IJHS

Original Article

# Functional role of human interleukin-32 and nuclear transcription factor-κB in patients with psoriasis and psoriatic arthritis

**Hani A. Al-Shobaili[1], Jalees Farhan[2], Uzma Zafar[3], Zafar Rasheed[2]**

[1]Department of Dermatology, College of Medicine, Qassim University, Buraidah, KSA, [2]Department of Medical Biochemistry, College of Medicine, Qassim University, Buraidah, KSA, [3]Department of Pathology, College of Medicine, Qassim University, Buraidah, KSA

**Address for Correspondence:**
Zafar Rasheed, Department of Medical Biochemistry, College of Medicine, Qassim University, P.O. Box 6655, Buraidah, KSA.
E-mail: zafarrasheed@qumed.edu.sa

**WEBSITE:** ijhs.org.sa
**ISSN:** 1658-3639
**PUBLISHER:** Qassim University

## ABSTRACT

**Objective:** Inflammation and its associated cell signaling events have been well documented in psoriasis and psoriatic arthritis. However, the potential for interleukin (IL)-32 and its associated signaling to provoke an inflammatory response or to contribute in the pathogenesis of psoriasis or psoriatic arthritis are still in early phase. This study determined the role of IL-32 and nuclear transcription factor (NF)-κB in patients with plaque psoriasis and psoriatic arthritis.

**Methods:** Levels of IL-32 were determined in the plasma samples of patients with plaque psoriasis, psoriatic arthritis, and normal healthy subjects by human IL-32-specific Sandwich enzyme-linked immunosorbent assays. To investigate the role of a transcription factor in these patients, activated NF-κBp65 levels were determined in the peripheral blood mononuclear cells (PBMCs) by highly sensitive NF-κB transcription factor kit.

**Results:** The levels of IL-32 in the plasma samples of plaque psoriasis or psoriatic arthritis patients were found to be significantly higher as compared with the levels of IL-32 present in the normal human plasma samples ($P < 0.01$). Levels of activated NF-κB were also found higher in plaque psoriasis or psoriatic arthritic patients as compared with the PBMCs of healthy humans ($P < 0.05$).

**Conclusions:** This study shows the role of IL-32 and NF-κB in plaque psoriasis and psoriatic arthritic patients. Results indicate that IL-32 and NF-κB promote inflammation in patients with psoriasis and psoriatic arthritis. Disruption of IL-32 or NF-κB signaling event might provide a novel target for the management of plaque psoriasis and psoriatic arthritis.

**Keywords:** Interleukin -32, NF-κB, peripheral blood mononuclear cells, psoriasis, psoriatic arthritis

## 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.[5-7] 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.[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[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.[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.[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.[12-23] Moreover, its role has also been demonstrated in skin biopsies of psoriasis patients.[23] Now, it is somewhat established that IL-32 exhibits pro-inflammatory features in many cell types.[24,25] As, it induces the excessive production of TNF-α, IL-1β, IL-6, INF-γ, and IL-8.[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.[26-31] Role of NF-κB has already been well described in various human disorders ranging from arthritis to cancer,[26-28] and now, NF-κB has now well considered as a therapeutic target in almost all inflammatory disorders.[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.

## Methods

### Patient's selection

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in Tokyo 2004) for humans and was approved by The General Directorate of Health Affairs, Al-Qassim Region, Ministry of Health, KSA (Ethical Approval # 45/44/781515; Registration # H-04-Q-001). Study subjects were recruited through the dermatology and rheumatology outpatient clinics of Qassim University. Patients were diagnosed after careful clinical examination and were classified as plaque psoriasis and psoriatic arthritis as described previously.[33] Venous blood samples from plaque psoriasis patients ($n$ = 19; age 29.62 ± 9.39 years), psoriatic arthritis ($n$ = 11; age 47.64 ± 12.3), and healthy human subjects ($n$ = 22; age 27.72 ± 7.87 years) were collected, and desired components from blood were isolated. Demographic details of study subjects have been summarized in Table 1.

