Biochemical and Biophysical Research Communications 424 (2012) 611–615

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Base excision repair gene polymorphisms are associated with inflammation in patients undergoing chronic hemodialysis

Zhenming Cai [a,b], Wenwen Guo [a,b], Huimei Chen [a,b,*], Jing Tao [c], Lili Cao [a,b], Wei Sun [c], Yaping Wang [a,b,*]

[a] Department of Medical Genetics, Nanjing University School of Medicine, Nanjing, China
[b] Jiangsu Key Laboratory of Molecular Medicine & State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing, China
[c] Jiangsu Province Hospital of TCM, Nanjing University of Traditional Chinese Medicine, Nanjing, China

ARTICLE INFO

Article history:
Received 27 June 2012
Available online 7 July 2012

Keywords:
BER gene
Hemodialysis patients
IL-1β
IL-6
Inflammation
Polymorphism

ABSTRACT

Chronic inflammation may increase the risk of mortality for patients undergoing hemodialysis, while enhanced oxidative stress and DNA oxidative damage are involved in the inflammatory response. The purpose of this study was to examine the associations between inflammation and polymorphisms in the base excision repair (BER) system, which protects against oxidative DNA damage, among hemodialysis patients. Data were analyzed from 167 hemodialysis patients and 66 healthy controls. All subjects were evaluated for the expression of inflammatory cytokines (IL-1β and IL-6) and genotyped for two BER genes, including *hOGG1* c.977C > G, *MUTYH* c.972G > C and *AluYb8MUTYH*. The results showed that the hemodialysis patients had significantly higher levels of IL-1β and IL-6 than the healthy controls. In the healthy controls, no patterns of association were observed between the *hOGG1* c.977C > G or *MUTYH* c.972G > C genotypes and IL-1β or IL-6 levels; however, patients with the *MUTYH* c.972G/G genotype presented higher levels of IL-1β than those with the C/C genotype. The *AluYb8MUTYH* genotype was strongly associated with increased IL-1β levels among controls and increased IL-1β and IL-6 levels among hemodialysis patients. Additionally, the synergetic effect of these variations of the BER genes on the levels of IL-1β and IL-6 was investigated. The combinations of the *AluYb8MUTYH* genotype with the *hOGG1* c.977 C > G or *MUTYH* c.972 G > C genotypes were associated with the IL-1β and IL-6 levels in hemodialysis patients. This is the first report showing an association between BER genetic polymorphisms and the inflammatory state during hemodialysis; this association might be mediated by impaired anti-oxidant defense mechanisms.

1. Introduction

Chronic inflammation has been widely documented in patients with end-stage renal disease (ESRD) who are receiving maintenance hemodialysis [1]. When compared with healthy controls, the levels of most inflammatory markers are several-fold higher in the patients undergoing hemodialysis [2]. The increased levels of inflammatory cytokines contributed to the high mortality and poor outcome of these patients [3–5]. IL-1β and IL-6 have been identified as independent predictors of mortality in hemodialysis patients [6–8]. Thus, an extensive understanding of the inflammatory response would be useful for improving the outcome and preventing mortality among hemodialysis patients.

Reactive oxygen species (ROS) are involved in the pathogenesis of inflammation [9,10]. A growing body of evidence indicates that ROS can cause damage to cellular macromolecules. DNA is the most sensitive biological target for damage from oxidative stress, as it is not well protected from ROS and has limited chemical stability [11,12]. Genomic damage that is either left unrepaired or is repaired with errors may cause mutations of critical genes and result in high levels of inflammation and an elevated risk for certain diseases, including cancer and atherosclerosis [13,14].

DNA repair enzymes continuously monitor chromosomes to correct nucleotide residues that are damaged after exposure to ROS. The base excision repair (BER) system, which includes the *MUTYH*, *hOGG1* and *MTH1* genes, is a key mechanism for the repair of oxidative DNA damage [15]. Inactivation of the BER genes causes an accumulation of 8-oxoguanine (8-OHdG) and a mutational phenotype that is characterized by the presence of G:C → T:A transversions [16].

Abbreviations: ESRD, end-stage renal disease; ROS, reactive oxygen species; BER, base excision repair; IL-1β, interleukin-1β; IL-6, interleukin-6.

* Corresponding authors at: The Department of Medical genetics, Nanjing University School of Medicine, Hankou Road 22, Nanjing 210093, China. Fax: +86 25 83686451.

