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A Multi-targeted Approach to Suppress Tumor-Promoting Inflammation

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Conflict of Interest Statement

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Abstract

Cancers harbor significant genetic heterogeneity and patterns of relapse following many therapies are due to evolved resistance to treatment. While efforts have been made to combine targeted therapies, significant levels of toxicity have stymied efforts to effectively treat cancer with multi-drug combinations using currently approved therapeutics. We discuss the relationship between tumor-promoting inflammation and cancer as part of a larger effort to develop a broad-spectrum therapeutic approach aimed at a wide range of targets to address this heterogeneity. Specifically, macrophage migration inhibitory factor, cyclooxygenase-2, transcription factor nuclear factor-kappaB, tumor necrosis factor alpha, inducible nitric oxide synthase, protein kinase B, and CXC chemokines are reviewed as important antiinflammatory targets while curcumin, resveratrol, epigallocatechin gallate, genistein, lycopene, and anthocyanins are reviewed as low-cost, low toxicity means by which these targets might all be reached simultaneously. Future translational

work will need to assess the resulting synergies of rationally designed antiinflammatory mixtures (employing low-toxicity constituents), and then combine this with similar approaches targeting the most important pathways across the range of cancer hallmark phenotypes.

Keywords

cancer; tumor; inflammation; hallmarks; phytochemicals

Introduction

In 1863, Rudolf Virchow first proposed the role of inflammation in cancer, after observing the presence of leukocytes in neoplastic tissue [1]. Since Virchow's initial observation that inflammation and cancer are linked, empirical evidence has underscored inflammation as both a cause and consequence of cancer [2, 3]. The inflammatory milieu promotes a cellular microenvironment that favors the expansion of genomic aberrations and the initiation of carcinogenesis [4]. While acute inflammation is predominantly considered to be a self-limiting process and an important component of the immune system with therapeutic significance, inadequate or incomplete resolution of inflammatory responses frequently leads to various chronic diseases, including cancer [5, 6]. In fact, numerous epidemiological and clinical studies have indicated that chronic unresolved inflammation promotes and exacerbates malignancy [7]. Several types of cancer arise in the setting of chronic inflammation suggesting a strong link between inflammation and cancer [3, 8].

It has been estimated that about 25% of all cancers are etiologically linked to chronic inflammation and infection [9]. For example, the risk of colorectal cancer has been found to be 10-fold higher in inflammatory bowel disease, such as ulcerative colitis and Crohn's disease [10]. The risk for cancer of the respiratory system is positively associated with the severity and duration of inflammatory diseases [11]. Possible associations have also been found between inflammatory diseases, such as esophagitis and Barrett's metaplasia, and esophageal cancer [12] and between chronic pancreatitis and pancreatic cancer [13]. Emerging studies have established a crucial role of chronic, unresolved inflammation in the promotion and progression of breast cancer, including the most aggressive type known as inflammatory breast cancer [14, 15]. The ovarian epithelial inflammation is linked to ovarian cancer [16]. Likewise, foreskin inflammation (phimosis) has been associated with penile cancer [17]. *Helicobacter pylori* (*H. pylori*) infection and associated inflammation in the gastrointestinal tract represent the leading cause of adenocarcinoma [12]. Hepatic inflammation, due to exposure to infectious agents including hepatitis B virus and hepatitis C virus as well as toxic compounds, represent an early step in the development of hepatocellular carcinoma [18]. Moreover, chronic prostatitis, due to persistent bacterial infection or noninfective stimuli, has been linked to prostate cancer [19]. All of this evidence supports an association between chronic inflammation and cancer development.

Chronic inflammation is linked to various phases implicated in tumorigenesis, such as cellular proliferation, transformation, apoptosis evasion, survival, invasion, angiogenesis and metastasis [7, 8, 20]. A number of proinflammatory molecules within the tumor

microenvironment participate in a complex signaling network that enables extravasations of tumor cells through the stroma, resulting in promotion of tumor progression [21]. Inflammation is known to contribute to the process of carcinogenesis mediated through the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) capable of damaging the DNA at the site of the tumor [22]. Free radicals and aldehydes, produced during chronic inflammation, can induce deleterious gene mutation and posttranslational modifications of key cancer-related proteins [23]. Damage can also occur in tissues that are distant from the tumor [24].

Other procarcinogenic products of inflammation include cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6), as well as chemokines, prostaglandins, oncogenes, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), 5-lipoxygenase, matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), nuclear factor-κB (NF-κB), nuclear factor of activated T-cells, signal transducers and activators of transcription 3 (STAT3), activator protein-1 (AP-1), cAMP response binding protein/p300 (CBP/p300), and CCAAT enhancer binding protein (C/EBP) [25–28]. Additionally, activation of various upstream kinases, including IκB kinase (IKK), protein kinase C (PKC), mitogen-activated protein kinase (MAPK), and phosphoinositide-3 kinase/Protein kinase B (PI3K)/AKT, are known to participate in inflammation-driven oncogenesis [28]. The pro-cancerous outcome of chronic inflammation is increased DNA damage, increased DNA synthesis, cellular proliferation, the disruption of DNA repair pathways and cellular milieu, the inhibition of apoptosis, the promotion of angiogenesis and invasion.

As well, chronic inflammation has an influence on immune system constituents that are directly linked with cancer progression. Under normal conditions, immune cells, including macrophages, granulocytes, mast cells, dendritic cells (DCs), innate lymphocytes, and natural killer (NK) cells serve as the front line of defense against pathogens. When tissue disruption occurs, macrophages and mast cells secrete matrix-remodeling proteins, cytokines and chemokines, which activate local stromal cells (fibroblasts, adipocytes, vascular cells and others) to recruit circulating leukocytes into damaged tissue (acute inflammation), to eliminate the pathogens [29]. However, when these processes are initiated in the tumor microenvironment, they are not resolved which leads to chronic inflammation of the “damaged” (tumor) tissue. Thus, while acute inflammation normally supports and balances two opposing needs for the repair of damaged tissues (apoptosis and wound healing), chronic inflammation represents a loss of this balance and the resulting confluence of factors has deleterious implications for the immune system [30].

For example, chronic inflammation is directly associated with immunosuppression mediated primarily by immature myeloid-derived suppressor cells (MDSCs) [31]. Several factors induce MDSC differentiation arrest thus suppressing the host's innate and adaptive immune systems, which are essential for effective antitumor responses [31]. For example, chronically activated leukocytes supply mitogenic growth factors that stimulate proliferation of cancer and stromal cells [29, 32]. Similarly, cluster of differentiation (CD)4+ T helper cells (e.g., subsets T_H1, 2, 9, 10, 17, and 22) are key regulators of inflammation in cancer, and these cells secrete cytokines which are needed in immune responses [33] and contribute to

tumorigenesis in a variety of ways, depending on context [29]. Indeed, the many effects that these chronically activated immune system constituents have on neoplastic progression have been the subject of intense interest by cancer researchers [3, 34, 35]

Our intent here is not to elaborate on these details, but rather to discuss the relationship between tumor-promoting inflammation and cancer as part of a larger effort to develop a broad-spectrum therapeutic approach aimed at a wide range of therapeutic targets relevant for cancer biology. A nonprofit organization, entitled Getting to Know Cancer launched an initiative called “The Halifax Project” in 2011 with the aim of producing a series of overarching reviews in each of the areas that are widely considered to be cancer hallmarks [36]. The basis of this novel approach is premised on many of the insights of genomic sequencing in cancers. Cancers harbor significant genetic heterogeneity [37], and patterns of relapse following many therapies are due to evolved resistance to treatment. While efforts have been made to combine targeted therapies, a lack of success, rising drug costs and significant levels of toxicity have stymied efforts to effectively treat cancer with multi-drug combinations using currently approved therapeutics [38]. Consequently, this approach aims to target many disease-specific pathways simultaneously - using low-cost chemistry with little to no toxicity - to address this heterogeneity (in contrast to the limited number of actionable targets that have become the norm in combination chemotherapy).

To accomplish this task, the concept of the hallmarks of cancer [36] was used as a broad organizing framework and tumor–promoting inflammation was one of the areas of focus. We were specifically tasked to assess the many target choices that exist for inflammation related to cancer, and identify up to ten important targets as well as prospective non-toxic approaches that could potentially be combined to produce a low-toxicity approach to the suppression of tumor-promoting inflammation. In theory, inclusive investigation towards inflammatory associated carcinogenic pathways and associated therapeutics would also be combined with similar approaches being recommended for the other hallmark areas under review in this special issue. To that end, a list of seven important therapeutic targets was identified by this team along with seven corresponding approaches (i.e., approaches that have been shown to have potential to reach those targets) to support this objective. In addition to looking at the traditional pathways associated with the chosen approaches, we also review the known impact of these approaches on microRNA, a relatively new area of intense interest in cancer research. The following is a description of those targets and approaches.

Therapeutic Targets

The following therapeutic targets are reviewed in relation to inflammation: macrophage migration inhibitory factor (MIF), COX-2, NF-κB, tumor necrosis factor alpha (TNF-α), iNOS, AKT and CXC chemokines.

Macrophage migration inhibitory factor (MIF)

The hypothalamic–pituitary–adrenal (HPA) axis (also known as the stress-axis) sits at the apex of the human inflammatory response. Daily fluctuations of bodily inflammation are managed and regulated in a diurnal pattern [39] by the release of cortisol from the adrenal

gland. The hypothalamus is comprised of a diverse group of nuclei at the base of the brain which integrates information from a range of stimuli (e.g., circulating hormone levels in the blood) and generates appropriate responses based on ambient conditions. In the HPA-axis, the secretory neurons within the hypothalamus secrete corticotrophin-releasing hormone (CRH), which in turn stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which subsequently acts on the adrenal cortex to promote cortisol release [40]. A negative feedback loop completes the HPA circuit resulting in cortisol suppressing the production of CRH and ACTH through feedback to both the hypothalamus and pituitary [40]. The stress-axis is therefore widely recognized for its role in the stress response, but *adrenal cortisol* is also a vitally important steroid hormone that plays a critical role in the ongoing modulation of the inflammatory and immune responses. Specifically, cortisol achieves this mediation of the inflammatory cascade, in part, by acting on the master immune/inflammatory cytokine MIF.

MIF is released from macrophages and T lymphocytes that have been stimulated by glucocorticoids, and is a potent proinflammatory cytokine that binds to the CD74 molecule on immune cells in an acute immune response, which provides the coupling between the HPA-axis and inflammation [41, 42]. In general, the HPA-axis is able to regulate inflammation with low concentrations of cortisol which induce MIF [41], and higher levels of cortisol which result in decreases in MIF secretions [42]. As proinflammatory cytokine, MIF overcomes the inhibitory effects of glucocorticoids on TNF-α, IL-1β, IL-6, and IL-8 production [43].

In cancer, MIF is frequently elevated [44] and it has been widely implicated in tumor growth and progression. Specifically, the effects of MIF extends to multiple processes fundamental to tumorigenesis such as proliferation, tumor suppressor downregulation, evasion of apoptosis, angiogenesis, and tissue invasion [45, 46]. MIF signaling is involved in COX-2 and PGE2 upregulation, the activation of the extracellular-signal-regulated kinases (ERK)-1/2 and AKT pathways, and the regulation of c-Jun activation domain-binding protein-1 (JAB1), p53, Skp1–Cul1–F-box-protein (SCF) ubiquitin ligases and HIF-1, which are central to growth regulation, apoptosis and cell cycle control [45, 47, 48]. MIF also upregulates TNF-α [49] which is believed to occur via an amplifying proinflammatory loop [50]. In chronic lymphocytic leukemia (CLL) cells, the binding of MIF to CD74 induces NF-κB activation [51]. MIF contributes to the immune escape of malignant gliomas by counteracting NK and cytotoxic T-cell-mediated tumor immune surveillance [52].

Anti-MIF therapeutics are therefore believed to have considerable promise for many types of cancer [53–57], Indeed several MIF-inactivating strategies have proven successful in delaying cancer growth, including ISO-66, a synthetic MIF inhibitor which caused a significant decrease in tumor burden when administered to mice with established syngeneic melanoma or colon cancer [58]. Recently human anti-MIF antibodies have been tested for their ability to influence growth rate and invasion of the human PC3 prostate cancer cell line *in vitro*, and in a PC3-xenograft mouse model *in vivo*. Treatment with human anti-MIF antibodies suppressed xenograft tumor growth in a dose-dependent manner [53].

However, it should be noted that MIF may also be crucial for controlling infection. In a Ugandan cohort, genetic low expressers of MIF were 2.4-times more frequently identified among patients with Mycobacterium tuberculosis (TB) bacteremia compared to those without. While MIF-deficient mice have been shown to succumb to infection more quickly (with higher organism burden and decreased innate cytokine production) and MIF-deficient macrophages show a decrease in cytokine production and impaired mycobacterial killing. So MIF is a crucial upstream mediator in the innate immune response to mycobacteria [59], and an increased risk of infection could be a concern in any therapeutic approach aimed a suppressing MIF.

COX-2

The arachidonic acid (AA) cascade (see Figure 1) plays a vital role in mediating either the suppression or induction of the inflammatory response [60]. COX-1 and COX-2 are the primary regulatory enzymes responsible for the translation of AA into the several prostanoids, lipid mediators involved in many biological functions [61]. While COX-1 is a constitutive enzyme responsible for several house-keeping functions, the inducible form, COX-2, is responsible for various inflammatory events. COX-2 is readily available to perform both oxygenation and reduction of AA [62]. COX-1/COX-2, also known as prostaglandin (PG) H synthase, transforms AA into PGG2, which is then reduced further by PGH synthase to form PGH2 [61]. PGH2 then further metabolizes via PG synthases into PGE2, PGD2, PGI2, PGF2α, and TXA2, which are then paired with distinctive G protein-coupled receptors [61, 63]. The proinflammatory messenger prostaglandin E2 (PGE2) has further been linked to carcinogenesis [64]. PGE2 is an agonist towards prostaglandin E receptors, which are divided into four subtypes, EP1–4 [63, 64]. The binding of PGE2 to four PGE receptors along with heterotrimeric GTP-binding proteins, results in the activation of adenylyl cyclase, stimulated via EP2 and EP4 binding, or phospholipase C, stimulated via EP1 and EP3 binding [65]. This stimulation of the PGE receptors thus results in the formation of cyclic AMP (cAMP) or the mobilization of intracellular calcium [65]. PGE2 has noted tumorigenic properties and contributes to carcinogenesis by promoting insensitivity to antigrowth signals, evasion of apoptosis, sustained angiogenesis, and tissue invasion/metastasis [61].

