Journal of Clinical and Nursing Research, 2025, Volume 9, Issue 4
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Research Progress of MAPK Signaling Pathway in Colorectal Cancer

Panpan Mao, Weiyun Wu*

Guangdong Medical University, Zhanjiang 524023, Guangdong, China

**Author to whom correspondence should be addressed.*

Abstract: Colorectal cancer (CRC) is one of the most common malignancies. In recent years, despite the widespread application of new endoscopic techniques and continuous advancements in treatment methods that have improved the early diagnosis rate of CRC, the disease often has an insidious onset. Many patients are already in the middle or late stages of the disease when diagnosed, leading to poor treatment outcomes and prognosis. Therefore, further investigation into the pathogenesis of CRC and exploration of new therapeutic targets remain hot topics of research. The mitogen-activated protein kinase (MAPK) signaling pathway belongs to the large family of serine/threonine kinases and is a crucial pathway for signal transduction in eukaryotes. The MAPK signaling pathway can be activated by various extracellular signals such as cytokines, growth factors, and oxidative stress, thereby influencing biological processes like cell cycle, differentiation, malignant transformation, metastatic potential, and apoptosis. It plays a significant regulatory role in the development and progression of malignancies [1]. The evolution of CRC involves abnormal regulation of multiple signaling pathways, among which dysregulation of the MAPK signaling pathway is a key molecular event. This article provides a comprehensive overview of the research progress on the MAPK signaling pathway in CRC.

Keywords: MAPK signaling pathway; Colorectal cancer; Regulation mechanism

Online publication: April 30, 2025

1. Introduction

Colorectal cancer is a common cause of death in patients with malignant tumors, which is related to factors such as changes in dietary structure and increased life pressure. The pathogenesis is complex, involving processes such as intestinal epithelial cell proliferation, cell differentiation, and apoptosis. Abnormal signal transduction networks can be involved in the entire pathogenesis of the disease, among which MAPK is a type of serine/threonine kinase that is sensitive to stimuli both inside and outside the cell. Its dephosphorylation reaction reduces kinase activity, regulates cellular biological responses, and the MAPK signaling pathway can evaluate the expression levels of tumor cell lines and primary tumors, which has a regulatory mechanism on the

pathological process of colorectal cancer.

2. Composition and function of the MAPK signaling pathway

The MAPK pathway transmits signals by sequentially activating multiple protein kinases, including MAPK kinase kinase (MAP3K), MAPK protein kinase kinase (MAPKK), and MAPK. This pathway regulates various important physiological and pathological processes such as cell proliferation, differentiation, apoptosis, migration, stress response, and inflammatory reaction [2, 3]. MAPKs can be divided into four subfamilies: extracellular signal-regulated kinases (ERK), c-Jun N-terminal or stress-activated protein kinases (JNK or SAPK), p38 MAPK, and ERK5. The p38 MAPK and JNK cascade reactions are primarily involved in transducing stress-related stimuli, while the ERK cascade reaction is mainly involved in transmitting mitotic signals. It is one of the most important pathways for cell proliferation, and its activation is crucial in intestinal epithelial differentiation [4]. Increasing evidence suggests that activation of the MAPK pathway is involved in the occurrence and progression of CRC.

3. Role of the MAPK Signaling Pathway in CRC

3.1. MAPK signaling pathway and CRC cell biology

3.1.1. Regulation of CRC cell proliferation, apoptosis, migration, and invasion

The MAPK signaling pathway is closely related to the proliferation, apoptosis, migration, and invasion of CRC cells. In HCT-116 and RKO cells, overexpression of phosphatidylinositol-binding clathrin assembly protein (PICALM) promotes cell proliferation and migration while inhibiting apoptosis. Mechanism studies have revealed that overexpression of PICALM upregulates the expression of phosphorylated p-ERK1/2, p-MEK1/2, p-p38 MAPK, and p-JNK proteins, activating the MAPK signaling pathway, increasing cell proliferation, and decreasing apoptosis. However, the addition of the MAPK inhibitor SB202190 inhibits cell proliferation and increases apoptosis, indicating that activation of the MAPK signaling pathway promotes the malignant behavior of CRC cells [5].

Overexpression of Mex-3 RNA-binding family member A (MEX3A) in CRC cells significantly promotes cell proliferation, migration, and invasion, upregulates the expression of GTPase-activating protein RAP1GAP, p-MEK1/2, and p-ERK1/2 proteins, and downregulates the expression of HIF-1α. Treatment with the ERK inhibitor U0126 reverses these effects, suggesting that MEX3A promotes the proliferation and invasion of CRC cells by activating the RAP1GAP/MEK/ERK/HIF-1α signaling pathway [6].

