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Research on the Mechanism of Marcks in the Pathogenesis of Digestive System Diseases

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Abstract: Marcks (Myristoylated Alanine-Rich Protein Kinase C Substrate) is broadly expressed across tissues and has emerged as a significant player in the pathogenesis of multiple organ systems. Dysregulation of this protein—whether through genetic alterations at the Marcks locus, aberrant phosphorylation, or unchecked activation of downstream signaling pathways—appears to drive disease development in varied contexts. In this review, we focus specifically on the digestive system, examining how Marcks contributes to hepatocellular carcinoma, cholangiocarcinoma, colorectal cancer, and gastric cancer. Rather than simply cataloging its presence in these malignancies, we dissect the mechanistic underpinnings of Marcks-driven tumor initiation and progression. These findings carry important implications for biomarker discovery and may ultimately inform strategies for clinical diagnosis and treatment.

Keywords: Marcks; Digestive System Diseases; Mechanism

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1. Introduction

Marcks is a membrane-bound PKC substrate present in nearly all eukaryotic cells. Phosphorylation by PKC—or binding to calmodulin—releases it into the cytosol, where it remodels the cytoskeleton, actin, and vesicle trafficking to activate downstream signaling[1-6]. Marcks is expressed across all three germ layers in vertebrate embryos. It regulates gastrulation, myogenesis, brain development, and other processes essential for embryogenesis[7-11]. Studies show mice with Marcks loss-of-function mutations die shortly after birth with multiple defects, including severe neural tube closure defects [12-16]. Marcks takes part in peripheral nerve, appendage, and tail regeneration in adult vertebrates, and is a promising therapeutic target in regenerative medicine[17]. Marcks also transduces PI3K-AKT, BCR, TLR, and ErbB2 signals. Its broad developmental roles led us to study its mechanisms in digestive diseases.

2. Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally and makes up 90% of primary liver cancers; incidence and mortality rise yearly [18]. Surgery prolongs survival somewhat, but high metastasis and recurrence mean poor outcomes. Late diagnosis largely explains HCC's high mortality, so finding early biomarkers is vital [19].

Proteomics on HCC and adjacent non-tumor tissues first showed Marcks overexpressed, suggesting it could be an HCC biomarker [20]. p-Marcks upregulation triggers many tumors. Marcks knockdown in liver cancer cells blocks proliferation, migration, and invasion in vitro [21]. RNAi and peptide mimetics targeting Marcks' phosphorylation site block its phosphorylation. PI3K/AKT drives HCC and other cancers; abnormal AKT expression and activation are highly oncogenic. Jianjun Song et al. predicted via database analysis that tumor suppressor miR-34c-3p directly targets Marcks' 3'UTR. In HepG2 cells, miR-34c-3p cut migration and invasion without affecting proliferation, mimicking Marcks knockdown. So miR-34c-3p targets Marcks to suppress HCC cell proliferation, migration, and invasion [22].

Another study found Marcks rose from chronic hepatitis to cirrhosis but fell from cirrhosis to HCC, and was lower in HCC than in matched non-tumorous cirrhotic tissue. p-Marcks was absent in normal liver and chronic hepatitis but present in cirrhosis and HCC; its loss and hyperphosphorylation may drive cirrhosis to malignant HCC. In short, Marcks rise and fall may track normal liver/hepatitis to cirrhosis, and cirrhosis to HCC, respectively [23].

3. Cholangiocarcinoma (CCA)

Cholangiocarcinoma (CCA) is a cancer of biliary epithelial cells and the second most common primary liver cancer, at 3% of GI tumors. Marcks drives invasiveness, metastasis, and chemoresistance. Its activity depends not just on presence, but on phosphorylation. In CCA, p-Marcks boosts cell migration, while unphosphorylated Marcks aids adhesion. Marcks rises during liver tumorigenesis and may drive hepatocellular tumor growth. Liver fluke-induced Marcks may underlie opisthorchiasis-associated CCA[24].

Hamsters given O. viverrini and NDMA showed Marcks rising during CCA and overexpressed in tumor and inflammatory cells. Liver fluke antigens boost Marcks mRNA and protein in U937 macrophages. IHC showed Marcks in human inflammatory tissue, sharply rising in inflammatory cells after fluke infection, likely acting via macrophages in fluke inflammation. O. viverrini antigens upregulate Marcks in macrophages via NF-κB, and fluke-driven Marcks may underlie opisthorchiasis-associated CCA[24].

