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ORIGINAL ARTICLE / ÖZGÜN MAKALE

ELEVATED ENDOGLIN LEVELS AND THEIR LINK TO THE INFLAMMATORY TUMOR MICROENVIRONMENT IN COLORECTAL CANCER

KOLOREKTAL KANSERDE ARTMIŞ ENDOGLİN DÜZEYİ İLE İNFLAMATUVAR TÜMÖR MİKROÇEVRE İLİŞKİSİ

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ABSTRACT

Objective: *Colorectal cancer (CRC) is one of the most common cancers worldwide and is one of the leading causes of cancer-related deaths. The causal link between inflammation and cancer has been proposed based on the observation that tumors often develop in a chronic inflammatory environment and that inflammatory cells are present in tumor biopsy specimens. Epidemiological studies have revealed that chronic inflammation provides a basis for different types of cancer. There is a great deal of evidence to suggest that chronic inflammation can support cancer development and that tumor-induced inflammation maintains tumor progression by creating a snowball effect. Endoglin is a transmembrane glycoprotein identified in vascular endothelial cells and has been shown to be associated with angiogenesis and inflammation in various diseases. This study aimed to investigate the relationship between endoglin and the inflammatory microenvironment in colorectal cancer patients.*

Material and Method: *50 patients diagnosed with colorectal cancer and 50 healthy volunteers were included in the study. In plasma samples, endoglin and commonly known inflammation markers such as $sPLA_2$, $cPLA_2$, NfκB, and $TGF\beta_1$ levels were measured by ELISA (enzyme-linked immunosorbent assay) method. In addition, endoglin and PLA_2 mRNA expression were determined by Real-Time PCR.*

Result and Discussion: *In colorectal cancer patients, plasma endoglin, NfκB, $TGF\beta_1$ levels were found to be significantly higher than in the control group, while no significant difference was found between the groups in $cPLA_2$ and $sPLA_2$ levels. A significant positive correlation was found between plasma endoglin levels and NFκB in the colorectal cancer group. Gene expression analyses showed that endoglin and PLA_2 mRNA expression levels were significantly higher in the colorectal cancer group than in the control group. In conclusion, this study showed that the increase in endoglin in colorectal cancer may be associated with the development of inflammation and may play a role in poor prognosis associated with the inflammatory microenvironment.*

Keywords: *Colorectal cancer, Endoglin, NFκB, PLA_2, $TGF\beta_1$*

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ÖZ

Amaç: *Kolorektal kanser (CRC) dünyada en yaygın görülen kanserlerden biri olup, kansere bağlı ölümlerin önde gelen nedenleri arasındadır. Tümörlerin sıklıkla kronik enflamasyon ortamında geliştiği ve tümör biyopsi örneklerinde enflamatuvar hücrelerin mevcut olduğu gözlemine dayanarak, enflamasyon ve kanser arasında nedensel bir bağlantı öne sürülmüştür. Epidemiyolojik çalışmalar, kronik enflamasyonun farklı kanser türlerine zemin hazırladığını ortaya çıkarmıştır. Kronik inflamasyonun kanser gelişimini destekleyebildiğini ve tümör kaynaklı enflamasyonun kartopu etkisi yaratarak tümör progresyonunu sürdürdüğünü gösteren çok sayıda kanıt bulunmaktadır. Endoglin, vasküler endotel hücrelerinde tanımlanmış bir transmembran glikoprotein olup, endoglinin çeşitli hastalıklarda anjiyogenez ve inflamasyon gelişimi ile ilişkili olduğu gösterilmiştir. Bu çalışmada, kolorektal kanser hastalarında endoglin ile inflamatuvar mikroçevre ilişkisinin araştırılması amaçlandı.*

Gereç ve Yöntem: *Kolorektal kanser tanısı almış 50 hasta ile 50 sağlıklı gönüllü çalışmaya dahil edildi. Plazma örneklerinde, endoglin ve yaygın olarak bilinen enflamasyon belirteçlerinden olan $sPLA_2$, $cPLA_2$, NfκB, TGF-β_1 düzeyleri ELISA (enzyme-linked immunosorbent assay) yöntemi ile ölçüldü. Ayrıca, endoglin ve PLA_2 mRNA ekspresyon düzeyleri Real-Time PCR ile belirlendi.*