### IL-32-specific Sandwich enzyme-linked immunosorbent assay (ELISA)

Levels of IL-32 in the plasma samples of plaque psoriasis and psoriatic arthritic patients were quantified by sandwich ELISAs as described previously[34,35] using human IL-32 antibodies (Abcam, Cambridge, UK). Briefly, polystyrene Polysorp 96-well microtiter plates (Nunc-ImmunoTM MicroWell, Sigma-Aldrich, St. Louis, MO, USA) were coated with anti-IL-32 polyclonal antibodies (catalog # ab37158, Abcam) overnight at 4°C. The plates were washed with tris buffer saline-containing tween 20 (TBS-T), and the nonspecific binding sites were blocked with TBS-containing 1% BSA (TBS-BSA) at room temperature for 1 h. After washing extensively with TBS-T, 100 µl of patient plasma (1:100 diluted) were added to duplicate wells of the coated plate and incubated at room temperature for 2 h and overnight at 4°C. The plates were washed 5 times with TBS-T, and 100 µl of anti-IL-32 monoclonal IgG1 (Abcam; diluted 1:100) were incubated at room temperature for 2 h. The plates were washed extensively, and 100 µl of anti-human IgG-HRP (catalog # sc2769, Santa Cruz Biotechnology, Inc., Dallas, TX, USA) were added for 2 h. After washing, 100 µl of TMB peroxidase substrate (Santa

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

| Parameters | Psoriasis patients | | NHS |
|---|---|---|---|
| Clinical type | PP | PA | - |
| Number of subjects | 19 | 11 | 22 |
| Age (years) | | | |
| Mean±SD | 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 $H_2SO_4$, 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 (±) SD of IL-32 levels in patients with plaque psoriasis, psoriatic arthritis, and normal healthy subjects were 0.079 ± 0.03, 0.127 ± 0.12, and 0.035 ± 0.010, respectively [Figure 1].

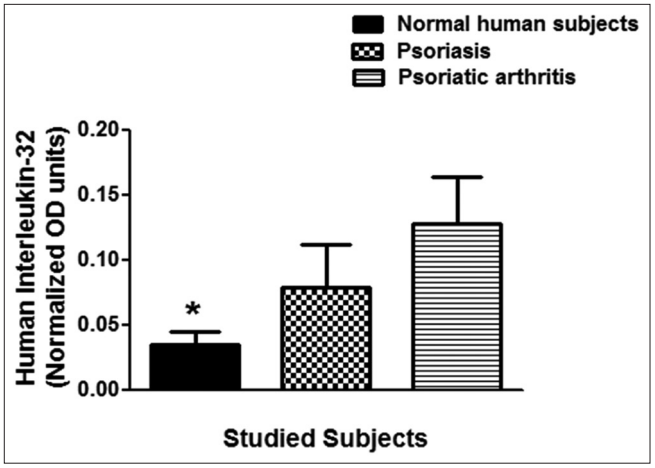


**Figure 1:** Human interleukin-32 in plasma samples of patients with psoriasis and psoriatic arthritis. Production of interleukin-32 protein was determined by sandwich enzyme-linked immunosorbent assay. Results are representative (mean±SEM) of duplicate experiments. *$P < 0.05$ versus psoriasis or psoriatic arthritis

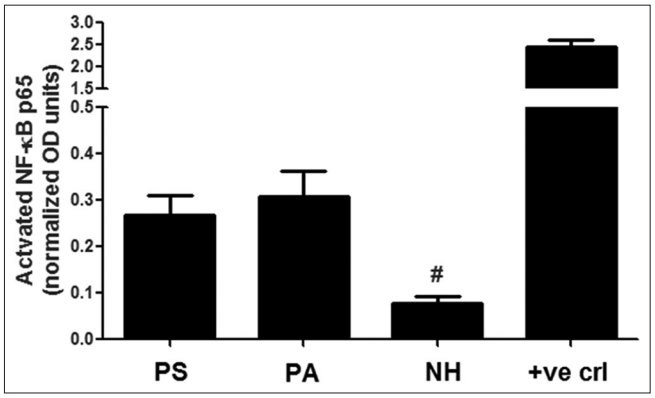


**Figure 2:** Activation of NF-κB in peripheral blood mononuclear cells of psoriasis and psoriatic arthritis. Activated NF-κB p65 was determined by highly specific transcription factor ELISA kit (Abcam). The positive control nuclear extract supplied with the kit was used. Data are represented as mean±SD.#$P < 0.05$ versus PS or PA. NF-κB: Nuclear transcription factor-kappa B, PS: Psoriasis, PA: Psoriatic arthritis, SD: Standard deviation

