**Reviewer’s Comments**

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**IL-22 serum levels in patients with rheumatoid arthritis in Sana'a city, Yemen**

***Abstract***

Interleukin (IL) -22 is a novel mediator of a member of IL-10 family cytokines that is produced by many different types of lymphocytes including both those of innate & adaptive immune system. This cytokine has potent proliferative & inflammatory effects on different cell lines. Recently, accumulated data has indicated that IL-22 plays an important role in the pathogenesis of rheumatoid arthritis (RA). We aimed to investigate the levels of IL-22 and its association with demographic, clinical data as well as serological markers in RA.

IL-22 serum levels were measured in 45 newly diagnosed RA patients without any treatment and 45 healthy individuals as control by a manual Enzyme linked immunosorbent assay (ELISA). Correlations of IL-22 serum levels were sought with demographic, clinical data and serological parameters.

IL-22 levels were significantly elevated in serum of RA patients (median= 86.89ng/ml & range = 896) compared to serum of healthy control (median=75.36ng/ml & range=459), p=.022. The IL-22 levels were correlated positively with C-reactive protein (CRP), anti-cyclic citrullinated peptide (ACCP) antibodies in RA patients.

A significant higher levels of serum IL-22 in RA patients compare with those in healthy control. Highly significant association between serum levels of IL-22 & the serological markers (CRP & ACCP antibodies) in the diagnosis of RA suggest the potential levels of IL-22 as a valuable biomarker for the evaluation of disease severity in RA patients.

**Key words:** Interleukin-22, rheumatoid arthritis, C-reactive protein, rheumatoid factor, anti-cyclic citrullinated peptide antibody.

**Introduction**

Rheumatoid arthritis (RA) is a chronic inflammatory disease that represents one of the most common autoimmune-related disease. Histologically, it is characterized by prominent infiltration of inflammatory mononuclear cells, such as T cells and macrophages, and the proliferation of synovial fibroblasts. 1 In RA, it is clear that inflammatory cytokines play a key role in driving T cell activation and migration that lead to joint destruction. 2

Interleukin (IL) -22 is a novel α-helical protein, the human IL-22 encoding gene is located in the longer arm (q15) of chromosome 12. 3 It belongs to a group of [cytokines](http://en.wikipedia.org/wiki/Cytokine) called the [IL-10](http://en.wikipedia.org/wiki/Interleukin_10) family which is a class of potent mediators of cellular inflammatory responses. [4](file:///E%3A%5CInterleukin_22.htm#cite_note-pmid15032600-4),5 IL-22 differs from other cytokines of [IL-10](http://en.wikipedia.org/wiki/Interleukin_10) family by being a potent proliferative and inflammatory agent for different cell lines. 3, 6 Many types of cells from lymphoid lineage can secrete IL-22, including both those of the innate and adaptive immune system. In humans, these cells include activated CD4+ T cells, CD8+ T cells 7-9 and γδ T cells 10 as well as various innate lymphoid cells such as Natural killer (NK) cells, NKT cells, 11-13 lymphoid tissue inducer (LTi) and LTi-like cells. 14 Several studies have shown that IL-22 has a major role in both defense against certain microbes and the development and maintenance of chronic inflammatory diseases. 15, 16 In addition, it plays an important role in mucosal tissue protection and wound healing. 16 , 17 Moreover, it induces proliferative and anti-apoptotic pathways in responsive cells allowing for tissue preservation. 18

