REVIEWS

Oxidative Stress in Keratinocytes as an Etiopathogenetic Factor of Psoriasis

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A new etiopathogenetic concept of psoriasis is proposed, which considers psoriasis as a typical inflammatory process characterized by increased antioxidant activity and overexpression of apoptotic receptors. Under these conditions, hyperstimulation of germinative layer cells proliferation dramatically accelerates keratinocyte passage towards apoptotic effect of atmospheric oxygen and its reactive species dooming to death cells with enhanced expression of apoptotic receptors. Oxidative stress of nondifferentiated keratinocytes triggers the formation of defective horny layer, the key mechanism of psoriasis.

Key Words: *psoriasis; apoptosis; inflammation; proliferation; oxidative stress; lipid peroxidation; reactive oxygen species; redox potential*

Peculiarities of skin damage are closely related to specific protective and barrier functions of this organ. Skin is characterized by permanent renewal of its structural elements and cells ensuring adequate responses to varying environmental conditions and participates in the maintenance of internal homeostasis. Exposure to damaging factors activates protective mechanisms, in particular, inflammation.

Cells which served their time are removed by apoptosis, programmed cell death. The balance between cell death and renewal provides the maintenance of cell homeostasis. In the skin, horny layer formed by dead epidermal cells protects the body from chemical and physical factors, while desquamation cleans skin from microbic dissemination.

Apoptosis is now considered as self-regulated cellular suicide controlled at the organ level [7]. This process is conventionally divided into several stages including reception of apoptotic factors, signal transduction to the nucleus, activation of lethal genes, synthesis of specific apoptotic proteins, and, finally, activation of endonucleases and DNA fragmentation [6].

Apoptosis is controlled by a number of external and internal factors [41]: hormones, cytokines, antioxidants, reactive oxygen species (ROS), Ca^{2+}, physical and chemical agents. It is suggested that all effects induced by apoptotic factors can be reduced to activation of several signal-transducing systems. At present, no apoptosis-specific system is known, and the action of apoptotic factors is attributed to their complex effects on phospholipase, sphingomyelin, tyrosine kinase, and protein kinase pathways involved in the regulation of cell differentiation and proliferation [6]. Oxidative stress plays an important role in modulation of apoptosis [6,16,18,20,22,43,44]. But most important, apoptosis is a gene-regulated process [7]. Genes APO-1/*fas*, c-*myc*, c-*jun*, c-*fos*, *nur*77, *p*53 were found to change their activity during cell death [15,19,21, 31,39], while other genes (*Bcl-2*, *Bcl-*x_L) block apoptosis [17,24-26,30,35,36].

Histoimmunochemical examination of skin biopsy specimens revealed a low level of apoptotic receptors *Fas* and antiapoptotic protein *Bcl-*x_L in healthy subjects and a considerably higher level of these proteins

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in patients with psoriasis [44]. In patients with basal cell carcinoma, keratinocytes expressed little *Fas* and extremely great amount of *Bcl-2*. High levels of apoptotic receptor in psoriasis and antiapoptotic protein in carcinoma are implicated in disturbances in differentiation and apoptosis programs [45].

The use of polyclonal antibodies also revealed an increased content of apoptotic protein *p*53 and proliferation marker *Ki*67 in psoriasis [40].

These data suggest that psoriasis is accompanied by activation of apoptotic genes *Fas* and *p*53 and antiapoptotic protective systems *Bcl-2*, *Bcl-*x_L, and *Ki*67.

At present, there is no clear notion of the mechanisms of apoptotic signal reception and the sequence of events triggering cell suicide. However, the metabolic state of the cell undoubtedly affects its reception and realization. The mechanism of programmed cell death is closely related to the tissue redox potential and concentration of ROS [18,27].

ROS are characterized by high reactivity and short lifespan and therefore are an efficient tool for local regulations. Recently, a broad spectrum of physiological effect of ROS was described, including regulation of proliferattion [16,22,24], vascular tone

