



Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: <https://www.sciopen.com/journal/2097-0765>

Overview on signal transduction cascades regulation roles of garlic and its bioactive constituents

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ARTICLE INFO

Article history:

Received 1 April 2023

Received in revised form 18 April 2023

Accepted 28 May 2023

Keywords:

Cancer

Nutrigenomics

Signaling

Apoptosis

Allium sativum

ABSTRACT

High-throughput technologies in combination with modern exciting advancements in mass spectrometry-based proteomics and data analysis pipelines have empowered comprehensive characterization of disease phenotypes and their mechanistic regulation by dietary agents and bioactive molecules at unprecedented dimensionality and resolution. Extra-ordinary breakthroughs in the field of nutrigenomics have leveraged our understanding altogether to a new level of maturity. Interdisciplinary researchers have extensively analyzed health promoting and pharmacologically significant properties of garlic (*Allium sativum*). Importantly, garlic and its biologically active chemicals targeted oncogenic signaling cascades. In this mini-review we have attempted to summarize how garlic and its bioactive constituents regulated signal transduction cascades in cell culture studies and tumor-bearing mice.

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1. Introduction

Cutting-edge research has helped us in the identification and comprehensive characterization of deregulated cell signaling pathways, leading to a greater appreciation of their widespread roles in carcinogenesis and metastasis^[1-5]. Ground-breaking findings in the recent years have comprehensively characterized the complexity of clinicopathological features as well as genomic and proteomic aspects of wide variety of cancers^[6-8]. Mechanistic insights gained from the pioneering scientific works of cellular signaling cascades in wide variety of cancers have enabled researchers to develop a deeper understanding of heterogeneous nature of cancer^[9-13]. Fine-tuning of

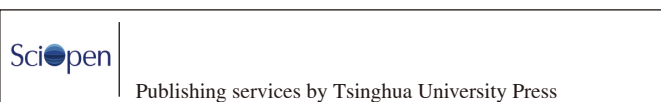
the cellular physiology in response to environmental and intracellular signals requires highly precise and complicated spatio-temporally controlled expression of gene networks^[14-15]. These pathways achieve considerable levels of selectivity and diversity through extensive crosstalk and integration. Understanding the mechanisms by which different oncogenic signaling cascades operate in different cancers has been enhanced greatly by recent mechanistic insights into how shared components are regulated independently and how the activity of one system is contextualized by others^[16-17]. Importantly, components of signal transduction cascades act with a high degree of autonomy and show pathway fidelity.

Drug developers are continuously in pursue for the next generation of cancer targets. Cutting-edge research unraveling the regulation of cell signaling pathways by natural products and dietary agents have grown exponentially^[18-22]. Undoubtedly, we have witnessed breakneck growth in the high-impact research works highlighting wide variety of molecules from natural sources which have shown

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Peer review under responsibility of Tsinghua University Press.



significant pharmacological properties. Cancer chemo-preventive features of dietary agents have attracted extra-ordinary appreciation and urged researchers to re-interpret the underlying mechanisms of carcinogenesis and metastasis, identification of tractable targets and how dietary agents prevent/inhibit cancer progression^[23-29].

Extracts and bioactive constituents of garlic (*Allium sativum*) have been shown to target oncogenic transduction cascades. Garlic contains diverse bioactive compounds, such as allicin, alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide and *S*-allyl-cysteine. There are some good reviews about cancer chemo-preventive roles of garlic in wide variety of cancers. Majority of the reviews have analyzed cancer chemo-preventive properties of garlic on the basis of their bioactive molecules and different cancers^[30-35]. However, we have exclusively addressed regulatory role of signaling cascades in cancers in this review. We have comprehensively provided a compendium of the key findings about the regulation of different signaling pathways by bioactive constituents of garlic in different cancers. We have summarized regulation of JAK/STAT, NF κ B, and PI3K/AKT pathways by garlic. We have also discussed regulation of endoplasmic reticulum stress-associated pathway and non-coding RNAs by garlic. We also discuss current knowledge on the tumor inhibitory and metastasis inhibitory effects of garlic-derived biomolecules in animal models.

2. Generalized overview of chemopreventive properties of garlic

Cancer chemopreventive role of garlic-derived bioactive molecules has engrossed significant attention^[36-37]. Garlic based biomolecules are being used as templates for drug design^[38]. Allium vegetables intake and the risk of gastric cancer has been evaluated in the Stomach cancer Pooling (StoP) project^[39]. However, more mechanism-oriented studies related to the chemo-preventive role of garlic are required.

Consumption of garlic and its sulphur-containing compounds such as alliin have been reported to be linked with a reduction in the risks associated with development of prostate cancer. The concentration of alliin and its metabolites has been tested in the prostate tissues of cancer patients^[40]. However, these findings need additional evidence and well-designed studies for a detailed understanding. Protective effects of dietary garlic have been reported to reduce the risk of colorectal cancer^[41]. Inhibition of NRF2 and its target genes are effective approaches for the prevention or reversal of radiotherapy-induced tumor recurrence and metastasis of NSCLC. Diallyl disulfide attenuated ionizing radiation-induced migratory and invasive potential of cancer cells by suppression of NRF2 signaling^[42]. Diallyl disulfide and diallyl trisulfide demonstrated high affiliations with a large extracellular loop of CD151 with a binding energy of -4.0 kcal/mol and transmembrane domain with a binding affinity of 11.7 and 13.6 kcal/mol, respectively^[43]. In the next section, we will discuss the role of garlic-derived chemicals in the modulation of JAK/STAT pathway.