The IL-22 receptor complex is composed of IL-22R1 and IL-10R2. 19-21 IL-22R1 subunit is restricted to cell lineages of a non-haematopoitic origin, in particular, pancreas, kidney & liver as well as barrier surfaces such as the skin, intestine & lung. 22, 23 It is important to note that the bone marrow, peripheral blood mononuclear cell, spleen, thymus do not express IL-22R, 5, 24 and therefore immune cells are not targets of IL-22. 23 In humans, Th22, a subset of CD4+ T cells that specifically express IL-22 is mainly found in tissues. 25 Animal models as well as human studies have identified both inflammatory 23 , 26 and protective roles 18 for IL-22 in autoimmune diseases. In RA, IL-22 is assumed to play a pathogenetic role. However, the mechanism by which IL-22 contributes to RA pathogenesis are not completely clear. The assumption was mainly based on the observed minimally reduced susceptibility of the IL-22-/- mice to collagen-induced arthritis (CIA) and decreased incidence of pannus information. In this model of inflammatory arthritis, IL-22 was found to promote osteoclastogenesis and this effect may be associated with the reduced severe arthritis in IL-22-deficient mice. 27 Previous studies suggest that IL-22, through the STAT3, ERKV2, & p38 MAKP pathways stimulate synovial fibroblasts proliferation & monocyte chemoattractants protein (MCP)-1production, leading to inflammation. 6, 28 Recently, Sakar *et al.* reported that IL-22 reduces the severity of CIA, when administered prior to the onset of the disease and showed that the mechanism of which is associated with increased with levels of IL-10. 29 Other recent study, has been shown that IL-22 significantly enhanced fibroblast-like synoviocytes proliferation in RA & suggests that its contribution to the synovium hyperplasia & joint destruction. This study showed that potential stimulus present in the rheumatoid joint, such as TNF-α & lipo-polysaccharides are able to induce IL-22 expression. 30 A more recent study, reported that IL-22 promoted osteoclastogenesis in RA by induction of receptor activator of nuclear factorkappa-B ligand (RANKL) in human synovial fibroblast. 31

This study was conducted to investigate the presence of IL-22 in the sera of patients with RA and healthy controls and to determine the association between the level of IL-22 and the blood parameters including C-Reactive Protein (CRP), rheumatoid factor (RF), and anti-citrullinated-peptide (ACCP) antibodies, as well as its association to demographic and clinical data in RA cases.

**Subjects and Methods**

This case-control study was conducted at Al-Thawra Modern General Hospital and University of Science and Technology Hospital, Sana'a city, Yemen during a period of one year starting in April 2015 and ending in April 2016. The study group; 45 patients with new onset RA were recruited and diagnosed, according to the revised criteria for classification of RA by the American College of Rheumatology (ACR) criteria. 32 These patients had never been treated with immunosuppressive drugs. The control group is 45 healthy subjects without RA were used as healthy controls. The personal and clinical information of patients and control are shown in table 1. We conducted the study in accordance with ethical standards, and verbal informed consents were obtained from all participants before their enrollment. Patients were excluded if they had any other autoimmune diseases or infection or he/she had received immunosuppressive or glucocorticoid therapies within the past 6 months.

Five ml of venous blood was collected from each subject. The specimens were allowed to clot at room temperature and centrifuged at 3500 rpm for five minutes. Serum was separated from each sample into three ependroff tubes; one tube for IL-22 test, second for RF test and CRP test and the third for ACCP test. They stored at -20°C till tested. The sera of the selected subjects were tested to determine the IL-22 by acommercially available manual enzyme linked immunosorbent assay (ELISA), Glory Science Co., Ltd,USA]. ACCP antibodies were determined by a manual ELISA kit manufactured by (INOVA Diagnostics Kits, San Diego, CA-USA). The levels of serum CRP, and RF were analyzed by latex tests (Vitro Science Co, Egypt).

**Data analysis**

According to data distribution, the quantitative data were expressed as median and range. 33 The demographic & clinical data were expressed as number & percentage. Independent sample T test was used for comparison between the patients & control groups. The potential correlation between variables was analyzed by the spearman rank correlation test. All statistical tests were performed by using the SPSS version 20 for windows (SPSS, Inc., Chicago, IL, USA) with 95% confidence interval. A two sided p-value of≤ 0.05 was considered statistically significant.

**Results**

The demographic data of healthy control and patients showed in Table 1.

**Table 1: Demographic data of control and cases of RA.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Demographic data** | **Healthy controls****(N=45)** | **Patients with RA****(N=45)** | ***p*** |
|  **Age (years)** | **Median** **Range Min-Max** | **40****80****(10-90)** | **40****50****(10-60)** | **.734** |
| **Gender** | **Female****Male** | **36****9** | **39****6** | **.402** |
| **Residence** | **R****U** | **10****35** | **19****26** | **.043** |
| **Smoking habit** | **No Yes** | **41****4** | **38****7** | **.340** |
| **Qat chewing** | **No****Yes** | **30****15** | **32****13** | **.653** |

**R/U:Rural/ Urban; Probability value (*p* )≤0.05 (\*: significant)**

At presentation, most of patients (97.8%) had joint pain and morning stiffness (93.3%), while 86.7% had swollen joints & 80% had fatigue.Twenty seven patients (60%) had symmetric arthritis, 19 (42.2%) had fever and only 8 patients (17.8%) had family history (table 2).

