

Investigation of Trpa1 and Trpc1 Immunreactivities in Colon Adenocarcinomas

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Purpose: As the normal colon epithelium differentiates into adenoma, invasive cancer and metastatic cancer, the cell acquires new characteristics such as apoptosis, proliferation, differentiation, invasion and metastasis. Many mechanisms are effective in acquiring these qualities. One of these is the regulation of the functioning of ion channels. This study aimed to examine TRPA1 and TRPC1 expression in colorectal adenocarcinomas showing different degrees of differentiation.

Patients and Methods: We examined the biopsy specimens of 60 patients diagnosed with colorectal adenocarcinomas, including those of patients with well-differentiated (n = 20), moderately differentiated (n = 20) and poorly differentiated (n = 20) carcinomas. Moreover, 20 biopsy specimens of individuals with normal colonic mucosa were examined. Histoscores were calculated for TRPA1 and TRPC1 based on the extent of diffusion and intensity of immunoreactivity, and these scores were compared statistically.

Results: A statistically significant increase in both TRPA1 and TRPC1 immunoreactivity was observed in low-grade and high-grade colon adenocarcinomas compared to the control group (p<0.001). A statistically significant decrease in both TRPA1 and TRPC1 immunoreactivity was observed in high-grade colon adenocarcinomas compared to low-grade colon adenocarcinomas (p<0.001).

Conclusion: TRPA1 and TRPC1 immunoreactivities are increased in colorectal adenocarcinoma tissue compared with the healthy tissue. Furthermore, the immunoreactivity decreases as the grade of cancer increases.

Keywords: colon cancer, adenocarcinoma, ion channels, ions

Introduction

Colorectal cancer (CRC) is the most common type of gastrointestinal cancer. Colorectal cancers are the third leading cause of cancer and cancer-related deaths in both men and women. Additionally, the incidence of colorectal cancer is increasing in young people.¹ It is a multifactorial disease with complex etiology, including genetic factors, environmental exposure (including dietary factors), and inflammatory conditions of the digestive tract, and the definitive treatment available is surgery.²⁻⁷ Local invasion and distant metastasis are the most common causes of mortality, and early diagnosis of such cancers reduces mortality by 18-33%.⁸⁻¹⁰ One of the most important factors affecting mortality is the tumor grade at the time of diagnosis.¹¹ Normal colon epithelium is susceptible to adenoma, invasive cancer and metastatic cancer. The cellular and molecular mechanisms underlying cancer differentiation have not been fully resolved.^{7,12} Ion channels in cells are very important for cancer cells to acquire their unique properties. These ion channels increase tumor cell apoptosis, proliferation, differentiation, invasion and metastasis through regulatory signaling pathways that are effective in cancer progression.¹³ Changes in intracellular calcium ion (Ca²⁺) concentration, increases in intracellular Ca²⁺ concentration required for exocytosis and contractions in muscles, cell processes that affect proliferation, cell cycle, cell control, cell migration, gene expression, and cell death.¹²⁻¹⁸ Since Ca²⁺ ions play a role in tumor development in addition to their normal physiological functions, the direct and indirect effects of these channels on tumor development are currently being investigated.^{19,20}

Transient receptor potential (TRP) channels are cellular sensors that respond to many changes, including osmolarity, pH, temperature, pressure, chemicals, and oxidation and reduction.²¹ Specifically, TRPA1 is activated by neutrophils, macrophages, and B and T cells in the tumor microenvironment.²² The TRPC subfamily consists of

seven members (TRPC1–7) and functions as non-selective cation channels permeable to Ca²⁺, Na⁺ and K⁺ ions.^{23,24} In contrast, TRPC1 channels inhibit Ca²⁺ overload, which causes cell death in aggressive metastatic tumors, as well as inhibitory pharmacological agents. It is a potential target for treatments aimed at suppressing tumor growth and metastasis via

Based on this information, this study aimed to examine TRPA1 and TRPC1 expression in colorectal adenocarcinomas showing different degrees of differentiation.

