Chapter 10
Attenuation of Multifocal Cell Survival Signaling by Bioactive Phytochemicals in the Prevention and Therapy of Cancer

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Abstract Extensive researches within the last decade have revealed the presence of a complex network of signaling pathways overtly active in cancer cells augmenting proliferation and suppressing apoptosis. In parallel, epidemiological literature summarized a casual association between consumption of well balanced diet comprising adequate fruits and vegetables with reduced risk of developing cancer. This was projected to be associated with the presence of well characterized bioactive compounds, e.g. flavonoids, isothiocyanates, catechins, phenolic acid and organic sulphur present in diet that lead to the development of preventive and therapeutic strategies. Emerging evidence narrate mechanistic insight relating to the pleiotropic role of these bioactive compounds in modulating proliferation linked signaling at multiple levels including Akt, nuclear transcription factor-κB, c-Myc, cycloxygenase-2, MAPK, STAT and other signaling pathways that are active during embryogenesis, such as hedgehog and Wnt signalings. Preclinical studies including genetically modified mouse models revealed that dietary bioactive compounds hitherto classed as 'chemopreventive agents' induce apoptosis in cancer cells and inhibit development and/or progression of tumor. This chapter presents a comprehensive overview of deregulated signaling mechanisms prevailing within tumor cells along with broad knowledge-based evidence intertwining biological and molecular basis of action of chemopreventive agents citing representative examples. Additionally, an important aspect relating to the noteworthy rationale of using bioactive chemopreventive agents for sensitizing tumors to improve efficacy of chemotherapy in clinics has been discussed briefly. Finally, to bring forward the potential of natural chemopreventive agents to full extent, the development of safe and tolerable pharmaceutical grade analogs with improved bioavailability is encouraged to reduce the incidence and mortality of cancer.

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10.1 Introduction

During ontogeny of development and adulthood in multicellular organisms, a complex well-coordinated circuitry of signaling pathways maintains a cohort of differentiated and committed cells which responds to external factors such as: growth factors, hormones, chemokines, cytokines, etc. Extensive research during the past decade has unraveled this complex network of signaling communication becomes aberrant in transformed cells and malignant tumors making them behave in disorderly conduct and loose tissue integrity. This reinforces the view that upregulation or constitutive activation of multiple oncogenic mitogenic signaling pathways due either to altered proteins produced from mutation, defects or amplification of genes stimulate tumor initiating cells to proliferate, evade apoptosis and invade into surrounding tissues and metastasize. It is predicted that proper restraining of abnormal mitogenic signal communication in cancer cells may restrict or attenuate the disorderly proliferative stimulus; the later believed to be paramount in the initiation of tumor formation and its progression thru distinct stages of malignancy under paradigm of functional tumor suppressor genes. Accumulating preclinical data indicates that tumor cells use a large number of clearly defined signaling pathways to regulate their activity and remain viable (Cho 2012). Arguably, this is the principal reason why single inhibitors that target only one pathway have often failed to show expected results in the clinics. Time has shown that even when a drug has a single target and great efficacy, like androgen antagonists in early prostate cancer, it is not uncommon for the regressing tumor to acquire addition mutations making them resistant to the drug on tumor recurrence (McCarty 2004). Current cell signaling targeted therapies include inhibition of survival signals and augmenting apoptosis by death ligands or proapoptotic proteins emphasizing features of new prevention-trial design (Wang et al. 2013).

Over the past decade, there has been a growing consensus to explore the major survival signaling pathways prevailing within tumor cells that are susceptible to modulation by chemopreventive agents. It has been known and widely accepted that several non-nutritive chemopreventive agents derived from fruits, vegetables or culinary spices are effective in inhibiting carcinogenesis. The molecular basis of their pleiotropic action is now emerging through examination of discreet regulatory pathways including Akt, NF-κB, mitogen-activated protein kinase (MAPK), *p53*, cyclooxygenase (COX)-2, Ras, and many other molecules that are known to regulate apoptosis without unacceptable side effects (Souza et al. 2012; Vinod et al. 2013). Moreover, clinicians often encounter challenge of treatment failure resulting from the induction of drug resistance in cancer cells. Interestingly, data from our laboratory and elsewhere have demonstrated that multidrug resistance (MDR), NF-κB, Akt and other complex molecular operations within the apoptosis signaling axis are involved in the development of drug resistance. Importantly, chemopreventive agents can also potentially synergize in sensitizing cancer cells to cytotoxic chemotherapeutics- or radiation-based therapy. Current state of knowledge has revealed some pivotal mechanisms regulating core signaling molecules and

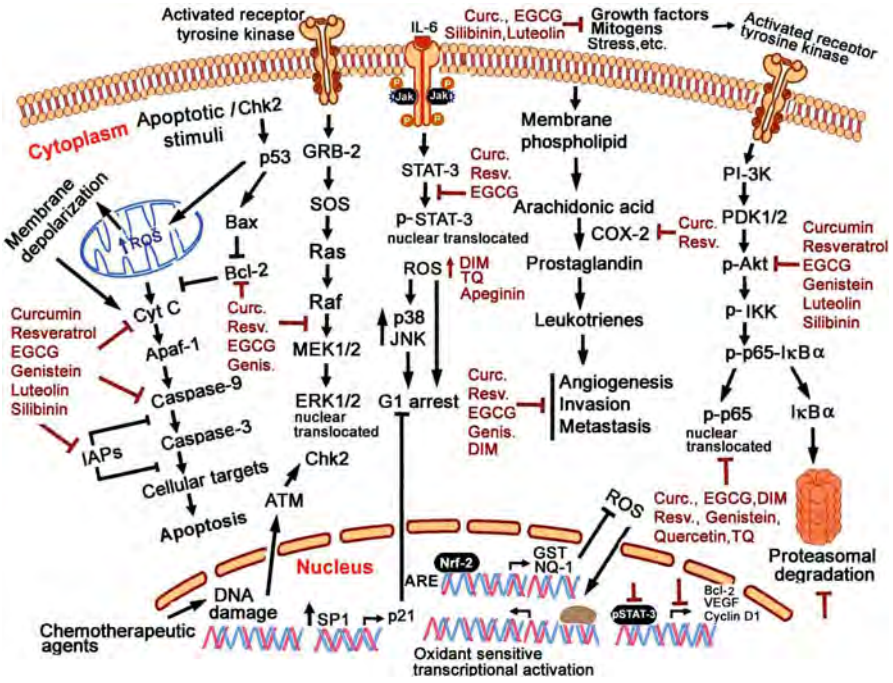

Fig. 10.1 A schematic summary of the molecular targets and cell signaling pathways altered by chemopreventive phytochemicals

apoptotic pathways. We summarize herein, a succinct overview of signaling mechanisms prevalent in most tumor types and their modulation citing representative examples of bioactive compounds that owe their origin to common food components (Fig. 10.1) and currently under clinical trials (www.clinicaltrials.gov). Conceptually, this justifies a strong rationale towards development of novel multitargeted pharmaceutical grade analogs primarily intended to abrogate key mitogenic signaling pathways within acceptable therapeutic window. Finally, continued focus could translate this aspect into novel therapeutic adjunct for treatment of different site specific cancers and attainment of long term disease free survival.

10.2 Regulation of the Akt Pathway

Akt is an evolutionarily conserved serine/threonine kinase and one of the most frequently hyperactivated signaling pathways in human cancers. Akt signaling and targeting the Akt protein kinase for cancer chemoprevention has been extensively reviewed (Vivanco and Sawyers 2002; Altomare and Testa 2005; Crowell et al. 2007). The principle role of Akt is to facilitate growth factor mediated cell survival, being negatively regulated by the tumor suppressor phosphatase and tensin

homolog on chromosome 10 (PTEN). Akt pathway does not operate in isolation but instead numerous studies point to Akt as a central molecule that tangentially integrates and cross-talk with other signaling entities including among others: receptor tyrosine kinase signaling, NF-κB signaling and extra cellular regulated kinase (ERK) signaling cascade. Additionally, it antagonizes the action of proapoptotic protein BAD (Hayakawa et al. 2000). Akt is essentially an inactive cytosolic protein which is recruited to the plasma membrane through binding by growth factor and becomes active through phosphorylation at two key sites: threonine 308 and serine 473 resulting in its full activation. Once activated, it dissociates from the plasma membrane and translocates to phosphorylate both cytoplasmic and nuclear target proteins, most notably glycogen synthase kinase (GSK)-3β, $p27^{Kip}$, mammalian target of rapamycin (mTOR) and forkhead transcription factor (Scott et al. 1998; Brunet et al. 1999; Testa and Bellacosa 2001; Shin et al. 2002); several of these are related to regulation of proliferation, progression, invasion and evasion of apoptosis. In different cell types it has been documented that diminution of phosphorylated Akt leads to induction of apoptosis and therefore there has been immense interest in developing novel Akt inhibitors for the treatment of cancer. Akt also counteracts the action of chemotherapeutics and radiation therapy leading to the development of chemo- and radio-resistance. In breast and pancreatic cancer cells with constitutively active Akt, the ability of standard chemotherapeutics and radiation to induce apoptosis is compromised (Sun et al. 2001; Arlt et al. 2003; Luo et al. 2003; Kucab et al. 2005). In contrast, PI3K/Akt inhibitors sensitize cancer cells to chemotherapy suggesting the importance of inhibition of phosphorylated Akt signaling as an important therapeutic target for cancer treatment.

