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ORIGINAL ARTICLE

Serum Cyclophilin A Correlates with Increased Tissue MMP-9 in Patients with Ulcerative Colitis, but Not with Crohn's Disease

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Abstract

Background Cyclophilin A (CyPA) is an immunomodulatory protein, high expression of which correlates with poor outcome of patients with inflammatory diseases. However, its role in inflammatory bowel disease (IBD) has not been studied.

Aim This study analyzes the correlation between cyclophilin A, matrix metalloproteinase (MMP)-9, and tissue inhibitor of MMP (TIMP)/MMP-9 complexes in the inflamed and non-inflamed colon mucosa of UC and CD patients.

Methods Serum and biopsy specimens from inflamed and non-inflamed colonic mucosa of 38 patients with IBD (19 with UC and 19 with CD) and 16 controls were included in our study. We measured serum and tissue level of CyPA, and tissue level of TNF-α, MMP-9, TIMP-1/MMP-9, and TIMP-2/MMP-9 using ELISA method.

Results Our results indicated that serum, but not tissue CyPA is increased in UC, rather than in CD patients, compared to the control. The increase correlated with higher tissue concentration of MMP-9 and TNF-α, especially in the UC group. Moreover, we observed significantly higher level of TIMP-1/MMP-9 in UC and CD group, which overlapped with the change in MMP-9. There was no change in TIMP-2/MMP-9 in the analyzed groups.

Conclusion The current study suggests that serum CyPA may be an independent additional marker of IBD, especially of UC. Higher CyPA level may be followed by increased MMP-9 in those patients. However, further studies are necessary to verify the role of CyPA in IBD development.

Keywords Crohn's disease · Ulcerative colitis · Cyclophilin A · Matrix metalloproteinase 9 · Tissue inhibitor of metalloproteinase

Introduction

Inflammatory bowel disease (IBD) is a group of chronic disorders primarily consisting of ulcerative colitis (UC) and Crohn's disease (CD). Both conditions can lead to an extensive damage of the gastrointestinal tract and are manifested by various clinical symptoms, such as visceral pain, diarrhea, rectal bleeding, weight loss and many others, all substantially lowering patients' quality of life. The clinical distinction between UC and CD is based mostly on the location and morphology of inflammatory lesions [1]. Ulcerative colitis is present in the rectum and colon; the pattern of inflammation is continuous and limited solely to the mucosa and submucosa of the intestine. By contrast, Crohn's disease can affect entire alimentary tract from mouth to anus; inflammation is usually discontinuous and transmural.

Although UC and CD are well-known inflammatory bowel diseases, the search for reliable disease markers continues [1, 2]. Among those factors is cyclophilin A,

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high expression of which correlates with poor outcome of patients with inflammatory diseases [3]. CyPA is a 18-kDa cytosolic protein that has an activity of cis–trans isomerase and may play an important role in immunomodulation and cell signaling. In the form of cytokine, CyPA promotes intracellular communication, has chemoattractant effect on inflammatory cells and exacerbates oxidative stress and inflammation [4].

It was showed that in inflammatory diseases CyPA stimulates monocytes production of matrix metalloproteinases (MMP)-9 and MMP-2 [5]. Furthermore, CyPA may regulate the expression of MMP-9 in the esophageal squamous cell carcinoma [6].

Previously Gao et al. [7] have shown that the expression of gelatinases, especially MMP-9, increases in relation to severity of inflammation in both UC and CD. Moreover, the lack of MMP-9 expression reduces inflammation and intestinal mucosa damage in dextran sulfate sodium (DSS)-induced UC mice [8]. Tissue concentration of MMPs is under control of tissue inhibitor of matrix metalloproteinases (TIMP). TIMP-1 and TIMP-2 are responsible for the activity of MMPs, and hence they maintain the correct balance between remodeling and degradation of extracellular matrix. It was showed that TIMP-1 levels tend to be up-regulated in IBD patients, while TIMP-2 levels were shown to be similar between IBD and healthy controls [9, 10]. However, during an ongoing inflammation an excessive amount of MMP-9 is produced by infiltrated neutrophils in response to pro-inflammatory proteins. Therefore, serum CyPA may influence MMPs and TIMPs, and may have prognostic significance in IBD patients.

