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An Overview of Psoriasis with Respect to its Protein Targets

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Abstract:

Psoriasis, a form of over-active wound healing response, is relatively common, chronic, inflammatory and hypersensitive disease of unsolved pathogenesis affecting skin and joints in 2-3% of the general population. At the cellular level, psoriasis is characterized by markedly increased epidermal proliferation and incomplete differentiation, elongation, dilatation and "leakiness" of the superficial plexus of dermal capillaries, and a mixed inflammatory and immune cell infiltrate of the epidermis and papillary dermis. Psoriasis is a skin disease driven by immune system which starts below the skin's surface and cause severe pain and adverse mental health effects. Our present study is an attempt to compile all most of the possible protein targets known so far for the treatment of psoriasis. The identified proteins are STAT3, Wnt5, Endothelin-1, enzyme - alpha secretase, S100 proteins, p53, Serum Response Factor, HSP70 and Bcl-x.

Introduction

Psoriasis comprises red, scaly patches of skin, which usually have very well defined edges, appear covered by silvery flaky surface [1]. These patches, which are sometimes referred to as plaques, usually itch or feel sore. The redness is explained by impressive growth and dilation of superficial blood vessels [2]. They most often occur on the elbows, knees, other parts of legs, scalp, lower back, face, palms, and soles of the feet, but they can occur on skin anywhere on the body [3]. The disease may also affect the fingernails, the toenails, and the soft tissues of the genitals and inside the mouth [4]. It is often symmetrical, affecting both sides of the

body. Psoriasis is often so mild it is barely noticed by the affected person, but it can occasionally be so severe that the patient must be admitted to hospital for treatment. The disease occurs in all age groups, primarily affecting adults. The most common ages for psoriasis to first appear are in the late teens and in the 50s. It affects men and women equally, although in children, girls are more commonly affected than boys [5]. Being characterized as dermatological disease, psoriasis is a non-contagious lifelong skin disease and also not an outcome of poor hygiene. Unfortunately it is often overlooked or dismissed because it is not typically life threatening [6].

Depending on the variability in morphology, distribution, severity and cause, they are divided into different types. Some can occur independently or at the same time as other variants, or one may follow another. Most common is the plaque psoriasis which starts off in small areas, then gradually enlarge and develop thick, dry plaque. They usually appear symmetrically, that is, in the same areas on opposite sides of the body. Eventually separate patches may join together to form larger areas as the disorder develops. In some cases, the patches can become very large and cover wide areas of the back or chest (known as geographic plaques because they resemble maps). Plaque psoriasis persists for long periods. Gutate psoriasis, from the Greek word "gutta" meaning droplet, includes teardrop-shaped patches 1-10 mm in diameter, usually distributed on the trunk and often on the extremities but can also occur on the head [7]. Gutate psoriasis can also develop in patients who have already had another form of psoriasis. Pustular psoriasis is characterized by white, sterile pustules surrounded by red skin. It tends to follow a cycle-reddening of the skin followed by formation of pustules and scaling. The pus consists of white blood cells. There are two types of pustular psoriasis, generalized pustular psoriasis (von Zumbusch) and palmo-plantar pustulosis (PPP). Generalized pustular psoriasis is rare and represents active, unstable disease. This form is very widespread and the eruptions often occur in repeated waves lasting days or weeks. PPP causes pustules on the palms and soles; it is uncertain whether it really is a form of psoriasis [8].

