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Impact of Lymphocyte Apoptosis on the Development of Psoriasis

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Abstract **Background:** The aim of the present study was to investigate the role of markers of activation and apoptosis of lymphocyte subpopulations in psoriasis. **Methods:** The content of the lymphocyte population in peripheral blood was determined using monoclonal antibodies to markers CD3, CD4, CD8, CD16, CD20, CD25, CD95 in 112 patients with psoriasis. **Results:** Different types of psoriasis exhibit diverse changes in the expression of markers associated with both positive and negative lymphocyte activation. **Conclusions:** Examining these activation markers helps identify various lymphocyte subpopulations and determine their role in the development and progression of psoriasis. These markers are linked to cellular cycle processes, including activation (CD25) and apoptosis (CD95).

Keywords Psoriasis, Immunology, Apoptosis

1. Introduction

Psoriasis is a lifelong immune-mediated inflammatory skin disease characterised by accelerated proliferation of epidermocytes and impairment of their differentiation [1,2].

The problem of psoriasis continues to be one of the most pressing issues in modern dermatology. WHO has emphasised the need for a better understanding of the global burden of psoriasis. In response to this need, the Global Atlas of Psoriasis was created to conduct comprehensive studies of the global prevalence and incidence of psoriasis [3,4].

The problem is also due to the unknown etiology and incomplete concepts of psoriasis pathogenesis [5,6,7]. The pathogenesis of psoriasis involves complex interactions between genetic, immunological and environmental factors, resulting in dysregulation of immune responses and excessive keratinocyte proliferation [8,9]. To date, there are a large number of publications in the literature indicating serious shifts in the immune status of psoriasis patients from both immunoregulatory and immune effector links, allowing us to consider this problem from the point of view of immunopathology [1,10]. Disorders of innate and adaptive cutaneous immune responses are responsible for the development and maintenance of psoriatic inflammation [11,12]. Recent studies have shown that epigenetic factors, including dysregulation of DNA methylation levels, abnormal histone modification, and microRNA expression, are involved in the development of psoriasis. The interaction between immune cells and cytokines is another critical factor in the pathogenesis of psoriasis [13].

The process of apoptosis (also called programmed cell death) is a basic, ordered physiological process that leads to cell death without induction of inflammation. Under conditions of homeostasis, it fulfils a regulatory function. It leads to the death of mutated, autoreactive or damaged cells in the body. The key role of apoptosis is to maintain internal tissue balance [14]. Apoptosis plays a crucial role in several physiological functions such as cell deletion during embryonic development, balancing the number of cells in continuously renewing tissues, and the development of the immune system [15]. The study of apoptosis has proven to be very productive in understanding a number of crucial phenomena and processes, including immune homeostasis. Apoptosis is used to remove unwanted or potentially harmful cells from the body, such as autoreactive T lymphocytes, tumour cells and virus-infected cells. Apoptosis is important in the termination of immune reactions [16].

It is considered that apoptosis is realized through activation of expression on the lymphocytes of the superficial CD95 receptor (Fas/APO-1) and its connection with ligand FASL. Classical specific receptors for apoptosis induction belong to the TNF-alpha receptor superfamily. They include Fas/CD95, TNF-alpha receptor type 1 (TNFR1), DR3/WS1-1, DR4/TRAIL-R1, DR5/TRAIL-R2, DR6, containing “the domain of death” in the cytoplasmatic site providing activation of the caspase cascades. Fas/CD95 expresses on the hepatocytes and circulating T-cells of memory. CD95 is not induced on the “testing” T-cells CD45RA+ and is poorly induced on the B-lymphocytes. At cell activation CD95 expresses predominantly on the neutrophils, hepatocytes, T-lymphocytes CD4+, that characterizes their high sensitivity

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to FASL-induced apoptosis. FASL expresses actively on activated T-lymphocytes and, cooperating (as membrane-associated or soluble protein) with Fas/Cd95, it becomes the basic mechanism of apoptosis of the cell-targets in various diseases [17,18].

The elucidation of the mechanisms of lymphocyte apoptosis disorders in psoriasis allows not only deeper understanding of pathogenesis of this dermatosis, but also planning new ways and approaches to immune correcting therapy.

2. Materials and Methods

The study included 112 patients with psoriasis. From heparinized peripheral blood of the patients on the 3% gelatin there were isolated intact lymphocytes. Blood samples obtaining was carried out before and after ending of the treatment.

The content of the lymphocyte population in the peripheral blood was determined with the help of monoclonal antibodies to markers CD3 (T-lymphocytes), CD4 (T-helpers/inducers), CD8 (T-suppressors/cytotoxic), CD16 (natural killers), CD20 (B-lymphocytes), CD25 (lymphocytes with receptor to IL-2), CD95 (lymphocytes with receptor to apoptosis) with indirect plaque assay. The principle of a method consists of attachment of human erythrocytes, sensibilized with monoclonal antibodies LT3, LT20, LT4, LT8, LT16, LT25, LT95, and LT HLA-DR on the surface of lymphocytes.

The group of comparison (n=54) included healthy people of the same age, as the studied patients.