3. JAK/STAT signaling

Greater than ever understanding of the molecular basis of JAK/STAT signaling pathway has garnered considerable interest, not only for the purpose of molecular and clinical research but also to refine our knowledge related to how deregulation of this cascade plays instrumental role in carcinogenesis. Cytokine binding results in the

activation of JAKs, which in turn phosphorylate cytokine receptors. Subsequently, this process promotes the binding of STAT proteins. These DNA-binding proteins become tyrosine-phosphorylated, undergo dimerization, and translocate into the nucleus for transcriptional regulation of target gene networks^[44-46].

Diallyl disulfide induced STAT1 expression in colon cancer colo-205 cells. It was shown that Diallyl disulfide mediated apoptosis was impaired in STAT1-silenced cancer cells^[47]. STAT1 has been shown to play dualistic role in carcinogenesis and STAT1-mediated functions in diallyl disulfide-treated cancer cell lines need to be tested in detail. SHP-1 (SH2-domain-containing protein phosphatase) is involved in inhibition of STAT3 phosphorylation by allicin (Fig. 1). Allicin mediated inhibitory effects on STAT3 phosphorylation were abolished in SHP-1-silenced HuCCT-1 cells. Intraperitoneal administration of allicin markedly impaired the growth of tumors in mice inoculated subcutaneously with HuCCT-1 cells (Fig. 1)^[48].

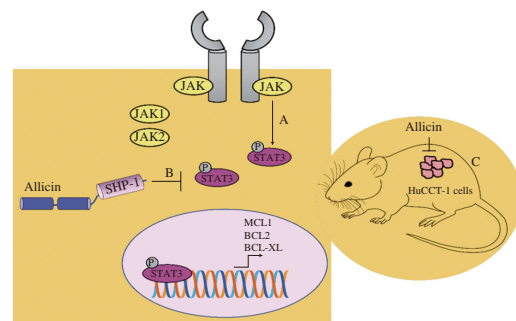


Fig. 1 (A) Regulation of JAK/STAT pathway by garlic-derived biomolecules. JAK-mediated phosphorylation of STAT proteins. Whereas SHP-1 dephosphorylated STAT proteins. (B) Allicin triggered SHP-1-mediated inactivation of STAT3. STAT3 has been shown to transcriptionally upregulate MCL1, BCL2 and BCL-XL. (C) Allicin impaired the growth of tumors in mice inoculated subcutaneously with HuCCT-1 cells.

Diallyl trisulfide-mediated inhibition of constitutive and interleukin (IL)-6-mediated nuclear accumulation of p-STAT3 as well as suppression of STAT3 dimer formation. Diallyl trisulfide efficiently reduced the incidence as well as burden of poorly differentiated cancers in male TRAMP mice without causing toxic side effects or weight loss^[49].

Allicin caused an inhibition of tumorigenesis in azoxymethane/dextran sodium sulfate (AOM/DSS) colorectal cancer rodent models. There was lesser weight loss reported in mice administered with allicin during every round of exposure to DSS as compared to the control group. Furthermore, recovery was more rapid in allicin treated mice as compared to the mice in model groups. Allicin treated mice revealed a notable suppression in size and number of tumors. Moreover, average tumor load was considerably reduced in allicin treated mice. Histological examination showed that allicin significantly reduced infiltration rate of the inflammatory cells in the colon tissues. Moreover, there was a noteworthy amelioration of mucosal hyperplasia and dysplasia in mice administered with allicin. Importantly, levels of p-STAT3 were noted to be concentration-dependently reduced by Allicin. Moreover, allicin also downregulated the expression of MCL1, BCL2 and BCL-XL (Fig. 1)^[50].

STAT3 signaling is oncogenic and existing evidence provides proof-of-concept about pharmaceutically targeting of JAK/STAT signaling by biomolecules derived from garlic. The JAK/STAT signaling pathway is a promising therapeutic target for the treatment of cancer and metastasis.

4. NFκB-driven signaling

The classical pathway for activation of the transcription factor NFκB is controlled by the IKK complex. This multi-component machinery consists of two active kinases (IKKα and IKKβ) and a regulatory molecule known as NEMO (IKKγ)^[51–52]. Activation of the IKK complexes leads to phosphorylation of IκBα, which is ubiquitinated and degraded by the proteasomal machineries, allowing NFκB to translocate to the nucleus and activate transcription of target gene networks^[53–54].

Diallyl trisulfide repressed IKK complex by inhibition of IKKβ phosphorylation (Fig. 2). IKKβ is a catalytic subunit of the IKK complex and triggers direct phosphorylation of IκBα for degradation. Essentially, as a ubiquitin ligase, TRAF6 is auto-activated by polyubiquitination of TRAF6 and induces phosphorylation of IKKβ by activation of TAK1-TAB2 complexes. TRAF6 catalyzes the synthesis of K63-linked polyubiquitination of TRAF6 and IKKγ. These K63-linked polyubiquitin chains serve as scaffolds for the recruitment of TAK1-TAB2 complexes. Diallyl trisulfide slightly reduced TRAF6-polyubiquitination but caused significant reduction in the levels of TRAF6. Diallyl trisulfide induced destabilization of TRAF6 in HeLa cells. Furthermore, proteasome inhibitor, MG132 hampered diallyl trisulfide-induced destabilization of TRAF6. Diallyl trisulfide induced TRAF6 degradation by the proteasomal machinery and diallyl trisulfide-mediated downregulation of TRAF6 suppressed IKKβ phosphorylation and activation of IKK complexes. Furthermore, IKK inactivation led to activation of IκBα and did not allow nuclear accumulation of NFκB. Diallyl trisulfide suppressed the ascites in the peritoneal cavities and the development of KSHV-infected cells in ascites of primary effusion lymphoma-xenografted SCID rodent model^[55].

