Review

Bioactive Food Components, Inflammatory Targets, and Cancer Prevention

Young S. Kim, Matthew R. Young, Gerd Bobe, Nancy H. Colburn and John A. Milner

Abstract
Various dietary components may modify chronic inflammatory processes at the stage of cytokine production, amplification of nuclear factor-κB–mediated inflammatory gene expression, and the release of anti-inflammatory cytokine, transforming growth factor-β. This review provides a synopsis of the strengths and weaknesses of the evidence that specific bioactive food components influence inflammation-related targets linked to cancer. A target repeatedly surfaced as a site of action for several dietary components is transforming growth factor β. Whereas the use of dietary intervention strategies offers intriguing possibilities for maintaining normal cell function by modifying a process that is essential for cancer development and progression, more information is needed to characterize the minimum quantity of the bioactive food components required to bring about a change in inflammation-mediated cancer, the ideal time for intervention, and the importance of genetics in determining the response. Unquestionably, the societal benefits of using foods and their components to prevent chronic inflammation and associated complications, including cancer, are enormous.

A variety of bioactive food components have been shown to modulate inflammatory responses and to attenuate carcinogenesis (1–3). However, the effects of diet on the molecular mechanisms accounting for the changes in inflammation and carcinogenesis are not well understood. Whereas inflammation is a crucial protective response to tissue injury or infection, uncontrolled chronic inflammatory responses can result in serious complications, including cancer (4). The frequency of cancer and overall mortality has major societal implications in the United States in terms of quality of life and loss of productivity (5–7). This review points to potential use of bioactive food components for modifying molecular targets involved with chronic inflammation and, as a consequence, the attenuation of carcinogenesis.

Inflammatory Processes and Cancer
Inflammation is initiated by the synthesis and secretion of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-12, and IFN-γ in macrophages in response to an inflammatory insult (8). The binding of proinflammatory cytokines to their receptors triggers the mitogen-activated protein kinase pathway, which ultimately results in the activation of two redox-sensitive transcription factors, nuclear factor-κB (NF-κB) and the c-Jun part of activating protein-1 (9). These transcription factors activate the expression of a wide variety of genes including cytokines (TNF-α and IL-1β), chemokines, adhesion molecules, and inducible effector enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), thereby generating a feed-forward loop that amplifies the inflammatory response (10).

The changes in proinflammatory cytokines have multiple links with the production of anti-inflammatory cytokines including IL-4, IL-10, transforming growth factor-β (TGF-β), peroxisome proliferator activated receptor-γ (PPAR-γ), and the cellular redox defense system including manganese superoxide dismutase, glutathione, and catalase (11). These feedback mechanisms serve as controlling points where the amplification of the inflammatory processes can be disconnected and thereby reduce subsequent cancer risk. The unchecked activation of NF-κB/COX-2 and the inactivation of TGF-β signaling are recognized to be fundamental to the formation of tumors (12, 13). Mouse models with mutations in the genes coding for the inhibitors of κB kinase (IKKα and IKKβ) have provided compelling evidence about the critical role for NF-κB in coupling inflammation and cancer (14). Overall, the imbalance between anti-inflammatory and proinflammatory mediators may precipitate the neoplastic transformation in various cancer sites (Fig. 1).

Modulating Effects of Bioactive Food Components on the Proinflammatory and Anti-inflammatory Molecules
Evidence exists that a host of food components, including α-linolenic acid, n-3 and n-6 polyunsaturated fatty acids,
conjugated linoleic acid, butyrate, (−)-epigallocatechin-3-gallate, curcumin, resveratrol, genistein, luteolin, quercetin, vitamin A, and vitamin D, can modulate various points in the inflammatory process (Tables 1 and 2; Fig. 2). For example, when the diet of diabetic Zucker rats is supplemented with 1% of conjugated linoleic acid, a mixture of positional and geometric isomers of linoleic acid, the levels of TNF-α in skeletal muscle significantly decreased by almost a third after 8 weeks compared with unsupplemented controls (15). Recently, evidence has surfaced that adding 1 g of green tea extract per kilogram of diet for rats decreased the enhanced TNF-α gene expression caused by high fructose by ∼30% in both liver and skeletal muscle (16). The authors suggested that this response was secondary to the induction of a tristetraprolin protein, which binds to and destabilizes TNF-α transcripts. These studies also point to the importance of understanding nutrient–nutrient interactions in establishing the balance of inflammatory indicators. Regardless, there remains a need to better characterize their physiologic significance in terms of the amount needed to bring about a response in vivo.

