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Chemopreventive potential of natural compounds in head and neck cancer

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is one of the most fatal cancers world-wide. Despite advances in the management of HNSCC, the overall survival for patients has not improved significantly due to advanced stages at diagnosis, high recurrence rate after surgical removal, and second primary tumor development, which together underscore the importance of novel strategies for cancer prevention. Cancer chemoprevention, the use of natural or synthetic compounds to prevent, arrest, or reverse the process of carcinogenesis at its earliest stages, aims to reverse premalignancies and prevent second primary tumors. Genomics and proteomics information including initial mutation, cancer promotion, progression and susceptibility has brought molecularly targeted therapies for drug development. The development of preventive approaches using specific natural or synthetic compounds, or both, requires a depth of understanding of the cross-talk between cancer signaling pathways and networks to retain or enhance chemopreventive activity while reducing known toxic effects. Many natural dietary compounds have been identified as multiple molecular targets, effective in the prevention and treatment of cancer. This review describes recent advances in the understanding of the complex signaling networks driving cancer progression using head and neck cancer as a prototype, and of molecularly targeted natural compounds under preclinical and clinical investigation.

Keywords

Head and neck squamous cell carcinoma; Chemoprevention; Molecular target; Natural compound

Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most common cancers worldwide and a major cause of significant morbidity and mortality. HNSCC accounts for 3.2% of all cancers in the United States with approximately 48,000 new cases and more than 11,000 expected deaths in 2009 (1). Despite substantial medical advances for HNSCC patients over the past 30 years in treatments, including surgery, radiation, and chemotherapy, the overall survival rate has not been improved significantly due to frequent presentation with advanced stage disease and the development of second primary tumors (SPTs) which remain challenging to control (2–4). Improvements in diagnostic and therapeutic techniques and in chemotherapeutic agents are likely to increase survival rates, and consequently more patients are at risk of developing SPTs, indicating the urgent need to deter HNSCC. Therefore, prevention and early diagnosis of high-risk premalignant lesions should be emphasized rather than directing efforts only at treating end-stage disease.

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Multiple epigenetic and genetic events, including the dysregulation of many cellular processes such as cell cycle, growth, apoptosis, and angiogenesis are highly associated with pathogenesis of HNSCC. The critical intracellular molecular targets and the mechanisms underlying the variable responses to therapies remain elusive. Damage to numerous regulatory genes ultimately results in the development of invasive and metastatic cancer, providing a strong rationale for a preventive approach to the control of this disease (5, 6).

Cancer chemoprevention is defined as the use of natural or synthetic substances to reverse, suppress or prevent the initiation, promotion, or progression of cancer. To be useful in humans, a chemopreventive agent must have an acceptable safety profile in addition to being effective at a dose low enough to not cause significant toxicity. Natural dietary agents such as fruit and vegetables hold great promise for chemopreventive research due to their potential ability to prevent and suppress cancer (7–10). The great chemical diversity of natural compounds suggests various approaches for cancer chemoprevention. The successes of several recent clinical trials in preventing cancer in high risk populations suggest that chemoprevention is a rationale and appealing strategy. Here, we will discuss recent advances in the understanding of the complex signaling networks driving cancer progression using head and neck cancer as a prototype, and the potency, efficacy and limitations of molecularly targeted natural compounds under preclinical and clinical investigation.

Aspects of chemoprevention for HNSCC

The clinical practice of chemoprevention is still in its early stage, although there is a wealth of data documenting its effectiveness in preclinical and clinical trials. Many cancer incidences could be preventable by consuming a healthy diet including vegetables and fruits, regular physical activity and maintenance of optimum body weight (11). In the planning of clinical trials for primary prevention of cancers, it is important to select agents for which there is a strong mechanistic or experimental basis for inhibition of carcinogenesis. Epidemiological studies into the effects of diet on cancer development are invaluable for giving clues regarding effective dietary components as potential chemopreventive agents (12, 13).

Premalignant lesions of the head and neck is an excellent model for studying chemopreventive approaches, as HNSCC has a high tendency to develop SPTs, which have been reported in over 20% of cases, and up to 47% in patients with previously treated laryngeal cancer (14, 15). Prevention of SPTs in patients who have undergone surgery for removal of a first primary tumor provides an even more meaningful endpoint and these subjects may be at an exceptionally high risk for new cancer. HNSCC well exemplifies the multistep carcinogenesis with stepwise accumulation of genetic alterations, (16, 17) and exhibits clinically defined premalignant lesions such as oral leukoplakia and erythroplakia that can be targeted by a chemopreventive approach. Chromosomal aneuploidy in upper aerodigestive tract cancer indicates the transformation from oral leukoplakia to head and neck cancer (18). Therefore, it is highly desirable to reduce the incidence of HNSCC by developing specific natural compounds as chemopreventive regimens.

Recent approaches for the development of cancer chemopreventive agents

The concept of chemoprevention was initially proposed in the 1920s (19) and was reintroduced with great hope for cancer research by Sporn *et al.* (20) in 1976. Proceeding from his concept, modern chemoprevention has achieved enormous progress over 30 years, with hundreds of cancer chemoprevention studies conducted, including over 70 randomized trials (21, 22).

