ASPECTS OF MicroRNA IN THE PATHOGENESIS OF ATOPIC DERMATITIS

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Summary

Atopic dermatitis is a widespread condition in which the atopic background associates (induces or modulates) inflammatory manifestations.

The discovery of microRNA, which can post-transcriptionally block the activity of a gene and which can also have numerous other actions on cellular DNA, has led to the investigation of the involvement of microRNA in numerous conditions, including atopic dermatitis.

Many studies have revealed numerous quantitative changes in microRNA in cells involved in the pathogenesis of atopic dermatitis, keratinocytes, inflammatory cells, but also in serum or urine.

The interpretation of the data of these studies is difficult to achieve due to the complex action of microRNA but also due to the selectivity of the investigations and the results obtained in a certain clinical context.

In our study we present the main types of microRNAs that showed quantitative changes in atopic dermatitis (over expression or reduced expression). At the same time we try a short critical interpretation regarding these results.

Even if they have not entered current clinical practice, in atopic dermatitis a series of microRNAs (microRNA155, microRNA146, microRNA203) retain their biomarker potential or therapeutic potential.

Key words: *atopic dermatitis, microRNA, pathogenic mechanisms*

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Introduction

Atopic dermatitis (AD) or atopic eczema is a chronic inflammatory skin condition with long periods of remission or minimal manifestations and rare periods of exacerbation. It can be considered that AD represents the main manifestation of atopy. The association of AD with other allergic manifestations (asthma, rhinitis) is frequent. The main symptoms of AD are: inflammation, erythema, blisters, sloughing, lichenification, itching, dry skin. Itching, usually of medium intensity, is the main symptom. The symptoms occur at all ages, but in the first 5-6 years of life they have a sharp evolution, both in terms of frequency and intensity and persistence [1,2,3].

The pathogenic mechanisms of AD overlap with those of eczema, with AD being considered a form of eczema. The pathogenesis of AD is extremely complex including genetic aspects, immunology (Th1/Th2 imbalance with predominance of Th2 cytokines), epidermal and skin microbiome dysfunctions, mechanisms of pruritus production via hisamine/histamine receptors or independent of histamine via TSLP

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(thymic stromal lymphoprotein/thymic stromal lymphoprotein) [4,5]. All these mechanisms contribute to the initiation, development and maintenance of skin inflammation.

Genetic pathogenic mechanisms have mainly highlighted filaggrin alterations. Filaggin is a protein found especially in the granulous layer, where it participates in the aggregation of keratin filaments but also in the formation of the cornified cell envelope through transglutaminase [6]. Filaggrin is also an important component of the stratum corneum and its degradation products contribute to the hydration and maintenance of skin pH [3,6].

Mutations found in the genes encoding filaggrin are associated with the alteration of the skin barrier and with an increased level of AD and certain forms of ichthyosis. But not all AD patients have these mutations [7,8]. Other genetic alterations of particular importance in AD are found at other levels, for example the polymorphism of type 2 cytokine receptors (IL-4R, IL-13R), the high-affinity receptor for IgE (FcƐR1), the receptor for TSLP [5,7] .

All these changes create the conditions for the development of a skin inflammatory response with the characteristics of AD.

Epigenetic modifications such as DNA methylation, histones modifications or microRNA investigation have sought to bring new data in AD pathogenesis especially in the relationship environmental factors/epigenetic modifications. Epigenetic changes are sensitive but influence over a period of time the environment in which the DNA is transcribed or blocked [9].

Investigation of different forms of non-coding RNA has been a relatively recent trend in elucidating the epigenetic mechanisms of AD.

Non-coding RNA (ncRNA). The transmission of genetic information from the nucleus to the ribosomes, where protein synthesis is carried out, is done by means of an RNA fragment called messenger RNA. It is expelled from the nucleus, passes through the cytoplasm reaching the ribosomes where it transfers the genetic information to more types of ribosomal RNA, finally realizing the protein synthesis. The messenger RNA structure has two components, one that contains genetic information and one that does not contain genetic information but can couple with other RNA-type polypeptide structures [10,11]. One way to interfere with this process is by the action of fragments of RNA that do not contain genetic information called non-coding RNA, but which have the ability to attach to the non-coding portion of mesangerRNA blocking the transport of genetic information to ribosomes and essentially blocking the activity of a gene [11,12].

