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総　説

Molecular Mechanisms of Anti-inflammation and Anti-cancer by 6-(Methylsulfinyl)hexyl Isothiocyanate

Takuhiro UTO
(Department of Pharmacognosy, Faculty of Pharmaceutical Science,
Nagasaki International University)

Abstract

Recently, a number of natural compounds with several chemoprevensive properties of anti-carcinogenesis, anti-tumorigenesis and anti-inflammation have been identified from our diet. Numerous epidemiological studies as well as experimental animal studies demonstrate that high intake of cruciferous vegetables such as broccoli, wasabi, cauliflower, and cabbage, protect against tumorigenesis. Thus, cruciferous vegetables have been a focus of constant attention for potential use in' cancer chemoprevention'. 6-(Methylsulfinyl)hexyl isothiocyanate (6-MITC) is a major allyl isothiocyanate occurring in wasabi (*Wasabia japonica*), which is a typical Japanese pungent spice. Several studies have reported that 6-MITC has anti-cancer activity *in vivo* and *in vitro*, but the molecular mechanism is not completely elucidated. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are important enzymes that mediate inflammatory processes. Excess up-regulations of COX-2 and iNOS have been associated with several types of cancers as well as inflammatory disorders. We found that 6-MITC has strongly inhibitory effects of COX-2 and iNOS expression at the signaling level and at the transcription factor/promoter levels. Moreover, molecular analysis demonstrated that 6-MITC blocked the expressions of COX-2 and iNOS by suppressing multiple signal transduction pathways to attenuate the activation of transcriptional factors. This review discusses the mechanisms underlying anti-cancer and anti-inflammation by 6-MITC with special focus on its effect on cellular signaling pathways regulating the expressions of COX-2 and iNOS.

Keywords

6-(methylsulfinyl)hexyl isothiocyanate, anti-inflammation, cancer chemoprevention, cyclooxygenase-2, inducible nitric oxide synthase

1. Introduction

Chemoprevention is a cancer preventive strategy to inhibit, delay or reverse carcinogenesis using naturally occurring or synthetic chemical agents. Numerous epidemiological studies as well as experimental animal studies clearly demonstrate that high intake of cruciferous vegetables such as broccoli, wasabi, watercress, cabbage, and cauliflower, protects against tumorigenesis. Thus, cruciferous vegetables have been great interest for potential use in the chemoprevention of cancer.

Isothiocyanates (ITCs) are a group of naturally occurring sulphur compounds containing characteristic functional group (−N=C=S), available often abundantly from many cruciferous vegetables. Numerous studies have demonstrated the chemopreventive properties of a significant number of ITCs. ITCs disturb several steps in the carcinogenic process by：(ｉ)

suppressing DNA damage by both inhibition of carcinogen activation through the down-regulation of Phase 1 enzymes such as cytochromes P450 (CYPs) and detoxification of reactive carcinogens through induction of Phage 2 enzymes [e.g., glutathione S-transferase (GST), NADPH:quinone oxidoreductase (NQO1)]; (ii)inhibiting cell proliferation by cell cycle arrest; (iii)removing pre-malignant and malignant cells through induction of apoptosis.[1-4] ITCs are therefore expected for effective strategy of cancer chemoprevention.

Wasabi (*Wasabia japonica*) is a very popular pungent spice in Japan. Accumulated studies showed that wasabi has a lot of physiological functions, such as appetite enhancement,[5] anti-microbial activity,[6] inhibition of platelet aggregation[7] and the suppression of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine-induced rat gastric carcinogenesis.[8] However, the anti-cancer and anti-inflammatory mechanisms of wasabi were not completely elucidated yet. Recently, we demonstrated 6-(methylsufinyl)hexyl isothiocyanate (6-MITC), a chemopreventive compound in wasabi, strongly suppresses inflammatory mediators.[9-11] This review aims to provide a novel mechanism of anti-inflammatory and anti-cancer effects by 6-MITC, and will give new insights into understanding for chemopreventive functions of ITCs at molecular level.

