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Cancer and diet: How are they related?

Bokyung Sung, **Sahdeo Prasad**, **Vivek R. Yadav**, **Afsaneh Lavasanifar***, and **Bharat B. Aggarwal**

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

*Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

Abstract

Extensive research in the past decade has revealed cancer to be a multigenic disease caused by perturbation of multiple cell signalling pathways and dysregulation of numerous gene products, all of which have been linked to inflammation. It is also becoming evident that various lifestyle factors, such as tobacco and alcohol use, diet, environmental pollution, radiation and infections, can cause chronic inflammation and lead to tumourigenesis. Chronic diseases caused by ongoing inflammation therefore require chronic, not acute, treatment. Nutraceuticals, compounds derived from fruits, vegetables, spices and cereals, can be used chronically. This study discusses the molecular targets of some nutraceuticals that happen to be markers of chronic inflammation and how they can prevent or treat cancer. These naturally-occurring agents in the diet have great potential as anti-cancer drugs, thus proving Hippocrates, who proclaimed 25 centuries ago, 'Let food be thy medicine and medicine be thy food'.

Keywords

Dietary agents; inflammation; cancer

Introduction

One of the earliest known examples of cancer is found in bone remains of Egyptian mummies, suggestive of the bone cancer osteosarcoma. The oldest description of cancer is also found in Egypt, in the Edwin Smith Papyrus, an ancient Egyptian textbook on trauma surgery that dates back to 1600 BCE. In that document, although the word 'cancer' is not used, a condition is described that is consistent with cancer: eight cases of tumours or ulcers of the breast, with the notation that there is no treatment for this condition and recommending cauterization. The word 'cancer' was first introduced by Greek physician Hippocrates (460–370 BCE), who used the term *Karkinos* (the Greek word for crab), which translates to 'carcinos' or 'carcinoma' in English, to describe 'non-ulcer forming' and 'ulcer-forming tumours '. The choice of the word *crab* stemmed from the similarity between blood vessels surrounding a tumour and the claws of a crab squeezing a malignant mass. Later, the Roman physician Celsus (28 -50 BCE) translated the Greek term into '*cancer*', the

Correspondence: Bharat B. Aggarwal, Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. Tel: 713-794-1817. Fax: 713-745-6339. aggarwal@mdanderson.org.

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Latin word for crab. Galen (130–200 CE), another Roman physician, used the word *oncos* (Greek for swelling) to describe tumours.

Today, cancer is considered a cluster of diseases involving alterations in the status and expression of multiple genes that confer a survival advantage and undiminished proliferative potential to somatic or germinal cells [1]. Only a minority of cancers are caused by germline mutations, whereas the rest (~ 90%) are linked to somatic mutations and environmental factors [2]. There is increasing evidence to suggest that cancer is also driven by 'epigenetic changes', such as DNA methylation and altered patterns of histone modifications, which can lead to alterations in chromatin condensation status, thereby regulating the expression of a certain set of specific genes [3,4]. The mutations and epigenetic changes found in the cancer cell genome accumulate over the lifetime of cancer patients. The rate of mutation increases in the presence of exogenous mutagenic exposures, such as lifestyle factors, tobacco smoke, naturally occurring toxic chemicals or various forms of radiation, including ultraviolet light. Substantial exposure to these environmental and lifestyle factors is associated with increased rates of lung, liver and skin cancer [5]. Similar factors have been linked to inflammatory responses. This suggests a strong relationship between inflammation and cancer [5–7].

How lifestyle and environmental factors lead to tumourigenesis is becoming ever more clear. However, one of the major contributors to tumourigenesis caused by these factors is believed to be chronic inflammation [8]. Although acute inflammation exerts therapeutic potential, chronic inflammation is a low-level inflammation that can persist for long periods, eventually causing chronic diseases, including cancer. It is estimated that ~ 15% of human cancers are associated with infections and inflammation [9]. The markers of chronic inflammation include pro-inflammatory cytokines (i.e. tumour necrosis factor [TNF] and interleukins [ILs]−1, −6 and −8) and chemokines, pro-inflammatory enzymes (cyclooxygenase-2 [COX-2], 5-lipoxygenase, matrix metalloproteinase [MMP] and urokinase plasminogen activator [uPA]), adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 and endothelial leukocyte adhesion molecule-1) and certain growth factors (such as epidermal growth factor [EGF] and platelet-derived growth factor [PDGF]) [8].

Although it is not yet possible to provide quantitative estimates of the overall risks, it has been estimated that 35% of cancer deaths may be related to dietary factors [10]. Diets that include fruits, vegetables and spices may provide substantial health benefits in terms of cancer prevention and treatment by suppressing the inflammatory processes that lead to transformation, hyperproliferation and the initiation of carcinogenesis. However, which component of these dietary agents is responsible for their anti-cancer effects and the mechanism by which they suppress cancer remain unknown. Dietary agents contain a variety of biologically active phytochemicals, many of which have been used in traditional medicine for thousands of years. Some phytochemicals are known to influence the transcription factors involved in carcinogenesis.

Transcription factors as a link between diet and cancer

Most oncogenes and tumour suppressor genes are transcription factors, which control gene expression and regulate numerous signalling pathways in cancer. Dysregulation of transcription factor activity is the result of numerous mechanisms, such as changes in gene expression, protein–protein interactions and post-translational modifications, leading to deregulation of gene products that are involved in both inflammation and carcinogenesis [11]. In this review, we will focus on selected transcription factors (e.g. nuclear factor –κB [NF-κB], activator protein-1 [AP-1], signal transducer and activator of transcription-3 [STAT-3], nuclear factor erythroid 2-related factor [NRF2], peroxisome proliferator-

activated receptor-γ [PPARγ], WNT/β-catenin, hypoxia inducible factor-1 [HIF-1] and hedgehog [Hh]) that are involved in tumour progression (Figure 1). In addition, we will review dietary nutraceuticals, including two powerful compounds, resveratrol and curcumin, that can modulate the activity of these transcription factors, playing a positive role not only in the prevention of various chronic diseases, including cancer, but also their treatment.

