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# Diet, nutrients, phytochemicals, and cancer metastasis suppressor genes

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**Abstract** The major factor in the morbidity and mortality of cancer patients is metastasis. There exists a relative lack of specific therapeutic approaches to control metastasis, and this is a fruitful area for investigation. A healthy diet and lifestyle not only can inhibit tumorigenesis but also can have a major impact on cancer progression and survival. Many chemicals found in edible plants are known to inhibit metastatic progression of cancer. While the mechanisms underlying antimetastatic activity of some phytochemicals are being delineated, the impact of diet, dietary components, and various phytochemicals on metastasis suppressor genes is underexplored. Epigenetic regulation of metastasis suppressor genes promises to be a potentially important mechanism by which dietary components can impact cancer metastasis since many dietary constituents are known to modulate gene expression. The review addresses this area of research as well as the current state of knowledge regarding the impact of diet, dietary components, and phytochemicals on metastasis suppressor genes.

**Keywords** Cancer · Dietary · Nutrients · Phytochemicals · Metastasis suppressor · Epigenetics

**Abbreviations**

| | |
|---|---|
| BRMS | Breast cancer metastasis suppressor |
| CTGF | Connective tissue growth factor |
| DHA | Docosahexaenoic acid |
| DLC | Deleted in colon cancer |
| EGCG | Epigallocatechin-3-gallate |
| EGF | Epidermal growth factor |
| EGFR | Epidermal growth factor receptor |
| EPA | Eicosapentaenoic acid |
| IFN | Interferon |
| KAI1 | Kangai 1 |
| MALL | Mal-like |
| MAPK | Mitogen activated protein kinase |
| MKK | Mitogen-activated protein kinase kinase |
| miR | Micro RNA |
| NDRG | N-myc downstream-regulated gene |
| NM23 | Nonmetastatic gene 23 |
| PDCD | Programmed cell death |
| PEBP | Phosphatidylethanolamine binding protein |
| PTEN | Phosphatase and tensin homolog |
| RASSF | Ras-associated domain family |
| RECK | Reversion-inducing-cysteine-rich protein with kazal motifs |
| RhoGDI2 | Rho GDP-dissociation inhibitor 2 |
| RKIP | Raf-1 kinase inhibitor protein |
| SNRP | Small nucleolar ribonucleoprotein |
| TIMP | Tissue inhibitor of metalloproteinase |
| TRAMP | Transgenic adenocarcinoma of the mouse prostate |

## 1 Introduction

A major contributor to cancer mortality is the metastatic spread of cancer. While diet, nutrients, and specific natural phytochemicals in plant-based foods such as fruits, vegetables, and spices are known to inhibit metastasis, most studies have to do with cancer prevention and inhibition of primary tumor growth. This review concerns the effect of diet and natural substances on metastasis suppressor genes,

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which are defined as those genes and their encoded proteins that inhibit the establishment of metastasis without affecting establishment of primary tumors. Results from the cancer prevention studies may not be directly applicable to metastasis prevention. This paper reviews the state of knowledge regarding the ways diet, nutrients, and phytochemicals affect expression and activity of metastasis suppressor genes.

Several reviews have recently been published about the effects of nutrients and phytochemicals on various aspects of cancer [1–6]. The reviews show the current state of knowledge regarding how natural substances' impact a multitude of molecular targets and signaling pathways that control gene expression, cell proliferation, angiogenesis, inflammation, apoptosis, invasion, and metastasis. However, it is notable that there has been little study of natural substances' effect on the expression and activity of metastasis suppressor genes. Not yet studied are the ways that major components of the diet such as protein, fat, and lifestyle issues impact the expression of metastasis suppressor genes [7–9].

It is increasingly clear that natural substances modulate genes through epigenetic mechanisms, which include altering DNA methylation status and histone acetylation and methylation [4, 10]. Because the expression of many metastasis suppressor genes can be regulated by epigenetic mechanisms, it stands to reason that dietary factors potentially would have a profound effect on these genes. There is a paucity of information regarding how diet, dietary components, and phytochemicals influence epigenetic mechanisms that control metastasis suppressor genes. This area also will be reviewed with the hope that the information will spur additional and more mechanistic approaches to research on metastasis suppressor genes.

Further supporting this call for research on the role of diet, nutrients, and phytochemicals on metastasis suppressor genes comes from the results of observational studies published in the last 15 years indicating that good adherence to dietary guidelines relating to decreasing cancer, published by The American Cancer Society and the American Institute for Cancer Research/World Cancer Research Fund, is associated with a 22 % reduced mortality that is cancer-specific [11]. Two of the guidelines recommended by these organizations are (1) eating foods of plant origin such as nonstarchy vegetables, fruits, and legumes, which contain a variety of anticancer phytochemicals, and (2) decreasing consumption of red meat as a source of protein.

