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Original Article

Clinicopathological characteristics of PRRX1 and PRRX2 gene expression in colorectal cancer patients

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Abstract

Colorectal cancer (CRC) ranks as the third leading cause of cancer-related deaths globally. It results from polyp growth or ulcers formation in the colon or intestinal lining. Genetic, environmental factors, unhealthy eating habits, and lifestyle choices contribute to CRC development. Genetic and epigenetic changes play a crucial role in tumor development. Homeobox (HOX) genes contain the homeodomain, encoding transcription factors that regulate gene expression. Paired Related Homeobox 1 (PRRX1) and Paired Related Homeobox 2 (PRRX2), homeobox genes, are intestinal overexpressed in diseases and involved in tumor metastasis, impacting cancer cell properties and metastasis. In this study, our goal was to analyze the presence of PRRX1and PRRX2 in both colorectal cancer and nearby normal tissues. The expression levels of PRRX1 and PRRX2 were evaluated in 100 colorectal tumor tissues and 100 adjacent control tissues using the Quantitative Real-Time PCR (qRT-PCR) method. Additionally, we assessed the diagnostic effectiveness of PRRX1 and PRRX2 by creating a receiver operating characteristic (ROC) curve. Our findings showed that the expression of PRRX1 and PRRX2 was significantly overexpressed in colorectal cancer patients compared to the adjacent control group sample. Examination of clinicopathological characteristics of patients revealed varied correlations between PRRX1 and PRRX2 gene expression and TMN stage ($p<0.0001$, $p<0.0001$). Also, the expression levels of PRRX1, PRRX2 between patients with LVI+ and those with LVI-, with p-values of $p<0.0001$, $p<0.0001$ for each. These findings suggest that PRRX1and PRRX2 levels could be used as possible diagnostic indicators for colorectal cancer.

Keywords: Colorectal Cancer (CRC), PRRX1, PRRX2, Diagnostic biomarkers.

1. Introduction

Colorectal cancer (CRC), which involves cancers occurring in the colon and rectum, is the third most prevalent cancer by incidence and mortality worldwide. In fact, it is estimated that by 2030, there will be globally >2.2 million new cases and 1.1 million deaths due to CRC [1].

From an etiological point of view, CRC can result from uncontrolled polyps' growth in colon or chronic ulcers on intestine lining. Some patients have a genetic and family history of CRC, while others may develop the disease sporadically while having a history of intestinal ulcers and gastrointestinal diseases [2].

Several environmental and genetic factors contribute to CRC development, but unhealthy eating habits, poor lifestyle choices, and family background are the major ones among them. High-fat and low-fiber food consumption per day has globally increased, leading to higher numbers of CRC cases [3].

Genetic and epigenetic changes are common in CRC and play a crucial role in the development of tumors.

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These changes often begin in early-stage adenomas and build up as the condition progresses to cancer. Chromosomal instability, microsatellite instability, and changes in the CpG island methylator phenotype are key factors contributing to genetic instability in CRC[4]. Essentially, cancer arises from the accumulation of somatic mutations, along with other genetic alterations, which lead to abnormal cell growth and the formation of tumors [5].

Homeobox (HOX) genes encode a peptide motif known as the homeodomain. Most HOX genes encode transcription factors that regulate the expression of other genes by binding to specific DNA sequences (mediated by the homeodomain) and interacting with protein cofactors [6]. These genes influence processes such as cell shape or phenotype, adhesion, migration, and the rate of mitosis or apoptosis. Paired Related Homeobox1 (PRRX1) is abnormally expressed in many diseases and plays a role in tumor metastasis. It is particularly associated with the epithelial-mesenchymal transition (EMT), maintaining the stem-like properties of tumor cells, thus affecting cancer cell proliferation and metastasis [7]. PRRX1 and Paired Related Homeobox2 (PRRX2), are members of a subfamily of homeobox genes, which could promote transcriptional activation. PRRX1 and PRRX2 have been confirmed as important factors for the development of mesenchymal tissues and are involved in the organogenesis of many tissues during developmental processes. In recent years, it has been demonstrated that changes in the expression of PRRX2 are related to the development of certain cancers, such as prostate cancer, esophageal squamous cell carcinoma and leukemia. Besides, PRRX2 expression has been found to be abnormally expressed in metastatic gastric cancer, which acted as a potential biomarker for gastric cancer metastasis [8].