Many chemopreventive agents have been documented to inhibit cancer cell growth and induce apoptosis through the inhibition of the Akt pathway (Crowell et al. 2007; Ko and Auyeung 2013). A few examples include curcumin, selenium, the flavonoids quercetin, kaempferol genistein, apigenin, and silibinin (Chaudhary and Hruska 2003; Gong et al. 2003; Spencer et al. 2003; Mallikarjuna et al. 2004; Way et al. 2004; Wu et al. 2006; Jeong et al. 2009). Kaempferol found in tea, propolis and grapefruit inhibits UV-B induced phosphorylation of Akt signaling suggesting kaempferol as a putative antitumor promoting agent (Lee et al. 2010b). Epigallocatechin-3-gallate (EGCG), a polyphenol constituent present in green tea, promotes apoptosis in T24 human bladder cancer cells by inhibiting PI3K/Akt activation that in turn, results in modulation of Bcl-2 family proteins, leading to enhanced apoptosis (Qin et al. 2007). Thymoquinone, derived from *Nigella sativa*, has been found to inhibit tumor growth and angiogenesis through downregulation of PI3/Akt pathway (Yi et al. 2008). In $Apc^{Min/+}$ mice, oral administration of the green tea component EGCG, or cruciferous vegetable component sulforaphane exhibited marked chemopreventive effects in association with inhibition of Akt signaling (Ju et al. 2005; Hu et al. 2006). Furthermore, other chemo protective bioactive derivatives from cruciferous vegetables: Phenethyl isothiocyanate (PEITC) and 3,3′-diindolylmethane (DIM) exhibited inhibition of the angiogenic features of human umbilical vein endothelial cells *in vitro* associated with the inactivation of Akt suppressing vascular endothelial growth factor (VEGF) secretion and down regulating VEGF receptor 2 protein levels (Xiao and Singh 2007; Kong et al. 2008). The growth inhibitory effect of SR13668, a synthetic

analog of DIM, in breast, ovarian and prostate xenografts *in vivo* and cell lines *in vitro* correlate with decreased pAkt and p-GSK-3β expression (Chao et al. 2007). In a study involving sulforaphane treated ovarian cancer cells both total Akt protein and active phosphorylated Akt (Ser473) were significantly decreased, signifying the inhibitory effect of sulforaphane on the Akt pathway (Chaudhuri et al. 2007). Deguelin, a member of the rotenoid family with chemopreventive activities has been found to decrease tumor incidence in animal models for lung, colon, mammary, and skin carcinogenesis through Akt inhibition (Udeani et al. 1997; Murillo et al. 2003; Gills et al. 2005; Lee et al. 2005a; Nair et al. 2006). Deguelin is also effective in reducing pAkt levels in the lung of Akt-inducible transgenic mice stimulating apoptosis and suppressing proliferation of premalignant and malignant human bronchial epithelial cells at doses in which only minimal effects were observed in normal bronchial cells (Lee et al. 2005a; Yan et al. 2005). We and other investigators have found that isoflavone genistein inhibit cancer cell growth and induce apoptosis through the downregulation of Akt in breast, lung, ovarian, prostate and pancreatic cancer cells (Li and Sarkar 2002; Gong et al. 2003; Banerjee et al. 2007). Collectively, these results reflect that Akt is an important target for action of chemopreventive agents in cancer prevention and towards therapeutic approach.

As mentioned previously evidence has also shown that activated Akt is critical for acquiring drug resistance in multiple cancers types (Kim et al. 2005a; Han et al. 2006; McCubrey et al. 2007; Tazzari et al. 2007; Huang and Hung 2009). This leads one to anticipate downregulation of Akt by chemopreventive agents would sensitize cancer cells to chemo- or radio-therapy. We and other investigators reported enhancement of chemotherapeutic and radiation effects by isoflavone genistein being partially mediated by the inhibition of Akt signaling (Akimoto et al. 2001; Banerjee et al. 2005; Yashar et al. 2005). It has been found that genistein also enhanced necrotic-like cell death with the significant inhibition of Akt activity in breast cancer cells treated with genistein and Adriamycin, suggesting that the enhanced growth inhibition by combination treatment is through the inactivation of the Akt pathway (Satoh et al. 2003). Phenoxodiol, one of the synthetic derivatives of genistein, inhibits Akt signaling pathway and subsequently activates the caspase system inhibiting X-linked inhibitor of apoptosis protein (XIAP), which in effect lead to increased chemosensitization (Kamsteeg et al. 2003). Curcumin, the polyphenol from the plant *Curcuma longa*, downregulates taxol-induced phosphorylation of Akt along with its interaction with NF-κB, revealing insight into improved antitumor effect of curcumin being mediated through the inactivation of the Akt and NF-κB pathways (Bava et al. 2005). In light of these prospective reporting's, it is believed that in future, Akt inhibition is likely to emerge as a prognostic marker for patient risk stratification.

10.3 mTOR Signaling

mTOR signaling is one of the major downstream signaling targets of PI3K/Akt and plays a critical role among other functions in promoting cellular proliferation and inhibiting apoptosis (Alayev and Holz 2013). mTOR exists as two functionally

distinct complexes: mTORC1 and mTORC2, differing in subunit compositions and biological functions. Dysregulated mTORC1 signaling is often observed in human tumors. Initially, rapamycin and its derivatives, CCI-779 and RAD001, showed much promise in clinical settings but later due to drug mediated hyperactivation of the Akt and ERK-MAPK pathways, increased tumor cell viability and drug resistance became prominent. Due to such unfavorable clinical activity in a limited number of tumor types, it has now been rationalized to combine drugs which inhibit both signaling network in therapeutic front. Recently, it has been reported that the combined use of resveratrol and rapamycin resulted in modest additive inhibitory effects on the growth of breast cancer cells, mainly through suppressing rapamycin-induced AKT activation (He et al. 2011). Similar findings have been reported in human glioma cells wherein rapamycin further enhanced resveratrol induced apoptosis (Jiang et al. 2009).

One study by our group reported using a newly recognized platelet-derived growth factor (PDGF)-D overexpressing PC3 cells (PC3 cells stably transfected with PDGF-D cDNA and referred to as PC3 PDGF-D) exhibited rapid growth rates and enhanced invasion associated with the activation of mTOR and reduced Akt activity (Kong et al. 2008). Interestingly, Bio-response DIM® (B-DIM, a formulated DIM with improved bioavailability) significantly inhibited both mTOR and Akt in these cells which correlated with decreased cell proliferation and invasion and elicited other beneficial therapeutic effects by inhibiting both mTOR and Akt activity (Kong et al. 2008).

PEITC inhibits mTORC1 activity and along with inhibition of mTORC1 contribute to optimal growth inhibition including the angiogenesis regulator HIF-1α RNA translation in MCF7 breast cancer cells (Cavell et al. 2012).

Beevers et al. (2009) reported that curcumin inhibited phosphorylation of the mTOR and its downstream effector molecules by dissociating raptor, a protein component of mTORC1 complex, from mTOR. Silibinin, a milk thistle plant derivate, inhibits translation initiation by inhibiting the mammalian target of rapamycin signaling pathway (Lin et al. 2009).

10.4 MAPK Signaling

The ubiquitous MAPK cascade pathway integrates various external stress signals into intracellular responses that dictate decision on cell fate for death or to survive and proliferate, and therefore MAPK signaling has received increasing attention as a target molecule (Sebolt-Leopold 2000; Wagner and Nebreda 2009; Santarpia et al. 2012). Accumulating evidence indicate constitutive and inappropriate activation of MAPK, due to amplified or over expressed growth factor receptors, along with oncogenic *Ras* as a critical component in a number of solid malignancies such as breast, prostate and gastric cancers (Dhillon et al. 2007; Kim and Choi 2010). Physiological interventions of the MAPK cascade by bioactive phytochemicals have been acknowledged as a promising approach to cancer therapy by several investigators. There are three distinct but parallel MAPK cascades identified in

mammalian cells: ERK, c-Jun N terminal kinase (JNK) and p38 (Cano and Mahadevan 1995). ERKs can be activated by mitogens and growth factors while JNK and p38 signaling can be activated by many environmental stress stimuli such as UV and γ-irradiation, as well as many anticancer drugs e.g. cisplatin or etoposide (Chen et al. 1996; Wada and Penninger 2004). Some chemopreventive agents exhibit selectivity, but ultimately the relative level of activation of ERK, p38 and JNK influences the cells decision to proliferate or undergo apoptosis or exit cell cycle (Xia et al. 1995). Constitutive activation of the ERK and p38 MAPK pathway have also been implicated in chemoresistance and therefore pharmacological inhibition of MAPKs hold additional promise in stimulating drug resistant cancer cells to undergo apoptosis upon treatment with chemotherapeutic drugs (Zhao et al. 2006; Guo et al. 2008). MEK1 is an important downstream component of MAPK signaling possess unique binding pocket adjacent to its adenosine triphosphate (ATP)-binding site. Computer modeling indicate that several phytochemicals including flavones quercetin, myricetin and equol can dock with this allosteric pocket strongly inhibiting MEK1 kinase activity (Ohren et al. 2004; Kang et al. 2007a; Lee et al. 2007, 2008).

Kong et al. (2000) reviewed flavonoids (EGCG, ECG) and isothiocyanate class of chemopreventive compounds on MAPK signaling and concluded high concentrations of chemopreventive compounds lead to activation of the caspase pathway of apoptosis and potentiate cytotoxicity. Similar observations have been reported by other investigators revealing inhibition of UVB-induced phosphorylation of ERK1/2, JNK, and p38 proteins by a variety of chemopreventive phytochemicals including silibinin, proanthocyanidins, apigenin, etc. EGCG inhibited the expression of ERK1/2 phosphorylation up to 93 % in the dorsolateral prostate of transgenic TRAMP mice (Harper et al. 2007). DNA microarray analysis of PC3 prostate cancer cells exposed to indole-3-carbinol or DIM rich in cruciferous vegetables showed parallel down regulation in the expression of upstream kinases MAP2K3, MAP2K4, MAP4K3, and MAPK3 (Li et al. 2003). Curcumin inhibits the activation of MAPK and shown to inhibit JNK activation induced by various agonists including PMA, ionomycin, anisomycin, UV, gamma radiation, tumor necrosis factor (TNF) and sodium orthovanadate (Chen and Tan 1998; Kim et al. 2005b). Furthermore, curcumin attenuates experimental colitis through a reduction in the activity of p38 MAPK and reduce drug resistance by its inhibitory effect on MAPK signaling (Salh et al. 2003; Sreekanth et al. 2011; Tsai et al. 2011). Resveratrol treatment on the skin of ICR mice resulted in a decrease in the ERK, as well as a decrease in catalytic activity of p38 MAPK (Kundu et al. 2004). Another study revealed topical application of resveratrol prevented UV-B light induced cutaneous damage including skin cancer by diminishing UVB-mediated upregulation of upstream kinase-MAPK kinase and MAPK signaling (Reagan-Shaw et al. 2004).