## 2 Overview of the effects of diet, dietary constituents, and phytochemicals on specific metastatic suppressors

The metastasis suppressor genes examined are those reviewed in the following references [12, 13] and Slc27a2, Mall, small nucleolar ribonucleoprotein (SNRP)b, and Ras-associated domain family (RASSF)2 genes, which were identified by comparative genomic hybridization in murine NE-10 prostate cancer and found to have metastasis suppressor activity [14]. The majority of the nutrition/phytochemical-oriented studies identified in this review indicate a beneficial effect on metastasis suppressor genes; however, they often do not associate these effects with suppression of metastasis directly. The effects of diet, dietary constituents, and certain phytochemicals on metastasis suppressor genes *in vitro* and *in vivo* are summarized in Table 1. From the table, it is very apparent that there is a variety of natural compounds from many different classes that exhibit effects on metastasis suppressor genes. Only the specific information from studies that identified some effect on metastasis suppressor genes is in the table. Many other nutritional substances exhibit antimetastatic effects (see reviews above); however, their impact on metastasis suppressor genes and the relationship to the control of metastasis were not examined in most cases. Examining the table, it is striking that the majority of these studies are conducted in cell lines treated *in vitro*, where the effects of a specific compound, extract, or combination of specific compounds are examined for various biological effects. While the preponderance of the *in vitro* studies has been conducted in human cell lines, most of the *in vivo* experiments examine effects on animal tumors in mice and rats. Few studies examine human tumor cell lines in immunodeficient mice or in human beings specifically. So far, the concentration of research in humans is limited and directed toward the effects of obesity, weight loss, and extended fasting on metastasis suppressor genes [7, 15]; the research is quite rudimentary. More intense research is needed in two areas: (1) identifying the effects of diet and lifestyle on metastasis suppressor genes, and (2) their contributions to control of metastasis and patient survival.

As shown in Table 1, phytochemicals can have dissimilar effects on metastasis suppressor genes in the same cancer cells. For example, two compounds found in cruciferous vegetables have opposite effects in AGS gastric adenocarcinoma cells. Phenethylisothiocyanate decreases mitogen-activated protein kinase kinase (MKK)7 expression [16], while benzylisothiocyanate increases expression [17]. Unfortunately, neither study examined the specific contribution of the effects on MKK7 to metastasis. These studies illustrate the complexity of examining specific foods on the metastatic process. Foods contain numerous constituents, and the overall biological effect will be a composite of the bioactive substances contained in the foods. Also, a specific substance can have different effects on multiple metastasis suppressor genes within the same cell line, as pointed out in the study by Wong et al. [18]. The investigators found that ethanol increased KISS1 and MKK4 but decreased

**Table 1** Diet, nutritional, and dietary constituents that modulate metastasis suppressor genes

| Constituent (source)/condition | Effect on metastasis suppressor genes | Reference |
|---|---|---|
| *In vitro* | | |
| **Fat, obesity, and fatty acids** | | |
| Adipocytes | B16BL6 melanoma cells incubated with media from 3T3L1-differentiated adipocytes exhibited decreased mRNA expression of KISS1 and E-cadherin. The effects were associated with increased B16BL6 melanoma invasion. | [75] |
| Ob/ob mouse serum | B16BL6 melanoma cells incubated with serum exhibited decreased KISS1 mRNA expression and decreased total E-cadherin protein expression and nuclear localization of E-cadherin. | [76] |
| ω-6 polyunsaturated fatty acids | Linoleic acid and arachidonic acid reduced NM23 protein expression and γ-linoleic acid increased NM23 protein expression in HT115 colorectal carcinoma and MDA-MB-231 breast carcinoma cells. Eicosapentaenoic acid had little effect. γ-Linoleic acid also increased NM23 mRNA expression in HT115 cells. mRNA expression in MDA-MB-231 was not examined. | [77] |
| c9,t11-Conjugated linoleic acid | SGC-7901 gastric carcinoma cells exhibited induced mRNA expression of TIMP-1, TIMP-2, and NM23. The effects were associated with inhibition of invasion. | [78] |
| ω-3 fatty acids | Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) increased protein expression and mRNA expression of CD44 in MDA-MB-231 breast cancer cells. | [79] |
| | DHA upregulated E-cadherin in MDA-MB-231breast carcinoma cells. | [80] |
| Fish oil | DHA and EPA increased protein expression and mRNA expression of CD44 in MDA-MB-231 breast cancer cells. | [79] |
| Sodium butyrate (a short-chain fatty acid in the colon produced by microbial degradation of microbial fibers | Butyrate increased TIMP-1, NM23A, and Kangai 1(KAI1) expression and decreased TIMP-3 expression as determined by microarray analysis in H460 non-small cell lung cancer cells. KAI1expression was confirmed by RT-PCR. Sodium butyrate also increased KAI1 protein expression in H460 lung carcinoma and HCT116 and SW620 colorectal cell lines. | [81] |
| | Butyrate increased E-cadherin protein expression in PC/AA/C1 and S/RG/C2 adenoma transformed PC/AA/C1/SB10 adenoma, and the colorectal carcinoma cell line, PC/JW/FI. | [82] |
| **Amino acids** | | |
| Tyrosine and phenylalanine | Deprivation increased MKK4 protein expression in MB-MBA-231 breast cancer cells and A375 melanoma cells. Tyrosine and phenylalanine deprivation also increased phosphorylation of MKK4 in A375 but not MB-MDA-231 cells. | [35] |
| **Amino acid, vitamin, and polyphenol mixture** | | |
| Lysine, proline, ascorbic acid, and green tea extract combination | The combination increased TIMP-2 protein expression in PC-3 prostate cancer cells. | [2] |
| Vitamins and derivatives | | |
| Vitamin D | 1α,25 dihydroxy vitamin D3 induced E-cadherin transcription and increased membrane-bound expression in SW480-ADH colorectal adenocarcinoma cells. 1α,25 dihydroxy vitamin D3 decreased mRNA expression of CD44 in these cells. | [83] |
| | The Gemini vitamin D analog, BXL0124, inhibited expression of CD44 protein, mRNA, and transcriptional activity of the CD44 promoter in MCF10DCIS.com cells. | [84] |
| γ-Tocotrienol (one compound in natural vitamin E) | γ-Tocotrienol up-regulation of TIMP-1, TIMP-2, and NM23-H1 in SGC-7901 gastric adenocarcinoma cells. | [85] |
| **Alcohol** | | |
| Ethanol | Ethanol inhibited retinoid acid differentiation of SH0SY5Y neuroblastoma cells That was associated with a concentration-dependent reduction in phosphatidylethanolamine binding protein (PEBP1) m-RNA and protein expression. | [86] |
| | Ethanol increased KISS1 and MKK4 and decreased NM23 mRNA expression in T47D breast cancer cells. Increased invasion was associated with down-regulation of NM23. | [18] |
| | Ethanol increased protein expression of E-cadherin and mRNA expression of KISS1, NM23m-1, and NM23m-2 in B16-BL6 melanoma cells and this was associated with inhibition of cell motility, invasion, and anchorage-independent growth. | [20] |
| **Triterpenoid glycoside mixture** | | |
| Ginseng extract | Ginseng transiently increased mRNA and protein expression of PEBP1 (RKIP) in MCF-7 breast carcinoma cells. | [87] |
| **Polysaccharide hydrocolloid gum** | | |
| λ-Carrageenan (component of carrageenans used in prepared foods) | λ-Carrageenan decreased gelsolin immunostaining in mammary myoepithelial cells. | [88] |