### 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 (±) SD of activated NF-κBp65 levels in PBMCs from patients with plaque psoriasis, psoriatic arthritis, and normal healthy subjects were 0.2687 ± 0.071, 0.3073 ± 0.096, and 0.0780 ± 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.[4-9] In plaque psoriasis, the role of inflammatory cytokines such as TNF-α, IL-1β, IL-6, and INF-γ is well defined.[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.[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-α, 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.[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.[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.[5-7] Furthermore, abnormalities in the production of potent inflammatory mediators such as IL-6, IL-1β, TNF-α, MIP1α, and neutrophils infiltrations have also been seen in the synovium of psoriatic arthritic patients.[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.[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.[13-18] It stimulates the production of TNF-α, IL-1β, IL-6, INF-γ, and IL-8.[13-25] Overexpression of IL-32 has also been observed in cells of endothelium from several origins.[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.[13-25] 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,[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-κB pathway has been well considered as a prime pro-inflammatory signaling pathway for many decades in numerous pathological conditions.[26,27] NF-κB complex is composed of RelA (p65), RelB, c-Rel, NF-κB1 (p105/p50), NF-κB2 (p100/p52), and also IκBs in the cytoplasm, where this complex is inactive. However, when the cells are activated through transmembrane receptor, IκBs are degraded and free NF-κB units including NF-κBp65 are moved to the nucleus and turn on its transcription factor.[26,27,32] NF-κB 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.[26-32,39] In psoriasis, the possible role of NF-κB has been described by Derakhshan in her excellent article.[40] All gathered information of genetic, immunohistochemical, and pharmacological studies strongly supported the involvement of NF-κB signaling events in the pathogenesis of psoriasis.[40] All major genes of apoptosis or pro-inflammatory cytokines in psoriasis have been regulated by NF-κB pathways.[40,41] Studies have shown that psoriatic lesional biopsies contained higher levels of NF-κB/Rel A as compared with non-psoriatic biopsies or with normal skin.[42] Moreover, NF-κB activation was also reported in keratinocytes proliferation and differentiation.[43] Mice with psoriasis-like inflammatory syndrome showed increased levels of active NF-κB as compared with normal mice.[44] Overexpression of NF-κB p50 and p65 in transgenic epithelium inhibits the production of hyperplastic epithelium, whereas application of NF-κB pharmacological inhibitors to transgenic murine or human epidermis produced hyperplastic epithelium.[45] Importantly, the role of NF-κB pathway on cytokine production in the pathogenesis of psoriasis has also been reported.[10,11,40,41] As, transforming growth factor-α stimulates IL-6 production through activation of NF-κB in human keratinocyte cell line.[40-45] Moreover, insulin-like growth factor-II also induces IL-6 production which is also through NF-κB activation in psoriasis patients.[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-κB transcriptional activity.[40,41]

To validate the involvement of NF-κB activation in the pathogenesis of plaque psoriasis and psoriatic arthritis, activated levels of NF-κBp65 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-κBp65 in PBMCs of normal human subjects. An increased level of activated NF-κB in these patients not only suggests that inflammation is increased in plaque psoriasis and psoriatic arthritis but also indicates a potential role of NF-κB 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-κB, 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.

## Acknowledgments

This work was funded by Qassim University Research Deanship Grants # SR-D-014-2829.