In CRC cell lines LOVO and HCT-116 infected with *Fusobacterium nucleatum*, the expression of phosphorylated p-JNK increases, and its downstream proteins c-Jun and p-c-Jun also significantly increase. Activation of the MAPK (JNK)-AP1 axis upregulates the expression of matrix metalloproteinase 7 and increases cell migration [7]. Aldolase A (ALDOA) expression is upregulated in clinical samples from CRC patients. In CRC cell lines SW480 and DLD1, knocking down ALDOA reduces the phosphorylation of p38 and ERK1/2, inhibits the MAPK signaling pathway, and decreases cell proliferation, invasion, and migration. In vivo experiments, mice in the ALDOA knockdown group show slow growth of subcutaneous tumor volumes and reduced lung metastatic lesions, indicating that the MAPK signaling pathway is the primary mechanism mediating the promotion of CRC development by ALDOA [8].

The RNA-binding protein MSI2 can interact with p-ERK, and knocking down MSI2 inhibits the proliferation, migration, invasion, and metastasis of CRC cells by inhibiting the MAPK signaling pathway and subsequently inhibiting HSPB1 phosphorylation. This leads to downregulation of PCNA and Ki67 expression and upregulation of ACSL4 expression, followed by induction of redox imbalance, iron accumulation, and mitochondrial shrinkage, ultimately triggering ferroptosis in cells. Therefore, targeting the MSI2/MAPK/HSPB1 axis to promote ferroptosis may be a potential therapeutic strategy for CRC.

Chromobox homolog 2 (CBX2) is highly expressed in CRC, and knocking down CBX2 attenuates the proliferation, migration, and invasion abilities of CRC cells by inhibiting MAPK signal transduction. G protein signaling regulator 16 (RGS16) is upregulated in CRC and inhibits cell apoptosis by inhibiting JNK/p38 MAPK pathway activation and subsequent expression of cleaved-caspase-3 and cleaved-PARP in CRC cells. DEAD-box RNA helicase 3 (DDX3) expression is reduced in advanced CRC tissues and associated with poor patient prognosis.

In vitro and in vivo experiments demonstrate that knocking down DDX3 expression promotes the proliferation, migration, and invasion of CRC cells by activating the MAPK pathway, enhancing E-cadherin expression and β-catenin signaling, thereby promoting tumor progression. The endoplasmic reticulum integral membrane protein Sec62 is upregulated in CRC tissues and promotes cell migration and invasion by activating MAPK/JNK signaling in HCT-116 cells, while a JNK inhibitor can inhibit the CRC metastasis process mediated by Sec62.

NADPH oxidase 4 (NOX4) is highly expressed in CRC tissues and associated with poorer survival rates. NOX4 promotes CRC cell colony formation, migration, invasion, and stemness by activating the MAPK-MEK1/2-ERK1/2 signaling pathway. It also promotes subcutaneous tumor growth and lung metastasis in nude mice. Treatment with the MEK inhibitor trametinib partially offsets the tumor progression effects mediated by NOX4, suggesting that the MAPK-MEK1/2-ERK1/2 axis promotes CRC progression. Li *et al.* found that the long non-coding RNA DICER1-AS1 is highly expressed in CRC tissues [8]. By inhibiting miR-650 and upregulating MAPK1, it increases ERK1/2 phosphorylation levels, activating the MAPK/ERK signaling pathway and enhancing the proliferation, migration, and invasion abilities of CRC. The sodium channel subunit SCNN1B is downregulated in CRC tissues and cell lines. Overexpression of SCNN1B inhibits CRC cell proliferation, induces apoptosis and cell cycle arrest, and suppresses cell migration in vitro and tumor growth in xenograft mice.

3.1.2. Regulation of epithelial-mesenchymal transition (EMT) in CRC cells

Tumor metastasis is the primary factor leading to treatment failure and cancer-related deaths in CRC. In this process, EMT plays a crucial pathophysiological role. During cell migration, epithelial cells lose polarity and intercellular connections, acquiring mesenchymal cell characteristics, making cancer cells more invasive and leading to metastasis. Epithelial cell markers include E-cadherin, cytokeratin, occludin, and claudins, while mesenchymal cells characteristically express N-cadherin, vimentin, and fibronectin. In EMT, the expression of N-cadherin, vimentin, and fibronectin is upregulated, while E-cadherin expression decreases. EMT-related transcription factors such as ZEB proteins, Twist, and TGF-β can stimulate EMT. Activation of the MAPK pathway can induce EMT in CRC cells.