Gingerol, the principle active constituent of ginger, inhibits COX-2 expression by blocking the activation of p38 MAPK and NF-κB in phorbol ester induced mouse epidermis (Kim et al. 2005c). Transcriptome and proteome profiling of colon mucosa of quercetin fed rats point to tumor preventive mechanism through downregulation of potentially oncogenic MAPK *in vivo* (Dihal et al. 2008).

Xue et al. (2005) showed that DIM can upregulate the expression and stimulate secretion of interferon-gamma (IFN-γ) in human MCF-7 breast cancer cell line which was shown to be mediated by activation of both JNK and p38 pathways. This novel observation offer an important clue that explains the anticancer effects of DIM, because it is well known that IFN-γ plays an important role in preventing the development of primary and transplanted tumors. Patten and DeLong (1999) reported increased activation of JNK in colon cancer cells upon treatment with benzyl isothiocyanate, and suggest that most likely such activation is involved in the induction of cytoprotective enzyme – NAD(P)H: quinine oxidoreductase. In breast cancer cells, trans-resveratrol induced apoptosis by activating the MAPK pathway (Filomeni et al. 2007). Guggulsterone, found in the resin of the plant *Commiphora wightii* induced prostate cancer cell undergo apoptosis instigated by ROS dependent JNK activation (Singh et al. 2007). These pieces of evidence clearly show that depending on the context of simulus and cell system, the modulation of MAPK signaling by bioactive natural products can be exploited to formulate targeted cancer therapy.

10.5 Regulation of the Growth Factor Signaling Pathway

Over the past decade evidence has emerged revealing the functional relationship and molecular characterization between growth factor specific receptors (GFR), and their ligands that drives cell proliferation and tumor growth. Typically, in a normal tissue, cell proliferation is initiated by the binding of extracellular growth factors with GFR that reside either at the cell surface or in the cytoplasm. This interaction then triggers a signaling cascade mediated by the assembly of signaling complexes *via* specific protein-protein interactions, or in case of cell surface GFR, the activation of multiple protein kinases. These process are held tightly in check by counter balancing signals in normal tissues but are activated by a variety of genetic defects in tumor cells that either lead to a constitutive activation or the loss of negative regulatory signals resulting in activating cellular proliferation along with suppression of apoptotic pathway and stimulating invasion and metastasis. Some of the growth factors implicated in carcinogenesis are epidermal growth factor (EGF), PDGF, fibroblast growth factors (FGFs), transforming growth factors (TGF-α and -β), erythropoietin (Epo), insulin-like growth factor (IGF), interleukin (IL)-1, 2, 6, 8, TNF, INF-α and colony-stimulating factors (CSF). The signaling initiated through their respective receptors has significant impact on tumorigenesis and amenable by many chemopreventive and chemotherapeutic agents. Several chemopreventive phytochemicals including curcumin, genistein, resveratrol and catechins have been shown to be potent inhibitors of several growth factor signaling pathways.

Curcumin inhibits ligand-stimulated activation of EGFR through its inhibitory effect on EGFR phosphorylation indicating that it has the potential to break the autocrine loops that are established in several advanced cancers. Seminal findings also indicate that curcumin enhances the growth inhibitory effects of 5-flurauracil

(5-FU) and oxaliplatin through EGFR and IGF receptor pathways (Korutla et al. 1995; Dorai et al. 2000; Patel et al. 2008). Blocking EGF receptor directs the cancer cells to enter apoptosis and also abrogate the invasive potential of the cancer cells. The molecular mechanism by which EGCG and other catechins exert their protective effects towards dysregulated receptor tyrosine kinases (RTKs) in cancer cells have recently been summarized by Larsen et al. (2010). It has been concluded from ligand binding assays that EGCG blocks the binding of EGF to its receptor to cause inhibition of EGFR phosphorylation (Fu and Chen 2006). In addition, it has been found that tea catechins inhibits receptor expression through a complex circuitry by inhibiting the activity of ERK which regulates the transcription factor Egr-1; it has been found that Egr-1 controls the expression of EGFR (Fu and Chen 2006). Inhibition of EGFR signaling has also been shown to decrease the production of VEGF in cancer cells (Masuda et al. 2002). Adachi et al. demonstrated that EGCG disrupts lipid order and membrane organization to cause internalization of EGFR such that EGF could no longer bind (Adachi et al. 2008). EGCG has also been shown to bind directly to EGF, VEGF and PDGF ligands (Kondo et al. 2002; Suzuki et al. 2004; Shimizu et al. 2008). Furthermore, EGCG treatment potentiated the effects of the tyrosine kinase inhibitor erlotinib in head and neck tumors (Masuda et al. 2001; Zhang et al. 2008). In pancreatic cancer, growth inhibition and apoptosis were associated with inhibition of EGFR tyrosine kinase activity by flavonoid luteolin, present abundantly in several green vegetables (Lee et al. 2002). Luteolin also inhibits VEGF induced angiogenesis and tumor growth in a murine xenograft model (Bagli et al. 2004). Quercetin is a potent inhibitor of EGFR tyrosine kinase activity. However, it does not directly inhibit EGFR, but interferes with different signaling pathways downstream of EGFR that regulate cell proliferation and survival (Jung et al. 2010a, b; Lee et al. 2004). The growth inhibitory and apoptotic effects of silibinin in prostate cancer cells could be achieved by targeting EGFR signaling. Silymarin and silibinin are also effective in inhibiting TGF-α and EGF-mediated tyrosine phosphorylation of EGFR along with its adapter protein Shc in androgen independent human prostate cancer cells harboring constitutively active EGFR (Zi et al. 1998; Sharma et al. 2001). IGF's are mitogenic ligands, their activity being firmly controlled by the presence of IGFBPs. Similar to EGFR, IGF receptor (IGFR) signaling also promotes growth and survival of cancer cells. It has been shown that silibinin, apigenin, EGCG and inositol hexaphosphate downregulates IGF-IR signaling and significantly increases the levels of IGF binding protein-3 (IGFBP-3) in prostate cancer inhibiting cell growth both *in vitro* and *in vivo* (Singh et al. 2002, 2004; Shukla et al. 2005).

10.6 Regulation of the Cyclin D/Cyclin-Dependent Kinase (CDK) Pathway

Pivotal to growth and hyperproliferation of tumor cells is deregulation of cell cycle check points and overexpression of growth-promoting cell cycle factors, such as cyclin D1 and CDKs, along with the suppression of associated CDK inhibitors.

Tumor cells progresses like normal cells through the four phases of cell cycle, G1, SG2 and M. Cyclin D1 along with component subunit of CDK-4 and CDK-6, controls the proliferative transition from G1 to S phase in the cell cycle. Cyclin D1 expression is regulated by NF-κB and the suppression of NF-κB activity by diet derived bioactive constituents have shown the potential to down regulate cyclin D1 in multiple studies. Studies from several laboratories have revealed that cyclin D1 is overexpressed in a wide variety of tumors including those derived from breast, esophagus, lung, head and neck, hepatocellular and pancreatic cancers and this can be targeted therapeutically for the treatment of cancer (Bartkova et al. 1994; Nishida et al. 1994; Adelaide et al. 1995; Gansauge et al. 1997; Caputi et al. 1999; Kim and Diehl 2009). To this end, not only inhibitors of cyclin D are being investigated, but also other component subunits that affects the complex signaling networks that could be of major clinical use as potentiators of standard chemotherapeutic drugs and/or radiation therapy. Curcumin, resveratrol, diosgenin, sulphorophane, thymoquinone, lupeol, DIM, genistein, acetyl-11-keto-boswellic acid, and betulinic acid have all been reported to down regulate cyclin D1 expression or its component subunits in different site specific cancers (Aggarwal and Shishodia 2006).

We earlier reported that curcumin can completely downregulate cyclin D1 expression through both transcriptional and post transcriptional mechanism(s) and showed a decrease in the formation of cyclin D1/Cdk4 enzyme complex resulting in suppression of proliferation and induction of apoptosis (Mukhopadhyay et al. 2002; Bharti et al. 2003b). Corollary to our findings, another independent study reported curcumin upregulated Cdk inhibitors (such as p21/Cip1/Waf1 and p27/Kip1) and downregulated cyclin B1 and Cdc2 (Park et al. 2002b). CDK inhibitors (such as the p21/Cip1/waf1 and p27Kip1 proteins) attenuate formation of these complexes and block cell cycle progression. 3′,4′,7-trihydroxyisoflavone, a metabolite of the soybean isoflavone daidzein, is a direct inhibitor of CDK2 and CDK4 (Lee et al. 2010a).

Citing other examples relating to modulation of cyclin D1 by chemopreventive agents, Benitez et al. (2007, 2009) found that treatment of prostate cancer LNCaP (androgen receptor positive) and PC-3 (androgen receptor negative) cells with resveratrol caused a significant reduction not only in the levels of expression of cyclins D1, E and CDK4, but also a reduction in cyclin D1/CDK4 kinase activity compromising cells capability to proliferate and also causing an increase in apoptosis in time- and dose-dependent manner. The predominating tea polyphenol-EGCG treatment to LNCaP and DU145 prostate cancer cells resulted in significant dose- and time-dependent downregulation of cyclin D1, cyclin E, cdk2, cdk4, and cdk6 (Gupta et al. 2003). Furthermore, in an *in vivo* model of intestinal tumorigenesis in $Apc^{Min/+}$ mice, feeding grape seed extract reduced the total number of intestinal polyps compared to control mice (Velmurugan et al. 2010). The findings paralleled with decreased cyclin D1 and c-Myc protein levels in small intestine along with downregulation in expression of other important molecules such as: COX-2, iNOS, β-catenin along with increased expression Cip1/p21 with reduced cell proliferation and increased apoptosis (Velmurugan et al. 2010). Thus, the suppression of cyclin D1 by natural agents could be an effective strategy in abating the proliferation of tumor cells *in vivo*.