Elevated levels of COX-2 have been associated with both carcinogenesis and cancer progression [66]. Overexpression of COX-2 has been associated with carcinogenesis in animal models, and in several human cancers [67–71]. In human UV-induced skin carcinogenesis, elevation of COX-2 activity is associated with the activation of proinflammatory transcription factors (NF-κB, AP-1, STAT3 and others) [72]. COX-2 is transcriptionally regulated and its promoter is activated by multiple transcription factors, either alone or in combination [73–75]. This leads to breast, gastrointestinal, hematological prostate and oral cancers [68–78]. COX-2 induces carcinogenesis through the aromatase pathway, particularly in estrogen positive breast cancers, and through the COX/lipoxygenase (LOX) pathway in estrogen-independent breast tumors [78]. Recently, elevated activity of COX-2 has been found to be correlated with chemoresistance through altered redox induced EGFR-mediated activation of the cell survival cascade (AKT/c-FLIP/COX-2), which results in diminished drug-induced apoptosis [79].

The indirect role of the COX-2/PGE2 pathway in regulating the tumor immune microenvironment has also been suggested through IL-17 promoting M2 macrophage differentiation [80]. The interplay between cancer and stroma via COX-2 and indoleamine 2,3-dioxygenase (IDO) promotes tumor progression and predicts poor patient survival [81]. COX-2 is also known to promote the development of MDSCs which directly suppress T cell immune responses. Indeed MDSCs accumulate in the blood, lymphoid organs, spleens and tumor tissues of cancer patients [82] and serve as critical mediators of tumor-associated immune suppression [83], but recently it was shown that a COX-2 blockade inhibited accumulation and function of MDSCs and restored T-cell response after traumatic stress [84]. So COX-2 inhibition may also prove to be an attractive target for counteracting MDSC-mediated immune suppression in cancer [83]. However, it should be noted that chronic inhibition of Cox-2 activity or expression, is noted to blunt the ability of B cells to produce antiviral antibodies, thereby possibly increasing susceptibility to viral infection [85], which has relevance for numerous cancers that are virus-related.

COX-2 expression and its activity are inhibited by small molecular inhibitors both synthetic and natural such as NSAIDS, capsaicin and curcumin [86, 87]. Recently, melatonin has also been found to enhance the antitumor effect of fisetin by inhibiting COX-2/iNOS and NF-κB/p300 signaling pathways [88]. However, clinically, the most effective way to inhibit COX-2 is with selective pharmacological inhibitors, notably rofecoxib, valdecoxib and celecoxib. Several clinical trials of COX-2 inhibitors, including rofecoxib and celecoxib were performed and their clinical usage was recommended for prevention of colorectal cancers. These studies showed unequivocally that up to 50% reduction in colonic polyps was achieved by daily use of 800 mg COX-2 inhibitors in patients with familial adenomatous polyposis [89]. However, this is not currently practiced due to the subsequent findings of severe cardiovascular risk associated with COX-2 inhibitors in a small patient subpopulation (resulting in the withdrawal of rofecoxib and valdecoxib in 2004 and 2005, respectively).

The search for more specific inhibitors of COX-2 for long-term preventative use has not been very successful, other than the classic NSAID, aspirin in lower dose. Long-term use of natural COX inhibitors, such as curcumin and capsaicin has significant potential, at least for the prevention of gastrointestinal tumors [90–93]. The low bioavailability of these natural compounds by oral administration is a challenge that has limited their use in other solid tumors.

NF-κB

NF-κB transcription factors are evolutionarily conserved, coordinating regulators of immune and inflammatory responses that play a pivotal role in oncogenesis [94]. NF-κB belongs to a class of transcription factor family designated as p65 (RelA), RelB, c-Rel, NF- κB1 and NF-κB2. NF- κB1 and NF-κB2 are synthesized as pro-forms, p105 and p100, which are proteolytically processed to active p50 and p52 respectively [95, 96].

All NF-κB family members form mono- or heterodimers and share common structural features including a Rel homology domain, which is essential for dimerization and binding to cognate DNA elements [97]. These dimers bind to inhibitory protein Iκ*B* family of proteins (inhibitors of NF-κ*B*) preventing their binding to DNA domains and localizing

them to the cytoplasm in most quiescent cells [98]. Furthermore, the complexity of this transcriptional regulation system is also amplified by the fact that different NF-κB dimers have differential preferences for variations of the DNA-binding sequence [99]. Therefore distinct NF-κB dimers induce different target genes. Low frequency shuttling between nucleus and cytoplasm is observed which might be the basis for low basal transcriptional activity of NF-κ*B* and indicative of rapid NF-κB /IκB association and re-association events.

NF-κB proteins are activated by phosphorylation and polyubiquitination of Iκ*B* and subsequent proteasomal degradation. Iκ*B* phosphorylation is catalyzed by an enzyme complex containing IκB kinases (IKK1/IKKα and IKK2/IKKβ)) and at least one non-catalytic accessory protein (NF-κB essential modulator, NEMO, also called IKKγ) [100, 101]. Furthermore, p105 and p100 are cleaved to active p50 and p52 forms respectively by targeted polyubiquitination and proteasomal degradation [102]. IκB and IKK complex bind to other components and interact with other upstream kinases [103]. NF-κB inducing kinase (NIK) phosphorylates and activates IKK1, mitogen-activated protein kinase kinase kinase 1 (MEKK1), MEKK2, MEKK3 and transforming growth factor beta (TGF-β) activating kinase 1 (TAK1) [104–106].

NF-κB is activated by canonical and non-canonical activation pathways. In the canonical activation pathway, ligands interact and activate toll-like receptors (TLRs), the IL-1 receptor (IL-1R), tumor necrosis factor receptor (TNFR) and antigen receptors. TNF-α, lipopolysaccharide (LPS) and IL-1-β are typical stimulating molecules [107, 108]. Alternatively, the non-canonical pathway originates from different classes of receptors including B-cell activation factor, lymphotoxin β-receptor (LTβR), CD40, receptor activator for NF-κB (RANK), TNFR2 and fn14 [109]. These receptors stimulate NF-κB by activation of the kinase NIK and phosphorylation of IKK1. IKK1 subsequently results in phosphorylation, ubiquitination and partial degradation of p100 to p50 [110]. Therefore, the non-canonical activation of NF-κB is independent of the activity of IKK2 and NEMO [111].

Upon activation, NF-κB dimers move to the nucleus and their Rel homology domains are free to bind cognate DNA-sequences in the enhancer elements of target gene promoters. Thousands of different target genes can be transcriptionally activated. Recent reports point to the role of NF-κB in inflammation and induction of cancer. Physical, physiological and/or oxidative stress results in activation of innate immunological processes leading to inflammation which is associated with canonical activation of the NF-κB signaling pathway [112]. NF-κB has a dual effect on inflammation. On one hand, the activation of NF-κB, as part of the acute immune response, activates cytotoxic immune cells against cancer cells [113]. However, the activation of NF-κB also results in up-regulation of antiapoptotic genes and the induced expression of other proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6, and IL-8) and adhesion molecules which leads to the recruitment of leukocytes to the site of inflammation [114]. Both, STAT3 and HIF1 pathways are interconnected with NF-κB signaling and interact with NF-κB. For example, the proinflammatory cytokine IL-6, encoded by NF-κB target genes, is important for STAT3 activation. STAT3 and NF-κB also co-regulate numerous oncogenic and inflammatory genes [115]. These observations suggest that NF-κB and STAT3 alone or in combination induce inflammation and an inflammatory microenvironment.

NF-κB activation is also involved in growth regulation [116], and contributes to tumor progression by controlling vascularization of tumors via upregulation of VEGF and its receptors [117, 118]. The activation of NF-κB also causes an increase in the expression of the transcription factor Snail, which is essential in the TNF-α-induction of the epithelial-mesenchymal transition (EMT) [119], which enables cancer progression and metastasis.

NF-κB-induced transcriptional regulation of HIF-1α is mediated by the recruitment of the NF-κB complex to the HIF-1α promoter [120]. Chronic expression of the proinflammatory protein tissue transglutaminase (TG2) reprograms the transcription regulatory network in epithelial cells via constitutive activation of NF-κB. TG2-induced NF-κB binds the functional NF-κB binding site in HIF-1α promoter and results in its increased expression at transcription and protein levels even under normoxic conditions. Like NF-κB, HIF-1α is also considered a negative prognostic factor because of its ability to promote chemoresistance, angiogenesis, invasiveness, metastasis, resistance to cell death, altered metabolism, and genomic instability [121]. So aberrant activation of NF-κB and its downstream events (HIF-1α, Snail, Twist, and Zeb expression) can induce EMT, stem cell-ness, and endow cancer cells with the ability to disseminate, survive in stressful environments, and regrow at metastatic sites, making NF-κB a very important target.

However, under normal conditions, NF-κB plays an important role in the maintenance of host defense responses so it may not be practical to inhibit NF-κB on a sustained basis. For example, in studies on mice, a prolonged inhibition of NF-κB activity resulted in animals that were more susceptible to bacterial infection [122]. So short-term treatment with specific bioactive inhibitors of IKK activity might be a preferred means to reduce systemic toxicity and avoid broad suppression of innate immunity. Ideally, an IKK/ NF-κB molecular-targeted inhibitor would prevent NF-κB activation without any effects on other signaling pathways, and be differentially active in tumor cells versus in normal cells. But one major shortcoming that will need to be addressed before targeted anti-IKK or NF-κB therapies become successful is the surprising but pronounced ability of NF-κB activation inhibitors to enhance the production of IL-1β and related cytokines (due to excessive inflammasome activation) during bacterial infections [123]. So any strategy that inhibits NF-κB will need to be carefully monitored for immune-related side-effects.

TNF-α

TNF-α is a key proinflammatory cytokine, secreted by inflammatory cells, which is involved in inflammation-associated carcinogenesis. It was named TNF-α because it can induce tumor regression through the induction of cell death [124]. TNF-α is involved in inflammation and immunity, but also in a multitude of biological processes including apoptosis, cell survival, angiogenesis and tumor cell migration and invasion [125].

TNF-α acts primarily via two receptors TNFR1 and TNFR2 [126]. TNF-α is a 17 kDa protein consisting of 157 amino acids that is a homotrimer in solution, and it is primarily produced in macrophages, T lymphocytes, and NK cells. However lower expression levels have been reported in other cells including fibroblasts, smooth muscle cells, and tumor cells. Although TNF-α binds TNFR2 five times higher than TNFR1, TNFR1 initiates the majority of the biological activities resulting from TNF-α [127]. TNFR1 (p60) is expressed in all cell

types whereas TNFR2 (p80) is expressed mainly in immune cells [128]. Only TNFR1 contains the death domain (DD) (i.e., TNFR2 does not contain the DD) making it an important member of the death receptor family that is capable of inducing apoptotic cell death [129].

Aside from death inducing activity, TNFR1 also has the ability to transduce cell survival signals. Binding to the homotrimer TNF-α, TNFR1 trimerizes the silencer of death domain (SODD) protein that is released [130]. The TNFR-associated domain (TRADD) binds to the DD of TNFR1 and recruits other adaptor proteins including the receptor interacting protein (RIP), TNFR-associated factor 2 (TRAF-2), and Fas-associated death domain (FADD)[131]. These adaptor proteins, in turn, are responsible for downstream cellular signaling. Apoptotic signaling mediated by TNFR1 results in FADD binding to caspase 8 and its activation. The chain of events leads to proteolytic activation of caspase enzymes and involves the mitochondrial cytochrome c release [132], which leads to the activation of endonucleases and DNA fragmentation.

Alternatively, TNFR1 may signal survival processes by recruiting TRAF-2 to the complex. TRAF-2 inhibits apoptosis by association with the cytoplasmic inhibitor of the apoptosis protein (cIAP). Once TRAF-2 associates with TNFR1, cell survival pathways are initiated through a series of phosphorylation steps resulting to the activation of cFOS/cJun transcription factors by MAPK and cJun N-terminal kinase (JNK) [133, 134]. Activation of TRAF-2 and RIP is associated with activation of the NF-κB transcription factor via a complex of NF-κB-inducing kinase (NIK) and an inhibitor, κ*B* kinase (IKK) [135]. The activation of cFos/cJun and NF-κB transcription factors mediates the transcription of anti-apoptotic, proliferative immunoregulatory, and inflammatory genes. NF-κB is the main survival transcription factor that prevents TNF-α-induced apoptosis, so NF-κB inhibition may be an efficient strategy for apoptosis-inducing cancer therapy [135–137].

Inhibition of NF-κB is known to sensitize cancer cells to TNF-α treatment [138, 139]. Furthermore, it has been shown that NF-κB-induced expression of iNOS increases cancer cell survival [140, 141]. Inhibition of NOS can potentially sensitize cancer cells to TNF-α treatment. ROS are generated by TNF-α-mediated apoptotic events, while NF-κB induces expression of ROS-neutralizing enzymes like superoxide dismutase [142]. Recent data also show that the mRNA-decay protein tristetraprolin (TTP) interacts with TNFR1 in a TRAF2-mediated fashion initiating cJun-kinase activation. Inhibition of TTP ubiquitination results in enhanced TNF-induced apoptosis in cervical cancer cells [143].

The role of TNF-α in carcinogenesis is controversial. While high concentrations of this cytokine display antitumoral response in murine model of sarcoma [144], low sustained TNF-α levels can induce a tumor phenotype [145]. The TNF-α tumor promoting mechanism is based on ROS and RNS which can induce DNA damage and facilitate tumorigenesis [146–148]. TNF-α-mediated inflammation has been linked to cancer; for instance, a recent report shows that *H. pylori* strains produce TNF-α-inducing protein (Tip-α), a carcinogenic factor in gastric epithelium. *H. pylori* isolated from gastric cancer patients secreted large amount of Tip-α, which is incorporated into gastric cancer cells by cell surface nucleolin, a Tip-α receptor. The nucleolin-Tip-α binding induces TNF-α and other cytokine genes

expression and results in NF-κB activation. Similarly, TNF-α through TNFR1, Noxo1, and Gna14 signaling leads to *H. pylori*-mediated gastric tumorigenesis [149]. These events are also associated with epithelial to mesenchymal transition (EMT) in human gastric carcinogenesis [150].

Direct evidence also points to the role of TNF-α in the metastatic cascade. Administration of TNF-α leads to significant increase of the number of lung metastases [151]. Conversely, tumor cells activate myeloid cells to generate a microenvironment favorable for metastasis. In Lewis lung carcinoma (LLC) cells-conditioned-medium, high levels of IL-6 and TNF-α were induced in bone marrow-derived macrophages [152], and TNF-$\alpha^{-/-}$ but not IL-$6^{-/-}$ mice injected with LLC cells showed improved survival and reduced lung tumor multiplicity, suggesting a critical role of TNF-α in LLC metastasis [152]. Others report that TNF-α-deficient mice are resistant to tetradecanoyl-phorbol-13-acetate-(TPA) induced skin carcinogenesis [153]. The role of TNF-α in angiogenesis was also studied recently, and Fajardo *et al* [154] showed that high TNF-α doses inhibited angiogenesis in mice subcutaneously implanted with angiogenesis disc-system, an experimental strategy used to induce new blood vessels, while low loses promoted vascularization of the area. The antiangiogenic action of TNF-α is related to downregulation of $\alpha v\beta 3$ and the angiotensin signaling pathway [155], while proangiogenic responses have been associated with increased VEGF, VEFGR, IL-8, and FGF expression [156]. Furthermore, low TNF-α increases tumor growth and induces angiogenesis of diverse tumors in mice [157, 158].

