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Transient receptor potential (TRP) channels in human colorectal cancer: evidence and perspectives

Theodoros Rizopoulos and Martha Assimakopoulou

Department of Anatomy, Histology and Embryology, School of Medicine, University of Patras, Patras, Greece

Summary. Colorectal cancer (CRC) is one of the leading causes of death in the civilized world. Transient receptor potential channels (TRPs) are a heterogeneous family of cation channels that play an important role in gastrointestinal physiology. TRPs have been linked with carcinogenesis in the colon and their role as potential therapeutic targets and prognostic biomarkers is under investigation.

Key words: Colorectal cancer, TRP channels, Transient receptor potential ion channels

Introduction

Colorectal cancer (CRC) is one of the most diagnosed types of cancer, affecting over one million people per year worldwide. Diet, western lifestyle habits, obesity (Dai et al., 2007; Hong et al., 2012; Ma et al., 2013), genetic factors (Wong and Xie, 2017; Xie et al, 2018), and inflammatory bowel disease (Herszenyi et al., 2015; Keller et al., 2019) seem to contribute to CRC pathogenesis. The key to its treatment is early diagnosis since patients may not manifest any remarkable symptoms. Colonoscopy is an important tool for primary prevention of the leading gastrointestinal tract cancer but many patients, even those with positive family history of colorectal cancer, do not cooperate, which leads to CRC diagnosis at advanced stage with metastasis for a significant number of patients. Therapy includes surgical resection, chemotherapy, radiotherapy, and immunotherapy but the five-year survival rate of patients with advanced CRC with metastasis has not changed dramatically over years and is less than 10% (Siegel et al., 2011).

The dysregulation of intracellular Ca^{2+} homeostasis has been correlated with colon tumorigenesis and with other gastrointestinal tract cancers (Villalobos et al., 2017). Store-operated Calcium entry (SOCE), transient receptor potential (TRP) channels, L-type Ca^{2+} channels, sarco/endoplasmic reticulum calcium-ATPases (SERCAs), and Na^{+}/Ca^{2+} exchanger seem to be involved in cells' proliferation, apoptosis and differentiation but it remains unclear whether the channels functional properties or the cellular Ca^{2+} concentration is the main mediator of tumorigenesis. Thus, SOCE is a novel key player in CRC therapeutic approach (Villalobos et al., 2017; Yang et al., 2019b).

The Transient Receptor Potential family (TRP) of selective and non-selective cation channels consists of TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPA (Ankyrin), TRPP (Polycystin), TRPML (Mucolipin) and TRPN (no mechanoreceptor potential C-NOMPC) channels, serving as cellular sensors for a wide range of stimuli and signal transducers. The last subfamily of channels is not represented in mammals and includes the recently introduced subfamilies of TRPVL (vanilloid-like), TRPS (soromelastin) and TRPF (fungus specific) channels (Pedersen et al., 2005; Himmel and Cox, 2020; Sakaguchia et al., 2020). Structurally, all members of the TRP family are tetramers consisting of subunits which include six putative transmembrane domains, cytosolic N- and C-terminal and a pore between transmembrane domains 5 and 6. Tridimensional diagrams of one member representative of each subfamily, namely TRPC5, TRPV1, TRPM4, TRPA1, TRPP2, and TRPML1 are demonstrated in Fig. 1 (Liao et al., 2013; Paulsen et al., 2015; Schmiege et al., 2017; Hulse et al. 2018; Duan et al., 2018, 2019).

Members of mammalian TRP subfamilies have been investigated in numerous diseases (channelopathies) (Kaneko and Szallasi, 2014; Dietrich, 2019) e.g. neurodegenerative (Nilius et al., 2005), cardiovascular (Inoue et al., 2019), and metabolic diseases (Zhu et al., 2011; Vasconcelos et al., 2016) whereas there is growing evidence supporting their role in carcinogenesis (Prevarskaya et al., 2007; Bernardini et al., 2015; Park et

Corresponding Author: Martha Assimakopoulou, PhD, Department of Anatomy, Histology and Embryology, School of Medicine, University of Patras, Biomedical Sciences Research Building, 1 Asklipiou, 26504 Patras, Greece. e-mail: massim@upatras.gr

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al., 2016; Shapovalov et al., 2016; Canales et al., 2019). In this context, some TRP members may be promising targets for novel chemotherapeutic drugs as they are involved in processes like tumor invasion, migration, and angiogenesis (Gkika and Prevarskaya, 2009). Novel chemotherapeutics targeting TRPs have already been tested in gliomas and prostate adenocarcinomas, breast, small cell lung tumors and in bladder cancer with promising results, while some TRPs, such as TRPP1 have predictive and prognostic significance for kidney cancer (Lee et al., 2011; Santoni and Farfariello, 2011; Vay et al., 2012; Gautier et al., 2014; Leanza et al., 2016; Bishnoi et al., 2018; Santoni et al., 2019).