The most extensively studied chemopreventive agents in HNSCC are retinoids (summarized in Table 1), which are structurally and functionally related to vitamin A, to reverse head and neck cancer progression (23–33). The first randomized clinical trial was conducted by Hong et. al. (23), with the vitamin A analog 13-cis-retinoic acid (13-cRA, isotretinoin) for a short period in patients, which appeared to be an effective treatment for oral leukoplakia. However, substantial toxicity and a high relapse rate upon discontinuation led to the conduct of a maintenance trial with a much lower dose of isotretinoin (26). Long-term maintenance with isotretinoin was more effective than with β -carotene(27). Phase III clinical trials in HNSCC patients who were at high risk for both recurrence and SPTs, low-dose isotretinoin for 3 years or high dose did not show any significant improvements in survival (24, 28, 31). Reduction of dose-related toxicity and durable efficacy are highly desirable for cancer chemoprevention. The high risk of advanced premalignant lesions progressing to malignancy and the resistance to single agent retinoid therapy have elicited the idea of combining retinoids with other agents. It was reported that 13-cRA along with alpha-2a-interferon provides synergistic antitumor effects (34–36). A biochemopreventive trial in patients with advanced premalignant lesions of the upper aerodigestive tract given one year of interferon- α (IFN- α), 13-cRA and α -tocopherol, reported the prevention of laryngeal lesions but no effect on oral cavity lesions (37). Shin et. al. conducted a phase II clinical trial, treating patients with stages III or IV HNSCC with the combination of interferon- α , 13-cRA and α -tocopherol after complete resection, postoperative radiotherapy, or both, and showed that biochemoprevention therapy was promising for the suppression of SPT development and had an excellent survival rate (29, 30). N-4-(hydroxycarbophenyl) retinamide (4-HPR), another retinoid analogue with an encouraging toxicity profile (38), has been studied to evaluate its efficacy in the treatment and prevention of cancer (39). In patients treated after surgical excision of oral leukoplakia, 4-HPR was well-tolerated and was effective in preventing relapses and new localizations during the treatment period (40). 4-HPR has appeared as a promising agent because of its ability to induce apoptosis even in neoplastic cells that are resistant to retinoic acid (41, 42).

Some promising chemopreventive agents other than retinoids have also been launched into clinical trials. Papdimitrakopoulou et al. conducted a pilot randomized phase II study of celecoxib in oral premalignant lesions (OPLs) (43), but found celecoxib to be ineffective in controlling OPLs. Identification of high risk patients and more active treatments are needed. Recently, Tsao et al. published a phase II randomized trial of short-term green tea extract (GTE) treatment in high risk OPL patients (44). High-dose GTE had a significantly higher response rate than placebo, providing a strong rationale for testing GTE in a longer term clinical trial.

The clinical benefit of chemoprevention was spectacularly demonstrated by the Food and Drug Administration (FDA)'s recent approvals of tamoxifen for breast cancer prevention (45) and celecoxib for the control of familial adenomatous polyposis (46). Efficient chemopreventive intervention requires the further development of molecular prognostic factors and the identification of patients at high risk of cancer who might benefit most from participation in chemoprevention trial.

Molecular targets for chemoprevention

Recent developments in genomics, proteomics and bioinformatics have raised new possibilities for the prevention of cancer. Genetic information regarding initial mutations, cancer promotion, progression and susceptibility has brought about the development of molecularly targeted therapies with high impact on patient outcomes. Designing new therapeutic strategies targeting multiple signaling pathways offers novel approaches to prevent and treat cancer. Several molecular targets, crucial signaling proteins in HNSCC are

presented schematically in Figure 1, and their function in HNSCC progression and inhibitory outcome discussed in the following sections.

Epidermal Growth Factor Receptor (EGFR)

EGFR, a member of the ErbB family of receptor tyrosine kinases, is overexpressed in 80–90% of HNSCC. It is a widely accepted biomarker for premalignant lesions and is particularly important in pathogenesis of HNSCC, being associated with advanced stages of HNSCC and poor survival (47, 48). Thus, EGFR has become one of the most pursued therapeutic targets for this disease. Mutations, gene amplification and overexpression of EGFR have been implicated as crucial contributors to a variety of cancers. EGFR alterations, specifically increased copy number in the tumor, are correlated with the overall patient survival rate of HNSCC (49). EGFR is activated upon ligand (EGF or TGF- α) binding through receptor dimerization and phosphorylation on multiple tyrosine sites and recruits signaling complexes to activate many downstream intracellular signaling pathways, including Ras/MAP kinase, phosphatidylinositol-3-kinase (PI3K), phospholipase-C γ (PLC- γ), protein kinase C (PKC) and signal transducer and activator of transcription (STATs) (50, 51) (Fig 1), which operate many important cellular processes such as tumor growth, survival, invasion, metastasis and angiogenesis (52). EGFR can be translocated to the nucleus and regulate the expression of several genes to drive cell-cycle progression, proliferation and metastasis development (53). EGFR expression is moderately upregulated in normal epithelium adjacent to tumor tissue, and increased when cells transition from dysplasia to HNSCC (54). Upregulated EGFR signaling correlated with growth and metastasis in a wide range of tumors, while downregulation protects HNSCC cellular growth (55). p53 status is crucial for EGFR-mediated cellular growth and apoptosis (56). p53 upregulated modulator of apoptosis (PUMA) is a critical mediator of EGFR inhibitor-induced apoptosis and the p63, p73 and PI3K/AKT pathways play vital roles in HNSCC (57, 58). EGFR is mechanistically involved in the link between tobacco smoke and oral cancer, since tobacco smoke activates EGFR signaling, which increases COX-2 signaling and thus tumor cell growth (52). Inhibition of EGFR by antibodies or selective inhibitors has been shown to induce growth suppression and apoptosis in HNSCC cells and xenograft tumors (52).

