INTRODUCTION

Skin is guardian of homeostasis in the face of varied environmental conditions. The constant renewal of keratinocytes provides protection as a barrier. External insults provoke protective mechanisms, particularly, inflammation. Removal of old cells occurs through biological process of apoptosis. There is a balance between keratinocyte renewal and apoptosis. The horny skin layer made of dead keratinocytes is protective against physical and chemical insults and desquamation sheds microbial contaminants.

THE PROCESS OF APOPTOSIS

Apoptosis is self-regulated cellular suicide controlled at the organ level [1,2]. This process proceeds in several stages. These include reception of apoptotic stimuli, transduction of signal to cell nucleus, activation of lethal or killer genes, and consequent transcription of specific apoptotic proteins. Finally, the endonucleases are activated causing breakdown of DNA. A number of internal as well as external factors control apoptosis. These include hormones, cytokines, antioxidants, reactive oxygen species (ROS), calcium ion fluxes (Ca2+), and different physical and chemical agents [3]. The influence of all these finds way through different signal transduction paths. Complex effects occur on phospholipase, sphingomyelin, tyrosine kinase, and protein kinase pathways that are regulating proliferation and differentiation of keratinocytes.

Oxidative stress is important in modulation of apoptosis [4-8]. Apoptosis is predominantly a gene regulated process with specific provoking [9-11] and blocking [12-14] determinants.

Higher expression of both the apoptotic signal receptors Fas and the anti-apoptotic proteins Bcl-x in skin is demonstrated in psoriasis [8]. This indicates the disturbance in differentiation and programming in apoptosis [15]. In addition, other apoptotic proteins and proliferation molecules are increased in expression in the disease [16]. Psoriasis accompanies activation of apoptotic genes Fas and p53 and anti-apoptotic protective Bcl2, Bcl, and Ki67 systems. Metabolic state of keratinocytes is a more responsive to apoptotic signals, through finite mechanism are not yet defined. The process of apoptosis is nevertheless, closely linked to the redox balance in the tissue [7].

KERATINOCYTE HYPERPROLIFERATION

ROS have high reactivity and short life span. They involved in local regulation of proliferation [6,12] vascular tone [17] and induction of specific genes [18]. ROS also participate as second messengers in activating apoptotic genes [5]. Several genes encoding cytokines are activated [4]. Synthesis of cyclic guanosine monophosphate, an important component of intra and extracellular communications is modulated by nitric oxide and carbon monoxide, functioning in tandem with the ROS [17-20].

Enhanced formation of ROS and lipid peroxidation (LPO) is implicated in pathogenesis of variety of diseases, but psoriasis uniquely exhibits low level of LPO. Such state of cell membranes favors ready proliferation. Enhanced synthesis of antioxidant and anti-apoptotic Bcl-x proteins [8,21] may support pathologic shift toward hyperproliferation of keratinocytes, seen in the disease. Conditions triggering differentiation and apoptosis in superficial keratinocytes hold key to pathogenesis of psoriasis and variety of stimuli have a determinant role [3]. Equally the keratinocyte readiness to perceive signals and the antioxidant extracellular milieu [7,21] are important.

Skin evolved in environment of oxygen which naturally impact [5] processes of development, maturation and death of keratinocytes, by continuous exposure to free environment. In psoriasis, keratinocytes grow rapidly within inflammatory environment and low LPO profile. This cuts short the proper differentiation or maturation events. Rapidly the cells face oxidative stress with an expression of apoptotic receptors Fas [15] and p53 [16]. Oxidative stress induced apoptosis of the granular layer cells results in the formation of defective horny layer; the key feature driving skin damage spread and chronicity of the disease.

Learning points
- Increased proliferation and apoptosis of keratinocytes is well known in psoriasis.
- It is increased sensitivity, mediated by metabolic effects and induced antioxidant enzymes that propels apoptosis in psoriasis. ROS are the obvious causal factors for such changes in psoriasis. They involve directly and also through various other secondary effective molecular processes crucial in hyper proliferation and apoptosis.
IMMUNE DYSFUNCTION

Current findings in psoriasis indicate to autoimmune pathogenesis. Elevated circulating immune complexes correlate duration and severity of the disease. Injuries by scratches provoke inflammation. Intense proliferation associating inflammation with activated proteolysis uncovers latent skin antigens liable to activating synthesis of autoantibodies. Normally, the lymphocyte clones engaging in synthesis of autoantibodies are eliminated by regulatory immune mechanism. The low LPO in psoriatic keratinocytes and ROS involved apoptosis impairs immunological regulatory mechanisms [22]. The vicious circle perpetuates to spread psoriasis lesions.

