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Cancer prevention and therapy through the modulation of the tumor microenvironment

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Abstract

Cancer arises in the context of an *in vivo* tumor microenvironment. This microenvironment is both a cause and consequence of tumorigenesis. Tumor and host cells co-evolve dynamically through indirect and direct cellular interactions, eliciting multiscale effects on many biological programs, including cellular proliferation, growth, and metabolism, as well as angiogenesis and hypoxia and innate and adapative immunity. Here we highlight specific biological processes that could be exploited as targets for the prevention and therapy of cancer. Specifically, we describe how inhibition of targets such as cholesterol synthesis and metabolites, reactive oxygen species and hypoxia, macrophage activation and conversion, indoleamine 2, 3-dioxygenase regulation of dendritic cells, vascular endothelial growth factor regulation of angiogenesis, fibrosis inhibition, endoglin, and Janus kinase signaling emerge as examples of important potential nexuses in the regulation of tumorigenesis and the tumor microenvironment that can be targeted. We have also identified therapeutic agents as approaches, in particular natural products such as berberine, resveratrol, onionin A, epigallocatechin gallate, genistein, curcumin, naringenin, desoxyrhapontigenin, piperine, and zerumbone, that may warrant further investigation to target the tumor microenvironment for the treatment and/or prevention of cancer.

Keywords

tumor microenvironment; cancer biology; cancer therapy; cancer prevention

1. Introduction

1.1 Tumor microenvironment as a therapeutic target

The tumor microenvironment is critical to both the initiation and maintenance of tumorigenesis [1,2]. The tumor microenvironment is comprised of a complex network that includes multipotent stromal cells/mesenchymal stem cells, fibroblasts, blood vessels, endothelial cell precursors, immune cells, and secreted factors such as cytokines [2]. During tumor progression, changes in the microenvironment occur through effects on a molecular as well as cellular level and involve interactions between incipient cancer cells and host structural as well as adapative and innate immune cells [3]. Many of the “hallmarks of cancer” are related to the tumor microenvironment, including the ability to induce proliferation and inhibit apoptosis, to induce angiogenesis and avoid hypoxia, to inhibit the immune system and avoid immune detection, and to activate immune cells to support invasion and metastasis [4]. Specific oncogenic pathways can be associated with dramatic changes in the tumor microenvironment [5–8]. Hence, the manipulation of the tumor microenvironment could be used as an approach to prevent as well as treat cancer.

Identification of therapeutic targets in the tumor microenvironment could be useful in the treatment and prevention of cancer. The typical biological approach has been to investigate specific molecular and cellular mechanisms and then to examine whether or not the inhibition or activation has the expected consequences for tumorigenesis. However, there are caveats to this approach. The same molecules and effector cells can have roles in both the prevention and initiation of tumorigenesis. Different cancers can occur through disparate mechanisms. What is limiting in some contexts may be in other circumstances of no importance. Some targets may have effects on multiple pathways and programs that can counteract their overall effectiveness. Hence, the ability to reconcile how to target the microenvironment and identify suitable therapies is daunting.

In this review, we have taken a different approach. Through an intiative supported by the Halifax Project, a group of investigators worked together as a team to identify both specific targets and novel approaches to therapeutically inhibit specific aspects of the tumor microenvironment. Through an integrative approach we have identified strategies for the treatment and prevention of cancer. Then, we examined the literature and thereby identified possible agents, in particular natural products, which could potentially inhibit some or several of these targets. Our goal was to identify existing agents that may be exploited for the prevention and/or treatment of cancer. Finally, the team utilized a cross-validation approach to examine how these targets and approaches, either alone or in combination, could be useful for the prevention and/or treatment of cancer.

We identified ten programs that could be or definitely appear to be targets and ten existing natural agents that may mediate their reported anti-cancer effects through the tumor

microenvironment (Figures 1 and 2, Tables 1 and 2). Our list is not a complete examination of all possible targets or therapeutic approaches but rather an attempt to identify existing broad-spectrum, lower toxicity therapeutics that could be combined with existing therapeutics.

The targets identified include metabolic programs that may broadly influence many cell biology programs that impact tumorigenesis and the tumor microenvironment (cholesterol synthesis and metabolites, reactive oxygen species (ROS) and hypoxia, inflammation, innate and adaptive immunity related programs (macrophage conversion, dendritic cell (DC) activation, immune signaling), host microenvironment associated cellular programs (fibrosis, angiogenesis), and cytokine mediated regulatory programs (interleukin (IL)-6, endoglin, and Janus-associated kinase (JAK)) (Figure 1, Tables 1 and 2).

We particularly focused on identifying approaches for inhibiting these targets, including natural products that may have significant anticancer activity. Some of these molecules may more generally influence tumorigenesis and the microenvironment (berberine), others more specifically target ROS (resveratrol, desoxyrhapontigenin) macrophage conversion (onionin A), indoleamine 2,3-dioxygenase (IDO) regulation of dendritic cells (epigallocatechin-3-gallate (EGCG)), cholesterol synthesis (genistein), fibrosis (naringenin), inflammation and immune signaling (piperine), vascular endothelial growth factor (VEGF) inhibition (curcumin), and JAK signaling (zerumbone). These approaches may warrant further investigation (Figure 1, Tables 1 and 2). These agents generally have low toxicity, suggesting that they could be combined with each other or existing therapies.

1.2 Cross-validation of approaches and targets

We identified approaches and targets through the analysis of the scientific literature via a team of investigators from a multitude of subspecialties. We made several assumptions. First, the complex biology and heterogeneity of cancer suggested that the most effective therapeutic approach may require simultaneous actions on mechanisms that are important for many of the hallmarks of cancer. Second, we anticipated that synergies would be achieved by combining specific targets and with specific approaches. Third, we considered that we could validate both targets and approaches through a cross-validation through the analysis of literature. Finally, we considered it was important to examine the relevance of the identified targets and the nominated approaches across different aspects of cancer biology.

Notably, the targets and approaches that we identified for the tumor microenvironment have been shown to be relevant to other cancer hallmarks. These are noted as having “complementary” effects, while those that were found to have pro-tumorigenic actions were noted as having “contrary” effects. Instances where reports on relevant actions in other aspects of cancer biology were mixed, where reports showing both pro-cancer potential and anti-tumorigenic potential, we have used the term “controversial.” 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 (Tables 1 and 2).

Our priority was to choose targets and approaches after consideration of potential cross-hallmark effects. We examined for possible incidental actions from therapeutic interventions. We assembled a reasonably complete view of the literature. However, we recognize that our results are a starting point. Future research on therapeutic combinations will require empirical testing of mixtures of constituents.

In some instances, published evidence of cross-hallmark relationships is robust. In other cases, the underlying evidence was weak, consisting of only a single *in vitro* study involving a single cell type. Dose levels and cell/tissue types were not used to discriminate when gathering together these reported actions. Hence, our results serve as a starting point, with caveats in mind and a degree of caution. We believe this heuristic approach will 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.

2. Targets

2.1 Cholesterol synthesis and its metabolites

The cholesterol pathway has general importance in the pathogenesis of many disease states, including cancer, through the regulation of cellular signaling, oncogene activation, hormone signaling, inflammation, and immune response, amongst many possible contributions.

Cholesterol synthesis and metabolites are intimate to the pathophysiology of carcinogenesis [9–11]. Cholesterol and its metabolites have an influence on many biological programs that are critical to cellular growth and signaling. Cholesterol and its metabolites are integral to the structure and fluidity of cellular membranes and are the templates for hormones and messengers and regulate cellular signaling and activation of oncogenes. Cholesterol is critical to normal host cellular and immune function. Cholesterol is specially localized in lipid rafts, which are membrane microdomains that assemble the signal transduction machinery and associate with proteins involved in key cellular signaling pathways. Many of these pathways closely associate with malignant transformations due to their effect on organization of the cytoskeleton, cell polarity, and angiogenesis [12].

Cholesterol was first identified in gallstones [13]. Subsequently, cholesterol was found to be important for many biological purposes, including core body temperature, the structural integrity and fluidity of cellular membranes, the production of bile salts, the synthesis of hormones such as vitamin D, testosterone, progesterone, cortisol and estradiol, the regulation of cellular signaling and activation of many gene products [9,10]. Indeed, cholesterol and its metabolites are critical to the regulation via prenylation of many oncogenes including RAS and perhaps MYC [14,15]. Cholesterol biosynthesis generally appears to be altered in cancer cells and its inhibition can impede tumorigenesis [16]. Hence, understanding cholesterol's metabolism could be important to understanding potential therapeutic approaches for cancer.

Cholesterol biosynthesis has been well defined [16,17]. Cholesterol is generally synthesized in the liver beginning with one molecule each of acetyl CoA and acetoacetyl CoA [18]. Cholesterol is regulated in the endoplasmic reticulum by sterol regulatory element-binding

protein (SREBP) 1 and 2 [19]. Cholesterol synthesis is controlled by a single enzymatic reaction mediated by beta-hydroxy- beta-methylglutaryl CoA reductase (HMG- CoA) [20]. Many studies suggest that cholesterol and its metabolites play a fundamental role in tumorigenesis.