We and other investigators have also shown that the overexpression of cyclin D1 contribute to the chemoresistance of pancreatic cancer cells because of the dual role of cyclin D1 in promoting cell proliferation and inhibiting drug induced apoptosis (Gansauge et al. 1997; Biliran et al. 2005). Therefore, we speculate that chemopreventive agents which downregulates c-Myc, cyclin D and CDK could be used in combination with chemotherapeutic agents to improve the treatment outcome in cancer therapy.

Kornmann et al. (1998) reported suppressing cyclin D1 expression in human pancreatic cancer cells not only inhibited pancreatic cell growth but also increased the cytotoxic actions of cisplatinum. The findings imply the dual role of cyclin D1 in promoting cell proliferation and further imply that cyclin D1 is critical in the maintenance of chemoresistance in these cells (Kornmann et al. 1998, 1999). In similar context, we also reported that cyclin D1-overexpressing Ela-myc pancreatic tumor cells exhibit significantly reduced chemosensitivity and a higher survival rate upon cisplatin treatment (Biliran et al. 2007).

10.7 Regulation of the c-Myc Pathway

c-Myc is an oncogene overexpressed in many types of human cancers leading to deregulated proliferation and survival of cancer cells through autonomous growth factor signaling. Intriguingly, c-Myc is also a strong inducer of cell death *via* induction of several proapoptotic signal transduction mechanisms; paradoxically, the proapoptotic signals generated by c-Myc become suppressed due to parallel activation of survival signals by the same growth factor signaling pathway. According to currently accepted dogma, c-Myc induced apoptosis involves first the activation of p19/ARF which sequesters Mdm2 into the nucleolus, this leads to a reduced ubiquitination of p53 by Mdm2 which causes subsequent accumulation of p53. In turn, p53 upregulates Bax and downregulates Bcl-2, this directly activates the apoptotic machinery. However, in many forms of human cancer both a mutation of *p53* and *Bax* or a hypermethylation of *p19/ARF* or amplification of *Mdm2* makes the apoptotic pathway redundant and the proliferative pathway overrides. Almost all types of human cancers show high frequencies of *c-Myc* amplification or overexpression of its protein product c-Myc. c-Myc can induce cyclin D1 which interacts with CDK4 and CDK6 to promote cell cycle progression (Daksis et al. 1994; Mateyak et al. 1999). As reported previously, we found that ectopic overexpression of *c-Myc* in human and murine pancreatic cancer cells resulted in increased sensitivity to cisplatin along with other chemotherapeutic drugs (Biliran et al. 2007). It has been reported that curcumin inhibits the expression of *c-Myc* and tumorigenesis (Kakar and Roy 1994; Han et al. 1999; Lin 2004). Other chemopreventive agents, including EGCG, sulforaphane and quercetin also show their ability to downregulate *c-Myc* (Csokay et al. 1997; Lin 2002; Tao et al. 2002; Bertl et al. 2006; Manna et al. 2006). Downregulation of *c-Myc* has been shown to be a critical molecular event of resveratrol mediated anti-medulloblastoma activity

causing growth suppression, cell cycle arrest and apoptosis of medulloblastoma cells (Zhang et al. 2006).

It has been reported that some chemotherapeutics including cisplatin, doxorubicin, paclitaxel and 5-FU can induce c-Myc expression (Park et al. 2002a). Interestingly, tumor cells surviving from cisplatin treatment display significant elevation in *c-Myc* expression (Walker et al. 1996). Thus, c-Myc could be an interesting potential chemoresistance and growth proliferative factor in cancer.

10.8 Regulation of the NF-κB Pathway

The NF-κB signaling plays critical roles in the control of cell proliferation, survival, inflammation, tumor invasion, metastasis, drug resistance and stress response. A large number of cancer cells, especially poorly differentiated cancer cells, show activated NF-κB in the nucleus, wherein it induces the expression of more than 200 genes that have been shown to suppress apoptosis, cause neoplastic transformation and promote cancer cell growth. So, it seems logical to target NF-κB for the prevention and/or treatment of cancer. Briefly, under non-stimulating conditions, NF-κB is sequestered in the cytoplasm through tight association with NF-κB inhibitory protein IκBα and following stimulation by factors such as cytokine binding to its receptor, free radicals, inflammatory stimuli, endotoxins, tumor promoters, UV light and X-rays, activation of IκB kinase (IKK) complex occurs. This leads to phosphorylation with subsequent degradation of the inhibitory protein IκB, allowing NF-κB to translocate into the nucleus and bind to specific DNA sequences in target genes designated as κB-elements. In addition, the expression of NF-κB target genes is also regulated through the recruitment of coactivators together with corepressors (Aggarwal 2004). Many of the target genes that are activated in cancer are critical to the establishment of the early and late stages of aggressive cancers. Examples include expression of cyclin D1, apoptosis suppressor proteins (such as Bcl-2 and Bcl-xL), and those required for metastasis and angiogenesis (such as matrix metalloproteases (MMP) and VEGF) (Aggarwal and Shishodia 2006). Akt pathway is also known to activate NF-κB (Aggarwal 2004).

Accumulating evidence from several laboratories including ours have concluded that several bioactive agents originating from dietary sources (like curcumin, resveratrol, guggulsterone, ursolic acid, betulinic acid, emodin, gingerol, flavopiridol, zerumbone, evodiamine, indole-3-carbinol, ellagic acid, anethole, green tea catechins, S-allyl cysteine, lycopene, diosgenin, garcinol, plumbagin, silibinin, thymoquinone, sulforaphane) have been found to be potent inhibitors of NF-κB (Aggarwal and Shishodia 2006; Banerjee et al. 2009a; Ahmad et al. 2010; Shanmugam et al. 2011). These inhibitors block one or more steps in the NF-κB signaling pathway such as the signals that activate the NF-κB signaling cascade, its translocation into the nucleus, DNA binding of the dimers, or interactions with the basal transcriptional machinery. Sulforaphane inhibits NF-κB DNA binding without affecting its translocation to the nucleus or phosphorylation of IκB (Heiss et al. 2001). In an *ex vivo* study reported by

our group, human volunteers received 50 mg of soy isoflavone supplements Novasoy™ (Archer Daniels Midland Company, Decatur, IL, USA, containing genistein, daidzein, and glycitein at a 1.3:1:0.3 ratio) twice daily for 3 weeks. TNF-α failed to activate NF-κB activity in lymphocytes harvested from these volunteers, while lymphocytes from these volunteers collected prior to soy isoflavone intervention showed activation of NF-κB DNA binding activity upon TNF-α treatment *in vitro* (Davis et al. 2001). These results demonstrated that soy isoflavone supplementation had a protective effect against TNF-α induced NF-κB activation in humans. DIM or the formulated B-DIM treatment could inactivate NF-κB DNA binding activity in prostate, breast, head and neck, and pancreatic cancer cells resulting in inhibition of NF-κB downstream genes-VEGF, urokinase-plasminogen activator and MMP-9 limiting cell growth concurrent with induction of apoptosis and inhibition of angiogenesis, invasion, as well as metastasis of tumor cells (Banerjee et al. 2011b).

5-FU, cisplatin, carboplatin, taxol, and gemcitabine have been reported to induce NF-κB activation in different cells. Our own findings along with other investigators have reported the inhibition of NF-κB by chemopreventive agents increases the sensitivity of cancer cells to the apoptotic action of chemotherapeutic agents and radiation exposure (Li and Sethi 2010; Nambiar et al. 2011). Inhibition of chemotherapy induced NF-κB activation by super repressor IκBα protein sensitized non-small cell lung cancer and pancreatic cancer cells to gemcitabine induced apoptosis in *in vitro* and *in vivo* (Jones et al. 2000; Fujioka et al. 2003). Therefore, targeting NF-κB by chemopreventive agents appear to be a promising strategy to enhance the antitumor activity of chemotherapeutics.

10.9 Regulation of the COX Pathway

COX enzymes play an important pivotal role in an organ specific manner in the conversion of free arachidonic acid released from membrane phospholipid to prostaglandins with prostanoids *via* an intermediary reaction catalyzed by the enzyme-phospholipase A2. Two isoforms of COX enzymes have been identified: COX-1 being constitutively expressed in almost every cell type that is involved in maintaining homeostasis of normal physiological functioning such as cytoprotection of gastric mucosa, regulation of renal blood flow along with control of platelet aggregation, while COX-2- the inducible isoform which is barely detectable under normal physiological conditions accounts for the elevated production of prostaglandins in response to various inflammatory stimuli, hormones, and growth factors. Mounting evidence reveals that COX-2 is overtly overexpressed in many premalignant, malignant and metastatic human cancers, including cancer of the colon, breast, lung, stomach, head, neck, pancreas, uterine cervix, urinary and gall bladder and the skin. The level of its overexpression significantly correlates with invasiveness, angiogenesis, prognosis, and survival (Subbaramaiah and Dannenberg 2003). Further studies have shown that in many cell types, NF-κB is a positive regulator of COX-2. Besides NF-κB, AP1 is also implicated in COX-2 transcriptional activation (Scheckel

et al. 2008). Since the initial observation that COX-2 inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) decreases the risk of various cancers (including colon and lung cancers), several evidences deem that the down regulation of COX-2 could be one of the molecular mechanisms by which tumor growth can be prevented and inhibited. Hence the notion that chemopreventive agents that can block COX-2 expression without affecting COX-1 got prioritized as novel target for chemoprevention. Moreover, it has been reported that forced expression of COX-2 caused enhancement in multiple drug resistance MDR1 expression and functional activity, suggesting the existence of a causal link between COX-2 activity and MDR1 expression (Sorokin 2004). Therefore, the use of COX-2 inhibitors to decrease MDR1 function may enhance the accumulation of chemotherapy agents, and decrease the resistance of tumors to chemotherapeutic drugs. Furthermore, laboratory findings have revealed that mice deficient in COX-1 or COX-2 enzyme develop few tumors when subjected to standard DMBA/TPA protocol of tumor development.

