Effect of Interleukin-2 on Interleukin-10 in vitro Production by Peripheral Blood Mononuclear Cells in Correlation with Hepatocyte Growth Factor Serum Levels in Patients with Chronic Renal Failure

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ABSTRACT

Chronic Renal Failure (CRF) is associated with dysfunction of immuno–inflammatory response manifested by imbalanced production of pro- and anti-inflammatory cytokines as well as decreased Th_1/Th_2 ratio. In the present work, the effect of interleukin 2 (IL-2) [as the main Th cell activator] on the production of interleukin-10 (IL-10) [as a potent anti-inflammatory cytokine] by Peripheral Blood Mononuclear Cells (PBMCs) in CRF patients was studied. The study was conducted on a group of 20 patients with CRF and 10 sex and age matched normal healthy individuals as a group of control. For both groups, the levels of IL-10 were measured in IL-2-supplemented and non-supplemented cell culture supernatants of PBMCs. The obtained results were correlated with serum levels of hepatocyte growth factor (HGF) as a marker of CRF associated inflammatory state. Results of the work revealed that IL-10 levels were significantly higher in both IL-2 supplemented (P=0.000) and non supplemented (P=0.000) PBMCs supernatants of CRF group when compared to normal one. This finding reflects the low grade systemic inflammation associated with CRF that is confirmed by significantly elevated HGF serum mean level (P=0.001) in CRF patients than normal subjects in the present study. These results have demonstrated that IL-2 may play a protective role in CRF patients through correction of Th_1/Th_2 ratio and keeping the balance between pro-and anti-inflammatory cytokines in those patients.

INTRODUCTION

Chronic renal failure (CRF) is associated with defective cellular and humeral immunity;[1] this is mainly due to disturbances of T helper (Th) cells subsets (i.e Th_1/Th_2) ratio[2] resulting in increased levels of circulating cytokines and other inflammatory markers such as proinflammatory cytokines including IL-1, IL-6, TNF[3].

In patients with CRF, increased serum hepatocyte growth factor (HGF) was found to be linked with the inflammatory status. It was

reported that HGF and IL-6 up regulate each other. This could explain the increased levels of HGF in sera of CRF patients.[4]

Human HGF is synthesized as a single polypeptide chain precursor of 728 amino acid residues. It has an appreciable homology with plasminogen, and it is processed proeolytically to release an N-terminal signal peptide of 31 amino acids to generate an active heterodimer after secretion.[5]

Hepatocyte growth factor (HGF) is emerged as multipotent growth factor that is involved in tissue regeneration, wound healing and normal tissue growth.[6] It is a powerful stimulator of DNA synthesis in a variety of cell types, especially hepatocytes.[7]

Patients with CRF are characterized by a low-grade systemic inflammation due to uremia reflecting consequences of an imbalanced production of pro-and anti-inflammatory cytokines.[8] High level of T-lymphocyte and monocyte expression of these cytokines has been reported and reflects the chronic immune system activation.[9]

IL-2 (Th$_1$ cytokine) as the main activator of other Th cells and IL-10 (Th$_2$ cytokine) as a potent regulatory and anti-inflammatory cytokine are examples of such cytokines that might have a role in CRF pathogenesis.

Interleukin-2 (IL-2) is an autocrine and paracrine T-cell growth factor. It is a polypeptide of M.Wt 15,400 Dalton consisting of 133 amino and encoded by single gene on human chromosome 4.[10]

It plays an important role in the immune systems by inducing cell cycle progression and protection from apoptosis.[11] Reduced cellular activity which exists in high proportion of CRF patients, could be attributed to a failure of monocyte population to support the process of primary T cell activation. This results in decreased production of IL-2 in those patients.[12,13]

Interleukin-10 (IL-10) is a Th$_2$ cytokines,[14] that is secreted by different cell population including T-cells, monocytes, B-cells, mast cells and keratinocyte.[15] IL-10 is an important negative regulator of cell mediated immunity and Th1 functions. However, it has a potent stimulatory effect for growth and differentiation of B lymphocytes, augmenting production of IgA, IgG and IgE. In vitro, IL-10 supresses the synthesis of reactive oxygen species and nitric oxide and blocks cycloxygenase-2-dependent synthesis of interstitial collagenase and gelatinase B.[16] It is considered to be a potent anti-inflammatory cytokine that is suggested to have a protective role against systemic inflammation by limiting the production of a broad range of pro-inflammatory factors in CRF patient.[3]

Thus, the aim of the present study was to investigate the relationship between IL-2 and IL-10 in CRF patients that could be useful in clarifying the mechanisms by which these two cytokines may participate in immunopathogenesis of the disease. To gain that aim, the plan of the work was to study the effect of IL-2 on in vitro production of IL-10 by PBMCs of CRF patients in correlation with serum level of HGF as a marker of CRF-associated inflammatory state.