First, mouse model studies suggest that cholesterol biosynthesis is causative for tumorigenesis [21–23]. Similarly, in transgenic mouse models of oncogene-induced lymphoma and liver cancer, tumorigenesis is prevented when mice are treated with inhibitors of HMG-CoA reductase [24,25], which was found to be associated with the inhibition of RAS and MYC oncogenes, respectively.

Second, epidemiological studies have shown that patients receiving agents that inhibit cholesterol metabolism reduce the risk of cancer [26]. Notably, serum cholesterol and cancer risk appears to depend upon the site of cancer [27].

Third, other studies have been reported demonstrating increased levels of cholesterol in tumors compared to normal tissue [28,29]. Fourth, cancers often exhibit alterations in programs that regulate cholesterol biosynthesis through the upregulation of HMG-CoA reductase activity [30,31], loss of feedback inhibition [20], increased uptake of extracellular cholesterol through the LDL receptor [32,33] and decreased expression of cholesterol exporter ATP binding cassette transporter A1 (ABCA1) [33–35]. Finally, obesity and high cholesterol level is associated with increased risk of breast cancer in postmenopausal women [11,36].

Cholesterol metabolites play a key role in the regulation of cellular and nuclear oncogene activation. Cholesterol metabolites are key to the regulation of many oncogenes through prenylation including the RAS oncogene [25]. In turn, this leads to the regulation of the MYC oncogene [24,25]. Thus, cholesterol metabolism is likely playing a role in tumorigenesis. Cholesterol is a key component of cellular membranes, a metabolite required to regulate oncogene activation, and a template for critical hormomes. The potential importance of cholesterol biosynthesis in cancer has led to significant interest in the use of HMG-CoA reductase inhibitors, statins, for the treatment or prevention of human cancer [37–41].

2.2 ROS

ROS influences the tumor microenvironment through many mechanisms that may be important for the treatment and prevention of cancer [42]. ROS can be defined as oxygen radicals and non-radical oxidizing agents that can be easily converted to radicals containing one or more unpaired electrons [43]. Major enzymes implicated in the generation of ROS are nicotinamide adenine dinucleotide phosphate (NADPH), myeloperoxidase (MPO) and xanthine oxidoreductase (XOR). The non-enzymatic reaction that produces ROS is through the mitochondria and generally involves the use of “catalytic” iron or copper ions. ROS are involved in various metabolic processes and enzyme reactions in the cells, in electron transport chain in the mitochondria, gene expression, signal transduction, activation of transcription factors [44,45]. Excess production of ROS may ultimately lead to tissue damage [43].

ROS contributes to tumorigenesis through mutagenesis as well as effects on the tumor microenvironment [46]. ROS levels in cancer cells are higher compared to those present in the normal cells [47,48], as cancer cells produce ROS via mitochondria [49]. Deregulation of the anti-oxidant machinery of the mitochondrial matrix has been shown to contribute significantly during cellular transformation. This is achieved by enhancement in the levels of ROS in the matrix [49] that may play an important role in the regulation of ROS [50–52].

The regulation of ROS is important to tumorigenesis. The mitochondrial enzyme superoxide dismutase 2 (SOD2) [53,54] regulates tumor hypoxia [55]. Oncogenes and tumor suppressor genes are regulated by ROS, including the phosphatase and tensin homologue (PTEN) tumor suppressor [56,57], the mitogen activated protein kinase (MAPK), and the extracellular signal regulated kinases (ERK) pathway [58–60]. ROS levels have been shown to influence tumor angiogenesis [61] and regulate tumor self-renewal/stemness associated with cancer stem cells [62]. Finally, the anti-neoplastic properties of some therapeutic agents may be mediated by their antioxidant properties [63], including tamoxifen [63,64] and sulphasalazine [65,66]. The manipulation of ROS levels could be therapeutically exploited for the treatment and prevention of cancer.

2.3 Macrophage conversion

Macrophage function and regulation contribute to tumorigenesis. Tumor associated macrophages (TAMs) and other innate immune cells have been found to regulate the tumor microenvironment, including the promotion of angiogenesis, initiation of fibrosis, and suppression of immune detection [67]. Recently, it has emerged that tumors can secrete factors that promote the conversion of macrophages from an “M1” to an “M2” phenotype [68]. Physiologically activated macrophages, or M1-type macrophages, produce cytokines such as IL-1β, IL-8, IL-12, IL-15, IL-18, IL-23 and tumor necrosis factor (TNF)-α in response to signaling through toll-like receptors triggered by damage associated molecular patterns present on bacteria, fungi, viruses and parasites [68]. These acute inflammatory mediators, in particular, IL-12, promote the development of a Th1 immune response to eliminate foreign pathogens and cancer cells [69]. However, macrophages within tumors are not exposed to danger signals and produce higher levels of IL-10, a cytokine that alters the differentiation of T cells away from the cytotoxic Th1 response [70]. M2 macrophages also secrete higher levels of transforming growth factor (TGF)-β, a cytokine that can dampen the ability of T cells to mount a targeted response and may lead to cancer cells attaining stem cell like features [71]. TGF-β also induces the activation of fibroblasts and other mesenchymal cells that eventually leads to tissue fibrosis. Thus, tumor associated macrophages can promote carcinogenesis, angiogenesis and immune escape.

Macrophages express major histocompatibility complex (MHC) class I and II. Thereby, they can present tumor antigens through MHC II to CD4+ T cells and to cross-present MHC-I to CD8+ T cells [72]. Following activation by toll-like receptors such as lipopolysaccharide (LPS) or interferon-gamma (IFN-γ), macrophages upregulate costimulatory molecules such as MHC-class I, CD80, CD83 and CD86, enabling T cells to fully mature and mount an antigen-specific immune response [73]. However, in a tumor microenvironment, macrophages do not appear able to present antigens. This may be reversible. Thus, IL-12 can

convert M2 into M1 macrophages. This can enable antigen presentation to CD8+ T cells and improved anti-tumor immunity [74].

TAMs can contribute to tumorigenesis by inducing the expression of immune checkpoints on tumor cells. For example, TAMs can induce the expression of programmed death-ligand 1 (PD-L1) [73]. This can engage the PD-1 receptors on T cells and inhibit their ability to respond to tumor antigens. Therapies that block PD-1 and PD-L1 may be effective for the treatment of many types of cancer. [75,76]. In general, increased TAMs correlates with poor prognosis of patients [77,78]. Hence, therapies that target TAMs or alter their function may be useful for the treatment of cancer.

2.4 IDO

DCs are antigen-presenting cells that link the innate and adaptive immunity and have been implicated in the immune regulation of cancer [79,80]. DCs are key players in inducing anti-tumor immune responses. DCs exposed to antigen in the absence of the correct costimulation can induce tolerance [81]. The tolerogenic function of DCs has been associated with low levels of specific molecules including the B7 family members and PD-L1, B7-H2, B7-H3, B7-H4 and BTLA [82–89].

The immune tolerance mediated by DCs appears to be mediated by enzymes that negatively regulate the function of effector lymphocytes in an antigen-independent fashion. These include inducible nitric oxide synthase, which generates nitric oxide, arginase-1, which depletes the milieu of arginine, and IDO, which degrades the essential amino acid tryptophan (TRP) and catalyzes the generation of kynurenine (KYN) [90–95].

The immune system can serve a protective role against tumor development [96–100]. DCs harboring active IDO have been detected in the tumor microenvironment or draining lymph nodes [101–103]. These cells can suppress T cell functions via IDO activation by two mechanisms. In the case of KYN, upon interaction with the aryl hydrocarbon receptor, this molecule has been shown to inhibit proliferation of T cells and NK cells, promote regulatory T cell (Treg) differentiation, and inhibition of DC immunogenicity [90,91,104]. In addition, rapid TRP depletion from the microenvironment sends stress signals to T cells, inducing anergy in CD8 cytotoxic T cells and promoting CD4 differentiation towards Tregs [90,91,105].

Tumor cells can synthetize IDO. But, it is not clear if the major contributors to KYN generation and TRP depletion in the tumor microenvironment are tumor cells or infiltrating leukocytes, in particular DCs or TAMs [90,91,106]. Regardless of the source, IDO activation can induce immunosuppression. High levels of IDO are correlated with poor prognosis [107–112]. IDO inhibition can suppress tumor growth in mouse models [113–117]. Hence, IDO inhibitors may be useful to target the tumor microenvironment for the treatment of cancer.

2.5 VEGF

VEGFs are critical regulators of tumor angiogenesis. They comprise a family (VEGF-A, -B, -C, -D, -E and placenta growth factor [PGF]) of growth factors that show a conserved pattern

of eight cysteine residues [118–120]. In particular, VEGF-A (the paradigmatic molecule of this family and usually referred to as VEGF) has the capability to act both as a mitogen, stimulating the proliferation of endothelial cells, and also a chemotactic factor with the capability to attract monocytes [118–120].