In this study, we investigated the concentration of serum and tissue CyPA in inflamed and non-inflamed areas of colon mucosa from UC and CD patients. Furthermore, to investigate whether serum CyPA may influence MMP-9 concentration, we analyzed the concentration of MMP-9 and its inhibitors, TIMP-1 and TIMP-2, in the colon mucosa of inflamed and non-inflamed areas of colon mucosa from UC and CD patients.

Materials and Methods

Patients

Serum and biopsy specimens from the total of 54 patients: 38 patients with IBD (19 with UC and 19 with CD, biopsies from inflamed and non-inflamed colonic mucosa) and 16 controls were included in our study.

In all IBD patients, endoscopic biopsies from the macroscopic inflamed and non-inflamed areas were obtained and all cases were histopathologically confirmed. Tissue was considered non-inflamed if there was an absence of macroscopic or histological evidence of inflammation. The control group included patients with dyspepsia that were diagnosed IBD-free during colonoscopy, and the results were confirmed in the histopathological examination.

Criteria for inclusion in the study groups were based on a diagnosis according to clinical, radiological, endoscopic, and histological criteria recommended by the European Crohn's and Colitis Organization. The exclusion criteria were low or high grade dysplasia, colorectal cancer, a history of cardiovascular disease, pulmonary and kidney disease, allergy, diabetes, lichen planus, psoriasis, atopic dermatitis, and other autoimmune skin lesions.

The study protocol was approved by the local ethic committee (No. RNN/515/13/KB), and all participants had given written informed consent to participate in the study.

Sample Collection

In each subject undergoing colonoscopy, two endoscopic biopsy specimens were taken from colonic inflamed and non-inflamed areas (UC, CD) and, in the control group, only from non-inflamed areas. Moreover, 5 ml of venous blood was collected from each patient to serum vacuum tubes. Samples were left to clot for 30 min at room temperature before centrifugation at 1,000xg for 15 min. Next, serum was collected and was stored at −80 °C for further biochemical analysis of CyPA.

Tissue Homogenate Preparation

Tissue biopsies from inflamed and non-inflamed colon were homogenized in RIPA lysis buffer (10 mg tissue in 1 ml) (Sigma-Aldrich Co., USA) using tissue raptor (Ultra-Turrax T25, IKA, Germany) at an rpm of 20,000/min for 30 s. Samples were incubated on ice for 15 min and, centrifuged for 10 min ($2000 \times g$, +4 °C) and supernatant was collected and stored at −80 °C for further analysis of CyPA, TNF-α, total MMP-9, TIMP-1/MMP-9, and TIMP-2/MMP-9.

Protein Assay of CyPA, TNF-α, MMP-9, TIMP-1/MMP-9, and TIMP-2/MMP-9 Complexes by ELISA

Human CyPA was measured in the serum samples and tissue homogenates (preparation described above), and TNF-α was measured in tissue using commercially available sandwich ELISA kits (Cusabio, USA; R&D Systems, Inc., Minneapolis, USA, respectively) according to the manufacturer's instructions. The results were presented as mean ± SEM in ng/ml for CyPA or pg/ml for TNF-α after normalization to total protein level.

Levels of MMP-9, TIMP-1/MMP-9 and TIMP-2/MMP-9 complexes were measured in appropriately diluted tissue homogenates using commercially available sandwich ELISA kits (R&D Systems, Inc., Minneapolis, USA) according to the manufacturer's instructions. The results were presented as mean ± SEM in pg/ml after normalization to total protein level. Each ELISA assay was forerun by total protein concentration assay using the Lowry protocol [11].

Statistical Analysis

Continuous demographic and biochemical data are presented as median, minimum and maximum, or mean ± SEM: demographic categorical data were described with absolute frequencies and percentages. Comparisons between groups were performed using the Kruskal–Wallis test (or non-parametric Mann–Whitney U test) and Chi-square test depending on the normality of distribution. One-way analysis of variance and the Dunns post-test were used to calculate differences. The outliers were excluded using the Grubbs' test. All p values lower than or equal to 0.05 were considered significant. Statistical analysis was performed using the software package Statistica 9.0.