E-mail addresses: chenhuimei@nju.edu.cn (H. Chen), wangyap@nju.edu.cn (Y. Wang).

0006-291X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbrc.2012.06.161

Oxidative stress is enhanced in patients undergoing hemodialysis due to reduced anti-oxidant systems and increased pro-oxidant activity [17]. However, an association between the inflammatory profile and the repair of oxidative DNA damage has not been documented. Furthermore, to the best of our knowledge, the biological significance of BER gene polymorphisms on the levels of circulating inflammatory markers in patients undergoing hemodialysis has not been elucidated. The polymorphic form in human DNA repair enzymes has been demonstrated to be involved in the control of damaged DNA repair and relevant events [18]. Our previous study has shown that a common variant of the *MUTYH* gene (*AluYb8MUTYH*) is associated with increased DNA oxidation as well as increased plasma IL-1 levels in healthy subjects [19]. In view of the different activity of BER proteins, we examined three BER gene polymorphisms (*hOGG1* c.977C > G, rs1052133; *MUTYH* c.972G > C, rs3219489 and *AluYb8MUTYH*, rs10527342) in the current study. We explored the individual and combined effects of these polymorphisms on the inflammatory state of hemodialysis patients by evaluating the plasma levels of the key pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-6 (IL-6).

2. Materials and methods

2.1. Subjects

A total of 167 patients who were undergoing hemodialysis treatment at two dialysis units in Nanjing, Jiangsu, China, between October 2009 and February 2010 were enrolled in the current study. All patients were older than 20 years of age and had been maintained on hemodialysis protocols for more than 3 months before this study began. The mean age of the patients (101 men and 66 women) was 54 ± 15 years. The primary diagnoses associated with ESRD were primary glomerulonephritis (n = 111), diabetic nephropathy (n = 19), congenital or inherited nephritis (n = 5), systemic lupus erythematosus (n = 3) and shrunken kidney resulting from unknown causes (n = 29).

Healthy individuals with normal renal function were recruited from volunteers who were receiving health check-ups in the same region. A detailed interview and various laboratory analyses were performed for every individual, including measurement of the albumin excretion rate (AER) and the serum creatinine level. The subjects were excluded if their albumin excretion rate (AER) was ⩾ 30 mg/24 h, their serum creatinine level was ⩾ 1.2 mg/dL or if an ultrasound of their kidney and ureter was abnormal in size and appearance. They were also ruled out if they suffered from certain diseases such as acute inflammation, diabetes, hypertension, autoimmune diseases or cancer, depending on the past history and the clinical and laboratory characteristics. Finally, 66 subjects were randomly selected for inclusion in the control cohort. The Institutional Ethics Committee of Nanjing University School of Medicine approved this study, and written informed consents were obtained from all participants.

2.2. Genotyping

To study the BER gene polymorphisms, cellular DNA was isolated from 1 ml of peripheral blood from the patients and the healthy individuals and was analyzed by PCR. In detail, the *OGG1* c.977C > G (rs1052133) and *MUTYH* c.972G > C (rs3219489) polymorphisms were genotyped using the dsDNA dye LCGreen in combination with High Resolution Melting (HRM) analysis, as described previously [20]. The PCR primers were designed by the LightScanner® primer design software (Idaho Technology) (Table 1). The 9-μL PCR reactions were supplemented with 1 μL of 1 × LCGreen® PLUS (Idaho Technology), and the 96-well plates (Bio-Rad) were analyzed on the Light Scanner (Idaho Technology). Fluorescence data were collected over a temperature range of 70–97 °C, and melting curve analysis was performed according to the manufacturer's software. For the *AluYb8MUTYH* (rs10527342) polymorphism, the genomic DNA was added to a 25-μl PCR mixture along with the appropriate primers (Table 1). The thermo-profile consisted of 35 cycles of denaturation at 94 °C for 30 s, annealing at 60 °C for 30 s and extension at 72 °C for 50 s, which was preceded by an initial denaturation step at 94 °C for 5 min and followed by a terminal extension step at 72 °C for 10 min. The PCR products were analyzed on 1% agarose gels (Invitrogen, Carlsbad, CA). Subjects that are heterozygous for this variation exhibit two fragments (500 and 826 bp products, absence/presence, *A/P*), while those that are homozygous display a single 826 bp fragment (presence/presence, *P/P*) [19].