2. Chemistry and extraction of 6-MITC

6-MITC is a major allyl isothiocyanate of wasabi[12] (Figure 1). The content of 6-MITC in wasabi is ~550-556 μg/g wet body weight of wasabi root.[13]

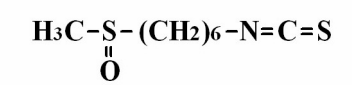


Figure 1. Chemical structure of 6-MITC

Ono *et al.* purified 6-MITC from the water-soluble fractions of wasabi by gel filtration and reverse-phase HPLC.[12] Wasabi roots were extracted with water, and the extract was fractionated into six fractions (P-1~P-6) by Sephadex G-15 gel filtration. The P-5 fraction exhibited the most marked suppressive effects of the growth of MKN-28 human stomach cells. P-5 was further fractionated into four fractions by the reverse-phage HPLC (F-1~F-4), and F-4 had the most suppressive activity of the growth of MKN-28. Final purification was carried out by preparative HPLC using Asahipak NH_2 P-50 column. The spectroscopic data, including fast atom bombardment mass spectrometry (FAB-MS) and electron ionization mass spectrometry (EI-MS), determined a molecular weight of 205 with a chemical composition of C8, H15, N1, O1, S2. Furthermore, IR and NMR completely identified that active compound is 6-MITC.

3. Inhibitory mechanism of 6-MITC on lipopolysaccharide-induced COX-2 expression

COXs catalyzes the synthesis of prostaglandins (PGs) from arachidonic acid. There are two isoforms of COX, designated COX-1 and COX-2, which are encoded by different genes. COX-1 is constitutively expressed in most tissues and believed to be responsible for normal

physiological functions.[14] In contrast, COX-2 is not detectable in most normal tissues or resting immune cells, but it could be induced by LPS, inflammatory cytokines, growth factors, and carcinogens[15,16] (Figure 2).

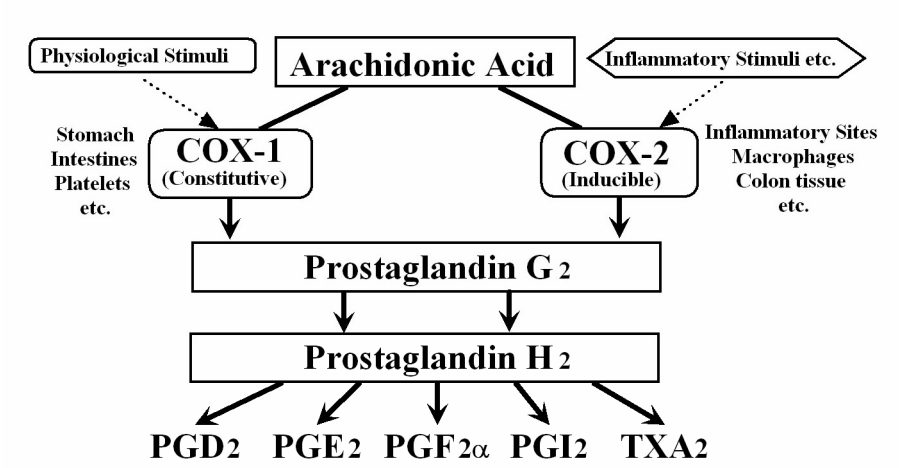


Figure 2. Arachidonic acid metabolism pathways by COX-1 and COX-2

Many cell types associated with inflammation such as macrophages, endothelial cells and fibroblasts, express the COX-2 upon induction.[17] COX-2 overexpression is also found in a variety of transformed cells and tumors.[18,19] Enhancement of COX-2 can stimulate the growth of malignant cells by increasing cell proliferation,[20] promoting angiogenesis,[21] and inhibiting immune surveillance[22] and apoptosis.[23] These effects were reversed by the nonsteroidal anti-inflammatory drugs (NSAID) such as etodolac, meloxicam and celecoxib, which are known as COX-2-specific inhibitors.[24-26] Thus, COX-2 plays an important role in inflammation and carcinogenesis, and the identification of COX-2 inhibitors is considered to be a promising approach to prevent cancer.

6-MITC suppressed lipopolysaccharide (LPS)-induced COX-2 expression and prostaglandin E_2 (PGE_2) release in murine macrophage cell lines RAW264 and human U937 monocytic cells without affecting the constitutive COX-1 expression,[9] suggesting that 6-MITC is a potent inhibitor of COX-2 expression. Molecular analysis demonstrated that 6-MITC blocked LPS-induced COX-2 expression in transcriptional level.