Results

Demographic Characteristic

Demographic data are shown in Table 1. The age range and number of women to men between the analyzed groups was comparable ($p > 0.05$). There was no significant difference in the percentage of smokers in the UC and CD groups (14 and 6%, respectively; $p = 0.364$). In the control group, none of the subjects received glucocorticosteroids (GCS), azathioprine (AZA), 5-aminosalicylic acid (5-ASA), or sulphasalazine (Sulpha). In the CD group, 2 patients were on GCS, 8 on AZA, 16 on 5-ASA, and 12 on Sulpha, while in the UC group, 3 patients were on GCS, 14 on AZA, 16 on 5-ASA, and 17 on Sulpha ($p = 0.768$, $p = 0.163$, $p = 0.303$, $p = 0.308$ in CD versus UC, respectively).

The level of white blood cells (WBC) was statistically higher in UC patients in comparison to control group (9.40×10^6 versus 7.31×10^6 ml $p = 0.015$), while the CD group had only slightly higher WBC concentration compared to the control; there was no significant difference between UC and CD group ($p = 0.145$ and $p = 0.608$, respectively). No sex-related difference in WBC was observed ($p > 0.05$). Patients in the UC group had statistically higher blood C-reactive protein (CRP) concentration compared to the control group ($p = 0.023$).

The Serum CyPA Is Increased in UC Patients

Our results indicated that patients with UC had significantly higher level of serum CyPA compared to the control and CD group ($p < 0.001$ and $p = 0.003$, respectively; Fig. 1a). There was also a tendency toward higher serum CyPA in the CD group compared to the control group ($p = 0.06$). The level of tissue CyPA in the inflamed and non-inflamed tissue samples was comparable (Fig. 1b).

The UC and CD Patients Have Higher Level of Pro-inflammatory TNF-α in Colon Mucosa

CyPA is known to influence pro-inflammatory cytokine level, such as TNF-α in inflammatory cells [12]. To determine if higher serum CyPA level correlates with elevated cytokine expression in IBD we measured the colon level of TNF-α. The changes are presented in Fig. 2. The results indicated that the level of TNF-α was markedly increased in inflamed areas of the colon mucosa in both UC and CD groups compared to the control ($p = 0.04$ and $p = 0.008$, respectively; Fig. 2). Also there was a higher TNF-α level in non-inflamed colon area of the UC group compared to the CD group ($p = 0.02$; Fig. 2).

Higher Level of MMP-9 and TIMP-1/MMP-9 in Inflamed Areas of Colon Mucosa from the UC and CD Groups

It was previously showed that serum CyPA may directly influence the MMP-9 level [13]. Also MMP-9 plays an important role in IBD's pathogenesis [14, 15]. In our study we measured the tissue level of MMP-9 alone or in complex with its inhibitors TIMP-1 and TIMP-2 in the inflamed and non-inflamed colon mucosa (Fig. 3). The results indicated that tissue level of MMP-9 was significantly higher in colon of UC and CD patients compared to the control ($p < 0.001$). Moreover, over-expression of MMP-9 was higher in the inflamed versus non-inflamed tissue in the UC and CD groups ($p = 0.01$; Fig. 3a). We also observed an increase in TIMP-1/MMP-9 the UC group but only in the inflamed colon areas compared to the control ($p = 0.027$; Fig. 3b). While in the CD group a significant increase of TIMP-1/MMP-9 was detected in non-inflamed and inflamed colon areas compared to the control ($p < 0.001$ and $p = 0.006$, respectively; Fig. 3b). Moreover, we noticed significantly higher level of TIMP-1/MMP-9 in the non-inflamed colon areas of the CD versus UC group ($p = 0.021$; Fig. 3b). Tissue concentration of TIMP-2/MMP-9 was comparable in all analyzed groups ($p > 0.05$; Fig. 3c).

