Cell Calcium 82 (2019) 102053

Contents lists available at ScienceDirect

Cell Calcium

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

Review

TRP channels in gastric cancer: New hopes and clinical perspectives

Andra M. Sterea[a], Emmanuel E. Egom[b], Yassine El Hiani[a,*]

[a] Departments of Physiology & Biophysics, Dalhousie University, Halifax, Nova Scotia, Canada
[b] Egom Clinical & Translational Research Services Ltd, Halifax, Nova Scotia, Canada

ARTICLE INFO

Keywords:
Gastric cancer
TRPC6
TRPM2
TRPM7
TRPV6
Therapy

ABSTRACT

Gastric cancer is a multifactorial disease associated with a combination of and environmental factors. Each year, one million new gastric cancer cases are diagnosed worldwide and two-thirds end up losing the battle with this devastating disease. Currently, surgery represents the only effective treatment option for patients with early stage tumors. However, the asymptomatic phenotype of this disease during the early stages poses as a significant limiting factor to diagnosis and often renders treatments ineffective. To address these issues, scientists are focusing on personalized medicine and discovering new ways to treat cancer patients. Emerging therapeutic options include the transient receptor potential (TRP) channels. Since their discovery, TRP channels have been shown to contribute significantly to the pathophysiology of various cancers, including gastric cancer. This review will summarize the current knowledge about gastric cancer and provide a synopsis of recent advancements on the role and involvement of TRP channels in gastric cancer as well as a discussion of the benefits of targeting TPR channel in the clinical management of gastric cancer.

1. Epidemiology

In 2018, the Global Cancer Statistics reported 18.1 million new cancer cases and 9.6 million cancer-related deaths of which gastric cancer represents 5.5% and 8.3%, respectively [1]. Interestingly, the incidence of gastric cancer shows a wide geographical distribution with the highest rates found in Eastern Asia, Eastern Europe, and Southern America, and lowest rates in Northern America, Northern Europe, Australia and New Zealand [2–5]. Obvious clustering of gastric cancer incidence also exists within individual countries [6–9]. For example, in China, the northern populations show higher incidence and mortality rates than the southern populations [10–13] which indicates the presences of an environmental component that contributes, at least in part, to the observed regional variation of gastric cancer occurrence. This is consistent with migration studies that have reported a decrease in the incidence/mortality of gastric cancer among second-generation Chinese and Japanese migrants to the US (the overall gastric cancer incidence of Asian migrants remains higher in the host population) [14,15]. In addition, this variation also exists within genders with 683,754 of the new gastric cancer cases being diagnosed in males and 349,947 in females (equating to 2/3 of all gastric cancer occurring in the male population) [16,17]. This difference was highlighted in an age-standardized study conducted in Korea where the incidence rate of gastric cancer in men was 32.1 per 100 000 compared to 13.2 per 100 000 in females [1,18,19]. However, despite the unsettling statistics, a steady decline in the incidence of gastric cancer has been observed over the last few decades in both, developed and developing regions. A 2.3% annual decrease in incidence rates is predicted until 2030 which is likely a result of improved hygiene and food conservation methods (for specific risk factor see Etiology section) [20–22].

2. Etiology

Cancer has long been known as a disease of many causes, some that have yet to be uncovered and some that have been established as the drivers of carcinogenesis. Today, there is a consensus that *Helicobacter pylori* (*H. pylori*) is the most important risk factor that contributes to the development of the majority of gastric cancers [23–26]. It is believed that chronic inflammation induced by *H. pylori* facilitates the epigenetic alteration of tumor suppressors genes and paves the way for uncontrolled cell proliferation, apoptosis evasion and cell invasion [27,28]. In addition, *H. pylori* infections can often result in the development of gastritis and polys [29–32] which can ultimately lead to gastric carcinogenesis [33–36]. Furthermore, the etiology of gastric cancer has also been linked with another pathogen known as the Epstein–Barr virus (EBV) [37–39]. In contrast to *H. pylori* which can be

* Corresponding author at: Dalhousie University, Department of Physiology and Biophysics, 5G, Sir Charles Tupper Building, 5850 College street, Halifax, Nova Scotia, B3H 1 × 5, Canada.
E-mail address: yassine.elhiani@dal.ca (Y. El Hiani).

https://doi.org/10.1016/j.ceca.2019.06.007
Received 1 April 2019; Received in revised form 14 June 2019; Accepted 14 June 2019
Available online 17 June 2019

found in normal and malignant gastric cells, increasing evidence shows that the EBV pathogen is found only in gastric cancer cells. However, the mechanism of action behind the ability of EBV to cause gastric cancer remains largely unknown [40].

Despite the contribution of extracellular microbes to the pathogenesis of gastric cancer, studies have provided enough evidence to suggest a "sweet and salty" relationship between dietary consumption and the incidence of gastric cancer [41–43]. The latest estimate of the World Cancer Research Fund International indicated that the daily intake of 5 g of dietary salt increased the relative risk of gastric cancer by 12% [44]. The proposed mechanism behind this phenomenon is the potential role that salt plays in mediating *H. pylori* colonization and maintaining the subsequent chronic inflammation [45–47]. On the other hand, studies have also shown that the daily consumption of 100 g of fruit lowered the risk of developing gastric cancer by 5% [22,48,49]. Health conscious dietary choices have always been regarded as the best medicine for many illnesses and in the case of gastric cancer, this theory proves true as the risk for gastric cancer has been linked to obesity [50–54]. Studies investigating the impact of a high body fat index and excess body weight on overall health have identified obese individuals as being at higher risk for gastric cancer [54,55]. This is in part due to the prevalence of *H. pylori* infections in obese patients [53]. Furthermore, other unhealthy habits such as alcohol consumption and tobacco use have also been associated with an increased risk of developing gastric cancer [56–62].

In addition to the aforementioned risk factors and although rare, there is also an inherited component that contributes to gastric cancer [63]. About 10% of reported gastric cancers are found among family members, but less than 3% are truly hereditary [64,65]. Currently, only a few high-penetrance genes have been identified in hereditary gastric cancer and these include *CDH1* and *CTNNA1* [40]. The *CDH1* gene encodes the cadherin 1 (also known as E-cadherin) protein while the *CTNNA1* gene is translated into the catenin a-1 protein (also known as a-E-catenin), both of which facilitate cell-adhesion and gene transcription. Attempts to map the genetic landscape of gastric cancer have also uncovered the presence of mutations in *TP53* (a tumor suppressor gene) and *SKT11* (regulator of autophagic processes), two mutations which are commonly found in many other cancers as well [40,63,66,67]. However, our knowledge of the genetic makeup of gastric cancer is limited and studies are currently ongoing to decipher the genetic predisposition underlying pre-cancerous gastric lesions.

3. Classification

There are several classification systems used for stomach cancer, but the most commonly used are the Lauren and World Health Organization (WHO) systems [40,68]. The Lauren classification distinguishes gastric cancer into two main classes based on histological differences: intestinal and diffuse [69]. The intestinal type tumors often occur in the antrum and incisura portions of the stomach and consist mainly of well differentiated cells that have a slow growth rate and the tendency to form glands. The incidence of this type of gastric cancer is often related to environmental factors and occurs predominantly in men and elderly individuals. In contrast, the diffuse type involves the entire stomach and it is made up of poorly differentiated cells lacking intercellular adhesions that tend to scatter throughout the stomach, which explains the increased incidence of metastasis and poor prognosis associated with this type of gastric cancer. Furthermore, the diffuse type is typically correlated with genetic abnormalities and is more frequently diagnosed in females and young patients [68]. The Lauren classification is complemented by the WHO classification which offers more histological patterns and differentiates gastric cancer into five groups: tubular (the most common type found during the early stages of the disease which consists of small branching tubules), papillary (occurs predominately in the proximal stomach of older patients), mucinous (characterised by a glandular architecture and extracellular mucinous pools), poorly cohesive (made up of signet ring cells arranged in clumps), and mixed carcinoma (involves a mix of different types of stomach adenocarcinomas) [70].

4. Diagnosis and treatment

Early stage gastric cancer is often silent or accompanied by non-specific symptoms including heartburn, nausea and poor appetite, all of which can be attributed to other illnesses. The characteristic symptoms (stomach pain with weight loss, and/or blood in stool) that allow for a differential diagnosis of gastric cancer usually emerge during the late stages or once the cancer has metastasized [40,63]. The diagnosis of gastric cancer relies primarily on imaging tests such as endoscopic ultrasounds (and laparoscopy) combined with biopsy [71–74]. The endoscopic ultrasound uses sound waves to create pictures of the inside of the stomach allowing for the identification of abnormal/tumoral structures that can be later confirmed using biopsies and immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH). The IHC test uses antibodies targeting the human epidermal growth factor receptor-2 (HER2) protein which has been demonstrated to be overexpressed in 20% of gastric cancers [75,76]. HER2 exhibits a progressive increase in expression which corresponds to the grade/stage of the gastric tumor (e.g. lower in low grade dysplasia and higher in gastric carcinomas) which establishing HER2 assessment as an accurate testing measure for the diagnosis of gastric cancer patients [75]. The HER2 IHC test generates a score between 0 and 3+ [77]. If the results are 0 or 1+, the cancer is classified as HER2-negative and patients are not treated with HER2-targeted therapies. If the score is 3+, the cancer is considered HER2-positive and patients can be treated with drugs targeting HER2, in particular trastuzumab. However, when the score is 2+, the HER2 status of the tumor is unclear and requires further testing. Often, tumors with a score of 2+ are tested using the FISH method which utilizes fluorescent pieces of DNA that specifically target *HER2* [40]. Once the cancer is detected and has an established HER2 status, laparoscopy is used to exclude the presence of small metastatic tumors and confirm that the tumor remains confined within the boundaries of the stomach [78–80].