Several natural or synthetic compounds have been identified for targeting EGFR-mediated signaling, providing a promising approach to inhibit cancer development and progression. Several EGFR-targeting agents including selective tyrosine kinase inhibitors (TKI), such as gefitinib (ZD1839/Iressa) and erlotinib (OSI774/Tarceva), and the monoclonal antibodies cetuximab (C225/Erbitux) and panitumumab (Vectibix) are approved by the FDA for use in certain types of cancer, and are currently being explored in clinical trials. However, a common challenge to their clinical potential is the development of acquired resistance. The development of preventive approaches using specific natural or synthetic chemical compounds alone or in combination has become highly desirable to reduce the incidence of HNSCC. The EGFR inhibitor erlotinib had synergistic growth inhibitory effects with either green tea-derived EGCG (56, 59) or COX-2 inhibitor (60–62) in cellular and animal models of HNSCC, thus providing an important rationale for chemoprevention or treatment trials. The National Cancer Institute has funded several grants for improving erlotinib efficacy by determining appropriate combination regimens for HNSCC (60, 61). A phase I/II study with a combination of EGFR inhibitor, erlotinib, and an anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab has shown the combination to be well tolerated in recurrent or metastatic HNSCC, with sustained benefit and complete responses (63). A follow up study of a phase III clinical trial in HNSCC patients using the anti-EGFR antibody cetuximab in combination with radiotherapy reported significantly improved overall survival

at 5 years (64). The above-mentioned studies suggest that EGFR is a potential candidate to be targeted for chemoprevention purposes in HNSCC.

Cyclooxygenase-2 (COX-2)

Overexpression of COX-2, a key enzyme for the formation of prostaglandins PGE₂ from arachidonic acid, an early and central event in carcinogenesis, provides an important target for chemopreventive drug development (65). COX-2 is widely overexpressed in variety of premalignant and malignant lesions including oral leukoplakia and HNSCC (66). Thus COX-2 appears to be a novel molecular target for the prevention and treatment of HNSCC. Treatment with selective COX-2 inhibitors reduces the formation of intestinal, esophageal, tongue, breast, skin, lung and bladder tumors in animals (65, 67–70). COX-2 protect cells from apoptosis by inducing anti-apoptotic Bcl-2 and by suppressing Bax proteins (65). COX-2 inhibitors have been shown to induce apoptosis in HNSCC (71), prostate cancer (72), colorectal cancer (73) and lung cancer (74). COX-2 expression promotes antitumor reactivity by restoring the balance between IL-10 and IL-12 in vivo (74, 75) and inhibitors of COX-2 activity have been shown to attenuate tumor-mediated immune suppression and also regulate invasion through CD44 and matrix metalloproteinase (MMP)-2 (66). COX-2 inhibitors suppress angiogenesis by reduction of VEGF, thus inhibiting growth of HNSCC (71) and lung cancer (74). Celecoxib, a selective COX-2 inhibitor abolished cigarette smoke-induced NF-Kb activity and suppressed cyclin D1 and matrix metalloproteinase-9 (76).

The first human clinical trial of celecoxib in cancer was conducted in familial adenomatous polyposis (FAP) patients treated with celecoxib, which led to a significant reduction in the number of colorectal polyps (46). On the basis of this result, celecoxib was approved by the FDA as an adjunctive therapy for patients with FAP. Combinations of celecoxib with other agents have been sought, given the advantages of combination therapy for cancer treatment and prevention, ie, allowing increased efficacy while reducing toxicity through lowered doses. The combination of celecoxib with the EGFR inhibitor erlotinib was highly effective in HNSCC chemoprevention, as mentioned earlier. The combination of a retinoid and a COX-2 inhibitor could be an effective chemopreventive strategy for HNSCC, since the transcriptional activation of COX-2 is blocked by retinoic acid in oral epithelial cells (77, 78), and retinoic acid has shown promising effects in HNSCC patients in a clinical trial. Cotreatment with a selective COX-2 inhibitor can increase the efficacy of chemotherapy or radiotherapy (79). COX-2 appears to be a novel molecular target and inhibitors need to be given in combination with standard therapy to improve its efficacy in cancer prevention.

p53

To evaluate the efficacy of chemopreventive agents, there is an urgent need to identify novel biomarkers which have predictive value for the clinical disease and risk stratification that can be used for precise chemoprevention. The p53 transcription factor is a known tumor suppressor protein, and one of the most promising biomarkers. p53 has been described as “the guardian of the genome,” referring to its role in conserving stability by preventing genome mutation. Activated p53 regulates genes including *p21*, *14-3-3*, *Noxa*, *Puma*, *Fas*, *Bax*, and many others to direct cellular processes such as cell cycle inhibition, apoptosis, genetic stability, and inhibition of angiogenesis (7, 80). p53 controls cell cycle arrest in G1 phase in response to DNA damage and thus protects against genomic instability, abnormal DNA replication and chromosome segregation (81, 82). p53 expression is highly associated with increased genetic instability during tumorigenesis in head and neck (81, 82), breast (83), ovarian (84) and renal cancer (85).