The response to specific dietary constituents, such as flavonoids, is recognized to depend on the form they are provided. Flavonoids are naturally occurring polyphenolic compounds that can be found in commonly consumed fruits, vegetables, and grains. These compounds not only exhibit potent anti-inflammatory properties but also possess unique metabolic responsiveness to inflammation. Usually, flavonoids exist as either aglycones or conjugates with glucuronide or sulfate in blood or tissues (17). During inflammation, however, the conjugates are hydrolyzed back to more active aglycones via β-glucuronidases that are released from stimulated neutrophils or certain injured cells (18). These results suggest that the active form of anti-inflammatory flavonoids and likely of other bioactive food components may be required by inflammatory cells to remove potentially harmful products such as reactive oxygen species.

Recent study on structure-activity relationship suggests that the double bond between C2 and C3 in flavonoids including luteolin, quercetin, and genistein may be necessary to bring about the highest anti-inflammatory effect (19). This observation can be supported by the lack of the anti-inflammatory property of flavanones such as hesperetin that belong to the same flavonoid family but do not contain the double bond between C2 and C3. When the anti-inflammatory properties of flavonoids were compared side by side, luteolin was the most potent and required the minimum concentration in inhibiting cytokine production in macrophages (20). However, quercetin, kaempferol, and genistein are the most widespread and commonly consumed flavonoids in foods and, thus, likely constitute major anti-inflammatory dietary components (21).

Another anti-inflammatory mediator that is modulated by diet is PPAR-γ. PPAR-γ is a ligand-activated transcription factor, and its activation results in the inhibition of various proinflammatory mediators such as IL-1, TNF-α, IL-6, COX-2, and INOS and thus behaves as an anti-inflammatory mediator (22–24). The expression of this nuclear receptor is shown to be impaired in ulcerative colitis, which is characterized by chronic inflammation (25). Dietary agonists that bind PPAR include n-3 fatty acids and other polyunsaturated fatty acids generated by the commensal flora, such as conjugated linoleic acid and a short-chain butyrate, all of which are known to suppress inflammatory responses (26). Whereas the mechanism that explains how diet-activated PPAR-γ regulates the inflammatory process and what is the temporal relationship between PPAR-γ and other inflammatory mediators remains unclear, it is possible that the binding of dietary components to PPAR-γ down-regulates the activity of NF-κB either by mediating the trans-repression of NF-κB target genes (27) or by promoting nuclear export of NF-κB subunit RelA to the cytoplasm (28). Overall, because these studies have been conducted with the isolated macrophages or tissue-originated cells, the requirement of specific metabolites, chemical structure, and the exposure for the modulation of proinflammatory and anti-inflammatory molecules needs to be verified in animal models with the physiologically achievable concentration. Likewise, because genetics can influence absorptive and conjugation reactions, it is likely that all people will not respond identically to specific bioactive food components (29).
TGF-β Is a Critical Target Linked to Diet and the Risk of Cancer

Among a variety of inflammatory molecules linked to the risk of cancer and modulated by dietary components, TGF-β is one of the most consistently reported to be differentially expressed between cancer versus normal (30). Because both NF-κB and TGF-β are closely linked with the inflammatory processes, changes in these molecules in cancer again suggest the significant role of inflammation in cancer development. In response to proinflammatory cytokines such as TNF-α and IL-1β, NF-κB activates the transcription of inhibitory Smad7, which in turn suppresses the TGF-β pathway (31). This ability of NF-κB to suppress the anti-inflammatory TGF-β pathway may explain the ongoing chronic inflammatory reactions in cancer.