In humans, there are thousands of types of non-coding ARN that can couple to different types of messenger RNA blocking the transcription process of a gene. Apart from the post-transcriptional regulation of a gene, non-coding RNA can regulate methylation and acetylation of histones, is a cofactor in the modulation of transcription, acts as an alternative mechanism in the splicing phenomenon. There are numerous types of ncRNA that they do not have a well-defined function [13].

Non-coding RNA is transcribed together with the messenger RNA transcription, it is expelled into the cytoplasm where the maturation process will take place, it may or may not couple with the complementary portion of the mRNA. This coupling depends on numerous poorly understood factors, possibly one of which is the status of the cellular microenvironment at any given time.

Depending on the number of nucleotides, three classes of non-coding RNA were differentiated: long ncRNA with more than 200 nucleotides, short ncRNA containing between 40 and 200 nucleotides and microRNA, below 40 nucleotides, most frequently between 17 and 24 nucleotides. A specific form of long ncRNA is circular RNA with a certain tissue specificity [14].

MicroRNA represents the smallest form of ncRNA having in mature form, a single chain of 20-24 nucleotides. MicroRNA is born in the nucleus by the transcription of its own genes with the help of RNA polymerase II, in the form of a precursor consisting of several hundred nucleotides, called primary microRNA (pri-microRNA) [15,16].

Pri-microRNA is processed/cleaved by an enzyme complex consisting of an RNAse III/ DROSHA and a nuclear protein DGCR8 or PASHA. The DROSHA/PASHA association cleaves the pri-microRNA into fragments of

approximately 70 nucleotides that form the micro-RNA precursor (pre-microRNA). The pre-microRNA is sent to the cytoplasm via a protein, exportin [17,18]. In the cytoplasm, pre-microRNA is cleaved into single-stranded chains of an average of 20-22 nucleotides by RNase III or DICIER, which attacks the hairpin structure of pri-microRNA. Blockade of the DICER enzyme is reported to be lethal in the mouse [19,20]. The small single-stranded chains that form microRNA associate with members of a protein family, the AGO proteins, forming the RISC complex (RNA-induced silencing compex). This complex associates with messenger RNA and the latter is destroyed by AGO proteins that have endonuclease activity. Coupling with messenger RNA is achieved by the fact that microRNA has a complementary structure with portions of messenger RNA that do not contain genetic information [17,18]. There are other ways of micro-RNA formation but of lesser importance.

The main function of microRNA is the post-transcriptional blocking of the activity of a gene by blocking or destroying the messenger RNA. About one-third of genes are thought to undergo the action of micro-RNAs. A micro-RNA can bind to and destroy several types of messenger RNA (dozens). Also, one type of messenger RNA can bind to and be destroyed by several types of microRNA [15,16,17].

Apart from blocking the activity of a gene, microRNA has other types of action: translation repression by inactivating translation activation factors, action at the promoter level of genes preventing to be activated, deadenylation, and occasionally produces DNA methylation at the promoter level of target genes and changes of histones. Also microRNA is a negative regulator for long ncRNA [16,21,22]. These processes at the subcellular level greatly influence a number of physiological and pathological processes. MicroRNA is involved in cell development and differentiation, innate and adaptive immunity, autoimmunity, apoptosis, inflammation and tumor development [23].

The possibility of investigating microRNA by various methods (PCR, RT-PCR), in situ hybridization, microRNA microarray, Northern blotting, both from lesional cells and from fluids (serum, urine, saliva) has led to numerous studies that have highlighted microRNA changes. These changes in microRNAs were especially aimed at the quantitative aspect, at a given time, in a lesional cell or immune cells [24]. In dermatology, microRNA variations, mostly quantitative, have been investigated in several types of conditions, psoriasis, vitiligo, bullous diseases, dermatomyositis, neurofibromatosis, melanic and non-melanic tumors, autoimmune skin diseases [25].