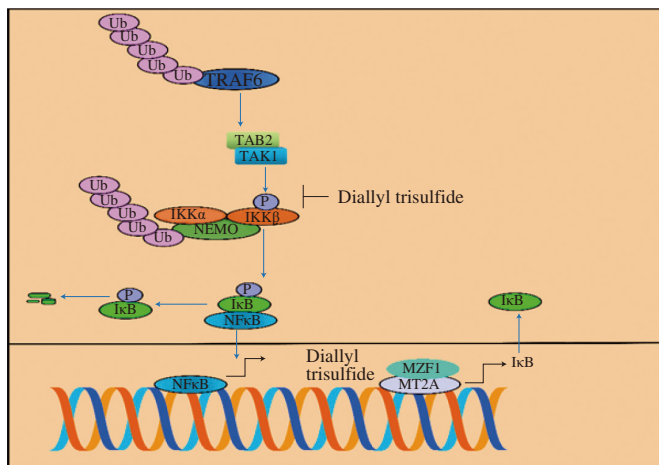


Fig. 2 Regulation of NFκB by bioactive components of garlic. Diallyl trisulfide inhibited IKK activation and IKK-mediated phosphorylation of IκB. Diallyl trisulfide promoted MZF1 and MT2A-mediated transcriptional upregulation of IκB.

Increasingly it is being appreciated that the negative regulators themselves are controlled by an intricate network of interactions that finetunes their effects on NFκB signaling. Further insight into the complex biochemical, functional, and pathophysiological interplay between NFκB and other transduction cascades may help to avoid such failures in the future.

Myeloid zinc-finger 1 (MZF1) worked synchronously with Metallothionein 2A (MT2A) and transcriptionally upregulated IκB. MT2A has also been demonstrated to upregulate MZF1 expression. Diallyl trisulfide promoted the interaction between MT2A and MZF1 and transcriptional upregulation of IκB in gastric cancer cells (Fig. 2). Essentially, MZF1 overexpression caused a significant reduction in volume of tumor xenografts in mice subcutaneously injected with MZF1-overexpressing BGC823 cancer cells^[56].

Diallyl trisulfide increased acetylation of histone-3 at lysine-9 (H3K9ac) and acetylation of histone 4 at lysine 5 (H4K5ac) accompanied with decline in the levels of HDAC1/2. Diallyl trisulfide reduced HDAC levels and potently enhanced histone hyperacetylation of *MT2A* gene. MT2A transcriptionally stimulated the expression of IκBα in BGC823 cancer cells. Diallyl trisulfide treatment increased the levels of MT2A and IκBα and promoted dephosphorylation of IκBα in tumor tissues of experimental rodent models. Immunohistochemistry evaluation of tumor sections from BGC823 tumor xenografts demonstrated an increase in the expression of MT2A and IκBα after combinatorial treatments with diallyl trisulfide and docetaxel^[57]. Diallyl trisulfide dose-dependently downregulated MMP2 and MMP9. IκBα phosphorylation was found to be reduced in diallyl trisulfide-treated-MDA-MB-231 cancer cells. IκB did not allow nuclear accumulation of NFκB and consequent upregulation of MMP2/9. The perivitelline cavity of embryos was injected with MDA-MB-231 cancer cells. The spread of cancer cells was observed throughout the body of zebrafish. After exposure to different doses of diallyl trisulfide, there was a significant reduction in the number of MDA-MB-231 cancer cells disseminated foci and the maximal distances of metastatic foci^[58].

Diallyl disulfide inhibited GSK-3β and suppressed the activation and nuclear localization of NFκB. Importantly, precursor protein p105 retains NFκB heterodimers in cytoplasm. Interestingly, GSK-3β phosphorylated p105 and accelerated proteolysis of p105 to p50. Furthermore, downregulation of GSK-3β in fibroblasts resulted in the inhibition of NFκB^[59].

5. PI3K/AKT/mTOR

PI3Ks (Phosphatidylinositol 3-kinases) are crucial regulators of intracellular transduction cascades in response to extracellular stimuli. Hyperactivation of PI3K pathway is one of the most frequently occurring mechanism in different cancers^[60–64]. Diallyl disulfide efficiently raised the levels of LC3B-II, an indicator of the formation of autophagosomes in MG-63 cells. 3-Methyladenine (3-MA) inhibited the formation of autophagosomes during the early stages by the blockade of class III phosphatidylinositol 3-kinases. Accordingly, diallyl disulfide-mediated increase in the levels of LC3-II was clearly reduced after treatment with 3-methyladenine. Diallyl disulfide reduced p-AKT, p-mTOR and p-p70S6K levels in osteosarcoma cells^[65]. *S*-Allylcysteine significantly suppressed the activation of the AKT/mTOR signaling cascade in tumor tissues of rodent models subcutaneously xenografted with A549 cells^[66].