This process of EMT leads to tumor progression, invasion of cancer cells, and resistance against treatment. Transcription factors such as those produced by SNAI gene family suppress epithelial gene expression, hence regulating this process. Several signaling pathways including (transforming growth factor-β1) TGF-beta1, (Interleukin 6) IL-6, (Protein kinase B) PKB or Akt and (Extracellular signal-regulated protein kinase 1 and 2) Erk1/2, stimulate EMT responses. In addition to regulatory transcription factors, non-coding RNA molecules (microRNA), miRNAs and long non-coding RNAs (lncRNAs) also initiate EMT [9].

EMT is driven by both internal and external factors within cells. This process is mainly triggered by external elements like TGF-β1, neurotrophins, and IL-6, which activate several signaling pathways, including WNT, Smads, STATs, Akt, and Erk1/2. These pathways then activate transcription factors such as Goosecoid, Snail, Slug, Twist, NRF2, and KLFs, which bind to specific DNA sequences. This binding primarily suppresses the expression of genes involved in maintaining epithelial characteristics. One of the most well-known changes in this process is the reduction of E-cadherin levels, regulated by the transcription factors SNAI, Snail, and Slug [9].

The expression of PRRX1 in cancer cells is high, which strongly correlates with metastasis, chemoresistance and poor prognosis in patients with CRC. In addition, PRRX1 remarkably enhances the proliferation, survival, stemness, and chemoresistance capacities of colorectal cancer cells [10].

This study will determine the levels of expression for the genes PRRX1 and PRRX2 in CRC patient tissue samples and correlate changes in their expressions with tumor grade, stage and lymphovascular invasion (LVI) in CRC patients. The linkage between gene expression transformation and CRC may open up novel strategies for controlling the disease.

2. Materials and methods

2.1. Patients and sample

This case-control study collected tissue samples from patients referred to endoscopy, oncology, or surgery clinics from July 2021 to December 2023 in different hospitals. In total, 100 patients and 100 control subjects were included in the study, with samples collected through biopsies or surgical resections. Additionally, normal specimens from colorectal cancer sample patients were collected, containing no tumor cells and located at least 2 cm away from the tumor site. Inclusion criteria for this study are patients aged 18–60 years old with a histologically confirmed diagnosis of colon adenocarcinoma, whose tumor tissue samples have been verified by a board-certified pathologist, and who have not received any colorectal cancer-associated therapy before the biopsy. This study excluded subjects who had received colorectal cancer-related treatments, such as surgical resections, as well as any other malignancies. Additionally, lifestyle, demographic, and histopathological information related to the clinical TNM staging and Lymphovascular invasion (LVI) were documented.

2.2. RNA extraction and cDNA synthesis

The commercial kit was used for RNA extraction (Cinnacolon, Tehran, Iran) and isolated RNA was eluted in 40 µl of RNase/free water. Its viscosity and integrity of the total RNA were assessed by measuring the A260/A280, using Nano Drop ND-1000 spectrophotometer (Thermo Fisher Scientific, USA). That each sample ratio was intended between 1.7 and 2.1, then RNA suspension was stored at −80°C for further analysis, and it was converted to cDNA. The reverse transcription reaction was using a cDNA kit (Cinnacolon, Tehran, Iran), and cDNA was prepared from 2 µg of total RNA, with Oligo (dT) and random hexamer primers. Consistent with the manufacturer's instructions the kit mix was run on a PCR thermocycler as follows: 10 min at 25°C, 2 h at 37°C, 5 min at 85°C, and thereafter on a PCR thermocycler. cDNA was diluted to a total concentration of 5 ng/µl.

