[Frontiers in Bioscience E4, 410-425, January 1, 2012]

Novel targets for detection of cancer and their modulation by chemopreventive natural compounds

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1. ABSTRACT

Cancer affects the lives of millions of people. Several signaling pathways have been proposed as therapeutic targets for cancer therapy, and many more continue to be validated. With the identification and validation of therapeutic targets comes the question of designing novel strategies to effectively counter such targets. Natural compounds from dietary sources form the basis of many ancient medicinal systems. They are pleiotropic i.e. they act on multiple targets, and, therefore, are often the first agents to be tested against a novel therapeutic target. This review article summarizes the knowledge so far on some actively pursued targets - Notch, CXCR4, Wnt and sonic hedgehog (shh) pathways, the process of epithelial-mesenchymal transition (EMT) as well as molecular markers such as uPA-uPAR, survivin, FoxM1, and the microRNAs. We have performed an extensive survey of literature to list modulation of these targets by natural agents such as curcumin, indole-3-carbinol (I3C), 3,3'-diindolylmethane (DIM), resveratrol, epigallocatechin-3-gallate (EGCG), genistein etc. We believe that this review will stimulate further research for elucidating and appreciating the value of these wonderful gifts from nature.

2. INTRODUCTION

The use of naturally occurring agents for the treatment and/or chemoprevention of cancer has long been advocated (1) and the search for such agents has often focused on chemical compounds that are typically found in fruits and vegetables (2). In pursuit of such beneficial compounds, a major prerequisite is that they should be physiologically non-toxic, and inert towards the normal cells. As a consequence, there has been a key interest in investigating the components of traditional medicines for possible therapeutic use against human cancers. While searching for novel therapeutic agents is crucial, a clear understanding of the physiological processes which contribute to cancer progression is equally important. A number of signaling pathways and their constituent members have been implicated in initiation, promotion as well as progression of human cancers. Also, there is substantial heterogeneity among different cancers as well as within the subsets of each cancer type. All this makes the field of cancer research particularly challenging wherein the pursuit for novel therapeutic targets as well as novel therapeutic agents goes hand in hand. It is highly desirable that the novel anti-cancer agents are multi-targeted

Table 1. Reports on down-regulation of uPA-uPAR system by anti-cancer natural compounds

Natural Compound	Study (reference)
Apigenin	Kim 2003 (19)
Curcumin	Aggarwal 2003 (16)
DIM	Kong 2007 (22); Ahmad 2009 (27); Ahmad 2009 (23)
DMC and BDMC	Yodkeeree 2009 (17)
DMC	Yodkeeree 2010 (18)
EGCG	Ho 2007 (20)
Genistein	Li and Sarkar 2002 (21); Kim 2003 (19)

(pleiotropic) and this holds true for most of the natural chemopreventive agents that are being tested for their effectiveness against various human cancers in laboratories across the globe (3;4).

Decades of innovative research has helped identify a plethora of putative targets for cancer therapy. Many of these targets have been unable to stand the test of time and quite a few of them are relevant to only specific human cancers. The purpose of our current review article is to give readers a broad view of therapeutic targets that are being actively investigated for putative role in cancer progression in multiple cancers. Additionally, for each such target, we have reviewed and grouped together studies that demonstrate the ability of naturally occurring chemopreventive agents to modulate the expression/ activity of the target in question, thus leading to the desired anti-cancer effect of the agent. We hope that such cataloging of novel targets and pleiotropic agents at one place would be of interest to many readers and would spark an interest in further validating the anti-cancer activity of naturally occurring compounds thus leading to a full realization of their potential.

3. THERAPEUTIC TARGETS AND THEIR MODULATION BY NATURAL COMPOUNDS

3.1. uPA/uPAR

uPA is a member of the urokinase plasminogen activator system, a serine protease family comprising of uPA, plasminogen activator inhibitors (PAI's), tissue-type plasminogen activator (tPA) and the receptor uPAR. The urokinase plasminogen activator system provides the most substantial amount of activated plasminogen when tissues are being degraded (5). uPA system is primarily associated with the degradation and regeneration of the basement membrane and extracellular matrix that leads to metastasis (6;7). uPA protein is 411 amino acid residues long, consists of two α helices and two anti-parallel β strands, and is secreted as a 53 KD zymogen (pro-urokinase). uPA catalyzes the activation of plasminogen into plasmin by cleaving the arginine-valine bond. In turn, plasmin facilitates the release of several proteolytic enzymes, including gelatinase, fibronectin, fibrin, laminin, and latent forms of collagenases and stromelysins (8;9). uPA is activated through cleavage of the Lys_{158}-Ile_{159} peptide bond after it binds to its receptor, uPAR. This activation of uPA is brought about by plasmin. Since activated uPA, in turn, generates active plasmin from plasminogen, such activation of uPA by plasmin completes the loop for a feed-back-type activation. The involvement of uPA family members in the progression of several human cancers is gaining interest (7) and uPA system is increasingly being recognized as a candidate target for gene therapy in cancers (10).