2.3. Quantitation of plasma IL-1β and IL-6

Venous blood samples were drawn from fasting healthy individuals or from fasting hemodialysis patients at the start of a dialysis session, before heparin administration. The plasma samples isolated from these subjects were stored at −80 °C, and the concentrations of IL-1β and IL-6 were quantified in single batch assays with a commercial ELISA kit (mouse monoclonal antibody against IL-1β, mouse monoclonal antibody against IL-6; R&D Systems, Inc., Minneapolis, United States of America).

2.4. Statistical analysis

All statistical analyses were conducted in SPSS 15.0. The descriptive statistical values used to describe the data included mean ± SE values for continuous data and percentages for categorical data. Separate comparisons of variables among subjects with different genotypes were conducted with ANOVA and Student's unpaired t test. In all cases, a P value of less than 0.05 was considered statistically significant.

3. Results

The clinical characteristics of patients undergoing hemodialysis are listed in Table 2. The age (P = 0.708) and gender (P = 0.407) of the patients and control groups were not significantly different.

Table 1
Sequences of the PCR primers used for genotyping.

Polymorphisms	Primer sequence (5′–3′)	Annealing temperature (°C)	Product length (bp)
rs1052133: *OGG1* c.977C>G (Ser326Cys)	F: 5′-actgtcactagtctcaccag-3′ R: 5′-ggaaggtgcttggggaat-3′	55	200
rs3219489: *MUTYH* c.972G>C (Gln324His)	F: 5′-cccattccagttcttcctct-3′ R: 5′-cctttctggggaagttgacc-3′	58	208
rs10527342: *AluYb8MUTYH*	F: 5′-tcttgacctggagaccttcc-3′ R: 5′-agctgcttcctccaaacagc-3′	60	500 or 826

Table 2
The demographic information and clinical profiles of the hemodialysis patients and the healthy controls.

	Hemodialysis patients (n = 167)	Healthy controls (n = 66)	P value
Age (yr)	54 ± 1.2	53 ± 0.74	0.708[a]
Male (%)	101 (60.5%)	36 (54.5%)	0.407[b]
Duration of hemodialysis (yr)	3.8 ± 0.61	–	–
IL-1β (pg/ml)	155 ± 5.51	110 ± 4.25	<0.001[a]
IL-6 (pg/ml)	7.67 ± 0.228	4.49 ± 0.325	<0.001[a]

[a] Comparison between the patients and the healthy controls by unpaired t test.
[b] Comparison between the patients and the healthy controls by Pearson's χ^2 test.

When compared with healthy controls, the patients undergoing hemodialysis had significantly higher levels of IL-1β (155 ± 5.51 versus 110 ± 4.25 pg/ml; $P < 0.001$) and IL-6 (7.67 ± 0.23 versus 4.49 ± 0.33 pg/ml; $P < 0.001$).

3.1. The effect of a single BER gene polymorphism on inflammation

The levels of plasma IL-1β were not significantly different with the various *hOGG1* c.977C > G genotypes among either hemodialysis patients or healthy controls ($P = 0.683$ and $P = 0.096$ by ANOVA, respectively; Fig. 1A1). Similar findings were detected when comparing the plasma IL-6 levels (Fig. 1A2).

For the *MUTYH* c.972C > G polymorphism, no patterns of association were observed among the healthy subjects in either the plasma IL-1β ($P = 0.722$ by ANOVA) or IL-6 ($P = 0.695$ by ANOVA) levels (Fig. 1B1, B2). However, a significant difference was observed among patients undergoing hemodialysis. When compared with the patients carrying the *MUTYH* c.972C/C genotype, those with the c.972G/G genotype had a statistically higher IL-1β level (173 ± 9.37 versus 132 ± 11.9 pg/ml; $P = 0.017$).

Moreover, the healthy controls with the *AluYb8MUTYH P/P* genotype had higher IL-1β levels than those with the *A/A* or *A/P* genotypes ($P = 0.002$, $P = 0.007$, respectively), although there was no difference in plasma IL-6 levels with the different *AluYb8MUTYH* genotypes. Among patients undergoing hemodialysis, however, those with either the homozygous or heterozygous *AluYb8MUTYH* genotypes had significantly increased IL-1β levels, when compared with those with the *A/A* genotype ($P = 0.006$ and $P = 0.007$, respectively; Fig. 1C1). Similarly, the level of IL-6 increased from 6.35 ± 0.360 pg/ml in *AluYb8MUTYH A/A* carriers to 8.03 ± 0.340 pg/ml in *A/P* carriers and to 8.60 ± 0.451 pg/ml in *P/P* carriers (Fig. 1C2).