2.3. Real-Time PCR

Real-time PCR analysis was conducted in duplicates using 2.0X Real Q-PCR Master Mix with SYBR Green (Ampliqon, Odense, Denmark). The reaction of each sample involves 10 µl 2 × RealQ-PCR Master Mix, 1 µl cDNA, 1 µl of each primer (10 pmol/µl), and 8 µl of distilled water. Reactions were run on the Step One Plus Real-time PCR System (Applied Biosystems, USA) using the thermal cycling parameters 95°C for 2 min and 40 cycles of 95°C for 5 s, 60°C for 30 s. The specificity of PCR products was verified by melting curve analysis. Gene expression levels were normalized to the housekeeping gene beta-2 macroglobulin (β2M) for each sample. Primers for PRRX1 and PRRX2 were designed to span exon-exon junctions to prevent the amplification of genomic DNA

Table 1. qRT-PCR primer sequences.

Genes	Primers	Sequences	Amplicon size (bp)
PRRX1	Forward Primer	CCCACAGCGTTTGGTGTTG	182
	Reverse primer	GCAGGTGACTGACGGAGAAG	
PRRX2	Forward Primer	GGTGCCTACGGTGAACTGAA	199
	Reverse primer	CCAAGGACAGAAGAGCTGGG	
Beta-2- macroglobulin	Forward Primer	TGTCTTTCAGCAAGGACTGGT	143
	Reverse primer	TGCTTACATGTCTCGATCCCAC	

Table 2. Patients' clinical pathological characteristics

Variable	Clinical pathological parameter	Number of samples (n = 100)
Age	≥ 45	54
	< 45	46
Gender	Male	48
	Female	52
TNM stage	II	29
	III	36
	IV	35
Tumor size	< 2	16
	2-3.5	25
	3.5-5	21
	>5	38
Localization	Colon	45
	Rectum	55
Lymphatic invasion	Positive	40
	Negative	60

and avoid false-positive results (Table 1).

2.4. Statistical analysis

Efficiency values and cycle threshold (Ct) for each sample [Figure 1], the amplification efficiency was determined using the Lin Reg software (version: 2017.1), and the expression ratio (Fold change 2 $^{-\Delta\Delta Ct}$) of the PRRX1 and PRRX2 was estimated using REST 2009 software. The means of statistical differences of PRRX1 and PRRX2 levels between patients and controls were analyzed with the Graph Pad Prism software version 8.0 (La Jolla, CA). That, using the Mann–Whitney test and unpaired t-test to compare PRRX1, PRRX2 mRNA levels in two groups. *P* value of ≤0.05 was considered significant.

3. Results

Overall, we studied 100 CRC patients (52 females and 48 males) aged between 20 and 65 years (mean ±SD = 43.91±9.73 years). The tissue location of malignancy in 45 (45%) was colon and 55 (55%) were rectum. Also, of these patients clinical TNM stage, 29(29%) were stage II, 36 (36 %) were stage III and 35 (35%) were stage IV. In the current study, LVI+ was observed in 40 (40 %) of 100 CRCs. The clinical characteristics of the selected subjects are shown in Table 2. Assessment of PRRX1, PRRX2 gene expression levels using qRT-PCR showed that the gene expression of PRRX1, PRRX2 is significantly up-regulated in CRC tissue samples compared to the normal tissues (p<0.0001, p<0.0001; Figure 1). ROC curve analysis revealed that the tissue may be a useful biomarker to distinguish colorectal adenocarcinoma patients from control subjects. We know that the larger the area under the ROC curve (AUC), the higher the diagnostic value. The area under the ROC curve for PRRX1 and PRRX2 is shown in Figure 2. Additionally, a significant difference was obser-

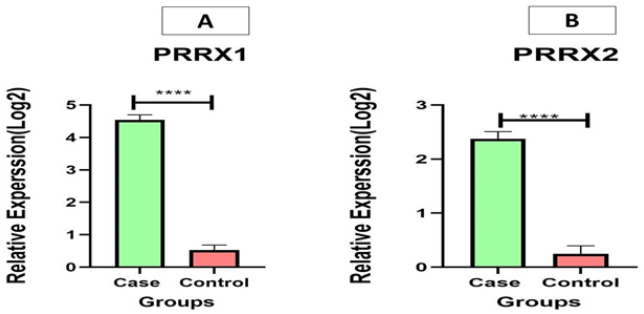


Fig. 1. The relative expression levels (−ΔCt) of PRRX1, PRRX2 and β2M. A. shows the differences PRRX1 expression between the control group. B. shows the differences in PRRX2 expression between the control group. (****: p<0.0001).