Mutations of p53 are commonly found in HNSCC (40–50%), and are strong determinants of more advanced oral cancer and poor survival (44). Restoring normal p53 function would be a potential chemopreventive approach in various types of cancers including head and neck. Many natural chemopreventive agents have been shown to induce p53 activation. In some clinical trials of HNSCC patients, retinoids have proven to be effective as chemopreventive agents but reduction of toxicity and better efficacy still remains challenging. p53 protein and retinoic acid receptor β (RAR- β) are expressed in most premalignant oral lesions (86) and wild type p53 expression is strongly associated with an increased clinical response to therapy with 13-cRA with or without IFN (80, 87). Thus, confirming p53 activation by suitable natural chemopreventive agents alone or in combination with other agents could be effective in future clinical trials.

Nuclear Factor-Kappa B

NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein that controls the transcription of DNA, usually in response to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, carcinogens, tumor promoters and bacterial or viral antigens (88–90). The genes regulated by NF- κ B include those controlling apoptosis, cell adhesion, proliferation, the innate- and adaptive-immune responses, inflammation, the cellular-stress response and tissue remodeling (90, 91). The major class of cellular targets of NF- κ B are chemokines (IL1 α and IFN γ), regulators of apoptosis (Bcl-xL, IAP), transcription factors (G-CSF, GM-CSF), and cell cycle regulators (cyclin D1, mdm2) (91). NF- κ B signaling pathways have been targeted for therapeutic applications in many cancers. Several drugs or inhibitors currently in clinical use have significant effects on NF- κ B activity and antitumoral activity (91–93) (Fig 1). Constitutively activated NF- κ B plays a vital role in pathogenesis and therapeutic resistance in HNSCC by regulating many genes including *cyclin D1*, *Bcl-XL*, *TRAF1*, *TRAF2*, and *mdm2* as cell cycle progressors and regulators of apoptosis; *IL-1*, *-6*, *-8*, *TNF α* and *VEGF* as angiogenic factors; *MMP-9*, *uPA*, *TIMP* as metastatic regulators; and *P-glycoprotein* and *GADD45* as therapeutic resistance factors (94). A recent phase I clinical trial was conducted using bortezomib (a proteasome inhibitor that inhibits NF- κ B) and cetuximab (EGFR inhibitor), which was found to be moderately effective in non-small cell lung or head and neck cancer patients (95). NF- κ B constitutes a potential target for chemoprevention. Thus, different combination approaches including natural chemopreventive agents need to be investigated. Understanding the pathways that regulate NF- κ B functions will be useful in developing NF- κ B inhibitors for the treatment and prevention of cancers.

Activator protein 1

Activator protein-1 (AP-1) is a transcription factor composed of a group of dimeric proteins belonging to the c-Fos, c-Jun, ATF, Maf and JDP families. AP-1 bind a common DNA sequence (TGAG/CTCA) and a dimeric structure formed by a leucine zipper. Several mechanisms have been shown for AP-1 activity involving growth factor receptor, proinflammatory cytokines and UV radiation (96). AP-1 proteins regulate many target genes such as *cyclin D1*, *p16*, *p19^{ARF}*, *p53*, *p21*, *Fas L* and execute different biological functions including cell proliferation, survival and apoptosis (97).

AP-1 is constitutively activated in HNSCC cell lines and promotes resistance to apoptosis by regulating many proteins including NF- κ B and COX-2 (98, 99). Blocking AP-1 activity augmented antitumoral efficacy in HNSCC cells (98). In vitro and in vivo evidence demonstrated that the antitumor effect of retinoid was enhanced by inhibiting AP-1 activity (100, 101). Retinoid has appeared a promising chemopreventive drug in several clinical

trials (Table 1). The combination of AP-1 inhibitor with retinoid or other chemopreventive compounds could be a useful tool for cancer chemoprevention.

Signal Transducers and Activator of Transcription (STATs)

STAT proteins are activated by tyrosine phosphorylation, dimerization and nuclear localization, where STATs bind to consensus elements in the promoter regions of targeted genes associated with many aspects of cell growth, survival, differentiation, angiogenesis and apoptosis (102–105). So far, seven mammalian STAT family members have been identified, named STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6. Several reports have indicated the important role of STATs in the progression of HNSCC. Autocrine or paracrine activation of TGF- α /EGFR is observed frequently in HNSCC and STAT3 is a vital signaling network downstream of TGF- α /EGFR (106). In primary tumors of HNSCC patients, STAT3 is constitutively activated and induces expression of cyclin D1 and is associated with a lower survival rate (107). Src kinase plays a vital role in EGFR-mediated STAT3 and STAT5 activation in HNSCC (108). Constitutive activation of STAT3 and STAT5 has been implicated in multiple myelomas, lymphomas and several solid tumors (109). Knockout studies have provided evidence that STAT proteins are involved in the development and function of the immune system and play a role in maintaining immune tolerance and tumor surveillance (110). Finding new agents and combination strategies that target STAT3 and STAT5 may be useful in the treatment and prevention of HNSCC.

PI3-K/AKT/mTOR signaling

PI3-K/AKT/mTOR has been reported as a key dysregulated signaling pathway in head and cancer (51). This pathway is an attractive therapeutic target in cancer because it plays a vital role in many growth stimuli, and controls cellular processes through its downstream substrates that contribute to the initiation and maintenance of cancer. Loss of function of the tumor suppressor PTEN, amplification or mutation of PI3K and Akt, activation of growth factor receptors, and exposure to carcinogens are strong contributors to the activation of PI3-K/AKT/mTOR signaling, which confers resistance to treatment and poor prognosis in many types of cancer (111). Constitutive activation of this signaling pathway is frequently found in HNSCC (112, 113) and is also associated with radioresistance (114). In preclinical and clinical studies, targeting this pathway by using several inhibitors is suggested as a promising approach in controlling tumor progression in many cancers including HNSCC (111, 115). Currently many inhibitors, both natural and synthetic, and their combinations are being used and developed to disrupt PI3-K/AKT/mTOR signaling (Fig. 1), and could prove beneficial for cancer prevention and treatment.