Inverse psoriasis is morphologically distinct from traditional plaques. It affects the flexures, particularly the armpits, the groin and under the breasts. Flexural lesions are devoid of scales and appear as red, shiny, well demarcated plaques. Erythroderma is a scaling, itching, inflammatory process that involves all or almost the entire body surface. It may either arise from chronic plaque which progresses, becoming confluent and extensive, or it may be a manifestation of unstable psoriasis precipitated by infection, drugs, stress or withdrawal of corticosteroids. Erythrodermic psoriasis can impair thermoregulation of the skin, leading to hypothermia; it can change metabolism due to loss of keratin, iron and folic acid during the profuse scaling and it can cause edema, especially around the ankles. Nail psoriasis is seen in 40-45 % of skin psoriasis patients; the commonest finding is small pits in the nail plate. The nail may also detach from the bed at its distal or lateral attachments, known as onycholysis. Psoriatic nails also often exhibit yellow-brown discoloration and are deformed and

thickened [9]. Psoriatic arthritis is a joint disease core common among patients with arithritis [10]. Other types of psoriasis include flexural psoriasis; characterized by smooth well-defined patches in body folds, scalp psoriasis; one or more scaly plaques in the scalp, sebopsoriasis, which is characterized by an overlap of seborrheic dermatitis and psoriasis, affects scalp, face, ears and chest, intraoral psoriasis which includes desquamation inside the mouth, most often associated with the more severe forms of cutaneous psoriasis, Koebnerised psoriasis which arises in healing wounds or scars and photosensitive psoriasis affecting sun-exposed skin.

Targets for Psoriasis

Signal Transducer and Activator of Transcription 3 (STAT3): [fig1]

It is a protein involved in transmitting extracellular signals to the nucleus, is crucial to the development of the skin disease psoriasis [11]. STAT proteins transmit signals from cytokines or growth factors that have cell-surface receptors associated with tyrosine kinase activity. Kinases, such as members of the Janus kinase family or SRC family, phosphorylate these receptors and provide docking sites for inactive STAT monomers, which are in turn phosphorylated and form activated dimers. Activated STATS move to the nucleus and are involved in regulating many genes that control fundamental biological process including apoptosis, cell proliferation and immune responses [12]. Blocking the function of STAT3 using antisense oligo-nucleotides inhibited the onset of, and reversed, established psoriatic lesions. Further analysis revealed a dual requirement of both activated STAT3 in keratinocytes as well as in T cells, indicating that the pathogenesis of psoriasis is rooted in a co-operative process involving STAT3-regulated genes in both skin cells and the immune system [13]. Another study revealed that phosphotyrosyl peptides block STAT3-mediated DNA binding activity, gene regulation and cell transformation. To identify small molecule inhibitors of STAT3 the ability of STAT3 SH2 domain binding peptide PY*LKTK (Y* represents phosphorylation) to disrupt STAT3 activity in vitro has been investigated [14]. The presence of PY*LKTK, but not PYLKTK or PFLKTK, in nuclear extracts results in significant reduction in the levels of DNA binding activities of STAT3.

Wnt5a:

It is a member of the wingless-type patterning regulators important in pre-natal development. Wnt5 and its receptors fzd3, fzd5 as well as fzd6 are restricted to specific layers in normal epidermis, analogous to their zonal distribution in hair follicles, suggesting a role in adult skin differentiation [fig.2]. Wnt5a and fzd5 are both over expressed and re-distributed in the epidermis of psoriasis which involves disturbed keratinocytes differentiation. Functionally, Wnt5a lowers the concentration of IFN required to induce target genes, and increases the magnitude of IFN target gene induction, suggesting a molecular mechanism underlying IFN