3.2. The synergetic effect of BER gene polymorphisms on the inflammatory state of hemodialysis patients

Furthermore, the synergetic effect of the *hOGG1* c.977C > G, *MUTYH* c.972G > C and *AluYb8MUTYH* polymorphisms on the inflammatory state was analyzed among hemodialysis patients; the wild-type genotypes for these genes were used as references (Table 3). The combination of the *hOGG1* c.977C > G and *MUTYH* c.972G > C polymorphisms had no association with the levels of IL-1β or IL-6 ($P = 0.275$ and $P = 0.415$ by ANOVA, respectively). However, the combination of the *hOGG1* c.977C > G or the *MUTYH* c.972G > C polymorphism with the *AluYb8MUTYH* polymorphism was significantly associated with increased IL-1β and IL-6 levels.

When compared with the patients carrying the *hOGG1* c.977 C/C genotype and *AluYb8MUTYH A/A* genotype, those carrying the c.977 C/G or G/G genotypes and the *A/P* or *P/P* genotypes had higher IL-1β levels ($P = 0.011$), as well as those carrying the c.977 C/C genotype and the *A/P* or *P/P* genotypes ($P = 0.017$). When using IL-6 as the inflammatory marker, the combination of the *hOGG1* c.977C > G polymorphism with the *AluYb8MUTYH* polymorphism presented a similar association between the combined polymorphisms and inflammation. Among patients with a combination of the *MUTYH* c.972G > C and *AluYb8MUTYH* polymorphisms, those with the c.972 C/G or G/G genotypes and the *A/P* or *P/P* genotypes had both significantly higher IL-1β and IL-6 levels than those with the c.972 C/C and *A/A* genotypes ($P = 0.030$ and $P = 0.022$, respectively).

4. Discussion

End-stage renal disease is a troublesome health problem worldwide, and the use of maintenance hemodialysis is consequently increasing with the epidemic of ESRD [21]. Recently, an increasing burden from ESRD and hemodialysis has been reported in China. At the end of 2008, there were 102,863 ESRD patients on maintenance hemodialysis or peritoneal dialysis, an increase of 52.9% over the previous year [22]. Previous studies have shown that hemodialysis patients have increased mortality rates compared to the general population, which is partly due to the increased inflammation in these subjects [3,23,24]. Interestingly, this study showed an increase in inflammation in hemodialysis patients and further demonstrated that this effect is genetically affected by gene polymorphisms in the BER system.

Chronic inflammation has, in fact, been widely documented in patients undergoing hemodialysis, and the predictive value of inflammatory markers has been discussed [25,26]. Hung et al. [8] showed that IL-1β, IL-6 and CRP were significant predictors of mortality during hemodialysis. The levels of plasma IL-1β and IL-6 were used as pro-inflammatory markers in the present study. When compared with healthy controls, IL-1β and IL-6 levels were significantly increased among hemodialysis patients, confirming that amplified inflammation is concurrent with hemodialysis.

Inflammation in hemodialysis patients is deeply interrelated with oxidative stress [27]. ROS can indiscriminately react with many cellular biomolecules, including proteins and lipids as well as DNA, to produce a variety of oxidative lesions [28]. Several repair pathways, including the base excision repair (BER) pathway, are involved in the repair of such DNA lesions [29]. It has been demonstrated that genetic polymorphisms in DNA repair genes might modulate their capacity to repair DNA damage, resulting in an accumulation of damaged DNA, and contribute to the level of inflammation and other complex diseases [30,31]. We have previously reported that BER gene polymorphisms could increase the risk of ESRD in the Chinese population and that they were also associated with increased oxidative DNA damage levels (i.e., 8-OHdG) in hemodialysis patients [20]. Moreover, homozygous subjects carrying the *AluYb8MUTYH* genotype were associated with a significant increase in plasma IL-1 in healthy individuals [19]. This study encouraged us to explore the relationship between BER gene polymorphisms and the levels of inflammation in hemodialysis patients.

