J Clin Periodontol 2008; 35: 365–370 doi: 10.1111/j.1600-051X.2008.01212.x

Journal of Clinical Periodontology

Interleukin-11, interleukin-1β, interleukin-12 and the pathogenesis of inflammatory periodontal diseases

Özlem Özer Yücel[1], Ezel Berker[1], Semra Gariboğlu[2] and Harika Otlu[3]

[1]Department of Periodontology; [2]Department of Immunology, Children's Hospital and [3]Department of Biostatistics, Hacettepe University, Ankara, Turkey

Yücel ÖÖ, Berker E, Gariboğlu S, Otlu H. Interleukin-11, interleukin-1β, interleukin-12 and the pathogenesis of inflammatory periodontal diseases. J Clin Periodontol 2008; 35: 365–370. doi: 10.1111/j.1600-051X.2008.01212.x.

Abstract

Objectives: The balance between pro-inflammatory and anti-inflammatory cytokines may be crucial for determining the immunopathology of gingivitis (G) and periodontitis. This study aimed to analyse interleukin-1β (IL-1β), IL-11 and IL-12 levels in gingival crevicular fluid (GCF) of patients with G and chronic periodontitis (CP).

Material and Methods: Fourty subjects including 12 CP, 14 G and 14 controls (C) were enrolled. GCF samples were collected from six maxillary sites per patient and analysed for IL-1β, IL-11 and IL-12 by an enzyme-linked immunosorbent assay.

Results: Significantly lower concentrations of IL-11 were detected in CP compared with both G and C groups ($p<0.05$). The CP group had a significantly higher total amount of IL-12 and IL-1β compared with the C group ($p<0.05$). The IL-11:IL-1β cytokine ratio was higher in both G and C groups compared with the CP group. The IL-11:IL-1β ratio became progressively lower with increasing probing depth ($p<0.01$).

Conclusions: Our data showed that IL-11 levels are significantly decreased in GCF from sites with periodontitis compared with G and healthy sites. Because of the possible preventive effect of IL-11 on inflammation, IL-11 may be an important factor in the therapeutic modulation of periodontal disease.

Key words: IL-11; IL-12; IL-1β; gingival crevicular fluid; gingivitis; inflammation; periodontitis

Accepted for publication 11 January 2008

Periodontitis is a multifactorial chronic inflammatory disease characterized by destruction of tooth-supporting tissues. The incidence and rate of progression of periodontal destruction involves a complex interaction between periodontopathic bacteria and cells of the immune system (Kinane & Lappin 2001, Bascones et al. 2005). The complex cytokine network that mediates the immune response includes pro-inflammatory cytokines, anti-inflammatory cytokines and specific cytokine receptors (Opal & Depalo 2000). As the other chronic inflammatory diseases, cytokines are considered to play an important role in the initiation, progression and the host modulation of periodontal disease (Bascones et al. 2005, Salvi & Lang 2005).

Because T-helper type 1 (Th1), Th2 and monocyte-derived cytokines in gingival tissues and gingival crevicular fluid (GCF) are involved in periodontal inflammation, even a minimal imbalance of cytokine production may affect induction of bone and collagen destruction in periodontal disease (Seymour & Gemmell 2001, Honda et al. 2006).

Interleukin (IL)-12 regulates the balance between Th1 and Th2 cells by inducing naive T cells in a Th1-specific manner and stimulating T cells and natural killer cells to synthesize multiple pro-inflammatory cytokines [interferon (IFN)-γ, IL-1β, tumour necrosis factor (TNF)-α, IL-8] (Trincheri & Gerosa 1996, Trincheri 2003, Watford et al. 2003). The interaction of IL-12 and many inflammatory cells may play an important role in periodontal disease as in other inflammatory diseases like active multiple sclerosis, rheumatoid arthritis and psoriasis (Comabella et al. 1998, Yawalkar et al. 1998, Kim et al.

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests.
This research was supported by a grant (05D07201001) from the Research Center of Hacettepe University.