Nuclear factor-kappa B (NF-κB)

NF-κB was first discovered in 1986 in the nucleus of the B-cell as an enhancer of the κ immunoglobulin chain [12]. NF-κB consists of homodimers or heterodimers of its five family members and is activated in response to several stimuli, including pathogen-associated molecular patterns, TNF-α, IL-1 and others stimuli related to environmental and lifestyle factors [13]. Once these ligands are engaged with their respected receptors, signalling impinges on a common molecular target, the inhibitor of κB (IκB) kinase (IKK) complex, leading to phosphorylation, polyubiquitination and subsequent degradation of IκBα, thereby allowing NF-κB to translocate to the nucleus and to exert its functions as a transcriptional regulator. NF-κB has been implicated in inflammation, cell survival, proliferation, invasion and angiogenesis. During the past decade, the crucial role of the NF-κB signalling in connecting inflammation to cancer has been subjected to intense investigation by a number of laboratories in a variety of experimental systems and this connection has been well established. The intimate relationship between NF-κB and cancer has already been extensively reviewed [8,14–16].

Constitutively activated NF-κB is found in several human cancer cell lines, including lymphomas and carcinomas of the breast, prostate, lung, colon, pancreas, head and neck and oesophagus. In addition to cell lines, activated NF-κB has been noted in tissue samples from cancer patients [17]. Studies of cancer-associated mutations have also reported that mutations in the upstream signal component of NF-κB that could direct to constitutive NF-κB activation in multiple myeloma (MM) cell lines and patient samples [18,19]. Because of the role of NF-κB in human diseases, including cancer, this transcription factor is an ideal target for anti-cancer drug development.

Our research group and others have described more than 700 inhibitors of the NF-κB pathway, including nutraceuticals derived from dietary agents [13,20,21]. Active components of spices, such as curcumin [22], diosgenin [23], gambogic acid [24], capsaicin [25], ursolic acid [26], noscapine [27], sesamin [28], anethole [29] and eugenol [29] can inhibit IKK and p65 phosphorylation *in vitro*, leading to the suppression of NF-κB that has been activated by various carcinogens. This NF-κB suppression leads to the down-regulation of its regulated gene products, including COX-2, MMP-9 and cyclin D1. Nutraceuticals derived from various kinds of ginger, such as crotepoxide [30], zerumbone [31], 1′-acetoxychavicol acetate [32] and [6]-gingerol [33], have been reported to suppress the NF-κB signalling pathway and induce apoptosis in a variety of human cancer cell lines. Recently, zerumbone has been shown to suppress the receptor activator of NF-κB ligand (RANKL)-induced NF-κB activation and osteoclastogenesis induced by RANKL and tumour cells, thus decreasing osteolysis in MDA-MB-231 breast cancer tumour-bearing athymic nude mice [34]. Nutraceuticals such as plumbagin [35], caffeic acid phenethyl ester (CAPE) [36], picroliv [37] and xanthohumol [38] have been shown to suppress NF-κB activation through direct inhibition of p65 binding to DNA. Butein [39], nimbolide [40], berberine [41] and xanthohumol [38] have been reported to sensitize tumour cells to chemotherapeutic agents through direct interaction with IKK. A novel form of vitamin E, γ-tocotrienol (γ-T3), has been shown to suppress the activation of NF-κB induced by inflammatory and carcinogenic agents [42]. γ-T3 has been shown to inhibit the growth of human pancreatic tumours and sensitize them to gemcitabine by suppressing NF-κB-mediated inflammatory pathways that have been linked to tumourigenesis [43].

Other dietary agents, including escin [44], pinitol [45], anacardic acid [46], 3,4-dihydroxybenzalacetone [47], morin [48], fisetin [49], simvastatin [50], resveratrol [51], indole-3-carbinol (I3C) [52], evodiamine [53], betulinic acid [54], silymarin [55] and emodin [56], have been found to inhibit both inducible and constitutive NF-κB activation; suppress the activation of IKK that leads to abrogation of phosphorylation and degradation of IκBα and nuclear translocation of p65; and suppress NF-κB-dependent reporter gene expression. Curcumin and resveratrol in particular have been extensively studied in both pre-clinical and clinical settings for their anti-inflammatory and anti-cancer properties, which are mediated through a down-modulation of NF-κB activation [51,57,58]. Because it is one of the most thoroughly studied transcription factors, compounds that inhibit NF-κB, especially those derived from dietary agents, hold great promise in the treatment and prevention of cancer.

Ap-1

AP-1 was first identified as a transcriptional factor that binds to an essential *cis*-element of the human metallothionein lla promoter [59]. The activation of AP-1 is stimulated by a plethora of physiological stimuli and environmental factors, including redox status. AP-1 is considered to be one of the key players in tumourigenesis given its role in a wide range of cellular processes, including inflammation, cell proliferation, death, survival and differentiation. AP-1 exists as dimeric combinations of basic leucine zipper proteins from the Jun, Fos, Maf and ATF sub-families, which recognize either 12-*O*-tetradecanoylphorbol-13-acetate (TPA, also called PMA) response elements (TREs) or cAMP response elements [60].

