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Review Paper

Role of Calmodulin Protein in Colorectal Cancer Cell Proliferation, Progression, and Metastasis

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ABSTRACT

Background: Colorectal cancer (CRC) is one of the most common malignancies and a leading cause of cancer-related mortality worldwide. Dysregulation of calcium homeostasis and calcium-dependent signaling pathways, particularly those mediated by calmodulin (CaM), plays a critical role in CRC initiation, progression, and metastasis. CaM acts as a central intracellular calcium ion (Ca^{2+}) sensor that integrates calcium signals with multiple oncogenic pathways.

Materials and Methods: This narrative review summarizes current evidence on the role of CaM in CRC. Relevant studies published between 2000 and 2025 were identified through systematic searches of PubMed, Scopus, and Web of Science using keywords related to CaM, calcium signaling, Ca^{2+}/CaM-dependent kinases, and CRC. Data from mechanistic, preclinical, and translational studies were qualitatively synthesized.

Results: The reviewed studies demonstrate that CaM promotes CRC cell proliferation through activation of Ca^{2+}/CaM-dependent kinases, particularly CaM-dependent protein kinases (CaM-KII), leading to stimulation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), and Wnt/β-catenin signaling pathways. CaM also enhances tumor progression and metastasis by regulating cytoskeletal dynamics, epithelial–mesenchymal transition, matrix metalloproteinase activity, and interactions with oncogenic partners, such as epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog (KRAS). Pharmacological inhibition of CaM in preclinical CRC models reduces cell growth, invasion, and resistance to chemotherapy.

Conclusion: CaM is a key signaling hub in CRC, linking calcium dynamics to proliferation, survival, and metastatic behavior. Selective targeting of CaM-dependent signaling or CaM–oncoprotein interactions represents a promising therapeutic strategy for precision management of CRC.

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Introduction

Colorectal cancer (CRC) is a major global health concern, ranking as the third most prevalent cancer and the second leading cause of cancer-related mortality, with over 1.9 million new cases and 935,000 deaths annually [1-6]. CRC arises from adenomatous polyps in the colon or rectum and progresses through multistep genetic alterations influenced by diet, lifestyle, and hereditary factors such as Lynch syndrome [1, 2, 5-7]. Key molecular signaling pathways, including Wnt/β-catenin for stemness and proliferation, rat sarcoma (RAS)/rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase kinase (MAPK)/extracellular signal-regulated kinase (ERK) for growth signals, phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) for survival and metabolism, and transforming growth factor beta (TGF-β) for epithelial-mesenchymal transition (EMT), orchestrate CRC initiation, invasion, and metastasis [1-5, 7-11].

Calmodulin (CaM) is a small, ubiquitous calcium-binding protein that functions as a principal intracellular calcium ion (Ca^{2+}) receptor. Upon binding Ca^{2+}, it undergoes conformational changes to regulate a variety of target enzymes, including Ca^{2+}/CaM-dependent protein kinases (CaM-Ks) and phosphatases [12, 13]. In CRC, dysregulated Ca^{2+} signaling and elevated CaM expression are associated with advanced tumor stages, lymph node involvement, and poorer survival outcomes. CaM-mediated pathways, such as CaM-KII-dependent phosphorylation, stabilize β-catenin, upregulate cyclin D1 to promote G1/S transition, and activate hypoxiainducible factor 1 alpha (HIF-1α) to drive angiogenesis and metabolic reprogramming. Additionally, CaM contributes to EMT by increasing vimentin and suppressing E-cadherin, facilitating invasion via matrix metalloproteinases (MMPs) and promoting metastasis to the liver and lungs [12, 14, 15].

This review synthesizes evidence on CaM's mechanistic roles in CRC cell proliferation (e.g. through cyclindependent kinase (CDK) activation), tumor progression (e.g. therapy resistance), and metastasis (e.g. motility enhancement), while evaluating the therapeutic potential of CaM inhibitors, such as trifluoperazine or novel peptides, to disrupt CaM-CaM-K interactions.

Materials and Methods

This narrative review was conducted to summarize current knowledge on the role of CaM in CRC. Relevant studies were identified through searches of PubMed, Scopus, and Web of Science using keywords related to CaM, calcium signaling, Ca^{2+}/CaM-dependent kinases, and CRC. Articles published in English between 2000 and 2025 were considered, with emphasis on recent mechanistic and translational studies. Original research articles, preclinical studies, and relevant review papers were included based on their relevance to CaM structure, function, and cancer-related signaling pathways. Data were qualitatively synthesized to describe CaM-dependent mechanisms involved in CRC proliferation, progression, metastasis, and therapeutic targeting.