Synaptotagmin 1 (SYT1) is downregulated in both CRC tissues and cell lines. Overexpression of SYT1 inhibits the ERK/MAPK signaling pathway by suppressing ERK1/2 phosphorylation, downregulates the

expression of EMT transcription factor Slug and vimentin, thereby inhibiting CRC cell migration and invasion, and also suppressing CRC metastasis in nude mice. Cell migration-inducing protein (CEMIP) promotes the degradation of GTP-activating protein GRAF1, downregulates its expression, activates CDC42/MAPK pathway-regulated EMT, and thus promotes the metastasis of CRC cells, suggesting that the CDC42/MAPK pathway plays a role in CEMIP-promoted colorectal cancer metastasis.

Ubiquitin-like protein (UBQLN1) is highly expressed in CRC tissues. Cellular experiments have found that UBQLN1 promotes CRC cell colony formation and EMT in vitro. In vivo experiments, knocking down UBQLN1 can inhibit the growth and metastasis of CRC tumors in nude mice. In addition, in LoVo cells with UBQLN1 knockdown, the expression of p-ERK1/2 and p-MEK1 is downregulated, ERK-MAPK pathway activation is inhibited, and c-Myc expression is reduced, suggesting that UBQLN1 knockdown inhibits CRC progression through the ERK-c-Myc pathway.

Compared with normal colorectal tissues, S100 calcium-binding protein A16 (S100A16) is downregulated in CRC and negatively correlated with the prognosis of CRC patients. In vitro and in vivo experiments have found that S100A16 can inhibit CRC cell proliferation, migration, invasion, and tumor growth in mice. In HCT-116 cells with S100A16 knockdown, the phosphorylation levels of p38, ERK1/2, and JNK increase, the expression of N-cadherin and vimentin increases, and E-cadherin decreases. However, treatment with JNK inhibitor SP600125 or p38 inhibitor SB203580 reverses these protein expression changes. This suggests that knocking down S100A16 promotes EMT by activating the JNK/p38 MAPK pathway, thereby promoting CRC progression. In CRC cells, knocking down the endoplasmic reticulum stress response protein GRP94 inhibits cell proliferation, migration, EMT, and tumorigenesis in xenograft nude mouse models by inhibiting the MAPK pathway, thereby inhibiting the development and progression of CRC.

In RKO, HCT-116, and SW480 cells, overexpression of aryl hydrocarbon receptor nuclear translocator-like protein 1 significantly upregulates the expression of RAF, p-MEK, p-ERK1/2, p-JNK, and c-Myc, increases the expression of N-cadherin and vimentin, and significantly reduces the expression of E-cadherin, activating EMT and leading to enhanced cell migration and invasion. However, treatment with ERK1/2 inhibitor PD98059 or JNK inhibitor SP600125 can reverse these effects, suggesting that the ERK/JNK pathway plays a role in affecting CRC metastasis.

3.2. MAPK signaling pathway and CRC tumor angiogenesis

Angiogenesis is controlled by angiogenic factors produced by various types of cells in the tumor microenvironment, including tumor cells, macrophages, endothelial cells, and tumor-associated stroma. Tumor-derived VEGFs, platelet-derived growth factors (PDGFs), fibroblast growth factors (FGFs), and angiopoietin-like proteins (ANGPTLs) are key growth factors for tumor angiogenesis. Xu *et al.* found that overexpression of the homeodomain transcription factor Six1 significantly promotes the growth and metastasis of CRC tumors in mice [1]. In the mouse CRC cell line MC38, overexpression of Six1 can increase the protein level of aldehyde dehydrogenase-1 and expand the CD44+/CD166+ cell population, suggesting that Six1 can enhance tumor stemness characteristics. Mechanism studies have shown that Six1 promotes angiogenesis by upregulating VEGF expression and recruits tumor-associated macrophages by increasing the expression of factors such as macrophage colony-stimulating factor and chemokine ligand 2/5, thereby synergistically promoting CRC growth and metastasis.

In addition, Six1 activates the MAPK signaling pathway in CRC cells, which may be the main mechanism

leading to tumor progression. Immunoglobulin-like transcript 4 (ILT4) is upregulated in CRC tissues and can promote angiogenesis in human umbilical vein endothelial cells by inducing the expression of vascular endothelial growth factor-A (VEGF-A) and fibroblast growth factor 1 (FGF-1) in CRC cells. In SW620 and HCT-116 cells overexpressing ILT4, the expression of p-ERK, VEGF-A, and FGF-1 proteins increases.

However, treatment with the ERK inhibitor U0126 downregulates the expression of these proteins, indicating that the activation of MAPK/ERK signaling and the upregulation of VEGF-A and FGF-1 expression are responsible for ILT4-induced angiogenesis and tumor progression in CRC. The m6A methyltransferase WTAP is highly expressed in CRC tissues and cell lines. By promoting m6A modification, it upregulates VEGF-A expression, activates the MAPK signaling pathway, thereby promoting angiogenesis and enhancing cancer cell proliferation, migration, and invasion abilities.

