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Pigment epithelium-derived factor in ulcerative colitis: Possible relationship with disease activity

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Abstract

Objectives: Pigment epithelium-derived factor (PEDF) is an endogenous most potential angiogenic inhibitor and increased expression of PEDF in intestinal mucosa specimens was shown in the course of ulcerative colitis (UC). The aim of the present study was to evaluate serum concentration of pigment epithelium-derived growth factor, a potent anti-angiogenic factor and its possible association with vascular endothelial growth factor (VEGF) levels and disease activity.
Methods: Concentrations of PEDF and VEGF were measured in sera of 33 patients (13 females and 20 males) with active UC.
Results: There was significant increase of serum PEDF (32.3±2.9 vs. 20.6±4.7 ng/mL, $P<0.05$) as well as VEGF (326.4±58.1 vs. 110.9±15.7 pg/mL, $P<0.05$) in UC patients compared to healthy controls. Serum PEDF showed strong, positive correlation with endoscopic score ($r=0.622$, $P<0.001$), while such association was absent in respect to VEGF ($r=0.05$, $P=0.77$). In contrast serum VEGF decreased in severe UC comparing to patients with a mild course of disease, however the difference was not significant (274.9±64.9 vs. 360.4±103.4 pg/mL, $P=0.53$).
Conclusions: Increase in serum PEDF during UC, especially in severe forms of disease suggests its involvement in UC pathogenesis.

Keywords: Pigment epithelium-derived factor; Vascular endothelial growth factor; Angiogenesis; Ulcerative colitis

1. Introduction

Ulcerative colitis (UC) is a disease of uncertain aetiology which affects the mucous membrane of the large intestine leading to its damage resulting in ulcerative lesions and intensive regeneration. Recent evidence increasingly suggests that inflammatory bowel disease (IBD) is the result of dysfunctional immunoregulation manifested by inappropriate production of mucosal cytokines. Moreover many reports provide evidence of abnormalities in the microcirculation in mucosa and muscular coat of the intestine of patients with inflammatory bowel disease proceeding to ischaemic lesions of the intestine wall [1]. Recently, angiogenesis-promoting cytokines have been suggested to play an important role in IBD because they promote inflammation by increasing vascular permeability and mediate tissue repair [2,3]. Hence, controlling of the angiogenesis is considered as an attractive approach for the therapy of IBD.

Pigment epithelium-derived factor (PEDF), a 50-kDa non-inhibitory member of the serpin family, is a potent, endogenous inhibitor of angiogenesis [4]. Originally isolated from human retinal pigment epithelial cells it was shown to protect retina from neovascularization [5]. PEDF is expressed in many tissues of the body, including brain, spinal cord, eye, liver, bone, heart, lungs, pancreas and prostate [6]. The presence of PEDF was demonstrated in cytoplasm and nucleus of mammalian cells as well as in blood as a secreted form [7]. PEDF seems to exert pleiotropic activities, such as neuroprotective, neurothropic, anti-angiogenic, anti-tumorigenic as well as anti-inflammatory [8,9]. The molecular mechanisms by which PEDF works in vivo still remain uncertain. The high affinity of PEDF to various proteins, including glycosaminoglycans, collagens and integrins was shown [10]. Moreover binding sites in retinal, neuronal and endothelial cells were demonstrated. Those observations suggest interaction of PEDF with an unknown receptor, however direct nuclear effect is considered.

Angiostatic activity of PEDF was proven to have a favourable effect on the pathogenesis of a variety of disorders affecting

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retina, central nervous system, arthritis, liver and pancreas cancers [11]. Recently Yamagishi et al. [12] showed that serum levels of PEDF were strongly associated with metabolic syndrome. PEDF was shown to induce apoptosis of proliferating endothelial cells induced by growth factors, to inhibit endothelial cells migration and proliferation thus playing an essential role in the control of angiogenesis [4,13–15]. Increased expression of PEDF was also observed in intestinal mucosa specimens in the course of UC [16]. Thus inhibition of endothelial cells migration and proliferation during mucosal regeneration could be crucial to the pathogenesis of UC [17].

After the injury, mucosal integration is reestablished by epithelial cells migration, proliferation and maturation. The repairing process in response to repeated mucosal damage also engages inflammatory processes, angiogenesis and matrix deposition. Many factors are engaged in this process. Vascular endothelial growth factor (VEGF) is supposed to play a crucial role in angiogenesis by stimulating migration and proliferation of endothelial cells as well as the expression of angiogenesis-related factors. The involvement of VEGF in tissue repair is complex and besides angiogenesis promotion, includes transforming growth factor β (TGF-β1)-mediated epithelial cell restitution [18].