Several natural agents have been shown to effectively down-regulate uPA leading to their anti-cancer effects (Table 1). There are reports on the ability of dietary components from ethnic foods to inhibit uPA expression and/or down-regulate its activity (11-15). Curcumin, a natural compound isolated from the plant Curcuma longa (turmeric), can down-regulate uPA which might, at least in part, be responsible for its anticancer effects in several preclinical studies (16). In a study to compare the anti-cancer effects of active components from turmeric, it was shown that demethoxycurcumin (DMC) as well as bisdemethoxycurcumin (BDMC) were more effective agents than curcumin (17). This conclusion was largely based on the relative ability of these compounds to inhibit uPA along with matrix metalloproteinases, all of which are crucial players in the degradation of extracellular matrix. A more recent report on DMC from the same research group (18) shows that this compound, at non-cytotoxic doses, can significantly inhibit the invasion of breast cancer cells, MDA-MB-231. Treatment with DMC was found to reduce the protein levels of uPA and uPAR and increase those of the inhibitor PAI-1 (18). Such down-regulation of uPA and related family members was suggested as the reason for observed inhibitory action of DMC on motility, invasion and metastasis of breast cancer cells. Similar observations have earlier been made with polyphenolic natural compounds flavonoids where it was shown that 3 representative flavonoids – genistein, apigenin and 3-hydroxyflavone blocked the generation of active uPA and also had modulatory effect on the expression of PAI-1 in human umbilical vein endothelial cell (HUVEC) model leading to inhibition of angiogenesis (19). In human oral cancer model, epigallocatechin- 3-gallate (EGCG), a polyphenol from green tea, has been demonstrated to inhibit the expression of uPA in a dose-dependent fashion resulting in the inhibition of invasion of these cells (20).

Li *et al.* (21) identified uPA and uPAR among several angiogenesis-related genes, that were down-regulated by genistein in prostate cancer cells. In this study, PC3 cells were treated with genistein and microarray analysis was performed. Later on, Kong *et al.* (22) showed that B-DIM, a formulated DIM (3,3'-diindolylmethane, an indole compound from cruciferous vegetables) with higher bioavailability, can repress extracellular matrix-degrading proteases, including uPA, leading to a reduced bioavailability of VEGF. Such biological activity of DIM led to the inhibition of angiogenesis and invasion of human prostate cancer cells. Taking a cue from this initial observation, it was later shown that silencing of uPA as well as uPAR leads to reduced cell growth and migration of highly aggressive PC3 cells (23). DIM- treatment also had similar effects but the silencing of uPA/uPAR significantly attenuated the ability of DIM to inhibit cell growth and migration of PC3 cells. This suggested an essential role of uPA-uPAR in mediating the biological activity of DIM against prostate cancer cells. Since we had earlier demonstrated an inhibitory effect of DIM on proliferation of breast cancer cells (24-26), we extended our

investigation to study the relevance of uPA-uPAR in breast cancer cells as well (27). We found that DIM treatment could inhibit cell growth and motility of MDA-MB-231 cells. Silencing of uPA-uPAR led to decreased sensitivity of these cells to DIM, thus implicating uPA-uPAR in DIM-mediated inhibition of cell growth and migration.

3.2. Survivin

Survivin, discovered more than a decade back (28;29), is an inhibitor of caspase-9 and, thus, is a key molecule that regulates apoptosis (30). Survivin is a member of the Inhibitor of Apoptosis (IAP) gene family. Survivin plays important role in multiple cellular pathways that are essential for tumor cell proliferation and viability (31) and is a molecule that favors cancer survival (32). It is expressed in most human cancers (33) and it is now believed that survivin is a universal requirement for successful tumor suppression in humans (34;35). Therefore, usefulness of survivin as an anti-cancer agent is now being tested in clinical settings and there are reports of some encouraging responses (31;35). In light of these evidences, survivin has been suggested as a potent cancer therapeutic target (36-38).

