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Expression patterns and clinical significance of MMP-8, MMP-9 and MMP-13 in colorectal cancer

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Abstract

Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal system in the world. By identifying specific gene expression patterns that indicate CRC in the early stages, it is possible to potentially diagnose the disease in the early stages and start treatment quickly. Matrix metalloproteinases (MMPs) play a crucial role in the degradation of the extracellular matrix and tissue remodeling. Among them, MMP-8, MMP-9 and MMP-13 have been found to be upregulated in various cancers, including CRC, and are associated with tumor invasion, metastasis, and angiogenesis. This study investigated tissue expressions of MMP-8, MMP-9, and MMP-13 in CRC patients and explored their possible associations with pathological and clinical factors. 100 patients with CRC and 100 control subjects were involved in the study. Tissue and blood samples were collected. The quantitative Real-Time PCR (qRT-PCR) technique was used to assess the expression levels of the MMP-8, MMP-9, and MMP-13 in CRC tissue samples in comparison with the adjacent control tissue. Our results revealed that the expression levels of MMP-8, MMP-9, and MMP-13 were significantly up-regulated in CRC tissues compared to the adjacent control group. Analysis of patients' clinicopathological features showed a statistically significant difference in the expression levels of MMP-8, MMP-9, and MMP-13 between CRC patients with and without lymphovascular invasion (LVI) and TMN stage. ROC curve results have shown that these genes are good candidate diagnostic biomarkers in CRC. These results indicated that MMP-8, MMP-9, and MMP-13 levels may serve as potential diagnostic biomarkers for CRC.

Keywords: Colorectal cancer (CRC), Matrix metalloproteinase 8, Matrix metalloproteinase 9.

1. Introduction

Colorectal cancer (CRC) ranks as the third most common form of cancer worldwide. It is currently the second leading cause of cancer-related fatalities globally, impacting both men and women equally in both developed and developing countries. It makes up 13% of all malignant tumors and is the most prevalent cancer in the gastrointestinal tract. It is anticipated that in the future, it will surpass the death rate caused by heart diseases [1,2]. In individuals with colorectal cancer, the clinical presentation varies depending on the location, size, as well as presence or absence of metastases. The clinical presentation includes symptoms such as stomach pain, adjustment of chronic bowel habits, changes in bowel movements, involuntary weight loss, nausea, vomiting, malaise, anorexia, and abdominal distension [3].

It is well established today that multiple variables contribute to the CRC pathogenesis, triggering complicated genetic and epigenetic processes that, ultimately, change normal colonic mucosa to cancerous tissue. CRC may originate from benign polyps with a mucosal origin and can evolve into carcinoma. Colorectal polyps, especially adenomas, are proliferative lesions that have been described as the precursor of CRC. Therefore, the early diagnosis and excision of these polyps can halt the progression of the adenoma-carcinoma sequence. Several molecular signaling pathways are involved in CRC initiation and progression, including ERK/MAPK, TGF-β, PI3K/Akt, Src/FAK, and β-catenin pathways. These pathways can promote the hallmarks of cancer involving inflammation, angiogenesis, metastasis, and invasion, also via the activation and overexpression of Matrix metallopro-

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teinases (MMPs). Thus, MMPs have been postulated as potential prognostic indicators for the malignancy risk of colorectal polyps [4]. MMPs are a member of the enzyme group that is capable of protein breakdown. MMPs are known as metalloproteinases because they require either zinc or calcium to accomplish their activities. Members of this family belong to the metzincin superfamily of proteases that can predominantly degrade or cleave numerous components of the extra-cellular matrix (ECM) during tissue remodeling. The ECM is an intricate network of macromolecules that gives biochemical and structural aid to surrounding cells by controlling physiological functions such as cell anchoring, migration, proliferation, differentiation, and metabolism. By degrading connective tissue between cells and in the lining of blood vessels, MMPs enable tumor cells to escape from their initial location and spawn metastases. A vast amount of experimental and clinical evidence has implicated MMPs in tumor invasion, neoangiogenesis, and metastasis. MMPs perform diverse and different roles in CRC [5].