Determination of microRNA in atopic dermatitis

Currently, a number of 2600 forms of mature microRNA have been identified and have been entered into numerous databases. Quantitative variations of various types of microRNAs in cells involved in a specific pathogenic process were followed.

In the case of atopic dermatitis, various types of microRNA have been determined in keratinocytes, immune cells (T or B lymphocytes) or related to inflammation in biological fluids: serum, urine. Results were reported to healthy subjects or in the same patient, in non-lesional areas.

The most important forms of microRNAs that were repeatedly found to be elevated or decreased are:

MicroRNA 146. Is a moderator of inflammatory processes with a strong anti-inflammatory action in atopic dermatitis, being involved in TNF-induced signals and NF-κB activation. In lesional skin, as in healthy skin, microRNA146 shows increased values. Inhibition of micro RNA146 increases the expression of proinflammatory factors in keratinocytes and the accumulation of inflammatory cells in the dermis [28]. By blocking the action of NF-κB, it suppresses the action of some genes such as: CARD10, IRAK1, CCL5, and decreases the level of IL-6 and IL-8, IFNγ in keratinocytes [29].

It has been shown that in patients with AD, the Th1/Th2 ratio decreases, a decrease correlated with the expression of microRNA146 compared to healthy subjects [30].

MicroRNA155. Is involved in innate but also adaptive immunity having an essential role in the regulation of allergen-dependent inflammatory

processes. It is also involved in Th17 differentiation in autoimmune processes. Also microAN155 is induced by activated T lymphocytes and overexpression of microRNA155 decreases the level of CTLA-4 and increases the proliferation of Th lymphocytes [31,32]. In AD microRNA155 is overexpressed and is positively correlated with disease severity. In the animal model, microRNA155-5p (a member of the microRNA155 family) was observed to be required for the development of inflammation in allergen-induced AD. Inactivation of microRNA155 is associated in AD with epidermal thickening and reduced inflammatory infiltrate and decreased Th2 cytokine secretion. Also microRNA155 has an action of modulating the skin barrier function by increasing the expression of the proteins that form the tight junctions of the epidermis [31,32]. One of the targets of microRNA155-5 is the gene encoding protein kinase inhibitor1 (PK1α) which is altered in AD. The inhibitor of protein kinase 1 can prevent the dysfunctions that occur at the level of tight junctions [31,32].

MicroRNA151. Is a potent inhibitor of the IL-12 receptor that has an important role in the differentiation of Thelper. MicroRNA151 has relatively consistently increased values in the plasma of AD patients and in blood mononuclear cells compared to healthy subjects [31,33].

MicroRNA124. It is a regulator of the inflammatory response at the level of keratinocytes in the inflammatory processes of the skin. In AD, it is low at the lesional level, especially in the case of chronic lesions. IFNγ and TNFα inhibit microRNA124 expression. On the other hand, microRNA124 inhibits NF-kB activation being the main target of microRNA124. It also has suppressive action on IL-8, CCL-5, CCL-8 [34,5].

MicroRNA143. The main target of micro RNA143 is the 3'-UTR region of IL-13 α1 receptors. Binding of microRNA143 with this receptor decreases IL-13 expression and subsequently IL-13-induced cytokine production. In AD the expression of microRNA143 is decreased in the skin. On the other hand, stimulation with IL-13 decreases microRNA143 expression in keratinocytes [31,36].

MicroRNA10a-5p.MicroRNA10a-5p has been shown to be increased in both lesional and healthy skin of AD patients. Overexpression of microRNA10a-5p in AD patients decreases keratinocyte proliferation, affecting skin barrier function. The genes encoding IL-1β, adhesion molecules as well as a series of signaling pathways mediated by cytokines are involved [31,37].

MicroRNA223.MicroRNA223 showed increased values in many blood cells but also in plasma having an important role in hematopoiesis. A positive correlation of increased microRNA223 values with disease progression was also revealed. It is also chemoattractant for Th2 lymphocytes. Although it has the ability to bind to the region of genes encoding HNMT (histamine-N-methyl transferase), which is increased in DA, this coupling does not occur and does not block the activity of these genes [34,38].