2000). It has been shown that IL-12 can promote both lipopolysaccharide (LPS)-induced IL-8 and IL-8-induced polymorphonuclear leucocyte influx (Ethuin et al. 2001). Peripheral blood mononuclear cells stimulated with *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans* and *Tannerella forsythensis* produce IL-12 and IFN-γ (Kobayashi et al. 2000). Higher levels of IL-12 have been found in GCF from chronic periodontitis (CP) sites than gingivitis (G) and healthy ones, suggesting that Th1 plays a potential role in the progression of periodontitis (Tsai et al. 2005).

IL-11 has been reported to have anti-inflammatory properties due to its inhibition of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, IL-12 and nitric oxide (Hill et al. 1998). It has been shown that IL-11 plays an important role in the modulation of immune response via the reduction of pro-inflammatory cytokine production and periodontal tissue damage in animal models (Martuscelli et al. 2000). Although IL-1β levels in periodontal disease have been studied extensively (Gonzáles et al. 2001, Rawlinson et al. 2000, Engebretson et al. 2002, Holmlund et al. 2004, Zhong et al. 2007), few studies have reported on the presence of IL-11 (Martuscelli et al. 2000, Johnson et al. 2004)

There is evidence that failure to resolve inflammatory periodontal disease may be the result of an imbalance in both Th1/Th2 response and pro- and anti-inflammatory cytokines (Gemmell et al. 2001, Seymour & Gemmell 2001, Honda et al. 2006). The aim of this study, therefore, was to assess the local cytokine response in relation to clinical periodontal status by determining the levels of IL-1β, IL-12 and IL-11 in the GCF obtained from G and CP patients.

Material and Methods

Selection of subjects

Fourty adult patients referred to the Department of Periodontics at Hacettepe University were included for the study. Informed consent was obtained from the patients and the protocol was approved by the Ethics Committee of Hacettepe University. The patients were diagnosed according to clinical and radiographic criteria as CP ($n = 12$), G ($n = 14$) and controls (C, $n = 14$). All the subjects were non-smokers and had at least 20 teeth. Patients with CP had moderate-to-advanced periodontitis [probing depth (PD) $\geqslant 5$ mm and bone loss $\geqslant 25\%$ at least in six sites] and had not received any periodontal treatment before the time of examination. G subjects had bleeding on probing (BOP), no sites with attachment loss and gingival index scores > 1. The C group consisted of individuals with no periodontal disease history and no clinical signs of inflammation [PD $\leqslant 3$ mm, clinical attachment level (CAL) $\leqslant 1$ mm]. None of the subjects had any known systemic disorders or had used antibiotics and anti-inflammatory medications in the last 3 months. Subjects with active infectious diseases such as hepatitis, HIV infection and tuberculosis or chronically treated with medications (phenytoin, cyclosporine-A or calcium channel blockers), as well as females who were lactating or pregnant were excluded.

Clinical parameters including PD, CAL, plaque index (PI) (Silness & Löe 1963), gingival index (GI) (Löe & Silness 1963) and BOP (Ainamo & Bay 1975) were recorded. PD and CAL values were obtained using a conventional periodontal probe (Hu-Friedy, Chicago, IL, USA). All clinical data were recorded by one examiner.

GCF sampling

Maxillary teeth were selected for sampling in order to reduce the possibility of contamination with saliva. GCF samples were collected from six maxillary anterior sites of each patient with 5 mm or more PD and bone loss $\geqslant 25\%$ for the CP group, and from six BOP-positive maxillary anterior sites with no attachment loss of each patient for the G group. Sampling teeth were isolated with cotton rolls and dried gently. A standard paper strip (Perio-paper, IDE Interstate, Amityville, NY, USA) was inserted into the sulcus to the depth until mild resistance was felt and left in situ for 30 s. Strips contaminated by blood were excluded from the sampled group. Following collection of GCF, the strips were moved immediately to a calibrated Periotron 8000 (Oroflow Inc., Amityville, NY, USA) to determine the GCF volume and placed in sterile Eppendorf tubes containing 10 mM NaH_2PO_4 and 150 mM NaCl, pH 7.2, followed by mixing and centrifugation at $800 \times g$. The GCF samples were stored at -80°C until subsequent analysis. The values were pooled to give a single median value for each patient.