Materials and Methods

For this study, approval was received from Firat University non-invasive research ethics committee before starting the study (2021/04-25). Informed consent was obtained from the patients included in the study and administrative permission was obtained from the hospital management. The study was designed in accordance with the Declaration of Helsinki. Hematoxylin and eosin stained sections were taken from patients operated on at the University Hospital between 2015 and 2020, and these sections were stored under appropriate conditions in the pathology laboratory. These sections were then examined under a light microscope by a single pathologist. Among these samples, three groups were created by including biopsy samples of 60 patients diagnosed with low-grade (n = 40) and high-grade (n = 20) colon adenocarcinoma according to the WHO classification and staging, and 20 samples containing normal colon mucosa.²⁵

Immunohistochemistry

Overall, 4–6 µm thick sections were obtained from paraffin blocks and mounted on polylysine slides. Deparaffinized tissues were treated with graded alcohol series and boiled in citrate buffer solution at a pH of 6 in a microwave oven (750 W) for 7 + 5 minutes for antigen retrieval. After boiling, the tissues were maintained at a room temperature for approximately 20 minutes and washed with PBS (Phosphate Buffered Saline, P4417, Sigma-Aldrich, USA) for 3×5 minutes; subsequently, they were incubated with hydrogen peroxide block solution for 5 minutes to prevent endogenous peroxidase activity (Hydrogen Peroxide Block, TA-125-HP, Lab Vision Corporation, USA). The tissues washed with PBS for 3×5 minutes were then treated with Ultra V Block (TA-125-UB, Lab Vision Corporation, USA) solution for 5 minutes to prevent background staining. Thereafter, the tissues were incubated with TRPA1 and TRPC1 primary antibodies (TRPA1 Polyclonal Antibody, Elabscience, E-AB-62987, Texas, USA and TRPC1 Polyclonal antibody, bs-10404R, Biossusa, USA) diluted at 1:200 for 60 minutes at room temperature in a humid environment. After incubation with primary antibodies, the tissues were washed with PBS for 3×5 minutes and incubated with secondary antibody (biotinylated Goat Anti-Polyvalent (anti-mouse / rabbit IgG), TP-125-BN, Lab Vision Corporation, USA) for 30 minutes at room temperature in a humid environment. Subsequently, these tissues were washed with PBS for 3×5 minutes and incubated with streptavidin peroxidase (TS-125-HR, Lab Vision Corporation, USA) for 30 minutes at room temperature in a humid environment and then placed in PBS. 3-amino-9-ethylcarbazole (AEC) substrate + AEC chromogen (AEC Substrate, TA-015 ve HAS, AEC Chromogen, TA-002-HAC, Lab Vision Corporation, USA) solution was dripped onto the tissues, and the samples were washed with PBS after a signal was obtained under the light microscope. These tissues were counterstained with Mayer's haematoxylin and treated with PBS and distilled water. Tissues were then fixed using the appropriate-mounting solution (Large Volume Vision Mount, TA-125-UG, Lab Vision Corporation, USA). The preparates were examined, evaluated and imaged under the Leica DM500 microscope (Leica DFC295). Histoscores were calculated based on the extent of diffusion (0.1: <25%, 0.4: 26%–50%, 0.6: 51%–75%, 0.9: 76%–100%) and intensity of immunoreactivity (0: no, +0.5: very low, +1: low, +2: moderate, +3: strong) as follows: Histocore = extent of diffusion × intensity

Statistical Analysis

The data obtained was determined as mean ± standard deviation. SPSS version 22 program (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Evaluation between groups was made with One-way ANOVA and Posthoc Tukey's test. P<0.05 values were considered statistically significant.

Results

Immunohistochemical Findings

TRPA1 immunoreactivity

As a result of light microscopy examination of the immunohistochemical staining performed to determine TRPA1 immunoreactivity; Compared to the colon tissue of the control group (Figure 1); A statistically significant increase in TRPA1 immunoreactivity was observed in low-grade (Figure 2) ($p < 0.001$) and high-grade colon adenocarcinomas (Figure 3) ($p < 0.001$). A statistically significant decrease in TRPA1 immunoreactivity was observed in high-grade colon adenocarcinomas compared to low-grade colon adenocarcinomas ($p < 0.001$). (Table 1 and Figure 4).