**Table 1** (continued)

| Constituent (source)/condition | Effect on metastasis suppressor genes | Reference |
|---|---|---|
| **Flavones** | | |
| Dietary flavones found in a variety of dietary sources including fruits, vegetables, and spices | Luteolin increased expression of E-cadherin protein in PC3 prostate cancer cells and this correlated with decreased invasion. | [89] |
| | 7-Hydroxyflavone increased and 5,6,7-trihydroxyflavone (also known as baicalein) and 4′,-5,7-trihydroxy-flavone decreased TIMP-2 protein expression in SCC-4 human tongue squamous cell carcinoma cells. All compounds inhibited invasion, migration and intravasation in the chicken chorioallantoic membrane assay. | [90] |
| | 3,3′4′,5,5′7′-hexahydroxyflavone (myricetin) inhibits TNF-α induced phosphorylation of MKK4 in JB6 P + mouse epidermal cells through direct interaction with the ATP binding site. | [91] |
| | Flavone increased mRNA expression of deleted in colon cancer (DLC-1) in HT029 colorectal carcinoma cells. | [92] |
| | Flavone restored DLC-1 mRNA expression in MDA-MB-468, MDA-MB-361, and BT20 breast carcinoma cells and HT-29 colorectal carcinoma cells. | [93] |
| **Isoflavones** | | |
| Genistein (an isoflavone in soy products) | Genistein inhibited MKK4 (referred to as MEK in the reference) activity in human 1532CPTX, 1532NPTX, 1542NPTX, 1542CPTX, PC3, and PC3-M prostate cell lines through specific binding to the active site of MEK4 protein. Genistein inhibited invasion of all cell lines between ~30–60 % depending on the cell line. | [33] |
| | Genistein increased KAI1 mRNA and protein (up to 2.5-fold) expression in a dose-dependent fashion, and also increased immunoreactivity in transgenic adenocarcinoma of the mouse prostate (TRAMP)-C2 prostate cancer cells. The effects correlated with decreased invasive ability. | [94] |
| | Genistein increased E-cadherin and decreased CD44 protein expression in ASPC-1 pancreatic cancer. | [95] |
| **Miscellaneous flavonoids** | | |
| Silibinin (a phenolic flavonoid from milk thistle seed, *Silybum marianum*) | Silibinin increased E-cadherin level that was mainly localized at the cellular membrane in PC-3, PC3MM2, and CA-2B prostate cancer cells. The effects were associated with antimigratory and antiinvasive activity. | [96] |
| | Silibinin decreased epidermal growth factor receptor (EGFR) ligand-induced CD44expression protein. | [97] |
| | Silibinin increased TIMP-2 protein expression in SCC-4 tongue cancer cells. | [98] |
| | Silibinin increased expression of TIMP-2 protein in A549 lung cancer cells. TIMP-2 mRNA was not affected. | [99] |
| | Silibinin increased PEBP1 (as known as Raf-1 kinase inhibitor protein (RKIP)) mRNA expression in HepG-2 hepatocellular carcinoma cells. | [100] |
| Isoliquiritigenin (a chalcone found in licorice, shallots, and bean sprouts) | Isoliquiritigenin decreased epidermal growth factor (EGF)-induced TIMP-1 and increased TIMP-2 secretion in DU-145 prostate cancer cells. Isoliquiritigenin inhibited migration and invasion in these cells. | [101] |
| **Glucosinolates** | | |
| Compounds found in cruciferous vegetables | Phenethylisothiocyanate decreased MKK7 protein expression in AGS gastric adenocarcinoma cells. | [16] |
| | Benzyl isothiocyanate increased MKK7 protein expression in AGS gastric adenocarcinoma cells. | [17] |
| | Indole-3-carbinol increased E-cadherin protein expression in MCF-7 MDA-MB-468 breast cancer cells. | [102] |
| | Indole-3-carbinol increased RECK protein in A549 alveolar basal epithelial adenocarcinoma cells. | [74] |
| **Carotenoid** | | |
| Lycopene (a carotenoid found in tomatoes and vegetables) | Lycopene increased mRNA and protein expression of the NM23-H1 in highly invasive SK-Hep-1 hepatic adenocarcinoma cells. The results were associated with inhibition of migration and invasion. | [103] |
| **Phenolic ether** | | |
| Anethole (major constituent in the volatile oil of fennel and anise) | Anethole increased mRNA expression of TIMP-1 but not TIMP-2 in HT-1080 fibrosarcoma cells. Anethole decreased invasion of these cells. | [104] |
| **Polyphenols** | | |
| EGCG (a tannin polyphenol found in tea, *Camellia sinensis*) | EGCG partially reversed hypermethylation and increased m-RNA expression of RECK in HSC3 and SCC9 oral squamous cell carcinoma cells. | [19] |