Assays of IL-1, IL-12 and IL-11

GCF samples were analysed for IL-1β, IL-12 and IL-11 using commercially available enzyme-linked immunosorbent assays (ELISA, Oroflow Inc.). Analyses were performed according to the manufacturer's protocol. All ELISA determinations were performed in duplicate. Results were calculated using the standard curves created in each assay. Concentrations of the cytokines were corrected for GCF volume and defined as pg/μl. The total amount of cytokines in GCF was expressed as picograms (pg).

Statistical analysis

The clinical parameters were expressed as mean $\pm$ standard deviation and analysed by the ANOVA test. Because the data were not normally distributed, cytokine levels in GCF were expressed as medians (minimum, maximum) and the significance of differences were assessed using the Kruskall–Wallis test and Conover comparison. A p value of < 0.05 was considered to be statistically significant. The cytokine ratios were compared by the Conover comparison. The non-parametric Spearman's coefficient was used to analyse the correlations between clinical parameters and GCF cytokine levels. SPSS software package was used for statistical analysis.

Results

The demographic data and the clinical characteristics of the patients are shown in Table 1. As expected, all the clinical parameters such as PI, GI, PD, CAL and BOP reached statistical significance among the groups.

Levels of IL-1β, IL-12 and IL-11 in GCF

Table 2 shows the median values of the total amounts and concentrations of IL-1β, IL-12 and IL-11 in GCF in the CP, G and C groups. CP subjects exhibited greater total amounts of IL-1β than G and C groups, and the difference between CP and C groups reached statistical significance ($p < 0.01$) while IL-1β concentrations were not different among the groups. Also, the total amount of IL-1β was significantly higher in the G group compared with

Table 1. Clinical and demographic characteristics of CP, G and C subjects

	CP ($n = 12$)	G ($n = 14$)	C ($n = 14$)	p value from ANOVA	Tukey–Kramer pairwise comparison		
					CP *versus* G	CP *versus* C	G *versus* C
Mean age	37.8	34.5	35.6	>0.710	NS	NS	NS
Female/male	7/5	5/9	9/5				
PD (mm)	5.1 ± 0.89	1.92 ± 0.32	1.49 ± 0.18	<0.001	*	*	Ns
CAL (mm)	5.78 ± 1.15	0.15 ± 0.20	0.0	<0.001	*	*	Ns
PI	1.65 ± 0.51	1.05 ± 0.17	0.35 ± 0.08	<0.001	*	*	*
GI	2.01 ± 0.73	1.2 ± 0.17	0.26 ± 0.08	<0.001	*	*	*
BOP (%)	92.84 ± 18.31	91.71 ± 14.12	0.0	<0.001	*	*	*

*Significantly different.
BOP, bleeding on probing; C, control group; CAL, clinical attachment level; CP, chronic periodontitis group; G, gingivitis group; GI, Gingival Index; NS, not significant; PD, probing depth; PI, Plaque Index.

Table 2. IL-1β, IL-12 and IL-11 levels in GCF in CP, G and C subjects

	CP ($n = 12$)	G ($n = 14$)	C ($n = 14$)	p value from Kruskall–Wallis test
IL-1β (pg)	40.66* (1.7–106.5)	23.58 (1.3–64)	10.23 (0.13–27.8)	<0.01
IL-1β (pg/μl)	20.82 (3.1–106.57)	39.80 (1–116)	23.80 (0.5–92)	>0.05
IL-12 (pg)	3.88* (0.52–7.8)	2.25 (0.4–20.7)	2.22 (0.3–10.5)	<0.05
IL-12 (pg/μl)	1.28 (0.33–8.5)	1.19 (0.6–14.2)	0.88 (0.4–16.9)	>0.05
IL-11 (pg)	54.42 (28.6–115.4)	75.06* (42.2–168.9)	49.73 (14–84.4)	<0.05
IL-11 (pg/μl)	35.19†,* (14.5–113.1)	101.46 (34.2–272.5)	98.5 (52.1–262.7)	<0.05
GCF (μl)	1.16†,* (0.54–2.97)	0.64* (0.42–2.2)	0.42 (0.2–0.9)	<0.05