In the *COX-2* gene, *cis*-acting elements including nuclear factor κB (NF-κB, −223/−214), CCAAT/enhancer-binding protein (C/EBP; −132/−124) and cyclic AMP-response element (CRE; 59/−53) have been found to play a critical role in regulating transcription (Figure 3).[27-31] Moreover, single site of NF-κB, C/EBP, or CRE cannot sufficiently response to induce *COX-2* transcription activity, and two of these *cis*-acting elements are at least recruited to achieve maximal induction of transcription.[27] 6-MITC inhibited LPS-induced COX-2 expression by suppressing transcriptional factors binding to the first 327 base pairs in the 5' flanking regions of *COX-2* gene. Moreover, mutation of a single NF-κB, C/EBP or CRE promoter element did not abrogate the effect of 6-MITC.[9] Thus, the inhibition of at least two of these *cis*-elements

is required to achieve the maximal inhibitory action of 6-MITC on *COX-2* gene expression, suggesting that the inhibitory effect of 6-MITC on COX-2 expression could be obtained by targeting the signaling pathways leading to at least two promoter elements including NF-κB, C/EBP and CRE sites.

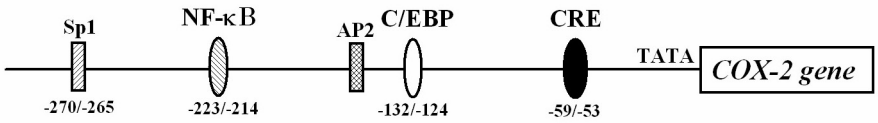


Figure 3. Regulatory elements in promoter regions of *COX-2* gene

One of the most extensively investigated intracellular signaling cascades involved in pro-inflammatory responses is mitogen-activated protein kinase (MAPK) cascades. Three distinct groups of well characterized major MAPK subfamily members including extracellular-regulated protein kinase (ERK), p38 kinase, and c-Jun NH_2-protein kinase (JNK). All of these MAPKs are activated through dual phosphorylation at tyrosine and threonine by an upstream MAPK kinase in responses to extracellular stimuli.[32,33] The activated form of each MAPKs phosphorylates and activates other kinases or transcriptional factors, thereby altering the expression of the target genes such as COX-2. 6-MITC blocked LPS-induced phosphorylation of MAPK including ERK, p38 kinase and JNK, and also blocked the phosphorylation of MAPK kinases (MAPKKs).[9] Thus, 6-MITC might inhibit LPS-induced COX-2 expression by blocking all of three MAPK signaling pathways.

LPS-induced phosphorylation of CREB and AP-1 can regulate *COX-2* gene expression through binding CRE site in *COX-2* promoter,[34-36] and LPS-induced nuclear translocation of C/EBP can stimulate *COX-2* gene expression through binding C/EBP site in *COX-2* promoter.[34,35] Several lines of studies have showed that the binding of CREB and AP-1 to CRE site depends on the phosphorylation of CREB and c-Jun, a component of the AP-1 transcription factor complex,[28,37,38] and that the binding of C/EBP to *COX-2* promoter is preceded by nuclear translocation of C/EBP.[28,34,39] Thus, the inhibition of phosphorylation of CREB and c-Jun, and nuclear translocation of C/EBP result in a binding suppression of those transcriptional factors to *COX-2* promoter. 6-MITC inhibited LPS-induced phosphorylation of CREB and c-Jun. In addition, 6-MITC blocked LPS-induced expression and nuclear translocation of C/EBPδ, but not C/EBPβ.[9]

NF-κB is one of the essential factors for COX-2 expression. Some chemopreventive compounds, such as capsaicin,[40] sauchinone[34] and apigenin,[41] inhibit LPS-induced COX-2 expression by blocking degradation of IκB-α in mouse macrophage cells. But, 6-MITC had no influence on phosphorylation and degradation of IκB-α, and on nuclear translocation of p65.[9] Thus, 6-MITC may inhibit COX-2 expression by a NF-κB-independent pathway, suggesting a novel type of inhibitor for COX-2.