The effect of TNF-α in induction of carcinogenesis, angiogenesis and metastasis and invasion has therefore been supported by several studies, so targeting TNF-α and TNFR may be a viable option for treatment of cancer.

Recently several TNF-α targeting drugs have also been used mostly to treat inflammatory diseases. Examples include infliximab, a recombinant IgG1 monoclonal antibody specific for TNF-α [159], Etanercept, a genetically engineered protein comprising two molecules of the extracellular domain of TNFR2 (p75) and the Fc portion of IgG1 [160], adalimumb, a monoclonal antibody of recombinant IgG1 [161], golimumab, a human anti-TNF-α monoclonal antibody [162], and certolizumab, a humanized anti-TNF-α antibody with high affinity to TNF-α [163]. However, major side effects of these anti-TNF-α agents are infection (tuberculosis, varicella, and other opportunistic infections) and malignancies especially when TNF-α antagonists are used concurrently with other therapies [164, 165]. For example, a subset of patients with inflammatory diseases may also have an increased risk of non-Hodgkin's lymphoma (NHL) [166], therefore treating these patients with anti-TNF-α may increase the rate of lymphoma [167–169]. Skin cancer has also been reported as a side effect in some studies involving TNF-α blocking [170, 171].

So, although TNF-α is a cytokine with well-known anticancer properties that has been utilized as an anticancer agent for the treatment of some patients with locally advanced solid tumors [172], its promise as a constituent within a multipronged approach aimed at a broad-spectrum of targets will need to be carefully assessed in light of these divergent outcomes.

iNOS

iNOS has been of interest in cancer since the discovery of its metabolite, nitric oxide (NO) in the 1990´s. Over the years, experimental data highlighted iNOS overexpression as a pivotal event ensuring tumor growth [173]. Indeed, more than 2,000 peer-reviewed publications support the iNOS-NO axis as a potential target in cancer. Under normal physiological conditions, NO is produced by the constitutive forms of NOS (cNOS and eNOS) and modulates pivotal cellular processes, such as vasodilatation, cell survival and growth. However, in chronic inflammatory conditions, the iNOS-NO axis is upregulated, and quickly yields NO-derived species with strong nitrosative properties, especially when other reactive species are also produced (such as the superoxide anion). Once formed, NO-derived species can quickly react with all cellular components, including proteins, lipids and DNA. Therefore, the main carcinogenic effect of NO-derived metabolites is related to their capability to potentiate genomic instability, as induced by the RNS peroxynitrite [174].

Experimental data and *in vitro* studies have supported iNOS as a viable target by demonstrating its overexpression in virtually all types of cancer cells, including glioma [175], hepatoma [176], mastocytoma [177], melanoma [178], B-cell lymphoma [179], neuroblastoma [180], mammary adenocarcinoma [181], and ovarian carcinoma [182], among others. In the same way, iNOS up-regulation has been documented in human cancerous tissues such as glioblastomas [183], brain tumors [184], prostate carcinoma [185], esophageal adenocarcinomas [186], B-cell CLL [187], primary lung cancer [188], transitional cell carcinoma of the bladder [189], pancreatic cancer [190], thyroid papillary carcinomas [191], buccal squamous-cell carcinomas [192], melanoma [193], colon carcinoma [194], gastric cancer [195], breast cancer [196], stomach cancer [197], malignant mesotheliomas and metastatic pleural adenocarcinomas [198], hepatocellular carcinoma [199] and ovarian carcinoma [200]. The enhanced activity and expression of iNOS in cancer cells seems to be a necessary mechanism for generating high levels of NO and its derived species, which promote genomic instability [201], cancer growth [202], and spreading [203]. Therefore interfering with this enhanced NO-iNOS machinery may represent a putative target for pharmacological intervention in cancer.

Interfering with the NO dynamic is not a simple task. In cancer, NO can be derived from both host and tumor cells [204]; therefore, blocking tumor-iNOS has potential implications for healthy cells. The mode of therapeutic delivery therefore needs a degree of specificity for cancerous cells (e.g. nano-carriers targeting membrane receptors unique to cancerous cells). In this context, strategies may be directed against a) iNOS activity, b) iNOS-derived NO and c) mainstream regulators of iNOS expression. Regarding the iNOS-NO axis, experimental approaches have been exploited to either block iNOS or to scavenge NO in cancer models, and interventions include treatment with aminoguanidine [197], N(G)-nitro-L-arginine methyl ester [205], carboxy-PTIO [206], tyrosine-kinase inhibitors [207], TGF-β-like molecules [208], S-methylisothiourea sulfate [173] and some natural compounds [209].

Interventions of the mainstream regulators of iNOS expression may be quite difficult because there are so many molecules involved in inflammation. It has been demonstrated that cancer-relevant mediators could include IL-1β [210], TNF-α [211], NF-κB [209] and

STAT-1 [212], among others. In fact, NO blockage has reached promising results in experimental models, inhibiting tumor growth [213], prolonging survival [214], and reducing metastasis [215]. These data indicate that the pharmacological impairment of iNOS functioning may be useful in patients diagnosed with metastatic disease, since sustained high levels of systemic NO are reported in such patients [216–219].

Clinical trials have tested the efficacy and safety of iNOS inhibitors in humans, and have provided support to encourage the use of such drugs in cancer, with no important adverse effects [220–222]. Vital functions such as blood pressure, pulse rate, or respiratory function – all pivotal functions physiologically controlled by NO - did not change after the systemic administration of the iNOS inhibitor L-N6-(1-iminoethyl)lysine 5-tetrazole amide (SC-51) on healthy volunteers [220]. In the same way, the use of nebulized aminoguanidine was tested in healthy individuals and patients with pulmonary diseases, and no adverse effects were reported regarding cardiovascular functioning after NO blocking [221, 222]. Although the evidence is promising, in-depth studies still need to be conducted to confirm that iNOS blockage will stop tumor growth without compromising normal functions that are dependent on NO.

In theory, interfering with the NO-axis could also affect immune function. For example, experimental knockout of iNOS enhances the mortality of mice in sepsis [223]. However, there is no evidence of immunosuppression after iNOS blockage in cancer models and none of the clinical trials using NOblockers have reported on immunosuppressive effects [220–222]

AKT

Protein kinases are an important family of regulatory enzymes required for the growth, division, and differentiation of cells, and they have been closely examined as possible mediators of oncogenesis. In particular, the kinase signaling pathway known as the phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K/AKT/mTOR) represents one of the intracellular cascades of utmost importance when examining cellular proliferation, differentiation, as well as cytoskeletal reorganization. The dysregulation of this pathway can direct the cell towards a carcinogenesis [224].

AKT was initially defined by three groups in 1991, Bellacosa et al. [225], Coffer et al. [226], and Jones et al. [227]. It possesses tumorigenic potential, which normally remains downregulated via the phosphatase and tensin homologue (PTEN) gene [224, 228, 229]. However, mutations in the PTEN gene, which are found in several human malignancies, lead towards the inhibition of AKT downregulation, which would would normally occur through the dephosphorylation of PIP3, a product of PI3K activation [229, 230]. The increased potential for cellular proliferation leading towards tumorigenesis initiated through PKB activation may also result from a response towards various cellular stimuli, such as heat shock, osmotic, and oxidative stress [229]. Mechanistic research has revealed a wide range of influences [231], including critical roles by AKT in proliferation [232], resistance to apoptosis [233], glucose metabolism [234], cell migration, [235] and the regulation of autophagy [236].

From an inflammation standpoint, studies of the role of AKT in phagocytosis, bacterial infections, LPS tolerance, production of proinflammatory cytokines, and migration during macrophage-mediated innate immunity strongly suggest a pivotal role in the functional activation of macrophages [237]. Evidence suggests that AKT promotes NF-κB activation [238]. *In vivo* tests on rodents (rat paw edema) also suggest that AKT inhibitors prevent AKT phosphorylation and downregulate the expression of inflammatory factors IL-6, MCP-1,TNFα and iNOS [239]. Similarly, in research on pancreatitis, researchers have found that AKT inhibition mediates a reduction in the activation of NF-κB and p38MAPK activity in SAP rats and a downregulation of NF-κB-dependent proinflammatory genes, including TNF-α, IL-1β and IL-6 [240].

From an immune perspective, PI3K-Akt pathway inhibitors are also attractive for their ability to selectively inhibit regulatory T cells (Tregs) with minimal effect on conventional T cells. In many cancers, an important tumor immune-evasion mechanisms involves the effects of suppressive immune cells, specifically regulatory T cells (Treg). So the depletion of Tregs has been found to be an effective strategy to enhance the immune response, but selective depletion of these suppressive cells (i.e., without affecting other immune cells) has not been very successful. Notably, however, PI3K-Akt pathway inhibitors selectively inhibit Tregs with minimal effect on conventional T cells (this has been shown in both human and murine CD4 T cells) and *in vivo* treatment with these inhibitors resulted in a significant and selective reduction in Tregs in both naïve and tumor-bearing mice (combined with a significant therapeutic antitumor effect). So PI3K-Akt pathway inhibitors appear to represent a promising approach to deplete Tregs in cancer [241].

Consequently, AKT inhibition is being aggressively pursued as a new therapeutic strategy for a range of cancer types, including ovarian [242], breast [243], lung [244], and bladder [245]. PI3K and AKT inhibitors are still in the early stages of development, but despite three generations of compounds targeting PI3K already having been developed, none have proved efficacious, mainly due to the emergence of therapeutic resistance [246, 247]. It is our opinion that this particular target, which appears to have strong promise, may still prove to be more effective when acted upon with a range of other therapeutic constituents that can address the alternate pathways that might otherwise serve to support this resistance.

CXC Chemokines

Chemokines were originally characterized by their ability to regulate the directional migration of leukocytes to inflammatory sites. This observation has key implications for tumorigenesis, as inflammatory cell infiltration is a common feature of many cancers and has varied functional consequences.

Chemokines or chemotactic cytokines are a group of small (8–14 kDa) heparin-binding proteins that interact with cognate cell-surface receptors and play important roles in a number of physiological processes such as development, host immunity, and cellular trafficking [248]. These functionally-related small secreted proteins constitute the largest cytokine family in humans [249]. Chemokines contain cysteine residues at their N-terminus and the position of these amino acids forms the basis for classification into four major

groups: CXC, CC, CX3C or C [248]. Most chemokines harbor a four-cysteine motif internally linked by disulfide bonds at conserved sites.

The mechanism whereby chemokines exert biological effects relies on their ability to bind to the extracellular domain of G protein-coupled chemokine receptors, which leads to production of second messengers, cytoplasmic calcium mobilization, and the activation of multiple downstream signaling cascades, including the PI3K/AKT pathway, the Ras/MAPK axis, and the Janus kinase (JAK)/STAT cascade [250]. Chemokines are produced by leukocytes, endothelial cells, fibroblasts, epithelial cells, and tumor cells [251]. This section will be limited to a discussion of CXC chemokines.

Chemokines produced by neoplastic and/or stromal cells control the nature of the inflammatory infiltrate by actively recruiting cells of the innate and adaptive immune systems [249]. The ability to regulate cell trafficking in and out of the tumor milieu has diverse and complex functional consequences. Some chemokines promote conditions favorable for tumor growth and progression, while others have antitumor activity [252]. For example, IL8/CXCL8 induces leukocyte cell migration during inflammation, and this response can promote tumor growth and development by generating a favorable microenvironment [252, 253].

In contrast, chemokines such as CXCL10 can have angiostatic properties owing to their ability to attract antitumoral lymphocytes *via* the receptor CXCR3. The extents to which chemokines recruit immune cells to tumor sites have dramatic, often opposite, functional effects. Indeed, chemokines recruit tumor-associated macrophages (TAM) that promote tumor progression, but when TAMs are recruited massively and appropriately activated, they can exert antitumor activity [249]. Neutrophils, lymphocytes and dendritic cells commonly are recruited to tumors such as bronchioloalveolar carcinomas, colon adenocarcinomas, myxofibrosarcomas, gastric carcinomas, and melanomas, where they can have pro- and antitumorigenic effects [254–261]. However, the presence of NK cells is relatively infrequent in tumors and their presence consistently correlates with good prognosis and increased survival [262, 263].

In addition to their role in cell migration and inflammation, the chemokine/chemokine receptor system impacts development and progression of malignant diseases by regulating tumor initiation, growth, survival, migration, adhesion, invasion, angiogenesis, and metastasis [248, 253]. In summary, chemokines and their receptors regulate tumorigenesis directly by acting on tumor cells, and indirectly by regulating the composition of the inflammatory infiltrate. The diversity of the chemokine/chemokine receptor system is such that it can both contribute to, and inhibit, key events relevant to the tumorigenic process.

CXC chemokines and their receptors are often over expressed in a variety of tumors, affecting proliferation, motility, cell survival and resistance to chemotherapeutic drugs [264–266] Chemokine receptors, unlike other cell surface receptors, are also promiscuous as they bind multiple ligands (chemokines), they can function in ligand-independent manners, and they can elicit multiple effects following binding to a single CXC chemokine [264, 267]. For example, each of the two cell surface receptors of IL-8, CXCR1 and CXCR2 has

diverse functions. IL-8 binding to CXCR1 results in activation of mitogenic signaling and increased ERK1/2 MAP kinase activity. CXCR2 mediates angiogenesis, motility, invasion and activation of NF-κB mediated cell survival pathways [267, 268]. Some receptors, e.g., the CXCL12 co-receptor CXCR7, also binds CXCL11 and MIF, and activates EGFRs independently of their ligands [269–272]. These complex and diverse functions of CXC chemokines and their receptors present significant challenges for cancer therapy, but also opportunities for investigating novel targeted approaches.

