The Impact of TRPV1 on Cancer Pathogenesis and Therapy: A Systematic Review

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Abstract
The transient receptor potential cation channel subfamily V member 1 (TRPV1) is a transmembrane protein that can be activated by various physical and chemical stimuli and is associated with pain transduction. In recent years, TRPV1 was discovered to play essential roles in cancer tumorigenesis and development, as TRPV1 expression levels are altered in numerous cancer cell types. Several investigations have discovered direct associations between TRPV1 and cancer cell proliferation, cell death, and metastasis. Furthermore, about two dozen TRPV1 agonists/antagonists are under clinical trial, as TRPV1 is a potential drug target for treating various diseases. Hence, more researchers are focusing on the effects of TRPV1 agonists or antagonists on cancer tumorigenesis and development. However, both agonists and antagonists may reveal anti-cancer effects, and the effect may function via or be independent of TRPV1. In this review, we provide an overview of the impact of TRPV1 on cancer cell proliferation, cell death, and metastasis, as well as on cancer therapy and the tumor microenvironment, and consider the implications of using TRPV1 agonists and antagonists for future research and potential therapeutic approaches.

Key words: TRPV1, proliferation, cell death, metastasis, therapy, microenvironment.

Introduction
Cancer is increasingly recognized as a serious public health concern worldwide; however, the mechanisms of tumorigenesis and development are complex and not well understood. The transformation from normal cells to cancer cells is caused by numerous alterations in various signaling pathways, which lead to enhanced cell proliferation, inhibition of programmed cell death, migration, and invasion.

Many proteins in cancer cells exhibit enhanced or reduced expression levels compared with the levels in normal cells, and these proteins play important roles in tumorigenesis and development. The recently identified transient receptor potential (TRP) channels are subject to expression changes in cancer cells [1, 2]. So far, the most studied members of the family have been TRPC1, TRPV6, TRPM1, and TRPM8 [3]. However, in the previous two decades, researchers have shown an increased interest in TRP subfamily V member 1 (V1), as it appears to play multiple roles in cancer [4, 5]. Alterations in both the expression and activity of TRPV1 are associated with tumorigenesis and therapy. The activation of the cation channel TRPV1 by heat and small molecules permeabilizes cells to allow Ca2+ and Na+ influx [6]. A considerable amount of literature has been published on the effects of TRPV1 agonists and antagonists on tumorigenesis and development.

In this review, we summarize the observations reported to date of the changes in TRPV1 expression and channel activity associated with cancers and the effects of these alterations on cancer cell proliferation, death, and metastasis, and the tumor...
microenvironment. We further discuss the therapeutic potential of targeting TRPV1 in cancer cells. To comprehensively understand the effects of TRPV1 activation on proliferation, cell death, metastasis, and therapy, we provide tables detailing the investigations reviewed so far regarding relevant drug applications, drug concentrations, tissue/cell types, and their effects on the treatment of tumors.

What is TRPV1

The human TRPV1 protein is encoded by the TRPV1 gene located on chromosome 17p13. TRPV1 belongs to the transient receptor potential channel vanilloid subfamily and is also known as the capsaicin receptor and vanilloid receptor 1 (VR1). TRPV1 predominantly forms a homotetramer, with each subunit consisting of six transmembrane segments, a pore-forming loop between the fifth and sixth transmembrane domains, and cytoplasmic C- and N-terminal domains [7-10]. Initially, TRPV1 was found to be expressed prominently in small-to-medium-sized neurons of the dorsal root, trigeminal, and vagal ganglia [8, 11], and was discovered to be involved in pain transduction [12]. Later, TRPV1 expression was reported in non-neuronal system cells, such as arteriolar smooth muscle cells [13, 14] and the bladder urothelium [15]. TRPV1 is a nonselective cation channel that can be activated by different physical and chemical stimuli, including temperatures over 43°C, acidic conditions (pH <6), and vanilloids [8, 9, 16]. The activation of TRPV1 induces the cellular influx of Ca²⁺ and Na⁺ ions [17-19], and the excess intracellular Ca²⁺ and Na⁺ leads to cell death [20]. Numerous putative endogenous and exogenous agonists and antagonists of TRPV1 have been identified and summarized (Table 1). Because TRPV1 is a promising therapeutic target in many human diseases and conditions [21, 22], about two dozen TRPV1 agonists/antagonists are being used in clinical trials, many of which are concerned with pain and inflammation [23, 24].

Expression of TRPV1 in cancers

TRPV1 expression has been reported to be higher in human primary brain tumors than tumor-free brains. Furthermore, its expression positively correlates with the grading of tumors [64]. Compared with in a normal pancreas, TRPV1 mRNA expression is significantly upregulated in human pancreatic cancer and chronic pancreatitis [65]. Elevated TRPV1 expression has also been verified in squamous cell carcinoma of the human tongue, prostate carcinoma, and breast cancer [66-68]. All the above published work indicated that TRPV1 expression is upregulated in cancers.

TRPV1 regulates proliferation

TRPV1 channel activation increases the intracellular Ca²⁺ concentration, and Ca²⁺ signaling plays an essential role in cancer cell proliferation, regulation, and survival [69]. A few studies have investigated the associations between changes in TRPV1 protein expression and the regulation of cancer cell proliferation. The majority of studies focused on the effects of TRPV1 agonists or antagonists on cell proliferation; however, some of these chemicals regulate proliferation independently of TRPV1 because they either play roles in cells

Table 1. Endogenous and exogenous ligands of TRPV1.

| Ligands | Ref. |
|---------|-----|
| Endogenous agonists: | |
| Anandamide | [25] |
| N-arachidonoyldopamine | [26] |
| N-oleyleldopamine | [27] |
| R(+)-methanandamide | [25] |
| 12- and 15-hydroperoxyeicosatetraenoic acid | [28] |
| 5- and 15-hydroxyeicosatetraenoic acid | [28] |
| Leukotriene B4 | [28] |
| 9- and 13-hydroxy-octadecadienoic acid | [12] |
| 9- and 13-oxo-octadecadienoic acid | [12] |
| Oleylethanolamide | [29] |
| Palmitoylethanolamide | [30] |
| Lysophosphatidic acid | [31] |
| Oxytocin | [32] |
| Exogenous agonists: | |
| 2-aminoethoxydiphenyl borate | [33] |
| 4α-phorbol-12,13-didecanoate | [34] |
| Orotic acid | [35] |
| Capsaicin | [8] |
| Piperine | [36] |
| Resiniferatoxin | [37] |
| Gingerol | [38] |
| Evodiamine | [39] |
| Cannabidiol | [40] |
| Cannabigerol | [41] |
| Polygodial | [42] |
| Vanillol | [43] |
| MD-652 | [44] |
| Linopirdine | [45] |
| Endogenous antagonists: | |
| Resolin D2 | [46] |
| Noradrenaline | [47] |
| Exogenous antagonists: | |
| Capsazepine | [48] |
| Iodo-resiniferatoxin | [49] |
| Hypericum perforatum | [50] |
| JNJ-17203212 | [51] |
| BCTC | [52] |
| Thapsigargin | [53] |
| Yohimbine | [54] |
| JYI.1421 | [55] |
| Caffeic acid | [56] |
| Asivatrep | [57] |
| SB-366791 | [58] |
| A-1165442 | [59] |
| AMG 9810 | [60] |
| AG489, AG505 | [61] |
| ABT-102, AMG-517, AZD-1386, DWP-05195, GRC-6211, JTS-653, MK-2295, PHE377, SB-705498 | [62, 63] |

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without TRPV1 expression or affect other receptors. In this section, we describe the roles and underlying mechanisms of the TRPV1 gene and the effects of TRPV1 agonists and antagonists, both independently of and dependent on TRPV1 and other receptors, on proliferation (Table 2).

**TRPV1 expression suppresses cell proliferation**

The overexpression of TRPV1 in intestinal epithelial HCT116 cells suppressed the phosphorylation of epidermal growth factor receptor (EGFR) at Y1068, a receptor that is associated with a variety of pro-proliferative signaling pathways [70]. According to the results of in vitro studies, the depletion of Trpv1 in mice led to the constitutive phosphorylation of EGFR at Y1068 and subsequently increased the expression of the oncogenes c-Fos and c-Myc, indicating that TRPV1 is a negative regulator in intestinal tumorigenesis [70]. The proliferation of human melanoma A2058 and A375 cells was inhibited after TRPV1 overexpression, as the overexpression induced apoptosis via the calcineurin-ATF3-p53 pathway in these cells [71]. It was reported that TRPV1 overexpression prevented the proliferation of human pancreatic cancer PANC-1 cells and human skin carcinoma A431 cells by promoting EGFR ubiquitination and degradation [72, 73]. The evidence presented thus far supports the hypothesis that TRPV1 acts to suppress cancer cell proliferation.