Data are presented as median (minimum–maximum).
*Significantly different from C.
†Significantly different from G.
C, control group; CP, chronic periodontitis group; G, gingivitis group; GCF, gingival crevicular fluid; IL, interleukin.

the C group (Table 2). Very little IL-12 was detected in any of the GCF samples. The total amount of IL-12 was significantly higher in CP than that in the C group ($p<0.05$). IL-12 concentrations did not differ among the groups. IL-11 concentrations were significantly lower in CP, compared with both G and C groups ($p<0.05$), while no significant difference was detected between G and C (Table 2). The total amount of IL-11 was significantly higher in the G group than the C group ($p<0.05$); however, statistical analysis revealed no significant difference between the G and CP subjects. A significantly higher GCF volume was obtained from periodontitis patients compared with G and healthy subjects (Table 2).

Cytokine ratios

The IL-11:IL-1β cytokine ratio (total amount) was higher in the G group than CP, and also a higher IL-11:IL-1β ratio was detected in the C group compared with the CP group ($p<0.05$) (Table 3). The IL-11:IL-1β ratio became progressively lower with increasing PD ($p<0.01$, $r=-0.478$). The IL-11:IL-1β cytokine ratio (concentration) was significantly higher in C group compared with the CP group ($p<0.05$) (Table 3).

Table 3. Ratios of the IL-11: IL-1β in GCF in CP, G and C subjects

Cytokine ratio	CP ($n = 12$)	G ($n = 14$)	C ($n = 14$)	p value from Conover comparison
IL-11:IL-1β†	1.33:1	3.18:1*	4.86:1*	<0.01
IL-11:IL-1β‡	1.07:1	3.05:1	4.98:1*	<0.01

*Significantly different from CP.
†Ratio of the total amount of IL-11 to IL-1β.
‡Ratio of the concentration of IL-11 to IL-1β.
C, control group; CP, chronic periodontitis group; G, gingivitis group; GCF, gingival crevicular fluid; IL, interleukin.

Correlation of IL-1β, IL-12 and IL-11 with clinical parameters

IL-1β and IL-12 were not correlated with any of the clinical parameters where both the total amount and the concentration levels of IL-11 in GCF were negatively correlated with BOP in the G group ($p<0.05$, $r=-0.580$; $p<0.01$ $r=-0.693$).

Discussion

The intensity, duration and resolution of inflammation depend on shifting the balance between the activities of pro-inflammatory and anti-inflammatory cytokines during the periodontal inflammation (Kinane & Lappin 2001, Honda et al. 2006).

The results of the present study have shown that the total amount of IL-1β in GCF increased in patients with CP whereas the IL-1β concentrations did not differ significantly. Numerous studies have reported increased IL-1β levels in GCF from diseased sites compared with healthy sites (Gonzáles et al. 2001, Rawlinson et al. 2001, Holmlund et al. 2004, Zhong et al. 2007). Engebretson et al. (2002) also demonstrated higher total amounts of IL-1β in patients with severe periodontitis

compared with those with mild periodontitis and healthy individuals, in agreement with our results. These data suggest that the amount of IL-1β in GCF is associated with increasing periodontal inflammation. Although a large amount of IL-1β is produced by monocytes/macrophages, it has been shown that IL-1β is also released by polyclonally activated B cells in CP (Murphy et al. 2000). On the other hand, Rawlinson et al. (2003) reported lower concentrations of IL-1β at diseased sites in comparison with healthy sites in both smokers and non-smokers, in contrast to previous studies. The range of IL-1β concentrations in GCF is often quite variable. (Lee et al. 1995, Rawlinson et al. 2001, 2003, Zhong et al. 2007). The sampling method, collection time and also inter-individual differences may have a significant influence on the results for studies on cytokines in GCF.

