Introduction

Psoriasis is a dermatologic autoimmune condition, linked significantly with social, functional, and psychological impairments.\(^1\) Plaque psoriasis (or psoriasis vulgaris) is the most common forms of psoriasis and causes painful itchy skin patches particularly on the lower back, elbows, knee, and also on scalp.\(^2\) Prevalence of this chronic inflammatory skin disorder is about 1–3% worldwide, and now, it is documented that it is gender or races independent as it appears on males and females equally and is seen in all races.\(^3\) Although it appears at any age of the patients, it mostly occurs between the ages of 15 and 20 or between 50 and 60 years.\(^3,4\) Psoriasis is often associated with numerous other disorders including psoriatic arthritis,\(^4,5\) and now, many dermatologist, rheumatologist, and scientist believe that both psoriasis and psoriatic arthritis underlying similar disease pathogenesis including abnormal functioning of stromal-immune cell and network of cytokines.\(^5,6\) Psoriatic arthritis is actually a form of chronic arthritis, where inflammation plays an important role in its onset, and it affects about 20% of total psoriasis patients.\(^5,6\) Importantly, it is observed that many individuals develop psoriasis first, and then, they were diagnosed as psoriatic arthritis, but often pain in the joints occurs before the appearance of psoriatic skin lesions.\(^5,6\) Psoriatic arthritis diagnosis is somewhat easy due to the appearance of psoriatic lesions with joint pain; however, it can also be diagnosed through joints deformities such as joints swelling, erythrocyte sedimentation rate, and duration of arthritis.\(^5-7\)

Role of pro-inflammatory mediator’s particular proinflammatory cytokines is well documented in the
induction of dermatologic inflammation in patients with plaque psoriasis and psoriatic arthritis.\textsuperscript{[5-7]} As tumor necrosis factor (TNF-α) is well known to induce the expression of various other pro-inflammatory mediators and various other pro-inflammatory activities which further induces inflammatory network in the psoriatic lesions. Furthermore, anti-TNF-α therapy was found to be an effective treatment for plaque psoriasis and psoriatic arthritis patients\textsuperscript{[8,9]} that showed clear evidence for the participation of inflammation in the induction of dermatologic inflammation in these psoriatic patients. Moreover, excessive expression of interleukin (IL-15) has also been reported in psoriatic skin and psoriatic arthritic synovium, and its blockade caused considerable reduction of inflammation in psoriatic lesions.\textsuperscript{[5,10]} Not only have these abnormal functioning of IL-1β, IL-6, IL-17, IFN-γ, IL-22 and IL-8 but also CXCL2 has been documented in psoriatic skin and synovium of these psoriatic patients, which give solid evidence for the involvement of inflammation in patients with plaque psoriasis and psoriatic arthritis.\textsuperscript{[5-11]}

Recently, the role of IL-32 has been discovered in a number of pathological conditions such as rheumatoid arthritis, gastric cancer, and pulmonary tuberculosis and also in many dermatological conditions including atopic dermatitis, leishmaniasis, systemic lupus erythematosus, and hidradenitis suppurativa.\textsuperscript{[12-23]} Moreover, its role has also been demonstrated in skin biopsies of psoriasis patients.\textsuperscript{[23]} Now, it is somewhat established that IL-32 exhibits pro-inflammatory features in many cell types.\textsuperscript{[24,25]} As, it induces the excessive production of TNF-α, IL-1β, IL-6, INF-γ, and IL-8.\textsuperscript{[12-25]} Nuclear factor kappa B (NF-κB) is a well-known inflammatory cell signaling event that plays a crucial role in the abnormal regulation and excessive production of numerous pro-inflammatory mediators including pro-inflammatory cytokines, chemokine, matrix metalloproteinase (MMPs), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) which have direct association with the disease pathogenesis.\textsuperscript{[26-31]} Role of NF-κB has already been well described in various human disorders ranging from arthritis to cancer,\textsuperscript{[26-28]} and now, NF-κB has now well considered as a therapeutic target in almost all inflammatory disorders.\textsuperscript{[26,27,32]} In this study, we hypothesized that overexpression of IL-32 in peripheral blood of psoriasis and psoriatic arthritis leads to increase inflammation which may be through activation of NF-κB signaling events. To assess this hypothesis and to establish an inflammatory link between IL-32/NF-κB and psoriasis and/or psoriatic arthritis, we examined the levels of IL-32 in the plasma samples of plaque psoriasis and psoriatic arthritis and also analyze the levels of activated NF-κBp65 in the peripheral blood mononuclear cells (PBMCs) of these psoriatic patients. Our results not only support an association between inflammation and plaque psoriasis or psoriatic arthritis but also pointed out that IL-32 and NF-κB might be important biomarkers for evaluation of inflammation in these psoriatic patients.

