Life Sciences 239 (2019) 116909

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Pathogenic roles of altered calcium channels and transporters in colon tumorogenesis

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ARTICLE INFO

Keywords:
Intracellular Ca^{2+} signaling
Ca^{2+} channels
Ca^{2+} transporters
Colorectal cancer

ABSTRACT

Cytosolic calcium $[Ca^{2+}]_{cyt}$ signaling plays a critical role in the regulation of multiple cellular functions, and Ca^{2+} channels/transporters are important to regulate calcium homeostasis whose abnormality may contribute human tumorogenesis including colorectal cancer (CRC). In this review, we summarized and discussed the current knowledge on pathogenic roles of the altered $[Ca^{2+}]_{cyt}$ and Ca^{2+} channels/transporters like SOCE, TRP channels, SERCA and Na + /Ca2 + exchangers in CRC tumorigenesis and progression. Understanding the detailed molecular mechanisms underlying the effects of $[Ca^{2+}]_{cyt}$ on CRC is essential to develop Ca^{2+} channels/transporters as diagnostic and therapeutic targets. Targeting Ca^{2+} signaling for cancer therapy has become an emerging research area nowadays, although our knowledge about the roles of Ca^{2+} channels/transporters in tumorigenesis is still in the early stage, we still believe that they will act as novel preventive/therapeutic targets for CRC with potentially extensive clinical significance.

1. Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide, and is diagnosed approximately over one million persons each year. Although the survival rate of five years is more than 90% for the early CRC [1], it is reduced to less than 10% for the advanced CRC with metastasis [2]. The current therapeutic principles include surgical resection for early CRC, immunotherapy, cytotoxic chemotherapy, radiotherapy, and other anticancer therapies for advanced CRC. Since patients may not have any remarkable clinical symptoms until it has developed to the advanced stage, so it is difficult to diagnose early and cure CRC. Therefore, it is important to enhance our understanding of the cellular and molecular mechanisms of CRC, which may help to design prospectively targeted diagnosis and therapy, as well as to improve the overall prognosis of CRC.

In eukaryotic cells, cytosolic free calcium ion ($[Ca^{2+}]_{cyt}$) is well-maintained at around 0.1 μM under the resting state with activated levels capable of exceeding 1 μM, while the extracellular free Ca^{2+} is about 2 mM. In recent years, the pathophysiological roles of intracellular Ca^{2+} signaling and Ca^{2+} channels that regulate intracellular Ca^{2+} homeostasis have been becoming one of the hot topics in the biomedical research field. It is well known that $[Ca^{2+}]_{cyt}$ is a ubiquitous intracellular second messenger to regulate multiple physiological and pathological processes, including mitochondrial energy production, cell proliferation, migration, invasion, and cell apoptosis [3]. The aberrance of intracellular Ca^{2+} signaling and membrane Ca^{2+} channels has been documented to be involved in several cancer hallmarks, such as self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis [4]. A growing line of evidence indicates that the dysregulation in intracellular Ca^{2+} signaling is also involved in the tumorigenesis and development of human digestive system, including esophageal carcinoma, gastric cancer, hepatocellular carcinoma, pancreatic cancer and CRC as well [5–9]. The roles of intracellular Ca^{2+} signaling and Ca^{2+} channels in CRC are complicated, in which many factors may participate. Since multiple lines of investigation have demonstrated that the abnormity of Ca^{2+} signaling played a critical role in recurrence, metastasis, and prognosis of CRC [10], a better understanding of the changes in Ca^{2+} signaling and Ca^{2+} channels in CRC will help to find novel therapeutic targets for drug

Abbreviations: $[Ca^{2+}]_{cyt}$, cytosolic free calcium ion; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; SOCE, store-operated Ca^{2+} entry; GPCR, G protein-coupled receptor; MCU, mitochondrial Ca^{2+} uniporter; ROS, reactive oxygen species; TRP, transient receptor potential; SERCAs, sarco/endoplasmic reticulum calcium-ATPases; PTP1B, protein tyrosine phosphatase 1B

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https://doi.org/10.1016/j.lfs.2019.116909
Received 3 July 2019; Received in revised form 12 September 2019; Accepted 23 September 2019
Available online 02 November 2019
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development.

In this review, we will concentrate on the pathogenesis roles of dysregulation of intracellular Ca^{2+} signaling and Ca^{2+} channels in colon tumorogenesis and progression since limited review on this topic exists in the literature. We anticipate that intracellular Ca^{2+} signaling and Ca^{2+} channels will be further studied in human CRC, and specific modulators will become promising new drugs to treat CRC in the near future.