Several dietary source derived bioactive compounds have shown the potential to suppress COX-2. Curcumin was one of the first chemopreventive phytochemical shown to possess significant COX-2 inhibiting activity through the suppression of NF-κB. We reported earlier that resveratrol suppressed mammary carcinogenesis in female Sprague Dawley rats and this suppression was in part associated with the inhibition of COX-2 and NF-κB activation. Other reports indicate that resveratrol inhibits COX-2 enzyme activity in phorbol ester treated human mammary epithelial cells through suppression of protein kinase C and AP-1 mediated gene expression abridging logical conclusion that both NF-κB and AP-1 can bind the COX-2 promoter and upregulate transcription of COX-2 gene (Newton et al. 1997; von Knethen et al. 1999; Allport et al. 2000). Thus, bioactive compounds that can suppress these transcription factors may have the putative potential to inhibit COX-2 expression. Furthermore, the effect of resveratrol pretreatment on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 expression in the skin of mice revealed an inhibitory effect in a dose-dependent manner (Kundu et al. 2004). Resveratrol also suppresses *N*-nitrosomethylbenzylamine-induced rat esophageal tumorigenesis with evidence of COX-2 overexpression at tumor site (Li et al. 2002). According to Zykova et al. (2008), resveratrol directly targets COX-2 to inhibit carcinogenesis. Ginger, an extensively consumed spice material and its constituents have shown to inhibit COX-2 and inducing apoptosis (Kim et al. 2005c). Gene expression analysis of sulforaphane treated HeLa cells reveals significant downregulation of COX-2 (Sharma et al. 2011). In LPS-activated murine macrophage cell line RAW264.7, the monoterpene D-limonene from orange peel oil, decreased the expression of COX-2 proteins along with the principle COX-2 product prostaglandin-E2 (PGE-2) production (Yoon et al. 2010). In COX-2 overexpressing pancreatic cancer cells, we reported thymoquinone and its analogs downregulated COX-2 protein along with reduction in PGE-2 (Banerjee et al. 2009a, 2010). Many other dietary source derived components, including galangin, luteolin, apigenin, kaempferol, sasanquol, genistein, wogonin, green tea catechins, have been shown to suppress COX-2 (Aggarwal et al. 2006; Koeberle et al. 2009; Lee et al. 2010c).

Green tea polyphenols have been reported to reduce COX-2 expression (24 %) in the TRAMP mice model (Harper et al. 2007). A reduction in invasive potential of highly metastatic human melanoma by EGCG has been recorded by targeting the endogenous expression of COX-2 and prostaglandin receptors (Singh and Katiyar 2011). However, the mechanism of EGCG-induced COX-2 inhibition appears to be through the suppression of transcription factor NF-κB compared to the protein binding/inhibition of COX-2 inhibitors (Smith et al. 2000). Other experimental studies have shown that curcumin and EGCG could down regulate COX-2 expression without any change in the expression of COX-1 at both the mRNA and protein levels in prostate cancer cells (Hussain et al. 2005). EGCG downregulates COX-2 in TPA-stimulated human mammary cells (MCF-10A) in culture (Kundu et al. 2003). Furthermore, green tea catechins (EGCG and EGC) as well as theaflavins from black tea inhibited COX-dependent arachidonic acid metabolism in microsomes from tumors and normal colon mucosa, indicative of tea polyphenols affecting arachidonic acid metabolism in human colon mucosa and also colon tumors reducing the risk for developing colon cancer in humans (Hong et al. 2001), a premise currently under clinical trial (NCT01360320, Table 10.1).

The synergistic growth inhibitory effect of curcumin and celecoxib has been demonstrated in colorectal cancer cells through the inhibition of COX-2 pathway (Lev-Ari et al. 2005). Genistein downregulates COX-2 promoter activity in colon cancer cells transfected with COX-2 reporter gene (Mutoh et al. 2000). Combination of 5-FU and isoflavone genistein revealed greater therapeutic effects than single agents in colon cancer through the COX-2 pathway (Hwang et al. 2005). Inhibition of tumor growth independent of the COX-2 pathway cannot be ruled out; further indepth mechanistic studies are needed to fully elucidate the mechanism of action of COX-2 inhibitors toward cancer prevention and therapy.

10.10 Regulation of the STAT Pathway

The STAT family of cytoplasmic latent transcription factors came to light while examining the transcriptional activation in response to interferon and other extracellular signal proteins (Darnell et al. 1994). Of the seven STAT family members identified till date with all sharing common structural elements, aberrant constitutive activation of STAT-3 have been identified in a number of human cancers including breast, lung, ovarian, pancreatic, skin, prostate and in multiple myeloma, leukemia and lymphomas. STAT-3 is tyrosine phosphorylated by three types of kinases: receptor tyrosine kinases (such as EGFR, FGF receptor, or PDGF receptor), Janus kinase family members which are constitutively bound to the cytoplasmic tails of cytokine receptors or non receptor associated tyrosine kinases (including Ret, Src, or the Bcl-Abl fusion proteins) (Brantley and Benveniste 2008). Active STAT-3 dimers bind to consensus sequences in the promoters of genes regulating cell proliferation and antiapoptotic behavior in cooperation with other transcription factors to regulate expression of genes, such as *Bcl-2* and *Bcl-xL, Mcl-1*, $p21^{WAF1/CIP1}$ along with cyclin D1 (Bowman et al. 2000; Reich and Liu 2006; Germain and Frank 2007).

Table 10.1 Current ongoing clinical trials

Genistein/isoflavone	
NCT01028001	Phase 2 trial of preoperative soy isoflavone supplementation and molecular markers in the prevention of head and neck squamous carcinoma
NCT01036321	Phase 2 clinical trial of purified isoflavones in prostate cancer: comparing safety, effectiveness and mechanism of action between African American and Caucasian men
NCT01174953	High risk prostate cancer prevention study
NCT01126879	Phase 2 trial of genistein in men with circulating prostate cancer cells
NCT00499408	Phase 2 trial of vitamin D and soy supplementation for biochemically recurrent prostate cancer following definitive local therapy
NCT01489813	Phase 2 randomized placebo-controlled clinical trial of genistein in reducing the toxicity and improving the efficacy of intravesical therapy
NCT01538316	Clinical trial on the effectiveness of the flavonoids genistein and quercetin in men with rising prostate-specific antigen
NCT01325311	Phase 2a, randomized placebo-controlled trial of single high dose cholecalciferol and daily genistein (G-2535) *vs* placebo in men with early stage prostate cancer undergoing prostatectomy
NCT01182246	Safety, pharmacokinetics and efficacy of AXP107-11 in combination with standard gemcitabine (Gemzar) treatment in patients with locally advanced or metastatic, unresectable, adenocarcinoma of the pancreas, stage III-IV: a prospective, open label, multicentre, sequential phase 1b /2a study (the drug substance, AXP107-11 is a crystalline form of genistein)
3,3′ diindolylmethane	
NCT00888654	Phase 2 trial of Bio-response 3,3′-diindolylmethane on intermediate endpoint biomarkers in patients with prostate cancer who are undergoing prostatectomy
NCT01391689	Evaluation of diindolylmethane supplementation to modulate tamoxifen efficacy in breast cancer, the diindolylmethane efficacy study
Curcumin	
NCT01160302	Exploratory biomarker trial of the food substances curcumin C3 complex in subjects with newly diagnosed head and neck squamous cell carcinoma
NCT01294072	Phase 2 clinical trial investigating the ability of plant exosomes to deliver curcumin to normal and malignant colon tissue
NCT00927485	Use of curcumin for treatment of intestinal adenomas in familial adenomatous polyposis
NCT00641147	Curcumin for treatment of intestinal adenomas in familial adenomatous polyposis
NCT00689195	Evaluation of curcumin formulation and ashwagandha root powder extract in the management of advanced high grade osteosarcoma
[a]NCT00969085	Phase 2 trial of curcumin in cutaneous T cell lymphoma patients
[a]NCT01490996	Phase 1/2a study combining curcumin (curcumin C3-complex, Sabinsa) with standard care FOLFOX chemotherapy in patients with inoperable colorectal cancer
[a]NCT01238198	Oral curcumin for radiation dermatitis in breast cancer patients
[a]NCT01608139	Pilot study of curcumin, vorinostat, and sorafenib in patients with advanced solid tumors
[a]NCT01219673	Study of reducing the symptom burden produced by chemoradiation treatment for head and neck cancer
[a]NCT01269203	Phase 2 randomized study of the efficacy of curcumin for reducing symptoms during maintenance therapy in multiple myeloma patients

(continued)

Table 10.1 (continued)