TRPs participate in numerous gastrointestinal tract functions such as taste, mucosal function and homeostasis, intestinal motility, visceral sensation and visceral hypersensitivity, while changes in TRP levels have been associated with a variety of gastrointestinal tract disorders, such as gastro-esophageal reflux disease, dyspepsia, irritable bowel syndrome (Boesmans et al., 2011; Holzer, 2011), inflammatory bowel disease (Zielinska et al., 2015; Rizopoulos et al., 2018) and several types of tumors including CRC (see reviews Alaimo and Rubert, 2019; Anderson et al., 2019; Yang et al., 2019b; Stokłosa et al., 2020). Thus, new pharmacologic strategies targeting TRP dysfunction have been proposed for gastrointestinal tract disorders (Vay et al., 2012; Alvarez-Berdugo et al., 2018; Bishnoi et al., 2018).

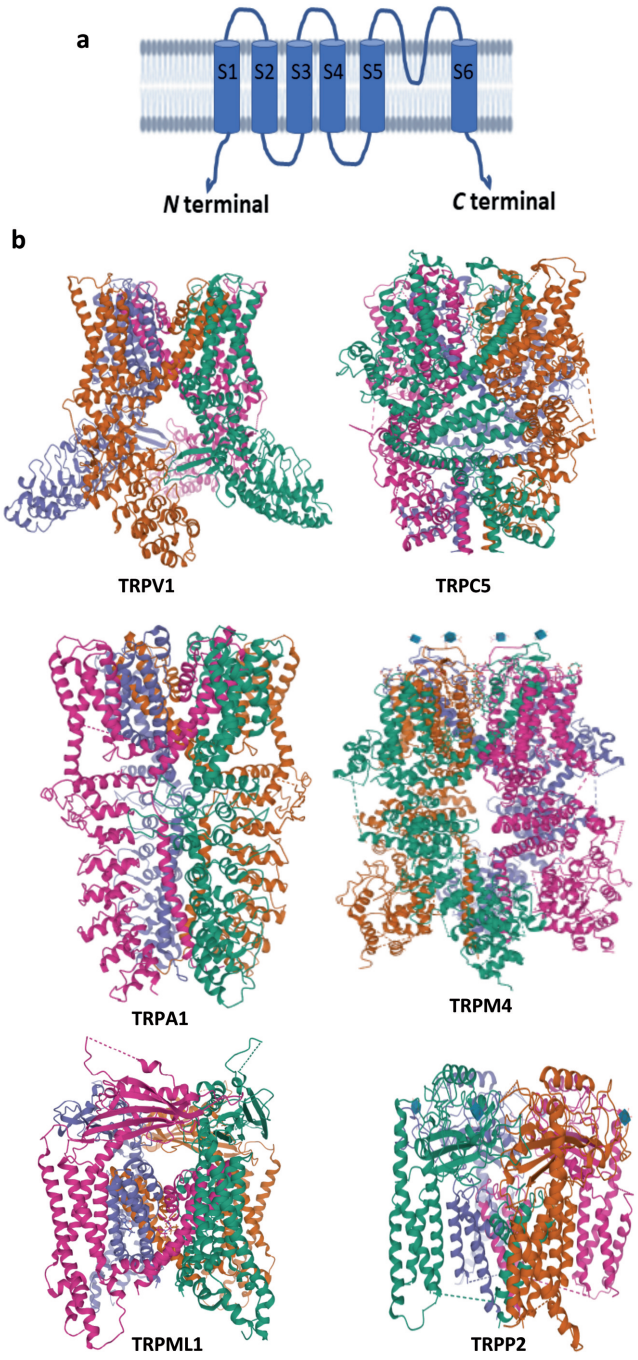

Fig. 1. a. Diagram of TRP channels subunit containing six transmembrane segments (S1–S6), a hydrophobic pore loop linking transmembrane S5 and S6, and large cytoplasmic N- and C-terminals. Four such subunits consist of TRP channels. Ankyrin domains (number variable) are present in the N-terminal region of TRPV, TRPA, TRPC subfamilies. The TRP domain (well-conserved region) and protein kinase domain are present in the C terminus region. **b.** Ribbon representation of the structure in perspective horizontal to the plane of the membrane, with four subunits colored differently of TRP channels exemplified by the TRPV1 atomic model (PDB 3J5Q), TRPM4 atomic model (PDB 6BWI), TRPML1 atomic model (PDB 5WJ9), TRPC5 atomic model (PDB 6AEI), TRPA1 atomic model (PDB 3J9P), and TRPP2 atomic model (PDB 6DU8) (Liao et al., 2013; Paulsen et al., 2015; Schmiege et al., 2017; Hulse et al., 2018; Duan et al., 2018, 2019).