Structure of CaM

CaM is a 148–amino acid protein with an approximately 17-kDa dumbbell-shaped structure, consisting of two globular N- and C-terminal lobes connected by a flexible central α-helix. Each lobe contains two EF-hand motifs (helix–loop–helix structures), giving CaM a total of four Ca^{2+}-binding sites with cooperative binding properties. In the Ca^{2+}-free (apo) state, CaM is more compact, whereas Ca^{2+} binding induces exposure of hydrophobic patches that are crucial for target recognition and binding [12, 16, 17].

General cellular functions

As a prototypical calcium sensor, CaM translates transient or sustained changes in cytosolic Ca^{2+} concentration into biochemical responses by undergoing conformational changes. Through this Ca^{2+}-dependent structural rearrangement, CaM acts as an allosteric activator or modulator of diverse targets, thereby coupling Ca^{2+} signals to processes, such as gene transcription, cytoskeletal dynamics, secretion, and cell cycle progression. Because Ca^{2+} signaling is highly spatiotemporally regulated, CaM functions as a versatile integrator, responding to both local and global Ca^{2+} oscillations [17-19].

Regulation of enzymes, channels, and pathways

CaM directly regulates many enzymes, including Ca^{2+}/CaM-Ks, calcineurin (a Ca^{2+}/CaM-dependent phosphatase), certain adenylyl and guanylyl cyclases, and nitric oxide synthases. It also binds to and modulates ion channels, such as voltage-gated Ca^{2+} channels, some potassium ion (K^+) channels, and ligand-gated channels, influencing membrane excitability and Ca^{2+} homeostasis. Through these interactions, CaM critically controls signaling pathways, such as CaM-K–MAPK, CaM-K–cyclic AMP response elementbinding protein (CREB), and Ca^{2+}/calcineurin–nuclear factor of activated T-cells

(NFAT) cascades, which in turn regulate proliferation, apoptosis, metabolism, and differentiation [17-21].

Importance in physiology and disease

In normal physiology, CaM is essential for cardiac contraction–relaxation cycles, neuronal excitability and synaptic plasticity, smooth muscle contraction, endocrine secretion, and immune cell activation. Mutations or dysregulation of CaM or its EF-hand Ca^{2+}-binding properties are linked to cardiac arrhythmias, neurodevelopmental disorders, and defective immune responses. In cancer, including CRC, overexpression or hyperactivation of CaM-dependent signaling can enhance cell proliferation, survival, migration, and metastasis, making CaM and its downstream effectors attractive therapeutic targets [19, 20, 22].

CaM across cancer types

Pan-cancer transcriptomic analyses have shown that CALM1 and related CaM genes are frequently upregulated in invadopodin-driven metastatic, lung, and several hematologic malignancies, where higher expression often associates with advanced stage and worse overall survival. In Kirsten RAS viral oncogene homolog (KRAS)-driven adenocarcinomas (such as many lung and pancreatic cancers), CaM is functionally required for full KRAS oncogenic signaling, underscoring its role as an enabling factor in RAS-addicted cancers [20-23].

CaM-Ks are hyperactive in leukemias and some solid tumors, contributing to uncontrolled proliferation, while CaM-regulated ion channels and pumps reshape Ca^{2+} handling in prostate, glioma, and nasopharyngeal carcinomas to favor a pro-tumorigenic Ca^{2+} signature. Although tissue-level CALM1 can be reduced in certain contexts (e.g. subsets of colorectal or prostate cancer), functional CaM signaling is often maintained or compensated via other CaM isoforms or enhanced sensitivity of downstream effectors [19-24].

Berchtold and Villalobo (2014) reviewed the role of CaM and CaM-dependent signaling systems in vertebrate cell proliferation, programmed cell death, and autophagy. They highlighted the importance of CaM in regulating cancer cell physiology, including tumor stem cells, and in processes essential for tumor progression such as growth, angiogenesis, and metastasis. The review also discussed the potential of targeting CaM-dependent pathways as a therapeutic strategy in cancer [24].