Diallyl trisulfide caused evident reduction in tumorigenesis and phosphorylated levels of AKT in the tumor tissues of rodent models xenografted with BGC-823 cancer cells^[67]. Diallyl trisulfide also effectively reduced AKT-mediated phosphorylation of BAD at serine-155 in DU145 cancer cells. In the dephosphorylated form,

BAD gets localized to the outer mitochondrial membranes. In the mitochondria, it binds to and antagonizes pro-survival protein BCL-XL (member of BCL2 family). Findings suggested that growth factor-mediated BAD phosphorylation resulted in its cytoplasmic retention. 14-3-3 proteins interacted with cytosolically located phosphorylated BAD and prevented interactions of BAD with anti-apoptotic BCL2 family members. Moreover, protein-protein interactions between BAD and 14-3-3 β were distinctly suppressed in diallyl trisulfide-treated DU145 and PC-3 cancer cells. Diallyl trisulfide promoted mitochondrial transportation of BAD. Importantly, ectopic overexpression of constitutively active PKB/AKT significantly prevented diallyl trisulfide-induced apoptotic death^[68].

S-Allylcysteine dose-dependently suppressed the phosphorylated levels of AKT and mTOR. *S*-Allylcysteine also markedly reduced the phosphorylated levels of I κ B α in tumor tissues of the mice inoculated subcutaneously with oral cancer CAL-27 cells^[69]. Bioactive constituents of garlic will be helpful in the development of rationally designed combinatorial therapies, which will be necessary to overcome activation of compensatory pathways and acquired resistance mechanisms and to maximize cancer inhibitory activities of PI3K inhibitors.

6. Regulation of TRAIL pathway

TRAIL-mediated pathway has attracted valuable consideration because of its unique capability to target cancer cells while leaving normal cells intact. Preliminary breakthroughs associated with TRAIL-mediated selective killing of cancer cells urged researchers to comprehensively characterize pro-apoptotic and anti-apoptotic proteins for a better understanding of the underlying mechanisms which have regulatory role in apoptotic cell death^[70-75]. Diallyl disulfide worked in combination with TRAIL and synergistically enhanced apoptotic death in SW620 cells. However, normal colon cells were found to be resistant to combinatorial treatments with diallyl disulfide and TRAIL. Pan-caspase inhibitors led to significant reduction in the sensitizing effects of diallyl disulfide to TRAIL-induced apoptosis in SW620 cells. Furthermore, diallyl disulfide and TRAIL efficiently restricted the growth of the tumors in mice subcutaneously injected with SW620 cancer cells^[76].

Diallyl trisulfide remarkably sensitized TRAIL-resistant glioma cells to apoptotic death. Co-treatments with diallyl trisulfide and TRAIL led to a marked increase in accumulation of sub-G1-phase cells and a typical ladder pattern of internucleosomal fragmentations in U87cells. Diallyl trisulfide stimulated the expression of DR5 to sensitize apoptotic death in TRAIL-resistant glioma cells. Combinatorial treatment-induced apoptotic death was severely impaired in DR5-silenced U87MG cells. U87MG cells treated with diallyl trisulfide demonstrated intracellular accumulation of ROS. Pre-treatment with N-acetyl cysteine markedly blocked diallyl trisulfide plus TRAIL-induced apoptotic death in U87MG cells^[77]. Diallyl trisulfide and TRAIL alone or in combinations caused minimal apoptotic death in melanocytes in spite of significant surface expression of DR4 and DR5. There was an evident increase TRAIL-induced apoptotic death after 24 h of treatment and later more pronounced effects were noted after 72 h of treatment. TRAIL dose-dependently increased the levels of XBPI. TRAIL dose- and time-dependently induced robust activation of caspase-12. Additionally, diallyl trisulfide considerably increased the effects of anti-DR5, anti-DR4

and TRAIL with varying degrees^[78]. Collectively, these findings suggested that diallyl trisulfide augmented TRAIL-mediated apoptotic death via activation of endoplasmic reticulum stress pathway.

Diallyl trisulfide induced the expression of BAX, BAK, PUMA, BIM and NOXA and downregulated the levels of MCL1, BCL2, BCL-XL, survivin, cIAP1, cIAP2 and XIAP. Diallyl trisulfide-treated PC-3 cells demonstrated an increase in the expression of DR4 and DR5 but did not show significant effects on the levels of decoy receptors DcR1 and DcR2. Likewise, diallyl trisulfide upregulated DR4 and DR5 expression in LNCaP cells. Diallyl trisulfide significantly enhanced tumor growth inhibitory effects of TRAIL in mice orthotopically implanted with PC-3 cells. Diallyl trisulfide and TRAIL profoundly enhanced the levels of DR4, DR5 and caspase-8 in the tumor tissues of xenografted mice. However, combinatorial treatment caused a reduction in the levels of BCL2 and BCL-XL. Diallyl trisulfide and TRAIL also effectively inhibited microvessel densities and the expression of VEGF and IL-6^[79].

Diallyl trisulfide increased the phosphorylation levels of BCL2 at threonine-56 in PC-3 cells. Phosphorylated BCL2 has been shown to lose its ability to undergo heterodimerization with BAX. Diallyl trisulfide triggered the activation of ERK1/2 and JNK1. Diallyl trisulfide-induced phosphorylation of BCL2 was abolished upon chemical inhibition of JNK. Collectively, these findings highlighted that activation of JNK1, and to some extent ERK1/2, contributed to Diallyl trisulfide-induced phosphorylation of BCL2 and apoptotic death in PC-3 cells^[80].