2. The roles of Ca^{2+} signaling in CRC

2.1. Cell proliferation

Activation of tissue factor (TF)-coagulation factor VIIa-protease-activated receptor 2 (PAR-2) axis enhanced proliferation, differentiation and migration of SW620 cells likely through causing $[Ca^{2+}]_{cyt}$ increase, which was inhibited by EGTA-mediated removal of extracellular Ca2+ and thapsigargin (TG)-induced depletion of intracellular Ca2+ stores. Therefore, Ca2+ signaling had an important role in the proliferation, differentiation and migration of SW620 cells [11]. PAR-2 stimulation by agonist peptide SLIGKV induced an increase in $[Ca^{2+}]_{cyt}$ and the proliferation of DLD-1 colon cancer cells, which was associated with the transient phosphorylation of MEK and MAP kinase pathway [12]. The mRNA of Kallikrein-related peptidase 14 (KLK14) is expressed in human colon adenocarcinoma cells but not in adjacent cancer-free tissue. Colon cancer cell lines but not in adjacent cancer-free tissue expressed and secreted KLK14 protein. KLK14 signal via activation of PAR2 increased $[Ca^{2+}]_{cyt}$ and stimulated ERK1/2/MAP kinase phosphorylation, and promoted proliferation of HT-29 cells [13,14]. Neurotensin (NT) promoted the proliferation of human colonic cancer HT29 cells by increase $[Ca^{2+}]_{cyt}$ and ERK1/2 phosphorylation [15]. Other study found KM20 colon cancer cell line expressed neurotensin receptor (NTR) gene. Binding to its endogenous NTR, neurotensin increased $[Ca^{2+}]_{cyt}$ and stimulated MAPK-signaling pathways and increased the levels of AP-1 transcription factor c-Fos, to stimulate cell proliferation [16].

Thrombin is now recognized as an important factor in many cancers. Evidence shown thrombin receptor proteinase-activated receptor 4 (PAR4) expressed on the human colon tumor tissues and lines but not on the normal human colonic mucosa and epithelial cells isolated from normal human colon. Activation of PAR4 increased $[Ca^{2+}]_{cyt}$ in HT29 cells, and the phosphorylation of ERK1/2 and epidermal growth factor receptor B-2 (ErbB-2) depended on the Src kinase activity, finally promoting proliferation of colon cancer cells [17]. Extracellular Zn2+ acting through ZnR induced Ca2+ release and ERK1/2 phosphorylation, subsequently, activation of NHE1 in HT29 colonocytes. By activation of ERK and NHE1, extracellular Zn2+ enhanced proliferation of colon cancer [18]. Take together, promoted proliferation of colon cancer depended on $[Ca^{2+}]_{cyt}$ increase and ERK1/2 and/or MAPK signaling pathway activation, such as coagulation gactor VIIa, peptide SLIGKV, KLK14, neurotensin, thrombin and extracellular Zn2+, which are summarized in Table 1.

HCT8 human colonic tumor cells produced pituitary adenylate cyclase-activating polypeptide (PACAP) hormone and expressed its receptor, PAC1. Activation of PAC1, PACAP elevated intracellular cAMP levels, and caused an increase in $[Ca^{2+}]_{cyt}$ and cellular proliferation [19]. Human colorectal cancers expressed cholecystokinin B/gastrin receptor (CCK-BR) and CCK-BRi4sv (intron 4-containing splice variant). CCK-BRi4sv exhibited spontaneous, non-synchronous, and oscillatory $[Ca^{2+}]_{cyt}$ increase and stimulated colorectal cancer cell proliferation though a gastrin-independent mechanism [20]. Activation of the M_3 muscarinic cholinergic receptor resulted in intracellular Ca^{2+} mobilization and induced significant proliferation of human colon cancer cell [21]. Human colonic carcinoma cells T84 expressed cancer-related K+ channels, but only voltage-gated K+ (Kv) channels influenced proliferation. Kv promoted proliferation of colonic carcinoma cells by affecting intracellular pH and Ca2+ signaling. Kv channels elicited $[Ca^{2+}]_{cyt}$ increase, probably by their hyperpolarizing effects, which induced intracellular Ca2+ release and extracellular Ca2+ influx through store-operated Ca^{2+} entry (SOC) mechanism [22].