**Table 2. Role of TRPV1 in Proliferation.**

| Drug      | Dose (μM) | Duration (h) | Tissue/Cell Type | Mechanism                                                                                     | Outcomes                                      | Ref. |
|-----------|-----------|--------------|-----------------|------------------------------------------------------------------------------------------------|-----------------------------------------------|------|
| Capsaicin | 100       | 24           | Human colorectal cancer HCT116 cells | Overexpression of TRPV1 suppressed EGFR phosphorylation at Y1068 and subsequently increased the expression of the oncogenes c-Fos and c-Myc | Proliferation ↓                              | [70] |
| Capsaicin | 50-400    | 24-48        | Human renal carcinoma 786-O cells | Activated p38 and JNK MAPK pathways to induce apoptosis                                      | Proliferation ↓                              | [75] |
| Capsaicin | 0.1-20    | 48           | Human prostate tumor androgen-responsive LNCaP cells | Activated PI3K and p44/42 MAPK pathways to suppress ceramide production and increased androgen receptor expression | Proliferation ↓                              | [76] |
| Capsaicin | 15        | 96-120       | Human ESCC cell lines Eca109 | Induced apoptosis by increasing the phosphorylation level of ERK and attenuating STAT3 phosphorylation | Proliferation ↓                              | [77] |
| Capsaicin | 100       | 24           | Human hepatocellular carcinoma PLC/PRF/5 cells | Disrupted mitochondrial membrane potential (ΔΨm) independently of TRPV1 synthesis to induce apoptosis | Proliferation ↓                              | [83] |
| Capsaicin | 100       | 24-72        | Human pancreatic neuroendocrine tumor BON and QCP-1 cells | Inhibited MKK3-induced p38 activation                                                        | Proliferation ↓                              | [84] |
| Capsaicin | 75        | 24-48        | Human nasopharyngeal carcinoma CNE2 and SUNE1 cells | Disrupted mitochondrial membrane potential and suppressed ATP synthesis to induce apoptosis | Proliferation ↓                              | [85] |
| Cannabidiol | 10        | 48           | Human breast carcinoma cell line MCF-7 cells | Induced apoptosis via activation of CB2 and TRPV1 to elevate reactive oxygen species | Proliferation ↓                              | [78] |
| Cannabidiol | 10        | 24           | Human colon adenocarcinoma cell line Caco-2 cells | Reduced the phosphorylation level of Akt, which was dependent on TRPV1 and CB1               | Proliferation ↓                              | [79] |
| Noradrenaline | 100    | 24           | Human prostate tumor androgen-resistant PC-3 cells | Activated both alpha 1D-AR and TRPV1 and, subsequently, elicited the PLC/PKC/ERK pathways     | Proliferation ↓                              | [80] |
| Cannabigerol | 10        | 24           | Human colon adenocarcinoma cell line Caco-2 cells | Stimulated ROS generation, increased CHOP expression level, and promoted apoptosis            | Proliferation ↓                              | [85] |
| AEA        | 10        | 24-72        | The murine neuroblastoma cell line N1E-115 | Seemed to occur via a lipid raft-dependent mechanism                                          | Proliferation ↓                              | [86] |

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TRPV1 agonist capsaicin affects cell proliferation dependent on TRPV1

Ligand-induced autophosphorylation of the EGFR results in phospholipase C (PLC) activation, which cleaves phosphatidylinositol-4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol triphosphate (IP3). Then IP3 triggers TRPV1 and Ca2+ influx, which activates calpain and subsequently protein tyrosine phosphatase 1B (PTP1B). PTP1B then dephosphorylates EGFR to inhibit intestinal epithelial HCT116 cell proliferation [70]. Amantini et al. found that the capsaicin-induced arrest of the cell cycle in the G0/G1 phase and apoptosis mediated by the ATM-p53 and ATM-Fas/CD95 pathways inhibited the proliferation of human urothelial cancer RT4 cells but not that of TCCSUP, J82, or EJ urothelial cancer cell lines, as TRPV1 showed high expression levels in RT4 cells [74]. Furthermore, this antiproliferation effect was completely rescued by capsazepine and SB366791, two antagonists of TRPV1 [74]. Another study illustrated the capsaicin suppression of human renal carcinoma 786-O cell proliferation, which was also reversed by capsazepine treatment [75]. Additionally, capsaicin induced apoptosis by activating the p38 and JNK/MAPK pathways, suppressing proliferation [75]. However, the opposite effect of capsaicin on proliferation has also been reported. For example, Malagarie-Cazenave et al. discovered that capsaicin promoted human prostate tumor androgen-responsive LNCaP cell growth by activating the PI3K and p44/42 MAPK pathways to suppress ceramide production as well as increasing androgen receptor (AR) expression [76]. The proliferative effect of capsaicin on LNCaP cells was reversed by the TRPV1 antagonists 5-iodo-resiniferatoxin (I-RTX), capsazepine, and SB366791 [76]. In a similar study, Huang et al. demonstrated that capsaicin treatment promoted the proliferation of human esophageal squamous cell carcinoma (ESCC) Eca109 cells, and the effect was abolished by the TRPV1 receptor antagonist AMG9810 [77]. The information detailed in Table 2 indicates that the effect of capsaicin on proliferation is dependent on its concentration: low-dose capsaicin promotes cancer cell proliferation, whereas high-dose capsaicin prevents proliferation.

Some agonists affect cell proliferation via both TRPV1 and other receptors

Some pharmacological regulators activate not only TRPV1 but also other reporters to affect cancer cell proliferation. For instance, cannabidiol prevented the proliferation of human breast cancer MBA-MD-231 cells through the activation of cannabinoid receptor type 2 (CB2) and TRPV1 to elevate intracellular Ca2+ and ROS generation and induce apoptosis [78]. The respective CB2 and TRPV1 antagonists SR144528 and I-RTX partially rescued the antiproliferation effect of cannabidiol [78]. Similarly, Aviello et al. suggested that cannabidiol reduces the phosphorylation levels of Akt to prevent human colon adenocarcinoma Caco-2 cells growth. This effect was counteracted by the CB1 receptor antagonists rimonabant and AM251 and the TRPV1 receptor antagonist capsazepine [79]. Noradrenaline has been shown to induce Ca2+ flux by activating alpha 1D-AR and TRPV1 and, subsequently, eliciting the extracellular signal-regulated kinase 1/2 (ERK1/2), PLC, and PKC pathways to promote the proliferation of human prostate tumor PC-3 cells. This effect was completely reversed by alpha 1D-AR/TRPV1 double-knockdown or treatment with a combination of clopenphendioxan and capsazepine [80].

TRPV1 agonists affect cell proliferation independently of TRPV1

Several research groups have reported TRPV1 agonists affecting cell proliferation in a TRPV1-independent manner. These agonists perform proliferation functions through two mechanisms. Firstly, the chemicals contribute to antiproliferation; for example, in the study carried out by Zhang et al., capsaicin induced apoptosis by increasing ERK phosphorylation and alleviating STAT3 phosphorylation, thus inhibiting the proliferation of a hepatocellular carcinoma cell line (PLC/PRF/5) cells. This was independent of TRPV1 [81] because no TRPV1 expression was detected in PLC/PRF/5 or the other hepatocellular carcinoma cell lines (HuH7 and HepG2) [81]. Capsaicin suppressed prostate cancer androgen-resistant PC-3 cell proliferation by inducing apoptosis via the production of ROS by the mitochondria and a decrease in perturbations in the inner transmembrane potential (ΔΨm), which could not be reversed by capsazepine treatment, indicating TRPV1 was not involved [82]. Capsaicin reduced the proliferation of human pancreatic neuroendocrine tumor BON and QGP-1 cells by disrupting the mitochondrial membrane potential and suppressing ATP synthesis to induce apoptosis, which was unaffected by a reduction in TRPV1 expression levels [83]. Recently, we found that capsaicin inhibited cell proliferation in nasopharyngeal carcinoma (NPC) CNE2 and SUNE1 cells by directly targeting p38, leading to MKK3-p38 axis blockage, in a TRPV1-independent manner [84].

Secondly, the chemicals play vital roles in proliferation by activating receptors other than TRPV1. For example, cannabigerol, an agonist of TRPV1, prevented human Caco-2 cells growth by
increasing CHOP mRNA levels and ROS production to stimulate apoptosis [85]. This effect was alleviated in TRPM8-knockdown cells but not in cells treated with the TRPV1 antagonist ruthenium red [85]. N-arachidonylethanolamine (anandamide, AEA) inhibited the proliferation of murine neuroblastoma N1E-115 cells, and proliferation was rescued by a lipid raft disruptor, methyl-b-cyclodextrin, but not by the TRPV1 antagonist capsazepine [86].

**TRPV1 regulates cell death**

Studies have demonstrated that pathological changes in or the pharmacological regulation of TRPV1 expression levels affect cell death. As mentioned in the previous section, TRPV1 overexpression or agonist treatment induces apoptosis, preventing cancer cell proliferation. Therefore, in this section, we focus on the roles of TRPV1 in cell death and provide a summary of the information (Table 3).