3. Results and Discussion

Study of activation markers enables defining various lymphocyte subpopulations, establishing their role in development and progress of psoriasis, as they characterize the processes of activation (CD25) and apoptosis (CD95) connected with the cellular cycle.

Table 1. The parameters of markers of positive and negative activation in the patients with different forms of psoriasis

Groups of patients	n	CD25	CD95
Control group	54	26.1±1.1	26.7±1.1
Stable stage	67	26.4±2.1	28.2±1.7
Progressing stage	45	28.6±2.2	24.07±1.6
Psoriasis vulgaris	52	28.8±1.7	26.8±1.8
Exudative form	20	34.75±2.33*	25.75±1.11
Psoriatic arthritis	24	18.3±0.86**	21.5±1.0*
Erythrodermic psoriasis	16	23.0±1.73*	17.0±0.67***

Note: * - $p<0.05$; ** - $p<0.01$; *** - $p<0.001$

As it may be seen from the data presented, the content of T lymphocytes with markers CD25 in the studied group of the patients was exceeded the data of the control, but not reliably. The analysis of data showed 1.1 times higher growth of these cells in the patients with a progressing stage of disease in comparison with the stationary form and control; but this difference was not reliable ($p>0.05$). At the progressing stage of disease the reliable growth of CD8 cytotoxic T lymphocytes was revealed.

The literature about the role APO-I/Fas (CD95) receptors in process of apoptosis shows that the degree of its expression may reflect level of the programmed cell death.

The study of level CD95 cells showed its little reduced content in the patients with psoriasis ($p>0.05$). The analysis of data in relation to the stage of disease has shown multidirectional changes. So, at the stationary stage the content of CD95 cells was registered above the control data, and at the progressing stage of disease was 1.1 times lower than the control. The difference between parameters CD95 cells was 1.2 times and reliable ($p<0.05$). The decrease in expression of CD95 receptor cells indicated about decrease of mature T cells in the blood flow which were rather resistant to apoptogenic stimulus.

The analysis of the data according to the forms of disease revealed that at vulgar form the content of CD25 lymphocytes was found 1.1 times higher than in the control, but not reliably ($p>0.05$). And exudative form differed by the high content of CD25 lymphocytes reliably exceeding the data of controls and parameters of vulgar form of psoriasis ($p<0.05$). Arthropathic form of psoriasis was characterized by the low content of CD25 lymphocytes, 1.4 times lower of the control data and 1.6 times lower than at vulgar form ($p<0.01$). At the erythrodermic form of psoriasis the content of CD25 lymphocytes was recorded 1.1 times below than the control values ($p<0.05$).

The analysis of the data of CD95 cells did not reveal reliable differences from the control at stable and progressing stages of psoriasis. There were also not revealed reliable differences from the control at vulgar and exudative forms of psoriasis. The arthropathic form of psoriasis was characterized by the 1.2 times reduced content of CD95 lymphocytes. At erythrodermic form of psoriasis the reduction of CD95 cells was 1.6 times lower of the control data ($p<0.001$). It is necessary to emphasize, that at erythrodermic form the content of CD95 cells were found reliably lower than in the other forms of psoriasis that indicated about suppression of apoptosis.

As we have noted, the investigated markers characterize connected with cellular cycle processes of activation (CD25) and apoptosis (CD95). The activated cells can participate in the cellular cycle resulting to mitotic cell division (positive activation). The opposite outcome of cell activation, that is, cell apoptosis induction and its death are also possible. In the patients with vulgar form of psoriasis there was noted small shift to increase in marker of positive activation. At the exudative form, the potential of positive cell activation grows comparing to both the control and other forms of psoriasis. It is known, that the result of outcome of activation depends on presence of the “survival factors”, which role some cytokines are capable to carry out (IL-2, IFN-gamma, IL-4). Increase of “grows factors” activates the T-cellular immunity, in the affected skin there is superexpression of cytokines of the T-helpers type 1 (Th-1) including interferon

-gamma and tumor necrosis factor, and reduction of cytokine expression of T helpers type 2 (IL-4 and IL-10). The arthropathic form of psoriasis was characterized by inhibition of receptor expression of both positive and negative activation; this was rather connected with different trigger mechanisms of this form of psoriasis, and possibly with therapy performed. For erythrodermic form of psoriasis there was characteristic inhibition of the expression of the markers of positive and negative activation.

4. Conclusions

Thus, at the various forms of psoriasis there are observed multidirectional changes of the expression of markers of lymphocyte positive and negative activation. Psoriasis induces changes of qualitative and functional parameters of cellular immunity that results in proliferation and predifferentiation of lymphocytes. Study of activation markers allows identifying the different lymphocyte subpopulations, establishing their role in development and progressing of psoriasis. At activation of T lymphocytes the cytokine IL-2 and its receptors play a key role in development, maturing and regulation of immune response supporting proliferation of activated T and B lymphocytes.

The study of the role of markers of activation and apoptosis in psoriasis seems to be significant because the results received will promote understanding of the complex mechanisms of the pathogenesis of disease and improvement of the methods of diagnosis and therapy.

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