MicroRNA335. Is a potent inducer of keratinocyte differentiation by inhibiting the SOX6 transcription factor. SOX6 has increased expression throughout the skin. In lesional skin microRNA335 is massively decreased [31,39].

MicroRNA1294. In DA microRNA1294 acts as an inhibitor of inflammation in the STAT3 pathway, inhibiting NF-kB. MicroRNA1294 is also increased in tumor processes having a suppressive role [40].

MicroRNA203. It has a certain specificity for the skin. It is significantly increased in the serum of AD patients compared to healthy children. Like microRNA483-5p, with which it is frequently associated, it is overexpressed in a series of conditions included in the atopia: bronchial asthma, allergic rhinitis. Although it is increased in the serum of atopic patients, in the same patients it has low values in the urine, these values being associated with increased levels of serum IgE [42].

MicroRNA483. It is overexpressed in the serum of children with AD but also in the serum of children with other atopic manifestations. It is also a modulator of fibrogenesis [42].

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Attempts to find a single microRNA showing significant expression changes in AD have been unsuccessful. An exception could be microRNA29. Decreased activation of microRNA29 in mouse B cells induces the expression of the atopic skin phenotype, being a negative regulator of the B lymphocyte receptor. MicroRNA29 promotes inflammation and microRNA29-deficient B cells

tend to switch immunoglobulin production to IgE formation in response to IL-4, IL-13 stimulation [43].

We searched for microRNA profiles that are characteristic of various conditions including AD. Such a profile highlights in the skin, increased values for the following types of microRNA: microRNA501, microRNA155, microRNA135b, microRNA142-3p, microRNA142 and low values for: microRNA204, microRNA486, microRNA 375, microRNA328, microRNA195 [28,44].

Another study by Gu et al (cited by Yu) identified in skin biopsies an increase in microRNA4270, microRNA201, microRNA4529, microRNA29b and a decrease in microRNA184, microRNA135a, microRNA4454 [45]. 44 microRNAs with variations from normal were identified in AD lesions. Of these, 34 showed increased values and 10 decreased values. MicroRNA135 presented in this study, a massive exacerbation [46,47].

Studies were conducted using data included in the databases available in SCORUS and PubMed. From the analysis of 118 articles investigating various types of microRNAs, the most common elevated values in lesions and peripheral blood cells showed microRNAs 155 and 146a, which can be used as diagnostic markers. MicroRNA203 correlates well with disease progression and can be used as a marker for disease severity [48].

MicroRNAs in serum and urine

A series of studies have identified the presence of microRNA in biological fluids such as: serum, urine, breast milk, saliva. The presence of 155 microRNAs was detected in serum and 166 in urine. In serum 9 were overexpressed (microRNA 205, microRNA539, microRNA122, microRNA203, microRNA483-5p,1 let-7g, microRNA 495, microRNA642, microRNA134) and only one microRNA was decreased: microRNA590-5p. There were 10 types of microRNA increased in the urine (microRNA: 142-3p, microRNA 20-a, microRNA 548-3p, microrna205, microRNA 19a, microRNA483-5p, microRNA222, microRNA 92-a, microRNA 584-3p. With low values they have there were 7 types of microRNA (microRNA203, microRNA125a-5p,microRNA 886-3p, microRNA 184, microRNA886-5p, microRNA 26a, microRNA 194) [28,41,46].

A special mention for microRNA203 and microRNA483 which are overexpressed in the serum of children with AD. MicroRNA 483-5p is associated with other atopic manifestations (asthma, rhinitis) while decreased urine microRNA 203 is associated with increased IgE levels [41].

Discussions

MicroRNA investigation in AD has revealed numerous quantitative changes, both in the lesional cells and in the cells involved in the inflammatory or immune response. Also, microRNA was highlighted in serum, urine, saliva, milk, without being able to highlight the involvement of serum microRNA in various pathogenic processes.