TRPC channels (TRPCs)

TRPCs is a group of calcium-permeable non-selective cation channels which exhibit the highest protein sequence similarity to the Drosophila melanogaster TRP channels and consists of seven members that are divided into four subgroups (TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7) based on their amino acid sequences and functional similarities. Forming homo- and heteromeric complexes, TRPCs contribute to a broad spectrum of cellular functions like cell proliferation and migration, synaptic plasticity and neurite extension, through regulation of membrane potential and calcium signaling and "sensing" different environmental cues, and seem to regulate various physiological processes such as neural development, vascular smooth cell tone, hormone and neurotransmitter secretion, kidney function and immune function, as they participate in mast cells degranulation and T-cell activation (Freichel et al, 2004; Nilius and Owsianik, 2011; Chen et al., 2020; Wang et al., 2020). Differences

in the localization and regulation of TRPCs result from their interaction with regulatory and scaffolding proteins (Ambudkar et al., 2006). The role of TRPCs and their interacting molecular partners in the biology of cancer, particularly in regulating migration and invasion and thus in the process of metastasis has been extensively investigated (Asghar and Törnquist, 2020).

TRPCs and intestine

TRPCs have been detected in intestinal neurons, smooth muscle, and interstitial cells of Cajal implying their involvement in muscle excitability and intestinal motility (Walker et al., 2002; Tsvilovsky et al., 2009; Boesmans et al., 2011; Dwyer et al., 2011). According to the study of Pérez-Riesgo et al. (2017), human colonic cells express only TRPC1 channels. Additionally, experimental data has shown that induced TRPC1 expression increases apoptosis of intestinal epithelium, through inhibition of NF-κB activation (Marasa et al., 2008) and TRPC1 may be involved in intestinal epithelial restitution as it seems to regulate capacitive and intracellular cytosolic Ca^{2+} entry, and cell migration after wounding (Rao et al., 2006). The role of TRPCs in inflammatory bowel disease has not been elucidated yet but there is data indicating that TRPC6 upregulation in myofibroblasts may promote fiber formation in Crohn's disease patients (Kurahara et al., 2015; Inoue, 2019).

TRPCs and colorectal cancer

Colon cancer cells display enhanced store operated Ca^{2+} entry (SOCE) compared with their non-cancer counterparts due to an abnormal expression of SOCE molecular players including TRPC1 channels (Villalobos et al., 2017, 2019). Furthermore, there is evidence that TRPC1 may contribute to the hallmarks of various types of cancer (Elzamzamy et al., 2020). Indeed, TRPC1 expression has been found to be significantly enhanced in CRC patients (Pérez-Riesgo et al., 2017; Ibrahim et al., 2019) which has been associated with poor prognosis (Ibrahim et al., 2019). It has also been reported that a reciprocal shift in TRPC1 and stromal interaction molecule 2 (STIM2) contributes to Ca^{2+} remodeling and cancer progression in colon (Sobradillo et al., 2014). In accordance with these findings, further results indicate that a decrease of TRPC1 expression inhibits migration of the HT-116 colon cancer cells towards EGFR deactivation (Guéguinou et al., 2016) implying a novel therapeutic strategy for metastatic CRC.

As regards the other members of the TRPC family, through a study of a large cohort of CRC patients, high expression of TRPC5 channels was associated with tumor grade and poorer disease-free and overall survival (Chen et al., 2017a). Experimental data has shown that overexpression of TRC5 induces the epithelial-to-mesenchymal transition (EMT) through the HIF-1α-Twist signaling pathway and promotes tumor metastasis in colon cancer (Chen et al., 2017b). Notably, patients with advanced CRC high expression of TRPC5 displayed chemoresistance which was GLUT1 dependent (Wang et al., 2017, 2018). Additionally, TRPC5 mRNA overproduction has been correlated with 5-Fluoruracil chemo-resistance in human CRC cells, via glucose regulation, while TRPC5 suppression ends in a remarkable reversal of 5- Fluoruracil resistance cancer cells (Wang et al., 2015). On the other hand, Sozucan et al. (2015) have shown lower levels of TRPC6 mRNA in CRC patients compared with controls. Added to TRPC properties in CRC is that 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol (20-GPPD), via TRPC activation, reduces tumor burden addressing interest in TRPCs to their usage as chemotherapeutic targets (Hwang et al., 2013). Furthermore, as aspirin and other NSAIDs have been reported to prevent CRC acting on remodeled Ca^{2+} entry pathways through TRPCs, the role of these channels in the pathophysiology of the gastrointestinal tract may be further clarified (Villalobos et al., 2017, 2019).