**Table 2:The distribution of clinical Data among cases of RA.**

|  |  |
| --- | --- |
| **Clinical data** |  |
| **Duration (years)** | **Median****Min-Max****Range** | **2.0****(0.16-10)****9.840** |
| **Family history N (%)** | **8 (17.8)** |
| **Fever N (%)** | **19 (42.2)** |
| **Joint pain N (%)** | **44 (97.8)** |
| **Morning stiffness N (%)** | **42 (93.3)** |
| **Swollen joints N (%)** | **39 (86.7)** |
| **Fatigue N (%)** | **36 (80)** |
| **Symmetric arthritis N (%)** | **27 (60)** |

IL-22 levels in serum of RA patients were significantly higher compared to that in the healthy control (p= .022). As we expected, there were significant differences between patients and healthy control in the levels of CRP, RF, and ACCP (p=0.000) Table 3.

**Table 3:The levels of Il-22 & serologic markers of RA in control and cases.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **Healthy controls****(N=45)** | **Patients with RA****(N=45)** | ***P*** |
| **IL-22 (ng/mL)** | **Median****Range Min-Max** | **75.36****459****(55-514)** | **86.89****825****(56-881)** | **0.022\*\*** |
| **CRP (mg/mL)** | **Median****Range Min-Max** | **.00****24****(0-24)** | **24.0****48****(0-48)** | **0.000\*\*** |
| **RF (IU/mL)** | **Median****Range Min-Max** | **.00****32****(0-320)** | **32.0****64****(0-64)** | **0.000\*\*** |
| **ACCP (U/mL)** | **Median****Range Min-Max** | **.00****320****(0-320)** | **221.0****517****(0-517)** | **0.000\*\*** |

**CRP: C-reactive protein; RF: rheumatoid factor; ACCP: anti-cyclic**

**citrullinated peptide. The normal ranges of CRP, RF & CCP, & are**

**0–25 U/mL, 0–15 mg/L& 0–15 IU/mL, respectively. Probability value**

**(*p*)≤0.05 (\*: significant)**

Correlational analysis between the serum levels of IL-22 in the patient and personal & clinical data show no significant difference. As regard serologic parameters, a significant positive correlation was found between the levels of serum IL-22 and CRP &ACCP (rho=.416 p=.004, rho=.559 p=.000, respectively), however, there was no significant correlation between levels of IL-22 and RF in RA patients (table 4 & fig. 1 & 2, respectively). (Table 4).

**Table4: correlation between the levels of IL-22**

**& different variables in patients with RA**

|  |  |
| --- | --- |
|  | **IL-22 (ng/ml)****(N=45)** |
| **Demographic data** |
| **Age (years)** | **rho=.272, p= .071** |
| **Gender (Female/Male)** |  **rho=.015, p= .922** |
| **Residence (R/U)** | **rho=.121, p= .428** |
| **Smoking habit (%)** | **rho=.012, p= .939** |
| **Qat chewing (%)** | **rho=.098, p= .521** |
| **Clinical data** |
| **Family History(%)** | **rho=.219-, p= .148** |
| **Joints pain (%)** | **rho=.128-, p= .403** |
| **Morning stiffness (%)** | **rho=.144-, p= .0345** |
| **Swelling joints (%)** | **rho=.078-, p= .610** |
| **Fever (%)** | **rho=.097, p= .526** |
| **Fatigue (%)** | **rho=.017, p= .911** |
| **Symmetric arthritis (%)** | **rho=.070-, p= .648** |
| **Duration (years)** | **rho=.280, p= .062** |
| **Serologic parameters** |
| **CRP (mg/mL)** | **rho=.416\*\*, p= .004** |
| **RF (IU/mL)** | **rho=.291, p= .053** |
| **ACCP (U/mL)** | **rho=.559\*\*, p= .000** |