Other molecular targets

VEGF and its receptor are overexpressed in HNSCC, and regulate angiogenesis, survival, and tumor growth (116, 117). In a phase I/II study in patients with recurrent or metastatic HNSCC, the combination of the EGFR inhibitor, erlotinib, and an anti-VEGF antibody, bevacizumab, was well tolerated and led to sustained benefit and complete responses (63).

Sorafenib, a bisaryl urea, is a multikinase inhibitor that acts on C-Raf, B-Raf, VEGF, VEGFR-2, VEGFR-3, PDGFR and FLT3. It mainly targets the EGFR-Ras-Raf-MEK-ERK (118) and VEGF-VEGFR (119) signaling pathways to regulate cell growth, differentiation, apoptosis, cellular transformation, angiogenesis and metastasis. A phase II clinical trial of sorafenib in HNSCC patients showed it to be well tolerated with modest anticancer activity (120).

The above-mentioned signaling networks play vital roles in carcinogenesis. It is very important to understand the dysregulated signaling pathways in HNSCC which could be potential targets for chemopreventive strategies.

Potential natural compounds as chemopreventive agents

Successful chemopreventive agents must be effective and safe enough for extended use because short term interventions are not expected to substantially reduce cancer risk over the long term. Several nutritional compounds, including those found in green and yellow vegetables, fruits, and spices belonging to different classes of chemicals, have been shown to prevent the occurrence of cancer in experimental animals. Chemoprevention with a great diversity of natural or synthetic products has already appeared to be a promising approach. The chemopreventive properties and molecular targets of selected promising natural compounds are discussed, and available agents, either natural or synthetic or both, targeting crucial signaling proteins in HNSCC are presented schematically in Figure 1.

Green Tea Polyphenols

Polyphenols (PPs) are most abundant in plant-derived foods such as fruits, seeds, leaves and beverages, and are reactive metabolites characterized by several hydroxylated aromatic groups. PPs have powerful antimicrobial activity and outstanding antioxidant activity, capable of scavenging a wide range of reactive oxygen, nitrogen, superoxide anions and metal ions (121, 122). PPs may derive their preventive effect against oral cavity and oral cancer by coming into direct contact with tissues before being absorbed or metabolized (123), allowing them to deliver the biologically active aglycones at the surface of the epithelial cells to inhibit proliferation of oral cancer cells (124).

One of the most widely consumed beverages in the world is tea, which contains abundant PPs with antioxidant properties. The preventive potential of tea, mainly green tea polyphenols has been reported in many epidemiological and preclinical studies (125–127). Green tea extract (GTE) has been reported to account for the reduction of human cancer risk in multiple organ sites (7, 128). GTE contains four major polyphenols: epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) (6). EGCG, the most abundant and the best studied among tea polyphenols has gained the most attention with respect to anti-carcinogenic activity.

Multiple proteins including EGFR, NF- κ B, tumor necrosis factor- α (TNF- α), AKT, mitogen activated protein kinase (MAPK), p53 and its multiple target genes play a critical role in EGCG-driven signal transduction pathways to inhibit cell proliferation, invasion, and angiogenesis (7, 129–131). EGCG has been identified as targeting EGFR-mediated signaling (Fig. 1), providing a promising target to inhibit cancer development and progression. We showed in our earlier study that EGCG synergistically increased the efficacy of EGFR inhibitor in growth inhibition of HNSCC (56, 59). Erlotinib and EGCG synergistically inhibit HNSCC growth via inhibiting NF- κ B in a p53-dependent manner (56). EGCG regulates cell cycle progression and drives apoptosis to inhibit overall cancer progression. In preclinical studies, EGCG treatment arrested cells in the G₀-G₁ phase, downregulated cyclin D1 (132), directed cell cycle progression in oral leukoplakia cell lines (133), and enhanced apoptosis by p53 stabilization upon induction of p14^{ARF}, p16 protein levels and interferon (134, 135). EGCG interrupted angiogenesis by inhibiting phosphorylation of VEGFR (136) and inhibiting VEGF secretion by tumor cells (137). EGCG regulated AP-1 target genes by suppression of AP-1 activity (138). EGCG appears to be a potentially promising agent to prevent oral carcinogenesis (139, 140). EGCG synergistically increased the efficacy of other drugs including curcumin, erlotinib, luteolin,

genistein, atorvastatin, tamoxifen, celecoxib, cisplatin, sulindac, adriamycin in cell culture and animal models (7).

In vitro and in vivo results of green tea polyphenols have recommended several clinical trials to pursue, and a few trials addressing the efficacy and toxicity of GTE have already been completed. A phase I clinical trial using GTE in patients with advanced cancer showed that 1000mg/m² three times per day was safe (141). A pilot study in smokers using GTE (2000 to 2500 mg/d) showed that smoking-induced DNA damage was decreased with a reduction in aneuploidy and increased apoptosis (142). Recently, Tsao et al. published the results of a phase II randomized trial of short-term GTE in high risk OPL patients, showed that higher doses had greater response rates (44). A longer treatment time and higher dose were suggested. Nanochemoprevention has also been explored, with nanoparticle-mediated EGCG delivery found to enhance bioavailability and reduce toxicity (143). Currently, several trials involving green tea alone or in combination with other drugs or oral EGCG analogues are ongoing, with the goal of improving bioavailability and efficacy and reducing toxicity (7). A phase I clinical trial using low dose erlotinib and EGCG has been planned at the Emory Winship Cancer Institute to assess the efficacy of this combination in patients with premalignant lesions of the head and neck.