Interpretation of altered microRNA values, either overexpressed or below control values, is difficult to appreciate. A possible difficulty is the fact that a microRNA can couple with several messenger RNAs and a messenger RNA can couple with several types of microRNAs. A second difficulty is given by the fact that a microRNA has a direct action on genes, namely methylation, acetylation, action on the promoter, or on transcription factors.

In the case of microRNA types that showed large variations in the determinations made, a series of connections related to the cells in which the determination was made, keratinocytes and immune cells in the case of AD, were individually followed. The connections made between the quantitative variation of a type of microRNA constituted an important step in the understanding of AD pathogenesis, especially related to the allergic inflammatory process. But the path from the modification of microRNA to the appearance of the inflammatory process in AD, has many stages, some of them carried out in a certain context. Moreover, in AD microRNA does not act on the genetic changes typical of atopy (changes in filaggrin, IgEƐR receptors), but on the inflammatory response and changes in keratinocytes and the alteration of the barrier function. It seems that the genes that microRNA acts upon are coding reglatory proteins despite structural proteins.

Thus, following the microRNA dysregulation profile in AD, it was established that there are 5 types of microRNA that present dysregulations

that exceed the frequency of the values determined in healthy subjects. Although they have a certain constancy, the disturbances are not pathognomonic, or strongly associated with the respective condition. An example for AD is microRNA146, microRNA155 and microRNA203. The latter being also involved in the production of IgE.

Even though databases of microRNA changes (over- or under-expressed) were followed, no characteristic pattern could be established for AD to highlight which types of microRNAs are consistently changed. In AD, the most frequent changes occur in microRNA155 (in keratinocytes and peripheral blood cells, microRNA146 (keratinocytes), microRNA 203 (serum keratinocytes) to which are added microRNA151, microRNA 483-5p, microRNA223 [28,45]. The association of a certain type of microRNA with a known patological process was sought, based on direct (microRNA blocking studies) or indirect evidence.

Also, if microRNA changes are followed in other types of skin conditions: vitiligo, pemphigus, lichen planus, hidradenitis suppurativa. MicroRNA 155, microRNA146, microRNA203, show AD-like changes in lichen planus and hidradenitis suppurativa [34]. This fact suggests that these types of microRNAs are related to or involved in the inflammatory processes in these conditions. Moreover, the changes found above in these microRNAs are also found in psoriasis (chronic autoimmune inflammation) [28, 32]. It seems obvious that microRNA is involved in inflammatory processes: the differentiation and activation of T, B lymphocytes, macrophages, dendritic cells and keratinocytes [34]. There is a possibility that microRNA is not an initiator of a pathogenic process but an intermediate link of this process. An example is IL-32γA overexpression of AD symptoms by inhibiting microRNA205 via NF-κB inactivation pathway (murine model) [48]. Taken as a whole, it cannot be said that there are established markers unanimously accepted in clinical practice, which can be used as diagnostic markers or biomarkers (constant expression, reproducibility, correlation with the evolution of the disease). Several types of microRNAs have been proposed for biomarkers, but microRNA 203 seems to come closest to the classical definition of a biomarker. As diagnostic markers, microRNA155, microRNA 151, but also keratinocyte-related markers such as: microRNA146a, microRNA143, microRNA29 would come into discussion [49].

Conclusions

The discovery of microRNAs and other types of non-coding RNAs that can block messenger RNA, post-transcriptionally blocking a gene, has led to the accumulation of numerous data on this process. Accumulated data aimed at connections and direct consequences of the process, allowed a better understanding of the pathogenic mechanisms in various conditions, including AD. In AD, it was highlighted that microRNA participates in a series of subcellular processes that contribute to the disruption of the cytokine network, typical of AD, but also to its modulation. It was also highlighted that microRNA disrupts a series of important processes in keratinocytes contributing to the development of pathogenic processes in AD.

The accumulation of data on microRNAs has raised the hope of their use in current clinical practice and therapy. To date, even if these data are of limited use, they constitute an important basis for further research.

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Conflict of interest
NONE DECLARED

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