Chemokines and their receptors are regarded as promising molecular targets for therapeutic intervention. Several antagonists of CXCL8-CXCR1/CXCR2-mediated signaling are in development, including neutralizing antibodies, orally active small-molecule antagonists (e.g., SCH-527123, SCH-479833 [273]), and adenoviral-mediated anti-sense gene transfer approaches [274, 275]. Studies have shown that chemokines and their receptors are closely linked to emergence of drug-resistant cancer stem cells following regular chemotherapy exposure [276]. Use of small molecule inhibitors of IL-8 binding to CXCR1, such as repertaxin, has been shown to enhance responses to chemotherapy in breast cancer [277]. Identification of the CXCL12-CXCR4/CXCR7 axis as a novel therapeutic target led to development of several therapeutic approaches [248, 278]. Examples of these are the anti-CXCR4 drug AMD3100 [279], the CXCL12 analog CTCE-9908 [280, 281, 282], the anti-CXCL12 aptamer NOX-A12 [283], the inhibitor of CXCR4 expression chalcone 4 [284], and the CXCR7-specific inhibitors CCX2066 [278, 283], CCX733 [285] and CCX754 [286, 287]. CXCR4 also has been targeted using monoclonal antibodies and small molecule antagonists [288–291]. In addition, administration of recombinant forms of chemokines with angiostatic and/or antitumorigenic effects such as CXCL4, CXCL9, and CXCL10 has been proposed as a potential strategy to inhibit tumor growth and limit spreading [252, 292–295]. Thus, currently there are several chemokines that are targets of therapy, such as CXCL-1, CXCL8 and CXCL12 and others in various stages of development [296, 297]

The intrinsic functional redundancy in the chemokine system suggests that blocking a single receptor upregulated in a particular tumor is unlikely to significantly affect the integrity of protective immune mechanisms. The redundancy of this system itself presents therapeutic challenges related to possible overlapping functions of multiple receptors, but this feature also offers attractive opportunities from a therapeutic standpoint. It may be possible to fine-tune experimental screening studies to identify agents that inhibit certain signaling pathways while sparing others. The ability to bias signaling responses opens the possibility of selectively targeting events that contribute to disease while preserving immunity. In addition, the receptor microenvironment can profoundly affect its function and downstream signaling, and there may be serendipitous and unique specificities built into target cancer cells that can be capitalized upon to maximize beneficial therapeutic action and minimize or block the loss of beneficial responses such as antitumor immunity [298].

Many recent studies have revealed that chemokines can regulate the movement of a wide variety of immune cells including lymphocytes, NK cells, and dendritic cells in both physiological and pathological conditions. So these features endow chemokines with crucial roles in immune responses [299]. But therapeutic approaches that focus on chemokines can produce a range of immune-related effects. For example, a recent study demonstrated in

several murine models of anthracycline-based chemotherapy that the inhibition of CCL2 or CCR2 might actually impair the anticancer immune response [300]. On the other hand, there are other chemokines that appear to have the potential to enhance the recruitment of antigen presenting cells and effector cells to sites where they are needed [301]. Given the range of chemokines and the complexity of the immune system, readers who are seeking more detail on this topic are encouraged to peruse several recent reviews that cover this topic in considerable detail [299, 302, 303]. Suffice to say that although the development of therapeutics based on targeting chemokines and their receptors has been challenging, but the lessons learned are leading to advances that should allow us to develop more refined strategies with better chances of success.

Low Toxicity Approaches

Several synthetic antiinflammatory molecules have been tested in cancer research with important preclinical results; however, the translation to clinical practice has been hampered by the abrupt finding of unpredictable serious side effects or by a lack of significant anticancer activity when tested in humans. For example, the use of nonsteroidal antiinflammatory drugs (NSAIDs), in particular aspirin, have been included as a factor in several epidemiological studies, and also clinical trials have been attempted in order to demonstrate chemopreventive activity. While epidemiological data do show association between long term ‘baby aspirin’ intake and colon cancer risk [304], many of the clinical trials designed to look for prevention of the onset of cancer or of pre-cancerous lesions have not reached satisfactory results for a variety of reasons (such as problems with the target population, duration of the study, and more importantly, side effects [305–308] that range from gastrointestinal bleeding to hemorrhagic stroke). Thus, the use of NSAIDs in clinical practice for cancer chemoprevention has always been outweighed by the possibility of serious complications.

At the same time, a wide spectrum of phytochemicals, present in edible, non-edible and medicinal plants, and endowed with potent antiinflammatory properties, have been shown to prevent tumor occurrence in several organs of experimental animals and inhibit the growth of neoplastic cells [309–315]. Indeed, several epidemiological and experimental studies provide convincing evidence that there exists a strong relationship between increased consumption of various vegetables, fruits, whole grains, legumes and spices and a decrease in cancer risk [316–319]. A large number of phytochemicals present in dietary sources are capable of suppressing carcinogenesis through inhibition of inflammatory cascade [320–322] as well as modulation of various signaling pathways implicated in cancer initiation, promotion and progression. We have therefore focused on the following chemicals from plants and foods as promising approaches with therapeutic potential to reach the targets that we have identified: curcumin, resveratrol, epigallocatechin gallate (EGCG), lycopenes, anthocyanins, and genistein.

Curcumin

Curcumin, (diferuloylmethane) is a component of golden spice *Curcuma longa* (commonly known as turmeric) which has been used for centuries in many Asian countries as part of diet or as a coloring agent. The anticancer and antiinflammatory effects of curcumin have

been demonstrated in many cell and animal studies, and recent research has shown that curcumin can also target cancer stem cells [323], which makes it a dietary substance of considerable interest.

In Nepal and India, where daily curcumin uptake in diet has been assessed as high as 50–100 mg per day, no toxicities or adverse effects have been reported at the population level [324, 325]. The National Toxicology Program of the National Institutes of Health evaluated the toxicology and carcinogenic effects of turmeric in 1993 at a dose of 0.2g/kg/day (CAS no. 8024−37−1) for 13 weeks and 2 years on rats and mice. No adverse toxicological effects and no histopathological changes in treated mice were found. Similarly, in a study undertaken by National Cancer Institute in the United States, the oral administration of 3,500mg/kg body weight curcumin for 90 days in rats, dogs, or monkeys did not cause any adverse effects and was well tolerated [326]. In 1996, the Food and Drug Administration of the United States recognized curcumin as a Generally Recognized As Safe (GRAS) compound [327]. Up to 1,000mg/kg/body weight oral administration of curcumin did not have any adverse effect on reproduction of rats, when fed for two successive generations [328]. Finally, in humans, a dose escalation study performed in 24 adults, found that single oral doses up to 12g were well tolerated and the observed adverse effects were not dose-related. Curcumin supplementation up to 8 g/day for three months was well tolerated in the patients with precancerous conditions or non-invasive cancer [329], and in another clinical trial in patients with advanced colorectal cancer, curcumin supplementation ranging from 0.45–3.6 g/day for four months was well tolerated by subjects [330].

However, curcumin may have adverse effect in the following situations: (a) curcumin increases contraction in the gallbladder and potentially could increase the risk of symptoms in people with gallstone. [331, 332]; (b) curcumin can increase the risk of bleeding in subjects taking anticoagulant medicines because it can inhibit platelet aggregation [333, 334]; and (c) curcumin also increases acid output in the stomach and can interfere with acid suppressing drugs in patients with duodenal ulcers [335].

Curcumin has garnered significant interest in cancer research because it can regulate signaling pathways that are dysregulated during tumorigenesis, including proliferation, differentiation, invasion, apoptosis, and cell cycle checkpoints [336]. *In vitro* studies indicate that curcumin can target numerous kinases, phosphatases, and enzymes [337]. For example, curcumin can inactivate NF-κB [338], and reduce COX-2 expression [339] and downstream targets as well [338]. It promotes apoptosis through interaction with p53 [340] and by increasing caspase expression [341], and it induces cell cycle arrest [342]. In animal models curcumin prevents cancer development through reduction of TNF-α, interferon-γ (IFN-γ), and COX-2 [343]. So the diverse biological effects of curcumin make this compound an attractive constituent therapeutic that has been widely evaluated for its anticancer activity [344].

Indeed, curcumin has been shown to inhibit the development of chemically induced tumors of the oral cavity, forestomach, duodenum, and colon of experimental animals [337]. For example, the combination of 480 mg of curcumin and 20 mg of quercetin (three times daily) for six months reduced the number of polyps in a small number of familial adenomatous

polyposis (FAP) patients without major side effects [345]. Similarly, 4 grams of curcumin daily for 1 month prevented the development of aberrant crypt foci in humans [346]. A preclinical study also suggests that curcumin could work as chemotherapeutic agent, by enhancing colon cancer cells sensitivity to oxaliplatin [347]. However, not all trials have been successful [348], and the systemic bioavailability of curcumin is extremely poor [349]. Nonetheless, at the US National Institutes of Health website (https://clinicaltrials.gov), there are 47 ongoing clinical trials with curcumin registered for different types of cancers, but most of them appear to be preclinical or pilot studies. For formal validation of the efficacy of curcumin as a chemopreventive or chemotherapeutic drug, randomized, placebo-controlled, and double-blind trials are required.

Chemical and photochemical instability/degradation, absorption, metabolism, and excretion of the curcumin are considered the reason for low systemic bio-availability in human subjects [350]. When curcumin was administered orally at a dose of 1,000 mg/kg in rats, the majority of the curcumin was excreted in feces and negligible amounts were detected in the urine [351]. Curcumin is biotransformed in the intestine, and the liver converts it into glucuronides and curcumin sulfates [352, 353]. Also, reduction of the curcumin to tetrahydrocurcumin and hexahydrocurcumin has been reported after oral administration in rats, mice, and human [353–355]. Even intravenous and intraperitoneal administration of curcumin in rats resulted in reduced curcumin and subsequently reduced curcumin converted to monoglucuronide conjugates [354]. Transformation of curcumin may result in loss of the biological activity of curcumin [353]. In pharmacokinetic and dynamic studies, serum curcumin concentrations peaked in 1–2 hours [356]. The peak serum concentrations of curcumin were 0.5, 0.6, and 1.8 micromoles/liter following an oral dose of 4, 6, and 8 g of curcumin, respectively. [356]

Although systemic availability of curcumin is very low, it has been shown in some studies that orally administered curcumin accumulates in gastrointestinal tissues [357, 358]. It has been reported that when colorectal cancer patients were administered 3.6 g/d of curcumin orally for seven days, curcumin was detected in normal surgical samples of colorectal tissue [357]. Recent advances that use implantable polymeric micelles as nano-delivery systems or phospholipid-based delivery systems for curcumin increase its accumulation in organs specifically in the gastrointestinal tract, that can target COX-2 as well as prostaglandin synthesis pathway more effectively [359–362]. *In vitro*, curcumin shows potential as a COX-2 inhibitor, inhibiting the expression of COX-2 mRNA and enzymatic activities of COX-2 protein in colonic epithelial and in macrophages [363, 364]. Curcumin also inhibited the expression of COX-2 mRNA and enzymatic activities of COX-2 protein in colonic epithelial and in macrophages [363, 364].

Because curcumin can target prostaglandin biosynthesis, it can be used in cancers where COX-2 activation plays an important role. New advancements in *in vivo* delivery systems of curcumin will result in a higher levels of curcumin accumulation in organs (specifically in the gastrointestinal tract) that can target COX-2 as well as prostaglandin synthesis pathway more effectively. Curcumin inhibited bile acid and phorbol ester induced COX-2 mRNA expression in gastrointestinal epithelial cells [365]. In mouse skin cells, curcumin inhibits phorbol ester-induced expression of COX-2 [348]. In a human non-small cell lung cancer

ectopic and orthotopic xenograft mouse model, curcumin reduced COX-2 expression in subcutaneous tumors *in vivo* and caused a 36% decrease in weight of intralung tumors accompanied by a significant survival rate increase [366]. Curcumin inhibition of COX-2 in NSCLC cells was associated with decreased survival [366].

Notably, *in vitro* treatment of curcumin also suppressed CXCL-8 production by human pancreatic carcinoma cell lines and downregulated the inflammatory cytokines CXCL1 and CXCL2 in breast cancer cells via NF-κB [367, 368]. In a Kras-mediated lung cancer model in mice, curcumin inhibited the expression of neutrophil chemoattractant keratinocyte-derived chemokine CXC-KC and subsequently inhibited progression of the cancer [369].

From an immune perspective, curcumin suppresses the type 1 immune response, which can increase susceptibility to infection [370]. But at the same time curcumin appears to act in a supportive manner for tumor-related immune effects. For example, in *in vitro* tests aimed at studying the role of curcumin in the prevention of tumor-induced dysfunction of T cell-based immune response, curcumin prevented the loss of T cells, expanded central memory T cell (T(CM))/effector memory T cell (T(EM)) populations, reversed the type 2 immune bias and attenuated the tumor-induced inhibition of T-cell proliferation in tumor-bearing hosts. Curcumin also inhibited the suppressive activity of Treg cells (by downregulating the production of TGF-β and IL-10) and enhanced the ability of effector T cells to kill cancer cells [371]. As well, curcumin significantly inhibited the induction of IDO expression (a key enzyme in T-cell suppression-mediated immune tolerance to tumors) and activity by IFN-γ in bone marrow-derived DCs, which appears to be an important immunomodulatory property of curcumin that may serve to strengthen its therapeutic potential [372].

Resveratrol

Resveratrol (3,5,4'-trihydroxystilbene), a compound found in the skins of red grapes, red wine, berries, peanuts and many other plants, has been shown to possess health-promoting properties. It is a bioactive polyphenol and has antiinflammatory, antioxidant, antimicrobial, anticancer, neuroprotective, and cardioprotective effects. Numerous preclinical animal studies provided encouraging evidence for cancer chemopreventive and chemotherapeutic potential of this phytochemical [373]. *In vitro* evidence of resveratrol efficacy is well described; however, many concerns regarding its effectiveness *in vivo* arise from its poor stability and rapid metabolism and bioavailability following oral ingestion. Peak plasma concentrations occur at around 1hr, and levels of the parent compound are very low [374, 375]. Adverse effects are mild, even at high doses (up to 5g daily) [376]. Resveratrol works in animal models [377] and humans; although the data for humans is more sparse and controversial [378, 379].

Resveratrol has been shown to have efficacy in multiple animal models of chronic inflammatory diseases. These diseases include hepatitis [380], esophagitis [381], and in particular, there are many confirmed studies that resveratrol suppresses colitis [382, 383] and pancreatitis [384–386]. Resveratrol targets many of the key players involved in inflammation, prevents DNA damage, and induces apoptosis in a p53-dependent manner [387–389]. Interestingly, resveratrol can induce the expression of the p53 target, NAG-1 [non-steroidal antiinflammatory (NSAID) drug-activated gene-1], a member of the

transforming growth factor-beta superfamily, that has pro-apoptotic and antitumorigenesis activities [390]. Also, resveratrol prevents pRb hyperphosphorylation and thus the inactivation of this tumor suppressor protein. Resveratrol also inhibits MMP-2 [391] and MMP-9 [392, 393], COX-1 [394], proinflammatory cytokines [395–397], and growth factors such as hepatocyte growth factor [398].