In humans, the major effect of IL-12 is to stimulate IFN-γ production by Th1 cells and regulate the transition from an early innate immune response to an adaptive immune response (Trincheri 2003). The results of the present study showed little total amounts of IL-12 in GCF, with the levels increasing in CP, suggesting that IL-12 plays a potential role in the progression of periodontal inflammation by inducing a Th1 response. Several studies have attempted to determine the IL-12 profile in periodontal disease. Tsai et al. 2005 showed that the total amount of IL-12 in GCF was significantly higher in CP than in G and healthy subjects, while they reported significantly higher concentrations of IL-12 in healthy compared with CP subjects. These authors suggested that IL-12 could be related to the pathogenesis of inflammatory periodontal disease. Another study demonstrated that very little concentrations of IL-12 in GCF were detected, with the levels decreasing with increasing inflammation (Orozco et al. 2006). Our study revealed no significant differences in IL-12 concentrations. The controversial results of the previous reports may have resulted from the expression of IL-12 levels in GCF as concentrations or total amounts. It is well established that with increasing inflammation, there are increasing amounts of GCF (Champagne et al. 2003, Hatipoğlu et al. 2007). This could partly be the reason for the higher concentrations of IL-12 in healthy sites in the previous studies. Although the expression pattern is variable, these findings, together with our results, indicate that there is an association between IL-12 and periodontal disease.

Several studies have demonstrated that anti-inflammatory cytokines such as IL-4 and IL-10 can downregulate pro-inflammatory cytokine production from effector cells such as macrophages (Balkwill & Burke 1989, Raziuddin et al. 1998). It has also been shown that IL-11 can inhibit the production of IL-1β, TNF-α, IL-6, IL-12 p40 and nitric oxide and downregulates LPS-induced cytokines through inhibition of NF-κB expression in vitro (Trepicchio et al. 1996a, b, 1997, Leng & Elian 1997). In this study, we also assessed the level of IL-11 exerting a protective effect on inflammation and bone resorption. We observed significantly higher total amounts of IL-11 in G than the C group. Johnson et al. compared the gingival concentrations of IL-11 and IL-17 in both healthy and diseased gingival biopsies. They found that IL-11 concentrations were significantly lower within gingiva adjacent to 4–5 mm pockets as compared with 3 mm diseased sites (Johnson et al. 2004). In the present study, GCF IL-11 concentrations were significantly lower in the CP group (PD = 5.1 mm) compared with the G (PD = 1.92 mm, GI $\geqslant$ 1) and C groups, supporting the results of these authors.

The present study also demonstrated that both the total amounts and the concentration levels of IL-11 were negatively correlated with BOP, indicative of periodontal inflammation, in the G group. In animal models, IL-11 appears to be important in controlling the development of an inflammatory response in periodontal tissues (Trepicchio et al. 1996a, b, Martuscelli et al. 2000). It was reported that the twice-weekly administration of recombinant human IL-11 (rh IL-11) in the developing periodontal disease model acted by blocking the cytokines most associated with inflammation, leading to a reduction in both attachment loss and bone resorption (Martuscelli et al. 2000). IL-11 therapy has been successful for chronic inflammatory diseases like psoriasis and rheumatoid arthiritis (Hermann et al. 1998, Trepicchio et al. 1999). Several investigators showed that IL-11 induces osteoblastic differentiation and bone formation in vivo and in vitro (Takeuchi et al. 2002, Suga et al. 2003, 2004). Various host modulatory therapies (HMT) have also been developed or proposed to block the pro-inflammatory pathways responsible for periodontal breakdown (Assuma et al. 1998, Delima et al. 2001, Oates et al. 2002). Taken together, these results allow us to suggest that IL-11 may be acting as a key mediator in preventing the progressive inflammation leading to periodontal tissue breakdown.

In the present study, the total amount of IL-11:IL-1β cytokine ratio was significantly higher in both the G and the C groups, compared with the CP group. The IL-11:IL-1β ratio became progressively lower with increasing PD. Johnson et al. also reported that the IL-11:RANTES ratio became progressively lower with increasing PD, suggesting that the inhibitory effects of IL-11 on pro-inflammmatory cytokine synthesis could be minimized in tissues adjacent to deep pockets (Johnson et al. 2004). Thus, the progression of periodontal inflammation may be due to a lacking or inappropriate response of anti-inflammatory cytokines.

In conclusion, the results of the present study have shown that the production of IL-11 is significantly lower in CP patients than in G and C patients. Further studies are needed to determine the therapeutic benefit of IL-11 for resolution of inflammation in periodontal diseases.