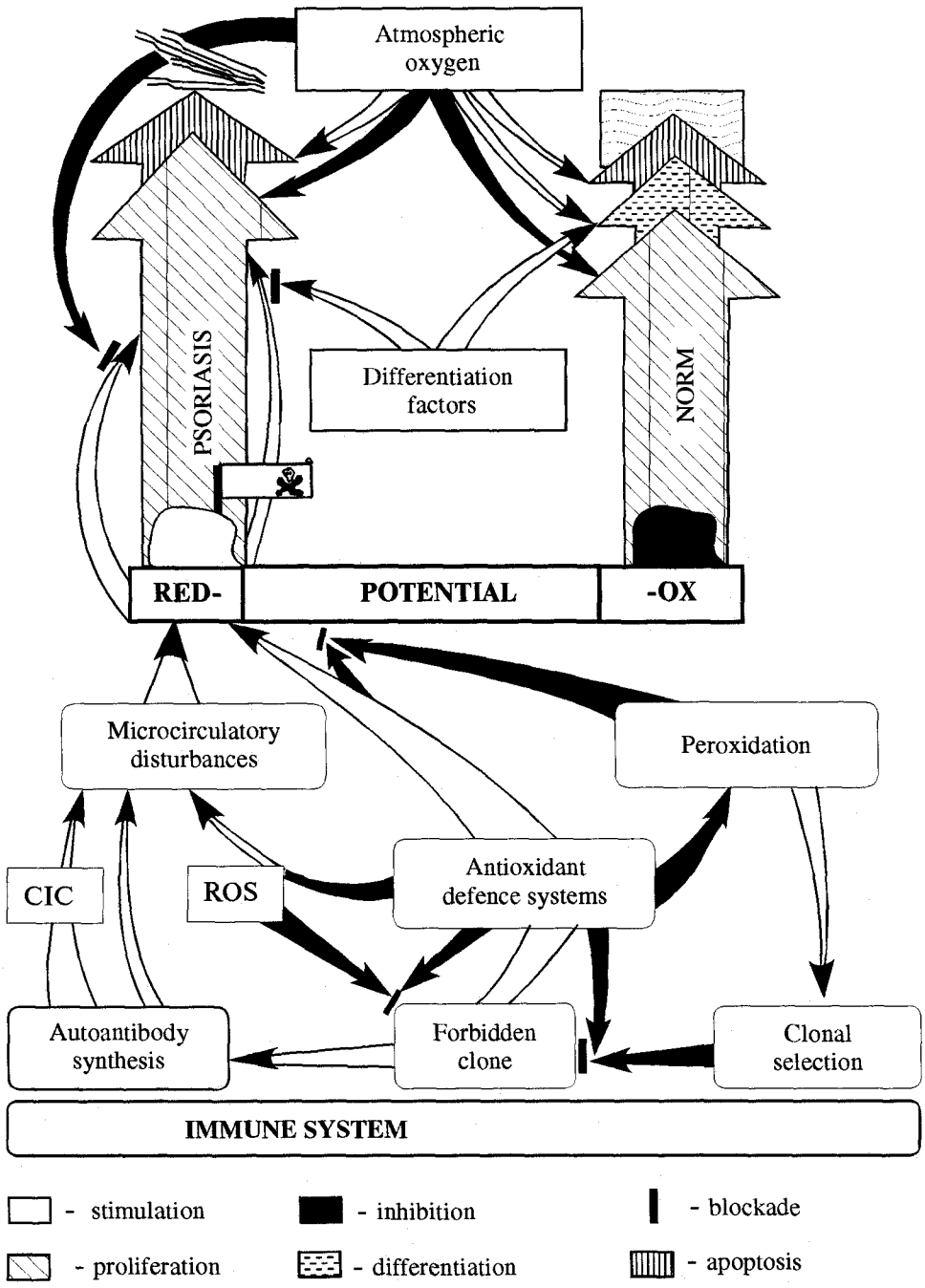

Fig. 1. Pathogenesis of psoriasis. Here and in Fig. 2: CIC: circulating immune complexes, ROS, reactive oxygen species.