## References

1. Nicholas MN, Gooderham M. Psoriasis, depression, and suicidality. Skin Therapy Lett 2017;22:1-4.
2. Pitlick M, Flesner J, Ballantini K. Plaque psoriasis: A review of recent guidelines and pharmacologic therapies. Formulary 2011;46:18-26.
3. Raychaudhuri SK, Maverakis E, Raychaudhuri SP. Diagnosis and classification of psoriasis. Autoimmun Rev 2014;13:490-5.
4. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. Can Fam Physician 2017;63:278-85.
5. Papoutsaki M, Costanzo A. Treatment of psoriasis and psoriatic arthritis. Biodrugs 2013;27:3-12.
6. Gan EY, Chong WS, Tey HL. Therapeutic strategies in psoriasis patients with psoriatic arthritis: Focus on new agents. BioDrugs 2013;27:359-73.
7. Weger W. Current status and new developments in the treatment of psoriasis and psoriatic arthritis with biological agents. Br J Pharmacol 2010;160:810-20.
8. Kane D, FitzGerald O. Tumor necrosis factor-alpha in psoriasis and psoriatic arthritis: A clinical, genetic, and histopathologic perspective. Curr Rheumatol Rep 2004;6:292-8.
9. Tobin AM, Kirby B. TNF alpha inhibitors in the treatment of psoriasis and psoriatic arthritis. BioDrugs 2005;19:47-57.
10. McIlnnes IB. Cytokine targeting in psoriasis and psoriatic arthritis: Beyond TNFalpha. Ernst Schering Res Found Workshop 2006;56:29-44.
11. Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. Cytokine 2015;73:342-50.
12. Dos Santos JC, Heinhuis B, Gomes RS, Damen MS, Real F, Mortara RA, *et al.* Cytokines and microbicidal molecules regulated by IL-32 in THP-1-derived human macrophages infected with new world leishmania species. PLoS Negl Trop Dis 2017;11:e0005413.
13. Hong JT, Son DJ, Lee CK, Yoon DY, Lee DH, Park MH, *et al.* Interleukin 32, inflammation and cancer. Pharmacol Ther 2017;174:127-37.
14. Cho JS, Kim JA, Park JH, Park IH, Han IH, Lee HM, *et al.* Toll-like receptor 4-mediated expression of interleukin-32 via the c-jun N-terminal kinase/protein kinase B/cyclic adenosine monophosphate response element binding protein pathway in chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol 2016;6:1020-8.
15. El-Far M, Kouassi P, Sylla M, Zhang Y, Fouda A, Fabre T, *et al.* Proinflammatory isoforms of IL-32 as novel and robust biomarkers for control failure in HIV-infected slow progressors. Sci Rep 2016;6:22902.
16. Joosten LA, Netea MG, Kim SH, Yoon DY, Oppers-Walgreen B, Radstake TR, *et al.* IL-32, a proinflammatory cytokine in rheumatoid arthritis. Proc Natl Acad Sci U S A 2006;103:3298-303.
17. Yousif NG, Al-Amran FG, Hadi N, Lee J, Adrienne J. Expression of IL-32 modulates NF-κB and p38 MAP kinase pathways in human esophageal cancer. Cytokine 2013;61:223-7.
18. Cui Y, Sun Z, Li X, Leng C, Zhang L, Fu X, *et al.* Expression and clinical significance of cyclooxygenase-2 and interleukin-32 in primary gastric B-cell lymphoma. Oncol Lett 2016;11:693-8.
19. Gasiuniene E, Lavinskiene S, Sakalauskas R, Sitkauskiene B. Levels of IL-32 in serum, induced sputum supernatant, and bronchial lavage fluid of patients with chronic obstructive pulmonary disease. COPD 2016;13:569-75.
20. Kitayama N, Otsuka A, Nonomura Y, Nakashima C, Honda T, Kabashima K, *et al.* Decrease in serum IL-32 level in patients with atopic dermatitis after cyclosporine treatment. J Eur Acad Dermatol Venereol 2017;31:e449-50.
21. Thomi R, Yerly D, Yawalkar N, Simon D, Schlapbach C, Hunger RE, *et al.* Interleukin-32 is highly expressed in lesions of hidradenitis suppurativa. Br J Dermatol 2017.
22. Wang Y, Zhou B, Zhao Y, Yu X, Liu Y, Zhang L, *et al.* Association of plasma IL-32 levels and gene polymorphisms with systemic lupus erythematosus in chinese han population. Dis Markers 2016;2016:2460206.
23. Kempuraj D, Conti P, Vasiadi M, Alysandratos KD, Tagen M, Kalogeromitros D, *et al.* IL-32 is increased along with tryptase in lesional psoriatic skin and is up-regulated by substance P in human mast cells. Eur J Dermatol 2010;20:865-7.
24. Dinarello CA, Kim SH. IL-32, a novel cytokine with a possible role in disease. Ann Rheum Dis 2006;65 Suppl 3:iii61-4.
25. Kim SH, Han SY, Azam T, Yoon DY, Dinarello CA. Interleukin-32: A cytokine and inducer of TNFalpha. Immunity 2005;22:131-42.
26. Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb Perspect Biol 2009;1:a001651.
27. Rasheed Z, Haqqi TM. Update on targets of biologic therapies for rheumatoid arthritis. Curr Rheumatol Rev 2008;4:246.
28. Rasheed Z, Al-Shobaili HA, Rasheed N, Mahmood A, Khan MI. MicroRNA-26a-5p regulates the expression of inducible nitric oxide synthase via activation of NF-κB pathway in human osteoarthritis chondrocytes. Arch Biochem Biophys 2016;594:61-7.
29. Rasheed Z, Haqqi TM. Endoplasmic reticulum stress induces the expression of COX-2 through activation of eIF2α, p38-MAPK and NF-κB in advanced glycation end products stimulated human chondrocytes. Biochim Biophys Acta 2012;1823:2179-89.
30. Rasheed Z, Anbazhagan AN, Akhtar N, Ramamurthy S, Voss FR, Haqqi TM, *et al.* Green tea polyphenol epigallocatechin-3-gallate inhibits advanced glycation end product-induced expression of tumor necrosis factor-alpha and matrix metalloproteinase-13 in human chondrocytes. Arthritis Res Ther 2009;11:R71.
31. Rasheed Z, Akhtar N, Haqqi TM. Advanced glycation end products induce the expression of interleukin-6 and interleukin-8 by receptor for advanced glycation end product-mediated activation of mitogen-activated protein kinases and nuclear factor-κB in human osteoarthritis chondrocytes. Rheumatology (Oxford)2011;50:838-51.
32. Alghasham A, Rasheed Z. Therapeutic targets for rheumatoid arthritis:

Progress and promises. Autoimmunity 2014;47:77-94.

33. Al-Shobaili HA, Ahmed AA, Rasheed Z. Recognition of oxidized albumin and thyroid antigens by psoriasis autoantibodies. A possible role of reactive-oxygen-species induced epitopes in chronic plaque psoriasis. Saudi Med J 2015;36:1408-19.
34. Al-Shobaili HA, Rasheed Z. Oxidized tyrosinase: A possible antigenic stimulus for non-segmental vitiligo autoantibodies. J Dermatol Sci 2015;79:203-13.
35. Al-Shobaili HA, Rasheed Z. Physicochemical and immunological studies on mitochondrial DNA modified by peroxynitrite: Implications of neo-epitopes of mitochondrial DNA in the etiopathogenesis of systemic lupus erythematosus. Lupus 2013;22:1024-37.
36. Alzolibani AA, Rasheed Z, Bin Saif G, Al-Dhubaibi MS, Al Robaee AA. Altered expression of intracellular toll-like receptors in peripheral blood mononuclear cells from patients with alopecia areata. BBA Clin 2016;5:134-42.
37. Rasheed Z, Akhtar N, Haqqi TM. Pomegranate extract inhibits the interleukin-1β-induced activation of MKK-3, p38α-MAPK and transcription factor RUNX-2 in human osteoarthritis chondrocytes. Arthritis Res Ther 2010;12:R195.
38. Rasheed N, Alghasham A, Rasheed Z. Lactoferrin from camelus dromedarius inhibits nuclear transcription factor-kappa B activation, cyclooxygenase-2 expression and prostaglandin E2 production in stimulated human chondrocytes. Pharmacognosy Res 2016;8:135-41.
39. Hoesel B, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer 2013;12:86.
40. Derakhshan N. NFκB inhibitors as a potential novel hypothesized treatment for psoriasis. Sao Paulo Med J 2011;129:433-4.
41. Goldminz AM, Au SC, Kim N, Gottlieb AB, Lizzul PF. NF-κB: An essential transcription factor in psoriasis. J Dermatol Sci 2013;69:89-94.
42. Moorchung N, Kulaar JS, Chatterjee M, Vasudevan B, Tripathi T, Dutta V, *et al.* Role of NF-κB in the pathogenesis of psoriasis elucidated by its staining in skin biopsy specimens. Int J Dermatol 2014;53:570-4.
43. Tsuruta D. NF-kappaB links keratinocytes and lymphocytes in the pathogenesis of psoriasis. Recent Pat Inflamm Allergy Drug Discov 2009;3:40-8.
44. Wang H, Syrovets T, Kess D, Büchele B, Hainzl H, Lunov O, *et al.* Targeting NF-kappa B with a natural triterpenoid alleviates skin inflammation in a mouse model of psoriasis. J Immunol 2009;183:4755-63.
45. Grinberg-Bleyer Y, Dainichi T, Oh H, Heise N, Klein U, Schmid RM, *et al.* Cutting edge: NF-κB p65 and c-rel control epidermal development and immune homeostasis in the skin. J Immunol 2015;194:2472-6.