TRPV channels (TRPVs)

TRPVs are a well-studied subfamily of TRPs. It consists of six non-selective calcium channels forming homo- or hetero-tetramers, TRPV1 to TRPV6 which are mostly located on cells plasma membrane. Besides, TRPV1-4 channels were shown to be expressed in the endoplasmic reticulum and their modulation by activators and/or inhibitors was demonstrated to be crucial for intracellular signaling (Haustrate et al., 2020). Some of these channels are named also thermo ion channels as they are expressed in primary sensory nerve terminals where they provide information about thermal changes in the environment (Vay et al., 2012). Furthermore, TRPVs serve as sensors of chemical, osmotic, and mechanical stimuli (Liedtke and Kim, 2005). Apart from the peripheral nerve terminals, expression of TRPVs is detected in neurons of PNS ganglia and brain (TRPV1-4), skin (TRPV1, TRPV3, TRPV4), pancreas (TRPV1, TRPV5, TRPV6), bladder (TRPV1), gastro-intestinal tract (TRPV1-6), spleen, mast cells, smooth, cardiac and skeletal muscle cells (TRPV2), tongue (TRPV3), testis, (TRPV3, TRPV4, TRPV6), kidney (TRPV4, TRPV5, TRPV6), heart, liver, osteoblasts, endothelium, urothelium, and cochlea (TRPV4), as well as prostate, brain and salivary gland (TRPV5, TRPV6) (Lee and Caterina, 2005; Nilius and Owsianik, 2011) and T cells (TRPV1,4), where an immunoregulatory role for these channels has been elucidated by Majhi et al. (2015). TRPV1 dysfunction has been correlated with various pathophysiological conditions and disorders such as inflammatory pain, thermal hyperalgesia, hippocampal long-term depression, diabetes, obesity, hyperactive bladder syndromes, hypertension, hypothermia and, renal excretory function (Liedtke and Kim, 2005; Nilius et al., 2005; Vay et al., 2012; Bujak et al., 2019). TRPV2 alterations have been investigated in muscular dystrophy

Duchenne, cardiac hypertrophy, and myocarditis (Zanou, 2009; Iwata and Matsumara, 2019) whereas skin disorders have been related to TRPV3 dysfunction (Nilius et al., 2014). Mutations in the TRPV4 gene are causative for several human diseases, which affect the skeletal and the peripheral nervous system (Nilius and Voets, 2013) while glomerular acidosis, osteoporosis and osteomalakia have been correlated with TRPV5 and TRPV6 levels of expression (Nilius et al., 2005) since these channels are implicated in bone metabolism and osteoclast function (van Goor et al., 2017).

TRPVs and intestine

TRPVs are expressed in many parts of the gastrointestinal tract, serving a broad spectrum of functions from taste and fluid secretion to Ca^{2+} absorption (Holzer, 2011). TRPV1, 2, 4 have been detected in visceral afferents. Intestinal epithelium demonstrates expression of all members of TRPVs. TRPV4 is mainly localized in the superficial mucosal cells. TRPV1,2 channels are also expressed by subtypes of enteric neurons in both the myenteric and submucosal plexus and TRPV3 is detected also in muscularis mucosa (Boesmans et al., 2011; Rizopoulos et al., 2018). Previous studies have correlated increased TRPV1 expression in sensory fibers with visceral hypersensitivity and hyperalgesia and neurogenic inflammation in inflamed bowel (Dömötör et al., 2005; Yu et al., 2010; Vinuesa et al., 2012; Vermeulen et al., 2013; Csekő et al., 2019). TRPV2 seems to be involved in colitis attenuation (Issa et al., 2014) while TRPV4 exerts a pro-inflammatory role in the intestine (Vergnolle, 2014). TRPV4 expression is significantly increased in the colonic epithelium of ulcerative colitis (UC) patients compared to controls (Rizopoulos et al., 2018) and a very recent gene expression study revealed that TRPV4 is higher in colonic tissue from patients with remission UC compared with active UC patients (Toledo Mauriño et al., 2020). In the same study, TRPV5 was demonstrated to have significantly higher mRNA levels in the control group compared with active UC patients whereas TRPV6 was significantly higher in the colonic tissue from patients with active UC compared with the control group (Toledo Mauriño et al., 2020).

TRPVs and Colorectal Cancer

Increasing evidence suggests that TRPVs are implicated in the pathogenesis of CRC. Hou et al. (2019) report that TRPV1 serves as a tumor suppressor in CRC. Particularly, TRPV1 expression was found to be significantly decreased in CRC tissues, compared with CRC-adjacent tissues and normal tissues. However, other studies showed no significant difference of TRPV1 expression between CRC and control tissues (Sozucan et al., 2015; Pérez-Riesgo et al., 2017). Experimental data have demonstrated inhibition of CRC growth and induced apoptosis by activating P53 in HCT116 cells treated with TRVP1 agonist capsaicin (Jin et al., 2014). In a recent study, the expression of fibulin-5, a multifunctional extracellular matrix (ECM) protein which regulates metastasis and invasion in many malignant tumors and contributes to colorectal cancer cell apoptosis via the ROS/MAPKand Akt signal pathways by downregulating TRPV1 was detected in lower levels in CRC tissues compared with peritumoral tissues (Chen et al., 2019). Additionally, capsazepine, a synthetic analogue of capsaicin with properties of TRPV1 antagonism has been proposed as a novel pharmacological tool for various tumors including CRC (Yang et al., 2019a). Indeed, Sung et al., 2012 have shown that capsazepine sensitizes colorectal cancer cells to apoptosis by TRAIL through ROS-JNK-CHOP-mediated upregulation of death receptors. There is little information regarding expression levels of TRPV2 in CRC. mRNA levels of TRPV3 were revealed to be lower in CRC tissues as compared with normal tissues by Sozucan et al. (2015) whereas no difference was detected by Pérez-Riesgo et al. (2017).