SUBJECTS & METHODS

The study was conducted on twenty proved CRF patients (5 females and 15 males) of different causes, attending the Medical Research Institute Hospital. Their ages ranged from 36 to 69 years, with a mean of 46 ± 2 years. Patients were on hemodialysis for a period more than 6 months. Hemodialysis was conducted for 3-4 hr/session, 2-3 times weekly.

Careful clinical examination was performed to exclude patients with diseases that might affect the different immunological parameter. None of the patients experienced signs of diabetes mellitus, malignancy, fever or infection at the time of sampling. Blood samples were drawn from the fistula needle before the dialysis session.

Part of the blood was pipetted in EDTA-coated tube for the determination of blood Hb, the serum was separated from the remaining blood for the determination of other parameters.

Ten normal healthy individuals (3 female and 7 males) with ages ranged 27-68 years with a mean age of 45 ± 4 years were taken as a control group.

Methods

Determination of HGF serum level

About three ml of venous blood were withdrawn just before dialysis from each subject. After clotting serum samples were separated and kept at -80°C till used for determination of HGF.

HGF was quantitatively measured in serum samples by ELISA Kit (RVD) system GmbH, Germany) according to the manufactures' procedures. A monoclonal antibody specific for HGF was pre-coated onto a microplate (microwells). Standards (125-8000 Pg/ml), and samples were pipetted into the wells. Any HGF present was bound by immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for HGF was added to the wells. Any unbound antibody-enzymes reagent was removed by washing with wash buffer. A substrate solution was added to the wells and color developed in proportion to the amount of HGF bound in the initial step. The color development was stopped by 2N sulfuric acid and the intensity of the color was measured by microplate reader at 450nm. HGF concentration in each serum sample was determined using a standard curve that was created by plotting the mean absorbance for each standard against its corresponding concentration.[17]

PBMCs were separated by density gradient centrifugation over histopaque under aseptic conditions and adjusted to 1×10^6 cells/ml in RPMI culture medium supplemented with 10% fetal calf serum, penicillin (100 IU/ml) and streptomycin (100μg/ml). Cells were cultured without/with 100 U/ml IL-2 in 5% CO_2 humid atmosphere at 37°C for 24 hours. After culture cell suspension was centrifuged at 1800 rpm for 10 minutes and the culture supernatant was stored at -80°C until IL-10 level was measured.

Determination of IL-10 level

IL-10 was quantitatively measured in IL-2 supplemented and non-supplemented PBMCs culture supernatants by ELISA (Bender Med

System GmbH, Vienna) according to the manufactures' procedures. Anti-IL-10 monoclonal coating antibody presented onto microwells. IL-10 standard (8.1-200pg/ml) concentration and samples were pipetted into microwells. IL-10 present in the sample was bound to antibodies adsorbed to the microwells. HRP-conjugated monoclonal anti-IL-10 antibody was added and bound to IL-10 captured by the first antibody. Following incubation, unbound enzyme conjugated anti-IL-10 were removed during a wash step and substrate solution reactive with HRP was added to the wells. A colored product was formed in the samples. The reaction was terminated by addition of phosphoric acid and absorbance was measured at 450 nm. IL-10 concentration in each serum sample was determined using a standard curve that was created by plotting the mean absorbance for each standard against its corresponding concentration.[18]

Levels of IL-10 in PBMCs supernatants and HGF serum samples are presented as mean ± SEM for each studied group.

Statistical analysis

Data of the present study were statistically analyzed using SPSS version 10 soft ware. For comparison of the means of more than two groups, one way analysis of variance (ANOVA) was applied. A difference was considered significant at P< 0.05.

RESULTS

Urea and creatinine mean serum levels were significantly increased in CRF patients when compared with normal controls (p = 0.00 for both). On the other hand Hb mean blood level in CRF patients was significantly lower than that in normal controls (p = 0.00), Table (I).

- IL-10 in Peripheral Blood Mononuclear Cells (PBMCs) of CRF patients was significantly higher than those of corresponding control groups ($p_4 = 0.000$, $p_2 = 0.000$) respectively. Table (II).
- Supplementation of IL-2 to PBMCs of control group significantly reduced IL-10 level ($p_1 = 0.003$). The same result was obtained after IL-2 supplementation of the PBMCs of CRF patients ($p_3 = 0.000$), Table (II).
- HGF was significantly higher in the sera of CRF patients when compared with that of control group. (p = 0.001), Table (III).
- On the other hand, no significant correlation was found between the levels of IL-10 released by PBMCs and HGF serum levels in CRF patients as well as in control group (r=0.23, p>0.05, r=0.31, p>0.05; respectively).