Human VEGF-A has four different isoforms (VEGF 121, 165, 189 and 206), a consequence of alternative exon splicing [118]. The properties of native VEGF most closely correspond to that of VEGF-165, which is the predominant VEGF-A isoform [118]. VEGF participates in different physiological processes such as angiogenesis, wound healing, and embryogenesis [118–120]. VEGF has been shown to participate in pathological processes such as diabetic retinopathy and oncogenesis [118]. Tumors require angiogenic factors to induce the formation of neovessels [121–123]. VEGF alone can initiate the angiogenic cascade [124]. VEGF is secreted by most human cancers [124], and VEGF expression can be correlated with a poor prognosis in ovarian [100] and other types of cancer tumors [125–128].

VEGF interacts with common receptors (VEGFR-1, VEGFR-2, VEGFR-3 and neuropilin-1) [129]. They comprise a family of receptor tyrosine kinases (RTKs) showing several immunoglobulin-like domains in the extracellular domain, a single transmembrane region and a consensus tyrosine sequence that is interrupted by a kinase-insert domain [118–120]. VEGF-A also interacts with the neuropilins family of co-receptors.

VEGFR-1 has a very high affinity for VEGF-A [130]. VEGF-A prevents binding to VEGFR-2 [118]. VEGFR-1 is able to induce mitogenic and pro-survival signal in some cells [131]. VEGFR-1 also has been linked to the induction of angiogenic molecules such as matrix metalloproteases (MMPs) and hepatocyte growth factor (HGF) [132,133]. VEGFR-1 may also participate in hematopoiesis, recruitment of endothelial progenitors, and migration of monocytes. Finally, VEGFR-1 can heterodimerize with VEGFR-2, leading to a transactivation of this molecule [134].

VEGFR-2 mediates mitogenesis and angiogenesis [118–120]. Upon ligand binding, VEGFR-2 dimerizes and autophosphorylates on multiple tyrosine residues. Ligation of VEGFR-2 by VEGF results in the phosphorylation of different proteins such as PI-3-kinase, RAS GTPase-activating protein, the SRC protein family, and the proteins from the RAF-MEK-ERK pathway [119,120,135]. VEGFR-2 signaling can promote endothelial cell survival, proliferation and angiogenesis. Thus, VEGF and its receptors are considered to be key molecules in the neovascularization process and consequent growth of many tumors.

VEGF has been the target for antitumor therapies [136]. A humanized monoclonal antibody targeting VEGF (bevacizumab/avastin) has been approved for treatment of different colorectal cancer, renal cancer, lung cancer or glioblastoma [137]. Some studies highlight its efficacy as part of combinatorial therapies [138–140]. Aflibercept/VEGF-trap can act as a decoy receptor for VEGF. This compound has antitumor efficacy [137,141–144]. Finally, RTK inhibitors such as sunitinib and sorafenib have activity in gastric cancer, renal cancer, pancreatic tumors or hepatic cancer [137,145].

2.6 Fibrosis

Tissue fibrosis is commonly observed in the tumor microenvironment associated with rapid proliferation of fibroblasts [67]. Fibroblasts also can secrete various cytokines and chemokines such as TGF-β, IL-1, IL-6, IL-8, CXCR4, CXCL12, and monocyte-chemotactic protein 1 (MCP-1) [146] and platelet-derived growth factor (PDGF), HGF, stromal-cell-derived factor 1 (SDF1), VEGF, and basic fibroblast growth factor (bFGF) [147].

Cancer associated fibroblasts (CAF) are often linked to more aggressive tumor biology due to the secretion of MMPs that enhance the breakdown of the ECM and aid in cancer cells escaping into the vasculature and metastasizing to distant sites [148]. MMPs are also implicated in inducing epithelial to mesenchymal transition (EMT), a process that triggers the de-differentiation of cancer cells of epithelial origin into mesenchymal cells with properties of stemness. EMT may be a biomarker of poor prognosis [149]. Fibroblasts can be associated with a worse clinical outcome in patients with many types of cancer [150–152]. Thus, the targeted inhibition of fibroblasts may be useful for treating cancer.

However, some studies suggest a more complex role for fibroblasts in tumorigenesis. Targeting the fibroblast activating protein (FAP) did not result in tumor regression but was associated with bone marrow toxicity [153]. The targeted deletion of smooth muscle actin positive myofibroblasts specifically associated with pre-malignant stages of pancreatic carcinomas (pancreatic intraepithelial neoplasia) [154]. This led to a more poorly differentiated and aggressive tumor phenotype. Hence, fibroblasts and myofibroblasts appear to play a critical role in the formation of the extra-cellular matrix and inducing fibrosis within growing tumors.

2.7 IL-6

IL-6 is an inflammatory cytokine associated with innate immune responses and defense against infection, but was more recently found to play a role in the tumor microenvironment. Macrophages, monocytes and T cells can produce IL-1α and TNFα [155]. The dysregulation of IL-6 is associated with inflammatory diseases, such as rheumatoid arthritis, insulin resistance, sepsis and cancer [155,156].

Signaling of IL-6 occurs through the collaboration of a membrane-bound receptor (IL-6Rα/gp80) and signal transducer glycoprotein (gp130), a receptor for cytokines such as IL-11 and IL-27 [155–158]. The expression of surface IL-6Rα is limited mostly to immune cells and hepatocytes. However, gp130 is ubiquitously expressed by many cell types, including endothelial and tumor cells [157,159–161]. The soluble form of the IL-6R (sIL-6R) is able to interact with IL-6 in solution and then contact the cell membrane to induce signaling through gp130. Thus, cells lacking membrane-bound IL-6Rα can still be influenced by IL-6 generated in the microenvironment [157,159–162]. IL-6 activates JAK and the signal transducers and activators of transcription (JAK/STAT) activating STAT3 [155,163,164]. STAT3 leads to cancer cell survival, proliferation, and metastasis; it also promotes angiogenesis and expression of immune suppressive factors in the tumor microenvironment [165]. IL-6 can promote growth of breast cancer [166], glioma [167], lymphoma [168], multiple myeloma [169], ovarian cancer [170], and prostate cancer [171]. High levels of

soluble IL-6 or high levels of IL-6 staining in tumor samples correlate with poor outcome [172–181]. Finally, IL-6 can induce the production of VEGF in cancer cells or tumor-associated cells [182–184]. Thus, IL-6 can promote tumorigenesis through many mechanisms.

IL-6 has been therapeutically targeted. Anti-IL6 antibody (siltuximab/CNTO 328) increases the cytotoxic effect of chemotherapeutic drugs such as paclitaxel or melphalan [185–187] and decreased tumor growth, macrophage infiltration and angiogenesis [185]. Siltuximab alone or in combination with cytotoxic drugs has been studied in human patients [188–190]. Some effect was observed when used in combinatorial therapies [191,192]. Similarly, a humanized anti-IL-6R antibody, tocilizumab, has been shown to inhibit IL-6 signaling in cancer cells in preclinical studies [193–195]. This antibody has been used for the treatment of inflammation [196] and cachexia [197].

2.8 Endoglin

Endoglin (CD105) is a homodynamic glycoprotein growth factor co-receptor for TGF-β in endothelial tissue that plays a critical role in angiogenesis and vascular remodeling [198,199]. Endoglin modulates SMAD phosphorylation and may control cell adhesion and migration by regulating the composition of focal adhesion complexes and can regulate angiogenesis. Aberrations of its co-receptor function are critical to many cell processes implicated in cancer [200]. Inflammation and tumor-associated angiogenesis may result from dysregulation of endoglin co-receptor functions [201]. Endoglin expression is observed in neo-angiogensis, tumor progression and metastasis [202]. Inhibiting the endoglin pathway may be useful for the treatment of cancer [203,204]. The TRC105 antibody has high avidity for endoglin-binding and may have activity as a single agent as well as combined chemotherapy with bevacizumab [205] and may overcome therapeutic resistance to bevacizumab [206].

2.9 JAK

The JAK family includes the receptor-associated tyrosine kinases JAK1, JAK2, JAK3 and Tyk2 that are important regulators of many normal signaling processes that have been implicated causally in tumorigenesis [207,208]. The JAK pathway is generally critical to normal cellular signaling [209,210]. Among classical examples is the JAK-mediated STAT3 tyrosine phosphorylation in response to IL-6 family cytokines (including IL-11) signaling through GP130 [211].

Mutations in JAK2 and more commonly in JAK2 or SOCS1 have been implicated in tumorigenesis [212]. The JAK/STAT3 pathway is constitutively active in the tumor cells [213,214] and in tumor associated stromal cells [163,164,184,215,216]. IL-6 – mediated JAK/STAT paracrine signaling is commonly observed in cancer [217–219].