**Fig. 1: The correlation between serum levels of IL-22 and CRP in RA patients.**

**Fig. 2: The correlation between serum levels of IL-22 and ACCP in RA patients.**

**Discussion**

IL-22 has been recently suggested to be involved in the pathogenesis of autoimmune arthritis. In our study, we observed significantly elevated levels of IL-22 in serum of RA patients compared to healthy controls (p=.022). Our data are in accordance with previous reports that found elevation of IL-22 in serum & plasma of patients with RA. 34-37 In consistent with our study, IL-22 m RNA was detected in synovial tissue directly as well as in synovial fluid mononuclear cells in patients with RA. 6, 37, 38 As regard to the sources of IL-22 in humans, many studies reported that the higher frequency of peripheral IL-22+CD4+T cells in RA patients than those in the controls. 36, 39 Moreover, Zhoa *et al*. showed that IL-22+CD4+T cells were correlated positively with the disease activity in RA patients and the percentage of these cells were correlated positively with the levels of plasma IL-22 in these patients. 36 Another recent study has been shown that the synovium in RA patients is infiltrated by T lymphocytes especially Th17 which is also a source of IL-22. 40

Correlation analysis revealed that a significant positive correlations between levels of serum IL-22 and CRP & ACCP antibodies (rho= =.0416, p=.004 & rho=.559, p=.000, respectively). In line with our result, kim *et al* 2011 found a significant association between serum IL-22 and ACCP antibodies. 37 Of potential implication, the strong association of elevated serum IL-22 with the more specific serologic marker, ACCP antibodies. In addition, many recent studies reported that IL-22 has been involved in joint destruction in RA, 27, 34, 35 thus, determination of ACCP antibodies & IL-22 levels may provide a novel means for predicting aggressive disease in these patients. Regarding to the correlation between IL-22 levels and RF in RA patients, our study showed no significant association between them, however, some previous studiesdemonstrated a positive correlation between them. 36, 37 While we did not find any previous study about the correlation between IL-22 and CRP.

To our knowledge, there is no report available on the correlation between IL-22 and the individual nor clinical data in RA. In our study, there is no correlations between serum IL-22 and demographic nor clinical data of our patients. In line with our observation, disease activity in IL-22 knockout mice of collagen-induced arthritis did not differ from that of their wild-type littermates. 27 In addition, recent study between high and normal levels of serum IL-22 in early untreated RA patients showed no differences in the clinical inflammatory parameters of the two groups of patients, although these studies showed an association between serum IL-22 levels & bone erosin. 34, 27 On the other hand, previous study on patients with RA have been a correlation between levels of Il-22 and disease activity or severity. 35 However, recent an experimental study has been shown that synovial inflammation was not affected in IL-22-/- mice and this study concludes that the local IL-22 produced by adaptive or innate immune cell have no direct contribution to the induction of T cell-mediated synovial inflammation. 29 Many studies suggest that the possible explanation for these differences is depending on different phases of the disease development. 29, 30, 41

**Conclusion**

In conclusion, our data indicated high levels of IL-22 in RA patients & that the strong association with ACCP antibodies suggest the potential of IL-22 & ACCP antibodies levels as predictive markers in this disease. It is also of interest that as immune cells do not express IL-22, targeting IL-22 & related signaling may be an effective therapeuticapproach for treating autoimmune RA.