Despite technological advancements and improvements in detection strategies, surgical resection remains the only therapeutic option that offers the best prognosis for gastric cancer patients [81]. Different types of surgery can be used to treat gastric cancer patients depending on the extent of the tumor(s) (e.g. endoscopic resection for small tumors, subtotal/total gastrectomy for advanced tumors) [82,83]. Surgery is typically coupled with the appropriate combination of chemotherapy drugs such as platinum, fluoropyrimidines or taxanes [84–87]. However, other treatment options have also been implemented and have shown some success over the years. Prompted by advances in molecular profiling and characterization of gastric cancer, two targeted therapies have been identified: anti- HER2 therapy (Trastuzumab) and anti-VEGF therapy (Ramucirumab) [88]. While these two treatment modalities have paved the way towards precise and personalized medicine, there are still challenges that pose a significant strain on the efficacy of these therapies as well as on the quality of life of the patient. However, recent discovers have shifted the scientific focus towards a new class of potential therapeutic targets, the transient receptor potential (TRP) channels [89–93]. TRP channels are often regarded as the Jack of all trades due to their extensive involvement in various physiological processes necessary for cell growth and survival, a characteristic which also renders them as suitable candidates for cancer therapy. The features that make TRP channels a favourable anti-cancer target can be summarized into three main points: 1) TRP channels are overexpressed in some cancers; 2) their activation triggers Ca^{2+} signalling cascades that have been shown to contribute to several hallmarks of cancer including uncontrolled proliferation, apoptosis-resistance, and cell migration and invasiveness, 3) most TRP channels are found on the cell surface which makes them more accessible to targeted therapies. The

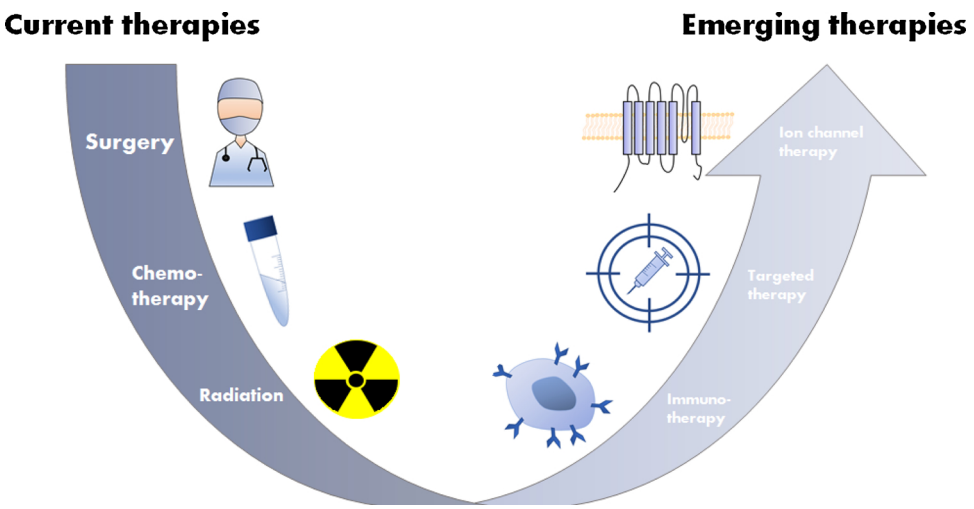

Fig. 1. Schematic depiction of the current and emerging therapies for gastric cancer patients. Surgery has long been the therapy of choice for gastric cancer patients (or any cancer type), in particular those with localized tumors and earlier stages of the disease. However, patients with late stage are often treated with chemotherapy, radiation or a combination of surgery, chemotherapy or radiation. Although successful to a certain extent, these approaches are not always curative and achieve varying clinical outcomes which are largely attributed to tumor heterogeneity. It is these challenges that led to the development of new therapies. Emerging cancer therapies are moving towards personalized medicine where each patient is treated according to their tumor expression profile and genetic makeup. These new therapy options include immunotherapy and targeted therapy which have shown good efficacy at treating gastric cancer patients, but various limitations still pose a significant strain on their effectiveness. Studies are now being conducted to assess the involvement of ion channels in the pathophysiology of gastric cancer in efforts of improving the efficacy of cancer treatment. Thus far, the TRP ion channel family (shown at the head of the arrow) has been demonstrated to play significant roles in gastric cancer cell survival and are currently under investigation as potential therapeutic targets for gastric cancer patients.

following sections of this review will introduce the TRP channel family and further discuss whether their function could be exploited for targeted cancer therapies (Fig. 1).

5. TRP channels (358 words)

TRP channels were first identified in 1969 by Cosens and Manning, but their structure and function remained a mystery until 1990s when studies revealed that these proteins harboured the defining characteristics of ion channels [94]. This initial discovery was carried forward and TRP channels have since been identified in various animal groups including the mammalian kingdom. In humans, TRP channels consist of transmembrane proteins typically assembled as homo- or hetero-tetramers that form gated pores and function to regulate the ion distribution across cellular compartments. Currently there are 28 members in the TRP superfamily which have been divided into six subgroups: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin) and TRPV (Vanilloid) [92,93]. Structurally, all members of the TRP family share a similar architecture consisting of six transmembrane segments with a pore flanked between the 5th and 6th segments, and cytoplasmic N- and C-termini [95,96]. In contrast to their shared structural similarities, physiologically, each member has a unique ionic signature, mechanism of activation and response to stimuli [97]. Notably, most TRP proteins are non-selective cation channels permeable to Ca^{2+} [98,99] – except for TRPMs 4 and 5 [100]. Ca^{2+} acts as a universal second messenger that interacts with a plethora of intracellular Ca^{2+}-binding proteins to regulate a wide range of cellular functions, from cell survival to cell death [101–103]. It has been suggested that the shape of the Ca^{2+} signals determines the cell's decision to differentiate, divide or die. For instance, local Ca^{2+} oscillations, waves and sparks have been associated with Ca^{2+}-mediated cell survival whereas a global sustained cytosolic elevation of Ca^{2+} has been linked to cell death [104]. When open, TRP channels mediate Ca^{2+} entry which activates Ca^{2+} signaling pathways (e.g. Ca^{2+}/Calmodulin kinase II (CaMKII), protein kinase C (PKC) and mitogen-activated protein kinase (MAPK)) which, in turn, shape the fate of a myriad of cell processes such as proliferation, apoptosis and migration [99,105–109]. Given the relationship between these processes with cancer cells and their ability to withstand stress and proliferate uncontrollably, it is not surprising that any alteration in the expression/function of TRP channels [89,92,110,111] and the subsequent disruption of Ca^{2+} homeostasis are often associated with the pathophysiology of cancer cells. Functional studies have demonstrated the incidence of altered expression and function of various TRP channels in many types of cancer including gastric cancer [112]. Furthermore, up to 30% of gastric cancer patients develop hypercalcemia and often have a poorer prognosis [113–115]. Over the past two decades, numerous research groups have identified six TRP channels (TRPC6, TRPM2, TRPM5, TRPM7, TRPV4, and TRPV6) that play an important role in the growth and survival of gastric cancer. These channels will be described in detail in the following paragraphs (Table 1).

Table 1
TRP channels involved in gastric cancer and their function.