**Table 1** (continued)

| Constituent (source)/condition | Effect on metastasis suppressor genes | Reference |
|---|---|---|
| | EGCG increased TIMP-1 and TIMP-2 protein expression in MCF-7 tamoxifen-resistant but not tamoxifen-sensitive MCF-7 cells. | [105] |
| | EGCG decreased gelsolin mRNA and protein and decreased E-cadherin mRNA In MCF-7 breast cancer cells. | [106] |
| Curcumin (major component of turmeric) | Curcumin suppressed CTGF protein expression in human stellate cells. | [107] |
| | Curcumin enhanced expression of TIMP-2, NM23, and E-cadherin proteins in B16-F10 melanoma cells. | [108] |
| | Curcumin upregulated CD44 mRNA 2.5-fold and down regulated MKK4 mRNA 4.3-fold in MDA-1986 squamous cell carcinoma cells. | [109] |
| | Curcumin decreased MKK7 protein expression in the mouse-rat hybrid retina ganglion cell line, N18, which was derived from retina ganglion cells hybridized with lymphoma cells. | [110] |
| Pomegranate juice | Pomegranate juice upregulated E-cadherin protein expression in DU145 prostate cancer cells. Pomegranate juice increased adhesion to gelatin-coated plates and inhibited migration and chemotaxis of DU145 and PC3 prostate cancer cells. | [111] |
| *In vivo* | | |
| **Body weight and dietary intake** | | |
| Extended fasting | Fasting decreased Rho GDP-dissociation inhibitor 2 (RhoGDI2) protein expression in peripheral blood mononuclear cells from 10 healthy volunteers subjected to a 36-h fast. | [15] |
| Obesity and weight loss | Obesity enhanced CD44 mRNA expression in the liver of obese patients with steatohepatitis. Weight loss was associated with a strong decrease in CD44 mRNA expression in subcutaneous adipose tissue of 6 originally morbidly obese patients 2 years after bariatric surgery. Male C57BL/6 mice fed a 36 % high fat diet for 15 weeks became obese and the diet-induced obesity resulted in increased CD44 mRNA expression in the fatty liver and epididymal white adipose tissue. Similar increases were also observed in *ob/ob* mice. | [7] |
| | Specific CpG methylation sites in the CD44 promoter were decreased as a function of weight loss in men with a body mass index of 30.5±0.45 kg/m$^2$ that participated in an 8-week 30 % energy-restricted dietary intervention. | [8] |
| **Fatty acids** | | |
| Fish oil | Fish oil consumption decreased mRNA and protein expression of CD44 in MDA-MB231 breast tumors after intracardiac inoculation into mice. The findings were associated with decreased bone metastasis. | [79] |
| **Protein** | | |
| Dietary protein | Five-week offspring from Wistar rats fed an isoenergetic diet containing 8 % protein compared to a control 20 % protein diet exhibited decreased NM23 mRNA expression in their mammary glands. | [9] |
| **Amino acids** | | |
| Tyrosine and phenylalanine | B16BL6 melanoma cells isolated from subcutaneous tumors expressed the NM 23 gene; however, there was no differential expression between cells isolated from mice fed a normal diet compared to mice fed a tyrosine and phenylalanine restricted diet. | [112] |
| **Vitamins** | | |
| Vitamin D | The Gemini vitamin D analog, BXL0124, repressed CD44 expression in MCF10DCIS.com cells injected into mammary fat pads of immunodeficient mice. | [84] |
| Folate | Feeding folate-depleted amino acid-defined diets to young (weanling), male Sprague Dawley rats for twenty weeks compared to feeding diets containing 8 g/kg folic acid lead to a 2-fold downregulation of TIMP-2 mRNA expression in the colonic mucosa. Old mice (12-months of age) fed the folate-depleted diets had 5.9-fold increased mRNA expression of DCC compared to young rats. | [113] |
| | Folic acid supplementation, 5 mg once daily for 1 year, prevented loss of heterozygosity of the DCC gene in the rectal mucosa of 100 % of 5 subjects that were selected to participate in the study that had at least one adenoma >0.5 cm in diameter. Folate supplementation also prevented loss of heterozygosity in 2 out of 4 subjects in the placebo group. Rectal mucosal protein levels of DCC were reduced in 7 out of 10 subjects in the placebo group and only 2 out of 10 in the folate group. | [114] |
| **Polyphenol** | | |
| Curcumin | Curcumin decreased B16-F10 lung metastasis by 8-fold in C57BL/6 mice. | [108] |