Colon derived cells, including SW-480, HT-29, and NCM-460 cells, expressed the calcium sensing receptor (CaSR), which activation induced $[Ca^{2+}]_{cyt}$ increase and proliferation inhibition of human colonic epithelial cells [23]. Ca^{2+} or calcimimetic R-568 activation of the CaSR decreased the phosphorylation of β-catenin at Ser-552 and Ser-675 with a decline of β-catenin in its nuclear localization and transcriptional activation and redistribution to the plasma membrane [24]. Similarly to colonic epithelial cells, acting on CaSR by thermostable direct hemolysin(TDH) increased $[Ca^{2+}]_{cyt}$ and inhibited proliferation of human CRC COLO-205 cells with the involvement of E-cadherin-β-catenin-mediated pathway and the inhibition of cell cycle regulators as well as upregulation of cell cycle inhibitors [25]. Therefore, the CaSR may serve as a tumor suppressor in CRC, and its activation induced $[Ca^{2+}]_{cyt}$ increase that inhibits CRC cell proliferation likely through anti-β-catenin pathway.

Bacterial heat-stable enterotoxins (ST) through acting on guanylyl cyclase C (GCC) was found to inhibit CRC cell proliferation, which was regulated by a mechanism of extracellular Ca^{2+}/CaSR signaling pathway [26]. Moreover, ST through stimulation of GCC to increase intracellular cGMP suppressed CRC cell proliferation, which was reversed by removal of extracellular Ca^{2+}, or chelation of intracellular Ca^{2+} [27]. Interestingly, the store-operated Ca^{2+} entry (SOCE) was found to be a key signaling mechanism that promoted cancer cell proliferation during ST-induced GCC and accumulation of cGMP to promote CRC cell cytostasis, serving as a tumor suppressor [28]. Therefore, a combination of GCC agonists and SOCE inhibitors may offer a novel paradigm for cGMP-directed therapy and prevention for CRC.

Gas2 dominant negative (Gas2DN) increased the activity of calpain and induced degradation of stabilized/mutated β-catenin, reducing the proliferation of colon cancer [29]. Limonin and limonin glucoside (LG) inhibited colon adenocarcinoma cell proliferation through facilitating the apoptosis process by increasing $[Ca^{2+}]_{cyt}$ level [30]. Verapamil inhibited proliferation of human colonic tumor cells via increasing $[Ca^{2+}]_{cyt}$ concentration. However, the complex biologic processes mediated by $[Ca^{2+}]_{cyt}$ to inhibit colorectal cancer proliferation were not well described [31]. Wnt5a expression was significantly diminished in colon cancer tissues and colon cancer cell and associated with clinicopathological characteristics. Wnt5a inhibited colon cancer growth in vivo and vitro with the involvement of increasing the $[Ca^{2+}]_{cyt}$ and mediating noncanonical Wnt/Ca^{2+} signaling in a calcium/calmodulin dependent kinase II (CaMK II) manner. This suggests that Wnt5a might

Table 1
Involvement of [Ca2+]cyt and ERK1/2 signaling pathways in pro-proliferative progress of CRC cells.

Stimulants	Receptors	Cell lines	Signaling pathways	Function	Reference
TF-coagulation gactor VIIa peptide SLIGKV KLK14	PAR-2	SW620 HT-29	Ca2+ ERK1/2 MAPK	Pro-proliferation	[11-14]
Neurotensin	Neurotensin receptors	KM20	Ca2+ ERK1/2 MAPK	Pro-proliferation	[15,16]
Thrombin	PAR-4	HT-29	Ca2+ ERK1/2 ErbB-2	Pro-proliferation	[17]
Zn2+	Zn2+ receptors	HT-29	Ca2+ ERK1/2 NHE1	Pro-proliferation	[18]

act as tumor suppressor in CRC by inhibiting cell proliferation through Wnt/Ca^{2+}/CaMK II [32].