AP-1 is also involved in inflammatory processes by regulating cytokine production, thus participating in the development of chronic inflammatory diseases such as inflammatory bowel disease, chronic obstructive pulmonary disease, rheumatoid arthritis, psoriasis and cancer. Indeed, this transcription factor has a critical role in the osteoclastogenesis activated by RANKL, thereby promoting bone resorption [61,62]. The role of AP-1 in tumour promotion was first discovered by Bernstein and Colburn [63]. They reported that transformation-resistant JB6 cells failed to activate AP-1 in response to tumour promoters such as TPA and EGF, whereas the AP-1 response was intact in transformation-sensitive JB6 cells. The requirement for AP-1 activation during tumour promotion in JB6 cells was later demonstrated by Brown et al. [64] by using a transactivation minus mutant of c-Jun (TAM67). Elevated AP-1 activity has been detected in a variety of cancers and tumour cell lines, suggesting a role for AP-1 in tumour progression [65]. Thus, AP-1 is a good target for both prevention and treatment for cancer.

Naturally occurring compounds such as curcumin, resveratrol, genistein, [6]-gingerol, capsaicin, epigal-locatechin gallate (EGCG), cyanidin-3-glucoside, nobiletin, 7,8-dihydroxyflavanone, theaflavin-3,3′-digallate, carnosol, silibinin, sulphoraphane, maslinic acid, ganoderic acid, lycopene, bavachin, kaempferol, berberine, momordin and caffeic acid phenethyl ester have been identified as inhibiting the activation of AP-1 [66–81].

Kundu et al. [82] demonstrated suppression by resveratrol of the TPA-stimulated activation of AP-1 in mouse skin *in vivo*. This stillbene, a component of grape and Japanese Knotweed, has also been shown to down-regulate PMA-induced IL-8 production and mRNA accumulation in U937 cells [83]. However, although resveratrol inhibited the PMA-stimulated DNA-binding activity of AP-1, it had little effect on PMA-induced NF-κB activation. These results suggest that suppression of IL-8 by resveratrol was, at least in part, due to the inhibition of AP-1 activation. Pterostilbene, a natural dimethylated analogue of resveratrol, is also known to suppress TPA-induced AP-1 activation, thereby inhibiting tumour invasion in HepG2 cells [84]. Takada et al. [85] found that a semi-synthetic flavone,

flavopiridol, which was initially thought to be a specific inhibitor of cyclin-dependent kinases, abrogated the activation of AP-1 stimulated by TNF or various carcinogens and inflammatory stimuli. As a result, flavopiridol suppressed the expression of various anti-apoptotic proteins such as inhibitor of apoptosis (IAP)-1, IAP-2, X-linked IAP, Bcl-2 and Bcl-xL and tumourigenesis-mediated proteins such as ICAM-1, c-myc and c-Fos.

Curcumin, a polyphenol derived from turmeric, has been shown to inhibit TPA-induced AP-1 activation in HL-60 cells and Raji cells [86,87]. Curcumin treatment has also been shown to abrogate constitutive AP-1 activity in prostate cancer cell lines [88,89]. Inhibition of AP-1 activity by curcumin also correlated with inhibition of Lewis lung carcinoma invasion in an orthotopic mice model [90]. Curcumin has been reported to suppress lipopolysaccharide-induced COX-2 gene expression by inhibiting AP-1 DNA binding in BV2 microglial cells [91]. More recently, Prakobwong et al. [92] showed that suppression of AP-1 activation by curcumin led to the down-modulation of cell proliferative gene products such as cyclin D1 and c-myc in a cholangiocarcinoma hamster model. These results suggest that chemopreventive agents specifically targeting AP-1 or its activating kinases could be promising agents for the treatment of several cancers.

Signal transducer and activator of transcription (STAT)–3

STAT3 is one of the members of a family of STAT transcription factors. It was first identified as a DNA-binding factor that selectively binds to the IL-6-responsive element in the promoter of acute-phase genes from IL-6-stimulated hepatocytes [93]. The binding of growth factors (e.g. EGF and PDGF) or cytokines (e.g. IL-6) to their receptors results in the activation of their receptor tyrosine kinase or of receptor-associated tyrosine kinases that subsequently phosphorylate the cytoplasmic part of the receptor and provide docking sites for monomeric STAT3. Once recruited, STAT3 is phosphorylated on a specific tyrosine 705 residue, allowing its dimerization and translocation to the nucleus [94,95]. Emerging evidence suggests that STAT3 plays a crucial role in the inflammatory microenvironment, both at the initiation of tumourigenesis and during cancer progression [6,96–99]. Rebouissou et al. [100] showed that STAT3 is linked to inflammation-associated tumourigenesis, which is initiated by genetic alterations in tumourous hepatocytes. In addition, elevated STAT3 activity has been detected in a wide variety of cancers, including head and neck, breast, colorectal, ovarian, pancreatic, renal and prostate cell carcinoma; leukaemia; lymphoma; and MM [94].

STAT3 has been reported to interact with NF-κB at several levels. For instance, inflammatory factors regulated by NF-κ B, most notably IL-6, are important STAT3 activators [93,96]. Lee et al. [101] showed that STAT3 directly interacts with NF-κB Rel A and prolongs NF-κB nuclear retention through acetyl-transferase p300-mediated RelA acetylation, interfering with NF-κB nuclear export and thereby contributing to constitutive NF-κB activation in cancer. These two transcription factors, STAT3 and NF-κ B, co-regulate numerous oncogenic and inflammatory genes [102–104], so agents that can sever this alliance are of particular interest for the prevention and treatment of cancer.