TRPC1 immunoreactivity

As a result of light microscopy examination of the immunohistochemical staining performed to determine TRPC1 immunoreactivity; Compared to the colon tissue of the control group (Figure 5); A statistically significant increase in TRPC1 immunoreactivity was observed in low-grade (Figure 6) ($p < 0.001$) colon adenocarcinomas. Compared to low-grade colon adenocarcinomas, a statistically significant decrease in TRPA1 immunoreactivity was observed in high-grade (Figure 7) colon adenocarcinomas ($p < 0.001$). (Table 1 and Figure 8).

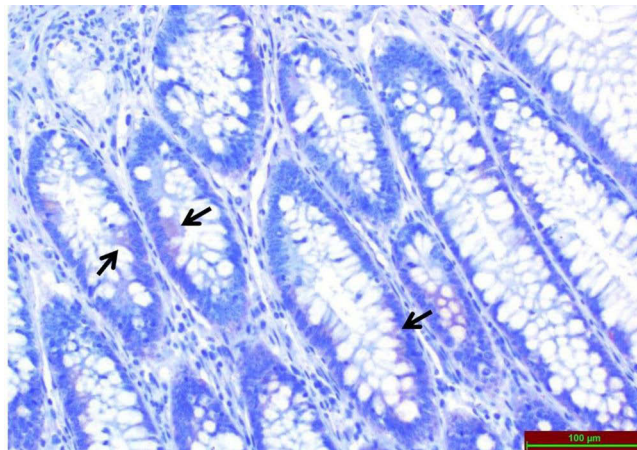


Figure 1 Light microscopic examination of TRPA1 immunoreactivity immunohistochemical staining in normal colon tissues. Arrows indicate areas of immunohistochemical staining.

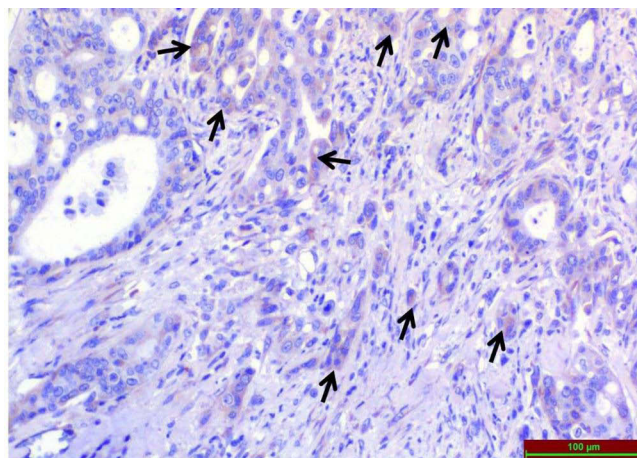


Figure 2 Light microscopic examination of TRPA1 immunoreactivity immunohistochemical staining in Low-Grade colon adenocarcinoma tissues. Arrows indicate areas of immunohistochemical staining.

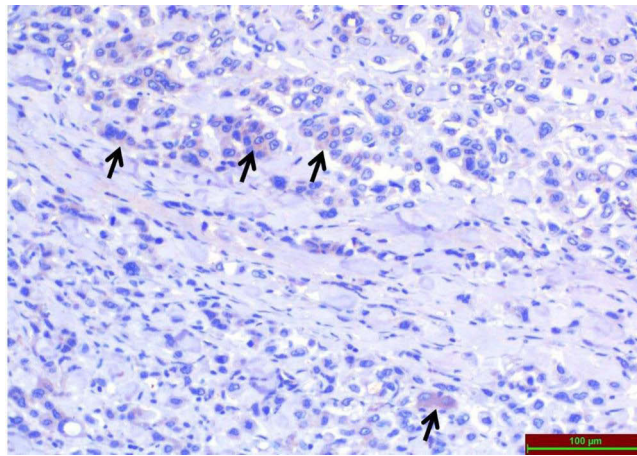


Figure 3 Light microscopic examination of TRPA1 immunoreactivity immunohistochemical staining in High-Grade colon adenocarcinoma tissues. Arrows indicate areas of immunohistochemical staining.

