Chapter 7
The Cancer-Suppressing and -Promoting Actions of Capsaicin

Pin Ju Chueh

Abstract Cancer chemoprevention is employed to block or reverse the progression of malignancies. To date, several thousand agents have been found to possess chemopreventive activity. One such compound is capsaicin, a component of chili peppers that exhibits anti-growth activity against various cancer cell lines. Capsaicin exerts its cytotoxic action by activating an array of signaling mechanisms, including generation of reactive oxygen species (ROS) as messengers to initiate apoptosis, a type I programmed cell death. However, numerous in vitro and in vivo studies have suggested that capsaicin also possesses tumor-promoting activity; possibly in part, reflecting activation of autophagy, an alternative (type II) programmed death process. This article reviews the recent literature on the paradoxical effects of capsaicin on cancer growth and the diverse capsaicin-induced signaling pathways that lead to cell death or tumorigenesis. Some of the most common cellular targets of capsaicin are also discussed.

Keywords Apoptosis • Autophagy • Cancer • Capsaicin • Cell death • Oxidative stress • Proliferation • Transient receptor potential vanilloid type 1 (TRPV1) • Tumor-associated NADH oxidase (tNOX; ENOX2)

Abbreviations

ATM	Ataxia telangiectasia mutated
C/EBP	CCAAT/enhancer-binding protein
DHC	Dihydrocapsaicin
DISC	Death-inducing signaling complex

P.J. Chueh (✉)
Graduate Institute of Biomedical Sciences, National Chung Hsing University, No. 250 Kuo-Kung Rd., Taichung, 40227 Taiwan, Republic of China
e-mail: pjchueh@dragon.nchu.edu.tw

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EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulation kinase
G153ADD153/CHOP	Growth arrest and DNA damage inducible gene
GFP	Green fluorescent protein
IL	Interleukin
JNK1	c-Jun N-terminal kinase 1
MAPKs	Mitogen-activated protein kinases
MEFs	Mouse embryo fibroblasts
NF-κB	Nuclear transcription factor κB
NO	Nitric oxide
PI3K	Phosphoinositide 3-kinase
PKCα	Protein kinase Cα
ROS	Reactive oxygen species
shRNA	Small interfering (hairpin) RNA
STAT	Signal transducer and activator of transcription
TNFα	Tumor necrosis factor-α
tNOX; ENOX2	Tumor-associated NADH oxidase
TPA	Tetradecanoylphorbol-13-acetate
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
TRPV1	Transient receptor potential vanilloid type 1
VEGF	Vascular endothelial growth factor

1 Introduction

Chili is commonly used in Mexican foods and now has become an indispensable element in a variety of cuisines. Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide), a pungent component of chili peppers, is consumed by humans all over the world for its flavor and spice taste (Dorai et al. 2004). Capsaicin has long been used as a pain reliever recognized for its ability to reduce inflammatory heat and noxious chemical hyperalgesia (Agakichiev et al. 2004). However, recent progress has focused on the chemopreventive effects of capsaicin, reflecting its anti-growth activity against various cancer cell systems, including human leukemic (Ito et al. 2004; Lawen et al. 1994; Wolvetang et al. 1996), prostate (Mori et al. 2006; Sanchez et al. 2006, 2007), colon (Kim et al. 2004, 2007), hepatoma (Baek et al. 2008; Lee et al. 2004), breast (Kang et al. 2003; Morré et al. 1995), and gastric cancer (Kim et al. 1997; Wang et al. 2009, 2011).

Capsaicin exerts its cytotoxic action by activating an array of signaling mechanisms, including generation of reactive oxygen species (ROS) (Ito et al. 2004; Macho et al. 2003; Zhang et al. 2008), up-regulation or activation of p53 (Ito et al. 2004; Mori et al. 2006), suppression of the signal transducer and activator of transcription (STAT) family of proteins (Bhutani et al. 2007), and NF-κB pathways

(Mori et al. 2006; Singh et al. 1996; Kim et al. 2003). The cytotoxicity of capsaicin is mainly associated with induction of type I programmed cell death—apoptosis—leading to inhibition of cancer growth. Accumulating evidence supports the idea that capsaicin also mediates autophagy, a type II programmed cell death. However, capsaicin-mediated autophagy may play a role in sustained cell survival (Choi et al. 2010a; Oh and Lim 2009; Yoon et al. 2011). Moreover, despite being commonly considered a chemopreventive agent, capsaicin has demonstrated mutagenic properties (Nagabhushan and Bhide 1985) as well as an ability to enhance prostate cancer cells proliferation (Malagarie-Cazenave et al. 2009). Furthermore, a tumor-promoting effect of capsaicin has been shown in animal and human studies (Toth and Gannett 1992; Agrawal et al. 1986; Serra et al. 2002; Archer and Jones 2002; Bode and Dong 2011), suggesting paradoxical actions of capsaicin in tumorigenesis. This article briefly reviews the recent literature on the suppressive and promoting effects of capsaicin on cancer growth as well as the signaling pathways that mediate its actions. In addition, some of the most common cellular targets of capsaicin are also discussed in light of their potential to account for the paradoxical effects of capsaicin on cancer growth.

2 Cellular Targets of Capsaicin

Capsaicin acts on an array of cellular targets, several of which have been identified, and initiates a number of signaling pathways. Numerous reports have demonstrated that capsaicin is differentially cytotoxic toward cancer cells and non-cancerous cells (Lo et al. 2005; Morré et al. 1995; Sánchez et al. 2006; Zhang et al. 2003); however, the specific target(s) of capsaicin and the resulting mechanisms that underlie this differential cytotoxicity are not yet fully understood. In this section, the focus is on the two most-often mentioned protein targets of capsaicin—transient receptor potential vanilloid type 1 (TRPV1) and tumor-associated NADH oxidase (tNOX; ENOX2)—and their role in capsaicin-induced cellular responses.

2.1 Transient Receptor Potential Vanilloid Type 1

TRPV1, a member of the TRP family of non-selective cation channels, is activated by several noxious stimuli, including hear and voltage, as well as by vanilloid ligands. Notable in the current context, TRPV1 has been identified as a capsaicin receptor (Nagy et al. 2004). TRPV1 is mainly expressed in the spinal cord and trigeminal ganglia and plays a role in the sensation of pain (Julius and Basbaum 2001). Because capsaicin functions as an agonist that transiently activates and then desensitizes TRPV1, it is commonly used as pain reliever. However, TRPV1 is also expressed in diverse tissues, suggesting that a broader context for its functions, and the actions of capsaicin, beyond pain perception.