Several nutraceuticals have been identified that can suppress STAT3 activation [94,95]. These include curcumin, resveratrol, caffeic acid, capsaicin, curcurbitacin, indirubin, piceatannol, parthenolide, flavopiridol, magnolol, guggulsterone, silibinin, ursolic acid, plumbagin, betulinic acid, γ-T3, butein and EGCG [94,105–108]. The mechanism of suppression of STAT3 varies depending on the compound. For example, guggulsterone, ursolic acid, betulinic acid, γ-T3 and butein transcriptionally up-regulate the expression of protein tyrosine phosphatase, which leads to inactivation of STAT3 [105–108]. By contrast, emodin suppresses IL-6-stimulated activation of Janus-activated kinase 2 and STAT-3; it also triggers the activation of caspases and down-regulation of Mcl-1. Ectopic expression of

Mcl-1 has been shown to reverse emodin-induced apoptosis in human MM cells. This observation indicates that emodin could induce apoptosis in myeloid cells via down-regulation of Mcl-1 [109]. Capsaicin has been reported to induce apoptosis in MM cells by inactivating STAT3 and down-regulating STAT3-regulated gene expression of Bcl-2, Bcl-xL and survivin. In a xenotransplant murine model of human MM, capsaicin has been shown to inhibit the tumour growth correlated with the inhibition of STAT3 [110].

Adult T-cell leukaemia is an aggressive malignancy of peripheral T-cells infected with human T-cell leukaemia virus type 1 (HTLV-1). Deguelin has been shown to induce apoptosis in HTLV-1-transformed T-cells via inhibition of survivin expression and dephosphorylation of STAT3 through the ubiquitin/proteasome pathway [111].

Curcumin has been known to suppress STAT3 activation and induce apoptosis in a wide range of human cancer cell lines, including ovarian [112], pancreatic [113], head and neck [114] and endometrial cancer [112]; melanoma [115]; Hodgkin lymphoma [116]; primary effusion lymphoma [117]; T-cell leukaemia [118]; and MM cells [119]. However, the inhibitory mechanisms of curcumin on STAT3 vary— for example (i) activating Src homology 2 domain-containing protein tyrosine phosphatises-2 [120]; (ii) up-regulating protein inhibitors of activated STAT, which are associated with inhibition of the JAK/STAT pathway; and (iii) decreasing nuclear STAT3 without affecting its phosphorylation [121]. Curcumin has also been tested in patients and was shown to down-regulate STAT3 pathways [119,122,123].

Numerous evidences indicate that resveratrol inhibits STAT3 activation and induces apoptosis in various cancer cell lines [51,124–126]. A report from our group showed that resveratrol was able to inhibit nuclear translocation of STAT3 in $CD138^+$ cells from patients with MM. Recently, Youn et al. [127] reported that oral administration of resveratrol (10 mg/kg body weight) for 7 constitutive days attenuated dextran sulphate sodium-induced inflammatory injury by suppressing inducible nitric oxide synthase expression and inhibiting NF-κB and STAT3 in a colitis mouse model. These results provide a rationale for testing resveratrol in patients with chronic inflammatory diseases, including cancer.

Nuclear factor erythroid 2–related factor (NRF2)

NRF2 is a transcription factor that regulates the expression of ~ 100 cytoprotective genes, including glutathione S-transferases (GSTs), heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), glutamate-cysteine ligase catalytic and modifier sub-units and peroxiredoxin 1, by binding to the DNA regulatory element, antioxidant response element (ARE). A negative regulator of NRF2, Keap1 (a 69-kDa protein), is located in the cytoplasm and is anchored to actin [128]. A site-directed mutagenesis study of Keap1 demonstrated that NRF2 is normally located in the cytoplasm by Keap1. Once NRF2 dissociates from Keap1, it translocates to the nucleus, heterodimerizes with small Maf and binds to ARE, resulting in responsive gene expression [129]. NRF2 also plays a major role as a central regulator of the adaptive response to oxidative stress, given that *nrf2*$^{-/-}$ mice have been shown to be sensitive to diverse oxidative stress conditions. When exposed to xenobiotics or chemicals that generate intracellular oxidative stress, *nrf2*$^{-/-}$ mice display increased tissue damage and prolonged inflammation; high amounts of DNA, lipid and protein oxidation; and increased incidence of cancer [130–132]. Numerous compounds that activate NRF2 are considered to be promising chemopreventive agents and some of these are now undergoing human trials of cancer chemoprevention. NRF2-activating substances include synthetic compounds (e.g. oltipraz), related dithiolthiones and novel triterpenoids, as well as natural products such as curcumin and sulphoraphane. The remarkable chemopreventive effects of these compounds are being tested in *nrf2*-knockout mouse models and gene deletion of

NRF2 reversed the chemopreventive effects of these agents, indicating that their anti-cancer activities are mediated by the induction of NRF2 [133–136].

Among the natural compounds that exhibit chemopreventive activity through activation of NRF2, sulphur-containing and phenolic dietary phytochemicals have attracted a lot of attention. Sulphur-containing compounds, such as isothiocyanates (i.e. sulphoraphane, phenethyl isothiocyanate and allylisothiocyanate) and dithiolethiones, which are derived from cruciferous vegetables—including broccoli, watercress, Brussels sprouts, cabbage and cauliflower—have been extensively studied for their chemopreventive properties via evoking NRF2 [137]. The diallyl sulphides (i.e. diallyl sulphide, diallyl disulphide and diallyl trisulphide) are another class of potential chemopreventive agents that are found in the *Allium* family, including garlic, onion and chive. A study by Chen et al. [138] indicated the positive action of these diallyl sulphides on ARE-mediated gene expression and expression of NRF2, NQO1 and HO-1 proteins.