The most compelling observation of this study is the effect of common BER system gene polymorphisms and their combinations on the level of inflammation in hemodialysis patients. The BER system mainly includes three genes, *MTH1*, *MUTYH* and *hOGG1*, and we have primarily focused on the two repair genes *MUTYH* and *hOGG1* for several years. We found that the *MUTYH* c.972G > C and *AluYb8MUTYH* polymorphisms directly increased plasma IL-β and IL-6 levels in hemodialysis patients. Patients with the *MUTYH* c.972G/G genotype or the *AluYb8MUTYH P/P* or *A/P* genotypes had significantly higher IL-β and IL-6 levels than patients with the wild-type genotype. The findings from Svilar et al. [32] confirmed this association, showing that base excision repair was involved in preventing cellular degeneration and death by suppressing

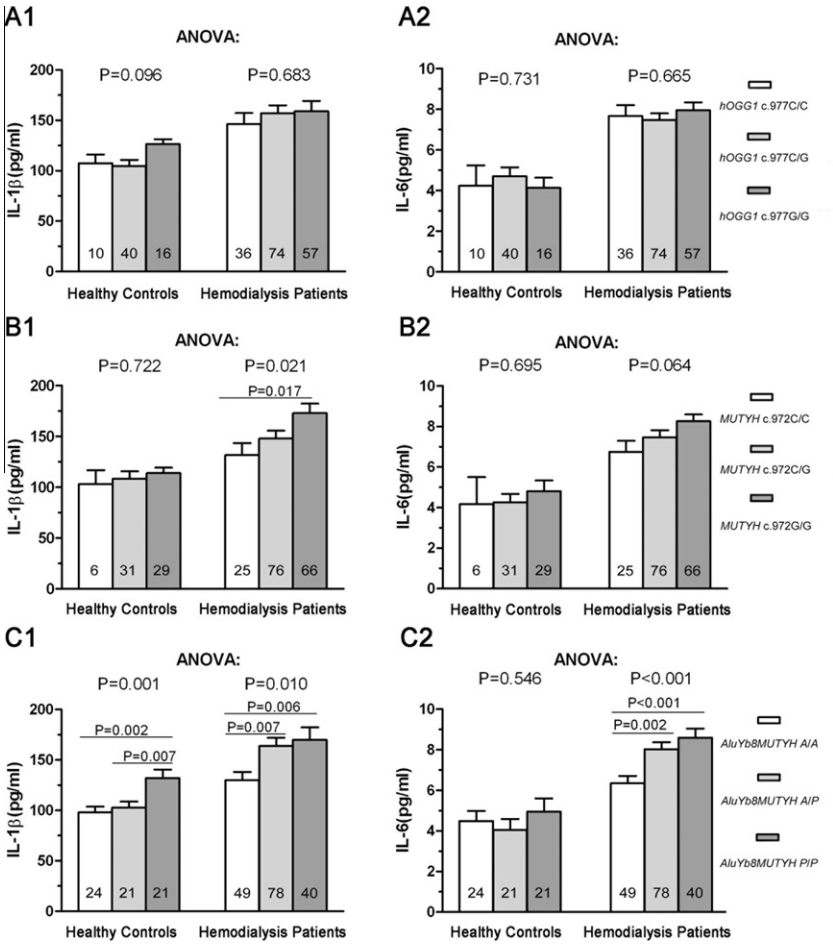

Fig. 1. Analysis of the effect of the BER gene polymorphisms on mean levels of IL-1β (A1, B1, C1) and IL-6 (A2, B2, C2) in the healthy controls and the hemodialysis patients. Every group includes three different bars stratified according to the polymorphism genotypes, and the number of each group is given in the corresponding bar. Statistical significance was calculated using one-way ANOVA testing followed by unpaired *t* test.

Table 3
The synergetic effect of the *BER* gene polymorphisms on inflammation in hemodialysis patients.