Channel family	Channel name	Involvement in gastric cancer
TRPC	**TRPC6**	Upregulated in GC Promotes GC cell growth and expression of EMT markers [120,121,122,123]
TRPM	**TRPM2**	Increased expression correlates with poor GC patient survival Regulates GC metabolism, enhances invasion and promotes GC survival Regulates gastric inflammation during *H. pylori* infection [127,128,157]
	TRPM5	Increased expression correlates with poor GC patient survival [129]
	TRPM7	Upregulated in GC Maintains GC cell proliferation and survival [132,133,134]
TRPV	**TRPV4**	Sustains GC survival Promotes GC cell proliferation [143,144]
	TRPV6	Upregulated in GC Activation induces GC cell death [145,146]

5.1. TRPC channels

The TRPC family includes seven members (TRPC1 through TRPC7), all of which function as mediators of Ca^{2+}-dependent signal transduction in response to G protein-coupled receptor activation and/or endoplasmic reticulum store depletion [116]. Longstanding evidence has demonstrated the expression of TRPC in different types of cancer cells. For instance, the expression of TRPCs 1, 3 and 4 was shown to influence the differentiation of non-small cell lung cancer cells [117]. while TRPC5 and TRPC7 have been demonstrated to contribute to the carcinogenesis of gliomas [118] and neuroblastoma [119], respectively. In gastric cancer, research is now beginning to uncover the central role of TRPC6. Cai et al., provided the first evidence to show that the expression level of TRPC6 is upregulated in human gastric cancer tissues as compared to the surrounding normal gastric tissues. In the same study, the authors demonstrated that TRPC6 is functionally expressed in gastric cancer cell lines and that pharmacological inhibition of this channel significantly reduced cell growth through G2/M cell cycle arrest [120]. These *in vitro* results were complemented with *in vivo* studies showing that inhibition of TRPC6 suppressed gastric cancer tumor growth in nude mice [120]. In addition to its proliferative role, TRPC6 was also found as a key player in gastric cancer epithelial-to-mesenchymal transition (EMT) [121]. EMT is the most common process involved in cancer metastasis and increased expression of EMT markers is often associated with poor prognosis [122]. Ge et al. demonstrated that the loss of TRPC6 function is concomitant with a reduction in the expression levels of many EMT proteins such as E-cadherin, vimentin and alpha smooth muscle actin (α-SMA). Mechanistically, it has been suggested that TRPC6 operates by modulating Ras/Raf/ERK1/2 signaling. Although the studies demonstrating the involvement of TRPC6 in gastric cancer were performed using pharmacological inhibitors (through the use of 2-APB and SKF), a method which lacks in specificity, these reports are still providing an important insight into the molecular mechanisms that mediate the progression of gastric cancer. In addition, these studies also suggest that drugs targeting the function of TRPC6 could be developed and used to improve gastric cancer treatment. For instance, pyrazolo [1,5-a]pyrimidine is a new potent TRPC6 antagonist that has been shown to be effective at inhibiting gastric cancer cell proliferation and migration *in vitro* as well as delaying tumor development in nude mice [123]. This prompts a very important question, could TRPC6 antagonists promote the efficacy of other chemotherapeutic agents such as paclitaxel, doxorubicin and cisplatin? Given that TRPC6 often exists as a hetero-tetramer with TRPCs 1, 3 and 7, and that all of these TRPCs are found in gastric cancer cells, it is likely that the answer to this question is not a straightforward one. To circumvent some of these difficulties, one possible approach could reside in the generation of individual knock out models of all TRPCs that form hetero-tetramers with TRPC6 and evaluate 1) their impact on the functional expression of TRPC6, 2) their role in gastric cancer survival, and 3) their response to TRPC6 antagonists, alone, and in combination other chemotherapeutics.

5.2. TRPM channels

Consisting of eight members (TRPM1 through TRPM8), the TRPM family share the common property of being activated in response to a variety of exogenous and endogenous ligands along with differential permeabilities and structural features. For instance, most TRPM channels are permeable to Ca^{2+} with the exception of TRPM4 and 5 that are Ca^{2+} impermeable. Additionally, three members within the family, TRPM2, 6 and 7 harbor enzymatic domains within their C-terminal regions and are commonly referred to as “chanzymes”. This diversity in structure and selectivity is in part responsible for the involvement of TRPM channels in many physiological processes as well as in various channelopathies [124,125]. The TRPM channels have also been implicated in numerous cancer types [126], but only TRPMs 2, 5 and 7 have been shown to contribute to the pathophysiology of gastric cancer.

TRPM2 was first demonstrated to play an active role in gastric cancer in 2018 by Almasi et al. The authors used two shRNA directed against TRPM2 to downregulate its expression and function in the AGS and MKN45 gastric cancer cell lines [127]. Results demonstrated that TRPM2 is functionally expressed as a plasma membrane ion channel permeable to Ca^{2+} in gastric cancer cells and that its inhibition reduced cell bioenergetics, suppressed cell invasion, and decreased cell survival. These results were further confirmed *in vivo* using a SCID mouse model where the loss of TRPM2 led to a decrease in tumor growth. The authors identified that TRPM2 operates via a JNK-dependent and mTOR-independent autophagy pathway to mediate gastric cancer survival [127,128]. Almasi et al. later confirmed that TRPM2 inhibition also promotes the effectiveness of chemotherapy drugs, specifically paclitaxel and doxorubicin, suggesting that TRPM2 inhibition in conjunction with known chemotherapeutics could represent an efficacious strategy for the treatment of gastric cancer [128]. Moreover, the authors reported that TRPM2 expression levels correlate with poor patient survival, in particular in those with late/advanced stages; thus, showcasing the possibility of a potential role for TRPM2 as a prognostic marker for late stage gastric cancer [128]. Similarly, other studies have found that high expression of TRPM5 was associated with shorter survival in gastric cancer patients [129]. However, further studies are needed to document the importance of TRPM2 and TRPM5 in gastric cancer patient survival and its clinical applicability.

TRPM7 is another member of the TRPM family that has captured the attention of certain research groups [130,131]. Results from Kim et al. showed that TRPM7 is upregulated in many gastric cancer cell lines including AGS, one of the most common human gastric adenocarcinoma cell lines [132]. In addition, using pharmacological tools and small interfering RNA as well as four gastric cancer cell lines (AGS, MKN45, SNU1 and SNU484), the authors demonstrated that TRPM7 inhibition caused a dramatic reduction in cell proliferation and a significant increase in apoptosis. These findings made TRPM7 a promising target for gastric cancer therapy. Accordingly, a variety of potent compounds against TRPM7 have been developed and their role in gastric cancer cell has been documented [133,134]. For instance, pharmacological studies showed that 5-lipoxygenase (LOX) inhibitors [135], nordihydroguaiaretic acid (NDGA), 3-[(p-chlorobenzyl)-5-(isopropyl)-3-tert-butylthioindol-2-yl]-2,2-dimethylpropanoic acid (MK886), 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone (AA861)) and waixenicin A [136] significantly decreased the TRPM7 current and caused gastric cancer cell death. Some fruit and vegetable extracts have also been proposed as promising TRPM7 antagonists (e.g. quercetin [137] and ginseng [131] have been shown to decrease TRPM7 activity and cause gastric cancer cell death). However, despite promising results following TRPM7 blockade, the development of anti-TRPM7 drugs faces its own challenges stemming from the ability of TRPM7 to exist as a hetero-tetramer with TRPM6. More studies are required to investigate whether the currently available inhibitors are specifically targeting TRPM7 or the TRPM7/6 hetero-tetramers. In addition, the function of TRPM7 in regard to some of the other major hallmarks of cancer is currently unknown (migration, invasion, and metastasis) and should be investigated in efforts to expand our knowledge of the underlying mechanisms of cancer cells. Although many questions remain open about the involvement of the TRPM family in gastric cancer, the quest for answers has already begun.

5.3. TRPV channels

Similar to the other TRP subgroups, the TRPV family consists of six members (TRPV1 through TRPV6) that function as Ca^{2+} entry mediators, either directly or indirectly following GCPR activation. Based on their function, two TRPV groups have been proposed: the non-selective group consisting of TRPVs 1–4, and the Ca^{2+}- selective group including TRPVs 5 and 6 [138]. The first group is characterised by its temperature

sensitivity and low Ca^{2+} conductance while the second group is not temperature sensitive and is highly selective for Ca^{2+} [139]. Many members of the TRPV family have been linked to various cancer types including breast cancer [140,141] and non-small cell lung carcinoma [142], but only TRPV4 and TRPV5 have been shown to play a prominent role in gastric cancer. Functional studies indicated that TRPV4 is upregulated in gastric cancer cells and its activation evoked a large outwarded rectifying current leading to a marked elevation in cytosolic Ca^{2+} [143]. Additional studies have also uncovered that the function of TRPV4 in gastric cancer cells is facilitated through the activation of GPCRs. For example, TRPV4 contributes significantly to the influx of Ca^{2+} through the calcium sensing receptor (CaSR)- and vasoactive intestinal polypeptide receptor 1 (VPAC1), both of which are GPCRs [143,144]. Furthermore, pharmacological inhibition and/or genetic depletion of TRPV4 expression markedly abolished CaSR and VPAC1-mediated gastric cancer cell proliferation and invasion, as well as tumor growth and metastasis. Interestingly, the mechanism behind these phenomena varies depending on the function of the GPCR receptor. CaSR/TRPV4 promotes gastric cancer survival through the Ca^{2+}/AKT/beta-catenin pathway while VPAC1/TRPV4 sustains survival via the Ca^{2+}/$ERK_{1/2}$/JNK/beta-catenin pathway [143,144]. Although these studies have provided convincing evidence on the role of TRPV4 in gastric cancer, further research is needed to determine whether TRPV4 alone has a biological role in gastric cancer and if targeting its function, alone or in combination with GPCR inhibitors represents a viable option for the treatment of this disease.