Phenolic compounds include various flavonoids, such as quercetin, rutin, genistein, tea polyphenols such as (–)-epigallocatechin and EGCG, black tea polyphenols and curcumin that can modulate the NRF2 signalling pathway [139]. Curcumin and CAPE disrupt the NRF2-Keap1 complex and lead to NRF2 binding to ARE [140,141]. Balogun et al. [140] have shown that both compounds stimulate the expression of NRF2, leading to a significant increase in the activity and expression of HO-1. Their findings indicate that p38 mitogen-activated protein kinase, which is upstream of NRF2, is involved in curcumin-induced HO-1 gene induction. In another study, curcumin increased the nuclear translocation of NRF2, ARE-DNA binding activity and glutamate-cysteine ligase expression [142].

Other natural chemopreventive agents that induce the NRF2/ARE pathway include indoles such as I3C and terpenoids. In HepG2 cells, I3C showed a weak induction of NRF2-reporter gene activity and NRF2 protein expression but had no effect on HO-1 protein expression [143]. Krajka-Kuźniak et al. [144] recently found that I3C significantly increased the activity of glutathione S-transferase (GST) and NQO1 in rat liver. This increase was correlated with nuclear translocation of NRF2. Treatment with I3C also significantly increased the activity of NQO1 in rat kidney. Therefore, the chemopreventive activity of I3C may occur through induction of the key detoxifying enzymes.

Among other examples, a mixture of coffee diter-penes, cafestol and kahweol palmitate has been shown to increase the enzymatic activities of NQO and GST in the small intestine of mice by 2-fold [145]. A sesquiterpene parthenolide derived from feverfew has been shown to stimulate ARE reporter-gene activity and to potently induce the expression of NRF2 and HO-1 proteins in HepG2 cells [143]. In addition, zerumbone was found to induce phase II enzymes, including GST-P1, γ-glutamyl cysteine synthetase, glutathione peroxidase and HO-1, through the NRF2 pathway and to reduce lipid peroxidation in hepatocytes [146]. These results suggest that nutraceuticals activating NRF2 may hold promise as a chemotherapeutic drug in the treatment of cancer and other diseases

Peroxisome proliferator-activated receptor (PPAR)–γ

PPARs, members of the nuclear receptor superfamily, are best understood as regulators of the lipid metabolism. There are three forms of PPAR: α, β/δ and γ [147]. These receptors also play an important role in modulation of the immune system through their ability to inhibit the expression of inflammatory cytokines by direct differentiation of immune cells toward anti-inflammatory sites. PPARs are involved in the regulation of cellular differentiation, development, metabolism and tumourigenesis [148]. In addition, they are known to directly down-regulate the expression of pro-inflammatory gene products in a ligand-dependent manner by antagonizing the activity of pro-inflammatory transcription

factors such as NF-κB and AP-1 [149–151]. PPARγ (also known as the glitazone receptor) is one of the nuclear receptor proteins that act as transcription factors and control the expression of different genes. PPARγ is normally present in such diverse systems as adipocytes, skeletal muscle cells, osteoclasts, osteoblasts and several immune-type cells. Interestingly, somaticmutations in PPARγ have been found in sporadic colorectal carcinomas [152]. These findings suggest an important role for PPARγ as a tumour suppressor. However, several murine models have suggested that, under certain circumstances, PPARγ ligands may stimulate cancer formation [153].

The ligands of PPARγ have been shown to exert profound inhibitory effects on the growth and differentiation of human liposarcoma [154]. Indeed, accumulated evidence has indicated an anti-growth and/or pro-differentiation response of PPARγ ligands in a variety of cancer cells, including colon, lung, ovary, breast, thyroid and prostate cells [155]. Targeting of PPARγ is of great potential interest to the food industry, given that several natural dietary constituents act as PPARγ ligands and can activate it, including curcumin, resveratrol [156], 7-chloroarctinone-b [157], deoxyelephantopin [158], macelignan [159] and honokiol [160].

Liang et al. [161] have demonstrated the anti-inflammatory effects of apigenin, chrysin and kaempferol in murine macrophages. These flavonoids transactivate PPARγ as allosteric effectors rather than pure agonists. The flavonoids baicalin [162] and cyanidin [163] are also known to act as antagonists of PPARγ. In addition, capsaicin from hot peppers has been found to induce apoptosis of melanoma as well as colon and prostate cancer cells and, at least in the case of colon cancer, this occurred through the activation of PPARγ [164–166]. However, although capsaicin acts as a PPARγ ligand, its anti-cancer effect is controversial [167,168]. Terpenoids, including glycyrrhetinic acid [169], betulinic acid [170], farnesol, geranylgeraniol [171], auraptene, bixin, norbixin, geraniol and phytol (see [172]), have also been reported to activate PPARγ very efficiently.

Curcumin has been reported to inhibit the proliferation of non-adipocytes through the activation of PPARγ. The level of PPARγ is dramatically decreased along with activation of hepatic stellate cells (HSC). However, curcumin was able to induce the expression of PPARγ and thus inhibit cell proliferation in activated HSCs. In contrast, blocking the trans-activity of PPARγ by its antagonist markedly decreased the effects of curcumin on the inhibition of cell proliferation [173]. Chen and Xu [174] also reported that activation of PPARγ by curcumin in Moser cells inhibited growth and suppressed the gene expression of cyclin D1 and epidermal growth factor receptor (EGFR). Overall, the activation of PPARγ by dietary agents could be one of the mechanisms responsible for their cancer preventive and chemotherapeutic effects.