Proliferation signaling

CaM activates CaM-K and other Ca^{2+}-dependent enzymes that directly interface with canonical growth pathways, such as PI3K/AKT, RAS–RAF–MAPK/ERK kinase (MEK)–ERK, Wnt/β-catenin, Janus Kinase (JAK)–signal transducer and activator of transcription (STAT), and Hippo signaling. Through these axes, CaM enhances cyclin D/E expression, drives G1/S transition, and stabilizes transcription factors (e.g. CREB, nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB], signal transducer and activator of transcription 3 [STAT3]) that support sustained proliferation and resistance to growth-factor withdrawal [24, 25].

In KRAS-mutant adenocarcinomas, CaM interacts both with KRAS and with RAF/MEK components, fine-tuning ERK activation dynamics and allowing tumor cells to maintain high proliferative drive without triggering excessive stress responses. This integration of Ca^{2+}/CaM with mitogenic cascades makes CaM a nodal point where calcium oscillations are "translated" into proliferative transcriptional programs [14, 24].

Apoptosis control

CaM influences apoptosis at several levels, often tipping the balance toward survival in cancer cells. By potentiating PI3K–AKT and certain MAPK branches, CaM signaling upregulates anti-apoptotic proteins (such as Bcell lymphoma 2 [BCL-2] family members) and downregulates pro-apoptotic effectors, contributing to chemoresistance and radioresistance. CaM-regulated pathways, including CaMK and calcineurin–NFAT, can also alter expression of death receptors and caspase regulators, further suppressing programmed cell death under stress conditions [24, 26].

Under extreme or dysregulated Ca^{2+} influx, CaM may participate in pro-apoptotic signaling by facilitating mitochondrial Ca^{2+} overload and activation of death-promoting enzymes, but in most tumor settings the net effect of elevated CaM activity is anti-apoptotic. This duality explains why context, Ca^{2+} amplitude/frequency, and the specific CaM targets engaged are critical in determining whether CaM signaling promotes survival or death [26].

Migration, invasion, and metastasis

CaM is a central regulator of the cytoskeleton and adhesion machinery that underpin tumor cell migration and invasion. By activating myosin light-chain kinase (MLCK) and coordinating actin–myosin contractility,

Table 1. CaM roles and mechanisms in CRC progression and metastasis

Cellular Process/Signaling Pathway	Role of CaM	Effect in CRC	Key Evidence/Studies	Ref.
Proliferation	Activates CaMKII and other Ca^{2+}/CaM-dependent kinases	Enhances β-catenin, CREB, cyclin D1/E; promotes G1/S transition; increases CDK4/6	CaM/CaMKII inhibition reduces proliferation and Ki-67 in HCT116 models	[24-29]
MAPK/ERK and PI3K/AKT signaling	Mediates Ca^{2+} signals to growth and survival pathways	Promotes pro-proliferative gene expression, resistance to growth factor withdrawal, cell survival	CaM inhibition reduces ERK and AKT activity and cell growth	[24, 27-31]
Apoptosis/therapy resistance	Activates PI3K/AKT and certain MAPK branches	Upregulates BCL-2, downregulates pro-apoptotic factors, chemoresistance	CaM inhibition increases apoptosis and therapy sensitivity	[24, 26, 30]
EMT and migration	Activates MLCK, RhoA/ROCK, Rac1/Cdc42	Increases vimentin, decreases E-cadherin, promotes lamellipodia/filopodia formation and motility	CaM inhibition reduces migration and invadopodia formation	[24, 27, 33]
Invasion and metastasis	Regulates focal adhesion, MMP-2/9, uPA/uPAR	Enhances ECM degradation, intravasation, metastasis	CaM inhibitors +5-FU reduce invasion and xenograft tumor growth	[27, 32-34]
Tumor microenvironment/ stress response	Interacts with EGFR, KRAS, Wnt/β-catenin	Maintains stem-like phenotype, therapy resistance	CaM binding to CALM1/CAMKK2 activates autophagy	[32, 34]
Therapeutic targeting	CaM antagonists (trifluoperazine, W-7)	Decreases growth, clonogenicity, migration; sensitizes to chemotherapy	Preclinical CRC models; combination with 5-FU effective	[24, 27, 34-39]