It has been shown that activations of MAPKs upregulate COX-2 expression by regulating transcription factors, and these signaling pathways depend on stimuli.[27,28] We identified the

relationship between MAPKs and transcriptional factors leading COX-2 expression in LPS-stimulated RAW264 cells by using MAPK inhibitors.[9] First, ERK and p38 kinase pathways cooperatively regulate COX-2 expression by activating CREB and C/EBPδ because ERK-specific inhibitor U0126 and p38 kinase-specific inhibitor SB203580 suppressed CREB phosphorylation and C/EBPδ expression but JNK-specific inhibitor SP600125 did not. Second, ERK and JNK signaling pathways cooperatively regulate COX-2 expression by activating AP-1 since SP600125 and U0126, but not SB203580, inhibited c-Jun phosphorylation. These data indicated that there is a redundancy at the signaling pathways, transcription factor and promoter levels for COX-2 expression in LPS-treated RAW264 cells. Finally, 6-MITC blocked LPS-induced COX-2 expression by suppressing ERK and p38 kinase signaling cascades leading to the activation of CREB and C/EBPδ, and by inhibiting JNK cascade leading to AP-1 activation (Figure 4).

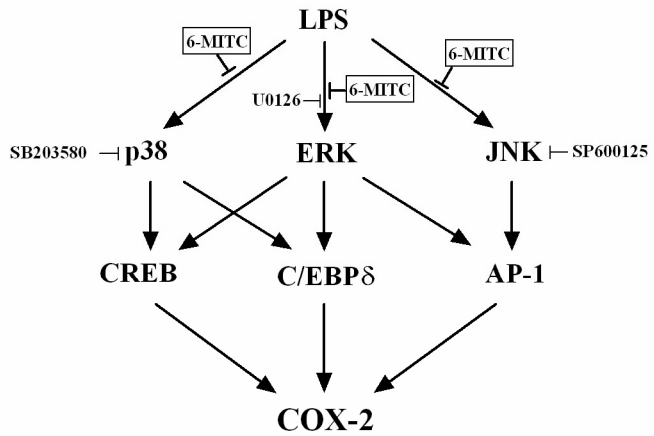


Figure 4. Schematic molecular model of 6-MITC on the suppression of LPS-induced COX-2 expression

4. Inhibitory mechanism of 6-MITC on LPS-induced iNOS expression

NO is produced endogenously during arginine metabolism by isoforms of NOS.[42,43] NO has a number of important biological functions, including tumor cell killing, host defense against intracellular pathogens, neurotransmission, and inhibition of platelet aggregation.[44] However, excess NO is recognized as a potent mediator and regulator of inflammatory responses.[45] The excess NO production also has a multifaceted role in process of cancer.[46,47] NO can damage DNA, directly or indirectly by several mechanisms[48]; it can also interfere with DNA repair,[49] and cause post-translational modification such as nitrosylation, potentially leading to tumor initiation and promotion/progression.[47,50,51] It is probable that the sustained high levels of NO can produce multiple types of damage under chronic conditions, which lead to an accumulation of gene mutations, including those of the tumor suppressor gene p53[52-54] that contribute to malignant transformation. Indeed, there is substantial evidence implicating NO in carcinogenesis as an endogenous mutagen,[55] an enhancer of oncogene expression,[56] and an

inhibitor of apoptosis.[57] Therefore, inhibition of NO production is a very important therapeutic target in the development of anti－cancer and anti–inflammation.

NO is produced from L–arginine by a chemical reaction catalyzed by NOS in living systems.[58] There are three distinct isoforms of NOSs. Endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) are constitutively expressed in endothelium and neural tissues, respectively.[59] On the other hand, inducible nitric oxide synthase (iNOS) is only induced by various inflammatory stimuli such as LPS and inflammatory cytokines in macrophages, hepatocytes, and endothelial cells[59－61] (Figure 5). iNOS catalyzes the formation of a large amount of NO, which plays a key role in the various forms of inflammation and carcinogenesis.[61－63] Therefore, NO production by iNOS may reflect the degree of inflammation and cancer, and provides a measure to assess the effect of chemopreventive agents on the inflammatory and cancer process.