The first indication of the potential involvement of TRPV6 in gastric cancer was provided by the Hediger group that showed an upregulation in TRPV6 expression in glandular gastric cancer cells [145,146]. Later, Chow et al. discovered the importance of TRPV6 when examining the role and selectivity of capsaicin in gastric cancer cell death [147]. Remarkably, capsaicin-mediated gastric cancer cell death was not mediated through TRPV1, a traditionally known capsaicin target [148], but rather through TRPV6. In the same study, the authors found that TRPV6 expression was upregulated in gastric cancer cells and its activation increased cytosolic Ca^{2+} levels. This discovery paved the way to uncovering that the mechanism behind Capsaicin/TRPC6-mediated gastric cancer cell death was mediated by the Ca^{2+}/p53/JNK pathway. While these findings indicate a therapeutic potential for TRPV6 in gastric cancer, they also raise several questions. Does capsaicin target TRPV6 directly to facilitate Ca^{2+} entry and gastric cancer cell death or does it activate TRPV6 indirectly through a complex signaling network? Is TRPV6 important in gastric cancer by itself or as a part of cascade signaling? Answering these questions will validate the clinical potential of TRPV6 and improve our understanding of the complex etiology of gastric cancer.

6. Conclusions and perspectives

Over the last two decades, a plethora of studies have demonstrated the involvement of TRP channels in various cancers, so much so that they are often regarded as *oncochannels* [104]. However, their contribution to the pathophysiology of cancer remains poorly understood and only a few TRP channels (TRPC6; TRPMs 2, 5 and 6; TRPVs 4 and 6) have been studied in the context of a gastric cancer model. It is of interest to examine the expression and function of TRP channels in correlation with oncogenes such as c-myc which is upregulated in more than 40% of gastric cancers [149–151] and it is often associated with *H. pylori* infections [152–156]. Some studies have demonstrated the involvement of TRPM2 [157] and TRPV4 [158] in *H. pylori* infections; therefore, it is important to establish the role of these channels in *H. pylori*-dependent tumours, especially when this pathogen remains the primary risk factor for gastric cancer.

Finally, despite marked progress in drug development, there are currently no pharmacological agents targeting any of the TRP channels that have successfully completed a clinical trial. Nonetheless, regardless of previous shortcomings, SOR-C13 (NCT03784677), a small, synthetic TRPV6 antagonist is currently undergoing a phase I clinical trial to validate its safety/tolerance and patient response in several solid tumors [159,160]. Upon binding, SOR-C13 disrupts the function of TRPV6 and inhibits Ca^{2+} entry [160]. As shown previously, TRPV6 is upregulated in different cancers including breast, ovarian and gastric cancer cells where it facilitates the entry of Ca^{2+}. Manipulating TRPV6-mediated Ca^{2+} transport using SOR-C13 may enable the inhibition of Ca^{2+}- dependent functions in cancer cell survival and growth. Thus far, pre-clinical studies have demonstrated that SOR-C13 is effective at inhibiting the growth of breast and ovarian tumors in animal models and it is currently classified as an orphan drug by the FDA for the treatment of ovarian and pancreatic cancer [160–162]. Although this molecule is still undergoing testing and validation, it does provide a foundation for its potential use in gastric cancer patients. TRP channels represent a relatively new field of research with most studies still in their infancy, but these channels hold tremendous potential that has yet to be uncovered in the hopes of achieving major clinical breakthroughs in the treatment of gastric cancer.

Declaration of Competing Interest

No conflicts.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424.

[2] Z. Kadar, I. Jung, J. Orlowska, Z. Szentirmay, H. Sugimura, S. Turdean, G. Simona, Geographic particularities in incidence and etiopathogenesis of sporadic gastric cancer, Pol. J. Pathol. 66 (2015) 254–259.

[3] S. Kummar, Gastric cancer: geographic differences in multidisciplinary management, Curr. Probl. Cancer 39 (2015) 314.

[4] O. Torgersen, The geographic distribution of gastric cancer in Oslo, Acta pathologica et microbiologica Scandinavica, Supplement 39 (1956) 86.

[5] Y. Yamaoka, M. Kato, M. Asaka, Geographic differences in gastric cancer incidence can be explained by differences between Helicobacter pylori strains, Intern. Med. 47 (2008) 1077–1083.

[6] T. Dendup, J.M. Richter, Y. Yamaoka, K. Wangchuk, H.M. Malaty, Geographical distribution of the incidence of gastric cancer in Bhutan, World J. Gastroenterol. 21 (2015) 10883–10889.

[7] N. Aragones, B. Perez-Gomez, M. Pollan, R. Ramis, E. Vidal, V. Lope, J. Garcia-Perez, E. Boldo, G. Lopez-Abente, The striking geographical pattern of gastric cancer mortality in Spain: environmental hypotheses revisited, BMC Cancer 9 (2009) 316.

[8] N. Montero-Oleas, S. Nunez-Gonzalez, D. Simancas-Racines, The remarkable geographical pattern of gastric cancer mortality in Ecuador, Cancer Epidemiol. 51 (2017) 92–97.

[9] M. Inoue, S. Tsugane, Epidemiology of gastric cancer in Japan, Postgrad. Med. J. 81 (2005) 419–424.

[10] J.J. Jing, H.Y. Liu, J.K. Hao, L.N. Wang, Y.P. Wang, L.H. Sun, Y. Yuan, Gastric cancer incidence and mortality in Zhuanghe, China, between 2005 and 2010, World J. Gastroenterol. 18 (2012) 1262–1269.

[11] L. Yang, Incidence and mortality of gastric cancer in China, World J. Gastroenterol. 12 (2006) 17–20.

[12] D. Liang, S. Liang, J. Jin, D. Li, J. Shi, Y. He, Gastric cancer burden of last 40 years in North China (Hebei Province): a population-based study, Medicine 96 (2017) e5887.

[13] S. Yan, B. Li, Z.Z. Bai, J.Q. Wu, D.W. Xie, Y.C. Ma, X.X. Ma, J.H. Zhao, X.J. Guo, Clinical epidemiology of gastric cancer in Hehuang valley of China: a 10-year epidemiological study of gastric cancer, World J. Gastroenterol. 20 (2014) 10486–10494.

[14] Y. Kim, J. Park, B.H. Nam, M. Ki, Stomach cancer incidence rates among Americans, Asian Americans and Native Asians from 1988 to 2011, Epidemiol. Health 37 (2015) e2015006.

[15] G. Maskarinec, J.J. Noh, The effect of migration on cancer incidence among Japanese in Hawaii, Ethn. Dis. 14 (2004) 431–439.

[16] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2015) 87–108.

[17] A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman, Global cancer statistics, CA Cancer J. Clin. 61 (2011) 69–90.

[18] S.S. Kweon, Updates on Cancer epidemiology in Korea, 2018, Chonnam Med. J. 54 (2018) 90–100.

[19] B.W. Eom, K.W. Jung, Y.J. Won, H. Yang, Y.W. Kim, Trends in gastric Cancer incidence according to the clinicopathological characteristics in Korea, 1999-2014, Cancer Res. Treat. 50 (2018) 1343–1350.

[20] A. Ferro, B. Peleteiro, M. Malvezzi, C. Bosetti, P. Bertuccio, F. Levi, E. Negri, C. La