Dietary Modulation of the TGF-β Signaling Pathway

A number of dietary components including butyrate (the end-product of dietary fiber fermentation in colon), vitamin D, and genistein are known to enhance TGF-β signaling and potentiate its tumor suppressor activity (32–34). The TGF-β members initiate signaling by bringing together a complex of serine/threonine kinase receptors that transmit signals through intracellular Smad proteins. The binding of TGF-β to its type II receptors (TβRII) induces a series of phosphorylation in the TGF-β type I receptor (TβRI) followed by Smad2 and Smad3. When phosphorylated by TβRI, Smad2 and Smad3 associate with Smad4 and then translocate to the nucleus where they associate with a DNA-binding partner and activate transcription of specific target genes (35). The exact mechanism by which these dietary components interact with TGF-β remains unresolved, but possible mechanisms include enhanced TGF-β–induced Smad protein phosphorylation (32, 34), function as a histone deacetylase (HDAC) inhibitor (36), and/or their ability to enhance the activity of 15-hydroxyprostaglandin dehydrogenase (15-PGDH; ref. 37; Fig. 3). Each of these is briefly discussed below.

Table 1. Proinflammatory mediators as potential molecular targets for bioactive food components

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Food component</th>
<th>Concentration/quantity</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>CLA</td>
<td>1% of diet</td>
<td>Diabetic Zucker rats (15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Curcumin</td>
<td>5 μmol/L</td>
<td>Human macrophage rat (76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EGCG</td>
<td>30 mg/kg i.p.</td>
<td>Rats (77)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genistein mixture</td>
<td>1 g green tea extract/kg diet</td>
<td>Rats (16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Luteolin</td>
<td>1 μmol/L</td>
<td>Macrophage cell line (RAW 264.7) (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n-3 fatty acids</td>
<td>9 g/d</td>
<td>Human feeding (82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quercetin</td>
<td>5 μmol/L</td>
<td>Macrophage cell line (RAW 264.7) (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
<td>1 nmol/L</td>
<td>Human peritoneal macrophage (83)</td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>Curcumin</td>
<td>5 μmol/L</td>
<td>Human macrophage cell line (Mono Mac 6) (76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n-3 fatty acids</td>
<td>9 g/d</td>
<td>Human feeding (82)</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Genistein</td>
<td>2 μmol/L</td>
<td>Estrogen-unresponsive fibroblasts (84)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Luteolin</td>
<td>1 μmol/L</td>
<td>Macrophage cell line (RAW 264.7) (20)</td>
<td></td>
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<tr>
<td></td>
<td>Quercetin</td>
<td>5 μmol/L</td>
<td>Macrophage cell line (RAW 264.7) (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
<td>1 μmol/L</td>
<td>Mast cells (86)</td>
<td></td>
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<tr>
<td>NF-κB</td>
<td>Butyrate</td>
<td>100 μmol/L</td>
<td>Human macrophage (87)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genistein</td>
<td>100 mg isoflavone mixed/d for 3 wk</td>
<td>Human lymphocytes (79)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resveratrol</td>
<td>5 mmol/L</td>
<td>Estrogen-unresponsive fibroblasts (84)</td>
<td></td>
</tr>
<tr>
<td>COX-2</td>
<td>Butyrate</td>
<td>4 mmol/L (HT-29)</td>
<td>Colon cancer cells (89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLA</td>
<td>20 μmol/L (MCF-7)</td>
<td>Human breast cancer cells (90)</td>
<td></td>
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<tr>
<td></td>
<td>Genistein</td>
<td>100 μmol/L</td>
<td>Human chondrocytes (91)</td>
<td></td>
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<tr>
<td>iNOS</td>
<td>Butyrate</td>
<td>3 mmol/L</td>
<td>Rat intestinal epithelial cells (IEC-6) (92)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CLA, conjugated linoleic acid; EGCG, (-)-epigallocatechin-3-gallate; iNOS, inducible nitric oxide synthase.
**TGF-β-Induced Smad Phosphorylation**