Several studies provide support for the idea that capsaicin exerts its anticancer actions through interaction with the TRPV1 (Amantini et al. 2009; Kim et al. 2006). For example, capsaicin elicits apoptosis in U373 glioma cells, which express relative high levels of TRPV1, but not in U87 glioma cells, which express low levels of TRPV1, suggesting TRPV1-dependent apoptosis (Amantini et al. 2007). Moreover, capsaicin induces up-regulation of the death receptors Fas/CD95 and promotes Fas/CD95-TRPV1 co-clustering, which leads to both extrinsic and intrinsic apoptotic pathways (Amantini et al. 2009). Capsaicin also activates ataxia telangiectasia mutated (ATM) kinase, which, in turn, phosphorylates serine residues of p53, resulting in enhanced transcription of Fas/CD95, establishing a novel connection between the ATM/DNA-damage-response pathway and Fas/CD95-mediated pathways triggered by TRPV1 (Amantini et al. 2009). TRPV1 is also involved in capsaicin-induced calcium entry, ROS generation, mitochondrial membrane depolarization and, ultimately, cell death in rat synovial fibroblasts (Hu et al. 2008). Interestingly, capsaicin-induced TRPV1-mediated apoptosis was recently reported to cause calcium release from the endoplasmic reticulum (ER) and increase transcriptional activation of growth arrest and DNA damage inducible gene (GADD153/CHOP), leading to ER-stress-mediated cell death (Thomas et al. 2007). However, TRPV1-independent mechanisms have also been documented (Mori et al. 2006; Morré et al. 1995), indicating that multiple molecular targets are involved in capsaicin-induced apoptosis.

Surprisingly, TRPV1 has been demonstrated to interact with the epidermal growth factor receptor (EGFR), a receptor tyrosine kinase that is up-regulated in many human epithelial cancers; this interaction leads to EGFR degradation and accounts for the anti-cancer effects attributed to TRPV1 (Bode et al. 2009). Additionally, TRPV1-knockout mice develop a striking increase in skin carcinogenesis following exposure to the phorbol ester, tetradecanoylphorbol-13-acetate (TPA), further supporting the suppressive role of TRPV1 in tumorigenesis (Bode et al. 2009). In contrast, recent evidence suggests that TRPV1 mRNA and protein expression are markedly down-regulated in poorly differentiated and undifferentiated urothelial cancer cell lines (Amantini et al. 2009), and TRPV1 is also reported to contribute to invasiveness and malignancy progression (Prevarskaya et al. 2007). Collectively, these findings provide a basic framework for understanding the TRPV1 protein and its association with capsaicin-induced inhibition of cancer.

2.2 Tumor-Associated NADH Oxidase

Capsaicin is one of several anticancer compounds that inhibit activity of tumor-associated NADH oxidase (tNOX; ENOX2) in association with a reduction in cancer cell growth (Hedges et al. 2003; Morré et al. 1995, 1997b, 2000, 2007). tNOX belongs a member of a family of growth-related NADH (or hydroquinone) oxidases (Bruno et al. 1992; Chueh 2000; Chueh et al. 2002a). Unlike the NADH oxidase activity identified in normal rat liver plasma membranes (CNOX; ENOX1), which

is responsive to growth factors and hormones, tNOX isolated from rat hepatoma cells is constitutively active (Bruno et al. 1992). Further studies have revealed that tNOX is present in numerous cancer cell lines, including those derived from breast, cervix, colon, lung, and stomach cancers, as well as leukemias (Morré et al. 1995; Chen et al. 2006; Liu et al. 2008; Mao et al. 2008; Wang et al. 2009, 2011); it is also detected in the sera of cancer patients but not in those of healthy volunteers, suggesting its clinical relevance (Chueh et al. 1997; Morré et al. 1997a; Morré and Reust 1997). tNOX cDNA has been cloned (Chueh et al. 2002a), and functional motifs of tNOX have been identified, including a quinone-binding site, an adenine-nucleotide-binding site, and a CXXXC cysteine pair that is important for tNOX activity (Chueh et al. 2002b).

Interestingly, capsaicin preferentially inhibits tNOX activity in cancer cells, resulting in apoptosis induction and reduced growth, while having little effect in non-cancerous cells (Morré et al. 1995). Chueh et al. used antisense oligonucleotides to down-regulate tNOX and found that tNOX deficiency decreases HeLa cell colony formation (Chueh et al. 2004). A subsequent study utilizing a small interfering (hairpin) RNA (shRNA) technique that effectively reduced tNOX protein expression showed that tNOX knockdown attenuates cell proliferation in HeLa cells (Liu et al. 2008). A key role for tNOX in regulating cell growth is further supported by the observation that the growth rate of mouse embryo fibroblasts (MEFs) from tNOX-overexpressing transgenic mice is approximately twice that of wild-type cells (Yagiz et al. 2007). Interestingly, Mao et al. suggested that tNOX protein is suppressed during capsaicin exposure and that tNOX down-regulation sensitizes cancer cells to stress-induced apoptosis, confirming that tNOX is required for transformed cell survival (Mao et al. 2008). Similarly, another report demonstrated that capsaicin induces a cytotoxic effect and tNOX down-regulation in SCM-1 gastric cancer cells through an apoptotic mechanism (Wang et al. 2009). However, the cytotoxic effects of capsaicin on other gastric cancer cell lines appear somewhat more complicated. As reported recently, capsaicin enhances oxidative stress and tNOX down-regulation in association with mitochondria-dependent apoptosis, leading to growth inhibition of SNU-1 cells, derived from a poorly differentiated human gastric carcinoma. In contrast, capsaicin is largely ineffective in inducing oxidative stress and tNOX protein repression in TMC-1 cells, a metastatic gastric carcinoma line; as a consequence, apoptosis induction is largely nonexistent and cell survival is augmented (Wang et al. 2011). Moreover, forced tNOX down-regulation restores capsaicin-induced apoptosis in TMC-1 cells, strongly supporting an essential role for tNOX in cancer cell growth (Wang et al. 2011). These results suggest that the paradoxical effects of capsaicin on cell growth are also reflected in its effects on tNOX protein expression.

Using shRNA, Liu and colleagues demonstrated that knockdown of tNOX expression attenuates HeLa cell migration by inhibiting membrane association of Rac protein (Liu et al. 2008). Conversely, tNOX overexpression in non-cancerous MCF-10A cells was shown to result in the acquisition of invasivity, an aggressive characteristic of cancer cells, confirming a key role for tNOX in cell migration (Chueh et al. 2004). These various lines of evidence suggest that tNOX

acts as a critical regulator of physiological and pathological outcomes in response to biological cues involved in redox signaling, cell proliferation, survival, and tumor progression.

3 Capsaicin-Induced Signaling Pathways

Capsaicin owes its reputation as a remarkable chemopreventive compound to its selective cytotoxicity toward malignant cells (Lo et al. 2005; Morré et al. 1995; Sanchez et al. 2006; Zhang et al. 2003). The differential susceptibility of cancer cells to capsaicin may result from modulation of diverse signaling pathways that contribute to cell death or sustained cell survival. Moreover, complicated cross-talk among such signaling pathways modulates cellular outcomes. In this section, the focus is on the signaling pathways stimulated by capsaicin.

3.1 Reactive Oxygen Species

Of the diverse array of cellular mechanisms involved in capsaicin-induced responses, one that is often highlighted is oxidative stress, which can lead to the subsequent loss of cell function and, ultimately, apoptosis (Ito et al. 2004; Sánchez et al. 2007; Lee et al. 2004; Zhang et al. 2008). The main contributor to cellular oxidative stress is the ROS, including hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and free radicals such as the hydroxyl radical (·OH) and the superoxide anion (O_2^-). Short-lived free radicals do not penetrate the plasma membrane easily and react rapidly with other molecules, consequently leaving little possibility for specific identification. On the other hand, hydrogen peroxide readily diffuses across the membrane and can function as a second messenger in redox signaling, mediating diverse cellular responses including cell proliferation, differentiation, and migration (Lambeth 2004). Capsaicin-induced hydrogen peroxide generation has also been shown to be an upstream event in capsaicin-induced apoptosis—specifically, mitochondria-dependent apoptosis—in gastric cancer SNU-1 cells (but not in TMC-1 cells), leading to decreased viability and increased apoptosis (Wang et al. 2011). As notes above, these divergent effects of capsaicin on the growth of gastric cancer cells parallel its effects on tNOX expression; the functional importance of tNOX in this context is highlighted by the demonstration that forced tNOX down-regulation restores capsaicin-induced growth inhibition in TMC-1 cells (Wang et al. 2011).