**Table 1:** Demographic details of studied subjects

| Parameters          | Psoriasis patients | NHS         |
|---------------------|--------------------|-------------|
| Clinical type       | PP                 | PA          | -           |
| Number of subjects  | 19                 | 11          | 22          |
| Age (years)         | 29.6±9.39          | 47.6±12.3   | 27.72±7.87  |
| Sex                 | Male (%): 10.19 (52.6) | 6.11 (54.5) | 09.22 (40.9) |
|                     | Female (%): 09.19 (47.4) | 5.11 (45.4) | 13.22 (59.1) |

Values in parenthesis represent percentage. NHS: Normal human subjects, PP: Plaque psoriasis, PA: Psoriatic arthritis, SD: Standard deviation
Cruz Biotechnology) was added to each well. This enzyme-substrate reaction was terminated after 15 min by 2M H$_2$SO$_4$, and optical density was measured at 405 nm using an automatic microplate reader (Anthos Zenyth 3100, Salzburg, Austria).

**Preparation of PBMCs and NF-κB activity assays**

Blood samples from plaque psoriasis and psoriatic arthritis patients and also from healthy humans were collected in ethylenediaminetetraacetic acid-treated tube (Thermo Fisher Scientific, IL, USA), and PBMCs were isolated by standard Ficoll density-gradient centrifugation using Histopaque-1077 reagent (catalog # 10771; Sigma-Aldrich) as described previously.[36] Total PBMCs cell lysates were prepared using the pierce RIPA cell lysis buffer (catalog #8990, Thermo Fisher Scientific) as described previously.[37] Activated NF-κB was determined in the PBMCs cell lysates using a highly sensitive NF-κBp65 transcription factor assay kit (catalog # ab133128, Abcam) as described previously.[38]

**Results**

**Levels of IL-32 in plasma samples of patients with plaque psoriasis and psoriatic arthritis**

In an attempt to investigate the role of IL-32 in psoriasis and psoriatic arthritis patients, the levels of IL-32 were determined in plasma samples of these psoriatic patients by human IL-32 specific sandwich ELISAs. Results showed that of 19 plaque psoriatic patients, ten patients showed significantly higher IL-32 levels in their plasma as compared to the IL-32 levels in the plasma of 22 normal healthy subjects ($P < 0.05$), whereas of 11 tested psoriatic arthritic patients, five patients showed significantly higher IL-32 levels in their plasma as compared with the levels of IL-32 present in the plasma of healthy human controls ($P < 0.05$). The average normalized OD units ($\pm$) SD of IL-32 levels in patients with plaque psoriasis, psoriatic arthritis, and normal healthy subjects were 0.079 $\pm$ 0.03, 0.127 $\pm$ 0.12, and 0.035 $\pm$ 0.010, respectively [Figure 1].

**Levels of activated NF-κBp65 in PBMCs from plaque psoriasis and psoriatic arthritis patients**

To investigate the mechanism responsible for the upregulation of IL-32 expression in patients with psoriasis and psoriatic arthritis, we examined the effect of NF-κB activation by estimating levels of NF-κBp65 in the PBMCs lysates using NF-κB transcription factor-specific assays kit. Levels of activated NF-κBp65 in PBMCs of plaque psoriasis and psoriatic arthritis were found to be significantly higher as compared with the levels of activated NF-κBp65 in PBMCs of normal human subjects ($P < 0.001$). The average normalized OD units ($\pm$) SD of activated NF-κBp65 levels in PBMCs from patients with plaque psoriasis, psoriatic arthritis, and normal healthy subjects were 0.2687 $\pm$ 0.071, 0.3073 $\pm$ 0.096, and 0.0780 $\pm$ 0.024, respectively [Figure 2]. These results may suggest that activation and DNA binding activity of NF-κB might have correlation with the upregulation of IL-32 expression in these psoriatic patients, but longitudinal studies are needed to show whether elevated levels of IL-32 in these patients are associated with the activation of NF-κB transcription factor.