Table 1 Patients' demographic

	Control $n = 16$	UC $n = 19$	CD $n = 19$	p value
Age (years)	45 ± 17	43 ± 15	35 ± 14	Control versus CD $p = 0.105$
				Control versus UC $p = 0.712$
				CD versus UC $p = 0.104$
Sex, n (%)				
Men	9 (56%)	6 (31%)	7 (37%)	Control versus CD $p = 0.757$
Women	7 (43%)	13 (68%)	12 (63%)	Control versus UC $p = 0.291$
				CD versus UC $p = 0.399$
BMI (kg/m^2)	25.6 ± 3.8	22.8 ± 3.6	21.93 ± 3.66	Control versus CD $p = 0.016$
				Control versus UC $p = 0.053$
				CD versus UC $p = 0.463$
Smokers (%, yes/no)	33%	14%	6%	Control versus CD $p = 0.046$
	(4/8)	(3/18)	(1/17)	Control versus UC $p = 0.198$
				CD versus UC $p = 0.370$
GCS (%, yes/no)	0%	14%	11%	Control versus CD $p = 0.232$
	(0/12)	(3/185)	(2/16)	Control versus UC $p = 0.170$
				CD versus UC $p = 0.768$
AZA (%, yes/no)	0%	67%	44%	Control versus CD $p = 0.007$
	(0/12)	(14/7)	(8/10)	Control versus UC $p < 0.001$
				CD versus UC $p = 0.163$
5-ASA (%, yes/no)	0%	76%	89%	Control versus CD $p < 0.001$
	(0/12)	(16/5)	(16/2)	Control versus UC $p < 0.001$
				CD versus UC $p = 0.303$
Sulpha (%, yes/no)	0%	81%	67%	Control versus CD $p < 0.001$
	(0/12)	(17/4)	(12/6)	Control versus UC $p < 0.001$
				CD versus UC $p = 0.309$
WBC (mln/dl)	7.3 ± 1.9	9.4 ± 2.6	8.9 ± 3.7	Control versus CD $p = 0.145$
				Control versus UC $p = 0.015$
				CD versus UC $p = 0.608$
CRP (mg/dl)	1.14 ± 1.11	13.59 ± 23.20	12.85 ± 29.22	Control versus CD $p = 0.108$
				Control versus UC $p = 0.023$
				CD versus UC $p = 0.931$

mean ± SD

CD Crohn's disease, *UC* ulcerative colitis, *GCS* glucocorticosteroids, *AZA* azathioprine, *5-ASA* 5-aminosalicylic acid, *Sulpha* sulphasalazine, *WBC* white blood cells, *CRP* C-reactive protein

Discussion

CyPA is an evolutionarily conserved protein, believed to be present only in the intracellular space; however, recent studies have shown that it is also secreted from cells in response to inflammatory stimuli and oxidative stress [4, 16]. Our results indicated that patients with UC, rather than CD, have higher serum, but not tissue level of CyPA. This effect may be in part explained by excessive concentration of inflammatory cells in the colon mucosa of UC patients. CyPA is also secreted by inflammatory cells during organ damage [17, 18].

Serum CyPA works via its receptor CD147, a single transmembrane glycoprotein, which is widely expressed in all leukocytes, platelets, endothelial cells, and intestinal epithelial cells [19, 20]. Activation of CD147 receptor by CyPA increases phosphorylation of pro-inflammatory extracellular matrix regulated signaling pathway (ERK1/2) [21, 22]. Activation of this pathway may further lead to an increase in MMP-2, MMP-9 and MMP-7 as it was shown in colon cancer cells [23]. Therefore, by acting through its receptor, CyPA increases gene expression of pro-inflammatory cytokines and MMPs including MMP-2 and MMP-9. Earlier study demonstrated that CyPA inhibition
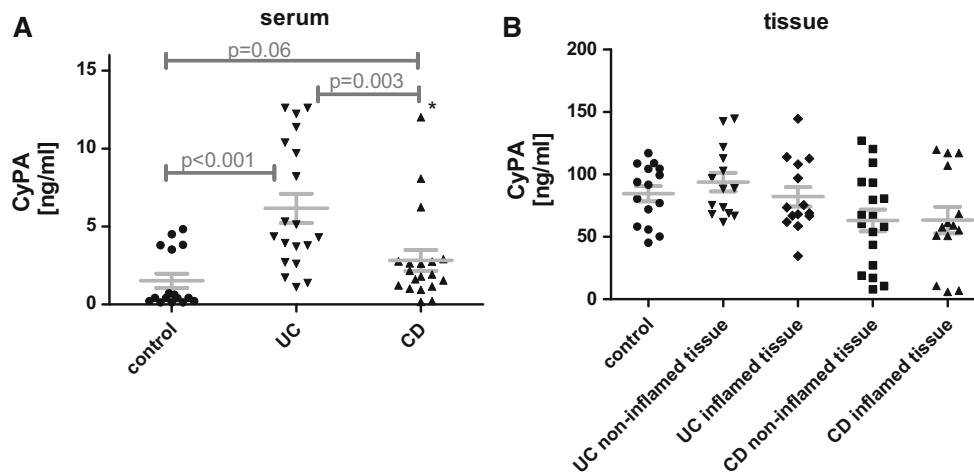
A