Additionally, resveratrol has potent NF-κB-dependent antiinflammatory and chemopreventive effects both *in vitro* and *in vivo*, and impacts multiple disease phenotypes in a favorable manner. For example, through the inhibition of NF-κB, resveratrol ameliorates diabetic vascular inflammation and macrophage infiltration in diabetic mice, inhibits the epithelial-mesenchymal transition, modulates autophagy, suppresses cell transformation, regulates miRNA levels, and reverses resistance to chemotherapeutic agents [399–405]. Notably, resveratrol has also been shown to inhibit other key modulators of inflammation and cancer discussed in this review, including COX-2 [406–408], MIF [409], TNF-α [410], iNOS [411], AKT [412], and the CXC group of cytokines [413]. For example, Cichocki et al. showed resveratrol inhibited 12-O-tetradecanoylphorbol-13-acetate activated NF-κB, AP-1, COX-2, and iNOS in mouse epidermis [414]. Similarly, Kundu et al. showed that resveratrol inhibits phorbol ester-induced expression of COX-2 and activation of NF-κB in mouse skin by blocking I-κB kinase activity [408]. Dietary resveratrol (50–300 mg/kg) was found to inhibit chemically-induced hepatocarcinogenesis in rats with simultaneous suppression of hepatic iNOS, 3-nitrotyrosine, COX-2 and NF-κB [415–417].

Several recently published clinical trials on resveratrol in humans have shown that it exhibits antioxidant and antiinflammatory activities. It can improve glucose and lipid metabolism, and favorably modify a number of important pathways involved in carcinogenesis (e.g., the insulin-like growth factor system [418], apoptosis [419] and others [420]). However, these effects can vary and depend on the protocols [376]. The plasma pharmacokinetics of resveratrol in humans are also now reasonably well defined, and daily doses up to 1 gram appear to be safe and well tolerated, although gastrointestinal toxicity is observed at higher intakes, and there is potential for drug interactions at higher doses[420].

In some of the earliest research on resveratrol and immune function, Falchetti *et al*. [421] showed that *in vitro* exposure to resveratrol produced a biphasic effect on anti-CD3/anti-CD28-induced development of both IFN-γ - IL2- and IL4-producing CD8+ and CD4+ T cells (with stimulation at low resveratrol concentrations and suppression at high concentrations). Similarly, it was found to induce a significant enhancement at low concentrations and suppression at high concentrations of both cytotoxic T lymphocytes and NK cell cytotoxic activity [421], and this biphasic modulation of NK cells has been confirmed in more recent research as well [422]. The administration of low doses of resveratrol also inhibited Renca tumor growth with regulatory T cells being decreased, and a massive amount of activated $CD8^+$ T cells accumulating in the tumor microenvironment. At the same time, the expression of T-helper (Th)-2 cytokines (e.g., IL-6 and IL-10) switched to Th-1 cytokines with dominance of interferon (IFN)-γ, which increases the expression of Fas in Renca cells. [423]. And resveratrol has also been shown to suppress tumor-derived CD4+CD25+ regulatory T cells (which are a negative regulator of the immune system and main obstacles to cancer immunotherapy in tumor-bearing hosts) in mice [424]. And

resveratrol at low and noncytotoxic doses has been shown to inactivate Stat3, preventing the generation and function of tumor-evoked regulatory B cells (tBreg), including expression of TGF-β in mice. This frees antitumor effector immune responses by disabling tBreg-induced conversion of forkhead box protein (FOX)p3(+) Tregs (without nonspecific inactivation of effector immune cells), which efficiently inhibited lung metastasis in mice[425]. So the effects of resveratrol on the antitumor capabilities of the immune system appear equally promising, and notably, this is accomplished with no apparent increase in susceptibility to risks of infection.

Epigallocatechin gallate (EGCG)

EGCG is the most abundant catechin in tea, is a potent antioxidant and antiinflammatory agent. It is found mainly in white tea, green tea and, in smaller quantities, black tea. Despite the demonstration of cancer prevention by EGCG in many animal studies, epidemiological studies have found mixed results concerning the effectiveness of EGCG as a superior medicine for prevention and therapy of cancer in humans [426]. Its limited *in vivo* activities can be attributed to metabolism and bioavailability. Methylation, glucuronidation, sulfation, and ring-fission metabolism represent the major metabolic pathways for tea catechins [427]. It has also been found that efflux transporters P-glycoprotein (Pgp), MRP1 and MRP2 play roles in the absorption and excretion of green tea catechins [428]. Several processes including intestinal metabolism, microbial metabolism, hepatic metabolism and chemical degradation are also involved in the fate of EGCG, resulting in its low availability in animals, and most likely also in humans [429].

Isbrucker et al. conducted toxicity studies on EGCG. An oral dose delivering 2000 mg EGCG preparation/kg was lethal to rats, whereas a dose of 200 mg EGCG/kg induced no toxicity. The dietary administration of EGCG to rats for 13 weeks was not toxic at doses up to 500 mg/kg/day. Similarly, no adverse effects were noted when 500 mg EGCG preparation/kg/day was administered to pre-fed dogs in divided doses. This dose caused morbidity when administered to fasted dogs as a single bolus dose, although this model was considered an unrealistic comparison to the human condition. From these studies a no-observed adverse effect level of 500 mg EGCG/kg/day was established [430].

There are multiple mechanisms that can explain the chemopreventive potentials of EGCG, among which are its ability to affect cancer cell signaling pathways, suppress cellular proliferation and induce apoptosis [426]. The diversified effects of EGCG may explain its broad pharmacologic activities. With regards to chronic inflammatory diseases associated with a high cancer risk, EGCG has been shown to suppress colitis [431], hepatitis [432] (and may have antiviral properties against HBV and HCV [433, 434]), and pancreatitis [435] in animal models. Excitingly, in a pilot study involving patients with mild to moderate ulcerative colitis, EGCG (400–800 mg daily) showed a therapeutic benefit for patients who were refractory to 5-aminosalicylic and/or azathioprine [436].

There is extensive evidence that EGCG targets key players in inflammation, providing a mechanism of its efficacy *in vitro* and *in vivo* against chronic inflammatory diseases and associated cancers. Noh et al. showed that EGCG improves *Dermatophagoides pteronissinus* extract-induced atopic dermatitis-like skin lesions in a mouse model by

suppressing MIF [437]. In addition, EGCG can inhibit TNF-α [438], iNOS [439, 440], AKT [441], the CXC group of cytokines [442], and by by reducing the transcriptional activity of NF-κB, COX-2 expression and PGE-2 synthesis [443–448]. Additionally, EGCG activates wild-type p53 [449–451], and protects from p53 mutation [452]. It promotes pRb hypophosphorylation and activation of this tumor suppressor protein [453], and inhibits MMPs such as MMP-9 [454].

In animal models EGCG prevents the development of adenomatous polyps in ApcMin/+ mice [455, 456]. Some epidemiological studies have shown that high consumption of green tea reduces the risk of several types of cancers, including the lung, colorectum, liver, esophagus and stomach [457, 458]. High urinary levels of tea polyphenol epigallocatechin (EGC) have been associated with reduction of colorectal cancer among a Chinese population [459] and a randomized clinical trial has shown a significant reduction in adenoma incidence among patients taking 1.5 g/day of green tea extract [460]. Doses of green tea polyphenols greater than 800 mg/day increase in liver enzymes, and there is possible hepatic toxicity in humans at this level [461–463]. Nonetheless, despite evidence from *in vitro* and non-human *in vivo* research on green and black tea as chemopreventive agents for colorectal cancer, data are still insufficient to conclude that either tea type is protective [464]. But EGCG does target and suppress many of the key players involved in the inflammation-to-cancer sequence, and therefore may be quite useful as a constituent within a mixture aimed at inflammation in cancer.

From an immune perspective, EGCG significantly suppressed IFN-γ production and the proliferation of peripheral blood mononuclear cells *in vitro* [465]. It was also shown to exert antitumor effects on colorectal cancer cells, at least in part by inhibiting the expression and function of IDO through the suppression of STAT1 activation [466]. In leukemic BALB/c mice that received 5, 20 and 40 mg/kg EGCG (orally) for two weeks, it increased the percentage of CD3, T-cell, CD19, B-cell, and Macrophage-3 antigen (Mac-3), and macrophages, but reduced the percentage of CD11b (monocyte) cell surface markers. It also promoted the phagocytosis of macrophages from 5 mg/kg treatment and promoted NK cell activity at 40 mg/kg, increased T-cell proliferation at 40 mg/kg, but also promoted B-cell proliferation at all three doses [467].

At the same time, EGCG appears to have a protective effect against bacterial infection. This was shown in EGCG treatment of nicotine-suppressed macrophages where it reconstituted the resistance to the infection and diminished a nicotine-induced inhibition of cytokine production [468]. It was also demonstrated in research against *Pseudomonas aeruginosa* and *Escherichia coli* isolated from skin wounds [469], and against burn wound infection by methicillin-resistant *Staphylococcus aureus* [470].

Lycopene

Lycopene is a phytochemical that belongs to a group of plant pigments known as carotenoids. Red colored lycopene is lipophilic and naturally occurs in many fruits and vegetables. The richest sources of lycopene are tomatoes and tomato products, however, apricots, guava, watermelon, papaya, and pink grapefruit are also sources of this phytochemical. Some studies suggest that cooking tomatoes in oil may increase the

bioavailability of lycopene [471, 472]. Research, dating as far back as the 1920s, has shown that naturally occurring carotenoids, specifically beta-carotene, have anticancer properties. Since the late 1980's when it was recognized that the antioxidant activity of lycopene was twice that of beta-carotene there has been a growing interest regarding lycopene as a possible anticancer agent.

Only 10–30% of the lycopene in dietary sources can be absorbed via the human digestive system [473]. Although there is conflicting data, it has been suggested that lycopene is better absorbed when taken in conjunction with fats due to its lipophilic properties [474]. Once ingested, lycopene is incorporated into lipid micelles and absorbed by the mucosa of the small intestine. The micelles are then transported to the liver as chylomicrons. Lipoproteins are the carriers of lycopene in the blood stream and the means by which bioactive lycopene gains access to the various organ systems. High concentrations of lycopene have been found in the testes, prostate, adrenal glands and liver [475].

Lycopene is a constituent of human diets that are rich in fruit and vegetables and epidemiological studies suggest that it may have a protective effect against various cancers [476]. Lycopene is a powerful antioxidant that blocks the action of free radicals which are activated oxygen molecules that can damage cells and have been shown to support the development of some cancers. For example, numerous studies suggest that lycopene and lycopene rich natural dietary products, when taken regularly, may decrease the incidence of a variety of malignancies including breast [477], ovarian [478] bladder mouth, esophagus, pancreas [479] and colorectal cancer [480]. There is also great interest regarding lycopene and prostate cancer; about 30 percent of the published human studies (16/54) that have considered lycopene concern prostate cancer. The association of a diet rich in lycopene from tomato-based foods with a lower risk of prostate cancer is supported by multiple studies [481–485].

Thus far, several researchers have investigated lycopene's mechanism(s) of action as regards its anticancer effects. Oxidative stress is a major factor implicated in chronic diseases and carcinogenesis. Lycopene has been found to increase the effects of deoxification proteins (such as epoxide hydrolase-1) and protective enzymes (such as glutathione-*S*-transferase-omega-1, peroxiredoxin-1 and sulphide-quinone oxidoreductase) [486]. Other studies have shown that lycopene downregulates the genes that regulate proteins involved in the generation of ROS, including ERO1-like protein-a and CLIC-1 [487]. In addition, lycopene may prevent cancers, especially prostate cancer, via other mechanisms. *In vitro* studies have shown that lycopene-induced activation of the peroxisome proliferator-activated receptors (PPAR)-*gamma*-LXR *alpha*-ABCA1 pathway is associated with decreased proliferation of LNCaP prostate cancer cells [488, 489]. When LNCaP cells were exposed to lycopene, a dose-dependent decrease of the G0/G1 phase-related protein, cyclin D1, and an increase in the cyclin kinase inhibitors, p53, p21 and p27 have been noted and were associated with cell cycle arrest [490]. Other *in vitro* studies suggest that lycopene may induce apoptosis in human prostatic epithelial cells. A protein expression profiling study revealed that lycopene may upregulate pro-apoptotic proteins as well as downregulate antiapoptotic proteins in human primary prostatic epithelial cells *in vitro* [487]. Lycopene has also been shown to

suppress the invasion and migration of prostate cancer cells by downregulating the expression of integrins [491].

Lycopene has also been shown to have antiinflammatory effects in both *in vitro* studies that assessed macrophages as well as rodent studies. In particular, lycopene has been associated with downregulation of TNF-α gene expression and/or inhibition of TNF-α secretion in LPS stimulated macrophages [492–494]. Also, in a rat model of pancreatitis, blood levels of TNF-α were notably lower in lycopene-treated versus control animals [495]. Similarly, decreased TNF expression and secretion results have been noted in a number of endothelial cell *in vitro* studies [496, 497]. Modulation of the following signaling pathways have been proposed as the mechanism of this antiinflammatory effects: ERK, NF-κB, JNK, and HMGB1 [492–494, 496, 497].

It is not clear whether or not lycopene predisposes patients to infections or immune system suppression. There is limited evidence that lycopene and other carotenoids have antiinflammatory effects that may impact native immune function [492] In some of the earliest animal studies, intraperitoneally or intravenously injected lycopene produced prolonged survival times in bacterially infected mice [498]. But according to Medfacts.com, a total of 143 lycopene drug adverse event reports were reported to the FDA between January 2004 and October 2012, including 21 infectious complications, but lycopene was not thought to be the cause of the infection in any of those cases (based on physician opinions - no further details provided).

From an anticancer perspective, lycopene treatment promoted promote spleen lymphocyte proliferation, and NK activity *in vivo* in mice [499]. But another study on mice showed that lycopene significantly attenuates the maturation of murine bone marrow-derived dendritic cells, and that it downregulated the expression of costimulatory molecules (CD80 and CD86) and major histocompatibility complex type II molecules, suggesting that it has immunosuppressive potential [500].

Studies in which lycopene was orally administered repeatedly, for a period of time, did not identify any clear organ toxicity related to the lycopene in rats or mice, however, in a dog, accumulation of lycopene and vitamin A in the liver, and excess vitamin A in the kidneys were noted. Skin pigmentation and colored fatty deposits in the liver were seen in a person who ingested high large amounts of lycopene daily over a period of years [501]. A study concerning 20 male and 20 female Wistar rats that were given lycopene in their diets (a range of levels were assessed, the highest being 1% of diet) for 90 days showed no evidence of toxicity based on: 1) clinical and neurobehavioral observations; 2) motor activity assessment; 3) body weight and food consumption measurements; 4) ophthalmoscopic examinations; 5) hematology, clinical chemistry, and urinalysis; 6) organ weights, 7) gross pathology, or 7) histopathology [502].