The anti-inflammatory cytokine TGF-β binds first to the TβRII, which leads to the recruitment and activation of the TβRI. The activated TβRI phosphorylates Smad3 at its COOH-terminal serine residue, which was enhanced with the 12-hour exposure of physiologically relevant concentration (5 mmol/L) of sodium butyrate in the culture medium for rat intestinal epithelial (RIE-1) cells (32). The phosphorylated Smad3, in turn, makes a complex with Smad4 and translocoates into the nucleus where it binds to a specific DNA site and various transcriptional cofactors, which may initiate the expression of potential tumor suppressor genes such as 15-PGDH (Fig. 3). The treatment of colon cancer cells such as Caco-2 and MC-26 with physiologically achievable concentrations of vitamin D (100 nmol/L) and genistein (60 μmol/L) was found to enhance the TβRI-mediated TGF-β/Smad pathway, suggesting the involvement of dietary components in this pathway mediating the induction of colon cancer cell apoptosis and the inhibition of their proliferation (33, 34).

TGF-β has been shown to antagonize the proinflammatory cytokine-mediated activation of NF-κB in human intestinal lamina propria mononuclear cells (38). Proinflammatory cytokines such as TNF-α and IL-1β stimulate the RelA subunit of NF-κB, which activates inhibitory Smad7 gene transcription. The Smad7, in turn, suppresses TGF-β signaling through its direct interaction with the TβRI on TGF-β ligand-receptor binding (Fig. 3). The increased Smad7-TβRII complexes bring about the inhibition of TGF-β-induced phosphorylation of Smad2/Smad3 and IκB, nuclear translocation of NF-κB, and DNA binding of SMAD signaling complexes by TNF-α (31). The expression of Smad7 has been altered in response to cholesterol-enriched diet, suggesting that the high-cholesterol diet may interfere with TGF-β signaling (39).

Recently, it has been shown that the phosphorylated TβRI is posttranslationally modified by binding to a small ubiquitin-like modifier (SUMO), or sumoylation, which leads to enhanced activation of the Smad-dependent TGF-β signaling pathway (40). A number of ubiquitin-like proteins including SUMO follow a mechanism similar to ubiquitination. It has been well established that the degradation process involved with ubiquitin is influenced by several dietary factors including tea constituents, fat, and sodium. For example, treatment of hepatocellular carcinoma HepG2 and human cervix epithelial adenocarcinoma HeLa cells with 30 μmol/L of green tea bioactive component, (−)-epigallocatechin-3-gallate, for 2 hours effectively inhibited the ubiquitin-mediated degradation of sterol regulatory element-binding protein 2 (41). This effect of green tea brought about the up-regulation of the low-density lipoprotein receptor, which is known to lower plasma cholesterol levels. Thus, the hypothesis that the sumoylation of TβRI can be modulated by dietary components and result in the changes in the TGF-β signaling pathway needs to be examined.

**HDAC Inhibition**

Another possibility may be because specific dietary components such as butyrate, diallyl disulfide, and sulforaphane can serve as HDAC inhibitors and thereby antagonize the Sp1/Sp3-associated HDAC activity and thus suppress tumorigenic events. The up-regulation of Sp1/Sp3 activity with a HDAC inhibitor, suberoylanilide hydroxamic acid, was shown to induce the expression of the TβRI and TβRII genes and restore TGF-β signaling in human breast cancer cells (42). Likewise, a deficiency in Sp1 transcriptional activity caused a decrease in TβRI gene expression in human colon carcinoma cells (43). The dependence of TβR expression on Sp1/Sp3 was shown to be associated with chromatin remodeling but not with DNA methylation (42, 44). Because both breast and colon cancer cells become unresponsive to TGF-β growth inhibition along the neoplastic processes, it is likely that the modification of chromatin structure via HDAC inhibitors recovers the TGF-β signaling pathway in colon as in breast. However, targeting these epigenetic events for therapeutic purposes requires caution because TGF-β can actually promote tumor progression as malignant transformation progresses (45). The exact mechanism for this switch from growth inhibition to growth promotion remains to be clarified.

