Mechanisms of Cancer Chemopreventive Agents: A Perspective

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Introduction

For individuals less than 65 years of age, cancer is now the leading cause of death in the United States [1]. Since this disease may stealthily progress for a decade or more prior to diagnosis, and only limited routine and robust early diagnostic markers are known, at risk individuals are advised to take preventive measures. Some cancer chemopreventive agents are available having the ability to prevent, delay, or reverse the risk of cancer development and/or progression. Those approved by the U.S. FDA include selective estrogen receptor modulators (SERMS), aromatase inhibitors, and celecoxib. In the general population, a diet highly enriched in fruits and vegetables may have preventative value; examples of natural products that show promise as cancer chemopreventive agents include epigallocatechin gallate (EGCG), capsaicin, resveratrol, curcumin, 6-gingerol, and lycopene [2], [3], [4].

Chemopreventive compounds can be identified in various ways. Some are isolated from plants with known medicinal properties, largely gleaned from epidemiological studies, while others are identified in massive screens of libraries of randomly collected samples. Irrespective of the method of identification, compounds with chemopreventive promise are ultimately purified and subjected to structure elucidation. Although structure identification is an important first step, it usually does not provide an explanation as to why a particular compound is active. Answering this question is exceedingly complex. Considering pharmaceutical agents that have been discovered throughout history, only a few are believed to have a clearly defined mechanism of action. For example, penicillin inhibits the formation of peptidoglycan cross-links in bacterial cell walls, 5-fluorouracil serves as a pyrimidine analogue, taxol stabilizes tubulin, tamoxifen is an SERM, and methotrexate interferes with one-carbon metabolism. Identifying a clearly defined mechanism of action for the majority of drugs, however, is the equivalent of finding a single needle in multiple haystacks, all equally complex. In most cases, the very composition of each haystack is largely uncharacterized or even yet undiscovered.

Abstract

A fundamental question addressed by drug development programs is how agents being tested function on a molecular level. Using resveratrol, curcumin and EGCG as examples, it is clear that a definitive mechanism of action for cancer chemopreventive agents is not available despite decades of exhaustive research. This is profoundly evident based on the myriad of biological responses that have been observed at the cellular level, and even more overwhelming when considering gene expression data that are now available. The situation is confounded further when chemopreventive agents are used in combination, even though superior clinical responses are anticipated. The best hope for delineating tangible, meaningful mechanisms resides in the use of complex physiological systems and computer models to decipher the most critical pathways that are appropriate for targeting with chemopreventive agents, their analogues, and combination treatments. Definitive answers concerning clinical efficacy are only available through human trials. Given the enormity of these tasks, together with the urgency of continuing the fight against cancer, it is adequate to move ahead with chemopreventive drug development on a semi-empirical basis, bearing in mind the importance of limiting toxic side effects.
The complexity of mechanistic definition is particularly apparent with cancer chemopreventive agents. As described herein, the anticancer effects observed from a single chemopreventive agent are the outcome of a combination of several distinct sets of intracellular effects, rather than limited to one established biological pathway. To elaborate on the mechanistic complexity of chemopreventive agents, as examples, we have surveyed the reported mechanisms of action of three compounds: resveratrol, curcumin, and EGCG. Presently, it is clear that a meaningful sequence of critical mechanistic events cannot be defined in a straightforward manner. These three chemicals also exemplify the structural diversity of chemopreventive agents (Fig. 1).

**Resveratrol**

Resveratrol is a stilbene that is found in several plants, the primary dietary source being grapes. It can function as a chemopreventive agent capable of inhibiting all stages of cancer development. Modes of action identified for resveratrol include induction of phase II drug-metabolizing enzymes, inhibition of cyclooxygenase (COX), and cellular differentiation [5]. Resveratrol inhibits cytochrome P450, cell invasion, transformation, and angiogenesis [6]. Resveratrol has been shown to up-regulate antioxidant enzymes, such as glutathione peroxidase, catalase and quinone reductase. It inhibits lipid peroxidation, ornithine de-carboxylase (ODC), protein kinases, and cellular proliferation [7]. Resveratrol effectively induces apoptosis modulated through multiple pathways including up-regulation of p53, activation of caspases, decreases in Bcl-2 and Bcl-xL, increases in Bax, inhibition of D-type cyclins, and interference with NF-κB and AP-1 mediated cascades [8].