Genotype combinations	IL-1β (pg/ml)	*P* value	IL-6 (pg/ml)	*P* value
OGG1 c.977 C > G and MUTYH c.972 G > C		0.275[a]		0.415[a]
c.977 C/C and c.972 C/C (*n* = 7)	129 ± 22.7		6.80 ± 1.39	
c.977 C/G or G/G and c.972 C/C (*n* = 18)	132 ± 14.3		6.73 ± 0.553	
c.977 C/C and c.972 C/G or G/G (*n* = 29)	150 ± 12.6		7.87 ± 0.587	
c.977 C/G or G/G and c.972 C/G or G/G (*n* = 113)	162 ± 6.93		7.83 ± 0.276	
OGG1 c.977 C > G and AluYb8MUTYH		0.017[a]		0.002[a]
c.977 C/C and *A*/*A* (*n* = 13)	112 ± 6.68	1	6.08 ± 0.827	1
c.977 C/G or G/G and *A*/*A* (*n* = 23)	136 ± 10.8	0.196[b]	6.45 ± 0.394	0.651[b]
c.977 C/C and *A*/*P* or *P*/*P* (*n* = 36)	166 ± 15.6	0.017[b]	8.56 ± 0.647	0.026[b]
c.977 C/G or G/G and *A*/*P* or *P*/*P* (*n* = 95)	166 ± 7.60	0.011[b]	8.14 ± 0.301	0.019[b]
MUTYH c.972 G > C and AluYb8MUTYH		0.018[a]		0.001[a]
c.972 C/C and *A*/*A* (*n* = 16)	125 ± 15.0	1	6.53 ± 0.595	1
c.972 C/C and *A*/*P* or *P*/*P* (*n* = 9)	132 ± 9.99	0.663[b]	6.27 ± 0.455	0.731[b]
c.972 C/G or G/G and *A*/*A* (*n* = 33)	144 ± 20.0	0.449[b]	7.14 ± 1.11	0.602[b]
c.972 C/G or G/G and *A*/*P* or *P*/*P* (*n* = 109)	168 ± 7.17	0.030[b]	8.31 ± 0.280	0.022[b]

[a] Comparison between the different genotype groups by ANOVA.
[b] Comparison with the reference genotype by unpaired *t* test.

ROS-induced inflammation. We have previously reported the effect of genetic polymorphisms in the BER system on DNA repair capacity and increased 8-OHdG levels in hemodialysis patients [20]. Thus, BER gene polymorphisms may be a predictive factor for inflammation and morbidity in hemodialysis patients, possibly through an accumulation of oxidative DNA damage.

Combinations of the common BER polymorphisms further increased the oxidative DNA damage and inflammatory levels. *MUTYH* and *OGG1* double-knockout mouse embryonic fibroblast cells were reported to be more sensitive to oxidants than single-knockout cells, and the double-knockout cells were found to have an S phase reduction and a G2/M phase increase when compared to

the wild-type cells. This suggested cooperative roles for *MUTYH* and *OGG1* in the maintenance of genome stability [33]. Additional evidence showed the combined effect of the DNA repair genes on several diseases, including ESRD [13]. In this study, we identified a combined effect of the BER gene polymorphisms on inflammation in hemodialysis patients. The patients with the *hOGG1* c.977 C/C genotype and the *AluYb8MUTYH A*/*P* or *P*/*P* genotypes, or the *hOGG1* c.977 C/G or G/G genotypes and the *AluYb8MUTYH A*/*P* or *P*/*P* genotypes had higher IL-1β and IL-6 levels than those with wild-type genotypes. A combination of the *MUTYH* c.972G > C and *AluYb8MUTYH* polymorphisms elicited a similar effect in patients undergoing hemodialysis.

It should be noted that different effects of the BER gene polymorphisms on inflammation were observed between healthy controls and hemodialysis patients. For instance, IL-1β levels among hemodialysis patients changed with three *MUTYH* c.972G > C genotype groups. The patients with the c.972G/G genotype had significantly higher IL-1β levels than those carrying the c.972C/C genotype. However, the IL-1β level was essentially the same among healthy subjects with the different genotypes. It is possible that these discrepancies are due to differences in inflammatory state between hemodialysis patients and healthy controls, as the levels of plasma IL-1β and IL-6 in hemodialysis patients were significantly higher than those in healthy controls. Additionally, as the levels of oxidative stress and DNA damage are thought to be greater in those patients, the demands for oxidative DNA repair would be increased. Thus, the effects of the BER gene polymorphisms would be amplified in patients undergoing hemodialysis, even if their impact is minimal in healthy controls. However, further studies are needed to explore the mechanisms mediating this process.

To our knowledge, this is the first study to examine the individual and combined effects of DNA repair gene polymorphisms on inflammatory state in hemodialysis patients. As predictors of mortality, plasma IL-1β and IL-6 levels were significantly higher in the hemodialysis patients than the healthy controls, and the increases were associated with the *MUTYH* c.972G > C and *AluYb8MUTYH* polymorphisms. These data suggest that common polymorphisms of DNA repair genes may play an important role in the chronic inflammation of hemodialysis patients and that oxidative stress-induced DNA damage might be involved in this process. Therefore, we propose that screening for these polymorphisms should be used as a predictive factor for the hemodialysis patients.