2.2. Migration and invasion

It is well established that intracellular calcium signaling regulates various cellular processes, particularly tumorigenesis and tumor progression, such as tumor metastasis, invasion and angiogenesis [3]. The significantly diminished expression of Wnt5a in majority of primary colon cancers was negatively related with epithelial-mesenchymal transition (EMT) biomarkers. Wnt5a induced $[Ca^{2+}]_{cyt}$ increase and activated non-canonical Wnt/Ca^{2+} signaling in colon cancer, attenuating EMT of CRC cells [32]. Coagulation factor VIIa (VIIa) and PAR2 agonist (PAR2-AP)-induced migration of SW620 cells via increasing $[Ca^{2+}]_{cyt}$, suggesting that intracellular calcium signaling have a vital role in the migration of SW620 cells, but the underlying mechanism remains elusive [11]. Chemokines and chemokine receptors are extensively and broadly involved in cancer metastasis. CXCL12 is a mixture of monomeric and dimeric species. Monomeric CXCL12 mobilized intracellular calcium, inhibited cAMP signaling, and stimulated colorectal carcinoma cell migration. Dimeric CXCL12 activated G-protein-dependent calcium influx, and the rapid activation of ERK1/2, and promoted chemotaxis [33]. It is well known that cancer cell motility is a key phenomenon regulating invasion and metastasis. Ca^{2+} bound lactate (CaLa) induced Ca^{2+} influx and increased CRC cell motility mediated by calpain activity through Focal adhesion kinase (FAK) and phosphorylated FAK (pFAK) protein destabilization [34].

2.3. Apoptosis

An increase in $[Ca^{2+}]_{cyt}$ resulted from both the endoplasmic reticulum (ER) Ca^{2+} release and capacitative Ca^{2+} influx through Ca^{2+} release-activated Ca^{2+} channels, has been proposed to be involved in apoptosis of CRC cells [35]. Intracellular Ca^{2+} plays a role in rotavirus-induced apoptosis because treatment with BAPTA-AM, an intracellular Ca^{2+} chelator, partially inhibited apoptosis [36]. L-type calcium channels are expressed in HT-29 and AZ-97 human colon cancer cells. Activation of L-type calcium channels increase intracellular Ca^{2+} and apoptosis in primary human colon cancer cells, but verapamil, a specific blocker of L-type calcium channels, completely abolishes both Ca^{2+} influx and apoptosis of these cells [37]. Diallyl disulfide (DADS) induces the elevation of $[Ca^{2+}]_{cyt}$ and apoptosis of human colon cancer HCT-15 cells [38]. It is known that thapsigargin (TG) causes the increase in $[Ca^{2+}]_{cyt}$ by depletion of Ca^{2+} within the ER. In HCT116 human colon cancer cells, TG-induced Ca^{2+}-mediated apoptosis is coupled with death-inducing receptors DR5 up-regulation and caspases 8 and 3 activation [39]. Sodium butyrate (NaB) also induces Ca^{2+} release from the ER, in turn causing extracellular Ca^{2+} influx. NaB-induced apoptosis of HCT-116 cells was inhibited by EGTA or BAPTA/AM, down-regulation of STIM1 or blockade of the SOC, indicating that the classical SOC is involved NaB-induced apoptosis [40]. Nifedipine can activate the CaSR to induce extracellular Ca^{2+} influx, in return down-regulating the expression of thymidylate synthase, a molecular target of fluorouracil (5-FU), and survivin, a key anti-apoptotic protein, finally augments the sensitivity of human colon carcinoma cells to 5-FU [41]. Paeonol exhibits antitumor effects by inducing apoptosis of human colon cancer cells through increase intracellular Ca^{2+} concentration [42]. Ganoderma lucidum polysaccharides induce apoptosis of HCT-116 human colon cancer cells through triggering intracellular Ca^{2+} release and Fas/Caspase dependent pathway [43]. Photodynamic therapy significantly increases intracellular Ca^{2+} and apoptosis of SW480 cells by activating ERK pathway [44]. Inhibition of HSP70 induces apoptosis of colon cancer cells by increasing $[Ca^{2+}]_{cyt}$ levels [45]. Taken together, an increase in $[Ca^{2+}]_{cyt}$, resulted from both intracellular Ca^{2+} release and etracellular Ca^{2+} influx, plays an important role in apoptosis of CRC cells (Fig. 1).