**Discussion**

This study determined the role of IL-32 and NF-κB signaling events in plaque psoriasis and psoriatic arthritis. In the past decade, it is clear that abnormalities of skin and joints are well correlated not only with psoriatic arthritic patients but also with plaque psoriatic patients, which affect significantly patients’ quality of life.[1,5,6] Despite advances in modern molecular approaches, still, etiologies of these psoriatic disorders are not completely understood; however, numerous studies suggest that inflammation is one of the responsible
factors, directly associated with the pathogenesis of plaque psoriasis and psoriatic arthritis.\(^\text{[4-9]}\) In plaque psoriasis, the role of inflammatory cytokines such as TNF-\(\alpha\), IL-1\(\beta\), IL-6, and INF-\(\gamma\) is well defined.\(^\text{[2-10]}\) These pro-inflammatory cytokines are also involved in the activation of myeloid dendritic cells, which present as antigens and secrete a number of other cytokines such as IL-12 and IL-23, which are involved in the differentiation of type 17 and type 1 helper T cells.\(^\text{[4-7]}\) Under psoriatic conditions, T cells produce a number of inflammatory mediators such as IL-22, IL-17A, and IL-17F which further involved in the activation of keratinocytes and lead to the induction of several other pro-inflammatory mediators including S100 proteins, cytokines TNF-\(\alpha\), IL-6, and IL-1, chemokine CXCL8 to CXCL11, and CCL20 all of these promote inflammation in the skin which lead to the generation of psoriatic lesions.\(^\text{[4-7]}\) As far as pathogenesis of psoriatic arthritis is concern, it is very much similar with the pathogenesis of plaque psoriasis in many ways. As T-cell mediated pathogenic changes observed in the synovial fluid of psoriatic arthritic patients.\(^\text{[5-7]}\) Moreover, serum p40 protein level was found to be abnormally high in psoriatic arthritis, suggesting an involvement of IL-12 and IL23 in its pathogenesis.\(^\text{[5-7]}\) Furthermore, abnormalities in the production of potent inflammatory mediators such as IL-6, IL-1\(\beta\), TNF-\(\alpha\), MIP1\(\alpha\), and neutrophils infiltrations have also been seen in the synovium of psoriatic arthritic patients.\(^\text{[5-7]}\) All of these studies clearly suggesting that abnormal functioning of T cells and inflammation are the most common features involved in the pathogenesis of plaque psoriasis and psoriatic arthritis.\(^\text{[5-7]}\)

In the present communication, the role of IL-32 was investigated in patients with plaque psoriasis and psoriatic arthritis. It is now well documented that IL-32 promotes inflammation in numerous ways.\(^\text{[13-18]}\) It stimulates the production of TNF-\(\alpha\), IL-1\(\beta\), IL-6, INF-\(\gamma\), and IL-8.\(^\text{[13-25]}\) Overexpression of IL-32 has also been observed in cells of endothelium from several origins.\(^\text{[25]}\) Several reports from the past 10 years or so show abnormal expression and production of IL-32 in many human disorders including rheumatoid arthritis, cancers, pulmonary tuberculosis, atopic dermatitis, and leishmaniasis.\(^\text{[11-25]}\) Moreover, in our previous study, we also found overexpression of IL-32 mRNA in PBMCs of psoriasis patients (unpublished data); furthermore, elevated IL-32 level was also reported in the sera of patients with atopic dermatitis and asthmatic patients,\(^\text{[19,20]}\) suggesting that IL-32 is secreted by blood cells. In view of these, this study determined the role of IL-32 in the plasma samples of plaque psoriasis and psoriatic arthritic patients. This study comprised 19 plaque psoriasis patients, 11 psoriatic arthritic patients, and 22 normal human controls. Plasma level of IL-32 was found to be significantly higher in 52.6\% of plaque psoriasis patients and 45.45\% of psoriatic arthritic patients as compared with their respective controls humans, indicating that IL-32 promotes inflammation and could be an important marker for the detection of inflammation in these psoriatic patients.