Dietary lycopene, from eating fruits and vegetables, has no known side effects and is thought to be safe for humans. The optimum dosage for lycopene has not been established, but the amount found helpful in studies generally falls in the range of 4 to 8 mg daily. Patients in some studies who took a lycopene-rich tomato supplement of 15 milligrams

twice a day had some intestinal side effects such as nausea, vomiting, diarrhea, indigestion, gas, and bloating. Lycopene at higher doses, especially when taken for long periods of time, has been associated with diarrhea, fat buildup under the skin, chest pain, heart attack, skin discoloration, stomach pain, stomach ulcer irritation, vomiting, and worsened hot flashes [503].

Supplements containing antioxidants such as lycopene may interfere with radiation therapy and chemotherapy if taken during cancer treatment [504]. Even though studies have not been done in humans, antioxidants are known to clear free radicals, which could interfere with one of the methods by which chemotherapy and radiation destroy cancer cells. Most of the human studies, thus far, have been case control or other types of observational studies which not as useful or predictive as clinical trials. More evidence from clinical trials is needed to confirm that lycopene-rich foods can help prevent or treat cancer. Further studies are needed to better document the benefits and effects of lycopene supplements and its mechanism of action *in vivo*.

Anthocyanins

A diet rich in polyphenolic anthocyanins (ACs) has been reported as a chemoprotective agent in *in vivo* models by regulating inflammatory cytokines. It inhibited the development of N-nitrosomethylbenzylamine- induced esophageal cancer in rats. The inhibition was mediated through decreased expression of inflammatory biomarkers like COX-2, iNOS, p-NF-κB, and soluble epoxide hydrolase (sEH)) and cytokine, pentraxin-3 (PTX3) expression [505]. AC-rich black currant skin extract showed chemopreventive activity through downregulation of abnormal lipid peroxidation, protein oxidation, and expression of iNOS and 3-nitrotyrosine (3-NT) in a dose-responsive fashion (100 and 500 mg/kg) and upregulation of the gene expression of a number of hepatic antioxidant (Nrf2-regulated antioxidant pathway) and carcinogen detoxifying enzymes, such as NAD(P)H:quinone oxidoreductase, glutathione S-transferase, and uridine diphosphate-glucuronosyltransferase isoenzymes in diethylnitrosamine (DENA)-initiated hepatocarcinogenesis in rats [506]. Black currant anthocyanins also abrogated elevated inflammatory markers, such as COX-2 and NF-κB, during DENA hepatocarcinogenesis in rats [507].

ACs also exerted an antiinflammatory effect in *H. pylori*-infected gastric epithelial cells. The inflammatory cytokine IL-8 and ROS increase in the *H. pylori*-infected gastric mucosa. First, ACs inhibit the phosphorylation of MAPKs, translocation of NF-κB and IκBα degradation. Secondly, they also inhibit *H. pylori*-induced iNOS and COX-2 mRNA expression and IL-8 production [508]. Additionally, *in vitro* studies showed that the anthocyanins inhibit the mRNA and/or protein expression levels of COX-2, NF-κB and various interleukins and exhibit antiinflammatory effects in multiple cell types [509, 510].

These studies suggest that anthocyanins significantly inhibit induced proinflammatory mediators, such as nitric oxide (NO) and prostaglandin E_2, as well as proinflammatory cytokines including TNF-α and IL-1β, without significant cytotoxicity. Anthocyanins also downregulated excessive expression of inducible NO synthase, COX-2, TNF-α, and IL-1β in a dose-dependent manner in different cancers. Moreover, anthocyanins inhibited nuclear translocation of NF-κB and IκBα degradation as well as phosphorylating MAPKs.

In addition to these antiinflammatory effects, anthocyanins have been shown to inhibit the growth and invasion of SKHep-1 cells through reduced expression of MMP-9 and urokinase plasminogen activator (u-PA) [511]. Similarly, a MMP-9 and u-PA mediated reduction of migration and invasion was observed in highly metastatic A549 human lung carcinoma cells through cyanidin 3-rutinoside and cyanidin 3-glucoside (anthocyanins). This inhibition was also through the downregulation of activation of c-Jun and NF-κB [512]. Treatment with anthocyanins (such as delphinidin, cyanidin, and pelargonidin) in normal human epidermal keratinocytes inhibited UV-B-mediated degradation and phosphorylation of IκBα and activation of IKKα which further inhibited nuclear translocation and phosphorylation of NF-κB/p65 at Ser (536) [513].

Some caution must be exercised, because anthocyanins are often addressed as a homogenous class of agents, but they represent a group of structurally dissimilar molecules. Some studies also look at anthocyanidins (which are similar to anthocyanins but without sugar moieties). Both anthocyanins and anthocyanidins (especially cyanidin and delphinidin) have been subjected to extensive mechanistic studies in relation to antiproliferation, induction of apoptosis and inhibition of activities of oncogenic transcription factors and protein tyrosine kinases. Water soluble anthocyanins are mostly 3-glucosides of the anthocyanidins. The most common anthocyanidins are pelargonidin, delphinidin, peonidin, petunidin, malvidin and cyanidin. Peonidin 3-glucoside and cyanidin 3-glucoside extracted from black rice (*Oryza sativa* ssp. *indica*) inhibit the growth and invasion of SKHep-1 cells through reduced expression of MMP-9 and urokinase plasminogen activator (u-PA) [511]. Similarly, MMP-9 and u-PA mediated reduction of migration and invasion was observed in highly metastatic A549 human lung carcinoma cells through cyanidin 3-rutinoside and cyanidin 3-glucoside (extracted from *Morus alba*). This inhibition was also through the downregulation of activation of c-Jun and NF-κB [512].

Treatment with pomegranate-derived delphinidin, cyanidin, and pelargonidin in normal human epidermal keratinocytes inhibited UV-B-mediated degradation and phosphorylation of IκBα and activation of IKKα which further inhibited nuclear translocation and phosphorylation of NF-κB/p65 at Ser [513]. Based on the accumulating evidence, pure anthocyanidins as well as berry extracts enriched with anthocyanidin showed higher chemopreventive activities than berry extracts with high anthocyanin. The major points of concern are pH, temperature and light-dependent interconversion of anthocyanins and anthocyanidins, a greater susceptibility of anthocyanidins (in comparison to the glycosides) to chemical decomposition, and shorter half-lives in the biophase.

Notably, a number of immunosuppressive effects of berry extract rich in anthocyanins have been reported by Hushmendy et al [514] who demonstrated that anthocyanidin rich fractions inhibit T-cell proliferation and IL-2 production on anti-CD3 plus anti-CD28-activated primary human T-lymphocytes in culture [514]. However, very little research on anthocyanidins and the immune system in cancer exists, suggesting that this is an area that needs further investigation.

In general, these findings suggest that anthocyanins offer substantial chemopreventative and therapeutic potential, although there is paucity of data regarding the bioavailability of

anthocyanin. Only a small portion of orally ingested anthocyanins is absorbed (<1 %). Maximum plasma levels are reached within 2 hours of consumption. About 68 % of absorbed anthocyanins are metabolized, and excreted as monoglucuronides [515]. Low bioavailability of the anthocyanins is due to to their extensive metabolism in the tissues and by the colonic microflora. The gut microflora degrades anthocyanins to release simple phenolics that conjugate in intestine and later in liver and hamper the absorption process. However, some reports contradict this observation and suggest that anthocyanin glycosides remain intact during absorption [516]. Although the bioavailability of cyanidin-3-glucoside and anthocyanin as shown through the above report is low, Mayrczylo *et al.* demonstrated systemic levels of parent cyanidin-3-glucoside and total anthocyanins as 1.7% and 3.3% respectively in C57BL6J mice that received cyanidin-3-glucoside by oral gavage or tail vein injection [517].

Overall, in most *in vitro* and *in vivo* assays anthocyanins are not genotoxic. Some evidence of genotoxicity was provided by a single *in vitro* study using pure anthocyanidins. However, the genotoxicity of grape seed extract was negative in a bone marrow micronucleus test *in vivo*. Moreover, in guinea pigs and dogs, no short-term or subchronic toxic effects were observed at 3 g/kg anthocyanins and 15 % of grape-skin extract respectively. In addition, in rats fed with 6 g/day unspecified anthocyanins extract or grape seed extract no toxic effect was observed. But because of a lack of data, no firm conclusion can be drawn with respect to long-term toxicity or carcinogenicity of anthocyanins [515].

Genistein

Genistein (GEN) is a prominent isoflavone which inhibits cell growth and induces apoptosis *in vitro* and *in vivo* without toxicity [518, 519]. It inhibits activated AKT, the downstream target of many pathways such as Notch [520], and IGF-1 in pancreatic cancer cells [521], and in osteosarcoma [522] and breast cancer [523]. Additionally, GEN inhibits the activity of Akt-targets like FOXM1 in pancreatic cancer cells [520] and FOXO3 [524] in colon cancer cells. AKT also forms a complex with human TERT, heat shock protein 90, p70S6 kinase and mTOR and GEN restrains the formation of this complex [525]. In pancreatic cancer cells GEN inhibits growth via inactivation of Notch- 1/AKT/FOXM1 [520]. Estrogen receptor-β/AKT mediated inhibition was also observed in DLD-1 human colon adenocarcinoma cells [526]. GEN also targets AKT and p21 WAF1/CIP1 in BRCA1-mutant human breast cancer cell lines [527], GEN induced AKT-mediated enhanced apoptosis/ downregulation of AKT has also been reported in combination with compounds like arsenic trioxide in human hepatocellular carcinoma [528], gefitinib in NSCLS [529], gemcitabine in human osteosarcoma [522, 530], cisplatin in cervical cancer cells [531], cetuximab in oral squamous cell carcinoma [532], photoactivated hypericin in breast cancer cells [533] and indole-3-carbinol in human colon cancer HT-29 cells [534]. GEN also inhibits the carcinogenic effect of 17 beta estradiol or bisphenol-A via ER/IGF-1/AKT pathway in BG-1 ovarian cancer cells [535] and also downregulates FOXO3 activity in colon cancer cells [524]. It also modulates MAPKs/AKT in cervical cancer cells. [536]. Repression of breast cancer stem cell-induced mammospheres by GEN was similar to the AKT inhibitor perifosine and was related to enhanced tumor suppressor PTEN expressions [537]. Increased ceramide and lipid raft cholesterol accompanied with genistein inhibited the cell viability of

prostate cancer cells via the partial contribution of EGFR-AKT/p70S6k pathway and down-regulation of androgen receptor [538, 539].

Some reports also show a distinct genistein effect whereby it induces PI3K/AKT nongenomic ER signaling to the histone methyltransferase enhancer of zeste homolog 2 (EZH2). As a result, this phosphorylates and represses EZH2 and reduces levels of H3K27me3 repressive mark in chromatin during developmental reprogramming, and promotes uterine tumorigenesis [540]. In colon cancer cells, membrane androgen receptors (mAR) activation inhibits the prosurvival signals AKT/Bad *in vitro* and *in vivo* and blocks migration of colon cancer cells via regulation of vinculin (a protein controlling cell adhesion) signaling and actin reorganization, supporting the powerful tumoristatic effect of mAR receptors. GEN inhibited actin reorganization and restored the motility of these cells and reversed the tumoristatic effect of mARs [541].

A number of concerns have been raised about the estrogen-like effects of natural isoflavones (i.e., the possible promotion of estrogen-sensitive cancers) [542–544]. However, a recent nested case-control study and meta-analysis of numerous epidemiological studies show an inverse correlation between GEN intake and breast cancer risk and a number of other clinical studies support the breast and uterine safety of purified naturally derived GEN administered for up to 3 years [545].

Most phase I and phase II clinical trials of GEN have considered normal dietary dose ranges (i.e., 0.3 mg to 1 mg per kg body weight per day [546]. In one study patients were treated with 2 mg GEN per kg body weight and compared against no treatment prior to undergoing radical prostatectomy for localized prostate cancer [547]. After treatment, it was shown that GEN decreased MMP-2 gene expression to 24% of the level seen in control subjects (blood concentrations of free GEN were approximately 140 nM in the GEN-treated cohorts while control group levels were below detection) [547]. Messing et al initiated a Phase 2 randomized, placebo-controlled trial with oral GEN (300 or 600 mg/d) as the purified soy extract G-2535 and found that GEN was more effective at lower dose on bladder cancer tissue through EGFR phosphorylation but the AKT pathway was unaltered in both *in vivo* conditions [548]. Another phase II clinical trial with GEN administered at a dose of 531 mg twice daily P.O. starting day -7 until the end of study participation with erlotinib, and gemcitabine in advanced pancreatic cancer did not appear to increase the survival of patients with advanced pancreatic cancer [549]. In another phase II trial, subjects with progressive prostate cancer were treated with soy milk three times daily for 12 months (approx 1 mg GEN per kilogram per day) which decreased the rate of increase of serum prostate-specific antigen (PSA) when compared to that which was seen in subjects prior to entering the study [550]. Finally, a third phase II study of GEN in men with various stages of prostate cancer used soy extract (6 mg GEN per kg per day for 6 months) [551] with 17% of the participants experiencing a decrease in their PSA levels.

From an immune perspective, a range of effects have been found. For example, Yellayi et al reported that sub-cutaneous GEN injections (8 mg/kg per day) in ovariectomized adult mice lead to estrogen receptor (ER) and non-ER-mediated inhibition of thymocyte and CD4(+)CD8(−) helper T cell lineage maturation as well as systemic lymphocytopenia [514].

Additionally, GEN produced suppression of humoral immunity. The significant thymic and immune changes in mice produced by serum GEN levels at 8 mg/kg per day was also comparable to those reported in soy-fed human infants [514]. GEN also appears to compete with endogenous 17beta-estradiol for estrogen receptors to suppresses Agspecific immune responses. Specifically 20mg/kg GEN downregulated OVA-specific proliferative responses, interferon-gamma production levels and immunoglobulin (Ig)G1 without reduction in responses to anti-CD3 monoclonal (m)antibody and Ag-presenting activity of CD11c(+) dendritic cells [552]. And GEN has also been shown to potently induce the granzyme B inhibitor, proteinase inhibitor 9 (PI-9) in MCF-7 human breast cancer cells inhibiting the ability of human NK cells to lyse breast cancer cells [553].