Curcumin

Curcumin, also called diferuloyl methane, is a hydrophobic polyphenol isolated from rhizomes of the plant *Curcuma longa L.*, widely used as spice. In the 1980s, Kuttan et. al. introduced new properties of curcumin as growth inhibition and cytotoxicity in vivo (144, 145). Extensive research over the last 30 years has revealed numerous therapeutic benefits of curcumin, including chemoprevention and therapy in cancer. In vitro and in vivo research revealed that curcumin has versatile properties such as cytotoxicity, anti-inflammation, antioxidant, immunomodulation, anti-angiogenic, cytokine release and apoptosis (128, 146–148). Curcumin has been shown to inhibit all three steps of carcinogenesis, initiation, promotion and progression, in an animal model (148) of skin cancer (149) and oral cancer (150). Curcumin has been shown to regulate the expression and activity of various molecules that play vital roles in cancer progression. As a single agent, curcumin can downregulate several molecular targets including COX-2, HER2, EGFR, AKT and VEGF (151) which are involved in crucial cellular processes discussed earlier in this chapter and in signaling networks summarized in Fig. 1. Curcumin has also been identified as an inhibitor of NF- κ B and its target genes and thus regulates several cellular processes: it inhibits cell growth and survival by suppressing Bcl-2, cyclin D1, IL-6, COX-2 and MMP-9 protein expression in HNSCC (152) and in colon cancer (153); it reduces cancer cell angiogenesis, invasion and subsequent cell migration by suppressing MMPs (154, 155); and it reduces cell cycle regulation by suppressing cyclin D (148).

The promising preclinical in vitro and in vivo results and the pharmacological safety of curcumin have advanced it into clinical trials. A phase I clinical trial was conducted by Cheng et. al. in patients with high risk or premalignant lesions and demonstrated that orally-administered curcumin taken for 3 months was not toxic up to 8g/day (156), but is not appropriate for clinical utilization due to its rapid metabolism in the liver and intestinal wall. A pharmacodynamic and pharmacokinetic study of oral curcumin in patients with colorectal cancer suggested that curcumin has low oral bioavailability in humans and undergoes intestine metabolism (157). In an attempt to improve curcumin's medicinal properties, there is a need to increase its potency. Many researchers are currently focusing on developing potent curcumin analogues and combination therapies. Curcumin has synergistic chemopreventive abilities with other diet-derived PPs including genistein (158) and green tea (159), and has been shown to increase the efficacy of some anti-cancer drugs including

fluorouracil (160) and gemcitabine (161). Combination treatment of curcumin with quercetin (162) or with piperine (163) has shown positive responses in clinical trials. EF-24 is an analogue of curcumin that has shown promising anticancer activity (164, 165). Several phase I and phase II clinical trials are now searching for improved chemopreventive efficacy of curcumin (7).

Resveratrol

Resveratrol is a phytoalexin produced by several plants including grapes, mulberries, peanuts, vines, and pines. In 1992 it attracted wider interest, when its presence in wine was associated with cardioprotective properties. Since then, several beneficial effects have been documented in many diseases including cancer. Jang et. al (166) showed that resveratrol reduced the incidence of skin tumors in a mouse model by inhibiting all stages of carcinogenesis. Resveratrol interacts with multiple molecular targets and has positive effects on breast, skin, gastric, colon, esophageal, prostate, and pancreatic cancer cells (167). Resveratrol has been shown to induce apoptosis in human breast cancer xenografts in vivo (168), in prostate cancer (169–171) and inhibits angiogenesis in human breast cancer xenografts in vivo (168, 172). Topical application of resveratrol in mice inhibited skin damage and decreased skin cancer incidence but orally given resveratrol was ineffective in treating mice inoculated with melanoma cells, or in leukemia and lung cancer (173, 174). Resveratrol (2.5 or 10 mg/kg via injection) slowed the growth of metastatic lewis lung carcinomas in mice (175) and (1 mg/kg orally) reduced the number and size of esophageal tumors in rats treated with a carcinogen (176). In several studies, small doses (0.02–8 mg/kg) of resveratrol, given prophylactically, reduced or prevented the development of intestinal and colon tumors in rats given different carcinogens (174).

Most of these results have yet to be tested in humans because even high doses of resveratrol are insufficient to achieve the resveratrol concentrations required for the systemic prevention of cancer. This is consistent with animal model studies showing that the effectiveness of resveratrol is limited by its poor systemic bioavailability (174, 177). Recent approaches using nanoparticle-mediated delivery of resveratrol indicate improved bioavailability as evidenced by increased solubility, stability and intracellular delivery (178). The strongest evidence of anti-cancer action of resveratrol exists for tumors it can come into direct contact with, such as skin and gastrointestinal tract tumors. Several clinical trials are ongoing to assess the efficacy of resveratrol in cancer chemoprevention (7).