TRPV4 is upregulated in colon cancer and is associated with poor patient prognosis, and TRPV4 silencing induces apoptosis and autophagy of colon cancer cells and suppresses human colon cancer development via activation of the PTEN pathway (Liu et al., 2019). Interestingly, recent data from a mouse model for colitis suggests that TRPV4, expressed in both vascular endothelial cells and bone marrow-derived macrophages, plays a significant role in colitis-associated tumorigenesis (Matsumoto et al., 2020). TRPV5 in CRC has been demonstrated to have lesser gene expression as compared with normal tissues (Sozucan et al., 2015). Finally, TRPV6 expression is significantly enhanced in CRC compared to controls (Pérez-Riesgo et al., 2017). It is worthy of mention that TRPV6 correlates with the pathogenesis of many tumors (Lehen'kyi et al., 2012). TRPV6 mutants, S692D and T702D could predispose to CRC, whereas the S824D TRPV6 mutant has been associated with increased invasion properties of CRC (Arbabian et al., 2020). Overexpression of TRPV6 was associated with early-stage colon cancer, and inhibition of TRPV6 expression, by small interfering RNA, inhibited proliferation, and induced apoptosis in colon carcinoma cells (Peleg et al., 2010). It has also been reported that the suppression of TRPV6 activity by a high calcium diet could have protective effects against CRC (Peleg et al., 2010). Interestingly, data from gastric cancer cells shows that TRPV6, rather than TRPV1, mediates capsaicin-induced apoptosis in these cells which is dependent on an abundance of TRPV6, suggesting that capsaicin may be a promising dietary candidate for cancer chemoprevention (Chow et al., 2007). Considering that TRPV6 is overexpressed in CRC further studies would elucidate this hypothesis. Recently, it has been found that drug-like dietary vanilloids induce anticancer activity through proliferation inhibition and regulation of bcl-related apoptotic proteins introducing the

chemopreventive properties of foods that contain vanilloids (Mai et al., 2018).

TRPM channels (TRPMs)

TRPMs consist the largest TRP subfamily, divided phylogenetically into four subgroups, TRPM1/3, TRPM6/7, TRPM4/5, and TRPM2/8. The TRPM subfamily includes members with completely diverse properties, forming homo- or hetero- meric channels (Huang et al., 2020). The diverse functional properties of these channels have a profound effect on the regulation of ion homoeostasis by mediating direct influx of Ca^{2+}, controlling Mg^{2+} entry, and determining the potential of the cell membrane (Fleig and Penner, 2004). TRPMs demonstrate a polymodal nature: they are regulated by stimuli including voltage, temperature, and the binding of ions, lipids, or other ligands. Additionally, TRPM2, TRPM4 and TRPM7, are modulated by oxidative stress (Simon et al., 2013) whereas TRPM2 and TRPM7 are implicated in cell death responses under stress (McNulty and Fonfria, 2005). TRPMs demonstrate a wide distribution in cells and organs (Nilius and Owsianik, 2011) but the tissues demonstrating highest expression for individual family members are brain (TRPM1,2,3,6), bone marrow (TRPM2), pituitary (TRPM3,7), intestine (TRPM4,5,6), prostate (TRPM4,5,8), pancreas (TRPM5), heart, bone, and adipose tissue (TRPM7), and liver (TRPM8) (Fonfria et al., 2006). The growing interest in these channels is raised due to their pivotal roles in diabetes, smooth muscle cell regulation, immunological responses, and cancer (Farooqi et al., 2011; Tabur et al., 2015; Trapani and Wolf, 2019; Wong et al., 2019). TRPMs have been proposed as potential therapeutic targets against pro-inflammatory diseases (Zierler et al., 2017), vascular diseases (Zholos, 2010) and cancer (Santoni and Farfariello, 2011; Gautier et al., 2014).