By contrast, however, the ingestion of GEN significantly increased lymphocyte proliferation and LDH release, and caused a significant increment in IFN-γ in a mouse model of Human Papillomavirus associated-cervical cancer resulting in a significant therapeutic effect (compared to a control group) [554]. GEN also produced a significant increase in ex vivo cytotoxic T lymphocyte (CTL), a potentiating effect on NK cells (but a decrease in the percentage of CD4(+)CD25(+) T cells), an increase in the production of IFN-γ, and the activation of STAT1 and STAT4 in a 7,12-dimethylbenz[a]anthracene (DMBA)-induced tumor model in mice. This resulted in an antitumor effect and an enhancement to host resistance in this study [555]. So the immunomodulatory potential of GEN appears to be quite nuanced and it may require further investigation before we fully understand how these effects impact various cancers.

MicroRNA (MiR)

In this section we also review the known impact of these approaches on microRNA (miRs), a relatively new area of intense interest in cancer research. miRs are small non-coding RNAs that regulate gene expression (post-transcriptionally) and target about 80% of the protein-coding mRNAs [556, 557]. They are master regulators of multiple cellular pathways, and the deregulation of miRNAs plays a fundamental role in the onset and progression of many cancers [556].

The miRBase database (http://www.mirbase.org) is a searchable database of published miRNA sequences and annotation. miRBase version 16.0 has 1048 miRNA sequences annotated in the human genome, and miRs and a single miR can target approximately 200 transcripts simultaneously. Each miR can target hundreds of messenger RNAs (mRNA)s and a single mRNA is often the target of multiple miRs within a given cell type [557]. Many housekeeping genes have evolved with shorter length of 3’-UTR to avoid miR regulation [558]. About 50% of annotated human miR genes are located in cancer associated genomic regions or fragile sites that are susceptible to amplification, deletion and translocation in a variety of tumors [23, 559]. Because of this, some miRs could act as either tumor suppressors or oncogenes (oncomir) [560–564].

The posttranscriptional fine tuning of mRNA and proteins levels by miR also plays an important role in developmental and immune regulatory processes [565–569]. They are involved in the regulation of nearly all aspects of cellular function including innate and

adaptive immune responses [570–573]. Deregulated miR expression has been found in several autoimmune disorders and inflammatory conditions [574–576]. Importantly, miRs have been found to be either upregulated or downregulated in tumors [577–580]. Epidemiological studies suggests about 25% of all cancer may be due to chronic inflammation [3, 8], and several miRs have been implicated in both inflammation and cancer [569, 581–584].

MicroRNA-155

miR-155 is found on chromosome 21 (human) and 16 (mice) [585] [586], and is generally considered to be an oncomir with mostly proinflammatory effects. This miR is upregulated by NF-κB [566, 587, 588], which is pivotal in inflammation and cancer [589]. miR-155 is upregulated/activated in B and T cells, macrophages and dendritic cells [566, 585, 590, 591]. miR-155$^{-/-}$ mice are highly resistant to experimental autoimmune encephalomyelitis (EAE) [592, 593]. Mechanistically, this appears to be due to the role of miR-155 in mediating the production of IL-17 (Th17) and IFN-γ (Th1) producing CD4+ T cells [592].

miR-155 has been found at high levels in human B cell lymphomas and other tumors [585, 590, 594–596]. Enforced overexpression of miR-155 in mouse B cells is sufficient to trigger murine B cell lymphoma [597]. It has also been reported that miR-155 acts as an oncogene by targeting tumor suppressor gene suppressors of cytokine signaling 1 (SOCS1) in breast cancer cells [598]. Additionally, the upregulation of miR-155 by mutant p53 was reported to drive breast cancer invasion [599] and this miR suppressed the expression of tumor protein p53 induced nuclear protein 1 (TP53INP1) [600]. miR-155 may also play a role in multiple sclerosis (MS) and rheumatoid arthritis (RA), where elevated levels have been found in brain lesions of MS patients [601] and in synovial samples of RA patients [602]. Overall, miR-155 is emerging, then, as a key oncomir linking inflammation and cancer.

MicroRNA-146

miR-146 is a miRNA family, consisting of two evolutionarily conserved miRNA genes: miR-146a and miR-146b. miR-146 suppresses inflammation and cancer. The distal region of chromosome 5q, which contains miR-146a gene (5q33) in humans is reported to harbor susceptibility loci for autoimmune diseases such as RA [603], Crohn’s Disease [604], asthma [605] and psoriasis [606]. miR-146a and miR-146b, when expressed in highly metastatic human breast cancer cells, function to negatively regulate NF-κB activity [607]. miR-146a and miR-146b have also been found to be highly expressed in RA synovial tissue [608]. Although RA is not a high cancer risk disease, other auto-immune, chronic inflammatory diseases such as inflammatory bowel disease (IBD) are treated in a similar manner (e.g. TNFα inhibitors). Therefore, it would be interesting to examine the role of this miR in such diseases. miR-146a also directly targets PGE2 synthase and increased expression of miR-146a in bone mesenchymal stem cells (BMSCs) is correlated with the inhibition of PGE2 synthase-2 (Ptges-2) and the inhibition of PGE2 release [609]. In contrast to miR-155, miR-146a limits T cell activation and promotes resolution of inflammatory responses [610]. miR-146a$^{-/-}$ mice develop spontaneous autoimmunity and myeloid cancers upon aging, due to hyperactivation of T cells via de-repression of the proinflammatory proteins, IL-1 receptor-associated kinase 1 (IRAK1) and TNF receptor

associated factor (TRAF)6 [610–612]. Finally, Xie et al. recently reported that the inhibition of miR-146 results in increased IL-1β, IL-6 and TNF-α secretion, as well as increased expression of IRAK1 [613]. Such studies, then, again highlight a key role of miR-146 in inflammation and cancer.

MicroRNA-21

miR-21 is an oncomir. Its oncogenic activity has been reported where it targets and represses important tumor suppressor genes such as PTEN [614], programmed cell death 4 (PDCD4) [615], tropomyosin 1 (TMP1) [616], B-cell translocation gene 2 (BTG) [617], components of the p53 pathway [618] and also modulates growth inhibitory and pro-apoptotic cytokine TGF-β signaling [618] to further enhance its tumorigenic effects. miR-21 deregulation is a very early event in the multistep progression of pancreatic ductal adenocarcinoma (PDAC) [619]. miR-21 expression is increased in breast and colorectal cancer and in the serum of patients with hepatocellular carcinoma (HCC) [620, 621]. With regards to its role in inflammation, miR-21 expression has been shown to be induced in macrophages and peripheral blood mononuclear (PBM) cells upon LPS challenge [622] and in mammary epithelial cells by inflammatory signals [582]. Similarly induction of miR-21 by IL-6 is a STAT3 dependent mechanism that is responsible for the survival of multiple myeloma cells [623]. It appears that STAT3 together with miR-21, miR-181b-1, PTEN and cylindromatosis (CYLD) is a part of the epigenetic switch that links inflammation to cancer in several cancer types including breast, colon, prostrate, lung and HCC [581]. Finally, Schetter et al. have reported a positive correlation of IL-6 with miR-21 expression in human colon cancer tissues [624], further supporting the role of miR-21 in linking inflammation and cancer.

MicroRNA-17~92 Cluster

miR-17~92 (OncomiR-1) [562] is a cluster of miRs located on human chromosome 13 and encodes a polycistronic miR gene for six mature functional miRs: miR-17, miR-18a, miR-19a, -20, -19b and -92 [625]. Overall, this cluster of miRs has cancer and inflammation-promoting properties. For example, SOCS1, a gene frequently silenced in multiple myeloma, and a strong antiinflammatory instigator, is targeted by miR-19, elucidating the proinflammatory property of miR-19 and its possible link to tumorigenesis [626, 627]. miR-17~92 clusters weaken TGF-β signaling by functioning both upstream and downstream of phospho-SMAD2 as well as through direct inhibition of TGF-β responsive genes [628]. miR-19b positively regulates NF-κβ signaling for proinflammatory cytokine production, is involved in controlling several negative regulators of NF-κB signaling, and plays a crucial role in the pathology of autoimmune diseases [629]. Additionally, miR-17~92 is a well-established player of oncogenesis and overexpression of this cluster and in a Myc-driven mouse model of B-cell leukemia accelerates tumor development [562]. miR-19 can exert its oncogenic effect through its repression of tumor suppressors PTEN and Protein phosphatase 2 (PP2A), pro-apoptotic molecule B-cell lymphoma 2 interacting mediator of cell death and Protein kinase, AMP-activated, alpha 1 catalytic subunit [630–632]. Overall, the miR-17~92 cluster, based on its role in inflammation and cancer could also serve as a potential therapeutic target.

MicroRNA-196

miR-196 is considered an oncomir, is upregulated in several cancer types [569] and is associated with Barrett's esophagus-to-adenocarcinoma disease progression [633]. Luthra *et al*. demonstrated miR-196a directly targets the antiinflammatory player, annexin 1 and has growth promoting and antiapoptotic properties in esophageal adenocarcinoma cell lines [634]. miR-196 is overexpressed in inflamed intestinal epithelial of Crohn's disease patients and downregulates immunity-related GTPase family M protein (IRGM) protective variant (c.313C) but not the risk associated allele (c.313T) [635]. Also, the Rs11614913 SNP in miR-196a-2 may promote susceptibility to breast and lung cancer [636]. These oncogenic and proinflammatory properties of miR-196a support its role in inflammation and cancer.

microRNA-663

miR-663 is currently reported as an antiinflammatory and tumor suppressor miR and impairs the upregulation of miR-155 by inflammatory stimuli [637, 638]. The overexpression of hypomethylated miR-663 induces chemotherapy resistance in human breast cancer cells by targeting heparan sulfate proteoglycan 2 (HSPG2) [639].

Other microRNAs involved in inflammation and cancer

miR-9 is canonically induced by NF-κβ following TLR4 activation in human neutrophils and monocytes and provides feedback to repress NF-κB signaling through direct targeting of p50 mRNA [640]. Overexpression of miR-9 by MYC/MYCN is involved in cancer metastasis [641, 642]. This elucidates a possible link between inflammation and cancer by miR-9. Several studies reported upregulation of miR-210 in hypoxic condition [643–645] and its importance for cell survival [646]. miR-210 is a sensor for hypoxic stress during tumorigenesis, where increased miR-210 expression inhibits tumor growth to provide tumor cells an opportunity to prevail in stressful hypoxic condition [647]. Thus, a possible connection between hypoxia and tumorigenesis is mediated by miR-210. miRNA-16 is a putative tumor suppressor miR, and is downregulated in a variety of human cancers [648–654]. One recognized function of miR-16 is that it controls the cell cycle primarily through a G1 cell cycle checkpoint [649, 655–662].

The finding that miR-16 is upregulated in high colon cancer risk, and chronic inflammatory disease possibly indicates an adaptive upregulation of this tumor suppressor miR in response to inflammatory stress. Finally, inhibiting the peptidyl arginine deiminase (PAD) enzyme, which catalyzes the post-translational conversion of peptidyl-arginine to peptidyl-citrulline ("citrullination") causes an increase in miR-16 [663]. The fact that citrullination is thought to be an inflammation-dependent process [664] supports the notion that miR-16 is involved in the suppression of inflammation. miR-125b expression is decreased after LPS challenge in macrophage cells [665], and additionally in several inflammatory condition such as psoriasis and atopic eczema [666]. Further down-regulation of miR-125b has been reported in several tumor types such as thyroid anaplastic carcinomas, hepatocarcinomas, oral, bladder cancer, ovarian and breast cancer [569]. Finally, miR-663 is currently reported as antiinflammatory and tumor suppressor microRNA and impairs the upregulation of miR-155 by inflammatory stimuli [637, 638].

Selected approaches that modulate miR involved in inflammation and cancer

Signaling pathways involving inflammation and cancer are clearly regulated by miRs so here we specifically discuss studies that relate to the therapeutic approaches reviewed above. For reference sake, additional details on other dietary components that regulate miRs have been reviewed in detail elsewhere [557, 667].

Resveratrol

Since both resveratrol and miR influence cellular homeostasis and disease conditions, resveratrol could act through miRs in modulating and targeting the factors involved in disease and cellular homeostasis. Tili and Michaille reviewed resveratrol, miRs, inflammation and cancer [668], and note that resveratrol has been shown to induce the expression of miR-663, a tumor-suppressor and antiinflammatory miR, while down-regulating proinflammatory miR-155 and oncogenic miR-21.

Curcumin

Curcumin regulates the expression of genes that are involved in the regulation of cellular inflammatory and cancer signaling pathways, such as NF-κB, AKT, MAPK and other pathways [669, 670]. These signaling pathways are in turn regulated by several miRs. In a spontaneously arising retinal pigment epithelia cell line (ARPE-19 cells), curcumin treatment lowers the expression of miR-17~92 cluster and its pre-treatment attenuates H_2O_2 induced expression of miR-15b, miR-21, miR-17, miR-196b and miR-9 [671]. The curcumin analog CDF decreases pancreatic cancer cell survival by increasing the expression of the tumor suppressor miRs, Let-7 and miR-146a, which are typically lost in pancreatic cancer [672]. The mesenchymal phenotype of gemcitabine-resistant pancreatic cancer cells has been shown to be reversed by simply treating the cells with either CDF or curcumin which upregulates the expression of miR-200b and miR-200c [673]. Curcumin also reduces miR-21 expression and activity via AP-1, suppresses tumor progression, and stabilizes the tumor suppressor Pdcd4 in colorectal cancer cells [674].

Genistein

Genistein enhances the apoptotic effects of exogenous miR-16 in murine CLL cells [675]. Isoflavones regulate miR function by inducing expression of miR-200 and let-7 to reverse EMT phenotype [676]. Isoflavones have also been shown to upregulate miR-146a and target EGFR and IRAK-1/NF-κB signaling to inhibit pancreatic cancer cell invasion [677]. These studies provide evidence that isoflavones regulate miRs involved in inflammation and cancer which may provide a prevention and/or treatment measure.

EGCG

EGCG is a major catechin in green tea and has been implicated in many pathways involved in inflammation and cancer. EGCG upregulates miR-210 in human and mouse lung cancer cells in culture which leads to reduced cell proliferation mediated by stabilization of HIF-1α [678]. EGCG antagonizes androgen action and down-regulates miR-21 and upregulates tumor suppressor miR-330 in prostate tumors of mice [679]. EGCG has also been shown to decrease expression of oncomirs (miR-92, miR-93, and miR-106b) and increase the

expression of tumor suppressor miRs (miR-7-1, miR-34a, and miR-99a) in neuroblastoma cells [680].

Cross-validation for Tumor Promoting Inflammation

Given that the heterogeneity that is present in most cancers, it is our assumption that the complete arrest of the various subpopulations of immortalized cells in any given cancer will require simultaneous actions on mechanisms that are important for several aspects of cancer's biology. We therefore believe that it is important to be able to anticipate synergies that might be achieved by acting on specific targets and with specific approaches (i.e., when contemplating an approach aimed at a broad-spectrum of targets). Accordingly, in this review the prioritized target sites and the approaches that have been identified (as potential ways to reach those targets) were all cross-validated by conducting a background literature research. A team of researchers consisting of specialists in each area specifically sought to determine the relevance of these targets and the nominated approaches across a number of important areas of cancer's biology.