Discussion

Colorectal cancer is a common and leading cause of cancer-related deaths. It is a group of diseases that show different clinics and results. The prognosis of colorectal cancer patients varies greatly in the literature, with 5-year survival rates ranging from 90% to 10%. The prognosis of colorectal cancer is based mainly on the stage of cancer defined by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM staging classification. Further risk stratification may be important to identify patients at the same stage who are at increased risk of recurrence or metastasis and to guide treatment.²⁶

Histological features such as tumor budding, perineural invasion, apical lymph node positivity, tumor grade, lymph node yield, lymph node ratio, and molecular features such as microsatellite instability (MSI), Kirsten rat sarcoma virus (KRAS), v-RAF murine sarcoma viral oncogene predict prognosis. Homolog B (BRAF) and caudal-type homeobox 2 transcription factor (CDX2) have been used to guide and optimize adjuvant therapy, but there is no consensus on their roles. Factors arising from molecular features are not routinely evaluated in all patients.^{26,27}

In our article, we will focus on tumor grade among many risk factors. The main limitations in tumor grading are the lack of a uniform system and significant inter pathologist variability in its assessment. Therefore, the same pathologist evaluated all our samples. We obtained our samples from surgical resection materials, completely focused on degree, regardless of localization. Tumor grade is based on the percentage of gland formation in the lesion and thus its similarity to the original tissue. The World Health Organization (WHO) classification of digestive tract tumors uses a two-tiered system: low-grade ($\geq 50\%$ glandular formation) and high-grade (poorly differentiated, $< 50\%$ glandular formation).^{26,27}

In this study, a significant increase in TRPA1 and TRPC1 immunoreactivity was observed in the low- and high-grade colon adenocarcinoma groups compared to the control group. However, TRPA1 and TRPC1 immunoreactivity was significantly reduced in the high-grade adenocarcinoma group compared with the low-grade adenocarcinoma group.

Table I TRPA1 and TRPC1 Immunoreactivity Histoscore

	TRPA1 Immunoreactivity Histoscore	TRPC1 Immunoreactivity Histoscore
Control	0,19±0,08	0,28±0,14
Low Grade Colon Adenocarcinoma	0,81±0,20 ^a	1,35±0,28 ^a
High Grade Colon Adenocarcinoma	0,45±0,24 ^{ab}	0,36±0,14 ^b

Notes: Values are given as mean \pm standard deviation. ^aCompared with the control group. ^bCompared to low-grade colon adenocarcinoma, ($p < 0.05$).

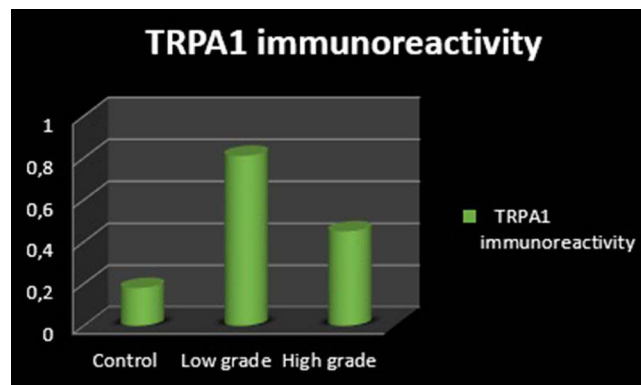


Figure 4 TRPA1 immunoreactivity.