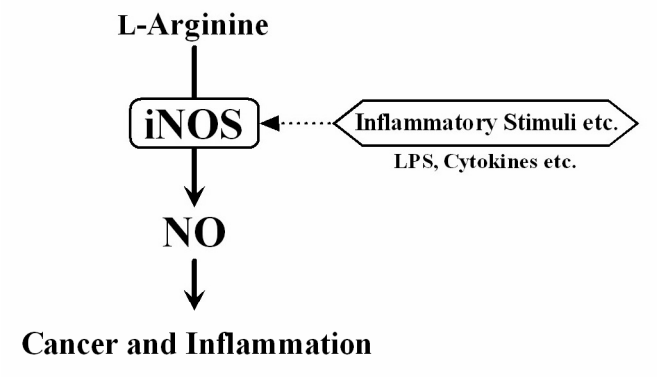


Figure 5. NO production catalyzed by iNOS

We reported that 6–MITC suppressed NO production and iNOS expression as well as COX–2 expression in LPS–stimulated macrophages.[10] NO production by iNOS is mainly regulated at the transcriptional level.[64] In the *iNOS* gene promoter, two transcription factors including AP–1 and NF–κB have been identified to bind the *cis*–acting elements, which regulate *iNOS* gene transcription (Figure 6).

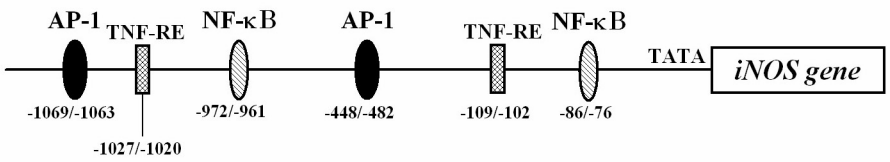


Figure 6. Regulatory elements in promoter regions of *iNOS* gene

AP–1 is one of the major transcription factors regulating iNOS expression,[65,66] and minimally activated under normal physiologic conditions, but is dramatically activated by inflammatory stimuli such as LPS.[67] As described above, 6–MITC markedly suppressed LPS–

induced c-Jun phosphorylation, a major component of AP-1.[9,10] Moreover, SP600125 also suppressed c-Jun phosphorylation. The data from MAPK-specific inhibitors showed that only JNK is required to LPS-induced iNOS expression, because only JNK-specific inhibitor SP600125 suppressed iNOS expression while ERK-specific inhibitor U0126 and p38-specific inhibitor SB203580 did not.[10] Thus, 6-MITC might inhibit iNOS expression by blocking JNK-mediated AP-1 activation.

NF-κB is also critical regulator involved in the induction of iNOS and activated by the inflammatory responses during viral and bacterial infections.[61,62] It is noticed that 6-MITC had no influence on the degradation of IκB-α and nuclear translocation of p65, suggesting that 6-MITC may inhibit iNOS expression without the degradation of IκB-α, and mainly by blocking AP-1 activation (Figure 7).[9,10]

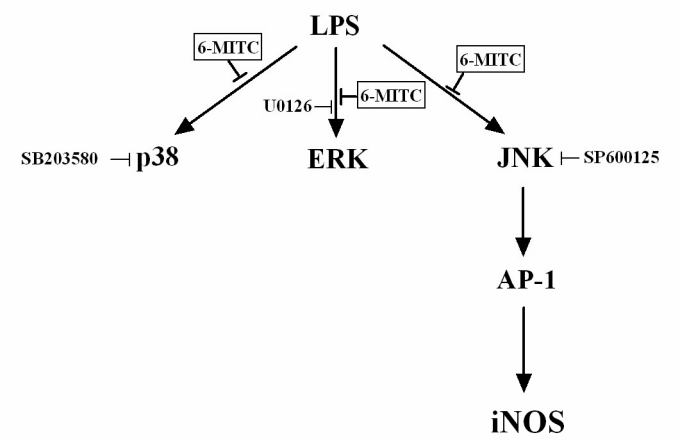
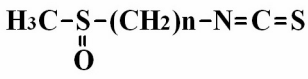


Figure 7. Schematic molecular model of 6-MITC on the suppression of LPS-induced iNOS expression

5. Structure-activity of MITCs on LPS-induced expression of COX-2 and iNOS

Depending on the length of the methyl chain of methylsulfinyl isothiocyanates (MITCs), there are a number of analogues of MITC in wasabi extracts (Figure 8). Although 6-MITC is one of major allyl isothiocyanate in wasabi,[12,13] other MITCs are minor components in wasabi. 4-MITC, also known as sulforaphane, is a major isothiocyanate of broccoli.[67]



n=2, 2-(methylsulfinyl)ethyl isothiocyanate (2-MITC)
n=4, 4-(methylsulfinyl)butyl isothiocyanate (4-MITC)
n=6, 6-(methylsulfinyl)hexyl isothiocyanate (6-MITC)
n=8, 8-(methylsulfinyl)octyl isothiocyanate (8-MITC)