**TRPV1 expression affects cell death**

In 2018, Yang et al. published a paper in which they described the overexpression of TRPV1 inducing a pro-apoptotic effect mediated by p53 activation [71]. In 2016, Pecze and co-workers demonstrated that the ectopic expression of TRPV1 in human breast cancer MCF-7 cells led to apoptosis [87]. The overexpression of fibulin-5, a multifunctional extracellular matrix (ECM) protein encoded by the FBLN5 gene, induced apoptosis in human colorectal cancer HT-29 and SW480 cells by enhancing the phosphorylation of p38 and ERK and alleviating the level of p-Akt by downregulating TRPV1 [88]. These studies indicate that TRPV1 can promote or inhibit cell death in a cancer- or tissue-specific manner.

**TRPV1 agonists affect cell death dependent on TRPV1**

Apoptotic or necrotic cell death can be triggered by calcium influx [89]. A large body of evidence shows the Ca^{2+}-channel-activating function of TRPV1 evoked by its agonists is responsible for these chemically induced cell deaths. The overexpression of TRPV1 in human breast cancer MCF-7 cells has been reported to have no effect on cell numbers; however, the increased expression of exogenous TRPV1 meant that necrosis was more effectively induced by the capsaicin activation of TRPV1 and the subsequent upregulation of c-Fos and the necrotic marker RIP3 [90]. Arachidonyl ethanolamide induced apoptosis in human uterine cervix cancer C299, Caski, and HeLa cells, and this was reversed by capsazepine [91]. Capsaicin induced apoptosis in human osteosarcoma G292 cells by activating endoplasmic reticulum TRPV1, which led to cytochrome C release [92]. TRPV1 agonists, capsaicin and MRS1477, stimulated ROS production and mitochondrial membrane depolarization to induce apoptosis, which was blocked by capsazepine [93]. In human endometrial cancer Ishikawa cells, AEA and cannabidiol caused apoptosis by activating TRPV1 to increase intracellular Ca^{2+} levels [94]. Capsaicin also induced apoptotic and necrotic cell death in human breast cancer SUM149PT cells, and the reduction in cell viability mediated by capsaicin was diminished by capsazepine treatment [68]. Taken together, it appears agonists of TRPV1, such as capsaicin, arachidonyl ethanolamide, MRS1477, AEA and cannabidiol, induce cell death by activating TRPV1 channels.

**TRPV1 agonists and antagonists affect cell death independently of TRPV1**

In contrast, several studies have revealed that certain TRPV1 pharmacological regulators trigger cell death independently of TRPV1. For example, the induction of apoptosis in human cutaneous melanoma A375 cells by the TRPV1-activator AEA was completely counteracted by methyl-β-cyclodextrin, a membrane cholesterol depletory, but not by capsazepine [95]. A similar effect was observed in non-melanoma skin cancer and colorectal cancer [96]. Capsaicin treatment induced apoptosis in methylcholanthrene-induced fibrosarcoma Meth A cells, and this could not be inhibited by the antagonists capsazepine and I-RTX [97]. Capsaicin induced apoptosis in human small cell lung cancer H69, DMS 114, DMS 53, and H82 cells by activating TRPV6 and, subsequently, inducing calpain-1 and calpain-2 activity. However, this pro-apoptotic effect was not abolished by the TRPV1 antagonist SB366791 [98]. Another report showed capsaicin-induced apoptosis in gastric cancer AGS cells was mediated by TRPV6 rather than TRPV1 [99]. Our recent results also indicate that capsaicin promoted apoptosis in NPC CNE2 and SUNE1 cells by inhibiting MKK3-induced p38 activation in a TRPV1-independent manner [84]. R(+)-methanandamide (MA) treatment increased COX-2 and PPARγ activity and induced the apoptosis of human cervical carcinoma HeLa cells, an effect that was unaltered by capsazepine [100]. The promotion of necrosis by resiniferatoxin was associated with mitochondrial dysfunction and was not reversed by I-RTX [101]. Furthermore, Gonzales et al. illustrated that both capsaicin and capsazepine induce cell death independently of TRPV1 in oral squamous cell carcinoma HSC3, SCC4, and SCC25 cells [102].
TRPV1 regulates cancer metastasis

Metastasis, which is one of the major causes of cancer-related deaths, requires two early events: migration and invasion [103]. Recently, calcium signaling was found to be closely related to carcinogenesis and metastasis [104-106], yet only a few reports mention the role of TRPV1 in cancer cell metastasis. As TRPV1 serves as the main Ca\(^{2+}\)-influx channel, it is reasonable to suggest that TRPV1 could act as an enhancer or inhibitor of migration and invasion in a tissue- or cell-specific manner.

TRPV1 agonists and antagonists affect cell migration dependent on TRPV1

Few published reports describe the direct impact of altering TRPV1 expression on cancer cell metastasis. Most of the studies using agonists or antagonists showed an ambiguous effect of TRPV1 channel activity on migration. On the one hand, Vriens et al. and Waning et al. reported that the activation of TRPV1 can be evoked by hepatocyte growth factor (HGF) and causes the influx of Ca\(^{2+}\) into HepG2 cells following capsaicin treatment, leading to increased cell migration [107, 108]. Another investigation into the pro-migration role of TRPV1 conducted on lymphatic endothelial cells by Nakaniishi et al. found TRPV1 functioning as a pH sensor and was activated by an acidic environment, upregulating the expression of IL-8, and therefore promoting cell migration and invasion [109]. On the other hand, Ramer et al. reported the activation of TRPV1 by MA did not affect cervix adenocarcinoma (HeLa) cell migration but inhibited cell invasion [110]. In addition, a recent study by Xu et al. focusing on the human endometrial cancer Ishikawa cells conducted on lymphatic endothelial cells by Nakanishi et al. found TRPV1 functioned as a pH sensor and was activated by an acidic environment, upregulating the expression of IL-8, and therefore promoting cell migration and invasion [109]. On the other hand, Ramer et al. reported the activation of TRPV1 by MA did not affect cervix adenocarcinoma (HeLa) cell migration but inhibited cell invasion [110]. In addition, a recent study by Xu et al. focusing on the human endometrial cancer Ishikawa cells conducted on lymphatic endothelial cells by Nakanishi et al. found TRPV1 functioned as a pH sensor and was activated by an acidic environment, upregulating the expression of IL-8, and therefore promoting cell migration and invasion [109]. On the other hand, Ramer et al. reported the activation of TRPV1 by MA did not affect cervix adenocarcinoma (HeLa) cell migration but inhibited cell invasion [110]. In addition, a recent study by Xu et al. focusing on the human endometrial cancer Ishikawa cells conducted on lymphatic endothelial cells by Nakanishi et al. found TRPV1 functioned as a pH sensor and was activated by an acidic environment, upregulating the expression of IL-8, and therefore promoting cell migration and invasion [109]. On the other hand, Ramer et al. reported the activation of TRPV1 by MA did not affect cervix adenocarcinoma (HeLa) cell migration but inhibited cell invasion [110]. In addition, a recent study by Xu et al. focusing on the human endometrial cancer Ishikawa cells conducted on lymphatic endothelial cells by Nakanishi et al. found TRPV1 functioned as a pH sensor and was activated by an acidic environment, upregulating the expression of IL-8, and therefore promoting cell migration and invasion [109]. On the other hand, Ramer et al. reported the activation of TRPV1 by MA did not affect cervix adenocarcinoma (HeLa) cell migration but inhibited cell invasion [110].