**Conflict of interest**

**References**

1. McInnes IB Shett G. Mechanisms of Diseases: The pathogenesis of Rheumatoid Arthritis. E New England and Journal of Medicine 2011; 365:2205-19
2. Christodoulou C, Choy EH: Joint inflammation and cytokine inhibition in rheumatoid arthritis. ClinExp Med 2006; 6: 13-9.
3. Wolk K, Sabat R. Interleukin-22: A novel T- and NK-cell derived cytokine that regulates the biology of tissue cells. Cytokine Growth Factor Rev 2006;7:367-80.
4. Zenewicz LA, Flavell RA. Recent advances in IL-22 biology. IntImmunol 2011; 23: 159-63.
5. Wolk K, Witte E, Witte K, Warszawska K, Sabat R: Biology of interleukin-22. SeminImmunopathol 2010; 32: 17-31.
6. Ikeuchi H, Kuroiwa T, Hiramatsu N, Kaneko Y, Hiromura K, Ueki K, *et al*. Expression of IL-22 in RA: Potential role as a proinflammatory cytokine. Arthritis Rheum 2005;52:1037-46.
7. Wolk K, Kunz S, Asadullah K, Sabat R. Cutting edge: immune cells as sources and targets of the IL-10 family members? J. Immunol. 2002; 5168: 97.
8. Kondo T, Takata H, Matsuki F, Takiguchi M. Cutting edge: phenotypic characterization and differentiation of human CD8+ T cells producing IL-17. J Immunol2009; 182:1794-8.
9. Ortega C, Fernandez AS, Carrillo JM, Romero P, Molina IJ, Moreno JC, Santamaria M. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. J LeukoBiolo2009; 86:435-43.
10. Ness-Schwickerath KJ, Jin C, Morita CT. Cytokine requirements for the differentiation and expansion of IL-17A- and IL-22-producing human Vγδ2Vδ2 T cells. J Immunol2010; 184:7268-80.
11. Nograles KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22-producing “T22” T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. J Allergy ClinImmunol 2009;123(6):1244–52.
12. Hughes T, Becknell B, Freud AG, McClory S, Briercheck E, Yu J, Mao C, Giovenzana C, Nuovo G, Wei L et al. Interleukin-1beta selectively expands and sustains interleukin-22+ immature human natural killer cells in secondary lymphoid tissue. Immunity 2010; 32:803-14.
13. Crellin NK, Trifari S, Kaplan CD, Cupedo T, Spits H. Human NKp44+IL-22+ cells and LTi-like cells constitute a stable RORC+ lineage distinct from conventional natural killer cells. J Exp Med 2010; 207:281-90.
14. Cupedo, T., Crellin, N. K., Papazian, N. et al. Human fetal lymphoid tissue-inducer cells are interleukin 17-producing precursors to RORC+ CD127+ natural killer-like cells. Nat. Immunol2009;10:66.
15. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. Immunity 2004; 21: 241-54.
16. Pickert G, Neufert C, LeppkesM*et al*. STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. J. Exp. Med. 2009; 206:1465.
17. Eyerich S, Wagener J, Wenzel V, Scarponi C, Pennino D, Albanesi C, Schaller M, Behrendt H, Ring J, Schmidt-Weber CB, Cavani A, Mempel M, Traidl-Hoffmann C, Eyerich K: IL-22 and TNF-α represent a key cytokine combination for epidermal integrity during infection with candida albicans. Eur J Immunol 2011, 41:1894-901.
18. Radaeva S, Sun R, Pan HN, Hong F, Gao B. IL-22 plays a protective role in T cell-mediated murine hepatitis: IL-22 is a survival factor for hepatocytes via STAT3 activation. Hepatology 2004; 39: 1332.
19. Xie HM, AggarwalS, HO WH, Foster G, Zhaing Z, Stinson G, Wood WA, Goderd AD, Jurney AL. IL-22 a novel human cytokines that signals through the interferon receptor-related proteins CRF2-4 and IL-22R, J BiolChem 2000;275:31335-39
20. Dumoutier L, Van Roost E, Colau D, Renauld JC (2000) Human interleukin-10-related T cell-derived inducible factor: molecular cloning and functional characterization as an hepatocyte-stimulating factor. ProcNatlAcadSci USA 97:10144–10149