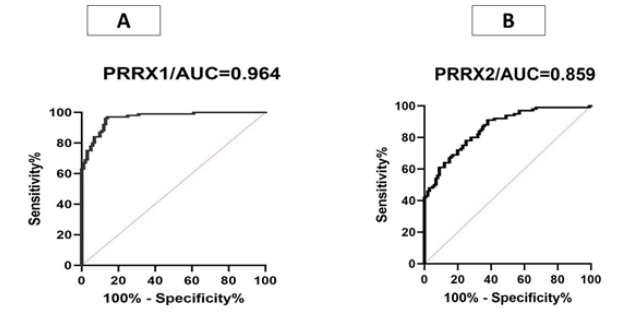


Fig. 2. ROC curve analysis of the diagnostic value of CRC-related genes to distinguish between CRC patients and healthy individuals.

ved in the tissue expression levels of PRRX1 and PRRX2 across TNM stages; notably, in stage IV CRC patients, the expression levels of these genes were significantly higher compared to those in stages II and III, with p-values of $p<0.0001$ and $p<0.0001$, respectively (Figure 4). In this study, lymphovascular invasion (LVI+) was present in 40 (40%) of the 100 CRC patients examined. Our analysis revealed statistically significant differences in the expression levels of PRRX1, PRRX2 between patients with LVI+ and those with LVI-, with p-values of $p<0.0001$, $p<0.0001$ for each. Specifically, the expressions of these genes were significantly higher in the LVI+ group compared to the LVI- group, as depicted in Figure 3.

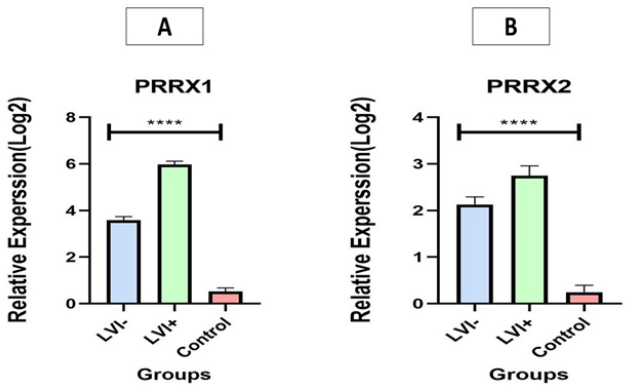


Fig. 3. The relative expression levels (−ΔCt) of PRRX1, PRRX2. A. shows the differences in PRRX1 expression between LVI+ group in CRC patients and the LVI- group. B. shows the differences in PRRX2 expression between LVI+ in CRC patients and the LVI- group. ($p<0.0001$, $p<0.0001$).

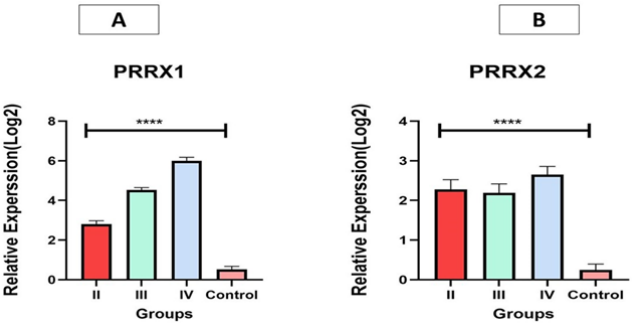


Fig. 4. The relative expression levels (−ΔCt) of PRRX1, PRRX2. A. shows the differences in PRRX1 levels between TMN stage in CRC patients. B. shows the differences in PRRX2 levels between TMN stage in CRC patients. ($p<0.0001$, $p<0.0001$).