Whereas it is uncertain how TGF-β induces tumor progression and metastasis, the aberrant expression of TGF-β1 during epithelial-to-mesenchymal transition in the cancer cell microenvironment is considered to play a critical role. Recently, it has been shown that trichostatin A, a HDAC inhibitor, prevented TGF-β1-induced epithelial-to-mesenchymal transition in cultured human renal proximal tubular epithelial cells (46). Because the epithelial-to-mesenchymal transition commonly occurs during carcinogenesis, the ability of HDAC inhibitors to prevent these morphologic changes may explain at least part of their antitumorigenic effects. Several dietary compounds such as butyrate, biotin, lipic acid, garlic organosulfur compounds, and metabolites of vitamin E hold structural features that are compatible with HDAC inhibition (47). Among these, butyrate, diallyl disulfide, and sulforaphane are already shown to exhibit HDAC inhibitory activity in vitro and/or in vivo. For example, when the tumor-bearing nude mice were fed 0.5 g sulforaphane/kg of diet for 21 days, these mice developed smaller size of tumors with the significantly

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**Table 2. Anti-inflammatory mediators as potential molecular targets for bioactive food components**

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Food component</th>
<th>Concentration/quantity</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β</td>
<td>Butyrate</td>
<td>5 mmol/L</td>
<td>Nontransformed intestinal epithelial cells (RIE-1)</td>
<td>(32)</td>
</tr>
<tr>
<td>IL-10</td>
<td>Luteolin</td>
<td>25 μmol/L</td>
<td>Colorectal carcinoma cell line (Caco-2)</td>
<td>(93)</td>
</tr>
<tr>
<td>PPAR-γ</td>
<td>CLA</td>
<td>200 μmol/L</td>
<td>Macrophage cell line (RAW 264.7)</td>
<td>(94)</td>
</tr>
<tr>
<td>Glutathione</td>
<td>Methionine</td>
<td>1 g/d</td>
<td>Humans</td>
<td>(95)</td>
</tr>
<tr>
<td>Catalase</td>
<td>Indole</td>
<td>0.4 mmol/L</td>
<td>Chinese hamster fibroblasts</td>
<td>(96)</td>
</tr>
</tbody>
</table>

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decreased HDAC activity in xenografts compared with controls (48). Likewise, the supplementation of Caco-2 colon cancer cells with 200 μmol/L diallyl disulfide in culture media decreased HDAC activity by 29% (49). Thus, it is likely that these dietary HDAC inhibitors have the similar effects as trichostatin A on the TGF-β1 mediated epithelial-to-mesenchymal transition at colon, which needs to be further examined.

**Effects on 15-PGDH**

TGF-β1 is shown to induce the expression of 15-PGDH in a time- and concentration-dependent manner in A549 and H1435 lung adenocarcinoma cells (50). 15-PGDH is a rate-limiting catabolic enzyme that converts prostaglandins to biologically much less tumorigenic 15-keto derivatives at sites of inflammation and cancer. This enzyme is universally expressed in normal colon but is routinely deficient in cancer cells, which contributes to the accumulation of prostaglandin E2 in colon and thus increasing the risk of developing cancer (51). Furthermore, the knockout of this enzyme has shown to increase the susceptibility to azoxymethane-induced adenomas and carcinomas in situ at colon, suggesting its tumor-suppressive role in colon (52).

Supplementations with sodium butyrate (2 mmol/L) and vitamin D (10 nmol/L) in lung and prostate cancer cells, respectively, has been reported to reduce the levels and biological activity of prostaglandin E2 (50, 53). Likewise, the treatment of HT29 colon cancer cells with curcumin (50 μmol/L) has been shown to suppress prostaglandin E2 activity (54). These effects of dietary components on prostaglandin E2 were correlated with the reduced expression of prostaglandin receptors and the increased expression of 15-PGDH, which is a potential tumor suppressor. Interestingly, the increasing effects of vitamin D on 15-PGDH activity have been enhanced by the addition of genistein (25 μmol/L), which is a soy isoflavone with phytoestrogenic effects (55). This is likely due to the known property of genistein that increases half-life of vitamin D by elevating the activity of its synthesizing enzyme CYP27B1 and inhibiting the activity of CYP24 that degrades vitamin D (56). Genistein (10 μmol/L) is also shown to increase vitamin D receptor expression by binding estrogen receptor β and thus facilitate the function of vitamin D in HT29 colon cancer cells (57). Therefore, nutritional supplementation of this soy isoflavone may optimize and/or enhance the cancer-preventive effects of vitamin D.