Previously we have shown that indole-3-carbinol (I3C) possesses anti-carcinogenic effects in experimental animals and inhibits the growth of human cancer cells (39-42). In one of the earliest reports on the modulation of survivin by a natural agent, Takada *et al.* (43) reported down-regulation of survivin by I3C treatment. Polyphenol phytoalexin resveratrol (3,4',5-trihydroxystilbene) is another well-studied natural agent (44;45) that has been shown to induce its anti-cancer and apoptosis-inducing effects through the down-regulation of survivin (46-51), and down-regulation of survivin leads to increased TRAIL-induced apoptosis (52;53). Further, flavonoid quercetin could also sensitize non-small cell lung cancer cells to TRAIL-induced cytotoxicity by suppression of survivin (54). Such survivin-dependent sensitization to TRAIL-mediated apoptosis has also been demonstrated for silibinin (55), a flavonoid that inhibits survivin expression resulting in apoptosis-induction in prostate (56), renal cancer (57) and urinary bladder cancer cells (58). Our own microarray gene profiling of DIM-treated breast cancer cells MDA-MB-231 revealed survivin as a gene that was significantly down-regulated by DIM (59). DIM was observed to inhibit cell growth and induce apoptosis in MDA-MB-231 MCF10CA1a breast cancer cells (26;60). Down-regulation of survivin by small interfering RNA prior to DIM treatment resulted in enhanced cell growth inhibition and apoptosis, whereas over-expression of survivin by cDNA transfection abrogated DIM-induced cell growth inhibition and apoptosis (59). In glioblastoma, EGCG has been shown to sensitize cells to ionizing radiations (61). In this study, transfection with survivin was observed to potentiate cytoprotective effect against ionizing radiations, however, treatment with EGCG, prior to survivin transfection, significantly increased the sensitivity of cells to radiation. The modulatory effect of flavonoids on survivin leading to cell cycle arrest has been discussed (62) and, on a similar note, curcumin has been shown to inhibit the expression of survivin (63) leading to cell cycle arrest and induction of apoptosis in leukemia cells while resveratrol has been shown to sensitize cancer cells to anticancer drug-induced apoptosis by cell cycle arrest and survivin depletion (64).

In a cellular model for angiogenesis, flavonoid deguelin has been shown to inhibit angiogenesis through the down-regulation of survivin (65). This natural agent has also been shown to induce apoptosis in breast cancer cell lines SKBR3 and MCF-7 through a dose-dependent down-regulation of expression of survivin (66). Further, deguelin was found to have no apoptosis-inducing effect in 'normal' human breast epithelial cells MCF-10A suggesting the ability of this agent to selectively target cancer cells. In prostate cancer cells LNCaP, betulin, a triterpene from birch bark, has been reported to activate proteasome-dependent degradation of transcription factors specificity protein 1 (Sp1), Sp3, and Sp4 leading to down-regulation of VEGF and survivin which, in turn, leads to induction of apoptosis and an efficient inhibition of angiogenesis (67). Our own studies on the effect of DIM, either alone or in combination with taxotere, using LNCaP and C4-2B prostate cancer cells revealed that DIM enhanced taxotere-induced apoptotic death in both the cell lines tested (68). These effects were related to down-regulation of survivin as well as androgen receptor and NF-κB-DNA-binding activity. Luciferase assays demonstrated a significant reduction of survivin-Luc and NF-κB-Luc activity in prostate cancer cells exposed to DIM and taxotere. Results were confirmed *in vivo* where combination treatment was observed to significantly inhibit C4-2B bone tumor growth and this correlated with the down-regulation of survivin. These studies clearly established that inactivation of survivin by DIM enhances the therapeutic efficacy of taxotere in prostate cancer cells (68).

Additionally, down-regulation of survivin by many naturally occurring compounds, such as, by curcumin in bladder cancer (69) and osteosarcoma cells (70); by berberine through suppression of NF-κB pathway (71); by silymarin in multiple models (58;72); by plumbagin in non-small cell lung cancer cells (73); by carotenoids fucoxanthin and its metabolite fucoxanthinol in leukemia cells (74); by psoralidin in androgen-independent PC3 and DU145 prostate cancer cells (75); by garlic extract in albino rats (72); by gingerol (76) and tea polyphenols (77) in skin tumors; by DIM (78), genistein (79) and maslinic acid (80) in pancreatic cancer cells; by naphthoquinone rhinacanthone in cervical cancer cell (81) and by sesamin in multiple cancer cells (82) is believed crucial for the apoptosis-inducing and anti-cancer effects of these agents.