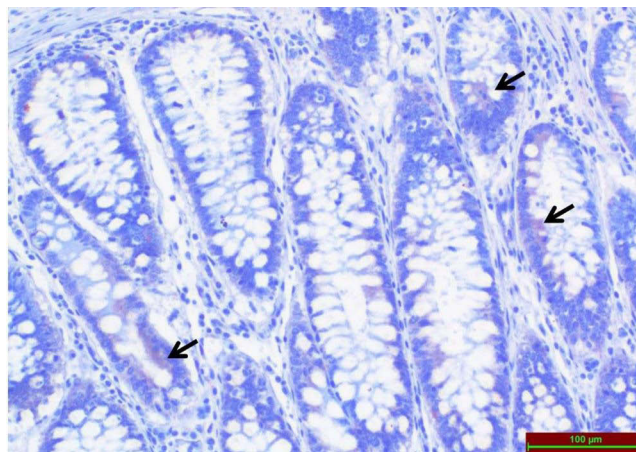


Figure 5 Light microscopic examination of TRPA1 immunoreactivity immunohistochemical staining in normal colon tissues. Arrows indicate areas of immunohistochemical staining.

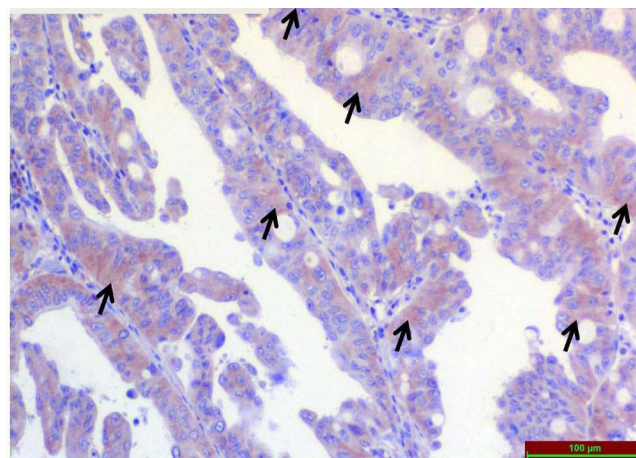


Figure 6 Light microscopic examination of TRPA1 immunoreactivity immunohistochemical staining in Low-Grade colon adenocarcinoma tissues. Arrows indicate areas of immunohistochemical staining.

Colorectal cancer is associated with Ca^{2+} , and a recent study has reported that mutations in oncogenes and tumour suppressors can promote changes in intracellular Ca^{2+} homeostasis in patients with colorectal cancer.²⁸ This mechanism may effectively increase the proliferation, invasion, metastasis and apoptotic resistance of cancer cells.^{24,29-31} In

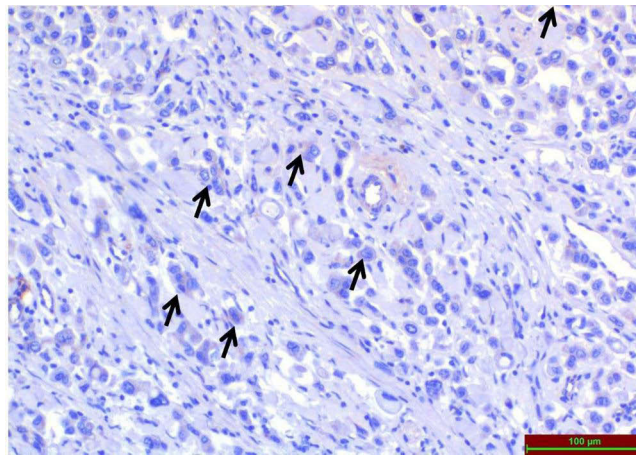


Figure 7 Light microscopic examination of TRPC1 immunoreactivity immunohistochemical staining in High-Grade colon adenocarcinoma tissues. Arrows indicate areas of immunohistochemical staining.

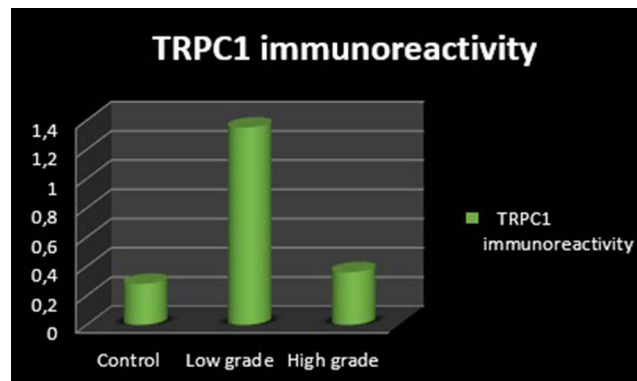


Figure 8 TRPC1 immunoreactivity.