7. Regulation of endoplasmic reticulum stress pathway

Structural and functional studies revealed that protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 α (IRE1 α) and activating transcription factor 6 (ATF6) are important stress sensors reportedly involved in modulation of UPR-dependent responses^[81-82]. Mechanistically it had been shown that ER transmembrane protein(s) transduced signals cytosolically and to the nucleus for restoration of protein-folding associated mechanisms via different pathways. IRE1 α RNase activity processed *XBPI* mRNA that upregulated a subset of target genes for regulation of folding of proteins, quality control of proteins, biogenesis of organelles and ER-associated protein degradation (ERAD). IRE1 α also selectively degraded different mRNAs by a distinct mechanism called regulated IRE1-dependent decay (RIDD). Functionally active PERK attenuated synthesis of protein by phosphorylating eIF2 α . Phosphorylated eIF2 α selectively translated *ATF4* mRNA, which encoded a transcription factor that transcriptionally controlled wide ranging genes involved in miscellaneous biological activities including apoptosis, amino acid metabolism and autophagy. There is evidence of transcriptional control of pro-apoptotic genes including CHOP and GADD34 by ATF4. GADD34 structurally associated with protein phosphatase 1C (PP1C) for dephosphorylation of eIF2 α . ATF6 has a Leu zipper (bZIP) transcription factor present in its cytosolically located domain and is localized at the endoplasmic reticulum in unstressed cells. In cells undergoing ER stress, distribution of ATF6 is noted in Golgi apparatus for proteolytic processing by site 1 protease (S1P) and site 2 protease (S2P) that resulted in release of its cytosolically located domain (ATF6f). ATF6f has been shown to upregulate expression of selective UPR target genes^[83-84].

BIP (GRP78), a member of the HSP70 family has been found to be distinctly induced upon circumstances leading to the accumulation of unfolded proteins in the endoplasmic reticulum (ER). HSPA5 (BIP) induced apoptotic cell death through several pathways. Furthermore, there is an evident increase in ubiquitin ligases which are involved in the ER stress response. These ligases target β -catenin for degradation. Importantly, RBX1 (RING box protein-1) and SKP1 (S-phase kinase associated protein-1) have been shown to target client proteins^[85].

BisPMB is a synthetically prepared analogue of ajoene. It has been reported to display better cytotoxicity as compared to ajoene. GRP78 is a Ca^{2+} dependent chaperone involved in folding of proteins. BisPMB increased GRP78 expression in WHCO1 cells. ERAD (endoplasmic reticulum-associated degradation) is a cascade in which misfolded proteins are transported to the cytosol from the ER for proteasomal degradation. The ubiquitin proteasome system is a core machinery of ERAD where misfolded proteins are ubiquitinated and tagged for degradation. It has been shown that bisPMB triggered ERAD by increasing the global levels of ubiquitinated proteins in WHCO1 cells. BisPMB activates the IRE1/XBP1 ER stress pathway. Importantly, XBP1 splicing is an early response to bisPMB in WHCO1 cells. Promoter region of *CHOP* gene has binding sites for XBP1, ATF4 and ATF6. CHOP upregulated GADD34 and ERO1 (ER oxidoreductin-1) which consequently promoted ER stress conditions. Furthermore, CHOP also downregulated BCL2 and promoted apoptosis. CHOP levels were found to be enhanced in bisPMB-treated WHCO1 cells^[86].

Se-methyl-*L*-selenocysteine dose dependently enhanced proteolytic cleavage of PARP and DFF45. Se-methyl-*L*-selenocysteine also caused an increase in the levels of GADD153 and GADD45 in COLO-25 cells^[87]. Diallyl trisulfide increased the levels of GRP78 and CHOP/GADD153 in basal cell carcinoma cells. BCL2 phosphorylation reportedly prevents the heterodimerization of BAX-BCL2. Consequently, unbound BAX proteins are available to form homodimers, resulting in induction of apoptosis. Phospho-BCL2 (serine-70) was dramatically increased in diallyl trisulfide-treated cancer cells. Diallyl trisulfide increased levels of cytochrome c and APAF1 (Fig. 3). Both these molecules formed a signalosome for the activation of caspase-9 and caspases-3. OMI/HTRA2, a serine protease contains an amino terminally located mitochondrial-targeting sequence that is removed upon translocation exposing a tetrapeptide IAP-binding motif (IBM). Diallyl trisulfide remarkably enhanced the mitochondrial release of OMI/HTRA2, AIF (apoptosis-inducing factor) and Endo G in cancer cells (Fig. 3)^[88].

Rapid increase in the expression of calreticulin has been demonstrated to be associated with activation of caspase-4 in glioblastoma cells. Calpain mediated degradation of α -spectrin resulted in the formation of two highly stable and characteristically distinct SBDPs. These SBDPs are of various molecular sizes 145 and 150 kDa (SBDP145 and SBDP150). While SBDP120 is largely derived from caspase-3 cleavage. Treatment of cells with diallyl sulfide and diallyl disulfide caused an increase in 145 kDa SBDP and 120 kDa SBDP. Importantly, high cleavage activity of calpain and caspase-3 was also noted. Proteolytic activities of calpain are controlled by an endogenous calpain inhibitor (calpastatin). Diallyl sulfide and diallyl disulfide markedly reduced the levels of calpastatin in U87MG and T98G cells. Caspase-3-mediated cleavage of ICAD (inhibitor of caspase-3-activated DNase) resulted in the release

of CAD. Importantly, free CAD translocated into the nucleus and triggered degradation of chromosomal DNA. Levels of nuclear CAD were reported to be profoundly enhanced in U87MG and T98G cells after treatment with diallyl sulfide and diallyl disulfide^[89].