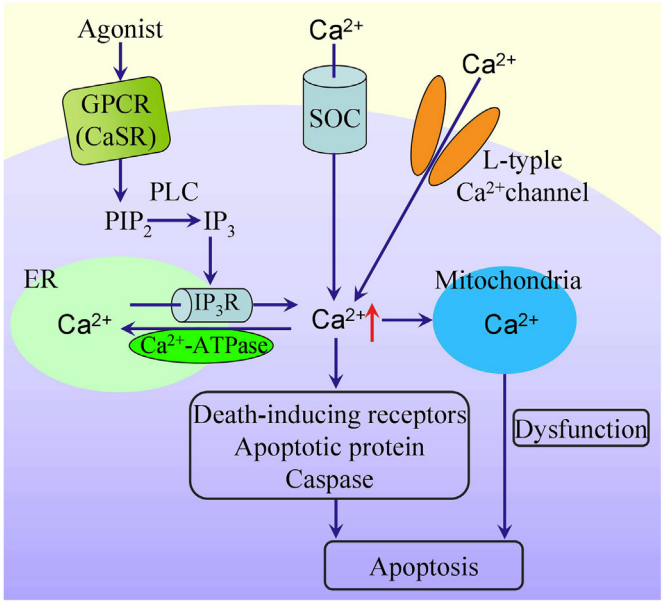

Fig. 1. Role of intracellular Ca^{2+} in the apoptosis of CRC cells.
Agonists stimulates GPCR such as CaSR to increase intracellular IP_3 concentrations, which activates IP_3 receptors to result in Ca^{2+} release from the ER, in turn inducing extracellular Ca^{2+} influx via the store-operated channels (SOC) to raise cytosolic Ca^{2+} concentrations ($[Ca^{2+}]_{cyt}$). Ca^{2+} influx via the L-type Ca^{2+} channels can also raise $[Ca^{2+}]_{cyt}$, but the ER Ca^{2+}-ATPase can pump $[Ca^{2+}]_{cyt}$ into the ER to reduce $[Ca^{2+}]_{cyt}$. An increase in $[Ca^{2+}]_{cyt}$ induces the apoptosis of CRC cells through death-inducing receptors, apoptotic protein and caspase. The mitochondrial Ca^{2+} overload resulted from the ER Ca^{2+} release also triggers mitochondrial dysfunction and apoptosis of CRC cells.

Growing lines of evidence suggest that apoptosis and necrosis are often linked to accumulation of excessive Ca^{2+} by the mitochondria and activation of mitochondrial membrane permeabilization [46,47]. Mitochondria uptakes Ca^{2+} and controls the Ca^{2+} concentration by removal of Ca^{2+} from cytosol in the cell, which is the so-called mitochondrial Ca^{2+} uniporter (MCU) [48]. Celastrol, an anticancer drug, induces paraptosis of colon cancer cell likely through IP_3R-mediated release of Ca^{2+} from the ER and subsequent MCU-mediated Ca^{2+} influx into the mitochondria [49]. Dihydroartemisinin triggers the ER stress through inhibiting SERCA activity to release the ER Ca^{2+}, and activates mitochondrial apoptosis pathway in HCT-116 cells [50]. Khz (a fusion mycelium of ganoderma lucidum and polyporus umbellatus mycelia) increases intracellular Ca^{2+} and disrupts mitochondrial membrane potential to finally induce apoptosis of human colon carcinoma HCT116 cells [51]. Laminarin increases reactive oxygen species (ROS) and Ca^{2+}, and activates intracellular mitochondrion permeability transition pore in human colon cancer LOVO cells, and finally induces apoptosis [52]. Emodin induces ROS and Ca^{2+}, leading to mitochondrial dysfunction and activation of caspase-9 and caspase-3 to cause human colon cancer cells apoptosis [53]. Na_2SeO_3 induces apoptosis of SW480 cells by an increase of intracellular Ca^{2+} and ROS production [54]. Cyclooxygenase-2 inhibitors dolastatin and celecoxib stimulate apoptosis by an increase in $[Ca^{2+}]_{cyt}$ and down-regulation of PI3–K/AKT pathway [55]. Diclofenac, another cyclooxygenase-2 inhibitor, induces apoptosis of colon cancer through targeting intracellular pH and Ca^{2+} signaling [56]. Capsaicin has been recently demonstrated to induce apoptosis in many types of malignant cells, including colon cancer cells. Capsaicin induces apoptosis of cancer cells through $[Ca^{2+}]_{cyt}$ increase and ROS generation [57]. Grape seed extract (GSE) induces apoptosis of Caco-2 human colon cancer cells by increasing ROS and intracellular Ca^{2+} to inactivate ERK [83].