Table (I): Statistical analyses of the mean values of serum urea, as well as creatinine and blood hemoglobin (Hb) levels in chronic renal failure (CRF) patients and normal control (NC) groups

Laboratory investigations		CRF	NC
Urea (mg/dL)	Range	90-233	15-30
	Mean ± S.E.M	167.95±8.6	20.25±1.8
	P	0.00*	
Serum creatinine (mg/dL)	Range	5.3-18.2	0.7-1.2
	Mean ± S.E.M	12.32±0.72	0.918±0.058
	P	0.00*	
Blood Hb (g/dL)	Range	6.4-13	11.8-16.2
	Mean ± S.E.M	9.28±0.41	14.03±0.48
	P	0.00*	

* p is significant at the level < 0.05.

Table (II): Statistical analyses of IL-10 (pg/ml) in peripheral blood mononuclear cells of chronic renal failure (CRF) patients and control group, with and without IL-2 supplementations

	Control	Control + IL-2	CRF	CRF + IL-2
Range	346.1–523.8	270.3–422.1	418.3–766.2	346.7–415.8
± Mean	421.78	286.22	541.06	391.65
± S.EM	15.62	21.04	32.72	7.40
(p₁)		0.000**		
(p₂)			0.003**	
(p₃)				0.000**
(p₄)				0.000**

(p_1): Level of significance between (control) and (control + IL-2) groups.
(p_2): Level of significance between (Control and CRF) groups.
 (p_3): Level of significance between (CRF and CRF + IL-2) groups.
 (p_4): Level of significance between (control + IL-2) and (CRF + IL-2) groups.
** Significant at p level < 0.01.

Table (III): Statistical analyses of serum hepatocyte growth factor (pg/ml) in chronic renal failure (CRF) patients and control group

	Control	CRF
Range	237.25-609.75	1522.25-7747.25
Mean	517.88	2935.44
± S.EM	83.73	412.75
(p)	(0.001) **	

** Significant at p < 0.01

DISCUSSION

The elevated levels of released IL-10 by IL-2 non-supplemented PBMCs of CRF patients than controls reflect intensive immuno-inflammatory state of those patients in response to chronic inflammatory stimuli including pro-inflammatory cytokines. This finding may form a counter-regulatory mechanism to limit inflammatory process in CRF patients.

Secretion of IL-10 is suggested by Grindt *et al.*,[17] to be a compensatory mechanism which controls monokine induction by CRF patients. In their more recent study, Grindt and his associates[3] has proven the protective role of IL-10 against systemic inflammation in CRF suggesting that IL-10 "high-producer" genotype is associated with a lower event rate and mortality than the IL-10 "low-producer" genotype.

Early studies of Matsumoto *et al.*[12] and Heidenreich *et al.*[18] suggested that elevated degree of apoptosis of T cell and monocytes in CRF contribute to the impaired cellular host defense seen in those patients. Now it is well established that in CRF patients, there is an increase in apoptosis of Th_1 than Th_2 cell subsets leading to decreased value of Th_1/Th_2 ratio. Such data together with ours explain findings of Libetta *et al.*,[13] who demonstrated that the constitutive release of IL-4 and IL-10 [mainly Th_2 cytokines] by PBMCs of CRF is increased by 5-8 times in comparison with healthy control. They, also, demonstrated that the ability of PBMCs of CRF patients to secrete interferon gamma (IFNγ was recovered after IL-4 and IL-10 neutralization.

Accordingly, the IL-2 supplementation to the PBMCs of CRF patients in the present study may partly compensate, in vitro, the loss of Th_1 cells caused by apoptosis in vivo. Thus, the lower level of IL-10 in IL-2 supplemented PBMCs than that in non-supplemented PBMCs of both normal and CRF group in the present study seemed to be due to the increased proliferation of Th_1 cell subset that in turn increased the production and activities of Th_1 cytokines that antagonized the secretion and activities of the type which belongs to Th_2 subset including IL-10. In addition, supplemented IL-2 could act directly on Th_2 cells to antagonize the secretion of Th_2 cytokines.[13]

It could, also, be suggested that decreased IL-10 level as a potent suppressor cytokine may allow different cell types to retain their normal activities including T-lymphocytes, monocytes and natural killer (NK) cells in CRF patients which confirm the protective role of IL-2 in those patients.[14] This protective role of IL-2 according to the current result may be relevant to the regulation of both pro-and anti-inflammatory cytokines since both are Th_2 cytokines.