ROS are highly reactive molecules that are produced primarily throughout the mitochondrial electron transport chain (Finkel 2003; Balaban et al. 2005). Capsaicin has been shown to induce apoptosis in pancreatic cancer cells in association with ROS generation and mitochondrial disruption (Zhang et al. 2008). More specifically, capsaicin obstructs mitochondrial electron transfer at complex I, possibly by

acting at or close to coenzyme Q binding (Hail 2003; Degli Esposti 1998). This disruption in electron transfer generates non-enzymatic ROS (Hail and Lotan 2009). Furthermore, Pramanik et al. demonstrated that capsaicin inhibits mitochondrial complex I and complex III activity and reduces ATP levels concurrently with decreased catalase and glutathione peroxidase, resulting in ROS production and apoptosis in pancreatic cancer cells, but not in normal HPDE-6 cells (Pramanik et al. 2011). Both in vitro and in vivo studies support a role for ROS generation, dissipation of the mitochondrial inner transmembrane potential, and caspase-3 activation in the action of capsaicin against androgen-independent prostate cancer PC-3 cells (Sanchez et al. 2006).

In addition to mitochondria, various cellular compartments and numerous enzymes also produce ROS, including peroxisomes (Schrader and Fahimi 2006) and cyclooxygenases (Pathak et al. 2005). Cyclooxygenase, a ROS-generating enzyme, has been shown to be involved in capsaicin-induced apoptosis in human neuroblastoma cells (Lee et al. 2002). Redox reactions at the membrane also play an important role in the control of many mechanisms that regulate cellular responses, such as cell proliferation, differentiation, and migration. The plasma membrane oxidoreductase system is proposed to act as a redox sensor that, in combination with growth factors, regulates cell proliferation and apoptosis; inhibition of this system by capsaicin can trigger Bcl-2-mediated apoptosis (Wolvetang et al. 1996). Moreover, capsaicin-induced apoptosis is mediated by the NADPH oxidase-modulated ROS production in HepG2 human hepatoblastoma cells (Lee et al. 2004).

3.2 Other Signaling Pathways

Capsaicin has been shown to enhance p53 gene expression in SNU-1 stomach cancer cells (Kim et al. 1997). It also triggers G1-phase arrest and apoptosis, leading to suppression of the growth of leukemic cells, but not normal bone marrow mononuclear cells. The signaling involved with this capsaicin-induced apoptosis is associated with intracellular ROS production (Ito et al. 2004). Alternatively, capsaicin induces elevation nitric oxide (NO) production, subsequent Mdm2 down-regulation and p53 activation, leading to Bax up-regulation and mitochondrial-dependent apoptosis (Kim et al. 2009). Capsaicin also inhibits constitutive activation of STAT3 in multiple myeloma cells in a dose- and time-dependent manner. This block of STAT3 activation by capsaicin subsequently alters protein expression of cyclin D1, Bcl-2, Bcl-xL, survivin, and vascular endothelial growth factor, resulting in G1 cell-cycle arrest and apoptosis (Bhutani et al. 2007).

The transcription factor, nuclear transcription factor κB (NF-κB), has drawn considerable attention for its importance in the mechanism of capsaicin action because the expression of many genes associating with the suppression of apoptosis and induction of cellular transformation, proliferation, invasion, metastasis, chemoresistance, and inflammation (Garg and Aggarwal 2002; Kumar et al.

2004; Shishodia and Aggarwal 2004). Capsaicin enhances the protein stability of IκB, an inhibitor of NF-κB, thereby repressing NF-κB activation (Singh et al. 1996). Similarly, capsaicin inhibited TPA-induced activation of NF-κB by blocking degradation of IκB and preventing the subsequent nuclear translocation of NF-κB/p65 in mouse epidermis cells. The repression of NF-κB by capsaicin leads to a reduction in neoplastic transformation and progression (Han et al. 2001). TPA-stimulated activation of NF-κB is also reduced by capsaicin in human promyelocytic leukemia cells (Han et al. 2002). Moreover, capsaicin inhibits tumor necrosis factor-α (TNFα)- and TPA-induced binding of AP-1 and NF-κB to their specific DNA binding sites in human chronic myelogenous leukemia cells (Duvoix et al. 2004).

Capsaicin selectively induced apoptosis in H-*ras*-transformed human breast epithelial cells, an action accompanied by marked activation of the mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinase 1 (JNK1) and p38, and deactivation of extracellular signal-regulation kinase (ERK) (Kang et al. 2003). Furthermore, experiments utilizing an animal model have demonstrated that capsaicin is involved in the reduced proliferation and suppressed activation of ERK and c-Jun in pancreatic carcinogenesis (Bai et al. 2011). However, studies employing specific inhibitors have shown that capsaicin induces activation of ERK, phosphoinositide 3-kinase (PI3K)/Akt and protein kinase Cα (PKCα) cascades, subsequently, triggering secretion of the pro-inflammatory cytokines, TNFα and interleukin (IL)-6, which synergize to decrease the cell viability of PC-13 prostate cancer cells (Malagarie-Cazenave et al. 2011). Another signaling pathway that might account for the anticancer effect of capsaicin is activation of phase I and phase II enzymes, which effectively detoxify carcinogens during experimental lung cancer (Anandakumar et al. 2009).

Capsaicin also impacts cell migration. In B16F10 melanoma cells, capsaicin was shown to significantly inhibit migratory activities without showing apparent cytotoxicity. This capsaicin-induced reduction in cell migration was correlated with PI3-K/Akt/Rac1 signaling (Shin et al. 2008). A recent study indicated that capsaicin inhibits vascular endothelial growth factor (VEGF)-induced p38 MAPK and Akt activation in human vascular endothelial cells, thus inhibiting VEGF-stimulated angiogenesis (Min et al. 2004).

4 Capsaicin in Programmed Cell Death

Physiological or programmed cell death is a closed regulated process, as opposed to necrosis, also known as uncontrolled cell death. Programmed cell death, including apoptosis (type I) and autophagy (type II), has attracted considerable attention as an important therapeutic target for many diseases, including cancer. Capsaicin has been shown to induce both apoptosis and autophagy; whether the net effect of these actions is decreased cell growth or enhanced cell survival is a central theme in this review.