In summary, mitochondria uptakes cytosol Ca^{2+} releasing from the ER, leading to mitochondrial Ca^{2+} overload, which induces

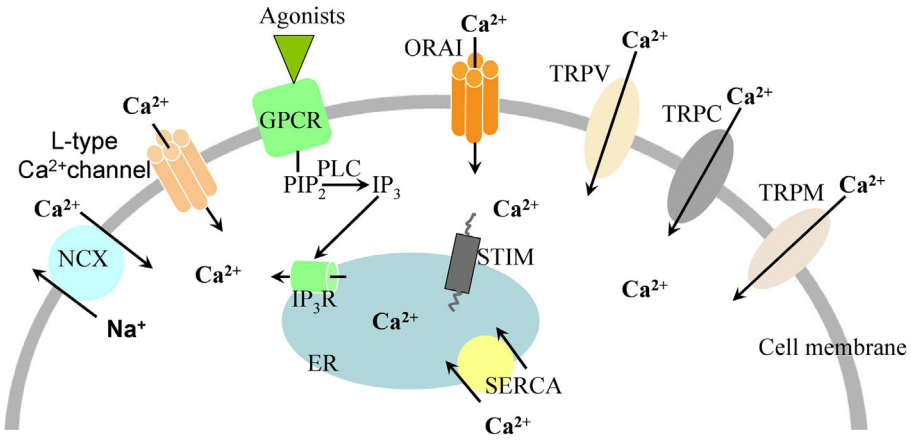

Fig. 2. Schematic diagram highlighting the involvement of some Ca^{2+} channels and transporters in the Ca^{2+} homeostasis of CRC and colon tumorigenesis.
Ca^{2+} influx is primarily mediated by L-type Ca^{2+} channels, TRPV, TRPC, TRPM, STIM/Orai and the Ca^{2+} entry mode of Na^+/Ca^{2+} exchanger (NCX). Intracellular Ca^{2+} release from the ER is induced by the activation of GPCR and phospholipase C to produce IP_3 that activates IP_3 receptors on the ER. The reuptake of $[Ca^{2+}]_{cyt}$ into the ER is primarily mediated by the S/ER Ca^{2+}-ATPase (SERCA). These channels and transporters play various roles in colon tumorigenesis. L-type calcium channels induce apoptosis of CRC cells. TRPV1 suppresses colon tumorigenesis, but TRPM8 and TRPC5 promote it. SERCA2 and SERCA3 affect CRC tumorigenesis and progression. STIM/Orai promotes proliferation, progression and metastasis of CRC.

mitochondrial dysfunction and apoptosis of CRC cells. Some anticancer drugs induce apoptosis of CRC cells by increasing ROS production, intracellular Ca^{2+} level to result in the changes in mitochondrial membrane potential and mitochondrial dysfunction. We summarize the different ways that mitochondrial Ca^{2+} uptake promote apoptosis of CRC (Fig. 1).

3. The roles of Ca^{2+} channels and transporters in CRC

In colon cancer cells, intracellular Ca^{2+} homeostasis is regulated mainly by SOCE, transient receptor potential (TRP) channels, L-type Ca^{2+} channels, sarco/endoplasmic reticulum calcium-ATPases (SERCAs), and Na^+/Ca^{2+} exchanger, which are summarized in Fig. 2. Here we discuss how Ca^{2+} channels or transporters might contribute to colon tumorigenesis and progression, and how these might be therapeutic targets for anticancer drug development.

3.1. Store-operated Ca^{2+} entry

Activation of G protein-coupled receptor (GPCR) could first stimulate phospholipase C to produce IP_3 that activates IP_3 receptors on ER membrane to induce Ca^{2+} release, and in return induce extracellular Ca^{2+} influx. This is the well-known SOCE mechanism. It is acknowledged that the SOCE is the major Ca^{2+} influx mechanism in non-excitable cells [58]. The stoma interaction molecule 1 (STIM1) and Orai1 were identified to be critical protein components of SOCE [59,60]. Previous studies found colon cancer cells display high protein expression of TRPC1, ORAI1, ORAI2, ORAI3, and STIM1. But the STIM2 protein expression is nearly lost. The Ca^{2+} stores in colon carcinoma cells are partially depleted relative to normal cells. Enhanced SOCE and depleted Ca^{2+} stores correlate with increased cell proliferation, invasion, and survival characteristic of human colon adenocarcinoma. Gene silencing experiments found that enhanced ORAI1, STIM1 and TRPC1 contribute to the enhanced SOCE and differential store-operated currents in colon tumor cells, whereas ORAI2 and ORAI3 are seemingly less important. Consistently, loss of STIM2 may underlie Ca^{2+} store depletion and apoptosis resistance in CRC. Therefore, a reciprocal shift in TRPC1 and STIM2 contributes to Ca^{2+} remodeling and tumor features in colon cancer [61].