Genistein/isoflavone	
Green tea/EGCG	
NCT01317953	Phase study of oral green tea extract as maintenance therapy for extensive-stage small cell lung cancer
[a]NCT01589887	Clinical and biologics evaluation of polyphenon E, an extract of green tea containing EGCG, in plasma cell dyscrasias-pilot study
[a]NCT00942422	Clinical and biologics evaluation of polyphenon E, an extract of green tea containing EGCG, in plasma cell dyscrasias-pilot study
[a]NCT00262743	Phase 1/2 study of daily oral polyphenon E in asymptomatic, Rai stage 0-II patients with chronic lymphocytic leukemia
NCT00917735	Phase 2, randomized, double-blind, placebo-controlled, study of the efficacy of Green tea extract on biomarkers of breast cancer risk in high risk women with differing catechol-*O*-methyl transferase genotypes
NCT01060345	Pilot study of chemoprevention of green tea in women with ductal carcinoma *in situ*
[a]NCT00676793	Phase 2 clinical trial to determine if polyphenon E inhibits c-Met signaling and activation of pathways contributing to breast cancer progression
[a]NCT00516243	Phase 1B randomized, double-blinded, placebo-controlled, dose escalation study of polyphenon E in women with a history of hormone receptor-negative breast cancer
NCT01360320	Minimizing the risk of metachronous adenomas of the colorectum with green tea extract
NCT00596011	Phase 2, randomized, double-blind, multi-centered study of polyphenon E in men with high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation
[a]NCT00233935	Phase 1B randomized, double-blinded, placebo-controlled, dose escalation study of polyphenon E in patients with Barrett's esophagus
[a]NCT01606124	Randomized phase 2 trial of polyphenon E *vs* placebo in patients at high risk of recurrent colonic neoplasia
NCT01116336	Phase 1 chemoprevention study with green tea and erlotinib in patients with premalignant lesions of the head and neck
NCT01032031	The effect of dietary bioactive compounds on skin health in humans *in vivo*
Resveratrol	
NCT01476592	A biological study of resveratrol's effects on Notch-1 signaling in subjects with low grade gastrointestinal tumors
NCT01489319	Evaluation of the ovarian dynamic response and the inflammatory response to oral lipid challenge in relation to body composition in polycystic ovary syndrome
Lycopene	
NCT00844792	Randomized, double-blind study of combination vitamin E, selenium and lycopene *vs* placebo in men undergoing radical prostatectomy for prostate cancer
NCT00669656	Phase 2 trial of a combination herbal therapy for men with biochemical recurrence of prostate cancer after initial local therapy

[a]Study is not yet open for participant recruitment

Under normal conditions, multiple STAT3 endogenous negative regulators such as suppressors of cytokine signaling proteins, protein inhibitors of activated STATs and protein tyrosine phosphatases (such as SHP-1 and SHP-2 that dephosphorylates

active STAT-3 complexes) abrogate STAT-3 signaling (Chung et al. 1997; Starr et al. 1997; Rakesh and Agrawal 2005).

Natural chemopreventive agents such as green tea, resveratrol and curcumin have shown to modulate STAT activation in tumor cells. In transgenic TRAMP mouse prostate cancer model, green tea polyphenol inhibited STAT3 expression precluding tumor growth and promoting apoptosis (Siddiqui et al. 2008). Zyflamend, a herbal preparation and non-selective inhibitor of cyclooxygenase activity inhibit STAT3 phosphorylation in LNCaP cells (Bemis et al. 2005). Polyphenon E, a standardized mixture of green tea polyphenols suppresses STAT-3 activation in breast cancer cells concurrent with inhibition of markers of angiogenesis (Leong et al. 2009). Resveratrol inhibits Src tyrosine kinase activity blocking STAT3 activation (Kotha et al. 2006; Bhardwaj et al. 2007). Bharti et al. (2003a) demonstrated that curcumin inhibited IL-6-induced STAT3 phosphorylation abrogating nuclear translocation of activated STAT. Administration of curcumin to athymic nude mice bearing ovarian HeyA8 tumors resulted in significant inhibition of STAT3 phosphorylation (Lin et al. 2007). Luteolin, a flavonoid abundant in green vegetables such as broccoli, cabbage celery green pepper and spinach inhibits phosphorylation of STAT3 and targets it for proteasomal degradation, in this manner inhibits the expression of cyclin D1, survivin, Bcl-xL and VEGF (Selvendiran et al. 2006). Capsaicin, a constituent of green and red peppers, suppresses both constitutive and inducible STAT3 activation pathway causing inhibition of the growth of multiple myeloma in nude mice (Bhutani et al. 2007). Thus, suppression of the STAT signaling pathway by dietary agents provides opportunities for both prevention and treatment of cancer.

10.11 Regulation of the Wnt and SHH Pathway

Our current knowledge relating to cell survival linked signaling pathways reveals existence of other prospective signaling targets, namely Sonic hedgehog (SHH) and Wnt. These pathways critically predominate during embryonic development. However, in cancer related context, activation of these pathways is linked with biological features related to acquisition of an epithelial to mesenchymal transition and cancer stem cell phenotype – the Holy Grail in cancer, that are intimately associated with cancer invasion and metastasis (Woll et al. 2008; Syn et al. 2009; Varnat et al. 2009; Takahashi-Yanaga and Kahn 2010). Available literature points to Wnt and hedgehog signaling as a vicious cycle for the maintenance for cancer cells towards aggressiveness and contributing to cancer related deaths. Wnt pathway is activated in over 85 % of sporadic colon cancers the end result of which is shortened overall survival. The role of nutraceuticals in the regulation of various components of Wnt and Sonic hedgehog signaling in cancer has been recently reviewed by our group and others (Teiten et al. 2011, 2012; Sarkar et al. 2010; Amado et al. 2011; Tarapore et al. 2012). Apigenin was the first described flavonoid as regulator of the Wnt pathway; it reduced the levels of β-catenin and disheveled

proteins and accelerated the degradation of β-catenin promoting cell cycle arrest in breast cancer cells (Song et al. 2000; Landesman-Bollag et al. 2001). Data accrued from animal study with microarray analysis showed that isoflavone genistein downregulated Wnt signaling in genistein treated animals (Su et al. 2007). Furthermore, curcumin, resveratrol, EGCG, DIM, lycopene, deguelin and the plant flavonoid fisetin have also been found to inhibit the expression of several molecules of Wnt signaling pathway in different tumor types and cells (Teiten et al. 2011, 2012; Pahlke et al. 2006; Hope et al. 2008; Wertz 2009; Syed et al. 2011). In breast cancer cells, Wnt signaling has been found to be inhibited by EGCG in a dose-dependent manner, an effect mediated by mRNA stability of a transcriptional repressor HBP1 which is a suppressor of Wnt signaling (Kim et al. 2006a). EGCG augment Wnt signaling antagonist (Wnt inhibitory factor-1) that binds directly to Wnt molecules in the extracellular space and inhibit Wnt signaling (Mazieres et al. 2004; Yang et al. 2009). In the $Apc^{Min/+}$ mouse, white and green tea extract intake, where the major compounds are catechins, reduced tumor multiplicity by inhibiting the translocation of Wnt mediator β-catenin to the nucleus (Dashwood et al. 2002; Ju et al. 2005; Bose et al. 2007). The chemopreventive effect of resveratrol in colon cancer is due to significant decrease in the amount and proportion of β-catenin in the nucleus along with reduced expression of the two regulators of β-catenin localization (Hope et al. 2008). The flavonoid silibinin is seen effective in colon tumor cell lines only where the Wnt pathway is found to be altered such as SW480 colorectal cancer cell line; silibinin treatment resulted in inhibition of cell growth, induced cell death, and decreased nuclear and cytoplasmic levels of β-catenin (Kaur et al. 2010). Quercetin suppresses the growth of several leukemia and lymphoma cells by inhibiting components of the Wnt signaling pathway (Kawahara et al. 2009).

The *in vitro* and *in vivo* effect of isoflavone genistein, EGCG and resveratrol in the regulation of hedgehog signaling has also been reported (Slusarz et al. 2010). The inhibition of hedgehog signaling correlates with delayed prostate tumor growth *in vivo* in TRAMP mice (Slusarz et al. 2010). An alternative to TRAMP model is the transgenic LADY model (Gipp et al. 2007). In this model, prostate tumors rarely produce metastasis due to lack of increased hedgehog signaling markers during tumor development, evidence that strengthens the importance of hedgehog signaling in the process of metastasis (Gipp et al. 2007).

10.12 Regulation of the Apoptotic Pathway

Apoptosis is an important defense mechanism against tumor development and the major mechanism of anticancer action of chemopreventive along with chemotherapeutic agents. It is now well recognized that there are two major signaling pathways for the induction of apoptosis: the intrinsic (or mitochondrial) pathway and the extrinsic (or receptor mediated) pathway. Apoptosis resulting from activation of either of these pathways usually precede through activation of a class of intracellular cysteine proteases (a family of caspases enzymes) that cleave a variety of

cellular substrates resulting in distinct morphological alterations associated with cell death phenomenon, most notably being the characteristic ladder-type fragmentation of the DNA in agarose gel electrophoresis. Additionally, in humans, the induction of apoptosis is closely related to normal *p53* functioning since lack of its expression or function is associated with increased risk of tumor development. Moreover, it has been well known that caspase inhibitors as well as, survival signaling molecules (such as Akt, c-Myc, NF-κB, and COX-2) intervene and antagonize the process of apoptosis. Accordingly, the premise that novel agent that may reverse the inhibition of apoptosis or induce apoptosis in cancer cells would be therapeutically advantageous. Indeed, many diet derived bioactive phytochemicals are being recognized to affect the cysteine proteases in the apoptotic pathway and shown effectiveness in downregulating survival signaling component at various levels by their interference as well as, disrupting mitochondrial membrane integrity.