hypersensitivity in psoriasis [15]. The marked over expression of Wnt5a and Fzd5 in psoriasis suggests that this ligand receptor pair may actively derive the chronic inflammatory and hyper-proliferative nature of this phenotype. This is supported by large number of evidences. First, Wnt5a induces IL-12 [16], which is central to psoriasis as indicated by therapeutic efficacy of antibodies targeted at IL-12 p40 and by the genetic association of IL-12 with psoriasis [17,18]. Second, Wnt5a itself is strongly induced by STAT3 [19], thereby acting as a potential effector molecule for psoriasis like skin disease seen in STAT3 over-expressing transgenic mice [20]. Wnt5a induces epithelial differentiation and stimulate endothelial cells proliferation; both are important elements in psoriasis. Wnt5a is unregulated in wound healing [21] and psoriasis lesions can classically be triggered by skin wounding. Wnt5a derived from endothelial signals through Fzd5 to induce the translocation of NFAT and subsequent induction of IL-2 in T-cells [22]. Wnt5a signaling in psoriasis may also be related to the activation of the nuclear hormone receptor. PPAR δ is identified as central mediator in psoriasis [15]. Thus, Wnt5a may synergize with IFN α to induce the expression of PPAR δ in activated T-lymphocytes [23]. Moreover, PPAR δ stimulates keratinocytes proliferation and in several biological processes acts by antagonizing another PPAR γ [24]. Wnt5a also represses PPAR γ trans-activation, thereby synergizing with PPAR δ functionally [25]. Conversely, PPAR γ inhibits STAT3 [26] which, when over expressed, induces Wnt5a and causes a psoriasis like phenotype in vivo [20].