4.1 Apoptosis

Much attention has focused on apoptosis as an important cell-death pathway, especially for its prominent role in cancer suppression. Apoptosis is a complex process that occurs in response to a variety of stress stimuli. The extrinsic pathway of apoptosis is dependent on binding of ligands to death receptors followed by formation of a death-inducing signaling complex (DISC), which subsequently activates initiator caspase-8 and effector caspases (Wajant 2002). An alternative intrinsic pathway has also been identified. This mitochondria-dependent mechanism is characterized by translocation of Bax/Bak to mitochondria and release of cytochrome c from mitochondria into the cytoplasm. These mitochondrial alterations subsequently activate a caspase cascade that induces an ordered series of events, culminating in degradation of the cell (Er et al. 2006; Kuwana et al. 2002; Lee et al. 2005; Jiang and Wang 2004; Vander Heiden and Thompson 1999). Capsaicin has been shown to potentiate tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-resistant human hepatocellular carcinoma cells to apoptosis through up-regulation of the cell surface TRAIL receptor DR5 by calmodulin-dependent protein kinase (Moon et al. 2011). Similar results were also reported in multiple malignant glioma cells, demonstrating that subtoxic doses of capsaicin effectively sensitize these cells to TRAIL-induced apoptosis via GADD153-mediated up-regulation of DR5 and down-regulation of the caspase inhibitor survivin (Kim et al. 2010). Capsaicin induces up-regulation of the death receptors Fas/CD95, but more importantly Fas/CD95 ligand independent, and triggers Fas/CD95-TRPV1 co-clustering, which results in both extrinsic and intrinsic apoptotic pathways (Amantini et al. 2009).

Recent findings have shed light on the importance of other organelles in integrating apoptotic signaling and initiating caspase activation and apoptosis; in particular ER stress, characterized by the unfolded-protein response and abnormal calcium homeostasis, has been implied (Kaufman 1999; Patil and Walter 2001; Ferri and Kroemer 2001). One of the many proteins induced as part of the adaptive ER stress response is GADD153/CHOP (growth arrest and DNA damage inducible gene 153). This member of the CCAAT/enhancer-binding protein (C/EBP) family of transcription factors has an essential role in regulating apoptosis (Zinszner et al. 1998; Oyadomari and Mori 2004; Friedman 1996). GADD153 functions as a transcription factor that regulates the expression of a panel of genes, including the anti- and pro-apoptotic Bcl-2 family members, Bcl-2 and Bim, respectively, resulting in mitochondrial cell death (McCullough et al. 2001; Puthalakath et al. 2007). To date, few studies have described the relationship between GADD153 elevation and capsaicin-induced apoptosis (Huang et al. 2009; Sánchez et al. 2008). In the studies of Ip et al., capsaicin was found to induce caspase-independent pathways through increases in the levels of GADD153 and calcium, resulting in ER stress and apoptosis in human tongue cancer cells and human nasopharyngeal carcinoma cells (Ip et al. 2010, 2011). Moreover, capsaicin triggers ER stress, in turn, activating GADD153 and calpain and leading to mitochondria-dependent apoptosis in human breast MCF-10A cells (Lee et al. 2009). Theses capsaicin-induced apoptosis processes are presumably major contributors to the anticancer properties of capsaicin.

4.2 Autophagy

Autophagy, often called type II programmed cell death to distinguish it from type I apoptosis processes, is a self-digestion and bulk-degradation process with adaptive catabolic and energy-generating features that promotes cellular survival in response to various forms of stress (Klionsky 2008; Yang and Klionsky 2010; Yorimitsu and Klionsky 2005). However, accumulating data now support the view that autophagy deficiencies enhance tumorigenesis, suggesting a tumor-suppressive function of autophagy (Liang et al. 1999; Mathew et al. 2009; Takamura et al. 2011). The fact that autophagy is induced when apoptosis is compromised further highlights its importance in cancer inhibition (Shimizu et al. 2004; Yu et al. 2004). During autophagy, cytosolic components are sequestered by a portion of isolated, membrane-forming autophagosomes, followed by fusion with lysosomes into autophagolysosomes. The contents of the autophagolysosomes are eventually degraded by digestive enzymes in lysosomes (Klionsky and Emr 2000).

To dates, only a very few studies have focused on the induction of autophagy by capsaicin or its derivatives. In 2008, Oh et al. reported that a saturated structural analog of capsaicin, dihydrocapsaicin (DHC), induces autophagy in human colon and breast cancer cells, as evidenced by the presence of punctuate structures of green fluorescent protein (GFP)-conjugated LC3, a marker of autophagosomes (Oh et al. 2008). These authors further suggested that catalase-regulated ROS generation functions as a key regulator of DHC-induced autophagy. Interestingly, blocking autophagy with inhibitors or using RNA interference sensitized cancer cells to DHC-induced apoptosis; conversely, blocking DHC-mediated apoptosis resulted in enhanced autophagy. Additionally, DHC-mediated autophagy is clearly associated with protection against apoptosis and necrosis in lung cells (Choi et al. 2010b). These various lines of evidence suggest a multifaceted role of capsaicin in cell-death regulation.

Recent progress also has shed light on ER-stress-mediated autophagy, indicating a new pathway for autophagy induction (Ogata et al. 2006; Yorimitsu and Klionsky 2005). Capsaicin and DHC have been shown to induce ER stress in human lung epithelial fibroblast WI-38 cells; this leads to autophagy, which, in turn, plays a role in cell survival (Oh and Lim 2009). Not surprisingly, blocking DHC-mediated autophagy enhances apoptosis in these non-cancerous WI-38 cells (Oh and Lim 2009). In another system, capsaicin increases autophagy in MCF-7 and MDA-MB-231 breast cancer cell lines and is less cytotoxic toward these cells than toward non-transformed MCF10A cells, where it shown greater apoptotic activity, indicating a protective role of capsaicin-induced autophagy (Choi et al. 2010a). A recent study, also the first to demonstrate that capsaicin triggers genotoxicity-induced autophagy through ATM–mediated DNA repair, showed that the resulting autophagy led to chemoresistance and sustained survival of breast cancer cells (Yoon et al. 2011). In cases of capsaicin-induced autophagy, the results almost invariably imply that autophagy is involved in cell protection rather than cell death, especially in cancer cells.

5 Capsaicin in Tumorigenesis

Capsaicin is one of the most commonly used anticancer drugs owing to its inhibitory effects on cell proliferation. However, data from epidemiologic studies suggest that capsaicin may exert dual effects—anti-tumor or tumor-promoting—depending on the dose (Lopez-Carrillo et al. 2003). Capsaicin has also been shown to act via EGFR signaling to function as a co-carcinogen in the TPA-induced skin cancer model (Hwang et al. 2010). Moreover, Erin et al. reported that capsaicin promotes a more aggressive gene-expression phenotype and represses expression of pro-apoptotic proteins in breast cancer cells (Erin et al. 2006), supporting the idea that capsaicin acts on other targets to activate unanticipated pathways, subsequently leading to tumorigenesis.

Tumor cell migration, which is a requirement for cancer metastasis and invasion, is often associated with epithelial-mesenchymal transition (EMT), a trans-differentiation process in which epithelial cells lose their characteristics morphology and adhesive properties and acquire a mesenchymal phenotype (Cannito et al. 2010). The work of Waning et al. provides a precedent for the reinforcing effect of capsaicin on cell migration. These researchers demonstrated a stimulatory effect of capsaicin on TRPV1 channels in hepatoma cells that enhances calcium influx, which is important for cell migration (Waning et al. 2007). Capsaicin has also been shown to stimulate calcium entry via TRPV4 channels, leading to a migratory phenotype (Vriens et al. 2004). However, capsaicin induces an invasive gene-expression phenotype in TRPV1-null urothelial cancer cells, and TRPV1 over-expression restores the sensitivity of cells to capsaicin-induced apoptosis and inhibition of capsaicin-enhanced invasion (Caprodossi et al. 2011). Seemingly, the expression and function of TRPV1 in different types of cells affects cellular outcome in response to capsaicin.