Whereas the preventive effects of dietary components on the inflammation and cancer are intriguing, their potential adverse effects cannot be ignored. For example, the addition of genistein (250 ppm) to the azoxymethane-induced colon cancer in mice is reported to increase the experimental tumorigenesis, possibly by interacting with the carcinogenic chemical azoxymethane.
(58). Similarly, in vitro study examining the chemopreventive activity of resveratrol reports that 24 hours of exposure to resveratrol (10, 50, and 100 μmol/L) was toxic to both nonmalignant B-cell lymphoblastoid cells (WIL2-N5) and malignant promyelocytic leukemia cells (HL-60) in a dose-dependent manner (59). Clearly, any bioactive food component can be toxic if provided in sufficient quantities, regardless if normal or neoplastic. Nevertheless, a wealth of evidence does point to a differential response. Finding the quantity needed to differentially influence cancer versus noncancer cells is certainly challenging. Because the mechanism for these conditional responses remains unclear, more research is warranted.

The loss of 15-PGDH expression in cancer is often associated with the increased COX-2 and epidermal growth factor receptor tyrosine kinase activity that occur in the majority of cancer (60, 61). The activated epidermal growth factor receptor is known to stimulate COX-2 production and its translocation to the nucleus in colon cancer cells (62). The increased COX-2 in turn generates additional prostaglandin E2, which rapidly phosphorylates epidermal growth factor receptor and triggers extracellular signal–regulated kinase 2 and its mediated mito-genic signaling pathway. The significance of COX-2 enzyme in tumorigenesis has been clearly shown by a marked reduction in numbers of intestinal polyps occurring in the COX-2−/− mice compared with COX-2 wild-type animals (63). Evidence exists that selected dietary components such as curcumin in curry spice, tea polyphenol (−)-epigallocatechin-3-gallate, dietary vitamin D, genistein in soy, resveratrol in red grapes, conjugated linoleic acid in dairy products, and butyrate generated through microbial metabolism of dietary fiber in colon suppress COX-2 expression by modulating various pathways in vitro and in vivo (64–70). However, it is likely that TNF-α-induced activation of COX-2 and its mediated tumorigenic cycle that leads to cancer cell proliferation may be vulnerable to only specific dietary constituents such as vitamin D, butyrate, and genistein, which are known to enhance the activity of 15-PGDH.

**Variations in Response to Bioactive Food Components**

Admittedly, the modulating effects of bioactive food components on various cytokine levels and inflammation-related molecules exhibit considerable variability in response. Individual sensitivities to the effects of diet may arise from a number of variables including the wide range of concentrations of bioactive food components adopted in studies, the lack of information on their timing of supplementation, and the genetic polymorphism encoded by or associated with inflammatory mediators such as TNF-α, IL-6, and TGF-β. Data from Grimble et al. (71) suggest that the different sensitivities of persons to the effect of diet, in this case fish oil, may arise from the genetic polymorphism encoded by or associated with inflammatory mediators such as TNF-α. According to the report, the ability of fish oil to decrease TNF-α production can be detected only in the individuals with high inherent TNF-α levels determined by genetic polymorphisms in TNF-α [−308 (G/A); ref. 71]. Fish oil supplementation decreased the mean TNF-α production significantly by 43% in the individuals with TNF-α [−308 (G/A)] genotype but did not change mean TNF-α production in the rest.

The influence of genetic polymorphism on the differential dietary response is further substantiated by the study showing that single nucleotide polymorphism in IL-6 [-174 (G→C)] is recognized to modulate glucose uptake and decrease inflammatory processes. Subjects homozygous for the C allele at this site have significantly higher metabolic rates for glucose with lower glucose uptake and lower fat accumulation than carriers of the G allele (72).