**Table 1** (continued)

| Constituent (source)/condition | Effect on metastasis suppressor genes | Reference |
|---|---|---|
| **Flavone** | | |
| Luteolin | Luteolin increased protein expression in PC3 tumor extracts implanted onto the dorsal flank of in BALB/cA-*nu* (*nu/nu*) mice. Luteolin also inhibited lung metastasis. | [89] |
| **Isoflavones** | | |
| Isoflavone mixture containing genistein, daidzein, and glycitein | Consumption of capsules containing the isoflavone mixture resulted in decreased levels of methylation at low serum genistein levels and hypermethylation at high serum genistein levels of CTGF (CCN2) DNA in breast tissue from premenopausal women. | [62] |
| Genistein | Female rat offspring were exposed to lactating dams treated with genistein in AIN-76A diet from day 1-21 postpartum. Gelsolin protein was increased in mammary glands at day 21 but not at day 50 as determined by proteomic analysis. | [115] |
| | Dietary genistein restored age-dependent decreases in KAI1 protein levels in the dorsolateral prostates of TRAMP/FVB mice. | [94] |
| **Phenolic flavonoid** | | |
| Silibinin | Dietary silibinin administration in TRAMP mice increased E-cadherin protein expression in prostate tumors. This was also associated with decreased vimentin and snail-1. The effects correlated with decreased invasion and metastasis. | [116] |
| **Glucosinolates** | | |
| Indole-3- carbinol | RECK RNA expression and protein expression increased in lung tissues of female A/J mice treated with the carcinogen, vinyl carbamate, and indole-3-carbinol in the diet for 15 weeks. | [74] |
| 3,3′Diindolemethane (the major *in vivo* metabolite of indole-3- carbinol) | Oral administration of 3,3′-diindolmethane inhibited metastasis to the lung of 4T1 breast cancer cells injected into the tail vein of Balb/c mice. Inhibition of metastasis was associated with decreased TIMP-1 and increased TIMP-2 in the sera and lungs. | [117] |
| **Carotenoid** | | |
| Lycopene | Lycopene increased expression of NM23-H1 in lung tissues of *nude* mice after tail vein injection of SK-Hep-1 hepatocarcinoma cells. | [118] |

The effects on metastasis suppressor genes are categorized according to the biological activity (*in vitro* or *in vivo*) and according to the major natural classification of the constituent

nonmetastatic gene 23 (NM23) gene expression in T47D breast cancer cells. NM23 downregulation was associated with increased invasion in this study. Whether the increase in invasion also correlated with increased metastasis was not evaluated. One can speculate that within a particular type of cancer there may be a hierarchy of importance associated with different metastasis suppressor genes and their function in the metastatic process. Results from these nutritional-based studies underscore the need to examine and interpret effects on multiple metastasis suppressor genes and the genes' involvement in controlling the metastatic process.

It is important to remember that a nutrient which modifies a metastasis suppressor gene in a specific type of cancer may not impact other cancers within the same classification of cancer. For example, differential effects are reported in the metastasis suppressor gene, reversion-inducing-cysteine-rick protein with kazal motifs (RECK), among the four oral squamous cell carcinoma cell lines, HSC3, HSC4, SCC9, and SCC25, in response to epigallocatechin-3-gallate (EGCG). In these cell lines, EGCG only enhanced mRNA transcription of RECK in SCC9 and HSC3 [19]. Additionally, ethanol *in vitro* increased NM23 gene expression in B16-BL6 melanoma cells [20] as opposed to decreasing the expression of this gene in T47D breast cancer cells [18].

## 3 Downstream signaling pathways modulated by metastasis suppressor gene activation

Metastasis suppressor genes do not act in isolation. They collaborate among themselves and, when activated, can independently or collaboratively influence a number of biochemical signaling pathways that can carry out the metastasis suppressor activity of these genes. The specific mechanisms that underlie the function of metastasis suppressor genes still are not unraveled, and the contributions of diet, nutrients, and phytochemicals to these mechanistic pathways have not been systematically studied. This is another area where research is needed.