6 Conclusions

Changes in intracellular redox homeostasis—a major signaling mechanism initiated by capsaicin—appear to regulate variety signaling pathways that lead to important cellular responses. Capsaicin, long considered a chemopreventive agent, may modulate redox signaling and subsequently produce divergent cellular outcome, from cell death to sustained cell survival. Much remains to be learned regarding the cellular targets of capsaicin and the molecular mechanisms initiated by capsaicin that mediate its apoptotic/tumor-promoting effects. The findings of future studies will assist us in understanding the biological function of capsaicin, and will possibly provide a rational framework for the further development of improved chemopreventive strategies based on capsaicin.

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References

Agakichiev G, Appelshauser H, Baur R, Bielcikova J, Braun-Munzinger P, Cherlin A, Drees A, Esumi SI, Filimonov K, Fraenkel Z et al (2004) Semihard scattering unraveled from collective dynamics by two-pion azimuthal correlations in 158A GeV/c Pb+Au collisions. Phys Rev Lett 92:032301

Agrawal RC, Wiessler M, Hecker E, Bhide SV (1986) Tumour-promoting effect of chilli extract in BALB/c mice. Int J Cancer 38:689–695

Amantini C, Mosca M, Nabissi M, Lucciarini R, Caprodossi S, Arcella A, Giangaspero F, Santoni G (2007) Capsaicin-induced apoptosis of glioma cells is mediated by TRPV1 vanilloid receptor and requires p38 MAPK activation. J Neurochem 102:977–990

Amantini C, Ballarini P, Caprodossi S, Nabissi M, Morelli MB, Lucciarini R, Cardarelli MA, Mammana G, Santoni G (2009) Triggering of transient receptor potential vanilloid type 1 (TRPV1) by capsaicin induces Fas/CD95-mediated apoptosis of urothelial cancer cells in an ATM-dependent manner. Carcinogenesis 30:1320–1329

Anandakumar P, Kamaraj S, Jagan S, Ramakrishnan G, Naveenkumar C, Asokkumar S, Devaki T (2009) Capsaicin alleviates the imbalance in xenobiotic metabolizing enzymes and tumor markers during experimental lung tumorigenesis. Mol Cell Biochem 331:135–143

Archer VE, Jones DW (2002) Capsaicin pepper, cancer and ethnicity. Med Hypotheses 59:450–457

Baek YM, Hwang HJ, Kim SW, Hwang HS, Lee SH, Kim JA, Yun JW (2008) A comparative proteomic analysis for capsaicin-induced apoptosis between human hepatocarcinoma (HepG2) and human neuroblastoma (SK-N-SH) cells. Proteomics 8:4748–4767

Bai H, Li H, Zhang W, Matkowskyj KA, Liao J, Srivastava SK, Yang GY (2011) Inhibition of chronic pancreatitis and pancreatic intraepithelial neoplasia (PanIN) by capsaicin in LSL-KrasG12D/Pdx1-Cre mice. Carcinogenesis 32:1689–1696

Balaban RS, Nemoto S, Finkel T (2005) Mitochondria, oxidants, and aging. Cell 120:483–495

Bhutani M, Pathak AK, Nair AS, Kunnumakkara AB, Guha S, Sethi G, Aggarwal BB (2007) Capsaicin is a novel blocker of constitutive and interleukin-6-inducible STAT3 activation. Clin Cancer Res 13:3024–3032

Bode AM, Dong Z (2011) The two faces of capsaicin. Cancer Res 71:2809–2814

Bode AM, Cho YY, Zheng D, Zhu F, Ericson ME, Ma WY, Yao K, Dong Z (2009) Transient receptor potential type vanilloid 1 suppresses skin carcinogenesis. Cancer Res 69:905–913

Bruno M, Brightman AO, Lawrence J, Werderitsh D, Morré DM, Morré DJ (1992) Stimulation of NADH oxidase activity from rat liver plasma membranes by growth factors and hormones is decreased or absent with hepatoma plasma membranes. Biochem J 284(Pt 3):625–628

Cannito S, Novo E, di Bonzo LV, Busletta C, Colombatto S, Parola M (2010) Epithelial-mesenchymal transition: from molecular mechanisms, redox regulation to implications in human health and disease. Antioxid Redox Signal 12:1383–1430

Caprodossi S, Amantini C, Nabissi M, Morelli MB, Farfariello V, Santoni M, Gismondi A, Santoni G (2011) Capsaicin promotes a more aggressive gene expression phenotype and invasiveness in null-TRPV1 urothelial cancer cells. Carcinogenesis 32:686–694

Chen CF, Huang S, Liu SC, Chueh PJ (2006) Effect of polyclonal antisera to recombinant tNOX protein on the growth of transformed cells. Biofactors 28:119–133

Choi CH, Jung YK, Oh SH (2010a) Autophagy induction by capsaicin in malignant human breast cells is modulated by p38 and extracellular signal-regulated mitogen-activated protein kinases and retards cell death by suppressing endoplasmic reticulum stress-mediated apoptosis. Mol Pharmacol 78:114–125

Choi CH, Jung YK, Oh SH (2010b) Selective induction of catalase-mediated autophagy by dihydrocapsaicin in lung cell lines. Free Radic Biol Med 49:245–257

Chueh PJ (2000) Cell membrane redox systems and transformation. Antioxid Redox Signal 2:177–187

Chueh PJ, Morré DJ, Wilkinson FE, Gibson J, Morré DM (1997) A 33.5-kDa heat- and protease-resistant NADH oxidase inhibited by capsaicin from sera of cancer patients. Arch Biochem Biophys 342:38–47

Chueh PJ, Kim C, Cho N, Morré DM, Morré DJ (2002a) Molecular cloning and characterization of a tumor-associated, growth-related, and time-keeping hydroquinone (NADH) oxidase (tNOX) of the HeLa cell surface. Biochemistry 41:3732–3741

Chueh PJ, Morré DM, Morré DJ (2002b) A site-directed mutagenesis analysis of tNOX functional domains. Biochim Biophys Acta 1594:74–83

Chueh PJ, Wu LY, Morré DM, Morré DJ (2004) tNOX is both necessary and sufficient as a cellular target for the anticancer actions of capsaicin and the green tea catechin (-)-epigallocatechin-3-gallate. Biofactors 20:235–249

Degli Esposti M (1998) Inhibitors of NADH-ubiquinone reductase: an overview. Biochim Biophys Acta 1364:222–235

Dorai T, Dutcher JP, Dempster DW, Wiernik PH (2004) Therapeutic potential of curcumin in prostate cancer – V: interference with the osteomimetic properties of hormone refractory C4-2B prostate cancer cells. Prostate 60:1–17

Duvoix A, Delhalle S, Blasius R, Schnekenburger M, Morceau F, Fougere M, Henry E, Galteau MM, Dicato M, Diederich M (2004) Effect of chemopreventive agents on glutathione S-transferase P1-1 gene expression mechanisms via activating protein 1 and nuclear factor kappaB inhibition. Biochem Pharmacol 68:1101–1111

Er E, Oliver L, Cartron PF, Juin P, Manon S, Vallette FM (2006) Mitochondria as the target of the pro-apoptotic protein Bax. Biochim Biophys Acta 1757:1301–1311