Recently, common polymorphisms in COX-2 genes were found to be associated with inflammatory and degenerative disorders including colon cancer (73). A case-control study of patients with adenomatous (n = 494) or hyperplastic polyps (n = 186) versus polyp-free controls (n = 584) revealed that carriers of the polymorphic allele in the COX-2 −765G > C promoter variant had significantly decreased COX-2 levels as well as the phosphorylation of TGF-βRII leads to the activation of intracellular signaling pathways including the phosphorylation of TGF-βRI/Smad2/3/4 (1), the inhibition of HDAC/Smad2 (2), and the increased expression of 15-PGDH (3), which down-regulates colon cancer cell proliferation. Specific dietary components such as butyrate, genistein, and vitamin D have been shown to modulate each of these pathways and thus enhance the apoptotic effects of TGF-β in colon. Smad-TF, Smad-associated transcription factor; HDACI, histone deacetylase inhibitor.

![Diagram](image-url)
as reduced risk of colorectal adenoma among nonusers of nonsteroidal anti-inflammatory drugs. In addition, the use of aspirin or other nonsteroidal anti-inflammatory drugs prevented risk of adenoma (~40%) only in those individuals with the increased COX-2 expression associated with the –765GG (wild type) and –765CG genotypes. Therefore, it is logical to assume that those with genetically enhanced COX-2 protein production would be more responsive to these dietary components.

Polymorphisms in anti-inflammatory factors may also influence the responsiveness to the bioactive food components. For example, a thymine-to-cytosine mutation in the coding sequence of TGF-β1 (29 T→C) results in a leucine-to-proline substitution and is associated with increased serum levels of TGF-β1 (74). It is reported that subjects with this polymorphism have lower rate of glucose metabolism compared with control (75). Phytanic acid, a metabolite of the chlorophyll molecule, has been found to enhance the uptake of glucose by increasing the expression of glucose transporters in rat primary hepatocytes. It is possible that the effect of phytanic acid may be maximized in individuals with polymorphic TGF-β1 (29 T→C). Inflammatory gene polymorphisms that are associated with the variations in response to bioactive food components are summarized in Table 3. Whereas these findings suggest that the genetic polymorphism in inflammatory mediators can alter the response to dietary components in carcinogenesis, much more information is needed to reveal the mechanistic relationship between genetic susceptibility and the utilization of diet in cancer prevention.

**Summary and Conclusions**

Undeniably, diet has an effect on the inflammatory process. However, the effect of specific bioactive food components depends on their interactions with an array of anti-inflammatory or proinflammatory mediators and their effectiveness at regulating specific targets. Because an individual’s dietary habits and genetic profile determine the response to inflammation and risk of diseases including cancer, it is imperative that a better understanding of the molecular events by which dietary constituents interact with cancer-related genes throughout the inflammatory process that creates chronic conditions be understood. Whereas unraveling diet-gene interactions in inflammatory is particularly challenging, the rewards will be enormous. Expanding strategies to use foods and their components for preventing chronic inflammatory processes will help foster normal cell function while minimizing a process that is needed for the initiation and progression of cancer. The utilization of experimental technologies combined with other molecular resources such as genomics, proteomics, and metabolomics will help identify the physiologic efficacy of dietary components needed to regulate inflammation under normal and diseased conditions. Expanding these “omic” endeavors not only will provide insights into molecular targets but will also serve as foundation for designing effective and personalized cancer prevention strategies.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**Table 3. Gene polymorphisms that are associated with inflammation and bioactive food components**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Food component</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>308 (G/A)</td>
<td>Fish oil</td>
<td>(71)</td>
</tr>
<tr>
<td>IL-6</td>
<td>−174 (G/C)</td>
<td>Glucose metabolites</td>
<td>(97, 98)</td>
</tr>
<tr>
<td>COX-2</td>
<td>−765 (G/C)</td>
<td>N-6 polyunsaturated fatty acids</td>
<td>(99)</td>
</tr>
<tr>
<td>TGF-β</td>
<td>29 (T/C)</td>
<td>Glucose metabolites</td>
<td>(75)</td>
</tr>
<tr>
<td>PPAR-γ</td>
<td>Pro12Ala</td>
<td>Lipids</td>
<td>(100)</td>
</tr>
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**References**

63. Rosmond R, Chagnon M, Bouchard C, Bjornor P. Increased abdominal obesity, insulin and glucose levels in nondiabetic subjects with a T29C


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