Many nutrients and phytochemicals produce antimetastatic activity by targeting downstream signaling pathways that are influenced by metastasis suppressors. One molecule targeted by a number of nutrients and phytochemicals is p38 mitogen-activated protein kinase (MAPK), which is a

signaling protein activated by the metastasis suppressors, MKK4 and MKK6, as well as other MAPKs [21]. Some natural compounds decrease and some increase p38 and/or its phosphorylation, and these effects are illustrated by the results from the following *in vitro* experiments. Glutamate supplementation [22], red grape skin polyphenolic extract [23], acacetin (a flavone found in honey and other sources) [24], isoalvaxanthone (a polyphenolic xanthone, which is biosynthetically related to flavonoids found in *Cudrania cochinchinensis*, Lour. and used in Chinese fold medicine) [25], and genistein (an isoflavone found in soy products) [26] inhibit p38 and/or its phosphorylation. Natural compounds that increase p38 and/or p38 phosphorylation in various cancer cell types include the following: glutamine, tyrosine and phenylalanine, and methionine restriction [27], lupulone (a prenylated flavonoid found in hops used in the manufacture of beer) [28], celastrol (a quinone methide triterpene extracted from the root bark of *Tripterygium wilfordii*, which in Chinese medicine is known as Thunder of God Vine) [29], berberine (an isoquinoline alkaloid with medicinal properties widely distributed in plants, notably Oregon grape, *Mahonia aquifolium*) [30], quercetin (a flavonol found in fruits, vegetables, leaves and grains) [31], and β-caryophyllene (a bicyclic sessquiterpene found in many essential oils, rosemary, hops, and black pepper) [32]. No consistent pattern is associated with p38 expression and tumor cell migration/invasion and survival. Perhaps, this is related to the differing effects of these nutrients in the various types of cancer. For example, genistein, which blocks activation of p38 in human prostate cancer cells, also inhibits cell invasion [26] and, specifically, inhibits MKK4 expression as well as metastasis of human prostate cancer cells in mice [33]. On the other hand, our laboratory, when looking at amino acids, showed that restriction of tyrosine and phenylalanine *in vitro* increases MKK4 protein expression by 2.5-fold in A375 melanoma cells [34] and also leads to increased p38 protein expression [27]. These changes were associated with an 80 % decrease in invasion [35]. Although the ability of tyrosine and phenylalanine restriction to inhibit metastasis of A375 melanoma or other human tumors has not been studied, dietary restriction of these amino acids inhibits metastasis in a wide variety of rodent tumors [36].

Celestrol, which activates p38 phosphorylation and decreases *in vitro* migration and invasion of B16-F10 murine melanoma and 95-D human lung cancer cells, also decreases pulmonary metastasis of B16F10-green fluorescent protein cells inoculated intravenously into C57BL/6 mice [29]. In this study, mice were treated with either 2 or 4 mg/kg intraperitoneally every 2 days beginning the day after tumor inoculation. Lung metastases were significantly decreased 3 weeks after tumor inoculation at both doses, $p<0.05$ at 2 mg/kg and $p<0.01$ at 4 mg/kg. The pulmonary tumor nodule count in the group receiving 4 mg/kg was about 50 % lower than the untreated group.

Some studies involving phytochemicals and nutrients show a positive correlation with p38 expression and/or phosphorylation and a particular biological effect associated with inhibition of metastasis. However, in most instances, the biological effect has not been linked to activation of a metastasis suppressor gene. More studies that examine the relationship between a particular metastasis suppressor and the downstream signaling pathways that are involved in mediating the gene's biological effect are needed. It will be especially important to conduct this evaluation in several different types of cancer, since the effect of the natural substance might be cell type dependent.

## 4 Epigenetic mechanisms

Epigenetics is an exciting area of science that involves studying changes in gene expression that are not correlated to changes in DNA sequence. It is well documented that nutrition and diet (as well as many other environmental factors) can epigenetically modify genes associated with cancer [37, 38]. This gives new meaning to the popular phrase, "You are what you eat." Epigenetic changes in cellular phenotype are inheritable so we can even say, "Your off-spring are what you eat." Mechanisms by which nutrition and specific phytochemical substances can epigenetically modify gene functions include modulation of DNA methylation, histone modifications and microRNA (miR)s. However, very little information is available on the specific epigenetic effects of diet and dietary constituents as they relate to regulation of metastasis suppressor gene activity. For some years, we have known that DNA methylation of genes plays an important role in invasion and metastasis [39]. Metastasis suppressor genes often are not expressed or inactive in cancer cells, but they can be re-expressed *via* epigenetic mechanisms. Epigenetic mechanisms, including alterations in DNA methylation, histone acetylation and methylation, and control of these processes by miRs have been reported for a number of substances: vitamins A, B, E, and D, selenium, fatty acids, polyphenols such as curcumin (a major constituent of the spice, turmeric), resveratrol (a phytoalexin and stilbene polyphenol found in the skin of red grapes and other fruits), EGCG and other tea catechins, ellagitannins (found in strawberries, raspberries, almonds, walnuts, etc.), various flavonoids, and indoles and isothiocyanates found in cruciferous vegetables. Studies of epigenetic mechanisms associated with these compounds were recently reviewed [4, 6, 40]. In another review, epigenetic regulations of these and several other bioactive dietary compounds were studied specifically for their effects in human breast cancer cells

[41]. Sulfur compounds found in garlic, particularly diallyl disulfide and allyl mercaptan, and butyrate (a major fermentation product largely found in the colon) modulate histone acetylation [42, 43]. Even though we know that many metastasis suppressor genes are modified by methylation and/or histone modulation, very little is known regarding how dietary factors alter these genes. The following sections identify what is known about these epigenetic mechanisms as they relate to the control of metastasis suppressor gene expression, with the goal of discovering future productive research.