Erin N, Zhao W, Bylander J, Chase G, Clawson G (2006) Capsaicin-induced inactivation of sensory neurons promotes a more aggressive gene expression phenotype in breast cancer cells. Breast Cancer Res Treat 99:351–364

Ferri KF, Kroemer G (2001) Organelle-specific initiation of cell death pathways. Nat Cell Biol 3:E255–E263

Finkel T (2003) Oxidant signals and oxidative stress. Curr Opin Cell Biol 15:247–254

Friedman AD (1996) GADD153/CHOP, a DNA damage-inducible protein, reduced CAAT/enhancer binding protein activities and increased apoptosis in 32D c13 myeloid cells. Cancer Res 56:3250–3256

Garg A, Aggarwal BB (2002) Nuclear transcription factor-kappaB as a target for cancer drug development. Leukemia 16:1053–1068

Hail N Jr (2003) Mechanisms of vanilloid-induced apoptosis. Apoptosis 8:251–262

Hail N Jr, Lotan R (2009) Cancer chemoprevention and mitochondria: targeting apoptosis in transformed cells via the disruption of mitochondrial bioenergetics/redox state. Mol Nutr Food Res 53:49–67

Han SS, Keum YS, Seo HJ, Chun KS, Lee SS, Surh YJ (2001) Capsaicin suppresses phorbol ester-induced activation of NF-kappaB/Rel and AP-1 transcription factors in mouse epidermis. Cancer Lett 164:119–126

Han SS, Keum YS, Chun KS, Surh YJ (2002) Suppression of phorbol ester-induced NF-kappaB activation by capsaicin in cultured human promyelocytic leukemia cells. Arch Pharm Res 25:475–479

Hedges KL, Morré DM, Wu LY, Morré DJ (2003) Adriamycin tolerance in human mesothelioma lines and cell surface NADH oxidase. Life Sci 73:1189–1198

Hu F, Sun WW, Zhao XT, Cui ZJ, Yang WX (2008) TRPV1 mediates cell death in rat synovial fibroblasts through calcium entry-dependent ROS production and mitochondrial depolarization. Biochem Biophys Res Commun 369:989–993

Huang SP, Chen JC, Wu CC, Chen CT, Tang NY, Ho YT, Lo C, Lin JP, Chung JG, Lin JG (2009) Capsaicin-induced apoptosis in human hepatoma HepG2 cells. Anticancer Res 29:165–174

Hwang MK, Bode AM, Byun S, Song NR, Lee HJ, Lee KW, Dong Z (2010) Cocarcinogenic effect of capsaicin involves activation of EGFR signaling but not TRPV1. Cancer Res 70:6859–6869

Ip SW, Lan SH, Huang AC, Yang JS, Chen YY, Huang HY, Lin ZP, Hsu YM, Yang MD, Chiu CF et al (2010) Capsaicin induces apoptosis in SCC-4 human tongue cancer cells through mitochondria-dependent and -independent pathways. Environ Toxicol 27(6):332–341

Ip SW, Lan SH, Lu HF, Huang AC, Yang JS, Lin JP, Huang HY, Lien JC, Ho CC, Chiu CF et al (2011) Capsaicin mediates apoptosis in human nasopharyngeal carcinoma NPC-TW 039 cells through mitochondrial depolarization and endoplasmic reticulum stress. Hum Exp Toxicol 31(6):539–549

Ito K, Nakazato T, Yamato K, Miyakawa Y, Yamada T, Hozumi N, Segawa K, Ikeda Y, Kizaki M (2004) Induction of apoptosis in leukemic cells by homovanillic acid derivative, capsaicin, through oxidative stress: implication of phosphorylation of p53 at Ser-15 residue by reactive oxygen species. Cancer Res 64:1071–1078

Jiang X, Wang X (2004) Cytochrome C-mediated apoptosis. Annu Rev Biochem 73:87–106

Julius D, Basbaum AI (2001) Molecular mechanisms of nociception. Nature 413:203–210

Kang HJ, Soh Y, Kim MS, Lee EJ, Surh YJ, Kim HR, Kim SH, Moon A (2003) Roles of JNK-1 and p38 in selective induction of apoptosis by capsaicin in ras-transformed human breast epithelial cells. Int J Cancer 103:475–482

Kaufman RJ (1999) Stress signaling from the lumen of the endoplasmic reticulum: coordination of gene transcriptional and translational controls. Genes Dev 13:1211–1233

Kim JD, Kim JM, Pyo JO, Kim SY, Kim BS, Yu R, Han IS (1997) Capsaicin can alter the expression of tumor forming-related genes which might be followed by induction of apoptosis of a Korean stomach cancer cell line, SNU-1. Cancer Lett 120:235–241

Kim CS, Kawada T, Kim BS, Han IS, Choe SY, Kurata T, Yu R (2003) Capsaicin exhibits anti-inflammatory property by inhibiting IkB-a degradation in LPS-stimulated peritoneal macrophages. Cell Signal 15:299–306

Kim CS, Park WH, Park JY, Kang JH, Kim MO, Kawada T, Yoo H, Han IS, Yu R (2004) Capsaicin, a spicy component of hot pepper, induces apoptosis by activation of the peroxisome proliferator-activated receptor gamma in HT-29 human colon cancer cells. J Med Food 7:267–273

Kim SR, Kim SU, Oh U, Jin BK (2006) Transient receptor potential vanilloid subtype 1 mediates microglial cell death in vivo and in vitro via Ca^{2+}-mediated mitochondrial damage and cytochrome c release. J Immunol 177:4322–4329

Kim YM, Hwang JT, Kwak DW, Lee YK, Park OJ (2007) Involvement of AMPK signaling cascade in capsaicin-induced apoptosis of HT-29 colon cancer cells. Ann N Y Acad Sci 1095:496–503

Kim MY, Trudel LJ, Wogan GN (2009) Apoptosis induced by capsaicin and resveratrol in colon carcinoma cells requires nitric oxide production and caspase activation. Anticancer Res 29:3733–3740

Kim JY, Kim EH, Kim SU, Kwon TK, Choi KS (2010) Capsaicin sensitizes malignant glioma cells to TRAIL-mediated apoptosis via DR5 upregulation and survivin downregulation. Carcinogenesis 31:367–375

Klionsky DJ (2008) Autophagy revisited: a conversation with Christian de Duve. Autophagy 4:740–743

Klionsky DJ, Emr SD (2000) Autophagy as a regulated pathway of cellular degradation. Science 290:1717–1721

Kumar A, Takada Y, Boriek AM, Aggarwal BB (2004) Nuclear factor-kappaB: its role in health and disease. J Mol Med (Berl) 82:434–448

Kuwana T, Mackey MR, Perkins G, Ellisman MH, Latterich M, Schneiter R, Green DR, Newmeyer DD (2002) Bid, Bax, and lipids cooperate to form supramolecular openings in the outer mitochondrial membrane. Cell 111:331–342

Lambeth JD (2004) NOX enzymes and the biology of reactive oxygen. Nat Rev Immunol 4:181–189

Lawen A, Martinus RD, McMullen GL, Nagley P, Vaillant F, Wolvetang EJ, Linnane AW (1994) The universality of bioenergetic disease: the role of mitochondrial mutation and the putative inter-relationship between mitochondria and plasma membrane NADH oxidoreductase. Mol Aspects Med 15(Suppl):s13–s27