### Table 3. Role of TRPV1 in Cell Death.

| Drug             | Dose (μM) | Duration (h) | Tissue/cell type | Mechanism                                                                 | Outcomes      | Ref. |
|------------------|-----------|--------------|------------------|---------------------------------------------------------------------------|---------------|------|
| Capsaicin        | 3         | 48/96        | Human breast carcinoma cell line MCF-7 cells | Activated exogenous TRPV1 and, subsequently, upregulated c-Fos and necrotic marker RIP3 | Necrosis [90] |      |
| Capsaicin        | 150       | 24           | Human osteosarcoma G292 cells | Activated endoplasmic reticulum TRPV1 and induced cytochrome C release | Apoptosis [92] |      |
| Capsaicin        | 10        | 72           | Human breast cancer MCF-7 cells | Stimulated ROS production and mitochondrial membrane depolarization | Apoptosis [93] |      |
| Capsaicin        | 150       | 48           | Human breast cancer SUM149PT cells | Activated TRPV1 | Apoptosis [68] |      |
| Capsaicin        | 100       | 72           | Human Methylcholanthrene-induced fibrosarcoma Meth A cells | Decreased Fas-associated factor1 (FAF1) expression level | Apoptosis [97] |      |
| Capsaicin        | 50        | 36           | Human small cell lung cancer H69, DMS 114, DMS 53, and H82 cells | Activated TRPV6 and, subsequently, induced calpain-1 and calpain-2 activation | Apoptosis [98] |      |
| Capsaicin        | 50        | 1/6/24       | Human gastric cancer AGS cells | Disrupted mitochondrial integrity, activated JNK and, thus, led to TRPV6-mediated p53 stabilization | Apoptosis [99] |      |
| Capsaicin        | 37.5/75   | 24/48        | Human nasopharyngeal carcinoma CNE2 and SUNE1 cells | Inhibited p38 phosphorylation mediated by MKK3 | Apoptosis [84] |      |
| Capsaicin        | 150       | 24           | Human oral squamous cell carcinoma HSC3, SCC4 and SCC25 cells | Activated TRPV1 | Apoptosis [91] |      |
| Arachidonyl      | 30        | 48           | Human uterine cervix cancer C299, Caski, and HeLa cells | Activated TRPV1 | Apoptosis [94] |      |
| Ethanalamide     | 50/25     | 48           | Human endometrial cancer Ishikawa cells | A complex mechanism comprising CB1 activation, COX-2, and LOX-derived product synthesis | Apoptosis [95] |      |
| Anandamide/      | 10        | 24           | Human cutaneous melanoma A375 cells | Increased oxidative stress and ER-stress apoptosis | Apoptosis [96] |      |
| Cannabidiol      | 20        | 4            | The murine squamous carcinoma cell line JWF2 and human colorectal cancer cell line, HCA-7 Colony 29 | Induced mitophagy | Apoptosis [93] |      |
| MRS1477          | 2         | 72           | Human breast cancer MCF-7 cells | Stimulated ROS production and mitochondrial membrane depolarization | Apoptosis [93] |      |
| Resiniferatoxin  | 10        | 24-72        | Human cervical carcinoma HeLa cells | Increased COX-2 expression and activity | Apoptosis [100] |      |
| Capsazepine      | 30        | 24           | Human oral squamous cell carcinoma HSC3, SCC4 and SCC25 cells | Induced mitochondrial dysfunction | Necrosis [101] |      |
| Resiniferatoxin  | 30        | 24           | Human bladder cancer T24 and 5637 cells | Stimulated ROS production | Apoptosis [102] |      |
Table 4. Role of TRPV1 in Metastasis.

| Drug       | Dose   | Duration | Tissue/cell type                          | Mechanism                                                                 | Outcomes | Ref.   |
|------------|--------|----------|------------------------------------------|---------------------------------------------------------------------------|----------|--------|
| Capsaicin  | 10 μM  | 400 s    | Hepatoblastoma HepG2 cell                | HGF evoked TRPV1 channel activity, causing Ca\(^{2+}\) influx              | Migration↑| [107]  |
| Capsaicin  | 100 nM | 5 h      | HGF pretreated hepatoblastoma HepG2 (20 ng/mL for 24 h) cells | HGF evoked TRPV1 channel activity, causing Ca\(^{2+}\) influx              | Migration↑| [108]  |
| Capsaicin  | 25/50/100 μM | 24/48 h | Human papillary thyroid carcinoma BCPAP cells | Capsaicin downregulated Twist1, Snail1, MMP2, and MMP9 and upregulated E-cadherin | Migration↓ | Invasion↓ | [111]  |
| Capsaicin  | 100 μM | 24 h     | Urothelial cancer 5637 cells (null-TRPV1) | Capsaicin treatment induced more aggressive gene expression, e.g., MMP1, MMP9, and S100A4 | Migration↑ | Invasion↑ | [115]  |
| Capsaicin  | 25/37.5/75 μM | 48 h    | Human nasopharyngeal carcinoma CNE2 and SUNE1 cells | Capsaicin directly targeted p38 and blocked the MKK3-p38 axis             | Migration↑| [84]    |
| 4α-PDD    | 1 μM   | 5 h      | HGF pretreated hepatoblastoma HepG2 (20 ng/mL for 24 h) cells | HGF evoked TRPV1 channel activity, causing Ca\(^{2+}\) influx              | Migration↑| [108]  |
| MA         | 10 μM  | 72 h     | Cervix adenocarcinoma HeLa cells          | MA elicited TRPV1 activation and upregulated TIMP-1 expression via MAPK pathway, causing decrease in MMP2 | Invasion↓ | [110]  |
| Cannabidiol| 3 μM   | 72 h     | Human lung cancer A549, H358, and H460 cells | CBD elicited TRPV1 activation, upregulated ICAM1 expression via phosphorylating p42/44, and subsequently upregulated TIMP-1 | Migration↑| [114]  |
| AM404      | 5/15/25 μM | 24 h    | Neuroblastoma cells SK-N-SH              | AM404 inhibited NFAT transcriptional activity, thus, downregulating MMP1, MMP2, and MMP7 | Migration↑| [116]  |
| Bortezomib | 10 nM  | 24 h     | Osteosarcoma HOS cell                    | Inhibited TRPV1 degradation                                                | Invasion↓ | [117]  |

**TRPV1 affects cell invasion**

Unlike its effect on migration, the effect of TRPV1 on cancer cell invasion has been relatively well characterized and studied, and TRPV1 is believed to function as an invasion repressor. In 2005, Lazzere et al. showed TRPV1 protein expression levels in urothelial cancer (UC) progressively decreased over progressive cancer metastasis stages [112]. In the same vein, Kalogris et al. found this reduction to be not only translational but also transcriptional in UC. They also showed TRPV1 expression was positively related to survival rate, suggesting TRPV1 could be used as a factor for estimating the prognosis [113].

Evidence suggests TRPV1 may regulate the ECM, which plays a critical role in cell metastasis [12, 13] and, thus, the regulation of cell invasiveness. Ramer et al. demonstrated that the TRPV1 agonist MA can inhibit cell invasion in HeLa cells by inducing the expression of tissue inhibitor of MMPs (TIMP)-1 and, thereby, downregulating MMP2, in a TRPV1 dependent manner [110]. In a later study, the same group found that intercellular adhesion molecule-1 (ICAM1) was upregulated by cannabidiol-elicted TRPV1-activation-mediated p42/44 activation in lung cancer cell lines A549, H358, and H460, subsequently inhibiting cell invasion [114]. Additionally, Xu et al. showed capsaicin-elicted TRPV1 activation downregulated Twist1, Snail1, MMP2, and MMP9 expression and upregulated E-cadherin expression, thereby inhibiting cell invasion by papillary thyroid carcinoma BCPAP cells [111].

**TRPV1 agonists and antagonists affect cell migration independently of TRPV1**

Investigations into TRPV1 commonly focus on the effects of treatment with agonists, e.g., capsaicin and cannabinoids, or antagonists such as capsazepine and AM404. However, the effects on metastasis either from TRPV1 activity alteration or the actions of agonists and antagonists should be interpreted with caution because of the reports of TRPV1 agonists and antagonists regulating cell migration and invasion in a TRPV1-independent manner. For instance, Caprodossi et al. found capsaicin promoted the more aggressive expression of genes, such as MMP1, MMP9, and S100A, and the invasiveness of null-TRPV1 urothelial cancer 5637 cells [115]. Whereas, in NPC, we found capsaicin inhibited cell mobility by blocking MKK3-induced p38 activation in a TRPV1-independent manner [84]. Caballero et al. reported AM404, an antagonist of TRPV1 and CB1, inhibited NFAT transcriptional activity and, thus, downregulated MMP1, MMP2, and MMP7 in neuroblastoma SK-N-SH cells via a mechanism unrelated to TRPV1 [116]. Furthermore, a recent investigation conducted by Punzo et al. reported JWH133 and resiniferatoxin enhanced the antiproliferation, anti-invasion, and apoptosis effects of bortezomib (BTX), a selective, reversible proteasome inhibitor, in osteosarcoma cells. However, this report does not include direct evidence to show if the synergism was exerted by BTX-mediated TRPV1 upregulation or if the TRPV1 upregulation was an unrelated effect of BTX [117].
Table 5. Role of TRPV1 in Cancer Therapy.

| Drug                  | Dose (μM) | Duration (h) | Tissue/cell type                      | Mechanism                                                                 | Outcomes                                      | Ref.   |
|-----------------------|-----------|--------------|---------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------|--------|
| Capsaicin             | 100       | 24           | Human hepatocellular carcinoma PLC/PRF/5 cells | Induced apoptosis by increasing phosphorylation of ERK and attenuating STAT3 phosphorylation | Increased antitumor sensitivity of sorafenib | [81]   |
| Capsaicin             | 150       | 12           | Human bladder transitional cell carcinoma 5637 cells | Inhibited PCNA translocation to the nucleus                               | Increased antitumor efficacy of pirarubicin   | [121]  |
| Capsazepine           | 10        | 6            | Human colorectal cancer HCT116 cells      | Mediated induction of expression of death receptors DR4 and DR5 via ROS-JNK-CHOP pathway, downregulated the expression of cell survival proteins, and upregulated the expression of proapoptotic proteins | Increased antitumor activity of TRAIL         | [125]  |
| Capsazepine/SB366791/ | 10        | 0.5          | Human lung cancer A549 cells              | Induced apoptosis via activation of TRPV1                                  | Enhanced cell death induced by γ-rays         | [118]  |
| AMG9810/BCTC          | 50        | 24           | Human breast carcinoma cell line MCF-7 cells | Increased apoptosis induced by doxorubicin                                | Increased antitumor sensitivity of cisplatin  | [120]  |
| Alpha-lipoic acid     | 300       | 2            | Human breast carcinoma cell line MCF-7 cells | Increased apoptosis induced by doxorubicin                                | Increased antitumor sensitivity of doxorubicin| [122]  |
| Melatonin             | 300       | 24           | Human breast carcinoma cell line MCF-7 cells | Downregulated apoptosis induced by 5-fluorouracil                         | Decreased antitumor sensitivity of 5-fluorouracil| [123]  |