DIM has been shown to down-regulate survivin in colon cancer cells and pre-treatment with DIM enhanced butyrate-induced apoptosis in colon cancer cells with APC (adenomatous polyposis coli) mutation (83) suggesting that a combination of DIM and butyrate is potentially an effective strategy for the prevention of colon cancer. In another study highlighting the efficacy of combinational treatment, I3C, an anti-cancer compound closely related to DIM, in combination with genistein, has been reported to effectively induce apoptosis in colon cancer cells through a mechanism that involves down-regulation of survivin (84).

Table 2. Reports on down-regulation of survivin by anti-cancer natural compounds

Natural Compound	Study (reference)
Berberine	Pandey 2008 (71)
Betulin	Chintharlapalli 2007 (67)
Curcumin	Magalska 2006 (63); Tian 2008 (69); Leow 2009 (70)
Deguelin	Peng 2007 (66); Dell'Eva 2007 (65)
DIM	Rahman 2006 (59); Rahman 2007 (24); Rahman 2009 (68); Bhatnagar 2009 (83); Banerjee 2009 (78)
EGCG	McLaughlin 2006 (61)
Genistein	Nakamura 2009 (84); Wang 2010 (79)
I3C	Takada 2005 (43); Nakamura 2009 (84)
Maslinic acid	Li 2010 (80)
Plumbagin	Gomathinayagam 2008 (73)
Psoralidin	Kumar 2009 (75)
Quercetin	Chen 2007 (54)
Resveratrol	Fulda and Debatin 2004 (64); Fulda and Debatin 2004 (52); Aziz 2005 (46); Fulda and Debatin 2005 (53); Aziz 2005 (47); Hu 2007 (48); Shankar 2007 (49); Shankar 2007 (50); Roy 2009 (51)
Sesamin	Harikumar 2010 (82)
Silibinin	Son 2007 (55); Singh 2007 (56); Li 2008 (57); Tyagi 2007 (58)
Silymarin	Tyagi 2007 (58); Shaarawy 2009 (72)
Tea Polyphenols	Roy 2009 (77)

Moreover, in addition to the parent natural compounds, even their synthetic analogs, such as the synthetic analogs of DIM (DIM-C-pPhBr and 2,2'-diMeDIM-C-pPhBr) could inhibit proliferation and induce apoptosis in SW480 colon and Panc28 pancreatic cancer cells, again through down-regulation of survivin (85). It was also reported that gamma-radiation-induced inhibition of pancreatic and colon cancer cell growth is associated with induced expression of survivin and, in cells co-treated with gamma-radiation plus DIM-C-pPhBr or 2,2'-diMeDIM-C-pPhBr, induction of survivin by gamma-radiation was inhibited after co-treatment with both compounds, suggesting applications for these drugs in combination cancer chemotherapy with gamma-radiation. Clearly, down-regulation of survivin by natural compounds (Table 2) is one of the mechanism by which these agents exert their anticancer properties.

3.3. FoxM1

Forkhead box protein M1 (FoxM1) belongs to a family of evolutionary conserved family of proteins that is characterized by the presence of a DNA-binding domain called the forkhead box. FoxM1 is known to be a key regulator of transition from G1 to S phase as well as for the progression to mitosis (86;87). Loss of FoxM1 expression has been reported to generate mitotic spindle defects and accumulation of cells in mitosis leading to mitotic catastrophe (88). FoxM1 signaling maintains a balance between cell proliferation, differentiation and apoptosis (89;90) and an abnormal activation of FoxM1 gene is a hallmark of many human cancers (91-94). Therefore, FoxM1 appears to be an attractive target for therapy (95;96) and it has rightly been pointed out that by inhibiting this single transcription factor it should be possible to target multiple facets of tumorigenesis (97). In addition to role in the regulation of cell cycle, FoxM1 has also been implicated in the processes of tumor development. In hepatocellular carcinoma (98), prostate cancer (93) as well as lung cancer (99), FoxM1 expression was shown to correlate with increased proliferation while siRNA transfections for the inactivation of FoxM1 resulted in the reduction of cell proliferation and anchorage-independent growth (93;99). Additionally, the role of FoxM1 in the progression of different cancers such as glioma (91;100;101), cervical cancer (102), gastric cancer (103), osteosarcoma (104), lung cancer (105) and colon cancer (106) has been reported.