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Abbreviations: EMT:Epithelial-mesenchymal transition; MAPK: Mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinase; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; CaMKII: CaM-dependent protein kinases; Ca^{2+}: Calcium ion; MLCK: Myosin light-chain kinase; RhoA: Ras homolog family member A; ROCK: Rho-associated coiled-coil containing protein kinase; MMPs: Matrix metalloproteinases; uPA: Urokinasetype plasminogen activator; uPAR: Urokinasetype plasminogen activator receptor; EGFR: Epidermal growth factor receptor; KRAS: Kirsten Rat Sarcoma viral oncogene homolog; CREB: Cyclic AMP response elementbinding protein; CDK: Cyclindependent kinase; BCL 2: Bcell lymphoma 2; ECM: Extracellular matrix; 5-FU: 5-fluorouracil.

Note: CaM acts as a central intracellular calcium sensor, integrating Ca^{2+} signals with multiple oncogenic pathways in CRC. This table summarizes CaM's involvement in key cellular processes, including proliferation, apoptosis, migration, invasion, and metastasis. Through activation of Ca^{2+}/CaM-dependent kinases (such as CaMKII), modulation of MAPK/ERK and PI3K/AKT pathways, and interactions with oncogenic proteins, such as KRAS and EGFR, CaM promotes tumor growth, therapy resistance, and metastatic progression. Pharmacological inhibition of CaM or its downstream effectors in preclinical CRC models demonstrates reduced cell proliferation, impaired motility, and enhanced sensitivity to chemotherapeutic agents. Collectively, these findings highlight CaM as a potential biomarker and therapeutic target for precision management of CRC.

CaM facilitates cell polarity, leading-edge protrusion, and tail retraction required for efficient motility. CaM also modulates focal adhesion turnover and integrin signaling, enabling cells to dynamically attach to and detach from the extracellular matrix (ECM) during invasion [27].

High CaM activity promotes formation and maturation of invadopodia, enhances MMP secretion and activation, and supports EMT programs characterized by increased vimentin and reduced E-cadherin, all of which correlate with metast atic potential in tumors, such as glioblastoma and carcinoma models. Pharmacological CaM antagonists (e.g. W-7, trifluoperazine) consistently reduce migration, invasion, and invadopodia-driven matrix degradation in vitro, reinforcing the concept that CaM-centered Ca^{2+} signaling is a key driver of metastatic behavior [27].

CaM in CRC

CaM integrates Ca^{2+} signals with major oncogenic pathways in CRC, shaping proliferation, tumor progression, and metastatic behavior. Its effects are largely mediated through Ca^{2+}/CaMdependent kinases, phosphatases, and CaM-regulated cytoskeletal and transcriptional programs [28].

CaM and cell proliferation: In CRC cells, growth factors, inflammatory cues, and microenvironmental stress generate spatially and temporally patterned Ca^{2+} signals that are decoded by CaM. CaM activates CaMKK–CaMK cascades (especially CaM-dependent protein kinase II [CaMKII]), which phosphorylate transcription factors such as CREB and modulate β-catenin activity, thereby enhancing expression of pro-proliferative genes, including cyclin D1, cellular MYC (c-MYC), and CDK4/6 [24-28].

At the cell-cycle level, CaM–CaM-KII signaling promotes G1/S transition by increasing cyclin D/E abundance, stimulating CDK activity, and facilitating phosphorylation and inactivation of Rb, while functionally antagonizing cell-cycle inhibitors such as p21 and p27. Pharmacological inhibition of CaM or CaM-KII in colon cancer models typically leads to G0/G1 arrest, reduced Ki-67 labeling, and decreased clonogenic growth, underscoring the dependence of CRC proliferation on the Ca^{2+}/CaM/CaMK axis [24-29].

CaM in tumor progression: Beyond simple proliferation, CaM acts as an adaptive hub that couples Ca^{2+} signaling to survival and stress-response pathways during CRC progression. Through CaM-KII, CaM-KKβ, and related effectors, CaM sustains PI3K/AKT/mTOR signaling, supporting anabolic metabolism, glycolysis, and resistance to intrinsic and therapy-induced apoptosis via upregulation of anti-apoptotic BCL-2 family members and suppression of pro-apoptotic mediators [24, 27-30].