Lee YS, Kwon EJ, Jin DQ, Park SH, Kang YS, Huh K, Kim JA (2002) Redox status-dependent regulation of cyclooxygenases mediates the capsaicin-induced apoptosis in human neuroblastoma cells. J Environ Pathol Toxicol Oncol 21:113–120

Lee YS, Kang YS, Lee JS, Nicolova S, Kim JA (2004) Involvement of NADPH oxidase-mediated generation of reactive oxygen species in the apototic cell death by capsaicin in HepG2 human hepatoma cells. Free Radic Res 38:405–412

Lee HJ, Wang CJ, Kuo HC, Chou FP, Jean LF, Tseng TH (2005) Induction apoptosis of luteolin in human hepatoma HepG2 cells involving mitochondria translocation of Bax/Bak and activation of JNK. Toxicol Appl Pharmacol 203:124–131

Lee MJ, Kee KH, Suh CH, Lim SC, Oh SH (2009) Capsaicin-induced apoptosis is regulated by endoplasmic reticulum stress- and calpain-mediated mitochondrial cell death pathways. Toxicology 264:205–214

Liang XH, Jackson S, Seaman M, Brown K, Kempkes B, Hibshoosh H, Levine B (1999) Induction of autophagy and inhibition of tumorigenesis by beclin 1. Nature 402:672–676

Liu SC, Yang JJ, Shao KN, Chueh PJ (2008) RNA interference targeting tNOX attenuates cell migration via a mechanism that involves membrane association of Rac. Biochem Biophys Res Commun 365:672–677

Lo YC, Yang YC, Wu IC, Kuo FC, Liu CM, Wang HW, Kuo CH, Wu JY, Wu DC (2005) Capsaicin-induced cell death in a human gastric adenocarcinoma cell line. World J Gastroenterol 11:6254–6257

Lopez-Carrillo L, Lopez-Cervantes M, Robles-Diaz G, Ramirez-Espitia A, Mohar-Betancourt A, Meneses-Garcia A, Lopez-Vidal Y, Blair A (2003) Capsaicin consumption, Helicobacter pylori positivity and gastric cancer in Mexico. Int J Cancer 106:277–282

Macho A, Sancho R, Minassi A, Appendino G, Lawen A, Munoz E (2003) Involvement of reactive oxygen species in capsaicinoid-induced apoptosis in transformed cells. Free Radic Res 37:611–619

Malagarie-Cazenave S, Olea-Herrero N, Vara D, Diaz-Laviada I (2009) Capsaicin, a component of red peppers, induces expression of androgen receptor via PI3K and MAPK pathways in prostate LNCaP cells. FEBS Lett 583:141–147

Malagarie-Cazenave S, Olea-Herrero N, Vara D, Morell C, Diaz-Laviada I (2011) The vanilloid capsaicin induces IL-6 secretion in prostate PC-3 cancer cells. Cytokine 54:330–337

Mao LC, Wang HM, Lin YY, Chang TK, Hsin YH, Chueh PJ (2008) Stress-induced down-regulation of tumor-associated NADH oxidase during apoptosis in transformed cells. FEBS Lett 582:3445–3450

Mathew R, Karp CM, Beaudoin B, Vuong N, Chen G, Chen HY, Bray K, Reddy A, Bhanot G, Gelinas C et al (2009) Autophagy suppresses tumorigenesis through elimination of p62. Cell 137:1062–1075

McCullough KD, Martindale JL, Klotz LO, Aw TY, Holbrook NJ (2001) Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state. Mol Cell Biol 21:1249–1259

Min JK, Han KY, Kim EC, Kim YM, Lee SW, Kim OH, Kim KW, Gho YS, Kwon YG (2004) Capsaicin inhibits in vitro and in vivo angiogenesis. Cancer Res 64:644–651

Moon DO, Kang CH, Kang SH, Choi YH, Hyun JW, Chang WY, Kang HK, Koh YS, Maeng YH, Kim YR et al (2011) Capsaicin sensitizes TRAIL-induced apoptosis through Sp1-mediated DR5 up-regulation: involvement of Ca(2+) influx. Toxicol Appl Pharmacol 259(1):87–95

Mori A, Lehmann S, O'Kelly J, Kumagai T, Desmond JC, Pervan M, McBride WH, Kizaki M, Koeffler HP (2006) Capsaicin, a component of red peppers, inhibits the growth of androgen-independent, p53 mutant prostate cancer cells. Cancer Res 66:3222–3229

Morré DJ, Reust T (1997) A circulating form of NADH oxidase activity responsive to the antitumor sulfonylurea N-4-(methylphenylsulfonyl)-N′-(4-chlorophenyl)urea (LY181984) specific to sera from cancer patients. J Bioenerg Biomembr 29:281–289

Morré DJ, Chueh PJ, Morré DM (1995) Capsaicin inhibits preferentially the NADH oxidase and growth of transformed cells in culture. Proc Natl Acad Sci U S A 92:1831–1835

Morré DJ, Caldwell S, Mayorga A, Wu LY, Morré DM (1997a) NADH oxidase activity from sera altered by capsaicin is widely distributed among cancer patients. Arch Biochem Biophys 342:224–230

Morré DJ, Kim C, Paulik M, Morré DM, Faulk WP (1997b) Is the drug-responsive NADH oxidase of the cancer cell plasma membrane a molecular target for adriamycin? J Bioenerg Biomembr 29:269–280

Morré DJ, Bridge A, Wu LY, Morré DM (2000) Preferential inhibition by (-)-epigallocatechin -3-gallate of the cell surface NADH oxidase and growth of transformed cells in culture. Biochem Pharmacol 60:937–946

Morré DJ, Chueh PJ, Yagiz K, Balicki A, Kim C, Morré DM (2007) ECTO-NOX target for the anticancer isoflavene phenoxodiol. Oncol Res 16:299–312

Nagabhushan M, Bhide SV (1985) Mutagenicity of chili extract and capsaicin in short-term tests. Environ Mutagen 7:881–888

Nagy I, Santha P, Jancso G, Urban L (2004) The role of the vanilloid (capsaicin) receptor (TRPV1) in physiology and pathology. Eur J Pharmacol 500:351–369

Ogata M, Hino S, Saito A, Morikawa K, Kondo S, Kanemoto S, Murakami T, Taniguchi M, Tanii I, Yoshinaga K et al (2006) Autophagy is activated for cell survival after endoplasmic reticulum stress. Mol Cell Biol 26:9220–9231

Oh SH, Lim SC (2009) Endoplasmic reticulum stress-mediated autophagy/apoptosis induced by capsaicin (8-methyl-N-vanillyl-6-nonenamide) and dihydrocapsaicin is regulated by the extent of c-Jun NH2-terminal kinase/extracellular signal-regulated kinase activation in WI38 lung epithelial fibroblast cells. J Pharmacol Exp Ther 329:112–122

Oh SH, Kim YS, Lim SC, Hou YF, Chang IY, You HJ (2008) Dihydrocapsaicin (DHC), a saturated structural analog of capsaicin, induces autophagy in human cancer cells in a catalase-regulated manner. Autophagy 4:1009–1019

Oyadomari S, Mori M (2004) Roles of CHOP/GADD153 in endoplasmic reticulum stress. Cell Death Differ 11:381–389