Our research investigations were the first to suggest that down-regulation of FoxM1 by a natural agent could be mechanistically associated with the inhibition of cell growth of breast cancer cells (59). While studying the molecular mechanisms underlying the observed anti-cancer properties of a DIM, we found that FoxM1 was one of the target genes that was significantly down-regulated by DIM in MDA-MB-231 breast cancer cell line (59). In a latter study in prostate cancer cells, we reported down-regulation of FoxM1 by DIM alone, as well as in combination with chemotherapeutic drug taxotere (68). Our detailed investigations in breast cancer cells have also yielded similar results (unpublished data). On a similar note, FoxM1 down-regulation has been reported by other researchers, using drugs, namely, antibiotic thiostrepton (107) and EGFR inhibitor Gefitinib (108). In a more recent study on the ability of a natural chemopreventive agent to modulate FoxM1 leading to its anti-cancer effects, the soy isoflavone genistein was reported to down-regulate FoxM1 expression and its downstream genes, including survivin, cdc25a, MMP-9 and VEGF, resulting in the inhibition of pancreatic cancer cell growth and invasion (79). These interesting results provide first evidence that FoxM1 is a legitimate target in pancreatic cancer and that the targeted inactivation of FoxM1, especially by natural agents, could be highly relevant to treatment of highly aggressive cancers. Additionally, down-regulation of FoxM1 was found to decrease cell proliferation and aggressiveness of breast cancer cells mediated by down-regulation of uPA, uPAR, MMP-2, MMP-9 and VEGF (109). Thus, there is evidence to suggest an important role of FoxM1 in aggressive cancers and reports on the anti-cancer effects of natural compounds through the down-regulation of this target are just beginning to emerge.

3.4. Notch

Notch signaling is associated with normal developmental processes (110;111) and loss of Notch signaling leads to embryonic lethality (112); however, increased activation of Notch signaling is believed to be the "hallmark" of aggressive cancers. There are four known

Notch-family receptors in humans, Notch-1, Notch-2, Notch-3 and Notch-4. The ligands for Notch receptors identified in mammalian cells are Jagged-1, Jagged-2, Delta-like1, Delta-like 3 and Delta-like 4. Binding of Notch ligands to their receptors initiates a proteolytic cascade resulting in the release of intracellular part of Notch that translocates to the nucleus and thereby regulates the transcription of target genes (113). In the context of cancer, activation of Notch signaling was first reported in T-cell lymphoblastic leukemia (114). Since then, a number of reports have demonstrated the relevance of Notch signaling in several other human cancers (115-121). Notch-1 expression has been reported in H-ras over-expressing breast cancers (122), is known to transform human breast epithelial cells (123) and, thus, implicated in mammary tumorigenesis (124;125). Further, while high expression of Notch-1 (126;127) and Jagged-1 (127) is associated with overall poor survival, high expression of Notch-2 has been linked with better survival (126). These reports clearly suggest the complex role of Notch signaling in human breast cancer (128;129). However, taken together, there is enough evidence to suggest that Notch signaling could be a valid therapeutic target in various human cancers.

With the emergence of reports detailing the contribution of Notch signaling to cancer progression in last few years, there has also been a realization that natural chemopreventive agents possess the ability to down-regulate various members of this signaling pathway in various cancer cells, leading to the desired anti-cancer effect. There is evidence to suggest that curcumin can efficiently down-regulate the expression of Notch-1 leading to apoptosis-induction in pancreatic cancer cells either alone (118) or in combination with soy-derived isoflavone (130). Curcumin has also been shown to down-regulate TNF-α-induced Notch-1 in leukemia cells (131). Similar activity in leukemia cells for resveratrol has also been reported (132). However, in medulloblastoma cells, resveratrol was found to have no effect on Notch signaling members (133) and the expression of Notch-1 and Notch-2 was actually found to be up-regulated by resveratrol in these cells. In pancreatic cancer cells, genistein has also been reported to inhibit the activity of Notch-1 resulting in inhibition of NF-κB and cell growth (134). Recently, inhibition of Notch-1 by yet another natural agent, withaferin-A, has been linked to inhibition of growth and induction of apoptosis in colon cancer cells (135).

3.5. CXCR4

CXCR4 is a chemokine receptor that is widely expressed in many different cancers (136). It is a G-protein-coupled receptor with seven trans-membrane domains. The ligand for CXCR4 is CXCL12 (also known as stromal cell derived factor-1, SDF-1). The role of CXCR4 and its ligand in progression of human cancers, especially in the process of metastasis, is widely recognized (137-148). As a result, signaling through CXCR4 receptor offers an attractive target for therapy.