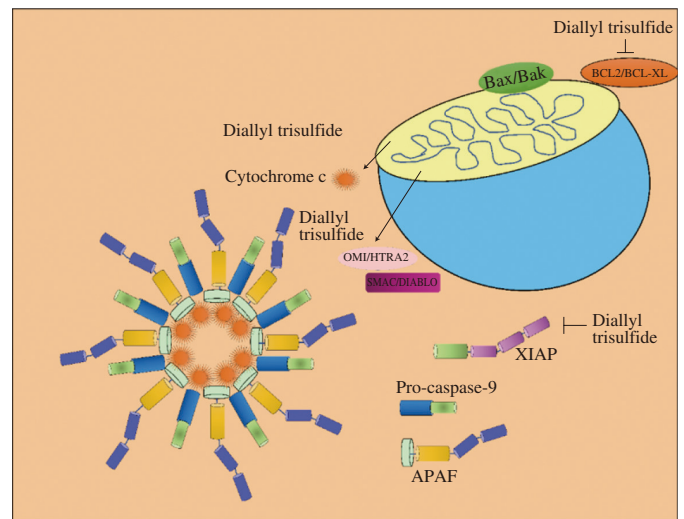


Fig. 3 Regulation of apoptotic pathway by bioactive components of garlic. Diallyl trisulfide facilitated the release of cytochrome c and OMI/HTRA2. Diallyl trisulfide inhibited XIAP and BCL2/BCL-XL.

8. Regulation of non-coding RNAs

Essentially, a conceptual shift in perception has occurred within the scientific communities and paradigmatically surpassed the classical view of “central dogma” of molecular biology. Technological advancements have assisted researchers in the discovery of characteristically and functionally novel types of non-coding RNAs. Different types of non-coding RNAs have been characterized including microRNAs (miRNAs), long non-coding RNAs and circular RNAs^[90-96].

Diallyl thiosulfinate and dexamethasone combinatorially reduced the levels of PI3K, p-AKT and p-mTOR in multiple myeloma MM cells. However, Diallyl thiosulfinate and dexamethasone did not reduce the levels of PI3K, p-AKT and p-mTOR in miR-127-3p-silenced multiple myeloma cells. Collectively, these findings indicated that miR-127-3p was necessary for Diallyl thiosulfinate and dexamethasone-mediated inhibitory effects on MM cells^[97]. miR-34a is a highly acclaimed tumor suppressor miRNA. Intratumorally injected miR-34a prolonged the survival of mice xenografted with A549 cells^[98]. Extensive analysis of miR-34a mediated cancer inhibitory effects has uncovered clinically targetable gene networks^[99-100].

SRC knockdown resulted in notable reduction in SRC levels, which caused suppression in the levels of Ras-GTP and p-ERK1/2. Whereas, SRC overexpression resulted in increased SRC levels, consequently resulting in an increase in Ras-GTP and p-ERK1/2. miR-34a overexpression led to decrease in SRC levels, less active Ras-GTP and subsequent decline in the levels of p-ERK1/2 in MDA-MB-231 cancer cells. miR-34a has been shown to directly target SRC. Diallyl disulfide (DADS) stimulated the expression of miR-34a. Moreover, diallyl disulfide and miR-34a mimics synergistically induced shrinkage in the tumor mass in mice subcutaneously inoculated with MDA-MB-231 cancer cells^[101]. It will

be pharmaceutically valuable to test the efficacy of garlic-derived biomolecules and miR-34a mimics in state-of-the-art animal models to propel a holistic understanding of the biology of metastasis, which will ultimately lead to the discovery of novel therapeutic prospects.

Another important tumor suppressor microRNA is miR-134 having notable features. Ruyiping (RYP), a traditional Chinese formula significantly reduced the tumor size and pulmonary metastasis in animal models. Ruyiping exerted anti-metastatic effects via upregulation of tumor suppressor miR-134^[102]. Different lncRNAs and circRNAs have been shown to inhibit miR-134 mediated tumor suppressive effects^[103-108]. Diallyl disulfide upregulated miR-134 expression in osteosarcoma cells. However, Diallyl disulfide-mediated tumor inhibitory effects were impaired by miR-134 inhibition in mice xenografted with U2OS cells. miR-134 directly inhibited FOXM1 and suppressed invasive potential of osteosarcoma cells^[109].

Existing evidence is insufficient about regulation of non-coding RNAs by garlic and its bioactive constituents. Future research works should converge on the identification of target tumor suppressor and oncogenic non-coding RNAs for a conceptual interpretation of the cancer chemo-preventive role of garlic and its constituents.