Lycopene

Lycopene is a red carotene, carotenoid pigment and phytochemical without vitamin A activity, found in tomatoes, fruits and vegetables, such as red carrots, guava, watermelons and papayas. Substantial scientific and clinical research has been devoted to exploring a possible correlation between lycopene consumption and a reduction in the incidence of cancer due to its antioxidant properties. Epidemiological studies have shown dietary intake of lycopene is inversely associated with the risk of many cancers including those of the digestive tract, prostate and cervix (179–182). In different studies, lycopene was found to have an inhibitory effect on different kinds of cancer cells including breast and endometrial cancer cells (183, 184), prostate carcinoma cells (182) and colon cancer cells (185).

Lycopene is a potent antioxidant and quencher of singlet oxygen (186), resulting in protection against oxidative DNA damage in vitro and in vivo, and is also involved in inhibition of growth and induction of differentiation in cancer cells by modulating the expression of cell cycle regulatory proteins (187, 188). Tomato products may control benign prostate hyperplasia by preventing disease progression (189) and by the induction of

apoptosis (190). Two phase II clinical trials suggested that lycopene alone (191) or in combination with soy isoflavones (192) suppresses the growth of prostate cancer.

The molecular mechanisms underlying the biological effects of lycopene as well as its pharmacological properties need to be further elucidated and clinical trials are needed to assess the relevance of lycopene for the prevention of cancer.

Luteolin

Luteolin is a flavonoid of the specific class of flavones, most often found in green vegetables such as celery, green pepper, thyme, broccoli, cabbage, spinach, olive oil, peppermint, rosemary and oregano (193). It plays an important role as an antioxidant, a free radical scavenger, an agent in the prevention of inflammation and in the prevention of cancer (194). Low systemic bioavailability of luteolin due to its metabolism by the liver and intestine is the major obstacle to its clinical application. However, epithelium of the oral cavity can absorb luteolin directly (124) and it has been reported that luteolin induced cell-cycle arrest by inhibiting cyclin dependent kinase and p-retinoblastoma, followed by apoptosis, leading to the growth inhibition of squamous cell cancer cells (195). Topical application also appeared to result in potent antitumor activity against skin papillomas in mice (196). Several studies have reported that luteolin was highly effective in inducing cell cycle arrest, apoptosis and cell growth inhibition in human esophageal adenocarcinoma cells (197), lung carcinoma (198), human colon cancer cells (199) and human hepatoma cells (200). Luteolin was highly effective in chemoprevention or therapy against HER2-overexpressing chemoresistant tumors (201). Recently, it has appeared with a role in inhibition of cell invasion in prostate cancer cells (202). Many *in vitro* and animal studies have been conducted but have yet to be replicated in human subjects. Thus, clinical trials are recommended to assess the chemoprevention potential of luteolin.

Other promising natural agents

Several other natural compounds besides the above mentioned agents are being extensively investigated to evaluate their chemopreventive potential. Pomegranate, genistein, ellagic acid, some triterpenes, polyunsaturated fatty acids and ginkgolid have appeared as promising chemopreventive agent. Pomegranate has been reported to be a potential chemopreventive agent for breast cancer (203, 204), prostate cancer (205), skin cancer (206) and prostate cancer (207). Genistein is a phytoestrogen mostly found soybeans, and an inverse correlation has been reported between genistein consumption and the risk of prostate (208), breast (209) and endometrial (210) cancer. Ellagic acid, found in many fruits and vegetables, has chemopreventive ability against skin, lung, esophageal, colon, prostate and breast cancers (211, 212). Triterpenes, polyunsaturated fatty acids and ginkgolid have shown their chemopreventive potency *in vitro* and *in vivo* in many cancers (7).

Future directions and conclusions

The five year survival rate of HNSCC patients has yet to be significantly improved despite the advances made in therapy including surgery, radiation and chemotherapy. Clinical trials, particularly for the prevention of second primary cancers have already validated the concept of chemoprevention. Multiple deviant or dysregulated signaling pathways involved in growth, survival and apoptosis in HNSCC challenge the clinical efficacy of chemopreventive agents. Thus, it is crucial to better understand these pathways and delineate how they network in the regulation of cancer progression, in order to develop diverse and complex agents that could be more effective in the prevention of HNSCC. Interfering with single steps of these pathways with single agent chemotherapy has been shown to have limitations of both toxicity and potency in patients, mandating the

development of new chemopreventive agents that have the potential to act on multiple targets. Alternatively the combination of chemopreventive agents with new targeted agents or with conventional chemotherapy or radiation treatments that target distinct specific pathways is likely to disrupt the malignant programming of the cells and inhibit prosurvival signals; this may also be an attractive approach to clinical therapy and prevention. Natural dietary agents hold particular promise for chemoprevention because of their safety profile. The broad chemical diversity features together with many epidemiological, preclinical and clinical studies suggest a definitive role for selected dietary products in various approaches to cancer chemoprevention. Low potency, poor bioavailability and toxicity of dietary agents constitute the major challenges to their clinical development. An important prospect is to standardize the formulation and contents of natural compounds. Many natural or synthetic agents target multiple signal transduction pathways and thus testing combinations could be a beneficial approach to enhance efficacy and bioavailability while reducing unexpected toxicities. An anti-proliferative agent and an inducer of apoptosis may be one beneficial combination of natural or synthetic compounds to overcome single agent resistance for more effective chemoprevention, and currently such clinical trials are in progress. For example, the combination of EGCG, a major polyphenol of green tea, with an EGFR-TKI represents a novel synergistic chemopreventive combination for HNSCC (59). To evaluate the efficacy of these chemopreventive agents there is an urgent need to identify novel biomarkers which have predictive value for the clinical disease and risk stratification that can be used for a more disease-specific approach. Natural agents appear to be highly promising molecular targets for chemoprevention and thus, innovative designs for chemopreventive treatment approaches based on appropriate patient selection are critical for meaningful impact.