Sonuç ve Tartışma: *Kolorektal kanser hastalarında plazma endoglin, NfκB, TGFβ_1 düzeylerinin, kontrol grubuna göre anlamlı olarak yüksek olduğu saptanırken, $cPLA_2$ ve $sPLA_2$ düzeylerinde gruplar arasında anlamlı bir farklılık bulunmadı. Kolorektal kanser grubuna ait plazma endoglin düzeyleri ile NFκB arasında anlamlı pozitif korelasyon saptandı. Gen ekspresyon analizi bulguları, kolorektal kanser grubunda endoglin ve PLA_2 mRNA ekspresyon düzeylerinin, kontrol grubuna göre anlamlı olarak yüksek olduğunu gösterdi. Sonuç olarak, bu çalışma endoglinin kolorektal kanserdeki artışının inflamasyon gelişimi ile ilişki olabileceğini ve inflamatuvar mikroçevre ile ilişkili kötü prognozda rol oynayabileceğini göstermiştir.*

Anahtar Kelimeler: *Endoglin, Kolorektal Kanser, NFκB, PLA_2, TGFβ_1*

INTRODUCTION

Colorectal cancer used to be the 4th leading cause of cancer-related death in humans, but today it has risen to the first in men and the second in women [1]. According to recent research findings, CRC accounts for 13% of all malignant tumors and is considered the most common malignant tumor in the gastrointestinal system. Less than 20% of CRC cases are inherited, with some being linked to specific syndromes like hereditary nonpolyposis colorectal cancer (lynch syndrome) and familial adenomatous polyposis [2]. It has been discovered that environmental factors, rather than inherited genetic alterations, are responsible for the majority of CRC cases. Colorectal cancer risk factors include some intestinal infections, environmental and food-derived mutagens, and persistent intestinal inflammation that precedes tumor growth [3].

It is well known that inflammation contributes to cancer development through various mechanisms. These include the direct carcinogenic effects of infectious agents [4], the promotion of chronic inflammation by immune-mediated diseases [5], subclinical inflammation conditions such as obesity [6], and exposure to environmental carcinogens [7].

With recent studies focusing on antibody-based therapeutic strategies in cancers, various potential antigens have been characterized. Endoglin, also known as CD105, has been identified within this scope and has gained widespread popularity in recent years. Endoglin is classified as a co-receptor for TGFβ (transforming growth factor-beta), a pleiotropic cytokine, and has been shown to be expressed in endothelial cells [8]. Its expression is regulated in actively proliferating endothelial cells [9]. Studies suggest that endoglin could serve as a suitable marker for tumor-associated inflammation and angiogenesis [10,11].

This study aims to investigate the relationship between endoglin levels, a transmembrane glycoprotein known to be upregulated in inflamed tissues, and the inflammatory microenvironment in CRC patients.

MATERIAL AND METHOD

Subjects

The study included 50 voluntary patients diagnosed with colorectal cancer who were receiving treatment at the Department of Medical Oncology, Faculty of Medicine, Ankara University. Blood samples collected from 50 healthy volunteers were used as the control group. To facilitate participant enrollment, informed consent forms and questionnaire forms were obtained from each participant, after attaining the necessary approval from the Clinical Research Ethics Committee. Considering these factors, collection of venous blood samples was carried out in EDTA-containing tubes, ensuring reliable sample extraction. Plasma and RNA samples obtained from these blood samples were used for analysis in this study.

Inclusion criteria included being diagnosed with colorectal cancer, not using anticoagulant medications, having no history of vascular disease or thromboembolic or hemorrhagic disorders, being an adult (20 years or older), and having no kinship relations among the participants. Volunteers who were related, using anticoagulant medications, or had a history of vascular disease, thromboembolic, hemorrhagic or inflammatory disorders were excluded from the study. No medications were used in this study.

ELISA Measurements

The plasma levels of endoglin and other inflammatory parameters were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (BTLab, China). The analytical sensitivity of the kit was 0.16 ng/ml, and the detection range was 0.3-60 ng/ml. The analytical sensitivities of the ELISA kits used for measuring plasma levels of $cPLA_2$ and $sPLA_2$ were 0.01 ng/ml and 0.32 ng/ml, respectively, with detection ranges of 0.05-15 ng/ml and 0.5-200 ng/ml, respectively.