JAK signaling is important to tumor-host interactions in the microenvironment. In head and neck cancer, IL-6 mediates EMT and increases metastatic potential of transformed cells [220]. In Waldenstrom macroglobulinemia, dysregulated CCL5 expression modulates IL-6 secretion in stromal cells, resulting in increased IgM secretion by malignant cells via the JAK/STAT pathway [221]. Pancreatic cancer-associated stellate cells secrete IL-6 and other

soluble factors that promote the accumulation of myeloid-derived suppressor cells via the JAK/STAT3-dependent mechanism [222]. In lung carcinogenesis, AZD1480 inhibits STAT3 activation in tumor-associated myeloid cells, reduces cell number, inhibits tumor metastasis, and myeloid cell-mediated angiogenesis. AZD1480 blocks angiogenesis, lung infiltration of myeloid cells and formation of pulmonary metastases in mouse syngeneic experimental and spontaneous metastatic models as well as in human xenografts. STAT3 activation in cancer cells is sufficient to overcome the microenvironment-mediated and AZD1480-inhibited lung cancer progression [223].

The therapeutic effects of the TLR4 and TLR9 agonist complexes against melanoma metastasis are dependent on the simultaneous use of inhibitors of the JAK/STAT pathway (such as the AG490 antagonist). Such combined therapy activates the autophagy-associated death of melanoma cells via IFN-γ/STAT1 activation and attenuated tumor metastasis [224]. In Barrett's carcinogenesis, the IL-6 blocking antibody and AG490 and JAK inhibitor I blocks STAT3 phosphorylation decreasing resistance to apoptosis [225]. The JAK/STAT3-dependent accumulation of Treg cells in tumors is dependent on an increase in S1PR1 protein in CD4+ T cells, while the JAK/STAT3 pathway inhibition in T cells diminishes accumulation of Treg cells in tumors and tumor growth. The Treg migration toward tumors is nearly completely blocked by AZD1480 [226]. The GP130-IL6ST/JAK1 signaling generates actomyosin contractility through Rho-kinase dependent signaling in both the tumor cells and the stromal cells. Hence, the inhibition of the JAK pathway could be useful to modulate tumorigenesis through many mechanisms, including targeting the tumor microenvironment.

3. Approaches

3.1 Berberine

Berberine (Figure 2) is quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids with general anti-neoplastic properites [227,228]. Berberine has a low bioavailabiliy with less than 5% of the ingested dose finding its way into the systemic circulation [229,230]; in rats the value is considerably lower (0.68%) [231]. In humans, doses of 1,000 to 1,500 mg per day have been shown to be effective in regards to berberine's impact on glucidic and lipidic profiles in patients with hypercholesteremia and type 2 diabetes. The metabolized product of berberine also acts as an original compound but with less potency [232,233]. The common form of the urinary excreted product of berberine is believed to be jatrorrhizine [234,235].

As a traditional medicine or dietary supplement, berberine has shown activity against fungal, *Candida albicans*, parasitic, and bacterial/viral infections [236]. Its clinical utility has been assessed for many diseases and conditions including hyperlipidemia, diabetes, obesity and fatty liver disease. Currently there are 17 completed and ongoing registered clinical studies regarding berberine (www.clinicaltrials.org).

Berberine's interactions with a variety of metabolic pathways have been widely investigated. Adenosine mono-phosphate kinase (AMPK) is a nutrient sensor protein; berberine activates AMPK in a dose and time-dependent manner [237,238]. The data suggests that berberine-

induced AMPK inhibits complex I of the mitochondrial electron transport chain [239]. This effect is also observed with the anti-diabetic drugs metformin and rosiglitazone. In lipid metabolism, the lipid-lowering effect of berberine is believed to be related to stabilization of the hepatic LDL-C receptor (LDLR) by an ERK-dependent pathway and also by increased transcriptional activity of LDLR promoter by a c-Jun N terminal kinase (JNK) [240,241]. In 3T3L1 cells, berberine has been shown to reduce key adipogenic enzymes *in vitro* such as fatty acid synthase, acetyl-coenzyme A (acetyl-CoA) carboxylase, acyl-CoA synthase, and lipoprotein lipase [242]. Furthermore, berberine has been shown to inhibit cholesterol and triglyceride synthesis in hepatic cells via activation of AMP kinase [243].

Berberine's anti-neoplastic effects have been noted [244,245]. Berberine appears to suppress inflammation in response to pro-inflammatory stimuli [246]. Berberine at 10–20 mcg/mL concentrations, *in vitro*, has been shown to slightly increase T cell proliferation in response to antigens, while concentrations above that level result in dose-dependent immunosuppression [247]. The selective inhibition of JAK3 by berberine may also mediate immunosuppression [248]. Berberine exerts its anti-tumor effects via various mechanisms that include inhibition of cell proliferation, induction of apoptosis, and suppression of angiogenesis and tumor metastasis. Berberine's immunomodulatory effects, via JAK3 inhibition, might also impact cancer growth [248]. Berberine has been found to enhance the cytotoxicity of doxorubicin, which suggests that this agent may have potential as an adjunct to some traditional chemotherapeutic agents [249]. The cytotoxic effect of berberine has been demonstrated for a wide variety of tumors including lung, breast, prostate, colorectal neuroblastoma, lymphoma, osteosarcoma and leukemia [228].

Berberine has a caspase-independent apoptotic effect on the IMCE colon cancer cell line but not a normal colonocyte cell line, YAMC [250]. Berberine also induces cytotoxicity via G1-phase cell cycle arrest and caspase-3-dependent apoptosis in glioblastoma, epidermoid and prostate carcinoma cells [251–253]. The apoptotic effect of berberine is associated with upregulation of the pro-apoptotic genes Fas, FasL, p53, and Bax [254–256]. Berberine has an anti-angiogenic effect related to decreased expression of MMP-1, MMP-2 and MMP-9 [257–259].

As a quaternary ammonium, berberine's solubility is low. Berberine use is hampered by its low bioavailability which is related to it rapid biotransformation during the lengthy period that it remains in the intestine. Various nano-particulate delivery systems have been used to increase the absorption of berberine, including the rotary-evaporated film-ultrasonication method [260], nanoemulsification with isopropyl myristate/glycerin [261], and lipisomal incorporation [262]. Berberine manufactured with the nanoparticulate delivery systems demonstrated improved bioavailability and optimization of its anti-inflammatory, anti-angiogenic [263], and anticancer effects [264]. Berberine has potential as an anti-cancer agent [250]. The molecular basis of its neoplastic effects, however, needs to be further investigated.

3.2 Resveratrol

Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) is a polyphenolic compound that functionally belongs to phytoalexins with anti-ROS activity. Resveratrol is produced through stilbene

synthase [265] in response to pathogen infections [266] or stress conditions [267] using malonyl- coenzyme A (CoA) and p-coumaroyl CoA as precursors. This compound may have potential for cancer prevention and treatment [268].

Resveratrol is naturally occurring in more than 70 plant species including peanuts, blueberries, raspberries, mulberries, pine, and grapes [269]. Relatively high levels of resveratrol present in fresh grape skin, which explain its high concentrations in red wine and grape juice [270]. Different conjugated forms of resveratrol were detected in plants. *Trans*-resveratrol exists in glycosylated forms and has *cis* and *trans* isomers. Other conjugations, including 1–2 methyl groups, sulfate group, and fatty acids, were also observed [270]. Glycosylation increases stability, solubility and absorption in human gastrointestinal tract. Additionally, it protects resveratrol from oxidative degradation [271].

Resveratrol metabolism in human body includes its conversion to water-soluble *trans*-resveratrol-3-O-glucuronide and *trans*-resveratrol-3-O-sulfate by liver phase-2 drug-metabolizing enzymes [272]. These metabolic products have a plasma half-life of about 9.2 h, which is significantly higher than the half- life of resveratrol (8–14 min) [272]. Concentrations between 32 nM and 100 μM were used for different *in vitro* studies, while concentrations of 100 ng to 1500 mg/kg (body weight) were used in animal studies [273]. Resveratrol and its metabolism products were detected in liver, stomach, kidney, bile and urine after a single oral administration of ^{14}C-*trans*-resveratrol in Balb/c mice [274], whereas 24.6% of resveratrol and its metabolites were detected in human urine after oral administration [275].

The biological activity is associated only with the *trans* form, which is a free radical scavenger [276]. Normal cellular respiration, environmental stress, and UV radiation are the main inducers of ROS production. The imbalance in the ratios between oxidized and reduced redox couples like glutathione (GSH/GSSG) or NADPH/NADP+ cause ROS accumulation [277]. High levels of ROS react with cellular components including DNA, proteins, and lipids leading to cellular and tissue damage [278]. Resveratrol and other dietary stilbenes reduce oxidative stress by acting either as a direct scavenger of ROS [279] or as an inhibitor of NADPH oxidase expression and xanthine oxidase activity [280]. Resveratrol has low toxicity [281]. Various studies report anti-cancer effects [282–284], including the suppression of metastasis [285], and induction of proliferative arrest [286].