TRPMs and intestine

TRPM expression and function have been described in the gastrointestinal tract. Particularly, TRPM4 channels are localized in mast cells and modulate their migration and degranulation. TRPM5 channels have been detected in enteroendocrine cells and brush cells and are responsible for nutrient sensing and release of endogenous opioids. TRPM6 and TRPM7 are important for Mg^{2+} absorption across intestinal epithelial cells whereas TRPM7 was suggested to be also involved in the pacemaker current of interstitial cells of Cajal (Holzer, 2011). Additionally, TRPM6 seems to be important for mucosal integrity since the reduction of TRPM6 expression is alleviated with Mg^{2+} supplementation which reduces the inflammatory status and fastens the mucosal healing in an experimental model of colitis (Luongo et al., 2018; Trapani et al., 2018). Apart from epithelial cells, TRPM7 channels are found in circular muscle. TRPM8 channels are expressed in primary extrinsic afferent nerves and participate in cold and menthol-induced sensory transduction. TRPM8 expression has been found to be increased in biopsies from IBD patients and has been correlated with higher TNFα levels. Added to those, TRPM2 channels have been found to participate in IBD development in a mouse model of colitis (see review papers Boesmans et al., 2011; Zielinska et al., 2015; Zierler et al., 2017) while TRPM2 levels were higher in peripheral blood mononuclear cells of ulcerative colitis and Crohn disease patients (Morita et al., 2020).

TRPMs and colorectal cancer

Accumulating evidence indicates that TRPMs may be oncogenes involved in the regulation of cancer cell growth, proliferation, autophagy, invasion, and EMT (Wong et al., 2019). Analysis of tumor tissue microarrays from 379 CRC patients has shown that high TRPM4 protein expression was associated with unfavorable tumor features characteristic for EMT and infiltrative growth patterns while results from cancer cell cultures indicate the pivotal role of TRPM4 in cancer cells' invasive properties. Additionally, TRPM4 was found to be highly expressed in tumor buds (Kappel et al., 2019). However, data from mRNA analysis are contradictory. In one study by Sozucan et al. (2015) mRNA levels of TRPM4 in 93 patients were significantly lower in CRC tissues compared to normal tissues whereas in another study by Pérez-Riesgo et al., (2017), using transcriptomic analyses, TRPM4 levels were equal between normal and CRC cells. In the same study, TRPM5 levels were lower in CRC compared to normal tissue samples (Pérez-Riesgo et al., 2017). Xie et al. (2018) identified 10 tumorigenesis-related genes for CRC in a microarray dataset containing 566 colon cancer samples and 19 non tumoral colorectal mucosae. Among them, TRPM6 was confirmed to be downregulated in 16 (80%) of 20 colon cancer tissues using quantitative polymerase chain reaction (qPCR) technology whereas high expression of TRPM6 was indicative of a prolonged overall survival (OS) in CRC patients. Since TRPM6 along with TRPM7 are the unique ion channels that mediate Mg^{2+} homeostasis, the above data indicate that Mg^{2+} intake may be associated with CRC pathogenesis. Indeed, Dai et al. (2007) have found that total magnesium consumption was linked to a significantly lower risk of colorectal adenoma, particularly in those subjects with a low Ca: Mg intake and TRPM7 polymorphisms are related with enhanced risk for adenomas. However, Huang et al. (2017) have shown that TRPM7 drives colon cancer cell proliferation in human HT-29 cells independently of systemic Mg^{2+} status. Su et al. (2019) have reported a markedly increased TRPM7 expression in CRC tissues which was associated with deeper tumor infiltration, positive lymph node metastasis, distant metastasis, and advanced clinical stage. Importantly, downregulated TRPM7 in vitro suppressed CRC cell proliferation, migration, and

invasion, reversed EMT, accompanied by down-regulation of N-cadherin and upregulation of E-cadherin, triggered cell cycle arrest at the G0/G1 phase, reduced the S phase, and promoted apoptosis. In a small scale study comparing TRPM6 and TRPM7 expression between human IBD-related and sporadic colorectal cancer with the adjacent non-neoplastic tissue the levels of TRPM6 and TRPM7 in both IBD and non-IBD patients were increased in malignant tissues without any statistically significant difference between IBD- and non IBD- tissue samples, although only TRPM7 expression was positively correlated with tumor grade (Pugliese et al., 2020). On the contrary, similar levels in normal colonic and CRC cells for TRPM7 have been reported by Pérez-Riesgo et al. (2017). Regarding TRPM8 there is evidence supporting its role in initiation and progression of tumors (Liu et al., 2016) including CRC, where a significant increase in its expression was found compared to normal tissues (Tsavaler et al., 2001). Finally, Sozucan et al. (2015) found similar levels for TRPM1 expression in cancerous and normal intestinal cells. As for TRPM3, an increased rate of mutated non-coding regions has been related to higher risk for CRC metastasis (Ishaque et al., 2018).

Referring to TRPMs as novel chemotherapeutic targets it has been published that the apoptotic effects of cyclophosphamide, 5-fluorouracil and leucoverin on human colon cancer cell lines Caco-2 were directly related to TRPM2 channels and that TRPM2 channels play an important role in the whole molecular pathway of apoptosis, leading to increased intracellular Ca^{2+} levels and mitochondrial depolarization (Guler and Ovey, 2018, 2020). Two different studies revealed that TRPM6 and TRPM7 levels are lower in LoVo resistant to doxorubicin cells than in LoVo sensitive to doxorubicin cells and this difference accounts for the different proliferation rate of sensitive and resistant colon carcinoma cells (Castiglioni et al., 2015; Cazzaniga et al., 2017). Thus, LoVo cell drug resistance is associated with alterations of magnesium homeostasis through modulation of TRPM7. Therefore, TRPM7 expression may be an additional undisclosed player in chemoresistance of CRC. Interestingly, cannabigerol (CBG), a non-psychotropic cannabis-derived cannabinoid with properties of TRPM8 blocker and TRPA1, TRPV1 and TRPV2 agonist, which inhibits CRC cell growth, is not effective in TRPM8 silenced cancer cells (Borrelli et al., 2014).