Acknowledgments

This work was supported by the Jiangsu Science and Technology Foundation (Grant Number: BK2009236), the National Natural Science Foundation of China (Grant Number: 81070579, 81070273) and Open Foundation of State Key Laboratory of Pharmaceutical Biotechnology (Grant Number: KF-GN-201201).

References

[1] C. Coskun, A. Kural, Y. Doventas, M. Koldas, H. Ozturk, B.B. Inal, A. Gumus, Hemodialysis and protein oxidation products, Ann. NY Acad. Sci. 1100 (2007) 404–408.
[2] J. Rysz, M. Banach, A. Cialkowska-Rysz, R. Stolarek, M. Barylski, J. Drozdz, P. Okonski, Blood serum levels of IL-2, IL-6, IL-8, TNF-alpha and IL-1beta in patients on maintenance hemodialysis, Cell. Mol. Immunol. 3 (2006) 151–154.
[3] P. Stenvinkel, Inflammation in end-stage renal failure: could it be treated?, Nephrol Dial. Transplant. 17 (Suppl. 8) (2002) 33–38.
[4] C. Zoccali, G. Tripepi, F. Mallamaci, Dissecting inflammation in ESRD: do cytokines and C-reactive protein have a complementary prognostic value for mortality in dialysis patients?, J Am. Soc. Nephrol. 17 (2006) S169–173.
[5] D.V. Barreto, F.C. Barreto, S. Liabeuf, M. Temmar, H.D. Lemke, C. Tribouilloy, G. Choukroun, R. Vanholder, Z.A. Massy, Plasma interleukin-6 is independently associated with mortality in both hemodialysis and pre-dialysis patients with chronic kidney disease, Kidney Int. 77 (2010) 550–556.
[6] R.M. Bologa, D.M. Levine, T.S. Parker, J.S. Cheigh, D. Serur, K.H. Stenzel, A.L. Rubin, Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients, Am. J. Kidney Dis. 32 (1998) 107–114.
[7] R. Pecoits-Filho, P. Barany, B. Lindholm, O. Heimburger, P. Stenvinkel, Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment, Nephrol. Dial. Transplant. 17 (2002) 1684–1688.
[8] C.Y. Hung, Y.A. Chen, C.C. Chou, C.S. Yang, Nutritional and inflammatory markers in the prediction of mortality in Chinese hemodialysis patients, Nephron Clin. Pract. 100 (2005) c20–26.
[9] S. Kumagai, T. Jikimoto, J. Saegusa, Pathological roles of oxidative stress in autoimmune diseases, Rinsho Byori 51 (2003) 126–132.
[10] S. Reuter, S.C. Gupta, M.M. Chaturvedi, B.B. Aggarwal, Oxidative stress, inflammation, and cancer: how are they linked?, Free Radic Biol. Med. 49 (2010) 1603–1616.
[11] R. Taha, E. Seidman, G. Mailhot, F. Boudreau, F.P. Gendron, J.F. Beaulieu, D. Menard, E. Delvin, D. Amre, E. Levy, Oxidative stress and mitochondrial functions in the intestinal Caco-2/15 cell line, PLoS One 5 (2010) e11817.
[12] T. Lindahl, Instability and decay of the primary structure of DNA, Nature 362 (1993) 709–715.
[13] S. Trabulus, G.S. Guven, M.R. Altiparmak, B. Batar, O. Tun, A.S. Yalin, A. Tunckale, M. Guven, DNA repair XRCC1 Arg399Gln polymorphism is associated with the risk of development of end-stage renal disease, Mol. Biol. Rep. 39 (2012) 6995–7001.
[14] R. De Bont, N. van Larebeke, Endogenous DNA damage in humans: a review of quantitative data, Mutagenesis 19 (2004) 169–185.
[15] A.B. Robertson, A. Klungland, T. Rognes, I. Leiros, DNA repair in mammalian cells: Base excision repair: the long and short of it, Cell. Mol. Life Sci. 66 (2009) 981–993.
[16] A. Yamane, K. Shinmura, N. Sunaga, T. Saitoh, S. Yamaguchi, Y. Shinmura, K. Yoshimura, H. Murakami, Y. Nojima, T. Kohno, J. Yokota, Suppressive activities of OGG1 and MYH proteins against G:C to T:A mutations caused by 8-hydroxyguanine but not by benzo[a]pyrene diol epoxide in human cells in vivo, Carcinogenesis 24 (2003) 1031–1037.