4. Discussion

CRC is a multifactorial digestive pathology and is an enormous problem facing not only clinicians but also scientific researchers [11]. It ranks as the third leading cause of cancer deaths worldwide, posing a significant threat to human health [12]. Factors such as a diet high in meat and saturated fats, low physical activity, obesity, smoking, alcohol consumption, and inflammatory bowel diseases seem to increase the risk of developing colorectal cancer. This type of cancer typically develops from benign precursors, the adenomatous polyps, which can gradually turn cancerous through a series of molecular changes, including mutations in oncogenes, inactivation of tumor suppressor genes, and microsatellite instability [13].

Homeobox genes encode DNA-binding transcription factors that are essential for metazoan cellular differentiation and embryonic patterning. Two of these highly conserved vertebrate genes are PRRX1 and PRRX2 [14]. Among these, PRRX1 and PRRX2 are particularly important for craniofacial and limb morphogenesis [15]. EMT is a process where cells lose their epithelial traits, such as cell-cell contacts and polarity, and gain mesenchymal characteristics like increased mobility. In CRC, EMT is linked to a more invasive and metastatic behavior. EMT can occur in various contexts: during embryonic development, wound healing and organ fibrosis, and cancer progression. In the case of cancer, EMT contributes to the invasive and metastatic abilities of cancer cells [16]. The PRRX1 gene is found to be abnormally expressed in many diseases and is involved in tumor metastasis. It is closely related to EMT and the stemness maintenance of tumor cells, thereby influencing cancer cell proliferation and spread. PRRX1 promotes EMT through the Wnt/β-Catenin and Notch signaling pathways and supports the stemness maintenance of tumor cells. It functions as both a transcription factor or transcription co-activator in these processes [7]. LVI is a significant risk factor for CRC. The lymphatic system often serves as a primary pathway for cancer metastasis, and the status of lymph nodes is crucial for determining patient prognosis, tumor staging, and treatment strategies [17]. IL-6 is a cytokine that plays a role in the development and progression of various cancers, including CRC. Studies in mice have shown that blocking IL-6 can significantly reduce tumor formation associated with colitis. Additionally, IL-6 has been found to promote CRC cell proliferation by activating the STAT, ERK/MAPK, and PI3K/AKT pathways. Increased IL-6 expression also enhances the resistance of CRC cells to chemotherapy [10].

This study aims to explore the expression levels of the PRRX1 and PRRX2 genes and their roles in the progression and LVI of CRC. The present study was conducted on a cohort of 100 treatment-naïve CRC patients with a mean age of 44 years, reflecting a comparatively younger demographic than often reported in Western populations. An almost equal gender distribution (52% female, 48% male) and a near-balanced anatomical origin of tumors (45% colon, 55% rectum) within our cohort strengthen the generalizability of our molecular findings across key clinical subtypes of CRC. Our core finding reveals a profound dysregulation of the mesenchymal transcription factors PRRX1 and PRRX2 in CRC pathogenesis. Quantitative analysis demonstrated a striking and highly significant upregulation of both genes in tumor tissues compared to their matched normal counterparts ($p < 0.0001$). This consistent overexpression strongly implies their active involvement in colorectal oncogenesis, potentially driving key malignant phenotypes such as enhanced cellular plasticity and invasive potential. According to our results, the study conducted by Rodríguez et al (2022) showed that the expression of PRRX2 is increased in CRC. They highlighted that androgen receptor inhibitors are the primary treatment for advanced prostate cancer, but resistance often develops. Their research identified PRRX2 as a gene contributing to resistance against enzalutamide, making it a key driver of treatment resistance [18]. By comparing our results with this research, we can conclude that the expression of PRRX2 has increased in prostate cancer and