The aim of present study was to evaluate the serum concentration of pigment epithelium-derived growth factor, a potent anti-angiogenic factor and its possible association with VEGF levels and disease activity.

2. Materials and methods

Studied population consisted of 33 patients (13 females and 20 males) with active ulcerative colitis, aged from 24 to 75 years (median 43 years). All patients had a history of diagnosed ulcerative colitis, which required typical clinical and endoscopical signs of distal part bowel involvement. Patients were treated with 5-ASA derivates in the standard dose of 3.0 g/24 h. None of them received any steroids at the time of the study.

Plasma PEDF and VEGF concentrations were compared with endoscopic pictures scored according to Meyers et al. [19]. Routine laboratory indices of the inflammatory process such as C-reactive protein (CRP), sedimentation rate (SR), white blood count (WBC) and platelet count (PLT) as well as hemoglobin, fibrinogen, total protein and albumin concentrations were also measured and compared with PEDF as well as VEGF.

Patients were divided into two groups with respect to severity of the disease. Severe UC was diagnosed when endoscopic score exceeded 10 and mild form of disease when equal or lower than 10. The median endoscopic score in studied UC population was 12 (minimum 6, maximum 18). Severe form of ulcerative colitis was diagnosed in 21 patients and a mild one in 12. Plasma PEDF and VEGF concentrations were also compared with those in 20 healthy volunteers (5 females and 15 males with a median age of 38, minimum 24, maximum 48 years). The study was approved by the Bioethical Committee of the Medical University of Bialystok. Informed consent was obtained from each patient.

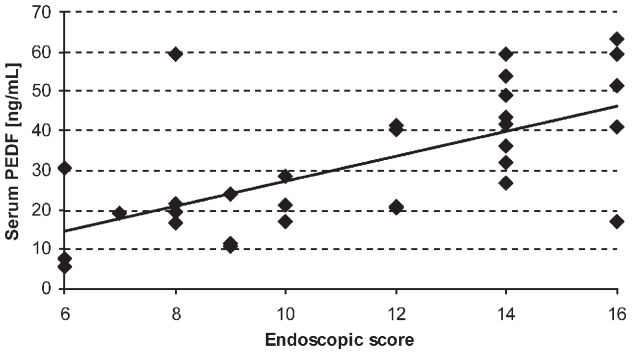

Fig. 1. Correlation between serum PEDF and UC activity reflected by endoscopic score according to Meyers et al. [19], (r=0.68, P<0.001).

Serum PEDF as well VEGF concentrations were measured by use of sandwich enzyme immunoassay kits (ChemiKine, Chemicon International) with sensitivity of 0.9 ng/mL and 26.6 pg/mL, respectively. In order to measure total PEDF the samples were treated with urea to a final concentration of 8 M. Applied VEGF test detects VEGF 165 isoform.

2.1. Statistical analysis

Values were expressed as mean±SE. The significance of differences was calculated by non-parametric Mann–Whitney U test. For correlation analysis, the Spearman non-parametric correlation was used. A P<0.05 was considered statistically significant. Statistical analyses were performed with Statistica 5.0 for Windows software (Statsoft Inc., Tulsa, USA).

3. Results

There was significant increase of serum PEDF (32.3±2.9 vs. 20.6±4.7 ng/mL, P<0.05) as well as VEGF (326.4±58.1 vs. 110.9±15.7 pg/mL, P<0.05) in UC patients compared to healthy controls. We observed no association between serum PEDF and VEGF and the age, sex of patients or disease duration. Among laboratory markers of inflammatory activity, only the mean values of CRP and SR exceeded the upper limit of normal range (Table 1).

Serum PEDF showed strong, positive correlation with endoscopic score (r=0.622, P<0.001) (Fig. 1), while such association

Table 1
Serum concentrations of PEDF and VEGF in healthy individuals as well as ulcerative colitis patients with regard to UC course

	Healthy controls (n=20)	Ulcerative colitis (n=33)	P	Mild UC (n=12)	Severe UC (n=21)	P
PEDF (ng/mL)	20.6±4.7	32.3±2.9	<0.05	20.5±4.5	38.3±3.2	<0.01
VEGF (pg/mL)	110.9±15.7	326.4±58.1	<0.05	360.4±103.4	274.9±64.9	0.53

SE. The significance of differences was calculated by non-parametric Mann–Whitney U test.