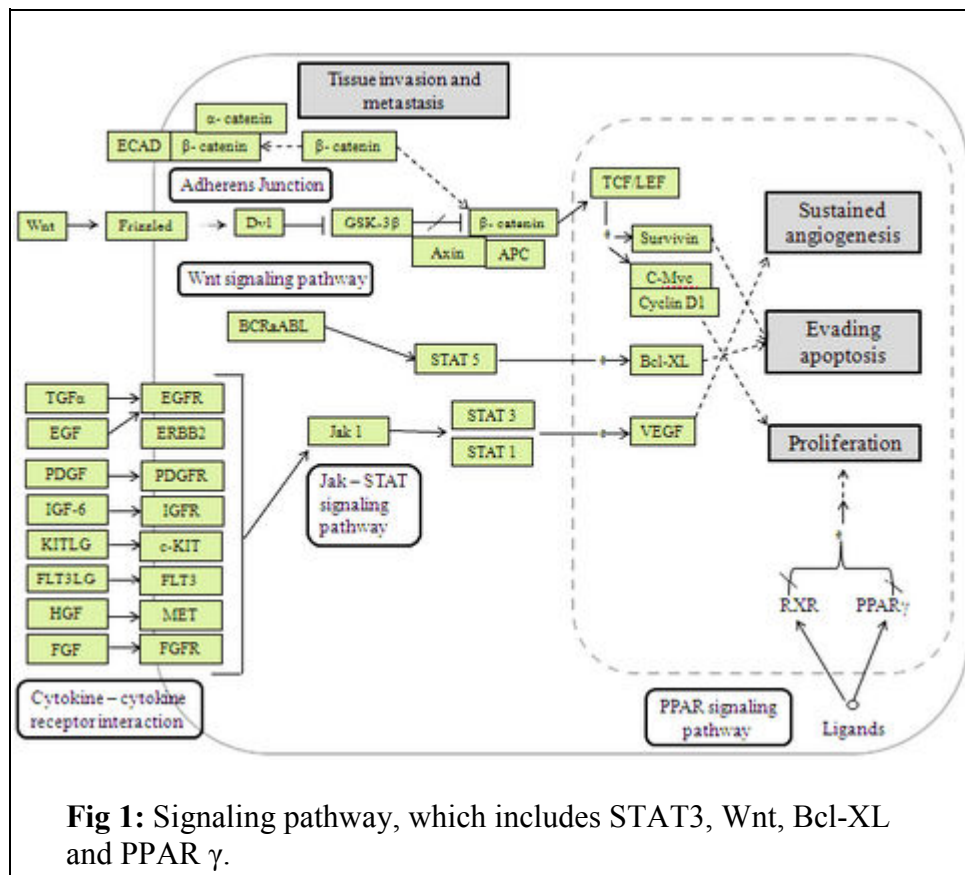
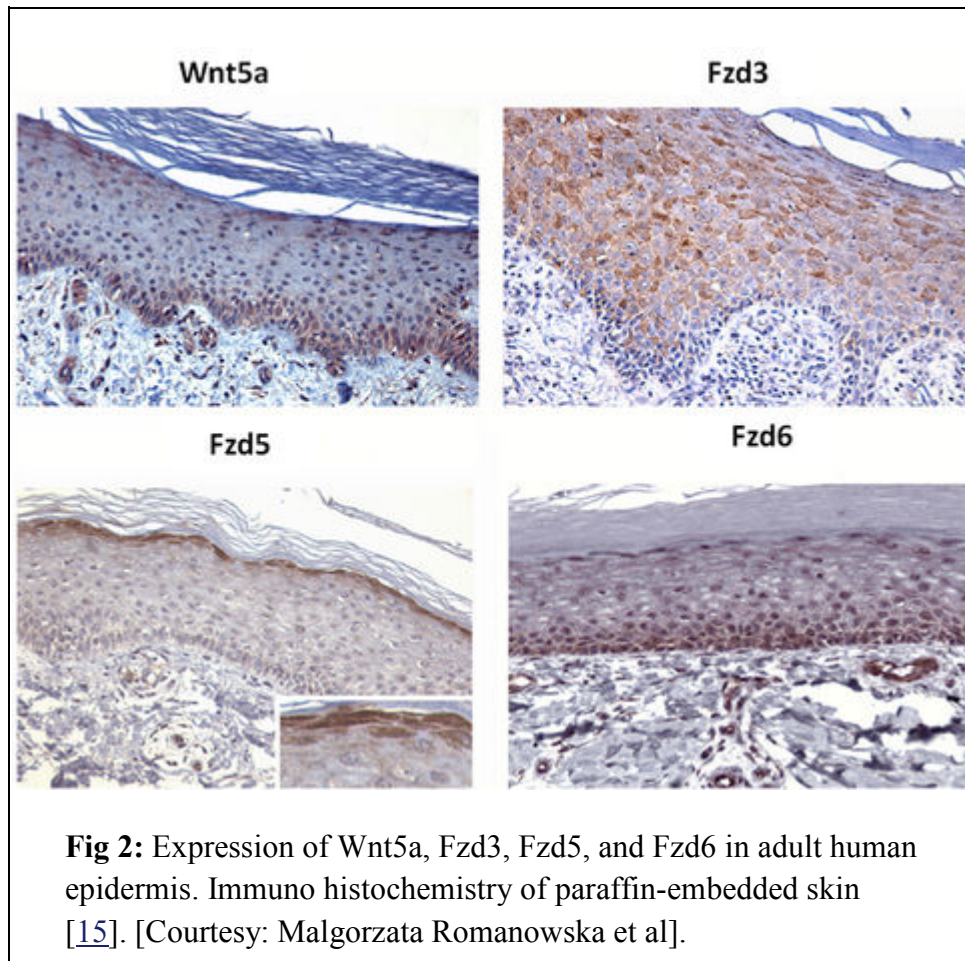


Fig 1: Signaling pathway, which includes STAT3, Wnt, Bcl-XL and PPAR γ .



Endothelin-1:

It could be one of the targets of psoriasis [27]. Endothelin (ET)-1 produced in keratinocytes acts through ETA receptor as an autocrine growth factor for these cells [28]. ETs are a family of three vasoactive peptides, termed ET-1, ET-2 and ET-3, which induce their biological actions through at least two major receptor subtypes that belong to the family of G-protein coupled receptors: a selective ETA receptor, which binds ET-1 and ET-2 with high affinity and ET-3 with low affinity, and a non-selective ETB receptor which binds all ET isopeptides with equal affinity. It has recently been reported that compounds that antagonize the action of ET-1 by blocking the ETA receptor may control the growth of tumor cells in which the ET-1 autocrine loop is up regulated [29,30]. High levels of ET-1 have been found in psoriatic skin and in the serum of patients with psoriasis [31,32]. Inflammatory cytokines such as interleukin-1 α increase the production of ET-1 that in turn may lead to the chronic stimulation of keratinocytes proliferation.