particular, Ca^{2+} is crucial for many functions of cells at biological, chemical and molecular levels, and intracellular and extracellular calcium levels are one of the fundamental signalling pathways for cellular functions. In addition, cellular calcium balance is maintained by voltage-, receptor-, and store-gated calcium channels; TRP channel proteins located on the endoplasmic reticulum (ER) and plasma membrane; and the IP₃ receptor and STIM protein located on the ER membrane.²² Some of these channels play a role in physiological and pathological processes in the organism and mediate Ca^{2+} signalling and remodelling in cancer cells.³² Ca^{2+} remodelling markedly contributes to carcinogenesis, including cell proliferation, motility and survival. The most prominent feature of Ca^{2+} remodelling in colorectal cancer cells is the depletion of intracellular Ca^{2+} stores owing to an increase in store-operated Ca^{2+} entry (SOCE).³³ SOCE is a Ca^{2+} entry pathway responsible for agonist-induced Ca^{2+} release from intracellular stores in the ER, and it was first reported in 1986 by James W. Putney. SOCE activation plays a role in colon carcinoma by activating TRPC1 channels in the plasma membrane via phospholipase C-bound inositol 1,4,5-triphosphate (IP₃) receptors.^{32,34} The results of this study showed that TRPC1 immunoreactivity was increased in patients with low-grade colorectal cancer but decreased in patients with high-grade colorectal cancer. Although the increase in patients with low-grade colorectal cancer is due to the pro-tumor effect of TRPC1, the decrease in patients with high-grade colorectal cancer may be due to depletion of intracellular Ca^{2+} stores due to SOCE. In addition, Type 3 IP₃ receptors (IP₃ R3s) can exert anti-oncogenic effects by directing proapoptotic Ca^{2+} signals to mitochondria. Moreover, as reported in a recent study, the upregulation of IP₃ R3 may trigger oncogenesis through ER-mitochondria Ca^{2+} transfer.³⁵ Although data on this topic are conflicting in the literature, based on the findings of this study, we believe that TRPC1 channels play a specific role in low-grade colon tumors.

In contrast, TRPA1 channels can be activated by endogenous electrophilic ligands released during oxidative stress and inflammatory and degenerative processes, and these channels may play a role in carcinogenesis by inducing intracellular increase in Ca²⁺ concentrations.³⁴ In a study examining the relationship between TRPA1 and colon adenocarcinoma, TRPA1 was reported to be secreted in the healthy colon but not in colorectal cancer.²² In another study, no difference in TRPA1 expression was found between colon adenocarcinoma and healthy colon tissues.³⁶ In this study, TRPA1 expression was significantly increased in low-grade colon adenocarcinomas. However, contrary to the results of the limited number of studies on the subject, TRPA1 expression was found to be significantly reduced in high-grade colon adenocarcinoma. The increase in the TRPA1 expression in well-differentiated colonic adenocarcinoma may be because of the activation of extracellular protein kinase (ERK1/2) and p38-mitogen-activated protein kinase (p38-MAPK), which are signalling pathways involved in carcinogenesis. A recent study reported that the activation of (ERK1/2) and p38-MAPK is mediated by TRPA1.³⁷

Similar to TRPC1, the decrease in TRPA1 expression in high-grade adenocarcinomas may be due to a decrease in intracellular Ca²⁺ stores. However, this is not a definitive conclusion. Based on the current evidence, it is safe to say that TRP channel protein expression may vary depending on various undiscovered variables and thus further studies are needed.

Conclusion

TRPA1 and TRPC1 protein levels are useful markers in distinguishing colon adenocarcinomas from healthy colons, regardless of degree. Therefore, the intensity of TRPA1 and TRPC1 expression can be used for the early detection of colon adenocarcinoma. Both ion channels may have pro-tumor effects, and pharmacological agents that block these channels may be candidates for use in the treatment of colorectal cancer.

Disclosure

The authors declare no conflicts of interest in this work.

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