Fig. 1 Changes of the serum (**a**) and tissue (**b**) CyPA in the colon mucosa of UC and CD patients. The results are presented as mean ± SEM in ng/ml of tissue homogenate after normalization to total protein level. *CD* Crohn's disease, *UC* ulcerative colitis.

Statistical analysis: Grubb's test for outliers followed by Kruskal–Wallis test. *An outlier—calculated with Grubb's test—that was removed from statistical analysis
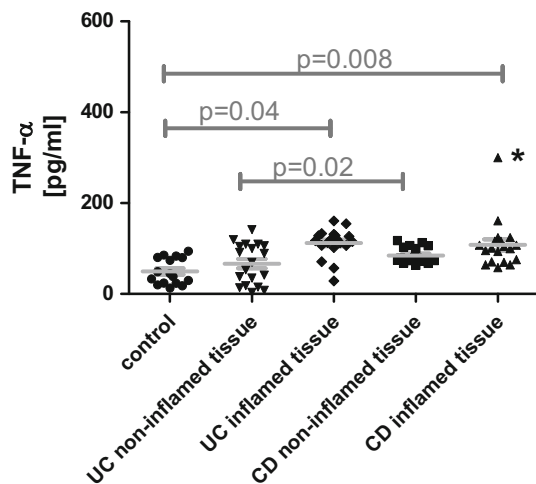

Fig. 2 Changes of the tissue TNF-α in the colon mucosa of UC and CD patients. The results are presented as mean ± SEM in pg/ml of tissue homogenate after normalization to total protein level. *CD* Crohn's disease, *UC* ulcerative colitis. Statistical analysis: Grubb's test for outliers followed by Kruskal–Wallis test. *An outlier—calculated with Grubb's test—that was removed from statistical analysis

significantly decreases MMP-9 and TNF-α in the mouse myocardial inflammation [13] and lung cancer cells [24]. This effect of CyPA on MMP-9 is in line with our results, which showed that serum CyPA correlated with higher tissue concentration of MMP-9 and TNF-α, especially in the UC group.

MMP-9 is synthesized predominantly in inflammatory cells; as a consequence of its release, more leukocytes are drawn to colon mucosa to worsen inflammation [25]. The mechanism behind CyPA influence on MMP-9 in IBD remains unknown; however, among factors that control

MMP-9 activity are TIMPs. Previously, Lakatos et al. [14] indicated that patients with UC and CD had elevated MMP-9 and TIMP-1 antigen levels, which correlated with disease activity. Recently Jakubowska et al. [26] showed that MMP-9 and TIMP-1 are over-expressed in the glandular epithelium plus inflammatory infiltration in UC patients and glandular epithelium of CD patients. Also Mao et al. [27] demonstrated a higher expression and activity of MMP-9 in the UC patients.

In our study we noticed a significant increase of MMP-9 in the inflamed colon areas of UC and CD patients. This is in line with previous reports were higher expression and activity of MMP-9 was detected in ulcerated areas compared with non-involved sites of the mucosa in patients with ischemic colitis [28].

The expression of MMP-9 is not only changed in tissue but also changed in serum of patients with IBD. Although we did not measure serum level of MMP-9 in our study, there are numerous reports that in IBD serum MMP-9 is elevated [10, 14]. Recently a large study on changes in serum level of MMP-9 in IBD patients described a significant elevation of serum MMP-9 in patients with UC, but only a tendency in CD [29]. Those authors also propose serum MMP-9 as a supportive marker for differentiation between active and inactive IBD.