Pathak SK, Sharma RA, Steward WP, Mellon JK, Griffiths TR, Gescher AJ (2005) Oxidative stress and cyclooxygenase activity in prostate carcinogenesis: targets for chemopreventive strategies. Eur J Cancer 41:61–70

Patil C, Walter P (2001) Intracellular signaling from the endoplasmic reticulum to the nucleus: the unfolded protein response in yeast and mammals. Curr Opin Cell Biol 13:349–355

Pramanik KC, Boreddy SR, Srivastava SK (2011) Role of mitochondrial electron transport chain complexes in capsaicin mediated oxidative stress leading to apoptosis in pancreatic cancer cells. PLoS One 6:e20151

Prevarskaya N, Zhang L, Barritt G (2007) TRP channels in cancer. Biochim Biophys Acta 1772:937–946

Puthalakath H, O'Reilly LA, Gunn P, Lee L, Kelly PN, Huntington ND, Hughes PD, Michalak EM, McKimm-Breschkin J, Motoyama N et al (2007) ER stress triggers apoptosis by activating BH3-only protein Bim. Cell 129:1337–1349

Sánchez AM, Sánchez MG, Malagarie-Cazenave S, Olea N, Diaz-Laviada I (2006) Induction of apoptosis in prostate tumor PC-3 cells and inhibition of xenograft prostate tumor growth by the vanilloid capsaicin. Apoptosis 11:89–99

Sánchez AM, Malagarie-Cazenave S, Olea N, Vara D, Chiloeches A, Diaz-Laviada I (2007) Apoptosis induced by capsaicin in prostate PC-3 cells involves ceramide accumulation, neutral sphingomyelinase, and JNK activation. Apoptosis 12:2013–2024

Sánchez AM, Martinez-Botas J, Malagarie-Cazenave S, Olea N, Vara D, Lasuncion MA, Diaz-Laviada I (2008) Induction of the endoplasmic reticulum stress protein GADD153/CHOP by capsaicin in prostate PC-3 cells: a microarray study. Biochem Biophys Res Commun 372:785–791

Schrader M, Fahimi HD (2006) Peroxisomes and oxidative stress. Biochim Biophys Acta 1763:1755–1766

Serra I, Yamamoto M, Calvo A, Cavada G, Baez S, Endoh K, Watanabe H, Tajima K (2002) Association of chili pepper consumption, low socioeconomic status and longstanding gallstones with gallbladder cancer in a Chilean population. Int J Cancer 102:407–411

Shimizu S, Kanaseki T, Mizushima N, Mizuta T, Arakawa-Kobayashi S, Thompson CB, Tsujimoto Y (2004) Role of Bcl-2 family proteins in a non-apoptotic programmed cell death dependent on autophagy genes. Nat Cell Biol 6:1221–1228

Shin DH, Kim OH, Jun HS, Kang MK (2008) Inhibitory effect of capsaicin on B16-F10 melanoma cell migration via the phosphatidylinositol 3-kinase/Akt/Rac1 signal pathway. Exp Mol Med 40:486–494

Shishodia S, Aggarwal BB (2004) Nuclear factor-kappaB activation mediates cellular transformation, proliferation, invasion angiogenesis and metastasis of cancer. Cancer Treat Res 119:139–173

Singh S, Natarajan K, Aggarwal BB (1996) Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a potent inhibitor of nuclear transcription factor-kappa B activation by diverse agents. J Immunol 157:4412–4420

Takamura A, Komatsu M, Hara T, Sakamoto A, Kishi C, Waguri S, Eishi Y, Hino O, Tanaka K, Mizushima N (2011) Autophagy-deficient mice develop multiple liver tumors. Genes Dev 25:795–800

Thomas KC, Sabnis AS, Johansen ME, Lanza DL, Moos PJ, Yost GS, Reilly CA (2007) Transient receptor potential vanilloid 1 agonists cause endoplasmic reticulum stress and cell death in human lung cells. J Pharmacol Exp Ther 321:830–838

Toth B, Gannett P (1992) Carcinogenicity of lifelong administration of capsaicin of hot pepper in mice. In Vivo 6:59–63

Vander Heiden MG, Thompson CB (1999) Bcl-2 proteins: regulators of apoptosis or of mitochondrial homeostasis? Nat Cell Biol 1:E209–E216

Vriens J, Janssens A, Prenen J, Nilius B, Wondergem R (2004) TRPV channels and modulation by hepatocyte growth factor/scatter factor in human hepatoblastoma (HepG2) cells. Cell Calcium 36:19–28

Wajant H (2002) The Fas signaling pathway: more than a paradigm. Science 296:1635–1636

Wang HM, Chueh PJ, Chang SP, Yang CL, Shao KN (2009) Effect of Ccapsaicin on tNOX (ENOX2) protein expression in stomach cancer cells. Biofactors 34:209–217

Wang HM, Chuang SM, Su YC, Li YH, Chueh PJ (2011) Down-regulation of tumor-associated NADH oxidase, tNOX (ENOX2), enhances capsaicin-induced inhibition of gastric cancer cell growth. Cell Biochem Biophys 61:355–366

Waning J, Vriens J, Owsianik G, Stuwe L, Mally S, Fabian A, Frippiat C, Nilius B, Schwab A (2007) A novel function of capsaicin-sensitive TRPV1 channels: involvement in cell migration. Cell Calcium 42:17–25

Wolvetang EJ, Larm JA, Moutsoulas P, Lawen A (1996) Apoptosis induced by inhibitors of the plasma membrane NADH-oxidase involves Bcl-2 and calcineurin. Cell Growth Differ 7:1315–1325

Yagiz K, Wu LY, Kuntz CP, James Morré D, Morré DM (2007) Mouse embryonic fibroblast cells from transgenic mice overexpressing tNOX exhibit an altered growth and drug response phenotype. J Cell Biochem 101:295–306

Yang Z, Klionsky DJ (2010) Eaten alive: a history of macroautophagy. Nat Cell Biol 12:814–822

Yoon JH, Ahn SG, Lee BH, Jung SH, Oh SH (2011) Role of autophagy in chemoresistance: regulation of the ATM-mediated DNA-damage signaling pathway through activation of DNA-PKcs and PARP-1. Biochem Pharmacol 83(6):745–757

Yorimitsu T, Klionsky DJ (2005) Autophagy: molecular machinery for self-eating. Cell Death Differ 12(Suppl 2):1542–1552

Yu L, Alva A, Su H, Dutt P, Freundt E, Welsh S, Baehrecke EH, Lenardo MJ (2004) Regulation of an ATG7-beclin 1 program of autophagic cell death by caspase-8. Science 304:1500–1502

Zhang J, Nagasaki M, Tanaka Y, Morikawa S (2003) Capsaicin inhibits growth of adult T-cell leukemia cells. Leuk Res 27:275–283

Zhang R, Humphreys I, Sahu RP, Shi Y, Srivastava SK (2008) In vitro and in vivo induction of apoptosis by capsaicin in pancreatic cancer cells is mediated through ROS generation and mitochondrial death pathway. Apoptosis 13:1465–1478

Zinszner H, Kuroda M, Wang X, Batchvarova N, Lightfoot RT, Remotti H, Stevens JL, Ron D (1998) CHOP is implicated in programmed cell death in response to impaired function of the endoplasmic reticulum. Genes Dev 12:982–995