Vecchia, N. Lunet, Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype, Eur. J. Cancer 50 (2014) 1330–1344.
[21] F. Bray, A. Jemal, N. Grey, J. Ferlay, D. Forman, Global cancer transitions according to the Human Development Index (2008-2030): a population-based study, the Lancet, Oncology 13 (2012) 790–801.
[22] T.L. Ang, K.M. Fock, Clinical epidemiology of gastric cancer, Singapore Med. J. 55 (2014) 621–628.
[23] J. Bornschein, M. Selgrad, M. Warnecke, D. Kuester, T. Wex, P. Malfertheiner, H. Pylori infection is a key risk factor for proximal gastric cancer, Dig. Dis. Sci. 55 (2010) 3124–3131.
[24] M. Plummer, S. Franceschi, J. Vignat, D. Forman, C. de Martel, Global burden of gastric cancer attributable to Helicobacter pylori, Int. J. Cancer 136 (2015) 487–490.
[25] H.J. Ahn, D.S. Lee, Helicobacter pylori in gastric carcinogenesis, World J. Gastrointest. Oncol. 7 (2015) 455–465.
[26] A. Sokic-Milutinovic, T. Alempijevic, T. Milosavljevic, Role of Helicobacter pylori infection in gastric carcinogenesis: current knowledge and future directions, World J. Gastroenterol. 21 (2015) 11654–11672.
[27] M.S. Krakowiak, J.M. Noto, M.B. Piazuelo, D.M. Hardbower, J. Romero-Gallo, A. Delgado, R. Chaturvedi, P. Correa, K.T. Wilson, R.M. Peek Jr., Matrix metalloproteinase 7 restrains Helicobacter pylori-induced gastric inflammation and premalignant lesions in the stomach by altering macrophage polarization, Oncogene 34 (2015) 1865–1871.
[28] F. Wang, W. Meng, B. Wang, L. Qiao, Helicobacter pylori-induced gastric inflammation and gastric cancer, Cancer Lett. 345 (2014) 196–202.
[29] S.Y. Nam, B.J. Park, K.H. Ryu, J.H. Nam, Effect of Helicobacter pylori eradication on the regression of gastric polyps in National Cancer screening Program, Korean J. Intern. Med. 33 (2018) 506–511.
[30] A. Archimandritis, C. Spiliadis, M. Tzivras, B. Vamvakousis, P. Davaris, Z. Manika, N. Scandalis, Gastric epithelial polyps: a retrospective endoscopic study of 12974 symptomatic patients, Ital. J. Gastroenterol. 28 (1996) 387–390.
[31] B. Horvath, R.K. Pai, Prevalence of Helicobacter pylori in gastric hyperplastic polyps, Int. J. Surg. Pathol. 24 (2016) 704–708.
[32] N. Sacca, Hyperplastic gastric polyps and Helicobacter pylori, Scand. J. Gastroenterol. 38 (2003) 904.
[33] S.C. Abraham, V.K. Singh, J.H. Yardley, T.T. Wu, Hyperplastic polyps of the stomach: associations with histologic patterns of gastritis and gastric atrophy, Am. J. Surg. Pathol. 25 (2001) 500–507.
[34] M. Stolte, Hyperplastic polyps of the stomach: associations with histologic patterns of gastritis and gastric atrophy, Am. J. Surg. Pathol. 25 (2001) 1342–1344.
[35] A. Ikai, H. Fujiwara, A. Shiozaki, K. Okamoto, T. Kosuga, H. Konishi, S. Komatsu, D. Ichikawa, R. Morimura, Y. Kuriu, H. Ikoma, M. Nakanishi, T. Ochiai, C. Sakakura, E. Otsuji, [Gastric cancer arising from gastric polyps in gardner syndrome - a case report], Gan to kagaku ryoho, Cancer & chemotherapy 41 (2014) 2262–2263.
[36] J.T. Jung, Gastric polyps and protruding type gastric cancer, Clin. Endosc. 46 (2013) 243–247.
[37] X. Su, Z. Ye, Z. Wang, Y. Long, M. Qiu, C. He, Epstein-Barr virus infection associated with pepsinogens and Helicobacter pylori infection in patients with gastric cancer, Virus Res. 256 (2018) 1–5.
[38] M.S. Wu, C.T. Shun, C.C. Wu, T.Y. Hsu, M.T. Lin, M.C. Chang, H.P. Wang, J.T. Lin, Epstein-Barr virus-associated gastric carcinomas: relation to H. Pylori infection and genetic alterations, Gastroenterology 118 (2000) 1031–1038.
[39] K. Shinohara, K. Miyazaki, N. Noda, D. Saitoh, M. Terada, H. Wakasugi, Gastric diseases related to Helicobacter pylori and Epstein-Barr virus infection, Microbiol. Immunol. 42 (1998) 415–421.
[40] E. Van Cutsem, X. Sagaert, B. Topal, K. Haustermans, H. Prenen, Gastric cancer, Lancet 388 (2016) 2654–2664.
[41] L. Strumylaite, J. Zickute, J. Dudzevicius, L. Dregval, Salt-preserved foods and risk of gastric cancer, Medicina 42 (2006) 164–170.
[42] M.J. Hill, Salt and gastric cancer, Eur. J. Cancer Prev. 7 (1998) 173–175.
[43] High salt intake can cause gastric cancer, Indian J. Med. Sci. 46 (1992) 58–59.
[44] X. Fang, J. Wei, X. He, P. An, H. Wang, L. Jiang, D. Shao, H. Liang, Y. Li, F. Wang, J. Min, Landscape of dietary factors associated with risk of gastric cancer: a systematic review and dose-response meta-analysis of prospective cohort studies, Eur. J. Cancer 51 (2015) 2820–2832.
[45] T. Toyoda, T. Tsukamoto, M. Yamamoto, H. Ban, N. Saito, S. Takasu, L. Shi, A. Saito, S. Ito, Y. Yamamura, A. Nishikawa, K. Ogawa, T. Tanaka, M. Tatematsu, Gene expression analysis of a Helicobacter pylori-infected and high-salt diet-treated mouse gastric tumor model: identification of CD177 as a novel prognostic factor in patients with gastric cancer, BMC Gastroenterol. 13 (2013) 122.
[46] C. Zhong, K.N. Li, J.W. Bi, B.C. Wang, Sodium intake, salt taste and gastric cancer risk according to Helicobacter pylori infection, smoking, histological type and tumor site in China, Asian Pac. J. Cancer Prev. 13 (2012) 2481–2484.
[47] X.Q. Wang, P.D. Terry, H. Yan, Review of salt consumption and stomach cancer risk: epidemiological and biological evidence, World J. Gastroenterol. 15 (2009) 2204–2213.
[48] M. Wiseman, The second world cancer research Fund/American institute for cancer research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective, The Proceedings of the Nutrition Society 67 (2008) 253–256.
[49] T. Wang, H. Cai, S. Sasazuki, S. Tsugane, W. Zheng, E.R. Cho, S.H. Jee, A. Michel, M. Pawlita, Y.B. Xiang, Y.T. Gao, X.O. Shu, W.C. You, M. Epplein, Fruit and vegetable consumption, Helicobacter pylori antibodies, and gastric cancer risk: a pooled analysis of prospective studies in China, Japan, and Korea, Int. J. Cancer 140 (2017) 591–599.
[50] H.J. Li, X.M. Che, W. Zhao, S.C. He, Z.L. Zhang, R. Chen, L. Fan, Z.L. Jia, Diet-induced obesity promotes murine gastric cancer growth through a nampt/sirt1/c-myc positive feedback loop, Oncol. Rep. 30 (2013) 2153–2160.
[51] H. Lim, G. Cho, S. Kim, Evaluation of nutrient intake and diet quality of gastric cancer patients in Korea, Nutr. Res. Pract. 6 (2012) 213–220.
[52] S. Sipetic, S. Tomic-Kundakovic, H. Vlajinac, S. Jankovic, J. Marinkovic, J. Maksimovic, [Diet and gastric cancer], Vojnosanitetski pregled 60 (2003) 697–705.
[53] Q. Li, J. Zhang, Y. Zhou, L. Qiao, Obesity and gastric cancer, Front. Biosci. 17 (2012) 2383–2390.
[54] P. Yang, Y. Zhou, B. Chen, H.W. Wan, G.Q. Jia, H.L. Bai, X.T. Wu, Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies, Eur. J. Cancer 45 (2009) 2867–2873.
[55] Y. Chen, L. Liu, X. Wang, J. Wang, Z. Yan, J. Cheng, G. Gong, G. Li, Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies, Cancer Epidemiol. Biomarkers Prev. 22 (2013) 1395–1408.
[56] Y.J. Choi, D.H. Lee, K.D. Han, H.S. Kim, H. Yoon, C.M. Shin, Y.S. Park, N. Kim, Correction: the relationship between drinking alcohol and esophageal, gastric or colorectal cancer: a nationwide population-based cohort study of South Korea, PLoS One 13 (2018) e0197765.
[57] A. Ferro, S. Morais, M. Rota, C. Pelucchi, P. Bertuccio, R. Bonzi, C. Galeone, Z.F. Zhang, K. Matsuo, H. Ito, J. Hu, K.C. Johnson, G.P. Yu, D. Palli, M. Ferraroni, J. Muscat, R. Malekzadeh, W. Ye, H. Song, D. Zaridze, D. Maximovitch, N. Fernandez de Larrea, M. Kogevinas, J. Vioque, E.M. Navarrete-Munoz, M. Pakseresht, F. Pourfarzi, A. Wolk, N. Orsini, A. Bellavia, N. Hakansson, L. Mu, R. Pastorino, R.C. Kurtz, M.H. Derakhshan, A. Lagiou, P. Lagiou, P. Boffetta, S. Boccia, E. Negri, C. La Vecchia, B. Peleteiro, N. Lunet, Alcohol intake and gastric cancer: meta-analyses of published data versus individual participant data pooled analyses (StoP Project), Cancer Epidemiol. 54 (2018) 125–132.
[58] M. Rota, C. Pelucchi, P. Bertuccio, K. Matsuo, Z.F. Zhang, H. Ito, J. Hu, K.C. Johnson, D. Palli, M. Ferraroni, G.P. Yu, J. Muscat, N. Lunet, B. Peleteiro, W. Ye, H. Song, D. Zaridze, D. Maximovitch, M. Guevara, T. Fernandez-Villa, J. Vioque, E.M. Navarrete-Munoz, A. Wolk, N. Orsini, A. Bellavia, N. Hakansson, L. Mu, R. Persiani, R.C. Kurtz, A. Lagiou, P. Lagiou, C. Galeone, R. Bonzi, P. Boffetta, S. Boccia, E. Negri, C. La Vecchia, Alcohol consumption and gastric cancer risk-A pooled analysis within the StoP project consortium, Int. J. Cancer 141 (2017) 1950–1962.
[59] K.A. Moy, Y. Fan, R. Wang, Y.T. Gao, M.C. Yu, J.M. Yuan, Alcohol and tobacco use in relation to gastric cancer: a prospective study of men in Shanghai, China, Cancer Epidemiol. Biomarkers Prev. 19 (2010) 2287–2297.
[60] L.E. Hansson, J. Baron, O. Nyren, R. Bergstrom, A. Wolk, H.O. Adami, Tobacco, alcohol and the risk of gastric cancer, Int. J. Cancer 57 (1994) 26–31.
[61] B. D'Avanzo, C. La Vecchia, S. Franceschi, Alcohol consumption and the risk of gastric cancer, Nutr. Cancer 22 (1994) 57–64.
[62] A. Agudo, C.A. Gonzalez, G. Marcos, M. Sanz, E. Saigi, J. Verge, M. Boleda, J. Ortego, Consumption of alcohol, coffee, and tobacco, and gastric cancer in Spain, Cancer Causes Control 3 (1992) 137–143.
[63] M.H. McLean, E.M. El-Omar, Genetics of gastric cancer, Nature reviews, Gastroenterol. Hepatol. 11 (2014) 664–674.
[64] C. Oliveira, H. Pinheiro, J. Figueiredo, R. Seruca, F. Carneiro, Familial gastric cancer: genetic susceptibility, pathology, and implications for management, the Lancet, Oncology 16 (2015) e60–70.
[65] C. Oliveira, G. Suriano, P. Ferreira, P. Canedo, P. Kaurah, R. Mateus, A. Ferreira, A.C. Ferreira, M.J. Oliveira, C. Figueiredo, F. Carneiro, G. Keller, D. Huntsman, J.C. Machado, R. Seruca, Genetic screening for familial gastric cancer, Hered. Cancer Clin. Pract. 2 (2004) 51–64.
[66] X. Liu, S.J. Meltzer, Gastric Cancer in the era of precision medicine, Cell. Mol. Gastroenterol. Hepatol. 3 (2017) 348–358.
[67] S.S. Kupfer, Gaining ground in the genetics of gastric Cancer, Gastroenterology 152 (2017) 926–928.
[68] B. Hu, N. El Hajj, S. Sittler, N. Lammert, R. Barnes, A. Meloni-Ehrig, Gastric cancer: classification, histology and application of molecular pathology, J. Gastrointest. Oncol. 3 (2012) 251–261.
[69] P. Lauren, The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An Attempt at a Histo-Clinical Classification, Acta pathologica et microbiologica Scandinavica 64 (1965) 31–49.
[70] F. Berlth, E. Bollschweiler, U. Drebber, A.H. Hoelscher, S. Moenig, Pathohistological classification systems in gastric cancer: diagnostic relevance and prognostic value, World J. Gastroenterol. 20 (2014) 5679–5684.
[71] N. Coburn, R. Cosby, L. Klein, G. Knight, R. Malthaner, J. Mamazza, C.D. Mercer, J. Ringash, Staging and surgical approaches in gastric cancer: a systematic review, Cancer Treat. Rev. 63 (2018) 104–115.
[72] N. Coburn, R. Cosby, L. Klein, G. Knight, R. Malthaner, J. Mamazza, C.D. Mercer, J. Ringash, Staging and surgical approaches in gastric cancer: a clinical practice guideline, Curr. Oncol. 24 (2017) 324–331.
[73] M.C. Russell, P.F. Mansfield, Surgical approaches to gastric cancer, J. Surg. Oncol. 107 (2013) 250–258.
[74] Gastric cancer–medical and surgical approaches, Hepatogastroenterology 36 (1989) 1–39.
[75] F. Grillo, M. Fassan, F. Sarocchi, R. Fiocca, L. Mastracci, HER2 heterogeneity in gastric/gastroesophageal cancers: from benchside to practice, World J. Gastroenterol. 22 (2016) 5879–5887.
[76] C. Gravalos, A. Jimeno, HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target, Ann. Oncol. 19 (2008) 1523–1529.

