types of lncRNA have been found that are different in the psoriasis lesion compared to healthy skin [57,58,59].

LncRNA also acts on genes involved in the immune response, thus being involved in the immune component of the pathogenesis of psoriasis. There are several types of lncRNA with obvious involvement in the pathogenesis of psoriasis: ANCR and TINCR. ANCR (anti-differentiation non-coding RNA) opposes keratinocyte differentiation while TINCR (terminal

differentiation-induced non-coding RNA) promotes keratinocyte differentiation [61].

Another type of lncRNA involved in the pathogenesis of psoriasis is PRINS [62,64]. It is over-expressed in healthy skin as well as in psoriasis lesion. It has a protective role against legislative stress and the presence of elevated levels of PRINS in the epidermis is correlated with an increased risk of developing psoriasis. At the same time, PRINS is a regulator of the G1P3 antiapoptotic gene. The expression of this gene is increased in keratinocytes from the psoriasis lesion and to a certain extent in healthy skin [62,63].

Although a profile of psoriasis lesions has not yet been established in terms of clinical miRNA changes, these molecules are strongly implicated in the pathogenesis of psoriasis. Thus, it has been observed that single nucleotide polymorphism encountered in microRNA can regulate EGFR expression by influencing keratinocyte proliferation. Other mutations in microRNA-146 may massively decrease keratinocyte proliferation [64]. The rs 290165G polymorphism of miRNA -146 is also a risk factor for psoriasis [64]. It can be seen that genetic polymorphism in miRNAs leads to the activation of genes that control the skin's inflammatory response [65].

However, there is some specificity of different types of miRNAs for psoriasis lesions. Thus, miRNA-21, miRNA-31, miRNA-146, miRNA-125, or miRNA-155 are more commonly associated with psoriasis lesions. In most cases, there is an over-expression of these miRNA types in the psoriasis lesion and in PBMC [51, 65].

A number of miRNAs, especially those with increased expression in the psoriasis lesion, were also followed after biological treatment with anti-TNF, anti-IL-2, and anti-IL-23 in the residual lesions. Only miRNA-135b. returned to low values after treatment [45]. Methotrexate therapy produces changes in the expression of various types of miRNAs but with low specificity and consistency [66]. There are studies that suggest that changes in miRNA after treatment would have some specificity depending on the treatment performed [45,66].

Although the expression of various types of RNA in the lesion and PBMC is variable in many studies, and the appreciation is high / low, it is possible that various groups of miRNAs may potentiate or inhibit each other. The study of miRNA may open up new therapeutic possibilities.

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Conflict of interest
NONE DECLARED

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