CaM also intersects with the MAPK pathway by influencing RAF/MEK/ERK activity and stabilizing nuclear effectors, such as ETS Like-1 protein (ELK-1) and activator protein 1 (AP-1), which drive expression of cyclooxygenase 2 (COX-2), matrix-degrading enzymes, and inflammatory mediators that favor a tumor-promoting microenvironment. Crosstalk between CaM/CaM-KII and Wnt/β-catenin—through modulation of components of the β-catenin destruction complex or glycogen synthase kinase 3 beta (GSK3β)—can augment nuclear β-catenin accumulation and transcriptional output, helping to maintain a stem-like, therapy-resistant phenotype in subsets of CRC cells [24, 27, 31].

Chen et al. (2017) investigated the role of Ca^{2+}/CaM-KII in colon cancer growth, proliferation, and migration. They found that CaM-KII was overexpressed in colon cancer tissues and correlated with tumor differentiation. Specific inhibition of CaM-KII with KN93 reduced proliferation, migration, and invasion of the human CRC cell line (HCT116) cells, with the ERK1/2 and p38 pathways also involved. These findings suggest that CaMKII is a key mediator in colon cancer progression and metastasis [28].

CaM and metastasis: CaM is a key regulator of the motility machinery that underlies CRC invasion and metastasis. By activating MLCK, CaM increases phosphorylation of myosin regulatory light chain, boosting actomyosin contractility and enabling tumor cells to squeeze through dense extracellular matrices and vessel walls. In parallel, CaM influences Ras homolog family member A (RhoA)/Rho-associated coiled-coil containing protein kinase (ROCK) and Rac1/Cdc42 signaling, coordinating actin polymerization, lamellipodia and filopodia formation, and front–rear polarity in migrating CRC cells [24, 27].

Zhou et al. (2025) investigated the effects of Erianin on 5-fluorouracil (5-FU)-resistant CRC cells. They demonstrated that Erianin restored sensitivity to 5-FU, reducing proliferation, migration, and invasion of resistant CRC cells and inhibiting xenograft tumor growth. Mechanistically, Erianin binds to CALM1, stabilizing it and enhancing CAM-KK2 phosphorylation, which promotes autophagy and tumor cell death. These findings suggest that combining Erianin with 5-FU may provide a promising therapeutic strategy for refractory CRC [32]. At the adhesion and ECM interface, CaM modulates focal adhesion turnover through effects on FAK and associated adaptor proteins, thereby optimizing cycles of attachment and detachment to the ECM and endothelium. CaM-dependent signaling enhances expression and activity of (e.g. MMP-2, MMP-9) and components of the urokinasetype plasminogen activator (uPA)/urokinasetype plasminogen activator receptor (uPAR) system, driving ECM degradation, basement-membrane breach, and intravasation. In conjunction with EMT-related pathways (TGF-β/Smad, nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB]), CaM contributes to downregulation of E-cadherin and upregulation of N-cadherin, vimentin, and EMT transcription factors, such as Snail and Twist, thereby consolidating an invasive, metastatic phenotype in CRC [24, 27, 33].

Higuchi et al. (2025, Japan) investigated the role of SEC61 Translocon Subunit Gamma (SEC61G) in CRC progression. They found that SEC61G is upregulated in CRC tissues and associated with poor patient prognosis. Overexpression of SEC61G increased cytosolic Ca^{2+} levels, activated the epidermal growth factor receptor (EGFR) pathway, and promoted cell cycle progression from G1 to S phase, enhancing CRC cell proliferation. Analyses of single-cell and spatial transcriptomic data

confirmed high SEC61G expression in tumor epithelial cells co-expressed with EGFR-related genes. These findings suggest that SEC61G drives CRC progression via Ca^{2+}/CaM-mediated EGFR activation and may serve as a prognostic biomarker and therapeutic target [34] (Table 1).

CaM inhibitors and modulators

CaM antagonists (e.g. classical phenothiazines, such as trifluoperazine and chlorpromazine, and non-phenothiazines, such as W-7, W-13) bind to Ca^{2+}/CaM and prevent activation of CaM-dependent kinases and phosphatases that drive proliferation and survival. These agents reduce CRC cell growth, clonogenicity, and migration in vitro, often via inhibition of CaM-KII, calcineurin/NFAT and downstream ERK and PI3K–AKT signaling, but at concentrations close to those that affect many other targets. Small-molecule modulators that more selectively disrupt CaM–oncoprotein interfaces (for example CaM–K-RAS or CaM–EGFR complexes) are being explored as a way to inhibit RAS/MAPK and EGFR signaling with less systemic CaM blockade, but these compounds remain at a discovery or early preclinical stage and none are clinically approved specifically as CaM-targeted anticancer drugs [24, 27, 34-39].