9. Metastasis inhibitory effects

Extracellular microparticles encapsulated with diallyl trisulfide demonstrate unique ability to inhibit pro-metastatic inflammatory microenvironment in local tissues. Intraperitoneal injections of diallyl trisulfide-loaded microparticles caused marked reduction in the number of pulmonary metastatic nodules in mice injected with B16BL6 melanoma cells into the left hind footpads of experimental C57BL/6 mouse models^[110]. Moreover, diallyl trisulfide-mediated anti-metastatic effects were also investigated in experimental metastasis models in which B16BL6 melanoma cells were injected intravenously into the tail veins of C57BL/6 mouse model to generate metastasis. Myeloid-related protein-8 (MRP8/S100A8) induces intracellular translocation of MyD88 (Myeloid differentiation primary response protein). Diallyl trisulfide-loaded microparticles effectively reduced fibronectin and MRP8 in lung tissues. MRP8/S100A8 triggered the activation of TLR4-mediated downstream intracellular signaling and recruitment of inflammatory cells. Diallyl trisulfide-loaded microparticles also suppressed the high infiltration rates of inflammatory cells. Furthermore, abnormal activation of TLR4-MyD88 transduction cascade in lung tissues was profoundly reduced by diallyl trisulfide-loaded microparticles^[110].

Diallyl sulfide prevented benzo[a]pyrene (BaP)-induced lung cancer in a murine model. Fatty acid synthase (FASN) upregulation was noted in the liver hepatocytes and lung alveoli in BaP-exposed mice. Diallyl sulfide reduced FASN expression and induced apoptosis^[111]. Chemical inhibition of thioredoxin (Trx-1) caused marked reduction in metastatic properties of MDA-MB-231 cancer. Cauliflower-like metastatic nodules were noted on the surface of livers and lungs in mice intravenously injected with MDA-MB-231 cancer cells. Diallyl trisulfide markedly reduced the number of pulmonary and hepatic metastatic nodules in mice intravenously injected with MDA-MB-231 cells. Diallyl trisulfide caused reduction in the metastatic tumor burden in the lungs and livers in mice orthotopically implanted with MDA-MB-231 cancer cells (Fig. 4). Diallyl trisulfide

exerted suppressive effects on Trx-1, matrix metalloproteinase-2/9 and NF κ B in the tissues of secondary tumors^[112].

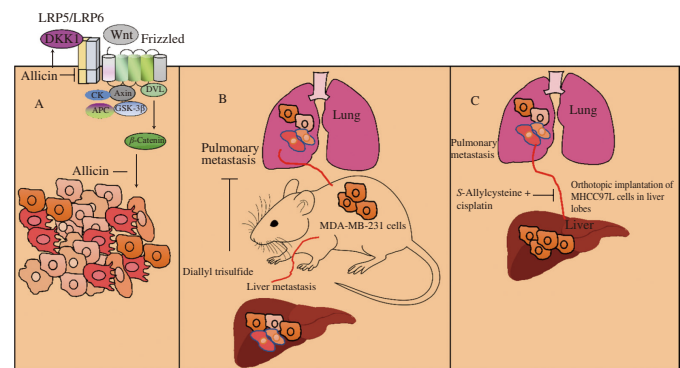


Fig. 4 (A) DKK1 inhibited Wnt pathway by interaction with extracellular domains of LRP5/6. Allicin increased the levels of DKK1 and reduced the levels of LRP5/LRP6, Dishevelled and β -catenin. (B) Diallyl trisulfide reduced metastatic tumor burden in the lungs and livers in mice. (C) *S*-Allylcysteine in combination with cisplatin reduced pulmonary metastatic nodules in mice orthotopically implanted with MHCC97L cells in liver lobes.

Garlic-derived *S*-allylmercaptocysteine downregulated the levels of p-LRP6, DVL2 (Dishevelled-2) and β -catenin in Huh-7 and Hep3B cells. Whereas *S*-allylmercaptocysteine induced an increase in DKK1 (Dickkopf Wnt signaling pathway inhibitor 1) levels. DKK1 inhibited Wnt pathway by interaction with extracellular domains of LRP5/6. β -Catenin pools as well as TCF/LEF activities were suppressed to a significant extent in LRP6 knockdown Huh-7 cells. Tumors derived from LRP6-knockdown Huh-7 cells were smaller in size. Moreover, *S*-allylmercaptocysteine further reduced tumor growth in mice xenografted with LRP6-knockdown Huh-7 (Fig. 4)^[113].

Exposure of MDA-MB-231 cells to diallyl trisulfides resulted in the inhibition of hypoxia-mediated metastasis in zebrafish embryos. MDA-MB-231 cancer cells were transplanted into the mammary fat pads of BALB/c animal model which developed into primary breast tumors that metastasized spontaneously to the lungs. Intragastrical administration diallyl trisulfides did not influence growth of primary tumors but it considerably reduced the number of pulmonary metastatic foci^[114].

Cell division cycle 25 (CDC25) are phosphatases and reportedly involved in the regulation of different proteins. CDC25 dephosphorylate and trigger activation of cyclin-dependent kinase (CDK)-cyclin complexes. *S*-allylcysteine reduced the levels of CDC25C, CDK1 and cyclin B1 in MHCC97L cells. *S*-allylcysteine reduced also efficiently suppressed the levels of anti-apoptotic proteins BCL-XL and BCL-2 in MHCC97L cells. More importantly, *S*-allylcysteine in combination with cisplatin synergistically reduced pulmonary metastatic nodules in mice orthotopically implanted with MHCC97L cells in liver lobes (Fig. 4)^[115]. Diallyl trisulfide significantly inhibited progression to poorly differentiated prostate carcinoma and multiplicity of the pulmonary metastasis in TRAMP mice^[116]. Diallyl trisulfide significantly activated different MAPKs, including p38, ERK and JNK. Pro-apoptotic protein BAX was enhanced and anti-apoptotic BCL-2 was suppressed in diallyl trisulfide-treated SGC-7901 cells. Besides, cytochrome c and p53 were also found to be profoundly enhanced in response to the diallyl trisulfide. Development of SGC-7901 tumor xenografts was slow in mice administered with diallyl trisulfide^[117].