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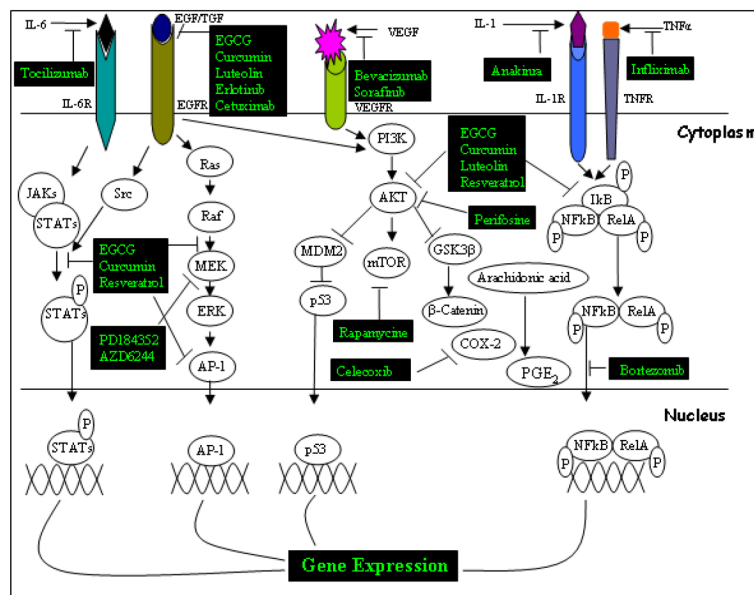


Figure 1. The consequences of signal cascades frequently dysregulated in HNSCC and the molecular targets of natural or synthetic chemopreventive agents
 Dysregulation of JAK/STAT, Ras/Raf, PI3K/Akt/mTOR, and the NF-κB signaling pathway contributes to HNSCC cancer progression upon activation of multiple growth factors and cytokine receptors. Several natural or synthetic compounds are summarized as potential inhibitors of these signaling pathways (blocking arrow).

Table 1

Selected chemopreventive trials in HNSCC patients.

Investigator	Year	Patient No.	Type	Agents	Results
Hong et al. (23)	1986	44	Oral leukoplakia	13-cRA at 1–2mg/kg/d for 3months vs placebo	13-cRA vs placebo response 67% vs 10%
Stich et al. (25)	1988	103	Oral leukoplakia from tobacco-containing betel quids	Beta-carotene (180mg/wk) with or without vitamin A (100,000 IU/wk) vs placebo	Remission of leukoplakia in beta-carotene (14.8%) vs beta-carotene plus vitamin A (27.5%) vs placebo (3%)
Stich et al. (33)	1988	64	Oral leukoplakia from tobacco-	Vitamin A (200,000 IU/wk) orally for 6months vs placebo	Complete remission vitamin A (57.1%) vs placebo (30%)
Hong et al. (24)	1990	103	Prior HNSCC	13-cRA at 50–100mg/m ² /d for 12 months vs placebo	Second primary tumors 13-cRA (24%) vs placebo (2%)
Han et al. (39)	1990	61	Oral leukoplakia	4-HPR (40mg/d) vs placebo	Complete remission 4-HPR (87%) vs placebo (17%)
Lippman et al. (26)	1993	70	Oral leukoplakia	13-cRA at 1.5mg/kg/d for 3months, followed by 13-cRA at 0.5mg/kg/d or beta-carotene 30mg/d for 9 months	Initial response 55% to high dose in 13-cRA and stable lesions 13-cRA (92%) vs beta-carotene (45%).
Chiesa et al. (40)	1993	137	Oral leukoplakia	4-HPR (200mg/d) for 52wk vs placebo	Local relapses or new localizations occurred 15% in placebo and 6% in 4-HPR group
Papdimitrakopoulou et al. (37)	1999	36	Advanced pre-malignant lesion	13-cRA (100mg/m ² /d) α-tocopherol (1200 IU/d) Interferon-α (3MU/m ²) twice per wk for 12 months	Laryngeal lesions 50% complete response vs placebo 0%.
Shin et al. (29,30)	2001 2005	44	Prior HNSCC	13-cRA (50mg/m ² /d) α-tocopherol (1200 IU/d) Interferon-α (3MU/m ²) thrice per wk for 12 months	2 years survival rate 91% and disease free 84%. 5 years overall survival rate 81.3%.
Khuri et al. (31)	2006	1190	Stage I and II HNSCC	13-cRA (30mg/d) vs placebo for 3 years	Low dose 13-cRA was not effective in reduction of SPTs or death.
Papdimitrakopoulou et al. (43)	2008	50	Oral premalignant lesions (OPLs)	Celecoxib 100mg or 200mg twice daily for 12 weeks	Ineffective in controlling OPLs
Papdimitrakopoulou et al. (32)	2009	162	OPLs	13-cRA (0.5mg/kg/d) for 1year followed by 0.25mg/kg/d for 2 years or beta-carotene (50mg/d) plus retinyl palmitate (25000IU/d) for 3 years.	Beta-carotene plus retinyl palmitate or retinyl palmitate alone are not equivalent to 13-cRA in controlling OPLs
Tsao et al. (44)	2009	41	High risk OPL	Green tea extract (GTE) 500 or 750 or 1000 mg/m ² vs placebo	Two higher dose GTE arms response rate 58.8% vs placebo (18.2%).