TRPA channels

The transient receptor potential Ankyrin 1 channel (TRPA1), the single member of the TRPA subfamily in humans, was initially identified as a temperature activated TRP channel but it is now known to be also a stress sensor (Himmel and Cox, 2020). TRPA1 is found in hair cells, sensory dorsal root and trigeminal ganglia neurons, fibroblasts, periodontal ligament and epithelial cells of the intestine, lungs, and urinary bladder (Nilius and Owsianik, 2011; Tsutsumi et al., 2013). An increased activity of TRPA1 channel has been linked with neurogenic inflammation and pain, thus TRPA1 is now considered as one of the targets for developing new anti-inflammatory and analgesic drugs (Logashina et al., 2019). Additionally, there is data indicating that TRPA1 antagonism could alleviate anxiety and depression (de Moura et al., 2014) but great interest in this channel was raised by its possible contribution in chemotherapy-induced peripheral neuropathy prevention (Trevisan et al., 2013). TRPA1 gene polymorphisms (SNPs) may augment the possibility of childhood asthma development as TRPA1 participates in the pathogenesis of airway constriction (Gallo et al., 2017).

TRPA and intestine

TRPA1 is expressed in epithelial cells of the small intestine and colon, muscularis externa and colonic myenteric neurons. Notably, TRPA1 is highly expressed in enterochromaffin (EC) cells, which are 5-hydroxytryptamine (5-HT)-releasing cells (Holzer, 2011). There is data showing that TRPA1 is implicated in intestinal inflammation and its role in colitis has been investigated in multiple ways (Boesmans et al., 2011). TRPV1 and TRPA1 levels were found to be increased in T-cells in the colon of patients with IBD, and TRPA1 silencing had protective effects against T-cell mediated colitis (Bertin et al., 2017). Activation and sensitization of TRPA1 and release of substance P induced and maintained colitis in mice (Engel et al., 2011). Furthermore, exposing rats to water avoidance resulted in upregulation of TRPV1 and TRPA1 in the colonic afferent dorsal root ganglia and stress-induced visceral hyperalgesia (Yu et al., 2010). It is well known that in the gastrointestinal tract TRPA1 is often co-expressed with TRPV1 in capsaicin-sensitive extrinsic sensory nerves, especially in the primary sensory neurons of the dorsal root ganglia, providing potential therapeutic value of TRPV1 and TRPA1 antagonists in colitis and visceral hypersensitivity (Vermeulen et al., 2013; Csekő et al., 2019). In addition to its role in inflammation, TRPA1 has been demonstrated to protect against intestinal fibrosis through its activation with steroids and pirfenidone in a mouse model of colitis (Kurahara et al., 2017) whereas TRPA1 agonists could also be helpful for patients with constipation and abdominal pain (Kojima et al., 2014).

TRPA and colorectal cancer

Two studies have investigated TRPA1 expression in human colorectal cancer. In one study, TRPA1 is expressed in normal colonic cells but not in colon cancer cells (Pérez-Riesgo et al., 2017). In the other study, there is no discrimination between normal and colon cancer regarding TRPA1 expression (Ibrahim et al., 2019).

TRPP channels (TRPPs)

The polycystine family of transient receptor potential channels, named by their causative role in polycystic kidney disease (Qamar et al., 2007), is formed by a group of highly conserved channels serving cell mechanosensation and follicle maturation and differentiation, usually located in intracellular membranes (Himmel and Cox, 2020). It is formed by TRPP1 (polycystin-1, PC1), TRPP2 (polycystin-2, PC2), which are widely expressed in human tissues as well as by TRPP3 and TRPP5, which are incompletely characterized (Pedersen et al., 2005). TRPP1 and TRPP2 are physically coupled and act as a signaling complex which is necessary for localization of TRPP2 to the plasma membrane. TRPP2 is a Ca^{2+} regulated, non-selective channel, which was identified to be mutated in autosomal dominant polycystic disease (Arif Pavel et al., 2016). It is localized in motile and primary cilia of renal epithelium and multiple subcellular compartments including the endoplasmic reticulum, Golgi apparatus, mitotic spindles, and the plasma membrane (Giamarchi et al., 2006). TRPP1 is expressed in renal tubular epithelial cells as well as a variety of other cell types during development and growth but is absent or weakly expressed in adult kidney and liver (Griffin et al., 1996). TRPP1 participates in cell proliferation, sperm fertilization and mating behavior in laboratory animals. TRPP3 and TRPP5 are Ca^{2+} permeable channels, participating in retinal and hair cell development and fertilization, respectively (Pedersen et al., 2005). Besides their role in polycystic kidney disease, alterations in expression profile of TRPP1 and TRPP2 may induce altered mechanotransduction which has been implicated in the pathogenesis of various diseases like cancer, cardiovascular defects, bone loss, and deformations, as well as inflammatory diseases (Gargalionis et al., 2019).