thus causes resistance to treatment. Beyond their general overexpression, the transcriptional activity of PRRX1 and PRRX2 exhibited a strong positive correlation with tumor progression. We found a stepwise and statistically robust increase in their expression levels across advancing TNM stages, culminating in the highest expression in stage IV metastatic disease ($p < 0.0001$). This stage-dependent escalation strongly suggests that these genes are not merely bystanders but active contributors to CRC aggressiveness and metastatic dissemination. According to our results, Zhu et al (2021) found that the COL11A1 gene is involved in cell proliferation in ovarian cancer. This gene is highly expressed in late-stage ovarian tumors. PRRX1 acts as an upstream regulator of this gene, promoting tumor progression and resistance to radiation therapy [19]. As a result, compared to our findings, the high expression of these genes in CRC at higher stages of cancer causes tumor progression and resistance to treatment. Most critically, our data establish a direct and potent link between PRRX1/PRRX2 expression and a key histological marker of metastatic competence: lymphovascular invasion (LVI). Tumors exhibiting LVI harbored significantly elevated levels of both transcripts compared to LVI-negative tumors ($p < 0.0001$). This finding provides strong circumstantial evidence that PRRX1 and PRRX2 are functionally involved in enabling cancer cells to invade vascular channels, a critical first step in the metastatic cascade. Similar studies have been conducted to investigate the expression level of these two genes and their effect on tumor progression and metastasis in various cancers. We will briefly describe some of them and then compare them with our results. Marchand et al (2019) discovered that PRRX1 is crucial in EMT and MET in pancreatic cancer, leading to liver metastasis. PRRX1 interacts with the transcription factor FOXM1, which is a downstream target. PRRX1 also regulates genes involved in DNA repair, potentially limiting DNA damage in pancreatic cancer cells [20]. Yao et al (2021) reported that PRRX1 expression is significantly higher in gastric cancer tissues compared to normal intestinal mucosa. PRRX1 may worsen lymph node metastasis in gastric cancer through EMT, making it a potential marker for predicting and preventing metastasis[21] . Wang et al (2017) indicated that PRRX1 plays a significant role in EMT in breast cancer, with its expression increasing in breast cancer tissues [22]. According to these studies, it can be concluded that PRRX1 and PRRX2 are overexpressed in some cancers and play a role in metastasis and tumor invasion. According to the obtained results, the expression of these genes increased more in cases where invasion and metastasis occurred (end stages of cancer). Similar to our research, Liu et al (2023) found that PRRX2 is highly expressed in lung adenocarcinoma tissues. PRRX2 promotes cell proliferation and inhibits apoptosis. It can bind to the promoter of PSMD1 gene, contributing to lung cancer cell malignancy [8]. In conclusion, the PRRX1 and PRRX2 genes are overexpressed in colorectal and other cancers, promoting metastasis and tumor progression. LVI is a key process in metastasis influenced by these genes. Despite understanding some pathways through which these genes operate, the precise molecular mechanisms remain unclear and need further research.

In conclusion, our study demonstrates that the mesenchymal transcription factors PRRX1 and PRRX2 are significantly overexpressed in colorectal cancer and that their elevated expression is robustly associated with advanced disease stage (IV) and the presence of lymphovascular invasion. These findings position PRRX1 and PRRX2 not only as potential diagnostic adjuncts but, more importantly, as promising prognostic biomarkers for identifying patients with aggressive, metastasis-prone tumors. Future research should focus on validating these associations in larger, independent cohorts and elucidating the precise molecular mechanisms through which these genes drive invasion and metastasis in CRC, with the ultimate goal of evaluating their therapeutic targetability.

Author contribution statement

AM: is the principal investigator in the study**, SZN:** laboratory manipulation, **ZM and SZN**: Concept, Data acquisition, Data analysis, Manuscript preparation. **AE**: Concept, Research. **ZS**: Literature search **AE**: Manuscript editing. **AA**: Manuscript formatting according to the Journal requirement. **AD**: contributed to drafting preliminary. All the authors contributed to the critical review, the approval of the final version and agreed to be responsible for all aspects of the work.

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None.

Ethical declaration

It is an approved grant by https://ethics.research.ac.ir/IR.SBMU.PHNS.REC.1404.107 Shahid Beheshti University of Medical Sciences. Tehran, Iran, and was conducted in agreement with the ethical guidelines of the Declaration of Helsinki.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Use of artificial intelligence tools

Some sentences in this manuscript were revised with the assistance of artificial intelligence, based language models to improve clarity and readability. All intellectual content, interpretations, and conclusions are solely the responsibility of the authors.

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