Techasen et al. found via IHC that Marcks and pMarcks rise in CCA, tracking with metastasis. High Marcks shortens survival, suggesting a prognostic marker. Unphosphorylated Marcks sits on the plasma membrane; phosphorylation shifts it to the perinuclear region, reorganizes actin, and drives migration and invasion. Without TPA, Marcks aids cell adhesion; with TPA, PKC phosphorylates Marcks, cycling it between membrane and cytoplasm to trigger migration or invasion. In short, PKC-driven Marcks phosphorylation and cycling govern CCA metastasis [25, 26].

4. Colorectal cancer (CRC)

Colorectal cancer (CRC) is one of the most common solid tumors worldwide. Marcks suppresses tumors in many cancers; losing it fuels proliferation in melanoma, neuroblastoma, and glioma lines. Most CRCs

are Marcks-high; loss predicts poor prognosis in MSS tumors. In 926 CRCs, Marcks was found in normal mucosa and most cancers but lost in 49% MSI-H and 9.5% MSS cases. Marcks loss affects MSI and MSS subtypes differently; it lowers motility and invasiveness in CRC, worsening outcomes [27].

Studies report that PKC-Marcks-actin axis alterations affect motility, proliferation, invasion, adhesion, cell spreading, and membrane trafficking [27]. In CRC cells, reduced Marcks enhances PI3K/AKT activity and proliferation; its inactivation renders MSS colon cancer cells anti-apoptotic, with loss serving as a prognostic marker for MSS CRC [27]. Krista Rombouts et al. modulated Marcks expression using chemical inducers in Marcks-expressing Clone A cells and Marcks frameshift-mutant LoVo cells to suppress colon cancer cell motility and invasion. Marcks loss inhibits proliferation and downregulates mitotic checkpoint kinase Aurora B (AURKB). shRNA-mediated Marcks knockdown in mouse CT26 cells reduced motility and invasion while abnormally prolonging mitosis. Compared to Marcks-deficient cells, control cells showed more liver metastases in tumor-challenged mice[28]. Marcks deficiency suppresses colon cancer cell motility, invasion, and proliferation.

Nam-Gyun Kim et al. identified multiple gene mutations in 38 out of 39 MSI-H colorectal cancers. Among these MSI-H tumors, the most frequently mutated novel genes were Marcks (72%), FLJ11383 (74%), and TAF1B (82%), with high-frequency frameshift mutations detected in all three. RT-PCR analysis confirmed the expression of both wild-type and mutant transcripts of these three genes in MSI-H colorectal tumors. It is hypothesized that Marcks inactivation is associated with tumorigenesis, which may provide a breakthrough point for developing novel diagnostic and therapeutic strategies in the future [29].

HNPCC is autosomal dominant, caused by germline mutations in DNA mismatch repair (MMR) genes. Knocking out both germline and somatic MMR alleles triggers HNPCC tumorigenesis. Frameshift mutations build up and drive tumor growth. Replication slip-ups in repetitive coding sequences of growth genes give HNPCC tumors a growth advantage. To connect frameshift mutations to clinicopathology during HNPCC onset and spread, Yamaguchi et al. screened 18 coding repeat genes in early (Dukes A) and advanced (Dukes B, C) CRCs. Eight genes, Marcks included, carried frequent mutations early in HNPCC-linked CRC. Earlier studies showed Marcks controls cell proliferation; its loss drives tumorigenesis. The authors proposed that frameshift mutations building up in Marcks and other genes trigger and advance HNPCC-linked CRC.

5. Globally, the incidence of gastric cancer (GC)

Globally, gastric cancer (GC) incidence is rising. Microarray analysis identified upregulated lncRNA LINC01268 in GC tissues, whose high expression positively correlated with lymph node metastasis, advanced TNM stage, and poor differentiation. Co-expression screening revealed Marcks was also highly expressed in GC tissues and cells, positively correlating with LINC01268 expression and prognosis. Marcks closely regulates PI3K/AKT pathway activation, which is linked to GC invasion and metastasis [30]. LINC01268 knockdown in GC cells significantly inhibited Marcks expression/activation, key pathway proteins, and cell invasion/migration. It is hypothesized that LINC01268 promotes GC invasion and metastasis by targeting and regulating Marcks to activate the PI3K/AKT signaling pathway [31].