Normal cells have antioxidant enzymes and molecules that keep ROS under normal physiological levels [287]. In cancer cells, oncogenic signals stimulate active cellular metabolism, which increase ROS production and cause permanent oxidative stress [288]. Additionally, tumor associated mitochondrial malfunction cause massive increases in ROS production [289]. Resveratrol inhibits ROS and reduces oxidative stress [290]. It decreases intracellular ROS production and oxidative stress by mechanisms involving degradation of Keap 1 protein, which is a repressor of Nrf2 [291]. In a rat model of hepatocarcinogenesis, resveratrol was found to upregulate hepatic Nrf2 [292]. In another study, the total oxidant levels in plasma, liver and brain were decreased and total antioxidant levels in these organs were increased in rats treated with resveratrol [293]. Additionally, resveratrol reduced oxidative stress and maintained mitochondrial function through its ability to activate sirtuin

1 (SIRT1), which has many roles in reducing oxidative stress and promoting mitochondrial functions [294]. Moreover, it decreased serum and hepatic oxidative stress in high-fat diets [295] and diabetic rats [296]. Resveratrol is a candidate for the treatment and prevention of different cancers by the inhibition of ROS.

3.3 Onionin A

Onionin A is a natural product in *Allium* vegetables that has recently been identified as a potential agent to regulate macrophage activity that could have anti-neoplastic activity. The consumption of *Allium* vegetables is associated with a decreased risk of several cancers. A European epidemiological study reported a 55–80% reduction of odds ratios of almost all major cancers, including oral, esophageal, laryngeal, colorectal, prostate, breast and ovarian cancers, in populations who frequently consumed considerable quantities of onions or garlic in their meals [297]. Vegetables including onions, garlic, leaks, chives and scallions belong to the *Allium* family. Previously identified bioactive compounds in onions (*Allium cepa*) are flavonoids and phenols [298]. Flavonoids are the largest family of polyphenolic compounds and as such the names “polyphenols” and “flavonoids” may, at times, be used interchangeably. These compounds are believed to limit and deter the development of cancers from damaged cells via their anti-inflammatory effects. [299–302].

The cytotoxic effects of onion-derived polyphenol extracts have recently been investigated. The polyphenol extract from *A. cepa* can induce caspase dependent apoptosis of human gastric cancer cells via a mitochondrial pathway by upregulating p53 and Bax proteins as well as by modulating Bcl-2 proteins. Furthermore, onion-derived polyphenol extract induced caspase-dependent apoptosis of several human leukemia cell lines *in vitro* has been attributed, at least in part, to inhibition of the PI3K/AKT signaling pathway [303]. The antioxidant and antimutagenic properties of onion extract against mutagens are related to their polyphenols and flavonoids [304]. The lipid soluble organosulfur compounds present in onion extracts inhibit proliferation of cultured human colon, skin and lung tumor cells [305]. One possible mechanism for the inhibition of carcinogen activation by onion extract derivatives may be inhibition of cytochrome P450 2E1, which is activated by a number of xenobiotic substances [306].

Onions are also rich in organosulfur compounds. These phytochemicals, including diallyl disulfide, S-allylcysteine and ajoene, protect against chemically induced cancer in animal models by altering carcinogen metabolism [307–310]. Recently, onionin A was purified [311] and identified as a 3,4-dimethyl-5-(1*E*-propenyl)-tetrahydrothiophen-2-sulfoxide-*S*-oxide. Onionin A may inhibit TAMs [68,312]. The toxic effect of onionin A on IL-10-induced activation of M2 macrophage by assessing the expression of the unique M2 marker CD163. Onionin A significantly suppressed the expression of CD163 at concentrations of 10 μM and 30μM. These results suggest that onionin A may suppress tumor cell proliferation. This agent may be useful as an anti-cancer agent.

3.4 EGCG

EGCG inhibits IDO expression in human cancer cells. Consumption of green tea, which is produced from the leaves of *Camellia sinensis* plant, has been associated with lower

incidence of human cancer [313]. Green tea contains many polyphenols, in particular EGCG, which have been shown to suppress tumor formation and progression in animal models [314]. The chemopreventive and therapeutic effects of EGCG are attributed to the broad-spectrum anti-cancer abilities of this polyphenol, including inhibition of proliferation, inflammation, apoptosis, and angiogenesis [314,315].

EGCG has also been found to inhibit the expression of IDO, which is a key enzyme in suppressing T cells and inducing immune tolerance to tumor cells through depletion of tryptophan. Many cytokine-dependent and independent signaling pathways are involved in IDO expression. Interferon-stimulated IDO activation is, however, mediated by the JAK/STAT signaling pathway [316]. There is a number of evidence suggesting that EGCG interferes with JAK/STAT-regulated IDO activation, resulting in the suppression of IDO and IDO-related downstream gene expression in human cancer cells.

EGCG has been shown to suppress IDO expression through inhibiting IFN-γ induced in human oral cancer cell lines [317]. The translocation of STAT1 into the nucleus, which consequently inhibits the transcriptional activation of IDO, was blocked by EGCG. Chen et al. [317] also showed that EGCG significantly suppressed the phosphorylation of protein kinase C (PKC-δ) and JAKs, resulting in inhibition of IFN-γ-stimulated STAT1 phosphorylation. Similarly, another group demonstrated that EGCG blocks IDO expression in human colorectal cancer at transcriptional level through inhibition of STAT1 phosphorylation, which consequently suppressed the activity of STAT1-activated sequence elements of the IDO promoter, IFN-stimulated response element (ISRE) and IFN-γ-activation sequence (GAS) [318].

EGCG was found to exhibit anti-IDO activities in murine bone marrow-derived dendritic cells (BMDCs) [319]. EGCG blocked the binding of phosphorylated STAT1 to INF regulatory factor-1 (IRF-1) promoter, in response to IFN-γ stimulation. The expression of prostaglandin E2 (PGE2) and cyclooxygenase (COX-2) was also significantly inhibited in EGCG-treated murine BMDCs. Over expression of PGE2, a bioactive lipid, and COX-2, the key enzyme in prostaglandin biosynthesis, is often associated with immune surveillance and cancer [320]. The inhibitory effect of EGCG on COX-2 expression has also been seen in other cancer cell lines such as human prostate carcinoma and colon carcinoma [321,322]. In an *in vivo* study, Ogawa et al. [323] demonstrated the effect of EGCG on azoxymethane (AOM)-induced preneoplastic lesions in F344 rat through suppression of IDO expression. EGCG-treated rats exhibited significantly reduced levels of aberrant crypt foci, which had overexpression of IDO. The mRNA expression of COX-2 in AOM-treated rat was also inhibited by EGCG treatment [323].

EGCG inhbits the JAK/STAT signaling pathway. Pre-treatment with EGCG lead to suppression of STAT1 phosphorylation and IRF-1 expression on different cancer cell lines such as mammary carcinoma, cervical carcinoma, and hepatocarcinoma [324,325]. STAT3 is associated with constitutive IDO expression in human cancer cells [326]. EGCG inhibits the phosphorylation and expression of both JAK3 and STAT3 proteins in pancreatic cancer cells [327]. EGCG decreases the levels of phosphorylated-STAT3 proteins stimulated by insulin-like growth factors (IGFs) in hepatocellular carcinoma cells, possibly through inhibiting the

bioavailability of IGFs [328]. EGCG inhibits STAT3 in head and neck cancer [329] and breast cancer [330]. The inhibition of the JAK/STAT pathway through EGCG may be useful to regulate IDO.

EGCG has anti-cancer properties. The ability of EGCG to act as a multi-targeting agent in regulating JAK/STAT signaling and JAK/STAT-mediated IDO is remarkable. The combinative efficacy of EGCG with a number of chemotherapeutic drugs such as tamoxifen and paclitaxel has shown synergistic effect [331], EGCG is a candidate as a cancer therapy by targeting IDO.

3.5 Genistein

Genistein (4′,5, 7-trihydroxyisoflavone), a polyphenolic isoflavone, is found in soy products and appears to modulate cholesterol metabolism. It has low bioavailability due to poor water solubility, extensive intestinal first-pass phase II metabolism, and subsequent excretion of their conjugated metabolites [332]. Epidemiological studies suggest that intake of soy rich diet may lower the incidence of breast and prostate cancer in Asian countries [333,334]. Genistein may mediate its anti-cancer effects through nuclear factor (NF)-κB modulation, reduction of AKT protein level, downregulation of androgen-mediated carcinogenesis, and/or more general antioxidation effects [334,335]. Genistein has potential anti-cancer activity against prostate [336,337], ovarian [338], breast [339], lung [340], and pancreatic cancer [341].

Elevated HMGR activity, mevalonate, and protein prenylation is associated with tumorigenesis [342]. Genistein has been shown to suppress HMGR and preent tumor growth [343,344]. Genistein also can increase LDL receptor and decrease HMGR expression in colon cancer cells [345]. Genistein has many other effects on lipid metabolism that could contribute to its anti-neoplastic properties [346]. However, it is important to note that genistein may have pro-proliferative effects in some contexts [347–350].