[77] L.F. Abrahao-Machado, C. Scapulatempo-Neto, HER2 testing in gastric cancer: an update, World J. Gastroenterol. 22 (2016) 4619–4625.
[78] V.V. Bintintan, A. Cordos, R. Chira, S. Cocu, P. Rus, A. Bintintan, G. Nagy, L. Ciule, E. Cata, A. Pop, V. Fagarasan, A. Ungureanu, V. Surlin, D. Timofte, K.Y. Woo, C. Ciuce, G. Dindelegan, The value of staging laparoscopy for optimal multidisciplinary treatment in patients with gastric Cancer, Chirurgia 113 (2018) 789–798.
[79] N. Machairas, P. Charalampoudis, E.P. Molmenti, S. Kykalos, P. Tsaparas, P. Stamopoulos, G.C. Sotiropoulos, The value of staging laparoscopy in gastric cancer, Ann. Gastroenterol. 30 (2017) 287–294.
[80] R.A. Possik, E.L. Franco, D.R. Pires, D.R. Wohnrath, E.B. Ferreira, Sensitivity, specificity, and predictive value of laparoscopy for the staging of gastric cancer and for the detection of liver metastases, Cancer 58 (1986) 1–6.
[81] H. Liang, [The precised management of surgical treatment for gastric Cancer: interpretation of the 5th edition of japanese gastric Cancer treatment guideline and the 15th edition of japanese classification for gastric Cancer], Zhonghua zhong liu za zhi [Chinese journal of oncology] 41 (2019) 168–172.
[82] T. Isobe, K. Hashimoto, J. Kizaki, M. Miyagi, K. Aoyagi, K. Koufuji, K. Shirouzu, Surgical procedures, complications, and prognosis for gastric cancer in the very elderly (&85): a retrospective study, Kurume Med. J. 59 (2012) 61–70.
[83] M.P. Lutz, J.R. Zalcberg, M. Ducreux, J.A. Ajani, W. Allum, D. Aust, Y.J. Bang, S. Cascinu, A. Holscher, J. Jankowski, E.P. Jansen, R. Kisslich, F. Lordick, C. Mariette, M. Moehler, T. Oyama, A. Roth, J. Rueschoff, T. Ruhstaller, R. Seruca, M. Stahl, F. Sterzing, E. van Cutsem, A. van der Gaast, J. van Lanschot, M. Ychou, F. Otto, E.G.C.C.E.P. First St Gallen, Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastro-esophageal and oesophageal cancer - differential treatment strategies for subtypes of early gastroesophageal cancer, Eur. J. Cancer 48 (2012) 2941–2953.
[84] K.C. Peeters, C.J. van de Velde, Improving treatment outcome for gastric cancer: the role of surgery and adjuvant therapy, J. Clin. Oncol. 21 (2003) 272s–273s.
[85] S. Fujimoto, R.D. Shrestha, M. Kokubun, K. Kobayashi, S. Kiuchi, C. Konno, M. Ohta, M. Takahashi, Y. Kitsukawa, M. Mizutani, et al., Positive results of combined therapy of surgery and intraperitoneal hyperthermic perfusion for far-advanced gastric cancer, Ann. Surg. 212 (1990) 592–596.
[86] R. Tamada, [Surgery and adjuvant therapy of gastric cancer], Gan to kagaku ryoho, Cancer & Chemotherapy 13 (1986) 1555–1563.
[87] S.C. Chang, K.H. Liu, C.Y. Hung, C.Y. Tsai, J.T. Hsu, T.S. Yeh, J.S. Chen, Y.C. Kuo, Y.S. Hung, W.C. Chou, Adjuvant chemotherapy improves survival in stage III gastric Cancer after D2 surgery, J. Cancer 9 (2018) 81–91.
[88] D.D. Yuan, Z.X. Zhu, X. Zhang, J. Liu, Targeted therapy for gastric cancer: current status and future directions (Review), Oncol. Rep. 35 (2016) 1245–1254.
[89] G. Shapovalov, A. Ritaine, R. Skryma, N. Prevarskaya, Role of TRP ion channels in cancer and tumorigenesis, Semin. Immunopathol. 38 (2016) 357–369.
[90] J. Chen, Y. Luan, R. Yu, Z. Zhang, J. Zhang, W. Wang, Transient receptor potential (TRP) channels, promising potential diagnostic and therapeutic tools for cancer, Biosci. Trends 8 (2014) 1–10.
[91] V. Lehen'kyi, N. Prevarskaya, Study of TRP channels in cancer cells, in: M.X. Zhu (Ed.), TRP Channels, 2011 Boca Raton (FL).
[92] G. Santoni, V. Farfariello, TRP channels and cancer: new targets for diagnosis and chemotherapy, Endocr. Metab. Immune. Disord. Drug Targets 11 (2011) 54–67.
[93] N. Prevarskaya, L. Zhang, G. Barritt, TRP channels in cancer, Biochim. Biophys. Acta 1772 (2007) 937–946.
[94] B. Minke, The history of the Drosophila TRP channel: the birth of a new channel superfamily, J. Neurogenet. 24 (2010) 216–233.
[95] M.R. Cohen, V.Y. Moiseenkova-Bell, Structure of thermally activated TRP channels, Curr. Top. Membr. 74 (2014) 181–211.
[96] M.Y. Song, J.X. Yuan, Introduction to TRP channels: structure, function, and regulation, Adv. Exp. Med. Biol. 661 (2010) 99–108.
[97] D.E. Clapham, L.W. Runnels, C. Strubing, The TRP ion channel family, Nature reviews, Neuroscience 2 (2001) 387–396.
[98] R. Hasan, X. Zhang, Ca(2+) regulation of TRP ion channels, Int. J. Mol. Sci. 19 (2018).
[99] B. Minke, TRP channels and Ca2+ signaling, Cell Calcium 40 (2006) 261–275.
[100] E.R. Liman, The Ca(2+)-activated TRP channels: TRPM4 and TRPM5, in: W.B. Liedtke, S. Heller (Eds.), TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades, 2007 Boca Raton (FL).
[101] H.P. Cheng, S. Wei, L.P. Wei, A. Verkhratsky, Calcium signaling in physiology and pathophysiology, Acta Pharmacol. Sin. 27 (2006) 767–772.
[102] O.S. Andersen, M.D. Cahalan, The 52nd annual meeting and symposium of the Society of General Physiologists, J. Gen. Physiol. 113 (1999) 153–159.
[103] C.D. White, D.B. Sacks, Regulation of MAP kinase signaling by calcium, Methods Mol. Biol. 661 (2010) 151–165.
[104] N. Prevarskaya, R. Skryma, Y. Shuba, Ion Channels in Cancer: Are Cancer Hallmarks Oncochannelopathies? Physiol. Rev. 98 (2018) 559–621.
[105] N.M. Conus, B.A. Hemmings, R.B. Pearson, Differential regulation by calcium reveals distinct signaling requirements for the activation of Akt and p70S6k, J. Biol. Chem. 273 (1998) 4776–4782.
[106] M. Naziroglu, D.M. Dikici, S. Dursun, Role of oxidative stress and Ca(2)(+) signaling on molecular pathways of neuropathic pain in diabetes: focus on TRP channels, Neurochem. Res. 37 (2012) 2065–2075.
[107] X. Cheng, J. Jin, L. Hu, D. Shen, X.P. Dong, M.A. Samie, J. Knoff, B. Eisinger, M.L. Liu, S.M. Huang, M.J. Caterina, P. Dempsey, L.E. Michael, A.A. Dlugosz, N.C. Andrews, D.E. Clapham, H. Xu, TRP channel regulates EGFR signaling in hair morphogenesis and skin barrier formation, Cell 141 (2010) 331–343.