The analytical sensitivity of the kit used for detecting plasma NfκB levels was less than 0.01 ng/ml, while the detection range was 0.03-10 ng/ml. Plasma levels of TGFβ1 were also determined using a commercially available ELISA kit, with a sensitivity of 5.11 ng/ml and a detection range of 10-4000 ng/ml.

Gene Expression Analyses

Whole blood samples, collected in EDTA-containing tubes, underwent RNA isolation using the RNA isolation kit (Qiagen, Germany). Then, utilizing the Qiagen RotorGene PCR system and the corresponding cDNA synthesis kit (Qiagen, Germany), cDNA samples were efficiently generated. Subsequently, quantitative real-time PCR analysis was executed via the Qiagen RotorGene system (Germany). For accurate normalization, β-actin served as the primary housekeeping gene. To ensure reliability and compliance with established protocols, the PCR reaction mix was meticulously prepared according to the manufacturer's instructions. Moreover, samples were assayed in duplicate to heighten data precision. The forward and reverse primer sequences were as follows: forward: 5'-CTGTGTCCACTTCTCCTGACC-3', and reverse: 5'-ACACTGCTGTTACACTGAGG-3' for endoglin; forward: 5'-GTTCAGGAGTGGGTGTGGAG-3', reverse: 5'-CTTAGAGGGTAGGCGATGGG-3' for PLA_2. β-actin was used as the housekeeping gene in the experiments. The fold changes were calculated according to $2^{-\Delta\Delta Ct}$ equation.

Statistical Analysis

Statistical analyses were conducted using the GraphPad Prism (GraphPad Inc., Version 6) program. The data collected from demographic analysis and ELISA tests were presented as the mean ± standard deviation and compared with Mann-Whitney U test. The real-time PCR results were evaluated with one-way ANOVA test. The correlation between endoglin and other cytokines were analyzed with Spearman correlation test. A p-value of less than 0.05 was deemed statistically significant.

RESULT AND DISCUSSION

Colorectal cancer is one of the most prevalent gastrointestinal cancers globally and remains a significant cause of cancer-related deaths [12]. The functional relationship between inflammation and cancer has long been recognized. This relationship is based on observations such as tumors emerging in regions of chronic inflammation, the presence of inflammatory cells, chemokines, and cytokines in tumors, the overexpression of cytokines and chemokines inducing cancer, and the activation or inhibition of similar molecular targets and pathways in both inflammation and carcinogenesis [13].

In this study, we investigated the relationship between endoglin, a transmembrane glycoprotein known to be associated with angiogenesis and inflammation, and the inflammatory microenvironment in patients diagnosed with colorectal cancer. The demographic data of the patient and control groups included in the study are presented in Table 1.

Table 1. Demographic data of CRC and control groups

Variable	Control (n=50)	CRC (n=50)	P value
Age, Mean±SD	34.20±13.59	61.05±8.83	<0.0001
Male, %	45.83	46.67	0.857
Site			
Left colon, %	-	10.52	
Right colon, %	-	31.57	
Sigmoid, %	-	47.36	
Rectum, %	-	10.55	
Bowel perforation at diagnosis, %	-	ND	
Bowel obstruction at diagnosis, %	-	ND	
Adenocarcinoma, %	-	78.95	
Mucinous adenocarcinoma, %	-	21.05	
Histological differentiation	-	ND	
Grade 2, %	-	76.92	
Grade 3, %	-	23.08	
CEA	-	16.44±41.73 (0.94-183.36)	

Abbreviations: CEA, carcinoembriogenic antigen, ND, not determined

The findings of the ELISA analyses are presented in Table 2. According to the results, plasma endoglin levels in the colorectal cancer group (6.71±3.51 ng/ml) were significantly higher compared to the control group (3.90±2.48 ng/ml) ($p<0.05$). Similarly, plasma NfκB levels (1.08±0.51 ng/ml) and TGFβ1 levels (565.03±395.14 ng/ml) in CRC group were significantly higher than control (0.41±0.24 ng/ml and 132.61±82.73 ng/ml, respectively) ($p<0.05$). Barely, no significance was observed between the groups for $cPLA_2$ and $sPLA_2$ levels.