Inflammation and leukocyte activation are initiated with the release of inflammatory mediators following deposition of immune complexes and binding of complement components in cutaneous microvasculature. Intense inflammation results in local hypoxia and lower antioxidant profile further stimulating of keratinocyte proliferation.

Psoriasis represents a genotypic multifactorial dermatosis. Genes encoding apoptotic receptor Fas and anti-apoptotic Bcl, and Bcl proteins, as well as enzymatic and nonenzymatic antioxidant mechanisms are prominently at focus of psoriasis molecular biology [15,23,24]. Clonal selection of autoantibody-producing cells is affected by changes in LPO and disturbances in apoptosis. On the other hand, activation of antioxidant mechanisms in reaction to infection only aggravates psoriasis. The infectious and immunological concept of psoriasis is based on such revelations.

Learning points

\* Autoimmune mechanisms are believed to be involved in pathogenesis of psoriasis. The current therapies attempt to control their effects and effectors but not the causal factors. 
\* ROS are linked to autoimmunity by exposing latent skin antigens as well as causing impairment of immune regulatory mechanisms. They have major causal relation to autoimmunity in psoriasis.

NEURO-ENDOCRINE DISORDER

The development of psoriasis with emotional and autonomic disturbances calls attention to role of Neuroendocrine mechanisms in pathogenesis. The pituitary-adrenal system has intricate role in the regulation of stress responses and inflammation [25]. The process of apoptosis is subject to hormonal influences and its disorder is crucial in the pathogenesis of psoriasis. This is confounded by psychophysiological disruptions consequent to stigma [26,27] and an impact of adverse personal habits [28]. Subtle impacts of the neuroendocrine disturbances may compromise microcirculation in skin hypoxia triggers paracrine mechanisms aggravating pathology with major involvement of ROS [29,30].

Learning points

\* Stress is well known to associate with and aggravate psoriasis.
\* The neuro-endocrine activity of stress affects microcirculation and is trigger to pathogenic mechanisms involving major role of oxidative stress.

INTERPLAY OF ROS, ANTIOXIDANTS AND CYTOKINES

Redox state (i.e., the balance between pro and anti-oxidant activities) of cells is regulator of fundamental process as signal transduction, gene expression, inflammation, and apoptosis [31,32]. Among the bio-molecules generated by influence of oxidative stress, cytokines are the major regulators of immune responses and are involved in driving inflammation, carcinogenesis, and apoptosis [33,34]. Antioxidant defense includes enzymes and low molecular compounds. Enzymes are superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. Low molecular antioxidants are glutathione, contributing to recycling of other oxidized antioxidants, uric acid, ascorbic acid, and lipid soluble α-tocopherol. Keratinocytes produce some cytokines physiologically but can be induced to produce and release pro-inflammatory cytokines that involve ROS as mediators [35]. Among the multiple cytokines produced, interleukin 1β and tumor necrosis factor-α (TNF-α) are known to induce cellular production of ROS. The relationship between the redox state and cytokines has a key role in cutaneous pathophysiology via cellular pathways. These pathways contain phosphorylation and gene expression which are mediated mainly by NFκB, nitric oxide radicals and proteins kinases [36].

The redox state and cytokines play a major role in redox cutaneous homeostasis and interference in ROS-induced immune modulation can associate immune disorder of skin [37]. Since antioxidant imbalance is implicated in the pathogenesis of inflammatory skin disease, supplementation of antioxidants appeals as a rational approach to restore homeostasis. Pro-inflammatory cytokines interleukin-8, TNF-α, and interferon-γ produced in excess from psoriatic keratinocytes also promote inducible nitric oxide synthase expression in the cell [38]. Under influence of the stated cytokines, the enzyme produces nitric oxide radicals which play a key role in recruiting T-lymphocytes and neutrophils. The immune-mediated inflammation is thus established and perpetuated.

PROSPECTS FOR PROTECTIVE/AMELIORATIVE DIETETICS

The dietetic perspectives based on contemporary understanding were earlier reviewed [36]. Psoriasis has distinct pathogenesis yet bears strong association with co-morbidity of metabolic syndrome [39]. This has to be based on the causative elements of metabolic syndrome and psoriasis sharing inflammation as feature [40]. There are reports of benefit of fasting and calories restriction in psoriasis also [41]. The specific dietetic perspective need to adapt to the same concerns that envisage advances in future psoriasis therapy [42]. There is need to develop phenotypic understanding toward refining preventive and ameliorative strategies in drugs and dietetic management. Focus is to be on bioregulatory agents that only check aberrant and not normal immune/inflammatory and proliferative function. These should target signaling pathways, regulate balance of lymphocyte subset functions, specifically counter aggressive cytokines, and mediators of various facets in disease pathogenesis.