TRPPs and intestine

TRPP1 and TRPP2 are localized in the cytoplasm of epithelial cells of intestine (Pérez-Riesgo et al., 2017). Particularly, TRPP1 is implicated in the establishment of cell-cell junctions in absorptive intestinal epithelial cells and exploits the microtubule-based machinery to be transported to the plasma membrane (Basora et al., 2010). TRPP3 is not expressed in human colon (Pérez-Riesgo et al., 2017). Through research in databases, no evidence exists referring to TRPP5 expression in human intestine.

TRPPs and Colorectal Cancer

Recent knowledge implicates TRPP1 and TRPP2 in CRC pathogenesis. Gargalionis et al. (2015) found that TRPP1 and TRPP2 overexpression is associated with aggressive phenotypes in colorectal cancer and poor prognosis of the patients. Moreover, experimental data in colorectal (HT29) cancer cell lines have shown that TRPP1 regulates signaling pathways that are constitutively activated in cancer such as mTOR and JAK pathways (Papavassiliou et al., 2019). In contrast, expression of TRPP1 in CRC tissues was found to the same extent with normal colon by Pérez-Riesgo et al., 2017. In the same study, TRPP2 was not expressed in colon cancer cells and TRPP3 was absent from both normal and colon cancer cells. Nevertheless, TRPP1 and TRPP2 are considered as novel biomarkers and putative targets of selective treatment in CRC cells (Gargalionis et al., 2018).

TRPML channels (TRPMLs)

TRPML1, TRPML2 and TRPML3 form the mucolipin family of transient receptor potential channels which participate in pH control, membrane trafficking, signal transduction, cellular autophagy, exocytosis, and vesicular transport (Cheng et al., 2010). TRPML1 is widely expressed and appears to reside in late endosomes/lysosomes and is found in brain, adrenal gland, lung, heart, bladder, placenta, thymus, kidney, liver and spleen and immune cells, with a prominent role in lymphocyte regulation (Schmiege et al., 2018). TRPML1 channels, which homo- or multimerize, were the first members of the subfamily discovered when loss of functional mutations in the TRPML gene were identified as responsible for a neurodegenerative disorder, mucolipidosis type IV, which is characterized by mental retardation, retinal degeneration, iron deficiency, achlorhydria and gastrointestinal abnormalities. (Sun et al., 2000; Curcio-Morelli et al., 2010). TRPML1 is also implicated in immune response (Spix et al., 2020). TRPML3 is localized in vesicle rich region of cochlea cells, early endosomes, and it is distributed in organs of the endocrine system, eye, thymus, kidney, spleen, intestine and lungs (Cheng et al., 2010; Grimm et al., 2014). TRPML2, which is expressed similarly to TRPML3 particularly in endosomes and lysosomes, has been detected in immune cells, thymus, heart, kidney, and spleen (Quian and Noben-Trauth, 2005; Spix et al., 2020). TRPML2 levels seem to be regulated by TRPML1 in lymphoid organs and kidney (Samie et al., 2009).

TRPMLs and intestine

Expression of TRPML1 and TRPML2 has been reported in colonic cells (Pérez-Riesgo et al., 2017).

TRPMLs and Colorectal Cancer

Although there is evidence implicating TRPMLs in cancer (Santoni et al., 2020), little information regarding the role of TRPMLs in CRC is provided. In the single published study, the first two members of TRPML, specifically TRPML1 and TRPML2, are significantly decreased in CRC cells compared with normal colon according to a transcriptomic analysis (Pérez-Riesgo et al., 2017).

Conclusions

CRC is a leading cause of death in the civilized world and the need for new diagnostic and prognostic markers is continuous. TRPs could be possibly used as novel biomarkers and may be promising therapeutic targets for CRC along with chemotherapeutic agents. For example, capsaicin combined with sorafenib in human hepatocellular carcinoma cells had better results on cell growth than either drug alone (Bort et al., 2017) indicating that chemotherapy along with agonists of TRPs have synergistic effects against tumorigenesis. Additionally, as some TRP channels are dietary players, chemoprevention of CRC through specific compounds of food e.g. vanilloids could be a novel era of investigation. The fact that the vast majority of TRPs are expressed in colonic cells and much more these channels display multiple functions and participate in several signal transduction pathways that are dysregulated in CRC, makes the issue more complex, which is poorly understood and thus, further study is required.

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