Enzyme blockers:

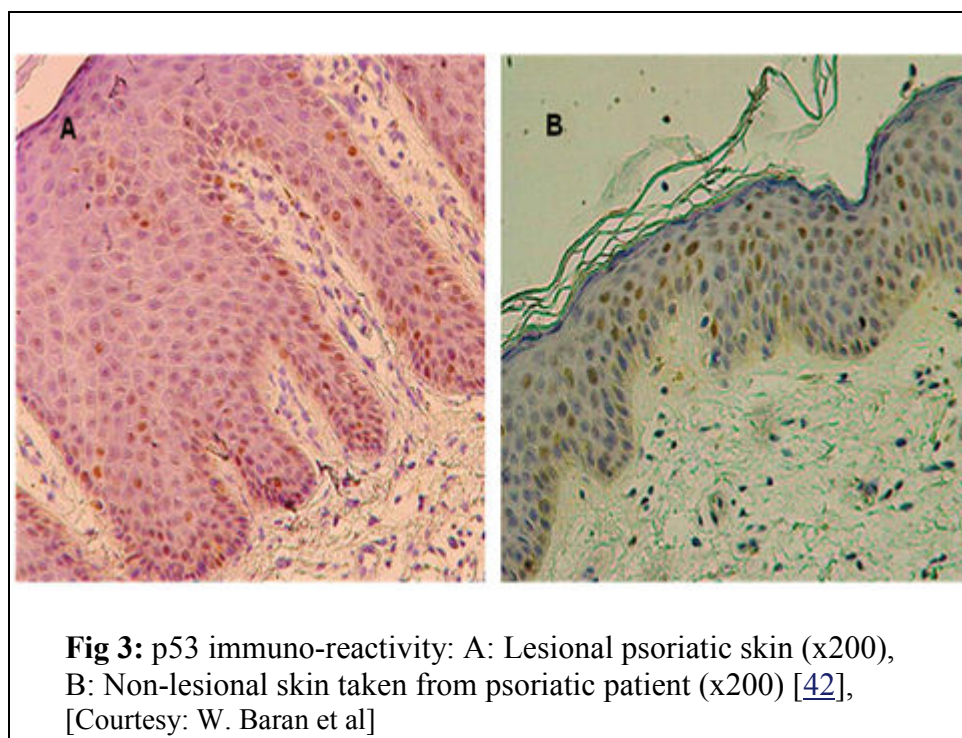
They could also be new psoriasis treatment. The keratinocytes produce an enzyme - alpha secretase - which cuts the APP down to size as sAPPa. After adding inhibitors, the team observed that the discharge of sAPPa was almost completely arrested in the cells of psoriasis patients. As a result, the greatly increased division rate of the keratinocytes dropped back to normal values, a reduction of 50 to 60 per cent [33].

S100 proteins:

They are calcium activated signaling proteins that interact with target proteins to modulate biological processes [34]. There are 18 identified S100 family proteins, thirteen S100 protein gene are located within the epidermal differentiation complex on human chromosome 1q21 [35]. Although eight S100 proteins are expressed in human epidermis [36], in psoriatic tissues S100A7, S100A8, S100A9 are markedly over expressed [37].

p53:

It is a phosphor-protein, which shows transcription factor-like properties [38], plays a central role in cell cycle regulation mechanisms and cell proliferation control. p53 protein acts as a "guardian" of the genome - its activation protects the organism from tumorigenesis. DNA damaging agents induce the activity of this protein, which leads to cell cycle arrest in the G1 or G2 phase and in the case of ineffective DNA repair apoptosis, is initiated [39]. Many genes, particularly oncogenes and tumor suppressor genes, could be involved in the deregulation of the cell-cycle (increased cell division), which is probably important in the development of psoriatic lesions [40,41]. In lesional psoriatic skin the count of p53 positive cells was significantly higher than in the skin samples taken from healthy individuals. p53 positive cells were located most commonly in the basal layer of the epidermis of both healthy skin and non-lesional psoriatic skin. In lesional psoriatic skin p53 positive cells were present in all layers of the epidermis [fig3] [42].