The inflammatory triggers release arachidonic acid from membrane phospholipids to generate 2-carbon series of potent inflammatory eicosanoid mediators. Meat products are rich in arachidonic acid. Mixed vegetable oils and sunflower oil contribute to linoleic acid consumption which gets converted to arachidonic acid. Monounsaturated fat, e.g., olive oil consumption avoids this. The omega-3 fats and gamma linolenic acid produce 1 and 3 carbon anti-inflammatory eicosanoids. Omega-3 fat Eicosapentaenoic acid is available in fish oil and cold water fish. Flax seed provides alfa-linolenic acid that gets converted to the eicosapentaenoic acid. Borage seed oil, black current oil, evening prim rose oil all promote 1-C series eicosanoid synthesis [43-46].

Antioxidant micronutrients as vitamin C, vitamin E, selenium, beta-carotene, etc., as well as vitamin B6, especially B6 and magnesium, selenium, serve as cofactors and coenzymes to enhance synthesis of the anti-inflammatory 1-C and 3-C series eicosanoids. These also to an extent disrupt inflammatory processes provoked by cytokine TNF-α [47].

Bioactive compounds in many herbs are directly inhibitory to enzymes cyclo-oxygenase and lipoxygenases which make inflammatory 2-C
series eicosanoids from arachidonic acid. Such usefulness is seen with curcumin, ginger, boswellic, white willow, etc., all of which are edible [48–50].

Inflammatory cytokines, e.g., TNF-α activate transcription factor NF-κB which then upregulates genes coding inflammatory proteins and hyperproliferative mediators as interleukins-1, 6, 8, etc. Natural agents as curcumin, quercetin, vitamin B, and catechins can downregulate TNF-α and NF-κB in over activated inflammatory cells as macrophages, without affecting blissfully, the normal level inflammatory capability. The effect is uniquely bioregulatory. Again the stated bioactive agents are easily available from edible plant resource. Reishi mushrooms and astragulus are very effective too [51].

Vitamin D has unique role to benefit immune-mediated inflammatory state by promoting formation of anti-inflammatory cytokines interleukin 4 and anti-inflammatory peptides, again exhibiting bioregulatory effect [52]. Folate is found to be particularly scavenger of peroxynitrite radicals, so important in psoriatic inflammation [53].

Prebiotics and probiotics exert a significant immunomodulatory effect as well [54–55]. The reports emphasize crucial need improve micronutrients in diet. This may summarily be helped by increasing consumption of fruits, nuts, seeds, non-starchy vegetables, and fish. Cruciferous vegetables are particularly protective. On the contrary above information suggests need to avoid excess dairy products, meat consumption, sugary refined foods and drinks. Very prudent is to give up alcohol and smoking.

**Learning points**
- Dietary items are known to have pro- and anti-inflammatory potentials and in psoriasis anti-inflammatory foods are preferable while pro-inflammatory food is avoidable.
- There are evolutionary and biochemical/immunological bases of choosing from available dietary options. The role of dietary factors in epigenome function is crucial to appreciate and consider in individual cases.
- The micronutrient balanced or enriched nutrition is suggestive of critical significance in management and prevention of psoriasis.
- Convergence with dietetic selection and application is integral to rational psoriasis management.

**EPILOGUE**
Traditionally, the topical agents as corticosteroids, retinoids, and vitamin D analogs, systemic methotrexate, ciclosporin, and retinoids as well as phototherapy form therapeutic means. Their inconvenience and adverse effects compromise the adherence to and success of therapy, particularly in early mild disease. The immunologicals developed through biotechnology advances are visibly too slow to find favor in dermatology practice at large. There is interest in immune-modulatory – anti-inflammatory less toxic and acceptable oral agents such as furamate [56], cannabinoids, alepapironol, and loratadine [57] and new class of the phosphodiesterase-4 inhibitors [58]. The overview of events in psoriasis pathogenesis reveals the significance of resting derailed index of cutaneous redox state for therapeutic rationale. Such a shift would reduce inflammation and improve microcirculation and proper tissue respiration, reducing risk of vascular endothelial growth factor production, which appears to be important in persistence and spread of psoriatic skin lesion [59]. Modern emphasis of evolving systems approach is on attempting personalized therapeutics [60]. The technical aids for the same are only developing. High and low responders to oxidative stress may involve genetic determinants but also nutrition shall answer such challenge. The advances in understanding on protective nutrients and harmful nutrients are impressive and represent very logical intervention to comprehensive rational management of psoriasis.

**REFERENCES**