3.6 Curcumin

Curcumin (diferuloylmethane), the active ingredient of the turmeric spice from plant *Curcuma longa,* belongs to the group of polyphenolic herbal compounds and has multiple beneficial effects including anti-tumorigenic action that appears to be related to VEGF inhibition. Powder of turmeric is widely used in Ayureveda, Unani, and Siddha medicine as a home remedy for various diseases [351]. In addition to curcumin, turmeric contains minor fractions such as demethoxycurcumin, bisdemethoxycurcumin, and the cyclocurcumin [352]. Curcumin has been implicated as suppressor of tumor initiation and promotion, angiogenesis, and metastasis [353,354].

Curcumin downregulates the expression of VEGF in prostate cancer cells in a dose-and time-dependent manner [355]. Osteopontin/integrin avb3 signaling through MMP9 activation increases VEGF and angiostatin expression in prostate cancer cells and conversely curcumin reduces VEGF expression [355], suppresses MMP9 activity in prostate cancer cells. The curcumin-derived analogue CDF inhibits VEGF as well as IL-6 and cancer stem cell signature genes Nanog, Oct4, and EZH2 *in vitro* and *in vivo* [356]. Similarly, CDF reduced VEGF and IL-6 expression in prostate cancer cells [357]. Curcumin inhibited

migration and invasion of human lung cancer cells through inhibition of MMP-2 and MMP-9 and suppression of VEGF expression [358]. Long-term exposure to curcumin was investigated in the liver of lymphoma-bearing mice. Curcumin treatment induced activation stress activated genes HIF-1a, MYC, and LDH activity to normal levels. Furthermore, it led to inhibition of angiogenesis as evidenced by reduced MMP-2, MMP-9, PKC-a and VEGF levels [359].

Similar to IL-6, IL-1 signaling is crucial to inflammatory and malignancy processes. IL-1 induced IkB alpha phosphorylation and inhibition of downstream NF-κB, which leads to expression of several genes that are associated with cell proliferation, invasion and angiogenesis [360]. Curcumin treatment blocked IL-1 and VEGF expression in chondrosarcoma cells. Further, curcumin inhibited IL-1 beta-induced angiogenesis and NF-κB-related gene expression [361]. Curcumin is one of the main constituents of turmeric spice, which has been used for centuries. A phase 1 human trial with 25 subjects using up to 8000 mg of curcumin per day for 3 months found no toxicity, and overall it has been considered to be safe in six human trials [362]. Curcumin has extremely low systemic bioavailability, owing to its low aqueous solubility and poor stability.

3.7 Naringenin

Naringenin has good prospects as an ideal therapeutic agent vis-à-vis an influence on metastasis and specific effect on fibrosis [363]. Naringenin significantly reduces lung metastases in mice (C57BL/6 and BALB/c) with pulmonary fibrosis and increases their survival by improving the fibrotic-immunosuppressive environment and reducing regulatory T cells [364]. In HSC-T6 cells, naringenin exerts antifibrogenic effects by directly or indirectly downregulating Smad3 protein expression and phosphorylation through TGF-beta signaling [365] and the downregulation of vimentin, N-cadherin, MMP2 and MMP9 [366]. Naringenin inhibits the viral assembly and long-term production of infectious hepatitis C particles [367]. It possesses agonistic [368] and antagonistic activities towards estrogen [369]. This also might its protective value against the food contaminant bisphenol A [370]. Hence, naringenin exerts inhibitory effects on cancer cell growth, migration and invasion, and also possess chemopreventive property.

Naringenin has low bioavailability (2.8% of intake) due to high excretion and low C_{max} in plasma. The principal metabolites, naringenin-7-O-glucuronide and naringenin-4′-O-glucuronide peaks at 6h after intake [371]. The distribution of metabolites also varies due to binding of metabolites to human serum albumin [372]. The binding modulates the half-life in plasma and tissue distribution. A NRG glucuronide have same affinity for human serum albumin as naringenin. Efforts are in way to increase the bioavailability through various techniques like combining NRG with β-cyclodextrin through solid dispersion and self nano emulsifying drug (SNEDDS) technique [373]. The mixture and nanoparticles enhanced a significant increase in NRG absorption compared to NRG alone. Area under the drug concentration time curve (AUC) 0–24h was significantly higher for SNEDDS as compared with pure drugs. Even NRG-loaded nanoparticles showed enhanced anti-lipid peroxidative antiproliferative effect and antioxidant potentials owing to increased chemo-preventive efficacy compared to free naringenin in 7, 12-dimethylbenz(a)anthracene (DMBA)-induced

oral carcinogenesis [374]. Naringenin flavonoids present in GJF demonstrate multiple interactions with drugs leading to loss of the therapeutic effects or increased side effects through a competitive or mechanism based inhibition of gut wall CYP3A4 isoenzyme, P-glycoprotein multi-drug resistance protein, and organic anion transporting polypeptide inhibition. Its safety has also been evaluated through *in vitro* and *in vivo* studies [375,376].

3.8 Desoxyrhapontigenin

Desoxyrhapontigenin (3,5-dihydroxy-4′-O-methylresveratrol) is an antioxidant [377]. Desoxyrhapontigenin may be useful in the modulation of the tumor microenvironment. It inhibits cytochrome P450 enzymes [378,379], inflammation, ROS, and associated pathways [380–385].

Desoxyrhapontigenin affects ROS and inflammation. This occurs through increased expression of antioxidant enzymes [383] and the inhibition of NF-κB and AP-1, reduced production of COX-2, TNF-α, and IL-6, and reduced inflammation in a carrageenan-induced animal inflammation model [385]. Desoxyrhapontigenin is produced by plants [386] and its cyototoxic and anti-proliferative effects are dose-dependent [387–390]. Thus, desoxyrhapontigenin may be useful as a therapeutic agent for cance through its effects on ROS and inflammation.

3.9 Piperine

Piperine (1-piperoyl piperidine) is the principal alkaloid in black (*Piper nigrum*) and long peppers (*Piper longum*) and has potentially multiple anti-cancer activities. It is widely used both as a spice in food as well as in traditional medicine [391].

Piperine has low toxicity [392]. Additionally, the *in vitro* absorption rate of piperine is relatively high compared with other natural products like curcumin without any metabolic modification of piperine during the absorption process [393]. Piperine is widely used as a bioavailability enhancer for a diverse group of therapeutic agents including the antimicrobial agent rifampicin [394], nevirapine which is a potent inhibitor of human immunodeficiency virus (HIV)-1 reverse transcriptase [395] and curcumin which has anticancer properties [396]. Piperine has various biological effects including antioxidant activity [397] anti-inflammatory effect by inhibiting PMA-induced COX-2 [398].

Piperine has significant anti-cancer effects [399]. Different mechanisms have been suggested, including apoptosis and suppression of metastasis [400], inhibition of angiogenesis [401], and blocked invasion by downregulation of MMPs [402,403]. Piperine exerts chemopreventive activity against some carcinogens including benzo(a)pyrene-induced lung carcinogenesis [404] and DMBA- induced skin carcinogenesis [405]. Piperine, with its low toxicity and potent anti-angiogenic activity, may be considered as a possible therapeutic agent in cancer prevention and treatment.

3.10 Zerumbone

Zerumbone, a sesquiterpene, exerts its anticancer effect through modulation of the JAK/STAT pathway. In renal cell carcinoma cell lines and xenograft mouse model, zerumbone

dose- and time-dependently, inhibits the activity of STAT-3 through suppressing its upstream kinases c-SRC, JAK-1 and JAK-2. Pervanadate, a protein tyrosine phosphatase (PTP) inhibitor treatment reversed the zerumbone -induced downregulation of STAT3, suggesting the involvement of a PTP. SHP-1 tyrosine phosphatase interacts with STAT3 and is induced by zerumbone. Upon knockdown of SHP-1 by siRNA, the ability of zerumbone to inhibit STAT3 activation-mediated apoptosis was suppressed, suggesting the involvement of SHP-1 in its action. Zerumbone not only suppresses STAT3 but also reduces the expression of downstream STAT3-regulated gene products that are involved in proliferation, survival, and angiogenesis [406]. Hence, zerumbone blocks STAT3 activation, leading to suppression of growth and sensitization of cancer cells.

Zerumbone is an inhibitor of constitutive JAK/STAT as well as IL-6 stimulated pathways, thereby blocking the activity of IL-6 in pancreatic carcinoma [407]. A synergistic effect of zerumbone with paclitaxel in prostate cancer cells is mediated through active JAK-2/STAT-3 pathway [407,408]. Zerumbone with cisplatin showed a synergistic anticancer effect on cervical intraepithelial neoplasia in female BALB/c mice through serum IL-6 [409]. In some cases, inhibition of JAK -2/STAT-3- mediated signaling pathways induced cytotoxicity through PARP cleavage in a human prostate cancer cell line (DU 145) [407]. However, other apoptotic mechanisms have also been reported through induction of G2/M arrest and decreased cyclinB1/CDK1 protein level in HL-60 cells [410]. G2/M arrest and Fas- and mitochondria mediated-apoptosis have been observed in T-acute lymphoblastic leukemia cells [411] and leukemia cells [412], and Bax- and Bak- mediated apoptosis has been observed in human breast cancer cells and othotopic xenografts [413]. It may modulate the Bax/Bcl-2 ratio in liver cancer cells independent of functional p53 [414], TRAIL-induced death receptor in human colon cancer [415], and Gli-1/Bcl-2 pathway mediated apoptosis in human renal carcinoma [416].