Protein SRF (Serum Response Factor):

It produced/ expressed in large amounts in normal healthy human skin cells (keratinocytes) and it maintains skin regulation. In psoriatic or wounded skin, SRF's are expressed at low levels. Without sufficient SRF, skin becomes dead i.e. skin divides excessively and no longer able to develop normally. As a result of their deficiency, the skeleton of the skin cells is disturbed and destroyed. The cells lose contact with their neighbours and the matrix that surrounds them. Consequently, the outer layer of skin loses its compact layering. Fissures form which enables water to evaporate more easily and the skin, dries out more quickly, thus making the intermediate spaces more susceptible to foreign bodies and bacteria. This in turn triggers an inflammatory reaction that induces the skin cells to divide and impairs their differentiation. Psoriasis patients lack SRF almost entirely. Triggers/factors that cause the down-regulation of SRF are still unknown. The suspects include other proteins, such as cytokines or other transcription factors [43].

Heat Shock Protein 70 (HSP70):

HSP represent a highly conserved class of molecules that increase during cellular stress response to a wide variety of stimuli. Based on molecular mass and sequence homology, HSPs are classified into families including ubiquitin, small HSPs of 20 to 28KDa, HSP60, HSP70 and HSP90. Antigenic sites of many pathogenic HSPs, particularly primary

target for B cell and T cell responses. In the HSP70 family are heat shocking cognate protein 70 (HSC70), which constitutively expressed during normal cell development and differentiation and the major heat or stress inducible protein HSP70 [fig4]. They are nuclear and cytoplasmic proteins exhibiting approximately 97% sequence homology and forming stable complex in stressed cells. HSP27, HSP60 and HSP70 and their ligands common HSP receptor CD91 have been reported to be increased in lesional psoriatic skin [44].