S-Allylmercaptocysteine reduced integrin β 1 but simultaneously enhanced E-cadherin in SKOV3 and HO8910 ovarian cancer cells. Intra-gastric administration of *S*-allylmercaptocysteine substantially suppressed the volume of subcutaneous tumor xenografts derived from SKOV3 and HO8910 cells^[118]. Metastatic growth was not detected in *S*-allylmercaptocysteine-treated tumor-bearing mice. Bioluminescence of the tumor-bearing mice was monitored, and results indicated that the photonic fluxes of the tumor-bearing mice treated with *S*-allylmercaptocysteine remained unchanged during 16 days of treatment with *S*-allylmercaptocysteine, but there was an evident increase in the photonic fluxes of the control mice inoculated with SW620 cancer cells^[119].

Researchers have designed different strategies to a directly visualize metastatic lesions in animal models. In accordance with this approach, androgen-independent metastatically competent prostate cancer PC-3 cells were engineered to constitutively express green fluorescent protein. Orthotopically implanted PC-3 cells not only induced primary tumor formation but also lymph node metastasis. Green fluorescent tumor deposits were noted in the lungs and adrenals of tumor-bearing rodent models. Low-doses of *S*-allylmercaptocysteine did not induce significant shrinkage of the tumors but high-doses of *S*-allylmercaptocysteine were found to be more effective in the inhibition of tumorigenesis as compared to the low dose. There was a significant reduction in the mean number of metastasis identifiable following high doses of *S*-allylmercaptocysteine. However, low-doses of *S*-allylmercaptocysteine did not cause evident reduction in lung metastasis formation. High doses of *S*-allylmercaptocysteine markedly abolished the metastases in adrenals^[120].

CUG2 overexpression induced the activation of Ras and enhanced the phosphorylation of JNK, ERK and p38-MAPK. Higher CUG2 expression also induced epithelial-to-mesenchymal transition through TGF β cascade. *N*-benzyl-*N*-methyl-dodecan-1-amine (BMDA) inhibited SMAD2 phosphorylation and reduced the expression of TGF β -target genes, including TWIST and SNAIL. BMDA significantly suppressed TWIST levels in the tumor tissues derived from CUG2-overexpressing-A549 cells in nude mice^[121].

CDK1 is maintained in an inactive state by WEE1-mediated phosphorylation at tyrosine-15 of CDK1. Diallyl trisulfide significantly suppressed CDK1 and its activator CDC25C. Whereas, WEE1-mediated phosphorylation of CDK1 was found to be enhanced. Essentially, Diallyl trisulfide reduced the activities of HDAC and potently induced histone H3/H4 acetylation. Diallyl trisulfide induced regression of the volume of U87MG tumor xenografts^[122]. Intraperitoneal administration of diallyl disulfide led to shrinkage of tumors in mice inoculated with MDA-MB-231 cancer cells. Diallyl disulfide caused evident decline in the levels of BCL2, MMP9, SNAIL and β -catenin and induced an increase in the expression of BAX in tumor tissues of xenografted rodent models^[123]. There was no significant evidence of loss in body weight and liver toxicity in *S*-allylmercaptocysteine-treated groups and all the mice survived the treatments. *S*-allylmercaptocysteine reduced levels of p-AKT and increased the phosphorylated levels of ERK, p38-MAPK and JNK^[124].

Importantly, cell migratory and invasive properties of SW620 cancer cells were suppressed significantly upon RAC1 knockdown, while these features were significantly demonstrated by RAC1-overexpressing-HT-29 cancer cells. RAC1 overexpression led to the upregulation of vimentin, N-cadherin and SNAIL1 and simultaneous

downregulation of E-cadherin. RAC1 overexpression also caused an increase in p-PAK1, p-LIMK1, and p-cofilin. Intraperitoneal injections of diallyl disulfide markedly reduced pulmonary metastatic nodules in mice injected with RAC1-overexpressing-HT-29 cells^[125].

10. Concluding remarks

The success of the Human Genome Project and the spectacular breakthroughs in genomics tools have ushered in a new era of nutrigenomics and cancer-related mechanisms. A ‘multi-pronged’ model for oncogenic signaling pathways for inhibition of metastasis might resolve some of the puzzles. Altogether, genomic characterization of metastasis has provided previously unprecedented important insights into the biology of tumor cell plasticity and metastasis. Conceptual knowledge of the context-specificity and regulatory effects of garlic-derived biomolecules on the diversity of signaling will open a path towards the design of therapeutic strategies and clinically efficient drugs to target deregulated oncogenic pathways more effectively. Multidisciplinary collaborations in rationally-designed clinical trials and therapeutic administration are vital in the continued progress of this exciting nutrigenomics field.

Conflicts of interest

Baojun Xu is an associate editor for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. Authors declare no conflict of interest.

Acknowledgments

The manuscript is funded by a grant (UICR202107) from BNU-HKBU United International College. Authors would like to pay sincere thanks to Maira Mariam for her helpful suggestions during language editing.

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