Corollary to this concept, a large number of studies have emphasized the potential of chemopreventive agents (such as resveratrol, curcumin, genistein, DIM, EGCG, etc.) exerting anticancer effects by causing cell cycle arrest and inducing apoptosis in numerous different cancer cell types. The induction of apoptosis has repeatedly been portrayed to be accompanied by increased caspase activity, cell cycle arrest in G1 phase or inhibition of cell cycle progression from S to G2 phase, decrease in Bcl-2, Bcl-xL, McL-1 oncoprotein levels and augmenting proapoptotic Bax levels (Bode and Dong 2006). EGCG, the principal flavonoid constituent of green tea polyphenols inhibits Akt and NF-κB signaling which is consistent with the concept that this generally promotes apoptosis. EGCG was found to promote apoptosis in T24 human bladder cancer cells by modulating PI3K/Akt pathway and Bcl-2 family proteins (Qin et al. 2007). EGCG induced the expression of p53 and its target p21 and Bax in prostate cancer cells with wild type p53 but not with inactive p53 (Hastak et al. 2005). EGCG also activates p53 and Bax in breast carcinoma cells (Roy et al. 2005). Our initial studies identified genistein, indole 3-carbinol (I3C), DIM, thymoquinone (TQ), garcinol, plumbagin, etc. as having anticancer effects through apoptosis as their primary molecular targets in a wide range of human cancer models regardless of their p53 status. Additionally, resveratrol together with DIM has been described to extend to another fundamental biological process and shown to interfere with mitochondrial functions by inhibiting mitochondrial ATP synthesis through its binding to F1-ATPase (Gong et al. 2006; Gledhill et al. 2007; Roy et al. 2008). This leads to generation of oxidative stress in cells through stimulation of ROS release from mitochondria perturbing signal transduction pathway and links ROS within mitochondria as playing an important role in augmenting proapoptotic activity. Interestingly, combination of chemopreventive agents demonstrate an additive effect in inducing apoptosis by significantly inhibiting downstream signaling molecules of the Akt-NF-κB pathway. We reported combination of resveratrol and curcumin significantly inhibits tumor growth in SCID mice implanted with HCT-116 colon cancer cells (Majumdar et al. 2009). Analysis of our *in vitro* results suggest that curcumin or resveratrol attenuated the constitutive activation of EGFR family members as well as IGF-1R, and that together, they cause a greater inhibition in

activation of the growth factor receptors than that observed with either agent alone. Further, the inhibition of IGF-1R activation in response to either mono or combinatorial treatment could be attributed to enhanced expression of IGF-binding protein (IGFBP-3) leading to increased sequestration of IGF-1 by IGFBP-3, rendering the growth factor unavailable for binding and activation of IGF-1R (Majumdar et al. 2009). Similarly, a combination of low doses of curcumin and PEITC substantially induced apoptosis by inhibiting NF-κB and EGFR signaling while inhibiting tumor growth in immuno-deficient mice (Khor et al. 2006b; Kim et al. 2006b). Profiling the gene expression in the small intestinal polyps of $Apc^{Min/+}$ mice fed sulforaphane, revealed that several proapoptotic genes (such as *MBD4, TNF-7* and *TNF ligand-11*) were upregulated while pro-survival genes (such as *cyclin D2, integrin-E1, Wnt-9A*) were downregulated (Khor et al. 2006a).

Phenoxodiol, the genistein derivative, under phase 2 clinical trials has been reported to bind to the tumor associated NOX receptor, block its function, and subsequently inhibit the anti-apoptotic proteins XIAP and FADD-like ICE inhibitory protein, eventually inducing apoptotic cell death (Kamsteeg et al. 2003). Additional findings reported from our laboratory and elsewhere have found that isoflavone genistein, DIM, TQ, sulforaphane, EGCG combined with either doxetaxel, cisplatin, oxaliplatin, or gemcitabine significantly inhibit Bcl-2, Bcl-xL, survivin and induced p21 WAF1, supporting that the enhanced antitumor effect in combination treatment is through the regulation of these important molecular entities in the apoptotic pathway axis. Furthermore, it has been found that curcumin combined with either cisplatin or paclitaxel decreased the expression of several apoptosis related genes including: *c-Myc, Bcl-xL, c-IAP-2*, neuronal apoptosis inhibitory protein and XIAP (Aggarwal et al. 2005; Notarbartolo et al. 2005).

The extrinsic pathway regulated by cytokines, mainly CD95L and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), secreted by cytotoxic T cells or natural killer (NK) cells is now being considered as important endogenous anticancer immuno-surveillance agent inducing apoptosis selectively in tumor cells (Mantovani et al. 2008). Mechanistically, it has been shown that the binding of cytokines to members of the superfamily of TNF receptors initiates receptor oligomerization and initiate cascade of signaling events leading to the activation of caspase-8 and effector caspase-3 (Ashkenazi 2008; Thorburn et al. 2008). Intriguingly, some cancer cells are resistant to TRAIL-mediated apoptosis and studies have examined the ability of bioactive chemopreventive agents to induce apoptosis targeting the extrinsic pathway. In this context, resveratrol has been shown to induce cell death in some tumor types expressing high CD95 (Fas, APO-1) by augmenting CD95 (FasL) expression thereby manipulating CD95-CD95L system as 'apoptotic trigger' inducing cell death (Gusman et al. 2001). Resveratrol, EGCG, genistein, and sulforaphane have been shown to sensitize tumor cells, but not normal human fibroblasts, to TRAIL-induced apoptosis (Fulda and Debatin 2004; Shankar et al. 2008c). The combination of curcumin and TRAIL induces the cleavage of procaspase-3, -8, as well as -9, truncation of Bid, along with the release of cytochrome c from the mitochondria, indicate stimulation of apoptotic pathway in these cells (Deeb et al. 2003). Quercetin from onions and apples is a potent

enhancer of TRAIL-induced apoptosis in prostate and hepatocellular carcinoma cells (Jung et al. 2010a, b; Kim et al. 2008). These findings suggest that bioactive chemopreventive agents also regulate the extrinsic apoptotic pathway extending the possibility to sensitize cells to proapoptotic cytokine stimuli during cancer prevention and therapy.

10.13 Regulation of Other Pathways

The forkhead transcription factors of the O class (FOXO) plays a direct role in cellular proliferation and regulate antitumor activities in cancer cells (Singh et al. 2011; Zhang et al. 2011a, b). It has been demonstrated that resveratrol, sulphorophane EGCG cause growth arrest and induce apoptosis through activation of FOXO transcription factors (Shankar et al. 2008a; Davis et al. 2009; Roy et al. 2010, 2011). We have reported that the isoflavone genistein enhances the antitumor and antimetastatic activities of docetaxel through the regulation of osteoprotegerin/receptor activator of NF-κB (RANK)/RANK ligand/MMP-9 signaling in prostate cancer, implying that isoflavone genistein could be a promising non-toxic agent to improve the treatment outcome of metastatic prostate cancer with docetaxel (Li et al. 2006). Another study by us revealed that soy isoflavone enhances prostate cancer radiotherapy through the downregulation of apurinic/apyrimidinic endonuclease 1/redox factor-1 expression (Raffoul et al. 2007). The NSAID activated gene (*NAG-1*) is a pro-apoptotic and anti-tumorigenic gene which is regulated by several transcription factors such as p53, activating transcription factor 3 (ATF3), and early growth response gene-1 (*EGR-1*) (Baek et al. 2004). An insight into modulation of *NAG-1* status in some tumor cells reveals upregulated *NAG-1* expression by ECG and DIM resulting in poly(ADP-ribose) polymerase cleavage and apoptosis (Baek et al. 2004; Lee et al. 2005b). There are evidence suggesting that for maintenance of biological homeostasis, peroxisome proliferators activated receptors (PPARγ) are molecular targets of resveratrol and TQ in the regulation of cell proliferation (Woo et al. 2011; Ulrich et al. 2006). PPARγ are ligand activated transcription factors whose activity induces apoptosis. Further, a combination of genistein and resveratrol downregulated PPARγ resulting in an enhanced effect on apoptosis (Rayalam et al. 2007). Another important aspect relates to the potential of genistein and isoflavone analog (daidzein and glycitein) to decrease the side effects of tamoxifen by inhibiting CYP1A2; this suppresses the formation of α-hydroxy tamoxifen and its sulfate conjugate believed to be responsible for DNA adduct formation (Umemoto et al. 2001; Chen et al. 2004). Likewise, resveratrol, restrains bioactivation of polycyclic aromatic hydrocarbons, a class of ubiquitous environmental chemicals, through reduced expression of the *CYP1A1* and *CYP1B1* genes in human bronchial epithelial cells (Berge et al. 2004); increased CYP1A1 expression and activity are associated with a high risk of lung and colorectal cancer (McLemore et al. 1990; Sivaraman et al. 1994). It has been shown that DIM interferes with regulation of the estrogen-metabolizing CYP enzymes (e.g. CYP3A1/2 activity) associated with cancer susceptibility and provides

an important mechanism for preventing the tumorigenic process in estrogen-responsive sites (Parkin and Malejka-Giganti 2004).

Significant findings emerging from field of experimental tumor immunology points to the absence of functional T cells or T cell derived cytokines such as, IL-6, IL-12 and IFN-γ or NK cells as playing a role in the onset of spontaneous and carcinogen-induced tumor in mice models (Dunn et al. 2004). It is conceivable that activation of functional T cells or production of cytokines (such as INF-γ or IL-12) would mount an antitumoral immune response in some types of human cancers and contribute to cancer prevention. It has been reported that quercetin is able to enhance susceptibility to NK cell-mediated lysis of cancer cells through the induction of NKG2 (NK group-2, member D) ligand (Bae et al. 2010). EGCG enhances $CD8^+$ T cell-mediated antitumor immunity induced by DNA vaccination (Kang et al. 2007b). Genistein modulates immune responses and increase host resistance to B16F10 tumor purportedly by enhancing the activities of cytotoxic T cells and NK cells (Guo et al. 2001). Sulforaphane inhibits prostate carcinogenesis and pulmonary metastasis in TRAMP mice in association with increased cytotoxicity of NK cells (Singh et al. 2009). Based on the preceding narrative, it becomes clear that chemopreventive agents are pleiotropic and thus, could be considered as efficient multitargeted agents for the design of anticancer therapy and likely to revolutionize our approach for the prevention and treatment of cancer.