Figure 8. Chemical structures of analogues of MITCs

The inhibitory potency on COX-2 and iNOS protein was showed in the order of 2-, 4-, 6- and 8-MITC,[9,10] suggesting that an increase in the methyl chain length is important for the inhibitory activity. Thus, MITC compounds which have the long methyl chain may be more effective in anti-inflammatory and anti-carcinogenic action within the non-toxic concentrations.

6. Different effect of 6-MITC on LPS-, IFN-γ- and TPA-induced COX-2 expression

COX-2 gene is expressed in response to proinflammatory factors including LPS, cytokines, hormones, growth factors, and oncogenes.[68,69] We investigated the ability of several inflammatory factors to activate COX-2 expression was examined in RAW264 cell line. Treatments of cells with LPS, interferon-γ (IFN-γ) and 12-*O*-tetradecanonoylphorbol-13-acetate (TPA) activated COX-2 expression, and 6-MITC suppressed LPS- or IFN-γ-induced COX-2 expression.[11] Interestingly, 6-MITC could not block TPA-induced COX-2 expression. Molecular analysis demonstrated that IFN-γ could not induce the activation of these transcriptional factors such as NF-κB, C/EBP, CREB and AP-1. Blanco *et al.* reported that a member of the interferon regulatory factor (IRF) family, IRF-1, regulates IFN-γ-induced COX-2 gene expression through two interferon stimulated response element (ISRE) sites in mouse peritoneal macrophages.[70] ISRE Ⅰ and ISRE Ⅱ are located in -1777/-1699 and -1354/-1345, respectively, in COX-2 promoter, and ISRE Ⅱ was more efficient at binding IRF-1 and IRF-2 complexes than ISRE Ⅰ. Therefore, the inhibitory effect of 6-MITC on IFN-γ-induced COX-2 expression is probably associated with IRF-1/2-ISRE Ⅱ pathway, which is interesting to be clarified in further study.

A number of studies reported that TPA increases protein kinase C (PKC) activity in several cell lines including RAW264.7 cells.[71] TPA as well as cytokines and LPS has been shown to upregulate COX-2 expression in several cell lines. TPA-induced PKC activation caused COX-2 expression through Ras/Raf-1/ERK pathway leading to NF-κB activation in human pulmonary epithelial A549 cell line.[72] TPA-induced PKC activation triggered AP-1 activation, and finally induced COX-2 expression by the binding of AP-1 to CRE site of COX-2 promoter in human mammary epithelial 185B5/HER cell line.[73] Thus, TPA-induced PKC activation is strongly linked with COX-2 induction. Although TPA induced COX-2 expression, 6-MITC did not suppress it in RAW264 cells.[11] In addition, 6-MITC did not suppress TPA-induced phosphorylation of CREB and c-Jun.[11] PKC activation induced by TPA might cause the activation of CREB and AP-1, and finally resulted in COX-2 expression. 6-MITC could not block TPA-mediated signaling pathway leading to the activation of CREB and AP-1 (Figure 9).

7. What is the molecular target of 6-MITC?

We showed the detailed inhibitory effects of 6-MITC on the intracellular signaling pathways related to COX-2 and iNOS expression. However, the molecular target(s) of 6-MITC was not identified yet. We tested the effect of 6-MITC on the binding of FITC-conjugated LPS to the LPS receptor were investigated by a flow cytometric assay, and the data suggested that 6-MITC could not affect the binding of LPS to the receptor in plasma membrane