**TRPV1 affects cancer therapy**

**TRPV1 agonists and antagonists affect cancer therapy dependent on TRPV1**

To date, there has been some evidence associating TRPV1 expression with the efficiency of radiotherapy and chemotherapy, and several investigators have published the impact of TRPV1 agonists and antagonists on these treatments. In 2016, Nishino et al. reported that pretreatment with the TRPV1 channel inhibitors capsazepine, SB366791, AMG9810, and BCTC suppressed repair of γ-ray-induced-DNA-damage in human lung cancer A549 cells, indicating TRPV1 antagonists may serve as radiosensitizers, enhancing the efficacy of radiation therapy [118]. Although there is no strong evidence that these chemicals impact the effectiveness of radiotherapy through TRPV1, Masumoto et al. demonstrated that depletion of TRPV1 suppressed the degree of DNA damage induced by γ-irradiation and UVB irradiation [119]. Therefore, it is likely TRPV1 is involved in DNA-damage responses induced by radiotherapy. However, not all the effects and mechanisms have been clarified.

There are many pharmacological regulators of TRPV1, and several studies have focused on the roles of TRPV1 agonists/antagonists in chemotherapy (Table 5). The toxicity of cisplatin on breast cancer MCF-7 cells was found to be increased by TRPV1-channel activation by alpha-lipoic acid (ALA), the effect of which was reversed by the TRPV1 blocker capsazepine [120]. Capsaicin increased the antiproliferative effects of pirarubicin, a major drug used in urinary bladder instillation chemotherapy, and the effect was reversed by capsazepine treatment [121]. In human breast cancer MCF-7 cells, doxorubicin treatment activated TRPV1, resulting in increased intracellular Ca^{2+}, which was reversed by the TRPV1 antagonist melatonin. Furthermore, a combination of doxorubicin and melatonin treatment led to higher apoptosis levels than doxorubicin treatment [122]. TRPV1 was also activated by 5-fluorouracil, inducing apoptosis; however, 5-fluorouracil toxicity was downregulated by the TRPV1-channel inhibitor Hypericum perforatum in breast cancer MCF-7 cells [123]. The TRPV1 agonist resiniferatoxin enhanced the antiproliferation effect of BTX in human osteosarcoma HOS cell lines by aggravating apoptosis [117]. The above-described cases indicate that TRPV1 agonists and chemotherapeutic agents may have synergic effects in cancer therapy. Nevertheless, the roles of TRPV1 antagonists in cancer therapy are controversial.

**TRPV1 agonists and antagonists affect therapy independently of TRPV1**

Several reports show that TRPV1 agonists/antagonists alter the sensitivity of chemotherapeutic agents without stimulating TRPV1. For instance, sorafenib is the standard systemic chemotherapy drug for the treatment of advanced hepatocellular carcinoma [124]; capsaicin enhanced the antitumor sensitivity of sorafenib in hepatocellular carcinoma PLC/PRF/5 cells without obvious TRPV1 expression [81]. Capsazepine amplified the antitumor activity of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) through multiple mechanisms, including promoting the expression of the death receptors DR4 and DR5 via the ROS-JNK-CHOP pathway; downregulating the expression of cell survival proteins cFLIP, survivin, Bcl-xL, Bcl-2, and...
cIAP-1; and upregulating the expression of proapoptotic proteins Bax and p53 [125]. However, these effects did not involve TRPV1 [125].

**TRPV1 regulates tumor microenvironment**

Tumors are not just a simple collection of cancerous cells, rather they are a complex of tumor cells and their interactions with the surrounding cells, forming the tumor microenvironment (TME). Recent reviews have indicated TME is an important mediator in cancer progression and is mainly composed of (a) ECM, which provides structural and nutritional support for tumor development; (b) tumor vasculature, which carries oxygen and nutrients to tumor cells and a provides a “highway” for metastasis; (c) cancer-associated fibroblasts, which contribute to tumor proliferation and metastasis, as well as regulating the formation of ECM; and (d) the immune system, which plays a critical part in tumor-related inflammation [126-128]. The contribution of the important intercellular and intracellular messengers, Ca2+ ions, to the TME has been reviewed elsewhere [105, 129-131]. As TRPV1 is a major Ca2+ channel, we summarize the relationships between TRPV1 and TME in the following section.

**TRPV1 and cancer-associated fibroblasts**

The final outcome of cancer development is not only determined by autonomous cancer cell defects but also by interactions between cancer cells and the TME. Cancer-associated fibroblasts are major components of the tumor stroma, and evidence collated over many years indicates that fibroblasts are key players in cancer development [132, 133]. Cancer-associated fibroblasts (CAF) can be recruited and activated by cancer-secreted growth factors, among which TGF-β is the main factor contributing to their activation [134-136].

Associations between TRPV1 and TGF-β in somatic cells have been reported for many years. For instance, Bodo et al. demonstrated that the activation of TRPV1 by capsaicin upregulated TGF-β2 mRNA and protein expression in human hair follicles through an unknown mechanism [137]. This was supported by further studies, which showed expression of TGF-β1 was attenuated in a TRPV1-knock-out animal model [138-140]. These findings hint at the possible regulation of TGF-β by TRPV1, yet currently, there is no evidence for correlation or interaction between TRPV1 and TGF-β in cancer. As fibroblasts act as important mediators for other TME components [132, 133], it would be interesting to further investigate the relationship between TRPV1 and TGF-β in cancer cells and cancer-related fibroblasts.

**TRPV1 and ECM**

ECM is mainly composed of the basement membrane, which primarily comprises collagen, and the interstitial matrix containing proteoglycans and fibrous proteins [141]. Hence, TRPV1 is a transmembrane protein that functions as a temperature and pH sensor and a non-selective cation channel; it is unsurprising, therefore, that the ECM and TRPV1 are closely linked. According to previous research, several components of the ECM are able to modulate TRPV1 activity; for instance, extracellular hyaluronan (hyaluronic acid) reduced the excitation of the TRPV1 channel, thereby reducing the activity of peripheral nociceptors [142]. Moreover, another ECM protein, fibulin-5, was reported to induce apoptosis in colorectal cancer cells by downregulating TRPV1 expression [88]. However, TRPV1 is also capable of regulating ECM proteins, including the main regulators of collagen in ECM matrix metalloproteinases (MMPs), which are highly relevant to the metastatic processes of cancer cells [143, 144]. In the immortalized somatic cell, TRPV1 was reported to directly mediate the expression of MMP-1 [145, 146], and Huang et al. further elucidated that TRPV1 regulates MMP1 expression via the Ca2+-ERK pathway [147]. In the field of oncology, there have been several reports showing that TRPV1 activation in cancer cells regulates MMP activity by modulating the expression of TIMP-1 [110, 148]. However, there were no details of the mechanisms and signaling pathways involved in the TRPV1-regulation of TIMP-1 expression, and these should be investigated in the future. Moreover, whether TRPV1 regulates other ECM proteins is unclear.

**TRPV1 and cancer-associated angiogenesis**

During angiogenesis, new blood vessels emerge from the existing vasculature via sprouting, which is vital for oxygen and nutrient transportation and is implicated in cancer metastasis. As early as 1995, the first links between the regulation of angiogenesis and calcium signaling were discovered by Kohn et al., who reported that carboxyamidotriazole (CAI), a non-voltage-operated Ca2+-channel inhibitor, inhibited vascular tube formation on Matrigel and angiogenesis in vivo [149]. Faehling et al. further suggested that angiogenesis requires Ca2+ influx; vascular endothelial growth factor (VEGF) induced Ca2+ influx into human umbilical vein endothelial cells (HUVEC), and adding CAI inhibited the VEGF-elicited Ca2+ influx, inhibiting endothelial cell proliferation [150]. There are several detailed reviews
available covering Ca\textsuperscript{2+} signaling and angiogenesis, which are not elaborated on here [151-153].