Table 2. Plasma levels of endoglin, NFκB, TGF-β1, $cPLA_2$, and $sPLA_2$ in CRC and control groups

	Control	CRC	P value
Endoglin (ng/ml)	3.90±2.48	6.71±3.51	0.0081
Nfκb (ng/ml)	0.41±0.24	1.08±0.51	<0.0001
TGFβ1 (ng/ml)	132.61±82.73	565.03±395.14	<0.0001
$cPLA_2$ (ng/ml)	3.84±1.28	4.80±2.57	0.3211
$sPLA_2$ (ng/ml)	43.59±32.50	55.94±30.13	0.3270

The correlation between the elevated endoglin levels detected in CRC patients and other inflammatory markers was analyzed, and the findings are presented in Figure 1 and Table 3. According to the results, a significant positive correlation was found between endoglin and NFκB levels.

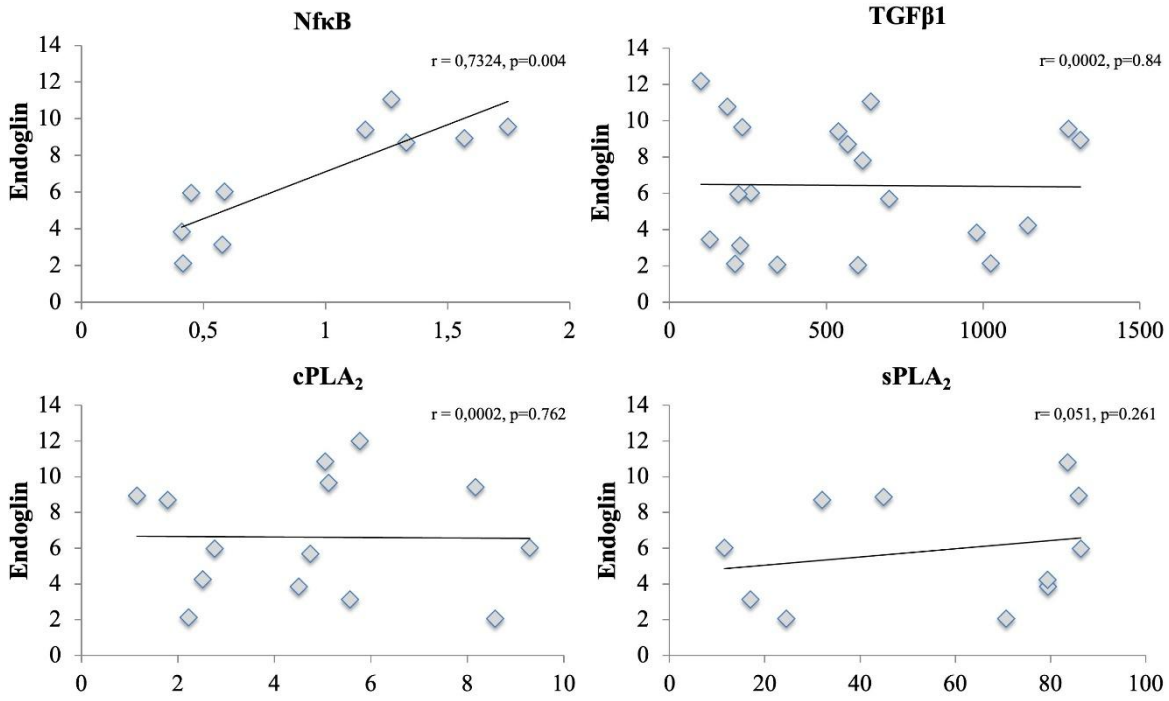

Figure 1. Correlation analyses of endoglin vs. other cytokines in CRC group

Table 3. The data of correlation analyses in CRC group

	Endoglin	
	r^2	**p value**
Nfκb	0.732	0.004
TGFβ1	0.00016	0.84
$cPLA_2$	0.00016	0.762
$sPLA_2$	0.0501	0.261

Recent research on antibody-based treatments for cancer has resulted in the identification of multiple potential targets for therapeutic intervention. Endoglin, also referred to as CD105, has been recognized within this context and has gained significant popularity in recent times. Endoglin as a TGFβ co-receptor, has been reported to be crucial for angiogenesis [14], since it is expressed in proliferating vasculature [15], and upregulated under hypoxic conditions [16]. It has been reported that endoglin is highly expressed in various tumors including lung, colorectal, and head and neck [15].