[108] A.J. Gustafsson, H. Ingelman-Sundberg, M. Dzabic, J. Awasum, K.H. Nguyen, C.G. Ostenson, C. Pierro, P. Tedeschi, O. Woolcott, S. Chiounan, P.E. Lund, O. Larsson, M.S. Islam, Ryanodine receptor-operated activation of TRP-like channels can trigger critical Ca2+ signaling events in pancreatic beta-cells, FASEB J. 19 (2005) 301–303.
[109] B. Minke, The TRP channel and phospholipase C-mediated signaling, Cell. Mol. Neurobiol. 21 (2001) 629–643.
[110] V. Lehen'kyi, G. Shapovalov, R. Skryma, N. Prevarskaya, Ion channnels and transporters in cancer. 5. Ion channels in control of cancer and cell apoptosis, American journal of physiology, Cell physiology 301 (2011) C1281–1289.
[111] H. Ouadid-Ahidouch, I. Dhennin-Duthille, M. Gautier, H. Sevestre, A. Ahidouch, TRP channels: diagnostic markers and therapeutic targets for breast cancer? Trends Mol. Med. 19 (2013) 117–124.
[112] X. Yu, M. Yu, Y. Liu, S. Yu, TRP channel functions in the gastrointestinal tract, Semin. Immunopathol. 38 (2016) 385–396.
[113] K. Takeda, R. Kimura, N. Nishigaki, S. Sato, A. Okamoto, K. Watanabe, S. Yasui, Humoral hypercalcemia of malignancy with a parathyroid hormone-related peptide-secreting intrahepatic cholangiocarcinoma accompanied by a gastric Cancer, Case Rep. Endocrinol. 2017 (2017) 7012520.
[114] T. Yoshii, T. Yoshikawa, O. Kobayashi, M. Sairenji, Y. Kameda, [Recurrent gastric cancer with hypercalcemia that represented elevated serum level of parathyroid hormone related protein (PTHrP) and rapid clinical course], Nihon Shokakibyo Gakkai zasshi = Japan. J. Gastroenterol. 97 (2000) 175–180.
[115] S. Monno, A. Nagata, S. Furuta, Hypercalcemia of cancer in the digestive tract, J. Clin. Gastroenterol. 9 (1987) 78–82.
[116] J. Abramowitz, E. Yildirim, L. Birnbaumer, The TRPC family of ion channels: relation to the TRP superfamily and role in receptor- and Store-operated calcium entry, in: W.B. Liedtke, S. Heller (Eds.), TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades, 2007 Boca Raton (FL).
[117] H.N. Jiang, B. Zeng, Y. Zhang, N. Daskoulidou, H. Fan, J.M. Qu, S.Z. Xu, Involvement of TRPC channels in lung cancer cell differentiation and the correlation analysis in human non-small cell lung cancer, PLoS One 8 (2013) e67637.
[118] V.C. Bomben, H.W. Sontheimer, Inhibition of transient receptor potential canonical channels impairs cytokinesis in human malignant gliomas, Cell Prolif. 41 (2008) 98–121.
[119] J. Nasman, G. Bart, K. Larsson, L. Louhivuori, H. Peltonen, K.E. Akerman, The orexin OX1 receptor regulates Ca2+ entry via diacylglycerol-activated channels in differentiated neuroblastoma cells, J. Neurosci. 26 (2006) 10658–10666.
[120] R. Cai, X. Ding, K. Zhou, Y. Shi, R. Ge, G. Ren, Y. Jin, Y. Wang, Blockade of TRPC6 channels induced G2/M phase arrest and suppressed growth in human gastric cancer cells, Int. J. Cancer 125 (2009) 2281–2287.
[121] P. Ge, L. Wei, M. Zhang, B. Hu, K. Wang, Y. Li, S. Liu, J. Wang, Y. Li, TRPC1/3/6 inhibition attenuates the TGF-beta1-induced epithelial-mesenchymal transition in gastric cancer via the Ras/Raf1/ERK signaling pathway, Cell Biol. Int. 42 (2018) 975–984.
[122] T. Brabletz, R. Kalluri, M.A. Nieto, R.A. Weinberg, EMT in cancer, Nature reviews, Cancer 18 (2018) 128–134.
[123] M. Ding, H. Wang, C. Qu, F. Xu, Y. Zhu, G. Lv, Y. Lu, Q. Zhou, H. Zhou, X. Zeng, J. Zhang, C. Yan, J. Lin, H.R. Luo, Z. Deng, Y. Xiao, J. Tian, M.X. Zhu, X. Hong, Pyrazolo[1,5-a]pyrimidine TRPC6 antagonists for the treatment of gastric cancer, Cancer Lett. 432 (2018) 47–55.
[124] B. Nilius, G. Owsianik, T. Voets, J.A. Peters, Transient receptor potential cation channels in disease, Physiol. Rev. 87 (2007) 165–217.
[125] Y. Kaneko, A. Szallasi, Transient receptor potential (TRP) channels: a clinical perspective, Br. J. Pharmacol. 171 (2014) 2474–2507.
[126] A. Hantute-Ghesquier, A. Haustrate, N. Prevarskaya, V. Lehen'kyi, TRPM family channels in Cancer, Pharmaceuticals 11 (2018).
[127] S. Almasi, A.M. Sterea, W. Fernando, D.R. Clements, P. Marcato, D.W. Hoskin, S. Gujar, Y. El Hiani, TRPM2 ion channel promotes gastric cancer migration, invasion and tumor growth through the AKT signaling pathway, Sci. Rep. 9 (2019) 4182.
[128] S. Almasi, B.E. Kennedy, M. El-Aghil, A.M. Sterea, S. Gujar, S. Partida-Sanchez, Y. El Hiani, TRPM2 channel-mediated regulation of autophagy maintains mitochondrial function and promotes gastric cancer cell survival via the JNK-signaling pathway, J. Biol. Chem. 293 (2018) 3637–3650.
[129] T. Maeda, A. Suzuki, K. Koga, C. Miyamoto, Y. Maehata, S. Ozawa, R.I. Hata, Y. Nagashima, K. Nabeshima, K. Miyazaki, Y. Kato, TRPM5 mediates acidic extracellular pH signaling and TRPM5 inhibition reduces spontaneous metastasis in mouse B16-BL6 melanoma cells, Oncotarget 8 (2017) 78312–78326.
[130] I. Dhennin-Duthille, M. Gautier, I. Korichneva, H. Ouadid-Ahidouch, TRPM7 involvement in cancer: a potential prognostic factor, Magnes. Res. 27 (2014) 103–112.
[131] B.J. Kim, C. Hong, Role of transient receptor potential melastatin type 7 channel in gastric cancer, Integr. Med. Res. 5 (2016) 124–130.
[132] B.J. Kim, E.J. Park, J.H. Lee, J.H. Jeon, S.J. Kim, I. So, Suppression of transient receptor potential melastatin 7 channel induces cell death in gastric cancer, Cancer Sci. 99 (2008) 2502–2509.
[133] B.J. Kim, Involvement of melastatin type transient receptor potential 7 channels in ginsenoside Rd-induced apoptosis in gastric and breast cancer cells, J. Ginseng Res. 37 (2013) 201–209.
[134] B.J. Kim, S.Y. Nah, J.H. Jeon, I. So, S.J. Kim, Transient receptor potential melastatin 7 channels are involved in ginsenoside Rg3-induced apoptosis in gastric cancer cells, Basic Clin. Pharmacol. Toxicol. 109 (2011) 233–239.
[135] H.C. Chen, J. Xie, Z. Zhang, L.T. Su, L. Yue, L.W. Runnels, Blockade of TRPM7 channel activity and cell death by inhibitors of 5-lipoxygenase, PLoS One 5 (2010) e11161.
[136] S. Zierler, G. Yao, Z. Zhang, W.C. Kuo, P. Porzgen, R. Penner, F.D. Horgen, A. Fleig, Waixenicin A inhibits cell proliferation through magnesium-dependent block of