21. Kotenko SV, Izotova LS, Mirochnitchenko OV, Esterova E, Dickensheets H, Donnelly RP, Pestka S (2001) Identification of the functional interleukin-22 (IL-22) receptor complex: the IL-10R2 chain (IL-10Rbeta) is a common chain of both the IL-10 and IL-22 (IL-10-related T cell-derived inducible factor, IL-TIF) receptor complexes. J BiolChem 276:2725–2732
22. Kunz S, Wolk K, Witte E, Witte K, Doecke WD, Volk HD, Sterry W, Asadullah K, Sabat R. Interleukin (IL)-19, IL-20 and IL-24 are produced by and act on keratinocytes and are distinct from classical ILs. ExpDermatol2006;15:991–100.
23. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R (2004) IL-22 increases the innate immunity of tissues. Immunity 21:241–254
24. Takatori H, kanno WT *et al.* Lymphoid inducer-like cells are an innate source of IL-17 and IL-22. JExpMed 2009;206:35.
25. TrifariS,KaplanCD, Tran EH, CrellinNK, SpitsH. Identification of a human helper T cell population that has abundant production of IL-22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. Nat Immunol 2009;10(8):864–71.
26. Ratsep R, Kingo K, Karelson M, *et al*. Gene expression study of IL10 family genes in vitiligo skin biopsies, peripheral blood mononuclear cells and sera. Br J Dermatol 2008; 159: 1275-81.
27. Geboes L, Dumoutier L, Kelchtermans H, Schurgers E, Mitera T, Renauld JC, *et al.*Proinflammatory role of the Th17 cytokine IL-22 in collagen-induced arthritis in C57BL/6 mice. Arthritis Rheum 2009;60:390-5.
28. Lejeune D, Dumoutier L, Constantinescu S, Kruijer W, Schuringa JJ, Renauld JC. IL-22 activates the JAK/STAT, ERK, JNK, and p38 MAP kinase pathways in a rat hepatoma cell line. Pathways that are shared with and distinct from IL-10. J. Biol. Chem. 2002; 33277: 33676.
29. SarkarS, Zhou X, Justa S *et al.* Interleukin-22 reduces the severity of collagen-induced arthritis in association with increased levels of IL-10. Arthritis Rheum 2013; 66: 950-71.
30. Carrion M, Juarranz Y, Martinez C, Gonzalez-A´lvaro I, PablosJ,Gutie´rrez-Can˜asI, and Gomariz RP. IL-22/IL-22R1 axis and S100A8/A9 alarmins in human osteoarthritic and rheumatoid arthritis synovial Fibroblasts. Rheumatology 2013; 52:2177-2186.
31. Kim KW, Kim HR, Park JY et al. IL-22 promotes osteoclastogenesis in rheumatoid arthritis through induction of RANKL in human synovial fibroblasts. Arthritis Rheum 2012;64:1015-23.
32. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31: 315–24.
33. Fagerland MW, Sandvik L. Performance of two-sample location tests for skewed distributions with unequal variances. ContempClin Trials 2009;30: 490–496.
34. Leipe J, Schramm MA, Grunke M, Baeuerle M, Dechant C, Nigg AP, *et al*. IL 22 serum levels are associated with radiographic progression in rheumatoid arthritis. Annals of the Rheumatic Diseases 2011; 70: 1453–1457.
35. da Rocha Jr LF, Duarte AL, Dantas AT, Mariz HA, Pitta ID, Galdino SL, *et al.* Increased serum IL-22 in patients with RA and correlation with disease activity. Journal of Rheumatology 2012; 39(7): 1320-5.
36. Zhoa L, Jiang Z, Jiang Y, Ning MA, Zhang Y, Feng L and Wang K.IL-22+CD4+ T cells in patients with RA. International Journal of Rheumatic Diseases 2013; 16: 518-26.
37. Kim S, Han S, Withers DR, Gaspal F, Bae J, Baik S, Shin HC, Kim KS, Bekiaris V, Anderson G et al (2011) CD117 CD3 CD56 OX40Lhigh cells express IL-22 and display an LTi phenotype in human secondary lymphoid tissues. Eur J Immunol 41:1563–1572
38. CascaoR, Moura RA, Perpetuo I  *et al.*  Identification of a cytokine network sustaining neutrophil and Th17 activation in untreated early RA Artheritis Res Ther 2010; 12 R196.
39. Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosingspondylitis and rheumatoid arthritis. Arthritis Rheum 2009; 60: 1647-1656.
40. Lubberts E. Th17 cytokines in arthritis. SeminImmunopathol 2010;32:43-53.
41. Yang X, Zheng SG. Interleukin-22: Alikely target for treatment of autoimmune diseases. Autoimmunity Reiew 2014; 13: 615-620.