In our study, endoglin mRNA expression was measured using RT-PCR, and the results are presented in Table 4. According to our findings, endoglin mRNA expression levels in the CRC group (1.86±0.17) were significantly higher than control (1.58±0.08) ($p < 0.05$). Similarly, higher PLA_2 mRNA expression levels were measured in CRC group (1.92±0.08) vs. control (1.54±0.07) ($p < 0.05$).

Table 4. Fold increase in expression of endoglin and PLA2 mRNA in CRC and control groups

Fold increase	Control	CRC	P value
Endoglin	1.58±0.08	1.86±0.17	<0.0001
PLA_2	1.54±0.07	1.92±0.08	<0.0001

Patients with metastatic breast and colorectal tumors showed significantly elevated levels of serum endoglin compared to the control [17,18]. Serum endoglin levels have been observed to decrease as a result of chemotherapy [18]. When combined, these results indicate that measuring endoglin levels in the blood could help categorize patients with advanced cancer and those who are at risk of developing metastases. Additionally, endoglin has been reported to be useful for monitoring recurrence in cancer patients following chemotherapy [19]. Consistent with the literature, our study also found higher plasma and mRNA levels of endoglin.

Intestinal epithelial cells are in constant interaction with various gut microorganisms and other luminal components. NFκB coordinates immune system defense against external threats by maintaining barrier integrity and regulating the inflammatory response. Disruption of this homeostasis leads to susceptibility to inflammatory bowel disease and colorectal cancer [20]. It has been reported that plasma cytokine levels are frequently elevated in CRC patients [21]. NFκB, a major regulator of inflammation has been implicated in tumorigenesis and this signaling pathway is triggered by cytokines such as IL-1 and TNF, as well as T-cell receptors and B-cell receptors [22]. In colon cancer specifically, the activation of NFκB in intestinal epithelial cells and chronic inflammation is thought to have a role in tumorcigenesis [23]. NFκB activation has been reported to contribute to immune defense, particularly in acute inflammatory responses, while also exhibiting pro-inflammatory properties associated with pro-tumorigenic functions [24]. In our study, plasma NFκB levels were found to be significantly higher in the CRC group compared to controls.

Studies have shown that TGFβ1 expression is increased in colorectal cancer compared to benign adenomas and non-cancerous tissue [25]. High TGFβ levels have been observed in primary tumor tissue and plasma samples from CRC patients, correlating with metastasis and poor prognosis [26]. It's been reported that disruption of TGFβ signaling has important role in pathogenesis of variable molecular types of CRC [27]. Some studies, consistent with our findings, have reported that circulating TGFβ levels are elevated in patients with hematologic malignancies and solid tumors compared to controls [28,29]. Pathological TGFβ levels have been shown to impair both innate and adaptive cellular immunity in cancer patients [30].

Colonic tumors have been suggested to release free arachidonic acid and typically produce a higher quantity of prostaglandins (PGs) than normal mucosal tissue [31]. $cPLA_2$ is a crucial enzyme in the synthesis of PGs and its role in the development of intestinal tumors has been defined. In 1996, Soydan et al. [32] were the first to demonstrate that human colon tumors, contain high-molecular-weight $cPLA_2$. Other research indicated that $cPLA_2$ is overexpressed in 35-50% of colorectal cancers [33,34]. Additionally, another study revealed that $cPLA_2$ was overexpressed in CRC tissue samples, but showed no correlation with clinicopathological parameters, except for its association with VEGF expression [35]. Our findings indicated no significant difference in $cPLA_2$ and $sPLA_2$ levels between CRC and control groups.

In conclusion, this study alerts the existence of a CRC predictor based on endoglin, as the analysis of the relation between inflammatory microenvironment and endoglin in CRC patients and found that endoglin plasma and mRNA levels were significantly elevated in CRC patients. The correlation between NFκB and endoglin suggests that the increase in endoglin levels may be linked to the development of inflammation in CRC. Endoglin can therefore be implicated in the tumor associated inflammation acting in the colorectal cancer microenvironment.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The study was conducted with the approval of the Clinical Research Ethics Committee of Ankara University with 04-225-18 number.

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