References

Ainamo, J. & Bay, I. (1975) Problems and proposals for recording gingivitis and plaque. *International Dental Journal* **25**, 229–235.

Assuma, R., Oates, T., Cochran, D., Amar, S. & Graves, D. (1998) IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis. *Journal of Immunology* **160**, 403–409.

Balkwill, F. R. & Burke, F. (1989) The cytokine network. *Immunology Today* **10**, 299–304.

Bascones, A., Noronha, S., Gómez, M., Mota, P., Gónzalez Moles, M. A. & Dorrego, M. V. (2005) Tissue destruction in periodontitis: bacteria or cytokines fault? *Quintessence International* **36**, 299–306.

Champagne, C. M., Buchanan, W., Reddy, M. S., Preisser, J. S., Beck, J. D. & Offenbacher, S. (2003) Potential for gingival crevice fluid measures as predictors of risk for periodontal diseases. *Periodontology 2000* **31**, 167–180.

Comabella, M., Balashov, K., Issazadeh, S., Smith, D., Weiner, H. I. & Khoury, S. J. (1998) Elevated interleukin-12 in progressive multiple sclerosis correlates with disease activity and is normalized by pulse cyclopho-

sphamide therapy. *The Journal of Clinical Investigation* **102**, 671–678.

Delima, A. J., Oates, T., Assuma, R., Schwartz, Z., Cochran, D., Amar, S. & Graves, D. T. (2001) Soluble antagonists to interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibits loss of tissue attachment in experimental periodontitis. *Journal of Clinical Periodontology* **28**, 233–240.

Engebretson, S. P., Grbic, J. T., Singer, R. & Lamster, I. B. (2002) GCF IL-1beta profiles in periodontal disease. *Journal of Clinical Periodontology* **29**, 48–53.

Ethuin, F., Delarche, C., Benslama, S., Gougerot-Pocidalo, M. A., Jacob, L. & Cholllet-Martin, S. (2001) Interleukin-12 increases interleukin-8 production and release by human polymorphonuclear neutrophils. *Journal of Leukocyte Biology* **70**, 439–446.

Gemmell, E., Yamazaki, K. & Seymour, G. J. (2001) Destructive periodontitis lesions are determined by the nature of the lymphocytic response. *Critical Reviews in Oral Biology and Medicine* **13**, 17–34.

Gonzáles, J. R., Herrmann, J. M., Boedeker, R. H., Francz, P. I., Biesalski, H. & Meyle, J. (2001) Concentration of interleukin-1beta and neutrophil elastase activity in gingival crevicular fluid during experimental gingivitis. *Journal of Clinical Periodontology* **28**, 544–549.

Hatipoğlu, H., Yamalik, N., Berberoğlu, A. & Eratalay, K. (2007) Impact of the distinct sampling area on volumetric features of gingival crevicular fluid. *Journal of Periodontology* **78**, 705–715.

Hermann, J. A., Hall, M. A., Maini, R. N., Feltmann, M. & Brenann, F. M. (1998) Important immunoregulatory role of interleukin 11 in the inflammatory process in rheumatoid arthritis. *Arthritis and Rheumatism* **41**, 1388–1397.

Hill, G. R., Cooke, K. R., Teshima, T., Crawford, J. M., Keith, J. C., Brinson, Y. S., Bungard, D. & Ferrara, D. L. (1998) Interleukin-11 promotes T cell polarization and prevents acute graft-versus-host disease after allogeneic bone marrow transplantation. *The Journal of Clinical Investigation* **102**, 115–123.

Holmlund, A., Hänström, L. & Lerner, U. H. (2004) Bone resorbing activity and cytokine levels in gingival crevicular fluid before and after treatment of periodontal disease. *Journal of Clinical Periodontology* **31**, 475–482.

Honda, T., Domon, H., Okui, T., Kajita, K., Amanuma, R. & Yamazaki, K. (2006) Balance of inflammatory response in stable gingivitis and progressive periodontitis lesions. *Clinical and Experimental Immunology* **144**, 35–40.

Johnson, R. B., Wood, N. & Serio, F. G. (2004) Interleukin-11 and 17 and the pathogenesis of periodontal disease. *Journal of Periodontology* **75**, 37–43.