Zerumbone inhibited CXC chemokine receptor-4 expression with subsequent inhibition of CXCL-12 induced invasion of breast and pancreatic tumor cells [417] and human tongue squamous cell carcinoma [417]. Zerumbone inhibited IL-6 and induces apoptosis in ovarian and cervical cancer cells [418]. It also decreased the levels of nitrite and prostaglandin (E2) with unchanged COX-1 expression in LPA and gamma irradiated increased NO synthase and COX-2 as well as release of TNF-α in RAW 264.7 mouse macrophages [419–421]. Zerumbone suppressed TPA-induced activation of EBV, LOX-1 mRNA expression [422], O_2- anion generation through NADPH oxidase in DMSO differentiated human promyelocytic leukemia (HL-60) cells and through xanthine oxidase in AS52 Chinese hamster ovary cells [423]

The safety of zerumbone has been demonstrated in normal human cells [424]. On oral ingestion of zerumbone (20/40 mg/kg/day) for 8 weeks reduced hyperglycemia induced p38 mediated inflammatory response (infiltration of macrophages and increased levels of IL-1, -6 and TNF-α) and also reduced expression of intercellular adhesion molecule-1, MCP-1, TGF-β1 and fibronectin in nephropathic rats. The proven *in vitro* and *in vivo* pharmacological efficacy of zerumbone provides a base to elucidate anticancer bioactivity. However to increase the bioavalability, zerumbone-loaded nanostructured lipid carriers have also been prepared and characterized for their antileukemic effect [410].

4. Discussion: Evaluating targets and approaches

We have identified 10 potential approaches to inhibit 10 identified targets to treat and prevent cancer by targeting specific aspects of the tumor microenvironment (Figures 1 and 2, Tables 1 and 2). Our list is not exhaustive but more illustrative. Several themes have emerged.

First, the consideration of the tumor microenvironment as a target for cancer prevention and treatment provides a unique perspective on both tumorigenesis and therapy of cancer. The majority of existing therapies have focused on the effect on the incipient cancer cell. However, the inhibition of biological programs that are associated with the tumor microenvironment may be critical to the prevention and treatment of cancer.

Second, there are many existing natural products that have been reported to have potential anti-neoplastic and/or tumor prevention properties. In many cases, these agents appear to have discrete and readily measurable effects on the host tumor microenvironment. However, it will be important to define the bioavailability as well as the kinetics of elimination of these compounds when used alone or in combination [425].

Third, the influence of agents that target the microenvironment requires the development of unique assays. Most targeted therapies can be evaluated through the examination of the expression and/or activity of the molecule that is being targeted. The consideration of the tumor microenvironment requires measurement of cellular, humoral, and cytokine mediated programs and this requires *in situ* analysis. For many clinical studies, this is a problem since it is not possible to obtain suitable clinical material for this evaluation. Hence, the development of therapies that target the microenvironment requires novel approaches to make these measurements either through more sensitive techniques that do not require direct examination of tumor material or through measurements in more easily obtained materials such as blood serum.

Fourth, the tumor microenvironment and incipient neoplastic cells coevolve temporally during tumorigenesis. Hence, in targeting the microenvironment, one must recognize that it is critical to consider when to introduce the therapeutic and to evaluate its efficacy at the right time. Thus, an agent that alters immune activation may be critical in preventing tumorigenesis. Hence, it would require examination of effects very early during tumor initiation as opposed to in a preclinical model or patient with an advanced cancer.

Fifth, the evaluation of agents that target the tumor microenvironment must be considered in the context of existing therapeutic approaches for tumor prevention. Thus, for many cancers there are accepted approaches for treating a primary or metastatic tumor, or for reducing the chance of early cancer lesions for progressing to more advanced cancers. Any considerations of the targets or approaches we suggest have to consider the current standard of care.

Sixth, the measurement of changes in the tumor microenvironment may be important endpoints for evaluating the preclinical and clinical efficacy of thereapeutics. Examining how individually or alone specific approaches are able to influence specific targets could provide intermediate measurements suggestive of therapeutic efficacy.

Finally, we realized that a broad multi-discplinary approach was important for identifying both approaches and targets. The tumor microenvironment by its nature occurs in different biological programs across multiple scales (molecule, cell, organ, host) over a long time period. Investigators with skills across many disciplines are required to consider this complexity.

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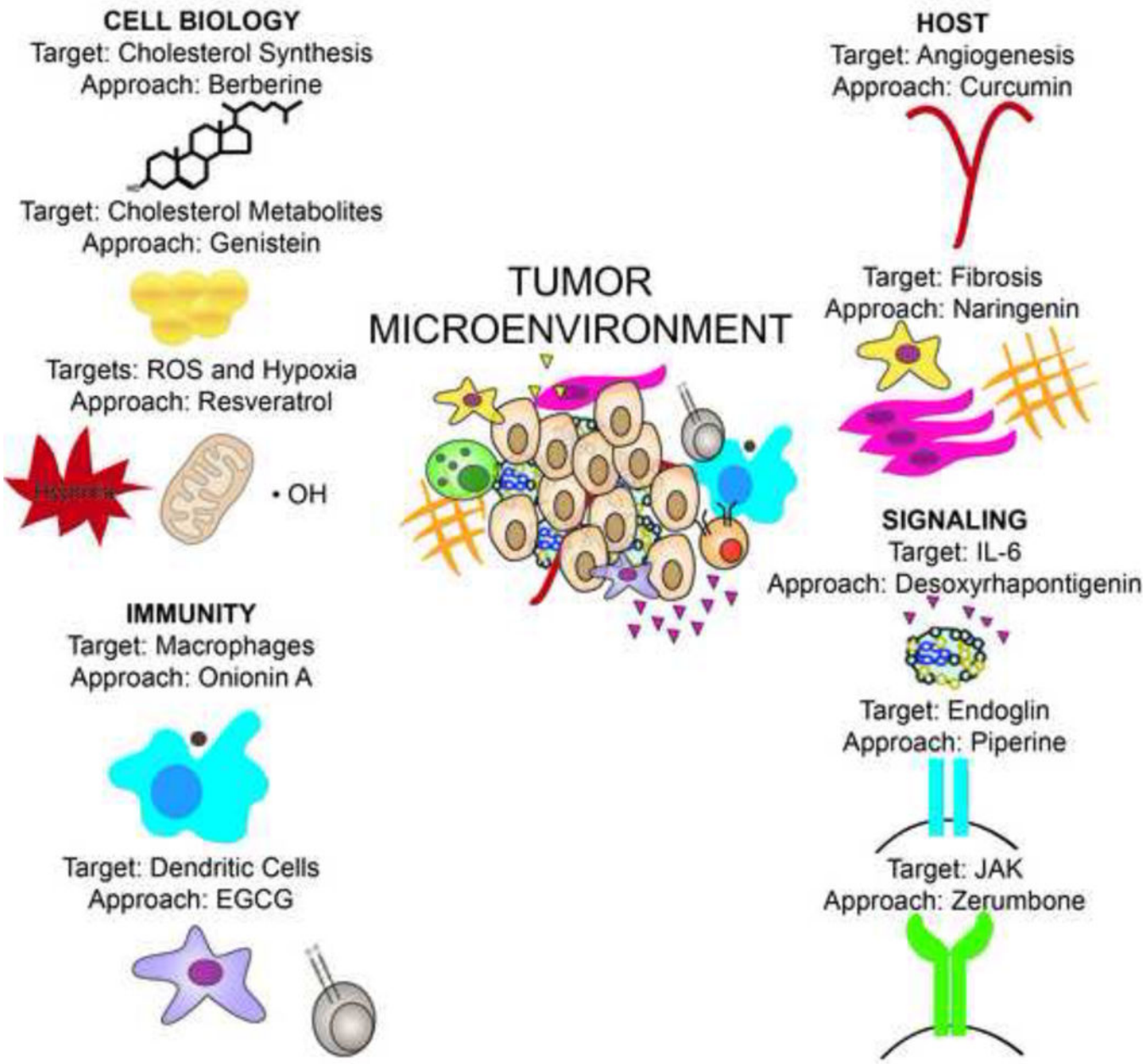

Figure 1. Targets and approaches identified that could modulate the tumor microenvironment to prevent or treat cancer

Key therapeutic targets identified include the inhibition of cholesterol synthesis and metabolites, reactive oxygen species and hypoxia, macrophage activation and conversion, IDO regulation of DCs, VEGF regulation of angiogenesis, fibrosis inhibition, endoglin, and JAK signaling. Potential therapeutic targets that have been identified and cross-validated, include many natural products including berberine, resveratrol, onionin A, EGCG, genistein, curcumin, naringenin, desoxyrhapontigenin, piperine, and zerumbone. These may warrant investigation as agents alone or in combination that target the tumor microenvironment for the treatment and prevention of cancer, although the specific target-approach combination as presented is not unique and other possibilities do exist.