transient receptor potential melastatin 7 (TRPM7) channels, J. Biol. Chem. 286 (2011) 39328–39335.
[137] M.C. Kim, H.J. Lee, B. Lim, K.T. Ha, S.Y. Kim, I. So, B.J. Kim, Quercetin induces apoptosis by inhibiting MAPKs and TRPM7 channels in AGS cells, Int. J. Mol. Med. 33 (2014) 1657–1663.
[138] L.J. Wu, T.B. Sweet, D.E. Clapham, International union of basic and clinical pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family, Pharmacol, Rev. 62 (2010) 381–404.
[139] M. Gautier, I. Dhennin-Duthille, A.S. Ay, P. Rybarczyk, I. Korichneva, H. Ouadid-Ahidouch, New insights into pharmacological tools to TR(i)P cancer up, Br. J. Pharmacol. 171 (2014) 2582–2592.
[140] L.V. Weber, K. Al-Refae, G. Wolk, G. Bonatz, J. Altmuller, C. Becker, G. Gisselmann, H. Hatt, Expression and functionality of TRPV1 in breast cancer cells, Breast cancer 8 (2016) 243–252.
[141] C. Lozano, C. Cordova, I. Marchant, R. Zuniga, P. Ochova, R. Ramirez-Barrantes, W.A. Gonzalez-Arriagada, B. Rodriguez, P. Olivero, Intracellular aggregated TRPV1 is associated with lower survival in breast cancer patients, Breast cancer 10 (2018) 161–168.
[142] H. Fan, Y.X. Shen, Y.F. Yuan, Expression and prognostic roles of TRPV5 and TRPV6 in non-small cell lung cancer after curative resection, Asian Pac. J. Cancer Prev. 15 (2014) 2559–2563.
[143] R. Xie, J. Xu, Y. Xiao, J. Wu, H. Wan, B. Tang, J. Liu, Y. Fan, S. Wang, Y. Wu, T.X. Dong, M.X. Zhu, J.M. Carethers, H. Dong, S. Yang, Calcium promotes human gastric Cancer via a novel coupling of calcium-sensing receptor and TRPV4 channel, Cancer Res. 77 (2017) 6499–6512.
[144] B. Tang, J. Wu, M.X. Zhu, X. Sun, J. Liu, R. Xie, T.X. Dong, Y. Xiao, J.M. Carethers, S. Yang, H. Dong, VPAC1 couples with TRPV4 channel to promote calcium-dependent gastric cancer progression via a novel autocrine mechanism, Oncogene (2019).
[145] J.B. Peng, X.Z. Chen, U.V. Berger, S. Weremowicz, C.C. Morton, P.M. Vassilev, E.M. Brown, M.A. Hediger, Human calcium transport protein CaT1, Biochem. Biophys. Res. Commun. 278 (2000) 326–332.
[146] J.G. Hoenderop, R. Vennekens, D. Muller, J. Prenen, G. Droogmans, R.J. Bindels, B. Nilius, Function and expression of the epithelial Ca(2+) channel family: comparison of mammalian ECaC1 and 2, J. Physiol. 537 (2001) 747–761.
[147] J. Chow, M. Norng, J. Zhang, J. Chai, TRPV6 mediates capsaicin-induced apoptosis in gastric cancer cells–Mechanisms behind a possible new "hot" cancer treatment, Biochim. Biophys. Acta 1773 (2007) 565–576.
[148] M. Tominaga, [Capsaicin receptor TRPV1], Brain and nerve = Shinkei kenkyu no shinpo 60 (2008) 493–501.
[149] L. Zhang, Y. Hou, H. Ashktorab, L. Gao, Y. Xu, K. Wu, J. Zhai, L. Zhang, The impact of C-MYC gene expression on gastric cancer cell, Mol. Cell. Biochem. 344 (2010) 125–135.
[150] J. Hajdu, L. Kozma, I. Kiss, Z. Szentkereszty, S. Szakall, I. Ember, Is the presence of distant metastasis associated with c-myc amplification in gastric cancer? Acta Chir. Hung. 36 (1997) 119–121.
[151] I. Ninomiya, Y. Yonemura, H. Matsumoto, K. Sugiyama, A. Yamaguchi, K. Miwa, I. Miyazaki, [Expression of c-myc product in gastric cancer: preliminary report], Nihon Geka Gakkai zasshi 90 (1989) 628.
[152] A.F. Tracz, L. Peczek, K. Zuk, K. Stec-Michalska, B. Nawrot, [Effect of Helicobacter pylori eradication on the expression level of SATB1 and c-Myc genes in gastric mucosa of patients with family history of gastric cancer], Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego 34 (2013) 269–276.
[153] N. Zhan, Y.Y. Xiong, J. Lan, B.C. Wang, S.F. Tian, S.P. Yu, [Relationship between Helicobacter pylori infection and expression of c-myc, Bcl-2, and Bax protein in different gastric mucosa lesions], Ai zheng = Aizheng = Chin. J. Cancer 22 (2003) 1034–1037.
[154] I.J. Silva-Fernandes, M.K. Alves, V.P. Lima, M.A. de Lima, M.A. Barros, M.V. Ferreira, S.H. Rabenhorst, Differential expression of MYC in H. Pylori-related intestinal and diffuse gastric tumors, Virchows Arch. 458 (2011) 725–731.
[155] G.X. Zhang, Y.H. Gu, Z.Q. Zhao, S.F. Xu, H.J. Zhang, H.D. Wang, B. Hao, Coordinate increase of telomerase activity and c-Myc expression in Helicobacter pylori-associated gastric diseases, World J. Gastroenterol. 10 (2004) 1759–1762.
[156] G.X. Zhang, Z.Q. Zhao, Y.H. Gu, S.F. Xu, H.J. Zhang, [Coordinated expression of c-Myc and telomerase activity in Helicobacter pylori infected gastric diseases], Zhonghua nei ke za zhi 42 (2003) 618–620.
[157] S. Beceiro, J.N. Radin, R. Chatuvedi, M.B. Piazuelo, D.J. Horvarth, H. Cortado, Y. Gu, B. Dixon, C. Gu, I. Lange, D.L. Koomoa, K.T. Wilson, H.M. Algood, S. Partida-Sanchez, TRPM2 ion channels regulate macrophage polarization and gastric inflammation during Helicobacter pylori infection, Mucosal Immunol. 10 (2017) 493–507.
[158] H. Mihara, N. Suzuki, J.S. Muhammad, S. Nanjo, T. Ando, H. Fujinami, S. Kajiura, A. Hosokawa, T. Sugiyama, Transient receptor potential vanilloid 4 (TRPV4) silencing in Helicobacter pylori-infected human gastric epithelium, Helicobacter 22 (2017).
[159] S. Fu, H. Hirte, S. Welch, T.T. Ilenchuk, T. Lutes, C. Rice, N. Fields, A. Nemet, D. Dugourd, S. Piha-Paul, V. Subbiah, L. Liu, J. Gong, D. Hong, J.M. Stewart, Erratum to: first-in-human phase I study of SOR-C13, a TRPV6 calcium channel inhibitor, in patients with advanced solid tumors, Invest. New Drugs 35 (2017) 397.
[160] S. Fu, H. Hirte, S. Welch, T.T. Ilenchuk, T. Lutes, C. Rice, N. Fields, A. Nemet, D. Dugourd, S. Piha-Paul, V. Subbiah, L. Liu, J. Gong, D. Hong, J.M. Stewart, First-in-human phase I study of SOR-C13, a TRPV6 calcium channel inhibitor, in patients with advanced solid tumors, Invest. New Drugs 35 (2017) 324–333.
[161] C.V. Bowen, D. DeBay, H.S. Ewart, P. Gallant, S. Gormley, T.T. Ilenchuk, U. Iqbal, T. Lutes, M. Martina, G. Mealing, N. Merkley, S. Sperker, M.J. Moreno, C. Rice, R.T. Syvitski, J.M. Stewart, In vivo detection of human TRPV6-rich tumors with anti-cancer peptides derived from soricidin, PLoS One 8 (2013) e58866.
[162] H. Xue, Y. Wang, T.J. MacCormack, T. Lutes, C. Rice, M. Davey, D. Dugourd, T.T. Ilenchuk, J.M. Stewart, Inhibition of Transient Receptor Potential Vanilloid 6 channel, elevated in human ovarian cancers, reduces tumour growth in a xenograft model, J. Cancer 9 (2018) 3196–3207.