Matrix metalloproteinase-9 (MMP-9) is one of the most complicated MMPs that belongs to the gelatinase B family. This gelatinase reveals a crucial role in carcinogenesis through the regulation of numerous processes, such as the survival of cancer cells, migration, stimulation of immune response, and creation of cancer microenvironment. Consequently, it has become a potentially interesting target for anticancer treatment. Several MMP-9 inhibitors have been produced and investigated for biological use. Extracellular matrix (ECM) remodeling is one of the key tasks of MMP-9. It involves the proteolytic cleavage of the most significant MMP-9 substrates, including gelatin, elastin, and collagen [6]. In addition, various substrates are particularly cleaved by MMP-9, including plasma membrane proteins, extracellular proteins, and intracellular proteins. The MMP-9 is involved in a number of biological activities, including the change of cell-cell and cell-ECM interactions, as a result of its proteolytic cleavage capacity. Additionally, as collagen type IV is the major component in the basement membrane, MMP-9 plays a vital role in its breakdown. Consequently, tumor cell invasion and metastases are often increased due to basement membrane degradation. The crucial contribution of MMP-9 in extracellular matrix (ECM) remodeling uncovers an important relationship between MMP-9 and each stage of cancer etiology and progression [7].

Matrix metalloproteinase 8 is a form of collagenase (collagenase-2 or neutrophil collagenase). Interstitial collagens (types I–III), the main structural elements of the extracellular matrix, are the most well-known substrates of MMP-8. MMP-8 exhibits greater proteolytic activity on types I and III than on type II. In addition, MMP-8 can also cleave non-matrix proteins such as serpins, bradykinin, angiotensin I, fibrinogen and many others. As a result of its known catalytic activities, MMP-8 is hypothesized to be involved in wound healing and tissue remodeling during inflammation [8].

Collagenase 3, or MMP-13, is a proteolytic enzyme that breaks down extracellular matrix. It is a member of a wide family of endopeptidases and is distinguished by the binding of zinc to its catalytic site. MMP-13 demonstrates versatility in the utilization of its substrate. In addition to being particularly active on type II collagen, MMP-13 breaks down other substrates, principally extracellular matrix macromolecules, but also molecules including the connective tissue growth factor (CTGF) and fibrinogen. It is overexpressed in numerous pathological circumstances, being implicated in the degradation of collagen, aggrecan, fibronectin, and tenascin, as well as other extracellular matrix proteins. Therefore, MMP-13 has a vital role in the progression of human carcinoma and metastatic processes [9].

Moreover, the dysregulated expression of matrix metalloproteinases (MMPs), specifically

MMP-8, MMP-13, and MMP-9, in colorectal cancer tissues, signify their crucial involvement in the pathogenesis and progression of this malignancy. This study was conducted to investigate the role of MMP-8, MMP-9, and MMP-13 in CRC. Using the Real-Time PCR method, the expression of MMP-8, MMP-9, and MMP-13 genes in tissue samples of colon cancer in patients with and without lymphovascular invasion was studied and the relationship between the expression pattern of these genes with the severity of the tumor progression was evaluated. We also wanted to explore the relationship between the expression of MMP-8, MMP-9, and MMP-13 pathway, which hasn't been investigated before. Accordingly, the current research aims to further investigate the cellular and molecular mechanisms of CRC. The evaluation of these genes increases our knowledge of cellular pathways involved in colon cancer, and the information obtained from this study can potentially help us in drug design.

2. Materials and methods

This case-control study collected tissue samples from patients referred to endoscopy, oncology, or surgery clinics from July 2021 to December 2022 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.

2.1. 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 NanoDrop 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. Reverse transcription reaction was using a cDNA kit (Cinnacolon, Tehran, Iran), cDNA was prepared from 2 µg of total RNA, with Oligo (dT) and random hexamer primers. Consistent with the manufacturer's ins-

tructions, 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.

2.2. 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, specificity of products was verified by melting curve analysis. Gene expression levels were normalized to the expression of beta-2 microglobulin (β2M), the housekeeping gene, for each sample. The primers were designed and positioned in a variety of exon junctions of TYK*2* to avoid false-positive results following DNA contamination (Table 1).

2.3. 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 MMP-8, MMP-9 and MMP-13 was estimated using REST 2009 software. The statistical differences of MMP-8, MMP-9 and MMP-13 levels between patients and controls were analyzed with the GraphPad Prism software version 8.0 (La Jolla, CA). That, using the Mann–Whitney test and unpaired t-test to compare MMP-8, MMP-9 and MMP-13 mRNA levels in two groups. *P* -value of ≤0.05 was considered significant.