CXCR4 in the tumor microenvironment may function to promote breast and prostate cancer proliferation, migration, and invasion, and our published data suggests that I3C could interrupt CXCR4/SDF-1α signaling pathway, resulting in tumor growth inhibition of breast cancer bone metastasis (42). Specifically, we showed that I3C significantly inhibited the bone tumor growth of MDA-MB-231 cells in a human mouse model of experimental bone metastasis through down-regulation of CXCR4-NF-κB pathway (42). These results further extend the potential therapeutic application of I3C for metastatic cancer. Modulation of CXCR4 and CXCL2 levels has also been suggested as a possible mechanism by which DIM can lower the invasive and metastatic potential of different human cancer cells (149;150). In addition to the usefulness of I3C against CXCR4, a synthetically developed derivative of I3C, OSU-A9, was reported to be more potent than the parent compound and down-regulation of CXCR4 was identified as one of the mechanism responsible for better efficacy of the compound against multiple breast cancer cells (151).

Curcumin has also been demonstrated to down-regulate CXCR4 in multiple cancer models. In follicular lymphoma, CXCR4 was found to be a major factor down-regulated by curcumin that was responsible for its anticancer properties (152). This study documented that attainable *in vivo* levels of curcumin are sufficient for inhibition of CXCR4 at mRNA as well as protein levels. Subsequently there have been reports on the down-regulation of CXCR4 by curcumin (153) and demethoxycurcumin (18) leading to anticancer effects in breast cancer cells. Curcumin has also been shown to sensitize colorectal cancer cells to chemotherapeutic drug capecitabine through the down-regulation of CXCR4 (154).

3.6. Wnt

The Wnt family of proteins is a family of glycoproteins that activate various intracellular pathways after binding to transmembrane frizzled (Fz) receptor family proteins or to a complex comprised of Fz and LDL receptor-related proteins 5/6 (LRP5/6). The best studied Wnt pathway, the Wnt/β-catenin pathway is also known as the "canonical" Wnt pathway. In the absence of Wnt ligands, β-catenin is recruited into a destruction complex comprised of adenomatous polyposis coli (APC) and axin, which induce the phosphorylation of β-catenin by casein kinase 1 (CK1) and glycogen synthase kinase 3 (GSK3) leading to ubiquitylation and proteasomal degradation of β-catenin. When Wnt proteins bind to Fz, dishevelled (DVL) is activated which recruits the destruction complex to plasma membrane, inhibiting GSK3 and thus preventing phosphorylation of β-catenin. β-catenin then accumulates in the cytoplasm and translocates to the nucleus, where it activates target genes (155). The role of Wnt signaling in human cancers has been recognized (156;157) and, thus, Wnt signaling offers an attractive target for therapy of human cancers.

Recently, sulforaphane, an isothiocyanate from cruciferous plants, has been demonstrated to modulate Wnt signaling leading to an efficient inhibition of breast cancer stem cells (158). This natural compound was found to be effective against an *in vitro* as well as an *in vivo* model for breast cancer stem cells. There are reports on ability of

components of traditional ethnic foods (159) and omega 3 polyunsaturated fatty acids (160;161) to inhibit Wnt signaling pathways resulting in reduced cancer growth in different cancer models. The Wnt signaling-inhibitory effect leading to inhibition of growth of breast cancer cells has also been reported for natural anti-cancer agents resveratrol (162), white currant berry (163), dietary triterpene lupeol (164), grape seed extract (165), silibinin (166), germinated brown rice (167) and deguelin (168). DIM has been found to significantly increase the phosphorylation of β-catenin and inhibit β-catenin nuclear translocation, suggesting a role of DIM in the down-regulation of Wnt signaling (169). The two natural chemopreventive agents that have been studied in relatively more detail with relation to their effect on Wnt signaling are curcumin and the green tea polyphenol EGCG. In addition to the documented role of curcumin in inhibiting Wnt signaling, particularly β-catenin (170-173), its synthetic analog, which is reported to be more potent, inhibits β-catenin leading to reduced growth of cancer cells and a prolonged survival time of colorectal carcinogenesis model mice (174). These studies confirm that modulation of Wnt signaling pathway represents a major mechanism of anti-cancer action of curcumin. Further, reduction of levels of β-catenin by green tea polyphenols in animal model of colon carcinogenesis (175;176) and in MDA-MB-231 breast cancer cells (177) points to the ability of green tea polyphenols, especially EGCG, to inhibit Wnt signaling pathway in different cancers.

3.7. Sonic hedgehog

The Hedgehog (Hh) pathway is primarily involved in the development of organs in most animals (178). The Hh gene was first identified in Drosophila and the three mammalian counterparts, Sonic Hedgehog (Shh), Desert Hedgehog, (Dhh), and Indian Hedgehog (Ihh), were identified thereafter (179). Shh binds to its 12-pass transmembrane receptor, Patched (Ptch1) resulting in de-repression of Smoothened (Smo) (178-180). This leads to the activation of Gli2 in the cytoplasm, which travels to the nucleus and regulates the transcription of Shh-pathway target genes, which include Gli1 and Ptch1. Shh signaling is increasingly being implicated in human cancers (181-184) and represents another attractive target for cancer therapy.