Kim, W., Min, S., Cho, M., Youn, J., Min, J., Lee, S., Park, S., Cho, C. & Kim, H. (2000) The role of IL-12 inflammatory activity of patients with rheumatoid arthritis (RA). *Clinical and Experimental Immunology* **119**, 175–181.

Kinane, D. F. & Lappin, D. F. (2001) Clinical, pathological and immunological aspects of periodontal disease. *Acta Odontologica Scandinavica* **59**, 154–160.

Kobayashi, H., Nagasawa, T., Aramaki, M., Mahanonda, R. & Ishikawa, I. (2000) Individual diversities in interferon gamma production by human peripheral blood mononuclear cells stimulated with periodontopathic bacteria. *Journal of Periodontal Research* **35**, 319–328.

Lee, H. J., Kang, I. K., Chung, C. P. & Choi, S. M. (1995) The subgingival microflora and gingival crevicular fluid cytokines in refractory periodontitis. *Journal of Clinical Periodontology* **22**, 885–890.

Leng, S. X. & Elian, J. A. (1997) Interleukin-11 inhibits macrophage interleukin-12 production. *Journal of Immunology* **159**, 2161–2168.

Löe, H. & Silness, J. (1963) Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontologica Scandinavica* **21**, 533–551.

Martuscelli, G., Fiorellini, J. P., Crohin, C. C. & Howell, T. H. (2000) The effect of interleukin-11 on the progression of ligature-induced periodontal disease in the beagle dog. *Journal of Periodontology* **71**, 573–578.

Murphy, K. M., Ouyang, W., Farrar, J. D., Yang, J., Ranganath, H., Asnagli, H., Afkarian, M. & Murphy, T. L. (2000) Signaling and transcription in T helper development. *Annual Review of Immunology* **18**, 451–494.

Oates, T. W., Graves, D. T. & Cochran, D. L. (2002) Clinical, radiographic and biochemical assessment of IL-1/TNF-alpha antagonist inhibition of bone loss in experimental periodontitis. *Journal of Clinical Periodontology* **29**, 137–143.

Opal, S. M. & Depalo, V. A. (2000) Anti-inflammatory cytokines. *Chest* **117**, 1162–1172.

Orozco, A., Gemmell, E., Bickel, M. & Seymour, G. J. (2006) Interleukin-1β, interleukin-12 and interleukin-18 levels in gingival fluid and serum of patients with gingivitis and periodontitis. *Oral Microbiology and Immunology* **21**, 256–260.

Rawlinson, A., Dalati, M. H., Rahman, S., Walsh, T. F. & Fairclough, A. L. (2000) Interleukin-1 and IL-1 receptor antagonist in gingival crevicular fluid. *Journal of Clinical Periodontology* **27**, 738–743.

Rawlinson, A., Grummitt, J. M., Walsh, T. F. & Ian Douglas, C. W. (2003) Interleukin1 and receptor antagonist levels in gingival crevicular fluid in heavy smokers versus non smokers. *Journal of Clinical Periodontology* **30**, 42–48.

Raziuddin, S., Bahabri, S., Al-Dalaan, A., Siraj, A. K. & Al-Sedairy, S. (1998) A mixed Th1/Th2 cell cytokine response predominates in systemic onset juvenile rheumatoid arthritis: immunoregulatory IL-10 function. *Clinical Immunology and Immunopathology* **86**, 192–198.

Salvi, G. E. & Lang, N. P. (2005) Host response modulation in the management of periodontal diseases. *Journal of Clinical Periodontology* **32** (Suppl. 6), 108–129.

Seymour, G. J. & Gemmell, E. (2001) Cytokines in periodontal disease: where to from here? *Acta Odontologica Scandinavina* **59**, 167–173.

Silness, J. & Löe, H. (1963) Periodontal disease in pregnancy. I. Correlation between oral hygiene and periodontal condition. *Acta Odontologica Scandinavica* **22**, 121–135.