10.14 Chemosensitization of Conventional Cancer Therapeutics by Chemopreventive Agents

Classical chemotherapy often remains the most used anticancer therapy. Unfortunately, one of the persistent problems with chemotherapy is the emergence of drug resistant clones after prolonged treatment. It remains clinically challenging to effectively target this resistant population of cells exhibiting repopulating capacities, high tumorigenicity and self renewal characteristics during course of disease management. Despite implication of novel and innovative strategies such as tumor-suppressor and suicide gene-based therapy, the tumor relapse rate remains high after these treatments. We and other investigators conceptualized the potential benefit of natural agents harboring pleiotropic effect, including inactivation of survival signaling and simultaneous activation of multiple death pathways as a rationale to sensitize tumor cells to therapy. Thus, rationally designed novel cocktail regimen including conventional cytotoxic chemotherapeutic agent and a chemopreventive agent are speculative to yield beneficial outcome, including potential for reduction in adverse side effect. In this direction of development, ongoing preventive trials demonstrate the beneficial effects of chemopreventive agents, including soy isoflavone, curcumin, tea polyphenols-EGCG, ECG, NSAIDs, resveratrol, quercetin and DIM against multiple cancers. Concurring preclinical study designs using xenograft and orthotopic models have convincingly shown that

isoflavone genistein could potentiate the antitumor effects of chemotherapeutic agents (gemcitabine, docetaxel, cisplatin, oxaliplatin) and targeted drug (erlotinib) resulting in greater apoptotic cell death parallel with the inhibition of tumor growth in pancreatic, osteosarcoma, and prostate cancers (Li et al. 2004; Banerjee et al. 2005, 2007, 2011a; El-Rayes et al. 2006; Zhang et al. 2010; Liang et al. 2012). Additionally, the effect of triple combination including gemcitabine and erlotinib against background of genistein treatment revealed more potent inhibitory effect on pancreatic cancer growth *in vitro* compared to monotherapy (El-Rayes et al. 2006). In a xenograft model, we reported that combination of curcumin and taxol enhanced drug cytotoxicity and inhibited lung metastasis of human breast cancer in nude mice (Aggarwal et al. 2005). Curcumin also sensitizes hormone refractory and TRAIL-resistant xenograft in the prostate suggesting this treatment approach could be useful for the prevention, as well as treatment of prostate cancer (Deeb et al. 2005, 2007; Shankar et al. 2008b). In another study, the chemosensitizing effect of liposomal curcumin in paclitaxel chemotherapy of cervical cancer has been reported (Sreekanth et al. 2011). To improve the drawbacks in bioavailability of curcumin, several novel analogs of curcumin have been developed and reviewed by Anand et al. (2008). Our laboratory reported a synthetic analog of curcumin named curcumin difluorinated (CDF) showing greater tissue bioavailability in pancreas and prostate of mice than natural curcumin, and enhancing the activity of gemcitabine in pancreatic cancer targeting cancer stem like cells (Padhye et al. 2009a, b; Ali et al. 2010; Bao et al. 2011).

The chemosensitizing effect of DIM in orthotropic mouse model of pancreatic cancer rendering significant inhibitory effect on pancreatic tumor growth in combination with erlotinib and third generation platinum drug oxaliplatin, currently in clinical use with major limitation of drug resistance, have been reported by us (Ali et al. 2008; Banerjee et al. 2009b). Similar growth inhibitory effects were also noted in an *in vivo* prostate tumor model treated with DIM and taxotere (Rahman et al. 2009). At the molecular level, this has been attributed to partaking by DIM in down regulating survivin, AR and NF-κB signaling (Rahman et al. 2006, 2009). Other bioactive compounds from cruciferous vegetables, PEITC and sulforaphane have been found to inhibit angiogenesis *in vitro* and *ex vivo* through a broad spectrum of anticancer and antiproliferative activity in multiple cancer types (Asakage et al. 2006; Bertl et al. 2006; Xiao and Singh 2007; Hudson et al. 2012). The prominent tea component, EGCG, enhanced the antitumor effect of tamoxifen in MDA MB-231 human breast cancer cells (Chisholm et al. 2004) and improved the therapeutic efficacy of temozolomide in an orthotopic mouse glioblastoma model (Chen et al. 2011). EGCG have been shown to sensitize xenograft tumors developed with drug resistant KB-A-1 human cervical carcinoma cells to doxorubicin *in vivo* through an increase in the accumulation of doxorubicin, and increased DOX-induced apoptosis in the tumors compared with DOX alone (Zhang et al. 2004). The synergistic action of EGCG and EGFR-tyrosine kinase inhibitor erlotinib on growth inhibition of squamous cell carcinoma of the head and neck (SCCHN) in a mouse xenograft model has also been reported (Zhang et al. 2008). The combined treatment resulted in significantly greater inhibition of tumor growth and delayed tumor progression as

a result of increased apoptosis, decreased cell proliferation and reduced pEGFR and pAKT compared to monotherapy proclaiming promising regimen for future chemoprevention and treatment strategy for SCCHN (Zhang et al. 2008). Another assessment found that PES (a combination of Polyphenon E, a highly characterized green tea extract standardized to EGCG) and siliphos (main component silibinin) inhibited colorectal tumor growth as well as hepatic metastases, but awaiting implementation as a perioperative anticancer therapy (Yan et al. 2012). In murine model of chemoresistant hepatocellular carcinoma (HCC), the tea catechins ECG and EGCG sensitized chemoresistant HCC cells to DOX by decreasing the level of P-glycoprotein while suppressing MDR1 expression, consequently increasing the intracellular accumulation of the drug (Liang et al. 2010).

Resveratrol has been reported to prevent and inhibit the development of tumors and exhibits anticancer properties in a variety of tumor cells including lymphoid, myeloid, skin, breast, prostate, pancreatic and colon cancer cells (Bishayee 2009). We recently reported that the biological effect of resveratrol could be enhanced in lower pH (Shamim et al. 2012); this is a provocative finding because the pH within the tumor is lower than the overall physiological pH *in vivo* and suggests that resveratrol could be effective in cancer in human patients because the pH within the tumor is lower than the overall physiological pH *in vivo*. It has been reported that resveratrol sensitizes human pancreatic cancer cells to gemcitabine therapy and the effect was found to be mediated by downregulation of cell survival molecules, including NF-κB, cyclin-D1, COX-2, MMP-9 and survivin (Harikumar et al. 2010). In human multiple myeloma cells, resveratrol inhibits cells proliferation, induces apoptosis and overcomes chemo resistance through downregulation of STAT-3, Akt, NF-κB, cyclin D1, Bcl-2, Bcl-xL, and XIAP (Bhardwaj et al. 2007). In murine liver cancer, resveratrol has been found to enhance the antitumor effect of 5-FU and markedly antagonizing its toxicity (Wu et al. 2004).

10.15 Clinical Trials for Cancer Therapies by Dietary Agents

Based on information available at http//www.clinicaltrials.gov several clinical trials are under way reflecting the clinical usefulness of natural chemopreventive agents in cancer patients (Table 10.1). It has been found that dietary supplements of pure unconjugated isoflavones (genistein, daidzein, and glycitein) given to humans in single doses exceeding normal dietary intake by many folds resulted in minimal clinical toxicity (Busby et al. 2002). Another phase 1 trial, using multiple-doses of isoflavone in men with prostate cancer also showed similar results (Fischer et al. 2004). Results from a clinical trial showed that supplementing early stage prostate cancer patients with soy isoflavones altered surrogate markers of proliferation such as: serum PSA and free testosterone, in large number of subjects in the isoflavone supplemented group than the group receiving placebo, suggesting the beneficial effects of isoflavone in early stage prostate cancer (Kumar et al. 2004). Several clinical trials are being conducted using isoflavone genistein or formulated

genistein in combination with IL-2 or gemcitabine in the treatment of melanoma, kidney and pancreatic cancers (Table 10.1). Phenoxodiol, is one of the isoflavone analogues that has shown a broad spectrum anticancer effect. Phenoxodiol is currently undergoing clinical trials in phase 2/3 trials to investigate the effects of phenoxodiol combined with carboplatin, docetaxel, cisplatin or paclitaxel in patients diagnosed with ovarian, fallopian tube, or primary peritoneal cavity tumors (Table 10.1).

Phase 1 data support the non-toxic nature of DIM in healthy volunteers (Reed et al. 2008). Other ongoing clinical trials have been recently summarized by us (Banerjee et al. 2011b). Polyphenon-E and other green tea polyphenols received investigational new drug status and are currently undergoing clinical trials. Recently, a phase 3 clinical trial is being conducted using combination of EGCG and erlotinib to chemoprevent head and neck cancer with premalignant lesions (NCT ID: 01116336). A phase 2 trial to evaluate the safety and effectiveness of administering several doses of lycopene to men with clinically localized prostate cancer has been reported showing that serum free testosterone decreased with lycopene supplementation, suggesting that steroid hormones related mechanisms are involved (Kumar et al. 2008). The results from another clinical trial showed that lycopene supplements reduced tumor size and PSA level in localized prostate cancer suggesting its promising effect on prostate cancer prevention and/or treatment (Kucuk et al. 2001, 2002).

10.16 Conclusion and Perspective

Studies reported over the past decade focusing specifically on signal transduction pathways have revealed the existence of complex deregulated cellular signaling networks unilaterally augmenting growth and survival of cancer cells. With increasing knowledge on bioactive food compounds along with aforementioned molecular events, the ability of chemopreventive agents to potentially intervene and slow down the initiation and progression of cancer by its effect on either one or multiple signaling pathways is unquestionable. Unfortunately, a regular diet cannot provide adequate amount of bioactive phytochemicals. Nevertheless, it is convincing to note as a ‘proof of principle’ that such strategy could be exploited rationally towards development of therapeutically relevant novel analogs aimed to establish greater bioavailability and potency to disrupt the cross talk between survival and anti-apoptotic signal transduction network circuitry primarily indicted in the initiation and progression of cancer and development of chemoresistance. This also calls for in-depth molecular characterization profiling of the compounds along with appropriate preclinical animal experimentation using genetically modified animal models of cancer. Finally, it is imperative that clinicians should enthusiastically pursue clinical trials to validate the usefulness of natural bioactive compounds or their analogs in the treatment of cancer either as single agents or combined with conventional existing cancer therapies to win the battle against cancer.

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