In this regard, targets and approaches that were not only relevant for this area of study, but also relevant for other aspects of cancer's biology (i.e., anticarcinogenic) were noted as having "complementary" effects. Those that were found to have procarcinogenic actions were noted as having "contrary" effects. In instances where reports on relevant actions in other aspects of cancer biology were mixed (i.e., reports showing both procarcinogenic potential and anticarcinogenic potential), the term "controversial" was used. Finally, in instances where no literature support was found to document the relevance of a target site or approach in a particular aspect of cancer's biology, we documented this as "no known relationship". These validation results are shown below in tabular form in Tables I and II.

The decision to review priority target sites and approaches for reports of cross-hallmark effects was driven by the fact that many individual studies and reviews fail to account systematically for the spectrum of incidental actions that can result from various forms of therapeutic interventions. It is our belief that this approach constitutes a better way to ensure that we had assembled a reasonably thorough review of the literature (i.e., where any sort of evidence of cross-hallmark activity had been reported).

Because future research on therapeutic combinations will likely involve empirical testing of mixtures of constituents, we wanted to create a starting point for other researchers who might be considering translational projects. We anticipated interest in approaches reported to exhibit a large number of anticarcinogenic actions across the hallmarks and we anticipated that a lack of procarcinogenic potential was important to identify (since targets or approaches that have been shown to exert procarcinogenic actions would potentially represent a confounding and unwanted influence/factor in empirical research). A summary of these reports is also provided in Tables I and II.

Note that, in some instances, the underlying evidence used to support the indication of a cross-hallmark relationship was robust, consisting of multiple studies involving detailed *in-vitro* and *in vivo* findings. In other instances, however, the underlying evidence that was used to report the existence of a cross-hallmark relationship was quite weak (e.g., consisting

of only a single in vitro study involving a single cell-type). Additionally, there are examples of approaches that are known to exert different effects at different dose levels and in different tissues but dose-levels and cell/tissue types were not used to discriminate when gathering together these reported actions.

Nonetheless, given that the overarching goal in this project was to create a foundation that would allow researchers to look systematically across the literature in each of these areas, the tables should serve as a useful starting point as long as they are approached with caveats in mind and a degree of caution. Essentially, we believe that this heuristic model should be useful to consider synergies that might be anticipated in testing that involves certain targets and/or mixtures of chemical constituents that are being considered for therapeutic effects.

Summary/Conclusions

In sum, it was our goal to explore a series of high priority antiinflammatory targets for therapeutic intervention in cancer as part of a larger effort to develop a broad-spectrum approach aimed at a wide range of targets that are relevant for cancer biology. The selected targets MIF, COX-2, NF-κB, TNF-α, iNOS, AKT and CXC chemokines represent a promising and interrelated set of targets that are pleiotropic, with demonstrated potential not only for inflammation, but also for a wide range of other effects that support the various hallmark phenotypes found in a wide range of cancer types.

At the same time, the approaches that we selected to act on those targets, (curcumin, resveratrol, EGCG, genistein, lycopene, and anthocyanins) are all agents than have demonstrated a range of anticancer effects. While we focused mainly on antiinflammatory effects, many of these approaches have demonstrated a range of anticarcinogenic actions as well. In addition to the most widely reported direct effects of these agents, we have also summarized miR regulated gene expression related to inflammation and cancer, and the known effects of these approaches on these MiRs.

Given the tight coupling between inflammation and the immune system, we also wanted to consider the possibility that proposed actions on important antiinflammatory targets, and/or the chronic administration of the antiinflammatory chemicals might predispose individuals to infection or modulate the immune system in a manner that might be relevant for immune-related antitumor effects. Perhaps not surprisingly, an increased risk of infection appears to be a concern for therapeutic approaches aimed at suppressing MIF, Cox-2, NF-κB, and TNF-α, and in the use of curcumin (as a therapeutic approach). By contrast, EGCG appears to have a protective effect against bacterial infection. Immunomodulation of antitumoral effects is also a nuanced picture. COX-2 inhibition and PI3K-Akt pathway inhibition both appear to be attractive targeting strategies that have antitumoral effects that are immune-related. Similarly, curcumin, resveratrol and EGCG have also been shown to act on the immune system in a favorable manner. However, lycopene and genistein have demonstrated a range of competing effects on the immune system making their utility from this perspective more difficult to discern.

Future research should address the ambiguities posed by the wide range of CXC Chemokines and their various effects, as precise targets are needed to better characterize the range of effects and synergies that might be anticipated. Similarly, within the selected approaches, specific anthocyanins that appear to have the greatest promise should be isolated and better characterized for effects across the range of cancer hallmark phenotypes, and for bioavailability and toxicity.

Ideally, future translational work would utilize the agents that we have identified in this review combined as constituents within a multi-pronged antiinflammatory approach with very little/no toxicity.

However, any multipronged strategy that focuses on these targets and/or approaches will need to carefully consider the potential for increased risks related to infection and anticipate the possibility for a range of immunomodulation that will have relevance for antitumoral effects.

Bioavailability challenges with a number of these agents are starting to be addressed, and foreseeably recent advances that uses implantable polymeric micelles, liposomes, microspheres, nano-delivery systems, phospholipid-based delivery systems and other systems (c.f. [359–362]) will help address this issue.

The cross-validation tables (Table I and II) are offered here as a simple heuristic framework that is intended to help researchers approach the topic of anticipated synergies. Although these initial results do not represent a homogenous set of underlying data, it is hoped that they can serve as a starting point for the translational research that will be needed. Rigorous experimentation will obviously be needed to determine whether or not actual synergies emerge that can be predicted using this approach. Other synergies may emerge depending on the specific constituents and model used.

The key is to recognize that a low-toxicity approach aimed at many important targets to reduce tumor-promoting inflammation is only a stepping stone. Most cancers harbor significant genetic heterogeneity [4], and patterns of relapse following many therapies are due to evolved resistance to treatment. Consequently, an antiinflammatory approach along these lines should be developed and then combined with other similar approaches that aim to target the many disease-specific pathways that have relevance across the range of hallmark phenotypes. A much broader range of targets overall may be the only chance we will have to address this heterogeneity. It is a promising approach, but a considerable amount of encompassing research needs to follow to determine methodological validity

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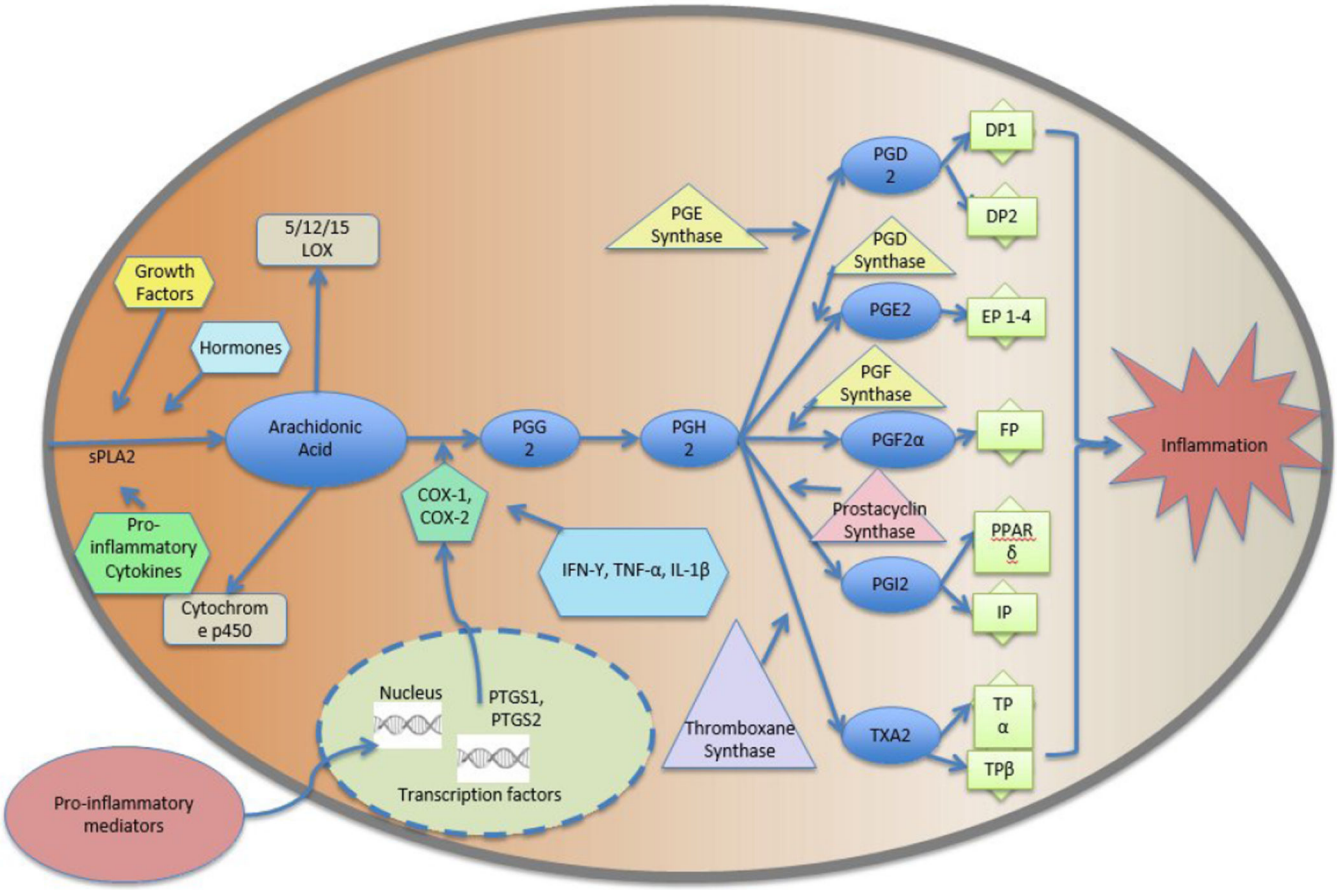

Figure I.
Arachidonic Acid Cascade

Table I

Cross validation of Targets

Prioritized targets evaluated for known effects in other cancer hallmark areas.

Potential targets for inflammation[1] / Other hallmarks	Inhibit Cox-2	Inhibit NF-κB	Block MIF	Block TNFα	Block iNOS	Block AKT	Inhibit CXC chemokines
Genomic Instability	+ [681]	+ [682]	0	0	0	+ [683–685]	0
Sustained Proliferative Signaling	+ [686–688]	+ [689–691]	+ [54, 692]	+ [693, 694]	+ [695]	+ [696]	+ [697]
Evasion of Anti-growth Signaling	+ [698, 699]	0	+ [53, 700]	+ [701, 702]	+ [703]	+ [704]	+ [705]
Resistance to Apoptosis	+ [706]	+ [707]	+ [708]	+ [709]	+ [710]	+ [711]	+ [712]
Replicative Immortality	+ [713–715]	+/− [716–718]	+ [719, 720]	+ [721]	0	+ [711, 722, 723]	0
Deregulated Metabolism	+ [724]	+ [725–727]	0	+ [728–731]	+ [732, 733]	+ [234, 734–736]	0
Immune System Evasion	+ [737, 738]	+ [739]	+ [740]	− [44]	0	+ [741]	+/− [742]
Angiogenesis	− [743]	+/− [744, 745]	+ [54, 55, 746]	+/− [154]	− [747]	+ [748]	+/− [749]
Tissue Invasion and Metastasis	+ [750–753]	+ [754]	+ [755, 756]	+ [757]	+ [758]	+ [759]	+ [760]
Tumor Microenvironment	+ [761]	+ [762]	+ [763]	+ [764]	+/− [765]	+ [766, 767]	+/− [768, 769]

[1] Targets that were found to have complementary, anticarcinogenic actions reported in another hallmark area were indicated with "+", while targets that were found to have procarcinogenic actions in another hallmark area were indicated with "−". In instances where reports on relevant actions in other hallmark areas were mixed (i.e., reports showing both anticarcinogenic potential and procarcinogenic potential), the symbol "+/− " was used. Finally, in instances where no literature support was found to document the relevance of a target in a particular aspect of cancer's biology, we documented this as "0". These cross-hallmark relationships are reported in the first eleven columns of the table. The number of anticarcinogenic, procarcinogenic and mixed cross-hallmark relationships for each target have been summed and are reported in the last three columns of the table.

Table II

Cross validation of Approaches

Selected approaches evaluated for reported actions in other cancer hallmark areas.

Approach[1]	Curcumin	Resveratrol	EGCG	Lycopene	Anthocyanins	Genistein
Other Hallmarks						
Genomic Instability	+ [770]	+ [682]	+ [771]	+ [772]	+ [770]	+ [773]
Sustained Proliferative Signaling	+ [774]	+ [775–777]	+ [678, 778]	+ [488, 779]	+ [780, 781]	+/− [782, 783]
Evasion of Anti-growth Signaling	+ [784, 785]	+ [786, 787]	+ [788, 789]	+ [790–792]	+ [793]	+/− [544, 794, 795]
Resistance to Apoptosis	+ [796]	+ [797]	+ [798]	+ [799]	+ [800]	+ [518]
Replicative Immortality	+ [774, 801, 802]	+ [803, 804]	+ [805, 806]	0	+ [807]	+ [808, 809]
Deregulated Metabolism	+ [810]	+ [811, 812]	+ [813–815]	0	0	+/− [816]
Immune System Evasion	+ [371]	+/− [425, 817–819]	+ [820]	0	0	+/− [554, 821]
Angiogenesis	+ [822]	+/− [823]	+ [824]	+ [825]	+ [826]	+ [827]
Tissue Invasion and Metastasis	+ [774, 828]	+ [829]	+ [312, 830, 831]	+ [832]	+ [833]	+ [830]
Tumor Microenvironment	+ [834, 835]	+ [836, 837]	+ [820, 838]	+ [772, 839]	+ [840]	+ [841]

[1] Approaches that were found to have complementary, anticarcinogenic actions in a particular hallmark area were were indicated with “+”, while approaches that were found to have procarcinogenic actions in a particular hallmark area were indicated with “ −”. In instances where reports on relevant actions in other hallmarks were mixed (i.e., reports showing both anticarcinogenic and procarcinogenic potential), the symbol “+/−“ was used. Finally, in instances where no literature support was found to document the relevance of an approach in a particular aspect of cancer's biology, we documented this as “0”. Threse cross-hallmark relationships are reported in the first eleven columns of the table. Finally, the number of anticarcinogenic, procarcinogenic and mixed cross-hallmark relationships for each target have been summed and are reported in the last three columns of the table.