Suga, K., Saitoh, M., Kokubo, S., Fukushima, S., Kaku, S., Yasuda, S. & Miyata, K. (2003) Interleukin-11 acts synergistically with bone morphogenetic protein-2 to accelerate bone formation in a rat ectopic model. *Journal of Interferon and Cytokine Research* **23**, 203–207.

Suga, K., Saitoh, M., Kokubo, S., Nozaki, K., Fukushima, S., Yasuda, S., Sasamata, M. & Miyata, K. (2004) Synergism between interleukin-11 and bone morphogenetic protein-2 in the healing of segmental bone defects in a rabbit model. *Journal of Interferon and Cytokine Research* **24**, 343–349.

Takeuchi, Y., Watanabe, S., Ishii, G., Takeda, S., Nakayama, K., Fukumoto, S., Kanetay Y., Inoue, D., Matsumoto, T., Harigaya, K. & Fujita, T. (2002) Interleukin-11 as a stimulatory factor for bone formation prevents bone loss with advancing age in mice. *The Journal of Biological Chemistry* **277**, 49011–49018.

Trepicchio, W., Ozawa, M., Walters, I. B., Kikuchi, T., Gilleaudeau, P., Bliss, J. L., Schwertschlag, U., Dorner, A. J. & Krueger, J. L. (1999) Interleukin 11 therapy selectively downregulates type 1 cytokine proinflammatory pathways in psoriasis lesions. *The Journal of Clinical Investigation* **104**, 1527–1537.

Trepicchio, W. L., Bozza, M., Pednault, G. & Domer, A. J. (1996a) Recombinant human IL-11 attenuates the inflammatory cytokine response through downregulation of proinflammatory cytokine release and nitric oxide production. *Journal of Immunology* **157**, 3627–3634.

Trepicchio, W. L., Bozza, M., Pedneault, G. & Dorner, A. J. (1996b) Recombinant human IL-11 attenuates the inflammatory response through down-regulation of proinflammatory cytokine release and nitric oxide production. *Journal of Immunology* **157**, 3627–3634.

Trepicchio, W. L., Wang, L., Bozza, M. & Domer, A. J. (1997) IL-11 regulates macrophage effector function through the inhibition of nuclear factor-kappa b. *Journal of Immunology* **159**, 5661–5670.

Trincheri, G. (2003) Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nature Reviews Immunology* **3**, 133–146.

Trincheri, G. & Gerosa, F. (1996) Immunoregulation by interleukin-12. *Journal of Leukocyte Biology* **59**, 505–511.

Tsai, I. S., Tsai, C. C., Ho, Y. P., Ho, K. Y., Wu, Y. M. & Hung, C. C. (2005) Interleukin-12 and interleukin-16 in periodontal disease. *Cytokine* **31**, 34–40.

Watford, W. T., Moriguchi, M., Morinobu, A. & O'shea, J. J. (2003) The biology of IL-12: coordinating innate and adaptive immune responses. *Cytokine and Growth Factor Reviews* **14**, 361–368.

Yawalkar, N., Karlen, S., Hunger, R., Brand, C. U. & Braathen, L. R. (1998) Expression of interleukin-12 is increased in psoriatic skin. *The Journal of Investigative Dermatology* **111**, 1053–1057.

Zhong, Y., Slade, G. D., Beck, J. D. & Offenbacher, S. (2007) Gingival crevicular fluid interleukin-1beta, prostaglandin E2 and periodontal status in a community population. *Journal of Clinical Periodontology* **34**, 285–293.

Address:
Özlem Özer Yücel
Department of Periodontology
University of Hacettepe
Ankara, 06100
Turkey
E-mail: ozlemozertr@gmail.com

Clinical Relevance

Scientific rationale for the study: There are few reports studying IL-11 in periodontal disease, although it has been suggested as a candidate molecule for HMT for many inflammatory diseases. In this study, we aimed to determine the possible role of IL-11 in periodontal pathogenesis, together with the pro-inflammatory cytokines IL-1β and IL-12.

Principal findings: Lower levels of IL-11 were detected in GCF of CP patients in comparison with G and healthy subjects. The IL-11: IL-1β ratio became progressively lower with increasing PD.

Practical implications: Further studies are needed to find out whether IL-11 could be one of the new treatment choices for therapeutic modulation of periodontal diseases.