[17] F. Locatelli, B. Canaud, K.U. Eckardt, P. Stenvinkel, C. Wanner, C. Zoccali, Oxidative stress in end-stage renal disease: an emerging threat to patient outcome, Nephrol. Dial. Transplant. 18 (2003) 1272–1280.
[18] E.L. Goode, C.M. Ulrich, J.D. Potter, Polymorphisms in DNA repair genes and associations with cancer risk, Cancer Epidemiol. Biomarkers Prev. 11 (2002) 1513–1530.
[19] C. Sun, H. Chen, W. Guo, K. Zhang, Q. Qi, X. Gu, D. Zhu, Y. Wang, A common mutation of the MYH gene is associated with increased DNA oxidation and age-related diseases, Free Radic. Biol. Med. 48 (2010) 430–436.
[20] Z. Cai, H. Chen, J. Tao, W. Guo, X. Liu, B. Zheng, W. Sun, Y. Wang, Association of base excision repair gene polymorphisms with ESRD risk in a Chinese population, Oxid. Med. Cell Longev. 2012 (2012) 928421.
[21] J. Punal, L.V. Lema, D. Sanhez-Guisande, A. Ruano-Ravina, Clinical effectiveness and quality of life of conventional haemodialysis versus short daily haemodialysis: a systematic review, Nephrol. Dial. Transplant. 23 (2008) 2634–2646.
[22] L. Zuo, M. Wang, Current burden and probable increasing incidence of ESRD in China, Clin. Nephrol. 74 (Suppl. 1) (2010) S20–22.
[23] A. Brymora, M. Flisinski, G. Grzesk, L. Szadujkis-Szadurski, G. Odrowaz-Sypniewska, J. Manitius, Inflammation, malnutrition and vascular contraction in experimental chronic kidney disease, J. Nephrol. 20 (2007) 423–429.
[24] W.W. Cheung, K.H. Paik, R.H. Mak, Inflammation and cachexia in chronic kidney disease, Pediatr. Nephrol. 25 (2010) 711–724.
[25] T. Eleftheriadis, C. Kartsios, E. Yiannaki, P. Kazila, G. Antoniadi, V. Liakopoulos, D. Markala, Chronic inflammation and T cell zeta-chain downregulation in hemodialysis patients, Am. J. Nephrol. 28 (2008) 152–157.
[26] V. Filiopoulos, D. Hadjiyannakos, P. Metaxaki, V. Sideris, L. Takouli, A. Anogiati, D. Vlassopoulos, Inflammation and oxidative stress in patients on hemodiafiltration, Am. J. Nephrol. 28 (2008) 949–957.
[27] B. Descamps-Latscha, T. Drueke, V. Witko-Sarsat, Dialysis-induced oxidative stress: biological aspects, clinical consequences, and therapy, Semin. Dial. 14 (2001) 193–199.
[28] O.A. Sedelnikova, C.E. Redon, J.S. Dickey, A.J. Nakamura, A.G. Georgakilas, W.M. Bonner, Role of oxidatively induced DNA lesions in human pathogenesis, Mutat. Res. 704 (2010) 152–159.
[29] R. Hakem, DNA-damage repair; the good, the bad, and the ugly, EMBO J. 27 (2008) 589–605.
[30] S. Maynard, S.H. Schurman, C. Harboe, N.C. de Souza-Pinto, V.A. Bohr, Base excision repair of oxidative DNA damage and association with cancer and aging, Carcinogenesis 30 (2009) 2–10.
[31] R.J. Hung, J. Hall, P. Brennan, P. Boffetta, Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review, Am. J. Epidemiol. 162 (2005) 925–942.
[32] D. Svilar, E.M. Goellner, K.H. Almeida, R.W. Sobol, Base excision repair and lesion-dependent subpathways for repair of oxidative DNA damage, Antioxid. Redox Signal. 14 (2011) 2491–2507.
[33] Y. Xie, H. Yang, J.H. Miller, D.M. Shih, G.G. Hicks, J. Xie, R.P. Shiu, Cells deficient in oxidative DNA damage repair genes Myh and Ogg1 are sensitive to oxidants with increased G2/M arrest and multinucleation, Carcinogenesis 29 (2008) 722–728.