### 4.1 DNA methylation and histone acetylation and methylation

DNA hypermethylation of metastasis suppressor genes is commonly associated with enhanced metastasis. One study looked at circulating tumor cells isolated from the peripheral blood of 56 patients with operable breast cancer, 27 breast cancer patients with confirmed metastasis, and 23 healthy individuals. Comparison showed that tumor suppressor and metastasis suppressor genes were silenced by methylation [44]. Promotor methylation of breast cancer metastasis suppressor (BRMS)1 was observed in 32 % of the patients with operable breast cancer and 44 % of patients with verified metastasis. Promoter methylation of BRMS1 was observed in only 4 % of the healthy individuals.

Many other metastasis suppressor genes are regulated by DNA methylation; however, the effects of diet, nutrients, and phytochemicals on methylation of their DNA have not been studied. The genes regulated by DNA methylation include NM23-H1 [45, 46], E-cadherin [46, 47], N-myc downstream-regulated gene (NDRG)1 [46], RECK [19], KISS1 [48], CD44 [49], RASSf2 and its specific isoform, RASSf2A [50, 51], DLC1 [52], caspase-8 [53], gelsolin [54], and connective tissue growth factor (CTGF) [55]. Many metastasis suppressor genes also are regulated by histone acetylation and methylation. Some examples include RECK [56], BRMS1 [57], E-cadherin [58], caspase-8 [53], tissue inhibitor of metalloproteinase (TIMP)-2 [59], NDRG1 [60], and gelsolin [61]. The fact that so many metastasis suppressor genes are influenced by epigenetic mechanisms and that natural substances modify genes epigenetically [4, 6, 10, 40] strongly supports the need for research to examine the potential for diet and dietary constituents to control the expression of these genes through DNA methylation and/or histone acetylation or methylation.

Little information is available on how natural substances control metastasis suppressor gene expression through modulation of DNA methylation and/or histone modification. This area of research shows promise because there are multiple cancer metastasis genes that could be influenced by natural substances. Below are the results from two studies that examine the effect of phytochemicals on methylation a single cancer metastasis suppressor gene.

In the first study, the four oral squamous cell cancers, HSC3, HSC4, SCC9, and SCC25, contain a hypermethylated RECK promoter [19]. HSC3 and HSC4 are highly methylated and express very low RECK mRNA. SCC9 and SCC25 contain unmethylated as well as methylated RECK promoter. RECK mRNA expression also is downregulated in these latter two cell lines. The four cell lines were treated with 20–50 μM EGCG for up to 6 days, and the treatment resulted in the appearance of specific unmethylated bands of the RECK gene. This finding is consistent with the fact that EGCG is known to complex with DNA methyl transferases to reduce methylation activity in cancer cells [4]. RECK mRNA transcription was enhanced by EGCG treatment in SCC9 and HSC3 cell lines; however, RECK mRNA levels were not altered in HSC4 and SCC25 cell lines after EGCG treatment [19]. The four cell lines were examined for their ability to invade three dimensional collagen gels. SCC9 and SCC25 were not invasive either in the presence or absence of EGCG. Invasion of HSC3 and HSC4 was inhibited by treatment with EGCG. This study does not indicate a consistent relationship between EGCG treatment, RECK methylation, and invasive ability, and the association with metastasis was not examined. Furthermore, *in vitro* invasive ability does not always correlate with *in vivo* metastatic potential. Interestingly, expression and activity of the invasive proteases, MMP-2 and MMP-9, were suppressed in HSC3 cells but not affected in HSC4 cell lines treated with EGCG. Thus, EGCG also may act through targets other than RECK to inhibit invasion.

In the second example, the methylation status of connective tissue growth factor (CTGF) was studied in a prospective, double-blind, randomized trial conducted in 34 healthy premenopausal women who received either 40 or 140 mg of a commercial isoflavone preparation daily through one menstrual cycle [62]. Serum genistein levels correlated with CTGF methylation at the end of treatment. CTGF methylation was significantly decreased ($p=0.011$) in subjects whose genistein levels were less than 200 ng/ml; however, methylation increased as a function of serum genistein levels >200 ng/ml, suggesting different mechanisms of action related to dose.

The results of these two studies indicate that metastasis suppressor gene expression can be regulated by phytochemicals through DNA methylation. While the results from these studies indicate that phytochemicals can control metastasis suppressor gene expression and are suggestive that this could translate into control of the metastatic process, more research in this area is needed before we can evaluate the potential for this epigenetic mechanism to have an impact on metastasis in humans.

Many phytochemicals also modify histones; however, no studies were identified in this review that specifically

examined effects on metastasis suppressor genes. This is another fruitful area of research.

### 4.2 MicroRNA

MicroRNAs (miRs) are noncoding RNAs that regulate a variety of biological processes, including cancer progression, by regulating gene expression. These RNAs are overexpressed in many types of cancer, are epigenetically regulated, and are implicated in all stages of the disease including promotion of tumor invasion, metastasis, and survival [63–66]. Many different dietary constituents are known to modulate miR including curcumin, indoles, isothiocyanates, polyunsaturated fatty acids, isoflavones, EGCG, ellagitannin, and resveratrol [40, 67]. While evidence is accumulating that miRs are important in regulating metastasis, the effects of diet and dietary constituents on metastasis suppressor genes have received little attention, and it is an exciting emerging area of research.