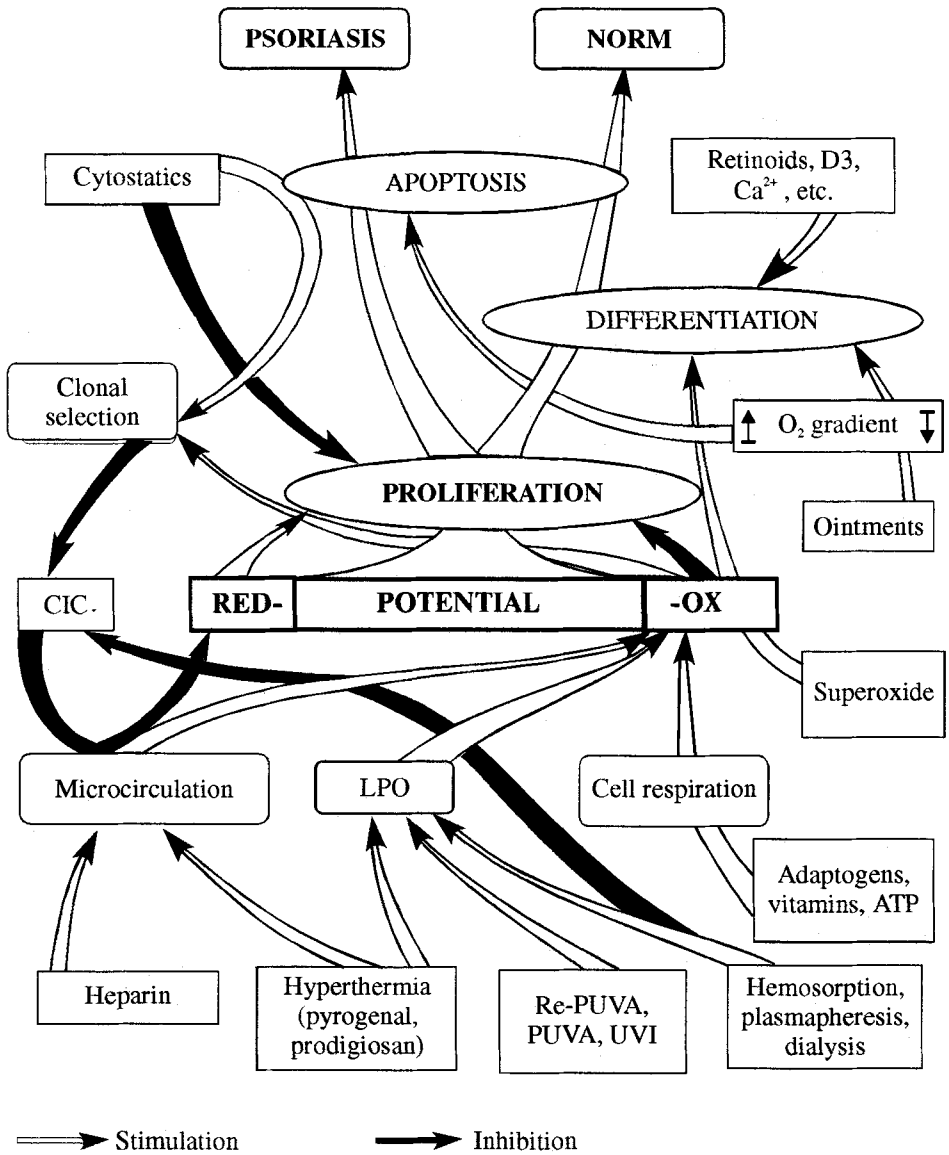

Fig. 2. Relationships between therapeutic methods and pathogenesis of psoriasis.

[33,34,37], and induction of some genes [18,43]. ROS were shown to participate as second messengers in the activation of apoptotic genes c-*mis* and c-*fos* [20]. $O_2^{\bullet}$ and H_2O_2 are involved in the activation of genes encoding a number of cytokines [22]. NO and CO bind to the heme site of guanylate cyclase and modulate the synthesis of cGMP, an important component of intra- and extracellular communcations [23,34,42].

A number of pathological conditions and diseases are accompanied by enhanced lipid peroxidation (LPO) and ROS formation [1]. However, psoriasis is a unique pathology characterized by a low LPO level. Our previous experiments revealed low levels of blood lipoprotein hydroperoxides and exhaled pentane in patients with psoriasis and LPO activation during extracorporal phototherapy [13,14]. A certain level of LPO activation (near or above normal), corresponded to clinical effects of phototherapy (regression and disappearance of psoriatic plaques).

Although the low intensity of LPO is indicative of high efficiency of the antioxidant protective systems in patients with psoriasis, it should be considered as a pathological shift. This is confirmed by the data on enhanced synthesis of antiapoptotic protein *Bcl-*x_L [44], which also possesses antioxidant properties [28]. The low level of LPO in psoriasis determines structural plasticity of cell membranes and permanent readiness to proliferation [11,12].

We think that conditions triggering differentiation and apoptosis in the upper epidermal layers are the keys to understanding the pathogenesis of psoriasis. They are determined by a variety of stimuli addressed to a cell [41], as well as by cell readiness to perceive signals, the time and intensity of stimuli, and redox potential of the extracellular space [3,18,28].

Since unique architectonics of the skin was formed during evolution in oxygen atmosphere, we assume that oxygen not only stimulates differentiation, but also triggers programmed death of epidermal cells.

It should be noted that the difference in partial oxygen pressure (Po_2) between the horny (158 mm Hg) and basal cell (below 20 mm Hg) layers is a necessary condition for cell proliferation [11]. Therefore, Po_2 increases almost 8-fold throughout the thickness of 10-12 epidermal cell layers. Insolation of the epidermis is accompanied by ROS formation. While moving from the basal to granular layer (the last layer of the germinative Malpighian layer), keratinocyte is exposed to increasing pressure of atmospheric oxygen and ROS, which inhibit proliferation and trigger cell differentiation (the necessity of other differentiation factors cannot be excluded). Apoptosis is triggered, when epidermal cells come into the clear layer, a layer with a still higher Po_2.