Curcumin has been shown to down-regulate Shh protein and its targets GLI1 and PTCH1 resulting in apoptosis induction through the mitochondrial pathway in medulloblastoma cells (173). In a recent study (185), seven agents - apigenin, baicalein, curcumin, EGCG, genistein, quercetin, and resveratrol were evaluated for their ability to inhibit Shh signaling in prostate cancer models. While genistein, curcumin, EGCG and resveratrol were found to inhibit Shh signaling by inhibiting Gli1 mRNA concentration by up to 95% and Gli activity by 80%, apigenin, baicalein and quercetin decreased Gli1 mRNA concentration but had no effect on Gli activity. Effect of EGCG on Hh signaling has also been reported in chondrosarcoma cells where EGCG was found to inhibit Ihh, as well as down-regulate Ptch1 and Gli1 levels (186).

3.8. Epithelial-mesenchymal transition

Progression of most carcinomas towards malignancy is associated with the loss of epithelial differentiation and a switch toward mesenchymal phenotype, which is accompanied by increased cell motility and invasion. The process of EMT by which epithelial cells undergo remarkable morphological changes is characterized by a transition from epithelial cobblestone phenotype to elongated fibroblastic phenotype. This process involves loss of epithelial cell-cell junction, actin cytoskeleton reorganization and up-regulation of mesenchymal molecular markers such as vimentin, ZEB-1, ZEB-2, fibronectin and N-cadherin (187). A disassembly of cell-cell junction, including down-regulation and relocation of E-cadherin and zonula occludens-1 (ZO-1) as well as down-regulation and translocation of β-catenin from cell membrane to nucleus, are known to be the mechanisms for the induction of EMT (188). Epithelial cells have a regular cell-cell junction and adhesion which inhibits cell movement of individual cells. In contrast, mesenchymal cells have weaker adhesion between cells compared to their epithelial counterparts, which renders mesenchymal cells more motile function, and confers more invasive characteristics. In addition to classical markers of EMT, such as e-cadherin, vimentin, ZEB-1/ZEB-2 etc, the process of EMT is also influenced by several other signaling molecules, particularly those from Notch and Wnt signaling pathways.

Since a switch from epithelial to mesenchymal phenotype is a good indicator of aggressiveness of cancer cells, it is desirable for an anti-cancer agent to reverse this phenomenon i.e. revert back from mesenchymal to epithelial phenotype (189). Consequently, an up-regulation of epithelial markers and/or down-regulation of mesenchymal markers is considered a reliable indication of the ability of any therapeutic agent to reverse EMT thereby reducing the invasion and metastasis of cancer cells (190). Curcumin has been reported to induce the expression of epithelial marker e-cadherin in melanoma (191), lung (192) and breast cancer cells (172). There is also evidence to indicate modulation of mesenchymal marker vimentin by curcumin leading to apoptosis induction (193). In one of the earlier studies on the subject, I3C was found to up-regulate e-cadherin in breast cancer cells leading to an inhibition of invasion and metastasis (194). Silibinin, an active constituent of silymarin isolated from milk thistle down-regulates the expression of vimentin in a dose- and time-dependent manner which leads to inhibition of invasion, motility and migration of prostate cancer cells (195). In a recent study with gemcitabine resistant pancreatic cancer cells, it was observed that exposure to DIM or isoflavone could up-regulate e-cadherin in these cells, and at the same time, down-regulate ZEB-1 and vimentin (196). Recently we found that treatment with DIM in combination with taxotere could up-regulate e-cadherin in MDA-MB-468, MCF7 and SKBR3 breast cancer cells and down-regulate vimentin in these cells including MDA-MB-231 (unpublished data).

3.9. microRNAs

microRNAs (miRNAs) are a group of small endogenous single-stranded non-coding RNAs, 19-25 nucleotides in length, that regulate gene expression by multiple mechanisms (197). microRNA (miRNA) profiling

is a rapidly emerging field that holds a lot of promise in cancer research (198). There has been an enormous spurt in research lately to suggest that the loss and gain of specific miRNAs is associated with the processes of invasion and metastasis. The regulation of oncogenes/tumor suppressor genes by miRNAs is increasingly being realized to be a key step in the progression of human malignancies (199). Further, expression of miRNAs is also known to regulate the acquisition of mesenchymal phenotype (200-202). New reports linking miRNAs with cancer progression are emerging everyday and this area of cancer research stands out as the most widely investigated one.