In this contest, Vella and his associates[19] demonstrated that IL-2 protects T-cells from death both in vitro and in vivo as tested in animal models. It was suggested by Wilhelm et al.,[20] that using IL-2 therapy for CRF increased T cells to normal levels, decreased gammopathy, returned renal function and gained apparently normal health status sustained for two years.

Results of the present study, also, revealed that serum HGF level was higher in CRF patients that of normal subjects. This reflects the inflammatory state of those patients as suggested by Malotino and his associates.[4] This finding is in agreement with results previous studies of Randers et al.,[21], Rampino et al.,[22]. The increased production of HGF in CRF was demonstrated to be correlated with kidney destruction and may be connected with glomerulopathy exacerbation. The higher serum HGF level in CRF is seemed to counteract inflammatory events as it was demonstrated that the beneficial effect of HGF in CRF is attributable, at least in part, to a direct anti-inflammatory action.[4]

Beside its anti-inflammatory effect, HGF is suggested to play a role in cell protection, anti apoptotic, antifibrosis and angiogenesis. Suggested mechanisms to explain these actions include, prevention of tubular cell apoptosis, blocking epithelial to mesenchymal transition and promotion of Extra Cellular Matrix degragation. Thus, the high serum HGF level in CRF may serve in ameliorating the progression of kidney disease as a potent growth-stimulating activator for a wide variety of cells.[6,23]

Although HGF was found to be stimulated by inflammatory cytokines,[24] and inhibited by tumour growth factor beta (TGFβ),[5] the role of HGF in the immune system is not well defined. However, the finding of Futamatsu et al.,[25] that HGF induces Th_2 cytokines may attribute the immune response shifting to Th_2 activties in CRF patients to the elevated HGF serum level in present study. Accordingly, it could be suggested that the anti-apoptotic effect of HGF in CRF patients may be directed to Th_2 cell subset rather than Th_1.

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تأثير الإنترليوكين–٢ على إنتاج الإنترليوكين–١٠ بواسطة كرات الدم البيضاء المفصولة وعلاقتها بمستوى عامل نمو خلايا الكبد فى مصل الدم لمرضى الفشل الكلوى المزمن

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مرض الفشل الكلوى يصاحبه ضعف فى الاستجابة المناعية – الالتهابية، تظهر كخلل فى إنتاج محركات الخلايا الالتهابية وكذلك نقص فى معدل الخلايا الليمفاوية ت المساعدة ١/ الخلايا الليمفاوية ت المساعدة ٢.

فى هذا البحث تم دراسة تأثير الأنترلوكين –٢ لـ كمحفز للخلايا الليمفاوية ت على إنتاج الأنترلوكين – ١٠ (كمضاد للالتهاب) بواسطة كرات الدم البيضاء المفصولة من مرضى الفشل الكلوى (٢٠ مريضاً) وأشخاص أصحاء (١٠ أشخاص) وقد تم زراعة كرات الدم البيضاء بعد فصلها فى وسط زراعى فى وجود وعدم وجود الأنترلوكين –٢. بعد انتهاء فترة زراعة الخلايا تم فصل الوسط الزراعى لقياس مستوى الأنترلوكين – ١٠ المنتج من هذه الخلايا. ومن جهة أخرى تم قياس مستوى عامل نمو خلايا الكبد فى مصل المرضى والأشخاص الأصحاء كدليل للحالة الالتهابية لمرض الفشل الكلوى المزمن.

وقد أظهرت النتائج زيادة ذات قيمة إحصائية لمستويات الأنترلوكين– ١٠ فى الوسط الزراعى وكذلك زيادة فى مستويات عامل نمو خلايا الكبد فى مرضى الفشل الكلوى المزمن عنه فى الأشخاص الأصحاء، وعلى الرغم من ذلك لم يكن هناك علاقة ذات قيمة إحصائية بين مستويات الأنترلوكين– ١٠ ومستويات عامل نمو خلايا الكبد من هذه النتائج يتضح أن الأنترلوكين –٢ يمكن أن يكون له دور حماية فى مرضى الفشل الكلوى المزمن وذلك بتصحيح معدل الخلايا الليمفاوية ت المساعدة١/ الخلايا الليمفاوية ت المساعدة ٢، وكذلك بتوازن محركات الخلايا الالتهابية والمضادة لها فى هؤلاء المرضى.