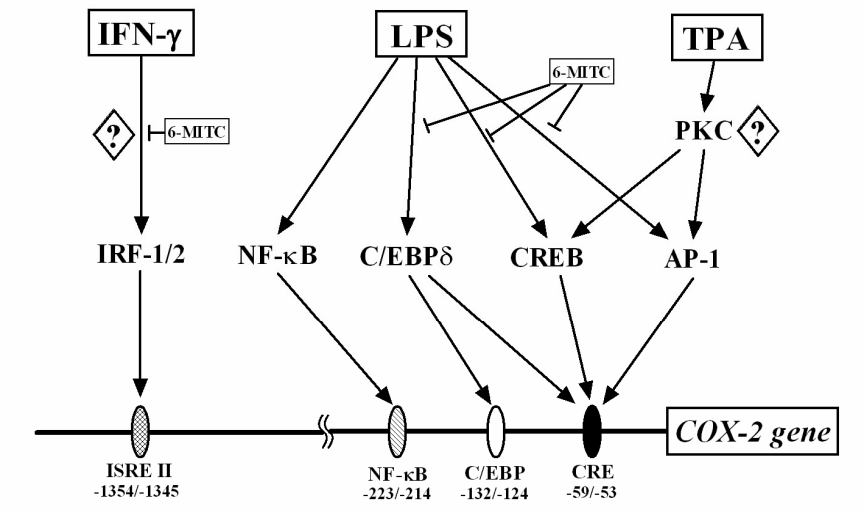


Figure 9. Induction mechanism of COX-2 expression induced by LPS, IFN- and TPA, and the inhibitory action of 6-MITC

in RAW264 cells (unpublished data). Thus, 6-MITC might target intracellular factors such as upstream kinases of MAPK to inhibit COX-2 expression. Several studies have revealed the metabolism of isothiocyanates (ITCs) in several cell lines.[74-76] ITCs appear to penetrate cells by diffusion, but entered ITCs rapidly conjugated with intracellular reduced glutathione (GSH). GSH is an important intracellular redox buffer that exits as a reduced predominant form, as a disulfide form (GSSG) or as mixed disulfide (GSSR) with protein thiols.[77] The redox status within the cells, reflected by GSH/GSSG,[78] has been shown to be relevant for the regulation of proinflammatory genes.[79] It was shown that the peak intracellular accumulation of GSH-conjugated ITCs was achieved within 0.5-3 h after the exposure of ITCs, reaching 100-200-fold over the extracellular ITCs concentration, and the total intracellular ITCs accumulation levels can reach the millimolar concentration range.[75,76] However, the relationship between GSH-conjugated ITCs and COX-2 or iNOS induction was not clear. Future studies are required to elucidate the role of GSH-conjugated 6-MITC on LPS-induced cellular signaling pathways leading to COX-2 and iNOS induction (Figure 10).

8. Can intake of 6-MITC prevents the inflammation and cancer ?

An important question is how much 6-MITC is absorbed into body. There is no report related to the absorption of 6-MITC. But, several lines of studies investigated the absorption of ITCs. Ye *et al.* reported that, when each human volunteer took broccoli sprout extract containing 200 μmole ITCs, the cumulative urinary excretion of ITCs equivalent at 8 h was 58.3 ±2.6% of the dose.[80] Shapiro *et al.* also reported that, after 74 μmole oral dose of horseradish ITCs, there was 42±5% recovery in the urine at 10 h. Thus, about half volume of ITCs may be absorbed into blood.[81] Hu *et al.* have showed the detailed phamacokinetics of 4-MITC in rat.[82] After oral administration of 50 μmol of 4-MITC, the plasma concentration of 4-MITC occurred

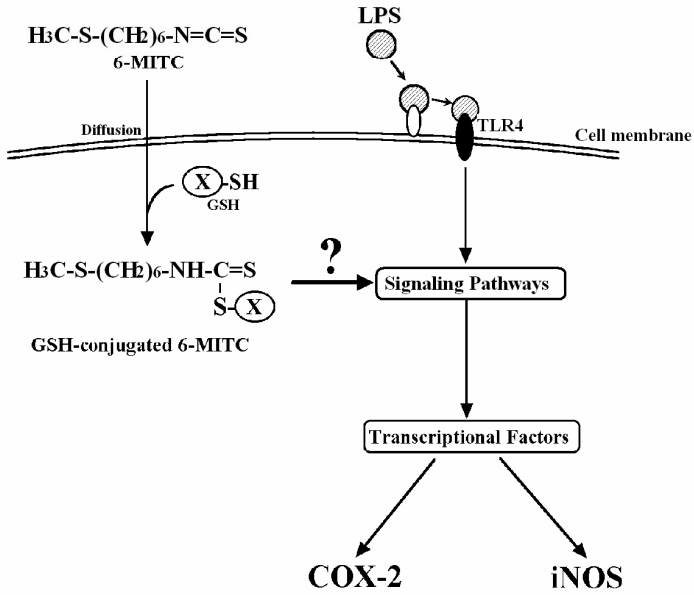


Figure 10. What role does GSH–conjugated 6–MITC play in signaling path ways leading to the expressions of COX–2 and iNOS ?