WNT/β-catenin

The mouse *wnt1* gene (originally called '*Int-1*') was first identified in 1982 by Nusse and Varmus [175] as a preferential integration site for the mouse mammary tumour virus in breast tumours. To date, 19 Wnt ligands have been identified in mammals that are known to activate β-catenin-dependent (canonical) and β-catenin-independent (non-canonical) signalling pathways on binding to the Frizzled-LRP co-receptor complex. Briefly, Wnt ligands bind to their receptors, proteins of the Frizzled family. These bindings result in the inactivation of a complex of cytoplasmic proteins (including adenomatous polyposis coli [APC] and axin) that promote the degradation of β-catenin, leading to cytoplasmic accumulation and nuclear localization. In the nucleus, β-catenin interacts with T-cell factor/lymphoid enhancer factors (TCF/LEF) to regulate the expression of target gene products. Wnt signalling is considered to be one of the fundamental mechanisms directing cell proliferation, cell polarity and cell fate determination during embryonic development and tissue homeostasis [176]. Thus, given the critical and pleiotropic roles of Wnt signalling, it

is not surprising that perturbations/mutations in Wnt signalling have been implicated in a variety of human diseases, including cancer [177].

The nuclear accumulation of β-catenin, a hallmark of activated Wnt signalling, has been clearly observed in cancer cells [178]. Hyperactive β-catenin turns on a genetic programme sufficient to initiate the development of a multitude of different tumour types, primarily those of gastrointestinal origin. Loss-of-function mutations in components of the β-catenin degradation complex have been observed in many human cancers. For instance, >70% of colorectal cancers have been shown to bear mutations in *APC*, such that it fails to degrade β-catenin. Similarly, inactivating mutations in the Axin scaffold protein have been implicated in hepatocellular carcinomas [179].

Several compounds have been reported to regulate the β-catenin/Wnt signalling pathway. Silibinin from milk thistle suppresses the intestinal carcinogenesis in $APC^{min/+}$ mice as well as 1,2-dimethylhydrazine-induced colon cancer in male Wistar rats through inhibition of the β-catenin/wnt signalling pathway [180,181]. Pterostilbene, a natural dimethylated analogue of resveratrol found in blueberry and grapes, also inhibits colorectal aberrant crypt foci and colon carcinogenesis via suppression of multiple pathways, including WNT/β-catenin signalling, in azoxymethane-treated mice [182]. Several flavonoids—such as genistein, kaempferol, isorhamnetin and baicalein—have been shown to inhibit the transcriptional activity of β-catenin in HEK293 cells transiently transfected with a constitutively active mutant β-catenin gene [183]. In addition, a plant flavonoid, fisetin, has been shown to induce apoptosis and suppress the growth of colon cancer cells by inhibiting the COX-2 and Wnt/EGFR/NF-κB signalling pathways [184]. In a study from Tarapore et al. [185], the dietary triterpene lupeol was reported to decrease the transcriptional activity of β-catenin and the expression of Wnt target genes. Interestingly, lupeol inhibited the translocation of β-catenin from the cytoplasm to the nucleus in melanoma cells. Tea has also been reported to modulate β-catenin and its regulated proteins, cyclin D and c-Jun, in polyps in the APC^{min} mice model [186]. Tea polyphenols, including polymeric black tea polyphenol and EGCG, have been shown to be potent inhibitors of the WNT/β-catenin signalling pathway [187,188]. Moreover, EGCG suppresses Wnt signalling by inducing the high mobility group-box transcription factor-1 transcriptional repressor through an increase in HBP1 mRNA stability in invasive breast cancer cells [189]. In addition to these examples, the hydroxylated polymethoxy-flavones shikonin and decursin are also known to suppress β-catenin signalling [190–193].

Curcumin also appears to be an effective inhibitor of the β-catenin/Wnt pathway. A study by Jaiswal et al. [194] demonstrated that curcumin induces apoptosis in colorectal cancer cells. Curcumin treatment was found to induce caspase-3-mediated degradation of cell–cell adhesion proteins, including β-catenin, which was linked with apoptosis, and caspase-3 inhibitor prevented this degradation. Choi et al. [195] reported that curcumin suppressed the level of β-catenin, leading to down-regulation of its regulated gene products, such as cyclin D1 and c-myc, by inhibition of Akt/glycogen synthase kinase-3 β in human prostate cancer cells. Interestingly, curcumin was able to modulate the self-renewal of both normal and malignant breast stem cells [196]. Curcumin inhibited the formation of mammospheres and decreased the population of aldehyde dehydrogenase-positive cells in normal and malignant breast cells by inhibiting Wnt signalling, which further suggests the potential for curcumin as a cancer preventive agent.

Hypoxia inducible factor (HIF)–1

The microenvironment of solid tumours differs from that of normal tissues and is characterized by low levels of pO_2 and low pH that are well below normal [197]. Hypoxia is a common feature of many cancers and it essentially occurs when the growth of the tumour

outstrips the accompanying angiogenesis [198]. A major factor in the hypoxic response is HIF-1 [199], which mediates the adaptive responses to hypoxia by affecting the transcription of numerous hypoxia-inducible genes.

A growing body of evidence suggests that the up-regulation of HIF has a crucial role in the progression of a broad range of human malignancies [200–202]. Accumulation of HIF-1α has been associated with poor survival of patients with a variety of cancers, including cervical cancer, breast cancer, ovarian cancer, endometrial cancer and oropharyngeal squamous cell carcinoma [203]. HIF can directly up-regulate a number of angiogenic factors, including vascular endothelial growth factor (VEGF), VEGF receptors, plasminogen activator inhibitor-1, angiopoietins (ANG-1 and -2), platelet-derived growth factor B, the TIE-2 receptor and MMPs [204]. As a transcription factor, HIF-1 can also induce the expression of gene products encoding the glycolytic enzymes phosphoglycerate kinase-1 and lactate dehydrogenase A, which provide energy for cancer cells under hypoxic conditions [205]. Indeed, HIF-1 has been shown to be a potent inducer of metastatic genes including chemokine receptor 4, its ligands (stromal cell-derived fator-1; SDF-1) and lysyl oxidase in a broad range of tumour cells [206], as well as E-cadherin, a key factor governing metastatic probability in the majority of epithelial cancers [1].