The process of angiogenesis requires the proliferation and motility of endothelial cells, in which several critical proteins, i.e., VEGF, EGFR, and fibroblast growth factor, play important roles [132, 154-156]. Among these, VEGF is considered the most potent factor for endothelial cell proliferation and migration. In the context of cancer, VEGF can be released from tumor cells or the tumor-related ECM and binds to VEGFR1/2 to induce the proliferation of vascular endothelial cells [157]. As mentioned above, VEGF is able to induce Ca\textsuperscript{2+} influx into HUVECs [150]. Indeed, VEGF has recently been reported to mediate Ca\textsuperscript{2+} influx by transactivating the channel function of TRPV1. In addition, VEGF secreted by human uveal melanoma cells transactivates TRPV1 function, causing intracellular Ca\textsuperscript{2+} influx into endothelial cells, which is essential for angiogenesis [158]. Interestingly, Su et al. showed Ca\textsuperscript{2+} influx by simvastatin elicited TRPV1 activation of the AKT signal, which subsequently activated calcium-calcmodulin kinase II (CaMKII) and eNOS, leading to angiogenesis [159]. VEGF transactivation of TRPV1 might share a similar pathway, although more experimental data is needed to support this hypothesis.

Whether TRPV1 activity regulates the expression and function of VEGF and its receptor is still largely unknown; however, hints have been provided by animal models. Vinuesa et al. showed that Trpv1-/- mice were more vulnerable to dextran-sodium-sulfate-induced colon cancer [160]. Their investigation demonstrated that the NF-κB and STAT3 signal pathways were hyperactivated in Trpv1-/- mice, resulting in the upregulation of a group of inflammatory factors, including IL-1 and IL-6, and invasion factors such as MMP9, which subsequently enhanced the carcinogenesis [160]. NF-kB and STAT3 are known to be regulators of VEGF in several cancers [161-163] and may be involved in the regulation of VEGF expression by TRPV1.

**TRPV1 in inflammation and leukocytes**

A considerable fraction of TME components is associated with inflammation and leukocyte activities. Cytokines released from tumor cells and TME components attract immune cells and trigger inflammation. Several systematic reviews have pointed out that inflammation contributes to tumorigenesis and helps to shape tumor progression, and modulating immune factors in the TME is a promising therapeutic approach for cancer treatment [164-166]. The characteristics of inflammation include heat and pain, and, because TRPV1 functions as a nociceptor, it may be highly relevant to this area of research.

TRPV1 is involved in key immune cell functions, and Ca\textsuperscript{2+} signaling is important for lymphocyte activation and differentiation [167, 168]. The functional expression of TRPV1 in mouse and human CD4+ T-cells was described by Bertin et al., who showed NFAT and NFKB, two key transcription factors of immune cell activation, were less expressed in the nuclear fraction of CD4+ T-cells isolated from Trpv1 knockout mice. This resulted in the reduced production of proinflammatory cytokines and indicated that TRPV1 is necessary for proper downstream T-cell signaling [169]. Moreover, TRPV1 was also shown to be expressed in dendritic cells (DCs), which are pivotal in antigen presentation and lymphocyte activation. Notably, the administration of capsaicin induced the maturation of DCs in Trpv1 +/+ mice but not in Trpv1-/- mice [170].

TRPV1 was also reported to be a modulator for inflammatory cytokines, although the exact regulatory network for TRPV1-inflammation is unclear. Okada et al. showed the expression of several pro-inflammation cytokines, such as MCP-1 and IL-6, was suppressed during the healing of eye injury in Trpv1-/- mice, and they suggested that TRPV1 may serve a pro-inflammatory role [138]. However, the story is completely reversed in cancer. In the AOM/DSS-induced colon cancer mouse model, several pro-inflammation factors, including IL-6 and IL-11, were found to be upregulated [160]. Further research demonstrated that Trpv1-deficient mice exhibited hyperactivation of the STAT and NFKB signal pathways; therefore, TRPV1 was believed to exert a protective role in colon cancer [160]. The findings of a recent study by Erin were in line with this view, as they showed the activation of TRPV1 by capsaicin downregulated the expression of TNF-a, IL-6, and IL-10 and suppressed lung metastasis in a breast cancer metastasis mouse model [171]. However, something that should be brought to the reader’s attention is that this study did not rule out the possibility that capsaicin functioned independently of TRPV1. Furthermore, because the above results were based on a TRPV1-deficient animal model, the regulation of inflammatory factors was more likely to be an outcome of systematic changes. Whether TRPV1 regulates the secretion of inflammatory cytokines by cancer cells is not fully understood, and the mechanisms need to be further investigated.

**Conclusion**

Based on the reviewed evidence, the following conclusions can be drawn. The expression of TRPV1 is
elevated in many cancers, and its overexpression suppresses cell proliferation in intestinal, melanoma, and pancreatic cancers and induces apoptosis in melanoma and breast cancers. These findings support the hypothesis that TRPV1 is a tumor-suppressor gene. However, TRPV1 either promotes or inhibits cell death, depending on cancer cell type, implying it has cancer- or tissue-specific functions. Further investigations and experimentations are strongly recommended.

From the current clinical and experimental data, it is likely that TRPV1 serves as a repressor of metastasis, which is in line with its tumor-suppressing role. Whereas the data showing TRPV1 to be a pro-metastasis factor suggest the role of TRPV1 in metastasis may be context-dependent.

As we mentioned, numerous studies have revealed that TRPV1 agonists/antagonists affect cancer proliferation, cell death, and metastasis by activating TRPV1 channels and subsequently increasing the levels of intracellular Ca$^{2+}$. However, the effects are complex and are determined by the concentration used and treatment duration. Additionally, agonists or antagonists may activate other receptors and, therefore, function in a TRPV1-independent manner. Thus, the effects and mechanisms are unclear, and further studies using combined gene silencing or knockout approaches are needed.

In cancer chemotherapy, the TRPV1 agonist capsaicin has a synergic effect with cisplatin. Nevertheless, capsaicin cannot be systemically administered in large doses, as it induces acute pain and neurological inflammation. In short, current evidence indicates TRPV1 plays certain roles in shaping the TME. However, the signaling networks interacting with TRPV1 have not been fully characterized, and the relationships between TRPV1 and TME need to be further explored. The effects of TRPV1 on cancer cell proliferation, cell death, migration, and invasion, as well as on radiotherapy and chemotherapy, are summarized in Figure 1. Moreover, the TRPV1 signaling pathways in cancer cell proliferation, cell death, migration, and invasion described in this review are summarized in Figure 2. The association between TRPV1 and TME are summarized in Figure 3.

Finally, a number of important issues need to be considered. Given the fact that TRPV1 also plays several intracellular roles, it remains unclear whether TRPV1 functions independently of its channel activity in cancer progression. Further research with more focus on the role of the TRPV1 gene in tumorigenesis and development using gene overexpression and knockdown (knockout) approaches is therefore suggested.

![Diagram](http://www.ijbs.com)

**Figure 1.** The effects of TRPV1 on cancer cell proliferation, cell death, migration, invasion, radiotherapy, and chemotherapy.
Figure 2. TRPV1 signaling pathways in cancer cell proliferation, cell death, migration, and invasion.

Figure 3. Interaction between TRPV1 and tumor microenvironment. Using transgenic mice, TRPV1 was shown to regulate TGF-β, which is the major factor that activates fibroblasts and transforms the fibroblasts into CAF. The CAF can secrete several cytokines and factors, most of which are TME components, e.g., MMPs (regulates collagen in ECM), TNF-α and IL-6 (trigger inflammation), and VEGF (promotes angiogenesis). In cancer cells, TRPV1 was shown to regulate the expression of several inflammation factors, probably through NFκB and STAT signaling pathways. In immunocytes, TRPV1 is important for T-cell signal transduction. Additionally, TRPV1 can regulate the ECM by promoting TIMP-1 expression. In turn, fibulin 5, an ECM component, downregulates TRPV1 expression in cancer cells. Furthermore, TRPV1 was shown to promote angiogenesis by mediating Ca²⁺ influx and, subsequently, activating the AKT-CalMII-eNOS signal pathway. The TRPV1 channel function can also be elicited by VEGF, but it is unclear if it shares the same downstream signal.
Abbreviations

TRPV1: transient receptor potential cation channel subfamily V, member 1; TRP: transient receptor potential; VR1: vanilloid receptor 1; EGF: epidermal growth factor receptor; PLC: phospholipase C; PLP2: phosphatidylinositol-4,5-bisphosphate; DAG: diacylglycerol; IP3: inositol triphosphate; PTP1B: protein tyrosine phosphatase 1B; AR: androgen receptor; I-RTX: 5-iodo-resiniferatoxin; ESCC: esophageal squamous cell carcinoma; ERK: extracellular signal-regulated kinase; NPC: nasopharyngeal carcinoma; AEA: anandamide; FAFI: Fas-associated factor1; ECM: extracellular matrix; MA: R(+) -methanandamide; HGF: hepatocyte growth factor; ICAM1: intercellular adhesion molecule-1; BTX: bortezomib; CAI: carboxyamidotriazole; VEGF: vascular endothelial growth factor; CaMKII: calcium-calmodulin kinase II; HUVEC: human umbilical vein endothelial cell; FGF: fibroblast growth factor.