Studies have found that, compared with adjacent non-tumor tissues, Marcks exhibits higher transcriptional and translational levels in GC tumors. Depletion of Marcks inhibits epithelial-mesenchymal transition, resulting in reduced cell migration and invasion. Upregulated Marcks expression is strongly

correlated with tumor cell differentiation and tumor stage, and high expression is associated with poor survival rates, serving as an independent prognostic marker for gastric cancer.

Using single genes as biomarkers for gastric cancer prediction lacks sufficient specificity. Combining the predictive capabilities of several genes into a gene signature represents a superior alternative [32]. To develop novel gene signatures and improve prognostic prediction for gastric cancer, Lan Zhao et al. analyzed marker gene sets from 375 GC patients in The Cancer Genome Atlas database. Gene enrichment analysis identified 189 gene signatures, and Cox proportional hazards regression modeling was used to identify a 5-gene signature including Marcks that predicts patient outcomes, with higher risk scores correlating with poorer prognosis.

Studies have found that LAP2 is widely expressed in various gastrointestinal cancers and is overexpressed in gastric cancer tissues. Knockdown of LAP2b reduces the motility of all tested cancer cells, while its overexpression increases motility. In liver metastasis xenograft models, LAP2b enhances the metastatic potency of gastric cancer cells and increases mouse mortality. DNA microarray analysis revealed that Marcks may participate in mediating LAP2b-regulated cancer cell motility through direct binding and cross-linking of actin filaments to the cell membrane [33].

6. Pancreatic cancer (PC)

Pancreatic cancer is a highly malignant digestive tumor. Young Eun Kim et al. performed proteomic analysis of oxaliplatin-sensitive PANC and resistant PANC-1R cells, finding upregulated Marcks in PANC-1R cells that activated PI3K/AKT signaling by regulating intracellular PIP2 levels [34]. Marcks knockdown reduced PI3K and AKT phosphorylation in renal and non-small cell lung cancers [35]. PI3K/AKT activation induces drug resistance in liver, colon, and cholangiocarcinoma cells [36]. This study found elevated AKT phosphorylation in PANC-1R cells, suggesting pancreatic cancer oxaliplatin resistance occurs through Marcks-mediated AKT pathway activation.

One study used omics approaches to compare the secretomes of pancreatic cancer cells and pancreatic cancer stem cells, analyzing differences at the protein level. The study found that Marcks and two other differentially expressed proteins were most highly secreted by Panc-1 cancer stem cells in the serum of pancreatic ductal adenocarcinoma patients. Marcks transcript expression was higher in pancreatic cancer cell lines with mutant K-Ras than in those with wild-type K-Ras genes [37]. Activating K-ras mutations occur in 80–95% of pancreatic cancers, where Marcks is overexpressed. Researchers transfected Marcks constructs to restore Marcks protein expression and thereby alter the phenotype. Results showed that Marcks-transfected Ras-transformed cells exhibited poor adhesion following treatment with PKC activators, suggesting an important role in the malignant behavior of cancer. The relationship between the expression of significantly differential genes such as Marcks and K-ras mutation status may help explore the pathogenesis of pancreatic cancer [38].

7. Conclusion

Marcks is a widely expressed membrane-associated protein that regulates cytoskeletal dynamics, vesicular transport, and various signaling pathways through PKC phosphorylation or calmodulin binding. This review summarizes the mechanisms of Marcks in digestive system diseases and the progress in clinical translational

research.

Marcks exhibits dual roles in digestive diseases: overexpression or abnormal phosphorylation promotes tumor proliferation, invasion, and metastasis via PI3K/AKT activation, serving as a poor prognosis biomarker; conversely, frameshift mutation-induced inactivation and loss of function also associate with tumorigenesis, with phosphorylation status determining its function. As a therapeutic target or biomarker, strategies include RNA interference, phosphorylation-site-targeting peptide mimetics, miRNA mimics, and natural compounds. Marcks frameshift mutation detection aids hereditary non-polyposis colorectal cancer screening. Future research should focus on precise regulation of Marcks phosphorylation status to advance its clinical application in early diagnosis, prognosis evaluation, and targeted therapy for digestive diseases, providing new targets for precision medicine.

Disclosure statement

The author declares no conflict of interest.

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