Recent studies show STIM1 and Orai1 are over-expressed in CRC specimens, and the expression levels of STIM1 positively correlated with tumor size, stage, depth of invasion, lymph node metastasis and the serum levels of carcinoembryonic antigen in CRC patients. STIM1 over-expression promotes CRC cell invasion and metastasis through up-regulating COX-2 expression levels, suggesting activation of SOCE promotes CRC progression and metastasis [62]. In contrast, inhibition of SOCE by aspirin and other NSAIDs may contribute to chemoprevention of colon cancer [10,63,64]. Sodium butyrate induces apoptosis of HCT-116 cells also via SOCE signaling networks [40]. These data strongly suggest a critical role for the changes in SOCE in tumorigenesis of colon cancer. Therefore, SOCE antagonists could be considered for colon cancer therapy.

3.2. Transient receptor potential channels

TRP channels are important components of calcium-peaceable channels, which are associated with several pathological processes like cancer. Evidence show the mRNA expression levels of TRPV3, TRPV4, TRPV5, TRPM4 and TRPC6 genes in CRC are lower in tumor tissue compared to normal tissue, suggesting they may serve as potential genes contributing to tumorigenesis [65]. At the present, the evidences about roles of TRP channels in CRC mainly concentrate on TRPV1, TRPM8 and TRPC5.

3.2.1. TRPV1

TRPV1 activation inhibits EGFR-induced epithelial cell proliferation via activation of Ca^{2+}/calpain and resulting activation of protein tyrosine phosphatase 1B (PTP1B), suggesting TRPV1 is a regulator of growth factor signaling in the intestinal epithelium through activation of PTP1B and subsequent suppression of intestinal tumorigenesis [7]. Besides, activation of TRPV1 decreases neuroinflammatory processes and restricts the initiation and progression of colon cancer [66]. Taken together, activation of TRPV1 inhibits colon tumorigenesis.

3.2.2. TRPM

In human colonic cancer goblet cell line, activation TRPM5 by ATP-mediated Na^+ currents and the subsequent Ca^{2+} uptake via Na^+/Ca^{2+} exchanger (NCX) to trigger Mucin 5AC (MUC5AC) secretion [67]. The expression of TRPM8 mRNA is high in human colon cancer tissue samples in the corresponding normal tissues, suggesting it may promote the progress of colon cancer [68]. Subsequent study found CRC cells expressed the mRNA of TRPM8 channels. Cannabigerol hampers colon cancer progression in vivo and selectively inhibits the growth of CRC cells by TRPM8 [69]. Therefore, TRPM8 may serve as a tumor promoter gene in CRC.

3.2.3. TRPC5

Although 5-Fluorouracil (5-Fu) is widespread used in the chemotherapy of CRC patients, its high drug resistance allows cancer progression. Whereas, suppressing ABCB1 (ATP-binding cassette, subfamily B, member 1) could overcome drug resistance. Study found in 5-Fu-resistant human CRC HCT-8 (HCT-8/5-Fu) and LoVo (LoVo/5-Fu) cells, TRPC5 and ABCB1 were overproduced at the mRNA and protein levels, and more nuclear-stabilized β-catenin accumulation. However,

suppressing TRPC5 expression inhibited the canonical Wnt/β-catenin signal pathway, reduced the production of ABCB1, weakened the ABCB1 efflux pump, and caused a remarkable reversal of 5-Fu resistance in HCT-8/5-Fu and LoVo/5-Fu cells, suggesting TRPC5 may serve as a promoter in CRC [70].

3.3. L-type Ca^{2+} channel

$Ca_v1.1$ (L-type Ca^{2+} channel, exons 41 and 41A)) and $Ca_v1.2$ (L-type α_{1C}) are over-expressed [71,72], but $Ca_v3.1$ (L-type α_{1G}) and $Ca_v3.3$ (L-type α_{1I}) are down-expressed in human colon cancer tissue samples and cell lines [3,73,74]. Activation of L-type Ca^{2+} channels increases intracellular Ca^{2+} and apoptosis in primary human colon cancer cells. However, there had been a lack of evidence expounding the mechanisms [37].