3. Results

Overall, 100 CRC patients (52 females and 48 males) aged 20 to 65 years (mean ± SD: 43.91 ± 9.73 years) were included in this study. The location of the malignancy was the colon in 45 patients (45%) and the rectum in 55 patients (55%). Among the CRC patients, 35 (35%) had a history of IBD, 30 (30%) had polyps, and 35 (35%) had colitis. According to clinical TNM staging, 29 patients (29%) were stage II, 36 (36%) were stage III, and 35 (35%) were

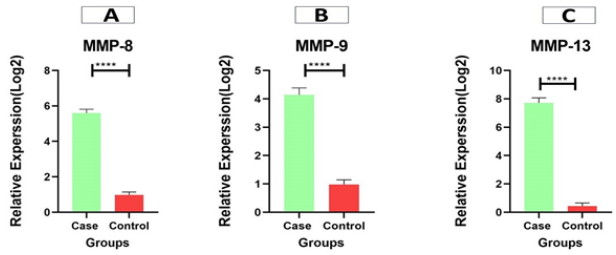

Fig. 1. The relative expression levels (−ΔCt) of MMP-8, MMP-9, MMP-13 and β2M. A. shows the differences MMP-8 expression between the control group. B. shows the differences MMP-9 expression between the control group. C. shows the differences MMP-13 expression between the control group. (****: $p<0.0001$)

Table 1. qRT-PCR primer sequences.

Genes	Primers	Sequences	Amplicon size (bp)
MMP-8	Forward Primer	GAGGAACTGCACTGATGCAA	182
	Reverse primer	ATTTGGCTTCCCCGTCACAT	
MMP-9	Forward Primer	TTGACAGCGACAAGAAGTGG	179
	Reverse primer	GCCATTCACGTCGTCCTTAT	
MMP-13	Forward Primer	GACTTCCCAGGAATTGGTGA	121
	Reverse primer	TGACGCGAACAATACGGTTA	
Beta-2-microglogulin	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

stage IV. In the current study, LVI+ was observed in 40 (40 %) of 100 CRC. The clinical characteristics of the selected subjects are shown in Table 2. Assessment of MMP-8, MMP-9 and MMP-13 gene expression levels using qRT-PCR showed that the gene expression of MMP-8, MMP-9 and MMP-13 is significantly up-regulated in CRC tissue samples compared to the normal tissues (p<0.0001, 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 is higher. The areas under the ROC curve for MMP-8, MMP-9 and MMP-13 are shown in Figure 2. Moreover, our analysis showed no significant differences in the tissue expression levels of MMP-8, MMP-9 and MMP-13 among CRC patients with a history of colitis, inflammatory bowel disease (IBD), and polyps, with p-values of 0.5690, 0.1903, and 0.1420, respectively. Additionally, a significant difference was observed in the tissue expression levels of MMP-8, MMP-9 and MMP-13 across TNM stages; notably, in stage IV CRC patients, the expression levels of this genes were significantly higher compared to those in stages II and III, with p-values of p<0.041, p<0.049 p<0.0001, respectively (Figure3). 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 MMP-8, MMP-9, and MMP-13 between patients with LVI+ and those with LVI-, with p-values of p<0.017, p<0.019, 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 4.

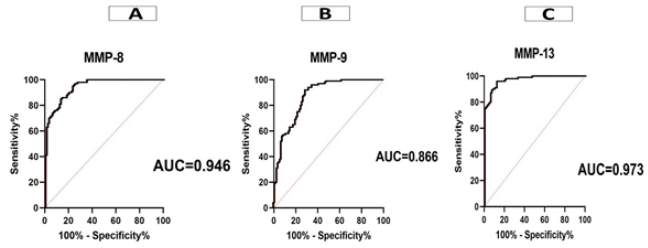

Fig. 2. ROC curve analysis of the diagnostic value of CRC-related genes to distinguish between CRC patients and healthy individuals.

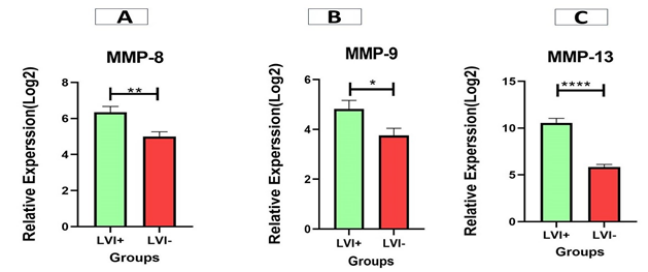

Fig. 3. The relative expression levels (−ΔCt) of MMP-8, MMP-9, MMP-13. A. shows the differences MMP-8 expression between LVI+ in CRC patients and the LVI- group. B. shows the differences MMP-9 expression between LVI+ in CRC patients and the LVI- group. C. shows the differences MMP-13 expression between LVI+ in CRC patients and the LVI- group. (p<0.017, p<0.019, p<0.0001).