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Authors’ contributions

LL and DZ provided the idea. LL and CC wrote the article. CYJ, TX, YCC, and YXY made suggestions for the article. All authors reviewed the manuscript and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

References

1. Ramsey IS, Delling M, Clapham DE. An introduction to TRP channels. Annu Rev Physiol. 2006; 68: 619-47.
2. Nilius B, Owsianik G, Voets T, Peters JA. Transient receptor potential cation channels in disease. Physiol Rev. 2007; 87: 165-217.
3. Shapovalov G, Ritaine A, Skryma R, Prevarskaia N. Role of TRP ion channels in cancer and tumorigenesis. Semin Immunopathol. 2016; 38: 357-69.
4. Zhai K, Liskova A, Kubatka P, Busselberg D. Calcium Entry through TRPV1: A Potential Target for the Regulation of Proliferation and Apoptosis in Cancerous and Healthy Cells. Int J Mol Sci. 2020; 21.
5. So CL, Milevskiy MJC, Monsteith GR. Transient receptor potential cation channel subfamily V and breast cancer. Lab Invest. 2020; 100: 199-206.
6. Bevan S, Quail T, Anderson DA. TRPV1. Handb Exp Pharmacol. 2014; 222: 207-45.
7. Kedri N, Szabo T, Lile JD, Treanor JJ, Olah Z, Iadarola MJ, et al. Analysis of the native quaternary structure of vanilloid receptor 1. J Biol Chem. 2001; 276: 28613-9.
8. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Neuron. 1998; 21: 531-43.
9. Helliwell RJ, Bjorklund TM, Kennan JS, Bevan S, McIntyre P. The cloned capsaicin receptor (VR1) mRNA in adult rat sensory ganglia. Neurosci Lett. 1998; 250: 177-80.
10. Patapoutian A, Tate S, Woolf CJ. Transient receptor potential channels: targeting pain at the source. Nat Rev Drug Discov. 2009; 8: 55-68.
11. Kark T, Bagi Z, Lisanetz E, Pasotor ET, Erdel N, Czisora A, et al. Tissue-specific regulation of microvascular diameter: opposite functional roles of neuronal and smooth muscle located vanilloid receptor-1. Mol Pharmacol. 2008; 75: 1405-12.
12. Moreau P, Koehly I, Darras M, Zourob S, Dugourd C. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 2011; 71: 5067-77.
13. Birder LA, Nakamura Y, Kiss S, Nealen ML, Barrick S, Kanaj AI, et al. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci. 2002; 5: 856-60.
14. Lord SE, Tominaga M, Julius D. Acid potentiation of the capsaicin receptor determined by a key extracellular site. Proc Natl Acad Sci U S A. 2000; 97: 8134-9.
15. Shapovalov G, Ritaine A, Skryma R, Prevarskaia N. Role of TRP ion channels in cancer and tumorigenesis. Semin Immunopathol. 2016; 38: 357-69.
16. Zhai K, Liskova A, Kubatka P, Busselberg D. Calcium Entry through TRPV1: A Potential Target for the Regulation of Proliferation and Apoptosis in Cancerous and Healthy Cells. Int J Mol Sci. 2020; 21.
17. So CL, Milevskiy MJC, Monsteith GR. Transient receptor potential cation channel subfamily V and breast cancer. Lab Invest. 2020; 100: 199-206.
18. Bevan S, Quail T, Anderson DA. TRPV1. Handb Exp Pharmacol. 2014; 222: 207-45.
19. Kedri N, Szabo T, Lile JD, Treanor JJ, Olah Z, Iadarola MJ, et al. Analysis of the native quaternary structure of vanilloid receptor 1. J Biol Chem. 2001; 276: 28613-9.
Ambrosio F, Sordelovi MV, Russo C, Tagliatalata M. Activation and desensitization of TRPV1 channels by the PPARα agonist palmitylolethanolamide. Br J Pharmacol. 2013; 168: 1430-44.

Norton-Poudrier T, Naria-Ouegnin A, Augustus N. TRPV1 channel gating kinetics. Curr Top Med Chem. 2011; 11: 2311-50.

Nersesyan Y, Demirkhanyan L, Cabezas-Bratesco D, Oakes V, Kusuda R, Davson T, et al. Oxytocin Modulates Nociception as an Agonist of TRPV1 and STING. Cell Rep. 2017; 21: 1686-94.

Hui HZ, Gu Q, Wang C, Colton CK, Tang J, Kinoshita-Kawada M, et al. 2-aminothiodiphenyl borate is a common activator of TRPV1, TRPV2, and TRPV3. J Biol Chem. 2004; 279: 37541-8.

Martin E, Dahman H, Guillemont G, Gillis-Duplantier J, Marthan R, Savineau JP, et al. Involvement of TRPV1 and TRPV4 channels in migration of rat pulmonary arterial smooth muscle cells. Pflugers Arch. 2012; 464: 261-72.

Bohlen CJ, Priel A, Zhou S, King D, Siemens J, Julius D. A bifavalent tarantula toxin activates the capsaicin receptor, TRPV1, by targeting the outer pore domain. Cell. 2010; 141: 834-55.

McNamara FN, Randall A, Gunthorpe MJ. Effects of piperine, the pungent constituent of black pepper, at the human vanilloid receptor (TRPV1). Br J Pharmacol. 2009; 155: 1025-42.

Szallasí A, Blumberg PM. Resiniferatoxin, a phorbol-related diterene, acts as an ultrapotent analog of capsaicin, the irritant constituent in red pepper. Neurosci. 1989; 30: 515-20.

Liu L, Welch JM, Ericsson RP, Reinhart RP, Simon SA. Different responses to repeated applications of zingerone in behavioral studies, recordings from intact and cultured TG neurons, and from VR1 receptors. Physiol Behav. 2009; 69: 177-86.

Pearce LV, Petukhov PA, Szabo T, Kedei N, Bizzik F, Kozikowski AP, et al. Evodiamine oxides: an agonist for the vanilloid receptor TRPV1. Org Biomol Chem. 2002; 4: 2281-6.

Bisogno T, Hans U, De Petrocellis L, Tchilibon S, Ponde DE, Brandi L, et al. Molecular targets for cannabinoids and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 2011; 163: 845-52.

De Petrocellis L, Vellani V, Schiano-Moriello A, Marini P, Magherini PC, Orlando P, et al. Plant-derived cannabinoids modulate the activity of the transient receptor potential channels of ankyrin type-1 and melastatin type-8. Pharmacol Ther. 2008; 121: 1007-15.

Andre E, Campi B, Trevisani M, Ferreira J, Malheiros A, Yunes RA, et al. Functional properties of the high-affinity TRPV1 (VR1) vanilloid receptor in dorsal root ganglia neurons. J Pharmacol Exp Ther. 2008; 325: 1007-15.

Siemens J, Zhou S, Piskorowski R, Nikai T, Lumpkin EA, Basbaum AI, et al. Prevention of multiple itch transmission pathways in mice. Eur J Pharmacol. 2010; 608: 298-305.

Yang Y, Guo W, Ma J, Xu P, Zhang W, Guo S, et al. Downregulated TRPV1 inhibits the cloned vanilloid receptor-1. Biochem Biophys Res Commun. 2002; 296: 134-9.

Voight EA, Gomtsyan AR, Daanen JF, Perner RJ, Schmidt RG, Bayburt EK, et al. Discovery of (8R,9S)-1-chloro-3-(3-methoxyisouquinolin-5-yl)urea as a (Ala165442): a temperature-neutral transient receptor potential vanilloid-1 (TRPV1) antagonist with efficacious analgesia. J Pharmacol Exp Ther. 2009; 329: 611-20.
vanilloid type 1 triggers prostate cancer cell proliferation. BMC Cancer. 2014; 14: 921.

81. Zhang S-S, Ni Y-H, Zhao C-Q, Rao Z, Yu H-X, Wang L-Y, et al. Capsaicin enhances the anti-cancer activity of sorafenib in hepatocellular carcinoma cells and mouse xenograft tumors through increased ERK signaling. Acta Pharmacologica Sinica. 2017; 39: 438-48.

82. Sanchez AM, Sanchez MG, Malagarie-Cazeneve S, Olea N, Diaz-Laviada I. Inhibition of prostate cancer tumor PC-3 cells and inhibition of xenograft prostate tumor growth by the vanilloid capsaicin. Apoptosis. 2006; 11: 89-99.

83. Skrzypski M, Sassek M, Abdelmessih S, Mergler S, Grotzinger C, Metzke D, et al. Capsaicin induces cytotoxicity in pancreatic neuroendocrine tumor cells via TRPV6. Cell Signal. 2014; 26: 41-51.

84. Chiang C, Zhang M, Wang D, Xiao T, Zhu L, Chen K, et al. Therapeutic potential of targeting MKK3/p38 axis with Capsaicin for Nasopharyngeal Carcinoma. Theranostics. 2020; 10: 7906-20.