3.4. SERCA pumps

Since SERCA pumps $[Ca^{2+}]_{cyt}$ into the ER and contributes to cell calcium homeostasis, the ER is crucial to control cell proliferation, differentiation and apoptosis. SERCA family consists of SERCA1, SERCA2, and SERCA3 by distinct genes encoding [75], but SERCA2 and SERCA3 are mainly studied in CRC. The mRNA of SERCA2 in human CRC tissue samples is significantly higher than that in corresponding noncancerous tissues. The patients with high SERCA2 expression in tumor tissue are significantly correlated with serosal invasion, more lymph node metastasis and advanced tumor stage and poorer overall survival, indicating that SERCA2 may be a molecular determinant in the development and progression of CRC [76]. Further evidence reveals that over-expression SERCA2 promotes proliferation and migration of SW480 cells via activating MAPK and AKT signaling pathways [77]. Taken together, these findings indicate that SERCA2 may play an advance role in colon carcinogenesis. Although the protein expression of SERCA3 is barely detectable in human colon cancer tissue samples and cell lines, $[Ca^{2+}]_{cyt}$ homeostasis becomes progressively anomalous during colon carcinogenesis result from deficient the SERCA3 expression, which is an early event of colon carcinogenesis [78,79]. Subsequent research found the decrease of SERCA3 expression seems to be linked to enhanced APC/β-catenin/TCF4 signaling and deficient Sp1-like factor-dependent transcription [80]. Therefore, the deficient SERCA3 expression in CRC leads to $[Ca^{2+}]_{cyt}$ homeostasis disorder and involves in colon carcinogenesis. Other evidence uncover inhibition of SERCA induced apoptosis of HCT-116 cells via up-regulated expression of CHOP activated mitochondrial apoptosis pathway, but it did not clarify the specific subtype of SERCA [50].

3.5. Na^+/Ca^{2+} exchanger

The Na^+/Ca^{2+}-exchanger (NCX) is a plasma membrane protein expressed ubiquitously in mammalian cells, which extrudes Ca^{2+} from the cytosol in exchange for extracellular Na^+ that maintains intracellular Ca^{2+} balance under different physiological conditions. But in the pathological conditions, NCX can increase $[Ca^{2+}]_{cyt}$ level. N,N-dimethyl-D-erythro-sphingosine, an inhibitor of PKC and sphingosine kinase (SK), induces $[Ca^{2+}]_{cyt}$ increase via NCX in HCT116 human colon cancer cells [81]. Heat-stress induces $[Ca^{2+}]_{cyt}$ increase in T84 cells through NCX-mediated Ca^{2+} entry [82]. Digoxin and ouabain increase Ca^{2+} influx via NCX, in turn inducing an increase in P-glycoprotein via activating CaMKII and HIF-1α. An increased amount of P-glycoprotein limits the absorption of drugs through epithelial cells, thus inducing resistance to chemotherapy [83].

4. Conclusions

The involvement of Ca^{2+} signaling in CRC is mainly investigated in proliferation, migration and invasion, and apoptosis. Increasing $[Ca^{2+}]_{cyt}$ may function as either tumor promoters or suppressors in CRC, depending on the activation of different downstream signaling molecules. For example, $[Ca^{2+}]_{cyt}$-induced activation of ERK1/2 and/or MAPK signaling pathway promotes proliferation of CRC cells; however, CaSR-mediated $[Ca^{2+}]_{cyt}$ suppresses proliferation of CRC cells likely through β-catenin pathway. It is currently unclear why and how an increase in $[Ca^{2+}]_{cyt}$ activates different downstream signaling pathways to play different or even opposite roles in colon tumorigenesis. In addition, $[Ca^{2+}]_{cyt}$ also mediates cell apoptosis of CRC likely through the ER- or mitochondria-dependent manner. So far, the roles of Ca^{2+} signaling in migration and invasion, autophagy and other progress of CRC have not been well explored.

Since the multiple functions of Ca^{2+} signaling in normal cells and the different ways of its dysregulation in cancer cells, our knowledge on the role of Ca^{2+} signaling in tumorigenesis is still in the early stage. Further studies are urgently needed to elucidate the detailed underlying mechanisms. Targeting Ca^{2+} signaling and Ca^{2+} channels for cancer therapy has become an emerging research area nowadays, and we therefore believe that Ca^{2+} signaling and Ca^{2+} channels are new preventive/therapeutic targets for CRC with potentially extensive clinical significance.

Consent for publication

We have obtained consents to publish this paper from all the participants of this study.

Availability of supporting data

Not applicable.

Funding

This study was supported by research grants the National Natural Science Foundation of China (No. 81660412 to XR; No. 81660099 to JY).

Authors' contributions

X.X.Y and J.L wrote the manuscript. W.X.S, Y.X.H, Q.D, and Q.S.L collect the literature. R.X. primarily revised and finalized manuscript J.Y.X revised the manuscript for clarity and style. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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