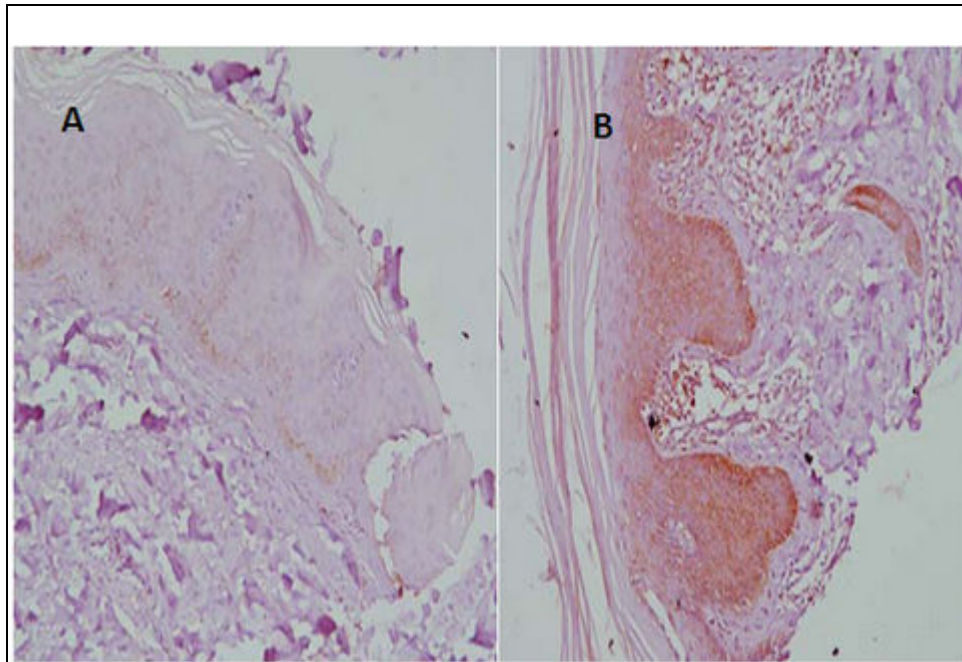


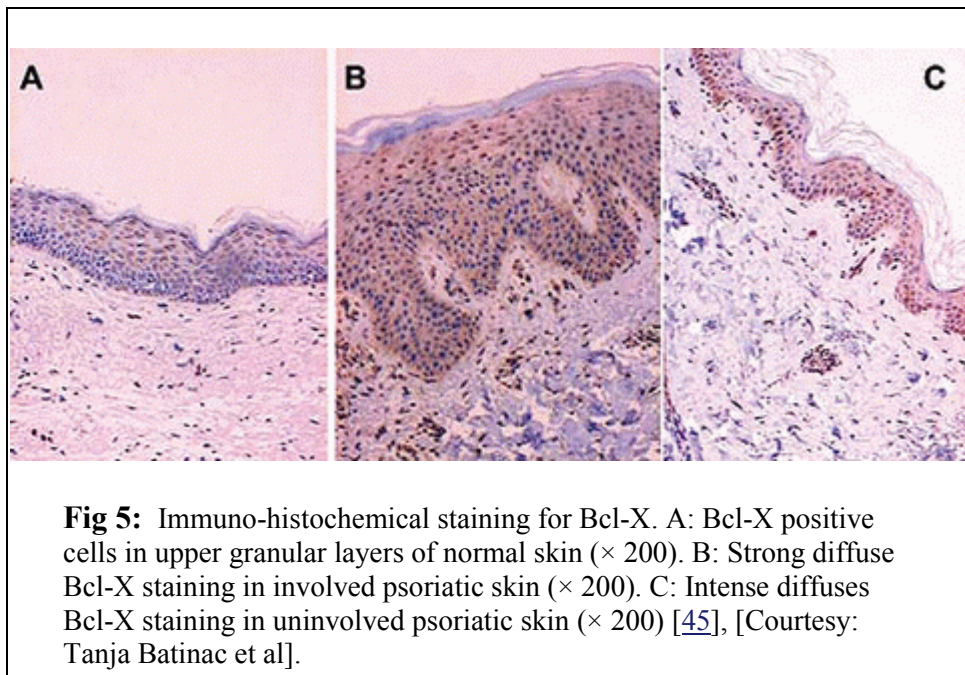
Fig 4:

A: Normal skin: light HSP70 immuno-staining in basal epidermal cell layer with negative immune-reactivity in supra-basal and superficial epidermal layers (immunoperoxidase X200),

B: Psoriasis vulgaris: intense HSP70 immuno-staining in basal and supra-basal epidermal cell layers with light superficial layer immuno-staining and dermal inflammatory infiltrate immune reactivity (immunoperoxidase X200). [44], [Courtesy: Amina Gamal el Din et al].

Bcl-2 family proteins:

Increased expression of Bcl-x protein is associated with psoriatic epidermal hyperplasia [fig5]. Strong Bax and Bak expression in involved psoriatic skin may probably have inhibitory mechanisms counteracting intensive proliferation [45].



Discussion

In this review, we have tried to extract the possible protein targets for psoriasis. As per the literature survey, all above discussed proteins i.e. STAT3, Wnt5, Endothelin-1, enzyme - alpha secretase, S100 proteins, p53, Serum Response Factor, HSP70 and Bcl-x have potential to serve as target for the treatment of psoriasis. By extensive review of number of research papers it seems that these proteins can play an important role in development of drug molecules which can prevent, mitigate and cure psoriasis.

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