Potential applications in CRC

In CRC models, CaM inhibition can: (i) induce cell-cycle arrest and apoptosis, partly through p21/p27 up-regulation and mitochondrial pathway activation; (ii) impair cytoskeletal dynamics and focal adhesion signaling, reducing invasion and metastasis; and (iii) modulate angiogenic and inflammatory mediators that shape the tumor microenvironment. On this basis, rational applications being discussed include using CaM inhibitors as chemosensitizers to 5-FU/oxaliplatin or targeted agents, to overcome resistance driven by CaM-dependent survival signaling, and combining CaM modulation with EGFR or RAS pathway inhibition to enhance blockade of MAPK/PI3K cascades while potentially allowing lower doses of each drug. Because CaM is ubiquitous and essential in excitable and non-excitable tissues, a key therapeutic concept is to favor context-dependent or protein–protein interaction-specific CaM modulators rather than global CaM blockade, to widen the therapeutic window [24, 27, 34-40].

Preclinical and clinical evidence

Preclinical data: Multiple CRC cell-line and xenograft studies show that phenothiazine-type CaM antagonists reduce tumor growth and can potentiate cytotoxics, but these effects are difficult to separate from dopamine-receptor and membrane-stabilizing actions, and cardiotoxicity, neurotoxicity, and QT prolongation limit direct translation. More recent work with structure-guided CaM–client interface inhibitors demonstrates suppression of RAS/MAPK signaling and tumor growth in RAS-driven models, including colon cancer lines, but these studies are still at the level of in vitro assays and mouse models with no human pharmacokinetic or safety data yet available. Clinically, there are no dedicated trials of CaM-selective inhibitors in CRC; phenothiazines and related drugs have only been evaluated indirectly (for example as antiemetics or repurposed psychotropics) and any anticancer effects remain exploratory, therefore, at present CaM-targeted therapy in CRC should be considered an experimental strategy supported by mechanistic rationale and early preclinical data rather than an established therapeutic option [24, 27, 38-42].

Limitations of current studies

Most studies rely on broad-spectrum CaM antagonists, such as phenothiazines, which exhibit off-target effects on dopamine receptors, ion channels, and membrane stabilization, complicating attribution of anti-CRC activity solely to CaM inhibition. In vitro and xenograft models predominate, but they inadequately recapitulate CRC heterogeneity, tumor microenvironment interactions, and patient-specific factors, such as microsatellite instability (MSI) status or KRAS mutations, leading to poor predictive value for clinical efficacy. Dosing issues persist, as effective anti-proliferative concentrations often approach toxicity thresholds, with insufficient pharmacokinetic data in humans to support safe translation [24, 27, 38-44]. Moreover, according to available studies, no specific clinical trial has been conducted on CaM inhibition in CRC.

Inconsistencies and knowledge gaps in CaM role in CRC

Inconsistencies in the literature on CaM's role in CRC primarily revolve around expression levels and functional outcomes of CaM and its effectors like CaM-KII. While numerous studies report CaM-KII overexpression correlating with poor tumor differentiation, enhanced proliferation, and metastasis [14, 30], conflicting evidence shows isoform-specific downregulation: for instance, CaMK2δ is reduced in advanced CRC stages [14, 30, 44-50], CaMK2β in Fusobacterium nucleatum-associated tumors [14, 15, 30, 49, 50], and CaM-K2γ in rectal cancers [50]. Additionally, CAM-K2N1, an

endogenous CaM-KII inhibitor, exhibits tumor-suppressive effects by repressing Wnt/β-catenin signaling [49, 50], challenging the dominant oncogenic paradigm.

These discrepancies may arise from isoform-specific functions, CRC subtypes (e.g. MSI-high vs stable), microbial influences, tumor microenvironment variations, or methodological differences such as transcriptomic versus proteomic analyses [14, 27-29, 51]. Knowledge gaps persist in elucidating CaM's context-dependent mechanisms across CRC heterogeneity, including its interactions with the microbiome (e.g. F. nucleatum's role in modulating CaM-K2β) and subtype-specific prognostic value [14, 30, 48-51].