In psoriasis, under conditions of low LPO and inflammation, enhanced repair processes are accompanied by a dramatic shift in the redox potential [11,13] and intense proliferation: rapidly growing keratinocytes skip the differentiation zone and come into the zone with apoptotic oxygen regimen with a great number of apoptotic receptors *Fas* [45] and *p53* [40]. Oxidative stress-induced transition of the granular layer cells to apoptosis results in the formation of defective horny layer, the key mechanism of psoriatic process determining the pattern of skin damage and the possibility of generalization and chronization of the disease.

Current data on the impairment of the immune system in psoriasis [9,10] suggest the involvement of autoimmune processes in its pathogenesis. Elevated serum content of circulating immune complexes in patients with psoriasis correlates with the duration and severity of the disease. Excoriations, scratches, and microinjuries cause inflammatory reactions followed by healing. Inflammation associated with activated proteolysis and intense proliferation unmasks latent antigens on skin cells [2]. Repeated contacts with latent antigens activate the synthesis of autoantibodies. On the other hand, the low intensity of LPO in patients with psoriasis [13,14] and the involvement of ROS in the realization of apoptosis [16,18,38] attest to impaired immunological control over cell clones responsible for autoantibody synthesis (normally these clones are eliminated). This vicious circle promotes the generalization of the psoriatic process.

The deposition of immune complexes in the vascular wall in the papillary layer of the dermis and epidermis and binding of complement components lead to the release of inflammatory mediators, initiation of inflammatory reactions, and leukocyte activation. Intensive local inflammatory reactions result in the formation of Munro—Sabouraud microabscesses and local hypoxia followed by further decrease in the redox potential and stimulation of proliferation [11,13, 14]. This local posttraumatic hypoxia occurring under conditions of a redox shift and overexpression of apoptotic receptors accounts for the appearance of new psoriatic elements (Koebner phenomenon) on apparently healthy skin.

In the proposed scheme (Fig. 1) we brought together all currently known disturbances involved in the pathogenesis of psoriasis.

The current concept of psoriasis considers this disease as a genotypic multifactorial dermatosis with incomplete gene penetration [5]. It was shown that the histocompatibility antigens B13 and B17 correlate with skin manifestations, while B17+B27+B35+B40 complex correlates with skin manifestations in combination with arthritis. On the other hand, the low intensity of LPO is provided by activity of gene-controlled antioxidant enzyme and nonenzyme systems [4]. It can be suggested that the high level of antioxidant protection in psoriasis is a genetically determined metabolic characteristic providing its possesser with some advantages, for instance, survival after dramatic increase in background radiation. Another genetic factor is activity of genes encoding apoptotic receptor *Fas* and antiapoptotic proteins *Bcl-2* and *Bcl-*x_L [17,24, 29,35,45].

Changes in LPO and disturbances in apoptosis affect clonal selection of cells producing autoantibodies. On the other hand, the adaptive activation antioxidant protection during infectious diseases and vaccinations accounts for provocation of psoriasis. These phenomena constitute the basis for the infectious and immunological concept of psoriasis [2].

The neuroendocrine concept [8] associates the development of psoriasis with emotional and autonomic disturbances, in particular with the involvement of the pituitary-adrenal system in the regulation of stress and inflammation, and possible hormonal regulation of apoptosis [7].

We hope that the proposed concept of the etiology and pathogenesis of psoriasis will stimulate the search for new efficient methods of its therapy.

The processes determining the pathogenesis of psoriasis and the targets for the most common therapeutic methods are presented in Fig. 2. Undoubtedly, the efficacy of treatment correlates with shifts in the redox potential (the principal index of a skin redox state) caused by this treatment. For instance, the therapeutic effect hemosorption therapy is associated with the sorption of psoriatic material, *i. e.* toxic medium-molecular-weight peptides, and the normalization of serum protein spectrum [10]. However, hemosorption is accompanied by considerable LPO activation due to

damage to blood cell membranes, as evidenced by a sharp increase in serum chemiluminescence after hemosorption observed in our study [10]. The decrease in the level of circulating immune complexes during hemosorption can also be attributed to activated oxidative processes, rather than their direct sorption. All these shifts improve microcirculation, activate respiration, and normalize tissue redox potential. In this connection, combined application of PUVA-therapy and hemosorption, modulating both skin redox potential and body antioxidant state gives a potent therapeutic effect [10].

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