With the identification of novel miRNAs, researchers are busy identifying novel therapeutic agents that can modulate the expression levels of different miRNAs leading to desired effects on genes that play a crucial role in tumorigenicity. The ability of naturally occurring agents to play a role in regulation of miRNAs has not gone unnoticed, and, slowly but surely, evidence is emerging that suggests a modulatory effect of natural chemopreventive agents on miRNAs (203). Resveratrol has been shown to modulate miR-146a (204) while EGCG has been found to modulate miR-16 (205). Curcumin is also reported to influence miRNA expression (206) and it has been shown to up-regulate miR-22 and down-regulate miR-199a in pancreatic cancer cells (207). Natural agent ellagitannin has been found to modulate a number of miRNAs in liver cancer cells which is suggested to be the basis of its anti-proliferative and anti-cancer properties (208). I3C has been shown to down-regulate miR-21 (209) in lung cancer model while its dimeric product DIM as well as isoflavone have been reported to up-regulate expression of miR-146a (210) and miR-200 and let-7 (196) in pancreatic cancer cells. It is important to note that the data on modulation of miRNAs by naturally occurring dietary chemopreventive agents is just beginning to emerge. Lot of studies report a list of miRNAs that might be modulated by the agent in question, with data on the miRNAs that are up-regulated Vs. those that are down-regulated. Since a majority of such miRNAs wait for validation, we have listed here only those miRNAs that were actually validated in different studies by either over-expression (treatment with respective pre-miRNAs) and/or silencing (treatment with respective anti-miRNAs) studies.

4. CONCLUSION AND PERSPECTIVE

Naturally occurring chemopreventive agents come across as promising agents in the fight against human cancers which is largely due to their pleiotropic effects. As discussed above, several of these agents such as resveratrol, curcumin, EGCG, I3C, DIM, isoflavone etc have, in particular, shown a modulatory effect against more than one therapeutic target. This stands testimony to their pleiotropic potential. Despite such promising activity against cancer cells, none of these agents has yet been approved as a standard anti-cancer therapeutic drug. A good example is the compound curcumin that has traditionally been used in Indian herbal medicines for centuries. It is also interesting to note that curcumin stands out as the candidate agent that has shown promise in inhibiting almost all of the pathways presented above. The predominant reason that has hindered the clinical utility of curcumin is its bioavailability. Towards this end, Sarkar and co-workers have synthesized a novel analog of curcumin, curcumin-difluorinated (211), which not only retains the biological properties of curcumin but is actually a better anti-cancer agent (212), and, on top of it, is significantly more bioavailable (213-215). Such innovative studies provide an insight into the future of drug design. While natural chemopreventive agents provide an advantage in the form of non-toxicity, more often than not, they have their own limitations. A carefully designed synthetic analog might be the need of the hour which brings together the beneficial features of natural agent and, at the same time, overcomes its limitations.

Cancer cells are programmed to favor pro-survival pathways. Therapeutic regimes that target a single molecule/pathway usually have limited success. This is partly due to the ability of cancer cells to immediately bypass the targeted pathway and, instead, utilize alternate pathway (s) as means for survival and proliferation. The pleiotropic nature of natural chemopreventive agents is highly relevant in this context because simultaneous inhibition of multiple signaling pathways ensures a more effective killing of cancer cells. As reviewed by us recently (38), a very interesting property of natural chemopreventive agents is their ability to sensitize various cancers to the standard chemotherapeutic regimes. In such combinational therapies, standard chemotherapeutic drug can be used at a significantly reduced dosage which reduces its associated toxicity. While novel targets for therapy continue to be unveiled and validated, it is expected that the usefulness of natural agents as anti-cancer will not diminish, thanks to their pleiotropic activity. However, it is urgently needed to start planning on translating their laboratory utility to clinics, which could be made possible, either by careful synthesis of novel and more potent analogs or through their use in combinational therapy as chemo-sensitizers.

5. ACKNOWLEDGEMENTS

This work was supported by Department of Defense (DOD) to KM Wahidur Rahman. Grants number: W81XWH-04-1-0689, W81XWH-05-1-0505 and W81XWH-07-1-0145.

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Key Words: Chemoprevention, uPA-uPAR, Survivin, FoxM1, Notch, CXCR4, Wnt, Sonic Hedgehog, Shh, EMT, miRNAs, indole-3-carbinol (I3C), 3,3'-diindolylmethane, DIM, Curcumin, Resveratrol, Epigallocatechin-3-Gallate, EGCG, Genistein, Review

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