There is limited data on CaM's activation states in diverse patient cohorts, with most studies relying on preclinical models that inadequately capture human tumor microenvironments or genetic diversity, such as KRAS/BRAF mutations. Furthermore, pharmacokinetic and safety profiles for selective CaM inhibitors remain underexplored, and no dedicated clinical trials exist, hindering translation from bench to bedside [14, 30, 41, 42, 49-53]. Addressing these gaps requires advanced models, such as patient-derived organoids and multi-omics approaches, to clarify dual oncogenic/suppressive roles.

Comparisons with other cancers highlight CRC's unique variability in CaM expression compared to consistent upregulation in KRAS-driven malignancies, pancreatic and lung adenocarcinomas, where CaM amplifies PI3K/AKT and MAPK pathways for aggressive growth [13, 16, 19, 54]. In breast and prostate cancers, CaM-KII overexpression uniformly promotes invasion and survival [14, 18, 24, 30, 49-55], mirroring CRC's oncogenic aspects but lacking the suppressive isoforms observed in CRC subsets [14, 30]. Melanoma and medulloblastoma show CaM-K-driven migration via MAPK/Rac1 [14, 24, 30, 49], similar to CRC, yet CRC's Wnt pathway dominance and inflammatory microenvironment may explain compensatory mechanisms, suggesting cancer-specific targeting strategies [14, 30, 49-55].

Need for further research

Deeper mechanistic studies are essential to dissect CaM's context-specific roles in CRC subtypes, including its interactions with oncogenic clients, such as KRAS, EGFR, and PI3K, using advanced models, such as patient-derived organoids and genetically engineered mice. Clinical correlative analyses should quantify CaM expression, activation states, and downstream signaling in CRC tissues versus normal mucosa to establish prognostic or predictive relevance. Comprehensive safety profiling of selective CaM modulators, including cardiac and neurological risks, requires dedicated Phase I trials in oncology settings [24, 27, 34, 40-45].

Future perspectives

CaM holds promise as a biomarker for aggressive CRC subsets with high Ca^{2+} signaling dependence, potentially guiding patient stratification via immunohistochemistry (IHC) or phospho-proteomic assays in liquid biopsies. Selective small-molecule or peptide inhibitors targeting CaM-oncoprotein interfaces could enable combination regimens with immunotherapy or chemotherapeutics, exploiting synthetic lethality in RAS-mutated tumors. Long-term, integrating CaM modulation with clustered regularly interspaced short palindromic repeats (CRISPR)-based screens and AI-driven drug design may yield first-in-class agents, positioning CaM as a viable therapeutic node in precision CRC management [24, 27, 40-48].

Conclusion

CaM serves as a pivotal calcium sensor in CRC, orchestrating proliferation through activation of CaM-dependent kinases, such as CaM-KII, that drive ERK/MAPK and PI3K/AKT signaling, while facilitating tumor progression and metastasis via cytoskeletal remodeling, NFAT transcription, and interactions with oncogenic partners such as EGFR and KRAS. Elevated CaM activity in preclinical models correlates strongly with enhanced tumor growth, invasion, apoptotic resistance, and metastatic potential, integrating calcium fluxes with core cancer hallmarks from early adenoma stages to advanced disease. These multifaceted roles underscore the critical importance of CaM-related pathways in targeted therapy development, where selective inhibition of CaM-oncoprotein interfaces promises synergy with chemotherapeutics or EGFR blockers to surmount resistance, particularly in KRAS-mutant subsets, thereby refining patient stratification and propelling precision oncology forward.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and study design: Mohammad Kordkatouli, Audrius Dulskas, Mahmoud Heidari, and Mohammad Amin Javidi; Resources: Mohammad Kordkatouli, Mehr Ali Mahmood Janlou, and Mohammad Amin Javidi; Data collection: Mohammad Kordkatouli, Mahmoud Heidari, Mehr Ali Mahmood Janlou, and Audrius Dulskas; Data analysis and interpretation: Mohammad Kordkatouli, Mahmoud Heidari, Mehr Ali Mahmood Janlou, and Mohammad Amin Javidi; Investigation: Mohammad Kordkatouli, Mahmoud Heidari, Mohammad Amin Javidi, and Mehr Ali Mahmood Janlou; Writing: All authors.

Conflicts of interest

The authors declared no conflicts of interest.

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