3.3. MAPK signaling pathway and CRC cell metabolism

Abnormal cell metabolism, such as increased aerobic glycolysis and anabolic pathways, plays a crucial role in tumorigenesis, metastasis, and drug resistance. The MAPK pathway can mediate the occurrence and development of CRC by affecting cell metabolism. In HCT-116 cells treated with a combination of FexMoyS-PEG bimetallic oxide nanoparticles (NPs) and hydrogen peroxide (H2O2), decreased phosphorylation of MEK and ERK was observed, leading to the inhibition of MAPK pathway activation and downregulation of MYC expression. This resulted in the suppression of glycolysis in cells, ultimately reducing tumor cell proliferation and energy metabolism.

In a xenograft mouse tumor model derived from CRC patient tumor cells, tumor growth was inhibited in the NPs-treated group compared to the PBS group. Both tumor volume and weight were significantly reduced, and the expression of MYC, p-MEK, and p-ERK was downregulated in tumor tissues, indicating the inhibition of MAPK pathway activation. This led to the suppression of tumor tissue growth and glycolysis, suggesting that NPs can affect cell proliferation, apoptosis, metastasis, and metabolic activities by inhibiting the activation of the MAPK pathway, thereby inhibiting CRC tumor growth. In HCT-116 and HT-29 cells with knocked-down GPCR receptor GPR37, the p38 MAPK signaling pathway was activated. This upregulation of stearoyl-CoA desaturase-1 expression was associated with increased saturated fatty acid (SFA) levels and decreased monounsaturated fatty acid expression. This induced lipid peroxidation, reduced reactive oxygen species levels, and inhibited ferroptosis, indicating that the p38 MAPK signaling pathway is involved in regulating lipid metabolism in CRC cells.

4. Conclusion

In summary, the MAPK signaling pathway mediates the occurrence and malignant progression of CRC by affecting the biological behavior of CRC cells, tumor angiogenesis, tumor cell metabolic activities, and resistance to antitumor drugs. It also impacts the prognosis of CRC patients. MAPK pathway-related inhibitors, such as vemurafenib, dabrafenib, and trametinib, have been used in the treatment of various tumors, but their efficacy still needs more comprehensive evaluation. Future research should explore the role of the MAPK signaling pathway in CRC, develop more targeted drugs, and facilitate the translation from basic research to clinical applications. This will improve the survival rate and quality of life of CRC patients.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Xu J, Zhu J, Liu P, et al., 2024, Protecting Cerebral Blood Flow Autoregulation: A Frontier Study on Aripiprazole's Inhibition of the MAPK Signaling Pathway After Cerebral Ischemia. Journal of Cerebral Ischemia Research, 38(5): 4349–4359.

[2] He X, Deng B, Zhang C, et al., 2025, HSPA1A Inhibits Pyroptosis and Neuroinflammation After Spinal Cord Injury via DUSP1 Inhibition of the MAPK Signaling Pathway. Molecular Medicine, 31(1): 1–20.

[3] Xiao P, Wang J, Zeng CZ, 2024, SSBP1 Is a Novel Prognostic Marker and Promotes Disease Progression via p38MAPK Signaling Pathway in Multiple Myeloma. Molecular Carcinogenesis, 63(4): 728–741.

[4] Liu S, Zhang H, Chen Y, et al., 2024, Resveratrol Treats Peri-Implantitis in Mice via Inhibiting the MAPKs/NF-κB Signaling Pathway. Journal of Prevention and Treatment for Stomatological Diseases, 32(11): 845–852.

[5] Yu YQ, Li SQ, Weng J, et al., 2024, LncRNA H19 Activates the RAS–MAPK Signaling Pathway via miR-140-5p/SOS1 Axis in Malignant Liver Tumors. Current Medical Science, 44(6): 1232–1240.

[6] Yu X, Ge J, Xie H, et al., 2024, MiR-483-3p Promotes Dental Pulp Stem Cells Osteogenic Differentiation via the MAPK Signaling Pathway by Targeting ARRB2. In Vitro Cellular & Developmental Biology – Animal, 60(8): 879–887.

[7] Zhou F, Wang L, Ge DWW, 2023, H3K27 Acetylation Activated–CD109 Evokes 5-Fluorouracil Resistance in Gastric Cancer via the JNK/MAPK Signaling Pathway. Environmental Toxicology, 38(11/12): 2857–2866.

[8] Li X, Mo K, Tian G, et al., 2023, Shikimic Acid Regulates the NF-κB/MAPK Signaling Pathway and Gut Microbiota to Ameliorate DSS-Induced Ulcerative Colitis. Journal of Agricultural and Food Chemistry, 71(23): 8906–8914.