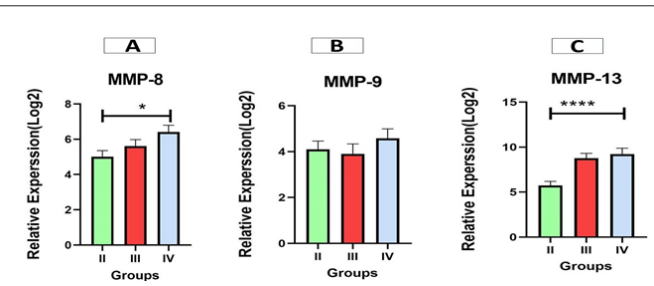

Fig. 4. The relative expression levels (−ΔCt) MMP-8, MMP-9and MMP-13 levels. A. shows the differences in MMP-8levels between TMN stage in CRC patients. B. shows the differences in MMP-9 levels between TMN stage in CRC patients. C. shows the differences in MMP-13 levels between TMN stage in CRC patients (p<0.041, p<0.049, p<0.0001).

4. Discussion

Several studies have indicated that MMPs are crucial in the development of most malignant tumor's activities such as growth, spread, formation of new blood vessels, and spreading to other parts of the body [10 -12]. A study conducted by Pezeshkian and colleagues demonstrated that MMPs were associated with the unfavorable outcome of CRC [11]. Rath et al. found that the genes MMP-7, MMP-2, and MMP-13 were upregulated in inflammatory tissues [13]. Another research conducted by Herszényi et al revealed an increase in MMP-9 expression in patients with colorectal cancer [14]. In the study by Waas et al, elevated levels of MMP-2 and MMP-9 were also observed in cancerous tissues [15]. In this research, we investigated the levels of MMP-9, MMP-8 and MMP-13 expression were focusing on the regulation of gene activity due to its importance in various biological processes. Proved that MMPs are mainly controlled at the transcriptional level. As anticipated, their levels of expression are substantially higher in colorectal cancer tissue samples when compared to normal samples. Discovering a connection between the representation of gene expression levels and tumor size, nearby lymph nodes, and metastasis categorization (TNM). One of the objectives of the present study was to conduct staging. We noticed that in this respect, the levels of our target genes show considerable variation across TNM stages; Specifically, when compared, patients in stages II and III had significantly elevated levels of these genes in patients with advanced colorectal cancer. Our examination also showed significantly higher levels of gene expression in patients with lymphovascular invasion (LVI+). This discovery aligns with earlier studies. Pointing out the various roles of MMPs in promoting cancer cell invasion, spread to other areas, and formation of new blood vessels a helpful environment for the tumor. A prior investigation, which focused on MMP-9 specifically, demonstrated that as colorectal cancer progresses from early stages to invasive and metastatic phases, the expression of MMP-9 RNA increases gradually. These findings provide additional evidence for the concept that raised MMP-9 expression in tumors is linked to increased metastatic ability [16]. As stated by Wang, according to this study, the decreased MMP-1 expression hindered the ability of colorectal cancer cells to undergo proliferation, migration, and invasion, all show the oncogenic impact of MMP-1 in colorectal cancer. Development of cancer, their findings also indicated that heightened MMP-1 expression

was connected to relating to the lymphatic system [17]. Another investigation focused on MMP-13 found that the disease stage was evaluated. Elevated MMP-13 expression was associated with the progression of adenoma and carcinoma [18]. A connection has been found between elevated MMP-13 levels and higher occurrences of liver metastasis, as well as poorer outcomes. The forecast and early return have been uncovered in recent studies [19,20]. This research showcases the important function of MMPs in the advancement of colorectal cancer, with a focus on their significance. Their participation in the spread, invasion, and movement to other parts of the body, indicating their possible impact as indicators for diagnosing CRC in its early stages. Continuing previous studies on the functions of MMPs in the research also identifies a link between heightened MMP levels and cancer cell invasion and metastasis. Development and sophisticated tumor classification, especially evident in patients at stage IV and LVI and above groups. Our study shows that MMPs could be valuable targets for diagnostic purposes and treatment methods in the advancement of CRC and needs more research to explore their exact processes in the formation of tumors and spread to other parts of the body.

These results, together with previously published peer-reviewed studies and additional data from other researchers, suggest that the expression levels of MMP-8, MMP-9, and MMP-13 may serve as potential diagnostic biomarkers for colorectal cancer (CRC). However, further investigation is required to draw definitive conclusions.

Conflict of interests

The authors have no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study IR.SBMU.MSP.REC.1403.719; Link: ethics.research.ac.ir/ https://pajoohan.sbmu.ac.ir/general/cartable.action#.

Informed consent

The authors declare that no animals were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Rezvaneh Ghadyani wrote the original manuscript, provided laboratory work; **Zahra Mozooni** analyzed the data, designed tables and scientific illustrations and supervised the laboratory work; **Zihab Sohbatzadeh** checked that the text corresponded with the references, text order according to the Journal format; **Latif Gachkar** checked the instructions to authors and statistical methodology**; Abolfazl Movafagh** checked the associated database, raw data, supervised and revised the final manuscript.

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