85. Borrelli F, Pagano E, Romano B, Panzera S, Maielli F, Coppola D, et al. Colon carcinoma is inhibited by the TRPM8 antagonist capsaicinol, a Cannabis-derived non-psychoactive cannabinoid. Carcinogenesis. 2014; 35: 2787-97.

86. Hamtiaux L, Hansoule L, Dauguet N, Muccioli GG, Gallez B, Lambert DM. Cancer cells induced apoptosis by the vanilloid Vanilloid 1. Int. J. Biol. Sci. 2021, Vol. 17 2048.

87. Pece L, Joway K, Blum W, Petrovics G, Vizier C, Olah Z, et al. Activation of endogenous TRPV1 fails to induce overstimulation-based cytotoxicity in breast and prostate cancer cells but not in pain-sensing neurons. Biochim Biophys Acta. 2016; 1863: 2054-64.

88. Chen Y, Li J, Jin L, Lei K, Liu H, Yang Y. Fibrinogen-5 contributes to colorectal cancer cell apoptosis via the ROS/MAPK and Akt signal pathways by downregulating transient receptor potential channel subfamily V member 1. J Cell Biochem. 2019; 120: 17838-46.

89. Orrenius S, Zivovitsovska B, Nicotera P. Regulation of cell death: the calcium-apoptosis link. J Bioenerg Biomembr. 2003; 35: 525-55.

90. Wu T, Peters AA, Tan PT, Thomson-Skjøth M, Montreith GE. Consequences of activating the calcium-permeable ion channel TRPV1 in breast cancer cells with regulated TRPV1 expression. Cell Calcium. 2014; 56: 59-67.

91. Contassot E, Tenan M, Schnuriger V, Pehe ME, Dietrich PY. Arachidonyl ethanolamide induces apoptosis of uterine cervix cancer cells via aberrantly expressed vanilloid receptor-1. Gynecol Oncol. 2004; 95: 182-8.

92. Chen CS, Ma KH, Lee HS, Liu PS, Li YH, Huang YS, et al. Dual effect of capsaicin on cell death in human osteosarcoma G292 cells. Eur J Pharmacol. 2013; 718: 350-60.

93. Naziroglu M, Cig B, Blum W, Vizler C, Buhala A, Marton A, et al. Targeting breast cancer cells by MRS1477, a positive allosteric modulator of TRPV1 channels. PLoS One. 2017; 12: e0179950.

94. Fonseca BM, Correia-da-Silva G, Teixeira NA. Cannabinoid-induced cell death in endometrial cancer cells: involvement of TRPV1 receptors in apoptosis. J Physiol Biochem. 2018; 74: 261-72.

95. Adinolfi B, Romanini A, Vanni A, Martinotti E, Chicca A, Fogli S, et al. Anticancer activity of anandamide in human cutaneous melanoma cells. Eur J Pharmacol. 2013; 718: 154-9.

96. Soliman E, Van Dross R. Anandamide-induced endoplasmic reticulum stress and apoptosis mediated by oxidative stress in non-melanoma skin cancer. Cancers. 2016; 8: 1807-21.

97. Ghosh AK, Basu S. Fas-associated factor 1 is a negative regulator in capsaicin-induced mitochondrial dysfunction and reduces tumor growth in a xenograft mouse model. Chem Biol Interact. 2014; 224: 128-35.

98. González CB, Kirmia NB, De La Chapa JJ, Chen R, Henry MA, Luo S, et al. Vanilloids induce oral cancer apoptotic independence of TRPV1. Oral Oncol. 2014; 50: 437-47.

99. Cheffler CL, Weinberg RA. A perspective on cancer cell metastasis. Science. 2011; 331: 1559-64.

100. Prevorska N, Ouadid-Ahidouche H, Skryma R, Shuba Y. Remodelling of Ca2+ transport in cancer: how it contributes to cancer hallmarks? Philos Trans R Soc Lond B Biol Sci. 2014; 369: 20130097.

101. Kadlo B, Yaya S, Baska A, Dye K, Gomes J, Meneghe C. Calcium role in human colon carcinogenesis: a comprehensive analysis and critical review of literature. Cancer Metastasis Rev. 2016; 35: 391-411.

102. Villalobos A, Benichot M, Meythaler R. The Role of Calmodulin in Tumor Cell Migration, Invasiveness, and Metastasis. Int J Mol Sci. 2020; 21.
135. Aoyagi Y, Oda T, Kinoshita T, Nakahashi C, Hasebe T, Okhohchi N, et al. Overexpression of TGF-beta by infiltrated granulocytes correlates with the expression of collagen mRNA in pancreatic cancer. Br J Cancer. 2004; 91: 216-26.

136. Yoshida GJ. Regulation of heterogeneous cancer-associated fibroblasts: the molecular pathology of activated signaling pathways. J Exp Clin Cancer Res. 2020; 39: 112.

137. Bodo E, Biro T, Telek A, Czifra G, Griger Z, Toth BI, et al. A hot new twist to hair biology: involvement of vanilloid receptor-1 (VR1/TRPV1) signaling in human hair growth control. Am J Pathol. 2005; 166: 985-98.

138. Okada Y, Reinaich PS, Shirai K, Kitano A, Kao WW, Flanders KC, et al. TRPV1 involvement in inflammatory tissue fibrosis in mice. Am J Pathol. 2011; 178: 2654-64.

139. Li HJ, Kanazawa N, Kimura A, Kaminaka C, Yonei N, Yamamoto Y, et al. Severe ulceration with impaired induction of growth factors and cytokines in keratinocytes after trichloroacetic acid application on TRPV1-deficient mice. Eur J Dermatol. 2012; 22: 61-64.

140. Nidegawa-Saitoh Y, Sumioka T, Okada Y, Reinaich PS, Flanders KC, Liu CY, et al. Impaired healing of cornea incision injury in a TRPV1-deficient mouse. Cell Tissue Res. 2018; 374: 329-38.

141. Mouw JK, Ou G, Weaver VM. Extracellular matrix assembly: a multiscale deconstruction. Nat Rev Mol Cell Biol. 2014; 15: 771-85.

142. Caires R, Luis E, Taberner FJ, Fernandez-Ballester G, Ferrer-Montiel A, Balaza EA, et al. Hyaluronan modulates TRPV1 expression in human peripheral nociceptor activity and pain. Nat Commun. 2015; 6: 8995.

143. Gonzalez-Avila G, Sommer B, Garcia-Hernandez AA, Ramos C. Matrix Metalloproteinases’ Role in Tumor Microenvironment. Adv Exp Med Biol. 2020; 1245: 97-131.

144. Wu T, Dai Y. Tumor microenvironment and therapeutic response. Cancer Lett. 2017; 387: 61-8.

145. Li WH, Lee YM, Kim JY, Kang S, Kim S, Kim KH, et al. Transient receptor potential vanilloid-1 mediates heat-shock-induced matrix metalloproteinase-1 expression in human epidermal keratinocytes. J Invest Dermatol. 2007; 127: 2328-35.

146. Lee YM, Li WH, Kim YK, Kim KH, Chung JH. Heat-induced MMP-1 expression is mediated by TRPV1 through PKCalpha signaling in HaCaT cells. Exp Dermatol. 2008; 17: 864-70.

147. Huang KF, Ma KH, Chang YJ, Lo LC, Jhap TY, Su YH, et al. Bicalutin inhibits matrix metalloproteinase 1 expression via activation of TRPV1-Ca-ERK pathway in ultraviolet B-irradiated human dermal fibroblasts. Exp Dermatol. 2019; 28: 568-75.

148. Ramer R, Merkord J, Rohde H, Hinze B. Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1. Biochem Pharmacol. 2010; 79: 955-66.

149. Kohn EC, Alessandro R, Sporzon J, Wester RP, Liotta LA. Angiogenesis: role of calcium-mediated signal transduction. Proc Natl Acad Sci U S A. 1995; 92: 1307-11.

150. Faehling M, Kro ll KJ, Fo hr KJ, Fellbrich G, Mayr U, Trischler G, et al. Essential role of calcium in vascular endothelial growth factor A-induced signaling: mechanism of the antiangiogenic effect of carboxamidotriazole. FASEB J. 2002; 16: 1805-7.

151. Moccia F, Negri S, Shekha M, Faris P, Guerra G. Endothelial nitric oxide synthase and angiogenesis. Acta Physiol (Oxf). 2014; 2328-35.

152. Earley S, Brayden JE. Transient receptor potential channels in the vasculature. J Mol Biol. 2002; 16: 1805-7.

153. Vig M, Kinet JP. Calcium signaling in immune cells. Nat Immunol. 2009; 10: 217.

154. Basu S, Srivastava P. Immunological role of neuronal receptor vanilloid receptor 1 expressed on dendritic cells. Proc Natl Acad Sci U S A. 2005; 102: 5120-5.

155. Erin N. Role of sensory neurons, neuroimmune pathways, and transient receptor potential vanilloid 1 (TRPV1) channels in a murine model of breast cancer metastasis. Cancer Immunol Immunother. 2020; 69: 307-14.