at 1 h and peaked around 20 μM at 4 h. Interestingly, the peak *in vivo* concentrations of 20 μM 4–MITC offers clear relevance for numerous *in vitro* cell culture studies, where between 1 μM and 30 μM 4–MITC was typically used for various signal transudation studies.

Dietary administration of wasabi suppresses rat glandular stomach carcinogensis. Wister WKY male rats received drinking water containing N–methyl–N'–nitro–N–nitrosoguanidine (MNNG) or tap water alone and a basal diet (PCE–2) or PCE–2 containing 10% (wt/wt) of wasabi powder for 40 weeks.[83] At autopsy, nine rats (30%) had 7 glandular stomach tumors and 3 duodenal adenomatous in MNNG+PCE–2 group, whereas in the MNNG+wasabi group, two rats (7%) had one forestomach epidermoid cyst and one duodenal carcinosarcoma. Yano *et al.* reported oral administration of 6–MITC exhibited a significant suppression against 4–(methylnitrosamino)–1–(3–pyridyl)–1–butanone (NNK)–induced lung tumorigenesis in mouse.[84] After admission of 6－MITC (5 μmol/day) for 4 consecutive days, the mice were given NNK solution (100 mg/kg weight). At week 16 after NNK injection, the treatment of 6–MITC did not significantly reduce the incidence population of mice that developed lung tumor, but resulted in an approximately 40% decrease in tumor multiplicity. Taken together, these animal experimental studies indicated that the oral administration of 6–MITC might indeed prevent the process of carcinogenesis.

9. Concluding remarks

This review focused on anti–inflammatory and anti–cancer properties of 6–MITC, and COX –2 and iNOS were chosen as target molecules. These findings provide the molecular view of the chemopreventive effect of 6–MITC, and support the results of animal experiments.

In recent years, numerous epidemiological studies and experimental animal studies many studies have shown strong chemopreventive effects of several naturally occurring compounds derived from vegetables and fruits. The elucidation of molecular mechanisms regulated by chemopreventive compounds may provide further insights on their beneficial uses as anti−inflammatory and anti−cancer agents. The author hopes that further studies focus on anti−inflammatory and anti−cancer properties of 6−MITC would greatly expand the understanding of the chemopreventive functions of 6−MITC.

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要　旨

近年、世界的な健康ブームの中、野菜や果物の摂取と健康状態の関係が注目されている。疫学的調査や動物実験などを基盤とした研究結果により、ブロッコリー、カリフラワー、キャベツ、ワサビなどのアブラナ科植物の積極的な摂取は癌のリスクを低減させることが報告されている。そのため、これらアブラナ科植物は「癌の化学予防」の戦略から注目されている。6–(methylsulfinyl)hexyl isothiocyanate (6–MITC) はワサビに含まれる主要 allyl isothiocyanate である。いくつかの *in vitro* 及び *in vivo* 実験で 6– MITC が強い抗癌効果を持つことが示唆されているが、その詳細なメカニズムはまだ解明されていない。著者は、これまで 6– MITC の持つ抗炎症及び抗癌作用の分子機構解明を目的として研究を進めてきた。Cyclooxygenase –2 (COX –2) 及び Inducible Nitric Oxide Synthase (iNOS) は炎症を制御する重要な酵素であり、それらの過剰発現は炎症性疾患と同様にいくつかの癌とも深く関与している。これまでの研究で 6– MITC は強い COX –2 及び iNOS 発現抑制効果を持ち、その抑制は転写レベルで発揮されていることが解明された。本総説では、現在明らかになっている 6– MITC の抗炎症及び抗癌作用について、COX –2 及び iNOS を制御するシグナル伝達系を中心に概説する。

キーワード

イソチオシアネート、抗炎症、化学癌予防、シクロオキシゲナーゼ –2、誘導型一酸化窒素合成酵素