The MMP-9 released from macrophages may be stimulated by CyPA via CD147 receptor and NF-κB pathway as it was shown in rheumatoid arthritis [30]. Another pathway stimulated by CyPA is ERK1/2, whose activation increases transcription of MMP-9 and TIMP-1, but not TIMP-2 in the biliary atresia [31]. This is in line with our results, where higher concentration of TIMP-1/MMP-9, but not TIMP-2/MMP-9, was observed. Moreover, in our study
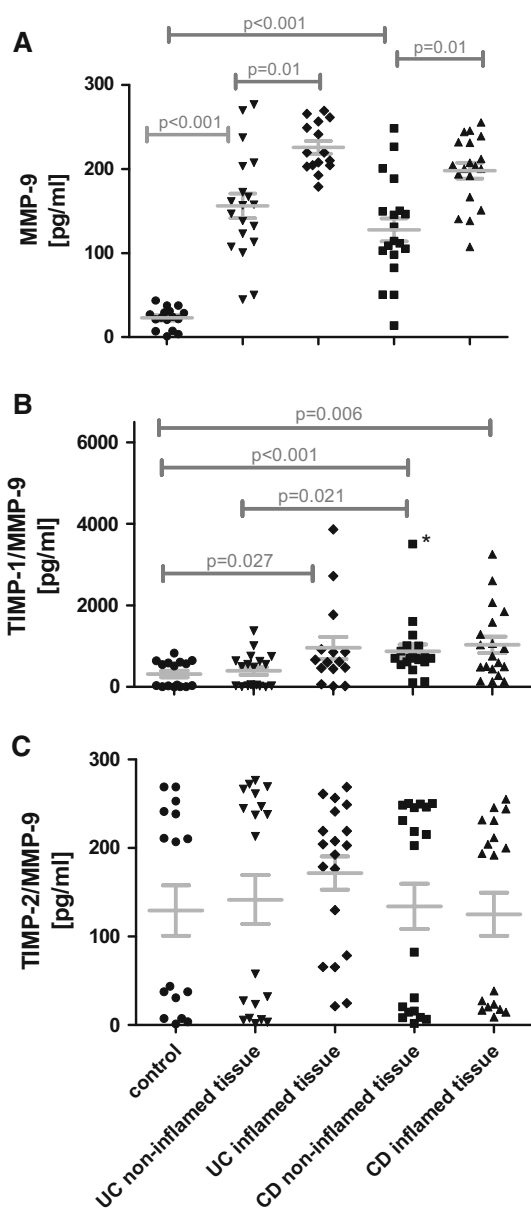
Fig. 3 The changes of MMP-9, TIMP-1/MMP-9 and TIMP-2/MMP-9 in the colon mucosa of UC and CD patients. The results are presented as mean ± SEM in pg/ml of tissue homogenate after normalization to total protein level. CD Crohn's disease; *UC* ulcerative colitis. Statistical analysis: Grubb's test for outliers followed by Kruskal–Wallis test. *An outlier—calculated with Grubb's test—that was removed from statistical analysis

TIMP-1/MMP-9 seemed to balance higher MMP-9 in both groups. These observations may be explained by the mechanism behind TIMP-1 regulation which involves CyPA. It was shown previously that the expression of TIMP-1, rather than TIMP-2 may be regulated by CD147, the CyPA receptor, in the in vitro studies [32]. Blockage of CD147 with siRNA decreases secretion of MMP-9 and MMP-2 in carcinoma cells and hepatocytes [32, 33]. Also, CD147 regulates TIMP-2 production in rats during

inflammation [34]. However, the direct link between CyPA–CD147–TIMP in inflammatory bowel disease needs to be verified.

In conclusion, the current study presents for the first time that patients with UC, rather than CD, have higher serum, but not tissue CyPA level. Higher level of CyPA in serum may influence tissue level of MMP-9 and TIMP-1/MMP-9; however further studies are necessary to verify the role of CyPA in IBD development.

Compliance with ethical standards

Conflict of interest None.

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