The NF-\(\kappa\)B pathway has been well considered as a prime pro-inflammatory signaling pathway for many decades in numerous pathological conditions.\(^\text{[26-27]}\) NF-\(\kappa\)B complex is composed of RelA (p65), RelB, c-Rel, NF-\(\kappa\)B1 (p105/p50), NF-\(\kappa\)B2 (p100/p52), and also I\(\kappa\)Bs in the cytoplasm, where this complex is inactive. However, when the cells are activated through transmembrane receptor, I\(\kappa\)Bs are degraded and free NF-\(\kappa\)B units including NF-\(\kappa\)Bp65 are moved to the nucleus and turn on its transcription factor.\(^\text{[26,27,12]}\) NF-\(\kappa\)B can induce transcription of numerous pro-inflammatory mediators such as several cytokines, chemokine’s, adhesion molecules, MMPs, COX-2, and iNOS which are having direct roles in the pathogenesis of various disorders ranging from dermatological disorders to cancer.\(^\text{[26-32,39]}\) In psoriasis, the possible role of NF-\(\kappa\)B has been described by Derakhshan in her excellent article.\(^\text{[40]}\) All gathered information of genetic, immunohistochemical, and pharmacological studies strongly supported the involvement of NF-\(\kappa\)B signaling events in the pathogenesis of psoriasis.\(^\text{[40]}\) All major genes of apoptosis or pro-inflammatory cytokines in psoriasis have been regulated by NF-\(\kappa\)B pathways.\(^\text{[40,41]}\) Studies have shown that psoriatic lesional biopsies contained higher levels of NF-\(\kappa\)B/Rel A as compared with non-psoriatic biopsies or with normal skin.\(^\text{[42]}\) Moreover, NF-\(\kappa\)B activation was also reported in keratinocytes proliferation and differentiation.\(^\text{[43]}\) Mice with psoriasis-like inflammatory syndrome showed increased levels of active NF-\(\kappa\)B as compared with normal mice.\(^\text{[44]}\) Overexpression of NF-\(\kappa\)B p50 and p65 in transgenic epithelium inhibits the production of hyperplastic epithelium, whereas application of NF-\(\kappa\)B pharmacological inhibitors to transgenic murine or human epidermis produced hyperplastic epithelium.\(^\text{[45]}\) Importantly, the role of NF-\(\kappa\)B pathway on cytokine production in the pathogenesis of psoriasis has also been reported.\(^\text{[10,17,40,41]}\) As, transforming growth factor-\(\alpha\) stimulates IL-6 production through activation of NF-\(\kappa\)B in human keratinocyte cell line.\(^\text{[40-45]}\) Moreover, insulin-like growth factor-II also induces IL-6 production which is also through NF-\(\kappa\)B activation in psoriasis patients.\(^\text{[40-45]}\) Furthermore, several pharmacological studies have shown that anti-psoriatic drugs such as acitretin, rottlerin, and dimethy fumarate perform their anti-psoriatic action through downregulation of NF-\(\kappa\)B transcriptional activity.\(^\text{[40,41]}\)

To validate the involvement of NF-\(\kappa\)B activation in the pathogenesis of plaque psoriasis and psoriatic arthritis, activated levels of NF-\(\kappa\)Bp65 were demonstrated in the PBMCs obtained from plaque psoriasis and psoriatic arthritis patients and were found to be significantly higher as compared with the levels of activated NF-\(\kappa\)Bp65 in PBMCs of normal human subjects. An increased level of activated NF-\(\kappa\)B in these patients not only suggests that inflammation is increased in plaque psoriasis and psoriatic arthritis but also indicates a potential role of NF-\(\kappa\)B in the pathogenesis of these psoriatic patients. The increased levels of IL-32 observed in plaque psoriasis and psoriatic arthritic patients in the present study, together with activation of NF-\(\kappa\)B, provide further evidence...
of the involvement of inflammatory signaling events in these psoriatic patients.

Conclusions

This study provides evidence that IL-32 and NF-κB play an active role in the induction of inflammatory processes in plaque psoriasis and psoriatic arthritis. The study pointed out that overproduction of IL-32 in plaque psoriasis or psoriatic arthritis might be associated with the activation of transcription factor NF-κB, but longitudinal studies are required to confirm whether elevated levels of IL-32 in these psoriatic patients are associated with the activation of NF-κB transcription factor. Targeting IL-32 or NF-κB signaling event might provide a novel strategy for the management of plaque psoriasis and psoriatic arthritis.

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