Flavonoids (e.g. quercetin, baicalein, luteolin, fisetin, galangin, (–)-epicatechin-3-gallate, apigenin, vitexin and chrysin), which are derived from various fruits and vegetables, have been reported to inhibit HIF-1α [207]. In addition, some flavonoids (e.g. quercetin, luteolin and kaempferol) have been reported to down-regulate HIF-1α by suppressing nuclear accumulation and thus altering HIF-1 transcriptional activity [208]. Deguelin has been shown to sensitize lung cancer cell lines that are resistant to radiation, rendering them more susceptible to anticancer therapy [209]. This effect is mediated through the inhibition of Hsp90 function and subsequent suppression of the interaction between HIF-1α and Hsp90 and reduction in HIF-1α expression by deguelin in radioresistant cells. Deguelin caused profound inhibition of tumour growth and angiogenesis when combined with radiation *in vivo*. This effect of deguelin on HIF-1α expression is supported by results from another study in which the compound inhibited retinal vascularization [210]. These results indicate that deguelin can be used in combination with other anti-cancer therapy to inhibit neovascularization and enhance the overall effectiveness of therapy.

Resveratrol has been shown to significantly inhibit both basal levels and hypoxia-induced HIF-1α protein accumulation in cancer cells but to not affect HIF-1α mRNA levels. Resveratrol shortened the half-life of HIF-1α protein by enhancing the protein degradation induced by 26S proteasome [211]. Cao et al. [212] also demonstrated the inhibitory effects of resveratrol on the HIF pathway through several mechanisms: (i) inhibition of AKT and mitogen-activated protein kinase activation, which play a partial role in the down-regulation of HIF-1α expression; (ii) inhibition of insulin-like growth factor 1-induced HIF-1α expression by inhibiting protein translational regulators, including M(r) 70 000 ribosomal protein S6 kinase 1, S6 ribosomal protein, eukaryotic initiation factor 4E-binding protein 1 and eukaryotic initiation factor 4E; and (iii) induction of HIF-1α degradation through the proteasome pathway in human ovarian cancer cells.

Similarly, curcumin also exerts an effect on the HIF-1 pathway. This polyphenol has been shown to decrease hypoxia-induced HIF-17alpha; protein levels in HepG2 hepatocellular carcinoma cells. Moreover, curcumin suppressed the transcriptional activity of HIF-1 under hypoxia, leading to a decrease in the expression of VEGF [213]. Choi et al. [214] reported that, of the two HIF-1 sub-units, only ARNT was destabilized by curcumin and that ARNT expression rescued HIF-1 repression by curcumin. They also found that curcumin stimulated the proteasomal degradation of ARNT via oxidation and ubiquitination processes. In mice

bearing Hep3B hepatoma, curcumin retarded tumour growth and suppressed ARNT, erythropoietin and VEGF in tumours [214]. These results suggest that chemopreventive agents specifically targeting HIF-1 expression or degradation could have potential in treatment of cancers.

Hedgehog (Hh)

The Hh signalling pathway was primarily identified in the development of the fruit fly, *Drosophila melanogaster*, as a segment polarity gene required for embryonic patterning [215]. The components of Hh signalling demonstrate high inter-species conservation. The mammalian Hh pathway has three family members, each named after their ligands: Sonic, Indian and Desert [216]. Hh signalling is involved in congenital development and cell growth; however, aberrant Hh signalling has been implicated in up to 25% of all cancers [217]. Dysregulation of the Hh signalling pathway can lead to an assortment of cancer types. Depending on the recipient cell of Hh signalling, a variety of cell-specific transcription factors may interfere with the developmental processes [216], including production of VEGF and ANG-1 and -2, which regulate angiogenesis [218]; cyclin D2, which regulates cell proliferation [219]; up-regulation of anti-apoptotic proteins that mediate cell survival [220]; transcription of SNAIL, which initiates the epithelial-mesenchymal transition in metastasis [221]; cell-cycle regulation; cell fate determination; and stem cell signalling [222]. Based on the importance of the Hh pathway in tumour development, the specific inhibitors that target Hh signalling could provide efficient therapy against a wide range of malignancies.

Hosoya et al. [223] identified zerumbone, isolated from *Zingiber zerumbet*, as an inhibitor of GLI-mediated transcription. In addition, they found that physalins F and B from the native gooseberry (*Physalis minima*) are potent inhibitors of the Hh pathway as well. These compounds also inhibited GLI2-mediated transactivation. By inhibiting the Hh pathway, zerumbone and physalins in turn down-regulated the expression of the anti-apoptotic protein Bcl-2 in human pancreatic PANC-1 cells. Similar results have been obtained in a study by Arai et al. [224] using the pentacyclic triterpenes colubrinic acid and betulinic acid, extracted from the Cambodian jujube (*Zizyphus cambodiana*). The inhibition of GLI-related protein expression with colubrinic or betulinic acid was observed in HaCaT cells with exogenous GLI1 and in human pancreatic cancer cells (PANC1), which express Hh/GLI components aberrantly. The expression of GLI-related proteins PTCH and Bcl-2 were clearly inhibited by both colubrinic and betulinic acid. Therefore, perturbing the Hh pathway may be one of the underlying mechanisms behind the anti-cancer activity of these compounds.