It is well established that all-*trans* retinoic acid, a biologically active metabolite of vitamin A, promotes cellular differentiation in many different types of cancer. The recent study by Ernst et al. [68] examined the molecular mechanisms associated with differentiation in five different cultures of glioblastoma spheroids prepared from glioblastoma tumors obtained from human patients. Among the 99 genes that were upregulated with a >2-fold change after treatment with 1 μM all-*trans* retinoic acid was the metastasis suppressor, CTGF. Interestingly, CD44 also was upregulated 1.6-fold. Expression of the miR-17-92 cluster, amplified and overexpressed in the glioblastoma cultures, was downregulated upon induction of differentiation by all-*trans* retinoic acid. Further analysis determined that the CTGF gene was a target of miR-17-92 and that it mediated the effects associated with differentiation of the glioblastoma cells during all-*trans* retinoic acid treatment.

miR-21 is commonly expressed in a number of different cancer types [69]. Known targets of miR-21 are phosphatase and tensin homolog (PTEN) and programmed cell death 4 (PDCD4), RECK and TIMP3 [69] among others. Inhibition of miR-21 leads to increased levels of TIMP3 and RECK protein in glioblastoma cells [70], and knockdown decreases cell migration medulloblastoma by increasing E-cadherin and TIMP2, two proteins also known to be regulated positively by PDCD4 [71]. Knockdown of miR-21 in B16 melanoma cells targeted PTEN and PDCD4 and sensitized these cells to interferon (IFN)-induced apoptosis [72]. Mice inoculated with these melanoma cells exhibited reduced metastasis and prolonged survival. In another study, curcumin treatment inhibited miR-21 promoter expression and activity and also inhibited migration and invasion of Rko and HCT116 colorectal carcinoma cells [73]. Curcumin inhibited primary tumor growth of Rko and HCT116 cells in chicken embryos and metastasis of Rko cells to the liver and lungs after implantation of cells into the chorioallantoic membrane. There was also a trend toward decreased metastasis of HCT116 cells. Curcumin also inhibited miR-21 expression in resected tumors from the chicken embryos in both cell lines. Dietary treatment of A/J mice with indole-3-carbinol administered in the diet for 15 weeks decreased miR-21 as well as miR-31, miR-130a, miR-143, miR-146b, and miR-377 in lung tissues, in addition to producing a 5-fold increase in RECK mRNA and increased RECK protein expression [74]. Indole-3-carbinol treatment of A549 alveolal basal epithelial adenocarcinoma cells *in vitro* also increased RECK protein expression in this study. The collective findings from these studies indicate that epigenetically targeting miRs with dietary constituents holds promise for the control of cancer and is wide open for exploration regarding the interaction between miRs and modulation of metastasis suppressor genes.

## 5 Summary and conclusions

Gaps in our knowledge regarding the effects of diet, nutrients, and phytochemicals on metastasis suppressor genes are huge. This is not surprising since the primary emphasis of funded research has been on inhibition of carcinogenesis and control of primary tumor growth. While it is clear that diet significantly impacts patient survival and that the major cause of death from cancer is due to metastasis, we are only beginning to understand the specific mechanisms associated with diet, dietary constituents, and other natural agents. This review of the literature indicates those unknowns that invite more research into the role of diet, nutrients, and phytochemicals and proposes the following areas of investigation as likely to be fruitful:

1. Define the effects of diet and lifestyle, nutrients, and phytochemicals on those metastasis suppressor genes known to have a role in controlling metastasis in a particular type of cancer. Once the effects are known, then one can determine the mechanism(s) underlying control of metastasis suppressor gene expression. This could include studying the downstream signaling molecules that mediate the antimetastatic effects of a specific gene and the interactions associated with activation or suppression of other impacted metastasis suppressor genes.
2. Determine the cell type specificity associated with natural substances as they affect metastasis suppressor genes. Is the dependency associated with a specific genotype and/or phenotype?
3. Define the specific biomarkers associated with selectivity and sensitivity of different types of cancer to dietary

and phytochemical factors. This is a necessary step before identifying the potential for effective therapeutic intervention.

4. Determine if genetic and biological differences within a particular type of cancer can predict responses to natural substances. For example, one could determine if an effect in a breast cancer that was estrogen positive differs from that of a breast cancer that is estrogen negative, and determine if breast cancer antigen (BRCA) and/or Her-2 positivity are associated with sensitivity to natural substances.
5. Determine if combining natural substances produces an additive or synergistic effect on the expression and activity of metastasis suppressor genes. This could preclude the need to achieve high concentrations of individual natural chemicals *in vivo* to activate metastasis suppressor genes.
6. Determine if combining natural substances that have beneficial effects on metastasis suppressor genes with other cancer therapies will prolong disease-free survival.
7. Evaluate the epigenetic mechanisms whereby natural substances control cancer metastasis genes. Very little is known about the ways natural substances regulate miR genes in relation to cancer in general and metastasis suppressor genes in particular. Identifying these mechanisms could lead to targeted approaches that control cancer metastasis and that increase patient survival.

Once it is established that natural agents play a significant role in controlling metastasis through their effects on metastasis suppressor genes, it may also be possible to develop them into effective antimetastatic agents to be used in combination with other treatments for cancer. With the recent advances being made in the pharmaceutical bioengineering field, it is likely that these natural agents also could be specifically formulated to improve their bioavailability, tissue distribution, and half-life.

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