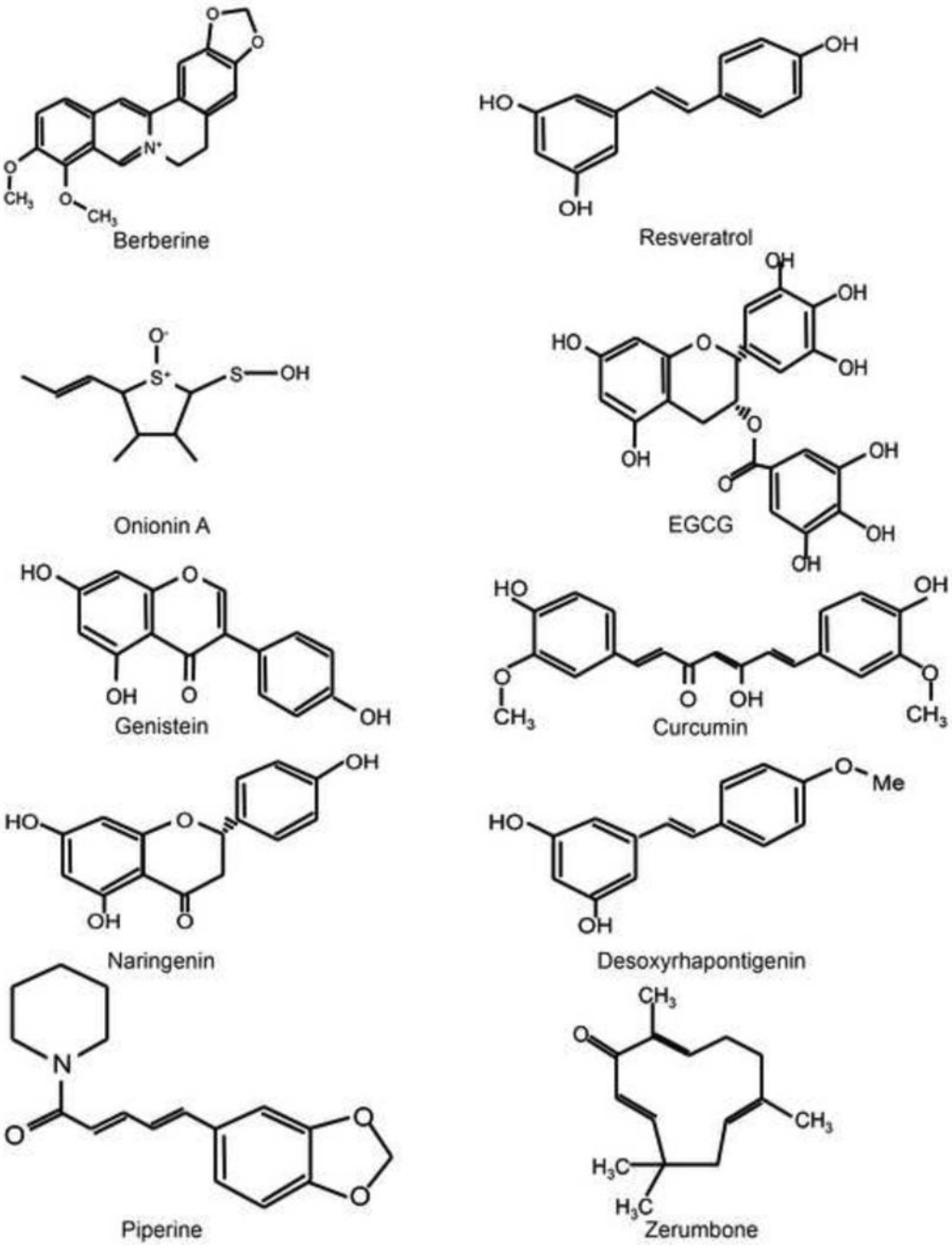

Figure 2. The structures of natural products identified that may target the tumor microenvironment for the treatment or prevention of cancer

Molecules shown include berberine, resveratrol, onionin A, EGCG, genistein, curcumin, naringenin, desoxyrhapontigenin, piperine, and zerumbone.

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Table 1

Cross-validation of Tumor Microenvironment Targets

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

Tumor Microenvironment Targets / **Other Cancer Hallmarks**	**Cholesterol synthesis (inhibition)**	**ROS (inhibition)**	**M2 macrophage conversion (inhibition)**	**IDO (inhibition)**	**Cholesterol metabolites (inhibition)**	**VEGF (inhibition)**	**Fibrosis (inhibition)**	**IL-6 (inhibition)**	**Endoglin (inhibition)**	**JAK (inhibition)**
Genomic Instability	+ [426]	0	0	0	0	+ [427]	0	+ [428]	0	0
Sustained Proliferative Signaling	+ [429,430]	+ [431–433]	0	+ [434,435]	+ [436–438]	+ [439,440]	+ [441,442]	+ [170,443]	+/− [444,445]	+ [446,447]
Tumor Promoting Inflammation	0	+ [448]	+ [449,450]	+ [451]	0	+ [452,453]	+ [364]	+ [454]	0	+ [223]
Evasion of Antigrowth Signalling	+ [455,456]	+/− [457,458]	+ [459]	0	+ [455,460]	+ [461,462]	0	+ [463,464]	+ [465,466]	+ [467,468]
Resistance to Apoptosis	+ [469]	+ [470]	+ [471]	+ [472]	+ [473]	+/− [474,475]	+ [476–478]	+ [479,480]	+ [481,482]	+ [483]
Replicative Immortality	+/− [484–486]	+/− [487–490]	0	0	0	+/− [491,492]	0	+/− [493,494]	0	+ [495,496]
Deregulated Metabolism	+ [497,498]	+ [499,500]	0	+/− [435,501]	+ [502,503]	+/− [504–506]	0	+ [507]	0	+ [507]
Immune System Evasion	+ [509]	+ [510–512]	+ [513,514]	+ [116,515–517]	+ [509]	+ [518–520]	+ [521]	+/− [522,523]	0	+ [512,524]
Angiogenesis	0	0	+ [525]	+ [526]	0	+ [527]	0	+/− [453,528]	+ [529]	+ [223]
Tissue Invasion and Metastasis	+ [530,531]	+ [532,533]	+ [513,534]	+ [535,536]	+ [537,538]	+ [539–541]	+ [542,543]	+ [544]	+ [545,546]	+ [467,547]

Targets that were found to have complementary, anti-carcinogenic actions reported in another hallmark area were indicated with “+”, while targets that were found to have pro-carcinogenic 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 anti-carcinogenic potential and pro-carcinogenic 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”.

Table 2

Cross-validation of Approaches and Hallmarks of Cancer

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

Phytochemical Approaches / **Other Cancer Hallmarks**	**Berberine**	**Resveratrol**	**Onionin A**	**EGCG**	**Genistein**	**Curcumin**	**Naringenin**	**Desoxyrhapontigenin**	**Piperine**	**Zerumbone**
Genomic Instability	+ [548,549]	+ [550,551]	0	+ [552,553]	+ [554–556]	+ [557,558]	+ [559]	0	+ [560,561]	0
Sustained Proliferative Signaling	+ [562,563]	+ [284,564]	0	+ [565,566]	+/− [567–571]	+ [572,573]	+ [574]	0 [387]	+ [391,575]	+ [413,576]
Tumor Promoting Inflammation	0	+ [577,578]	0	0	0	+ [579]	+ [364]	0	0	0
Evasion of Antigrowth Signalling	+ [580,581]	+ [582]	0	+ [583]	+ [584]	+ [579,585]	0	0	+ [586]	0
Resistance to Apoptosis	+ [587,588]	+ [589]	0	+ [590]	+ [591]	+ [592]	+/− [593,594]	+ [387]	+ [560]	+ [595]
Replicative Immortality	+ [581,596]	+ [581,596]	0	+ [599,600]	+ [601,602]	+ [603–605]	0	0	0	0
Deregulated Metabolism	+ [606,607]	+ [608–610]	0	+ [611–614]	+ [615,616]	+ [617–619]	+ [574,620]	0	+ [391,621]	+ [415,622]
Immune System Evasion	− [623–625]	+/− [626–631]	0	+/− [632–636]	+/− [637,638]	+/− [639–642]	+/− [364,643,644]	0	− [645–648]	+ [418,649]
Angiogenesis	+ [650]	+ [651]	0	0	+ [652]	+ [653]	0	0	0	0
Tissue Invasion and Metastasis	+ [654,655]	+ [627,656]	0	+ [657,658]	+ [659,660]	+ [661,662]	+ [364,366,663]	0	+ [400,403]	+ [654,655]

Approaches that were found to have complementary, anti-carcinogenic actions in a particular hallmark area were were indicated with “+”, while approaches that were found to have pro-carcinogenic 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 anti-carcinogenic and pro-carcinogenic 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”.