Curcumin is also a potential inhibitor of the Hh pathway. Curcumin induces apoptosis in medulloblastoma cells, presumably by suppressing Shh protein and its downstream targets, GLI1 and PTCH1. This response has been associated with a down-regulation of the anti-apoptotic protein Bcl-2 [225]. These results indicate that dietary agents targeting the Hh/GLI signalling pathway could be good leads for the development of new agents for the treatment of cancer.

Conclusions

Based on the descriptions above, it is clear that inflammation is tightly linked with cancer and that dietary agents can suppress chronic inflammation and thus help prevent and treat cancer.

This evidence regarding dietary nutraceuticals is fascinating and warrants greater attention. The recommendations made by the US National Cancer Institute are that a chemopreventive

agent should be non-toxic to normal and healthy people, should have high efficacy against multiple sites, should be orally bio-available, should have a known mechanism of action, should be easily accessible and should be acceptable to most of the human population. Among the nutraceuticals, curcumin appears to meet most of these requirements. As described above, curcumin can modulate multiple transcription factors and their related cell-signalling pathways known to be involved in prevention and treatment of cancer. Cancer is a disease caused by dysregulation of multiple cell-signalling pathways. Because dietary agents such as curcumin can control several of these pathways, it has enormous potential for cancer prevention. However, use of nutraceuticals as part of cancer prevention or a treatment regimen in the clinic awaits the answer of several unresolved questions, including those about bioavailability and safety as well as the specific anti-cancer molecular targets of these dietary agents. Future studies are needed to accurately characterize these nutraceuticals and gain a better understanding of their molecular mechanisms of action, to determine their *in vivo* bioavailability and efficacy in proper animal models of cancer and to elucidate their safety and efficacy in clinical trials.

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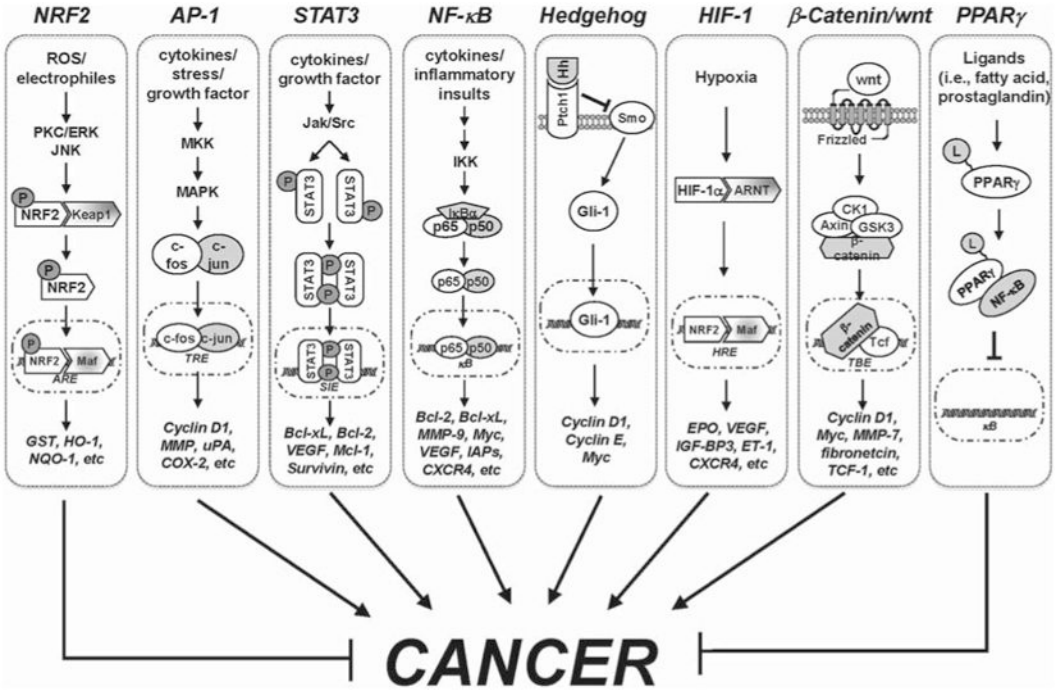

Figure 1.

Molecular mechanism of selected transcription factors in cancer. AP-1, activator protein-1; ARE, antioxidant response element; ARNT, aryl hydrocarbon receptor nuclear translocator; CK1, casein kinase 1; COX-2, cyclooxygenase-2; CXCR4, C-X-C chemokine receptor type 4; EPO, erythropoietin; ERK, extracellular signal-regulated kinases; ET-1, endothelin-1; Gli-1 glioma-associated oncogene homologue 1; GSK3, glycogen synthase kinase 3; GST, glutathione-S-transferase; Hh, hedgehog; HIF-1, hypoxia inducible factor-1; HO-1, heme oxygenase-1; HRE, hypoxia responsive element; IAPs, inhibitor of apoptosis proteins; IGF-BP3, insulin-like growth factor-binding protein 3; IKK, inhibitor of κB (IκB) kinase; Jak, Janus kinase; JNK, c-Jun N-terminal kinases; L, ligands; MAPK, mitogen-activated protein kinase; MKK, MAPK kinases; MMP, matrix metallopeptidase; NF-κB, nuclear factor-κB; NQO-1, NAD(P)H:quinone oxidoreductase; NRF2, NF-E2-related factor-2; P, phosphorylation; PKC, protein kinase C; PPARγ, peroxisome proliferator-activated receptor; Ptch1, protein patched homologue 1; ROS, reactive oxygen species; Smo, smoothened; STAT3, signal transducer and activator of transcription 3; TBE, Tcf/β-catenin binding element; Tcf, T-cell factor; TRE, 12-O-tetradecanoylphorbol-13-acetate (TPA)-responsive element; uPA, urinary plasminogen activator; VEGF, vascular endothelial growth factor.