A multitude of in vitro and in vivo studies implicate resveratrol in a large web of anticancer pathways (recently reviewed in [8], [9]). Resveratrol treatment resulted in growth arrest at G1 and G1/S phases of the cell cycle by inducing the expression of p21 and p27 [10]. It reduced inflammation via inhibition of prostaglandin production and COX-2 activity. Resveratrol has been shown to regulate cathepsin D, inhibit hypoxia-induced protein, and down-regulate telomerase. Resveratrol pretreatment suppressed activation of ERK2, JNK and p38 in association with inhibition of protein kinase C (PKC) and protein tyrosine kinase [11]. Resveratrol blocked activation of NF-κB through suppression of iκB activation, inhibited activation of MEK, and abrogated TNF-induced caspase activation.

**Curcumin**

Curcumin (diferuloylmethane), a yellow pigment from the rhizomes of turmeric, has been recognized as a chemopreventive agent due to its antitumor, antioxidant, antiproliferative, and proapoptotic effects. Curcumin suppresses transformation, proliferation, angiogenesis, and metastasis. Similar to resveratrol, curcumin mediates its anticancer effects through regulation of various transcription factors, growth factors, inflammatory cytokines, and protein kinases (reviewed in [12]).

Many mechanisms of action for curcumin have been identified, including modulation of the expression of genes involved in proliferation, apoptosis, invasion, metastasis, angiogenesis, and resistance to chemotherapy [13], [14]. Curcumin inhibits cell-cell adhesion and blocks cell cycle transition from G2 to M [15]. It suppresses cytochrome P450 and decreases P-glycoprotein expression [16], [17], [18]. Curcumin inhibits the catalytic activity of ERK1/2, activates caspases 8 and 3, down-regulates cyclin D1, suppresses the activation of NF-κB, AKT-P13K, AP-1, STATs, TNF, MAPK, PKC, and modulates the expression of PPAR-γ, β-catenin, and Nrf-2 [13], [19], [20], [21], [22]. Curcumin inhibits histone deacetylase [23] and down-regulates the expression of p53, EGR-1 and c-myc [24]. Curcumin treatment activates proapoptotic members of the Bcl-2 family and reduces the activity of EGFR and HER2/neu [25]. Curcumin up-regulates enzymes such as catalase, glutathione transferase, glutathione peroxidase, and superoxide dismutase (SOD). Curcumin inhibits production of IL-8 by tumor cells and augments the cytotoxic effects of chemotherapeutic drugs [26].

**Epigallocatechin Gallate (EGCG)**

EGCG is an antioxidant polyphenol that is found in green tea. It exhibits a wide variety of anticancer properties, including inhibi-
ition of extracellular mitotic signals, inhibition of the cell cycle at G1 phase, suppression of INOS, and induction of apoptosis (reviewed in [27]). EGCG has been reported to inhibit invasion and angiogenesis, processes that are essential for tumor growth and metastasis [28]. Similar to resveratrol and curcumin, mechanisms contributing to the anticarcinogenic and antimutagenic effects of EGCG include antioxidant activity, induction of phase II enzymes, blocking carcinogen formation, inhibition of carcinogen binding to DNA, and inhibition of DNA synthesis and cell proliferation [29], [30], [31].

EGCG has been reported to act through a myriad of mechanisms [27]. It suppresses MMP-9 secretion and phosphorylation of focal adhesion kinase and ODC activity. EGCG activates caspases 3 and 9, SOD activity, and catalase activity. EGCG inhibits DNA synthesis [29], MAPK signaling [32], NF-κB activity, STAT3, PI3K activation [33], [34], Raf, MEK, ERK, JNK, p38 kinase, EGFR, and Iκκ [27]. EGCG reduces signaling via P13K-AKT-NF-κκ mediated changes may also have biological significance. Columns four and five contain a sampling of commonly recognized genes. In the first example, microarray analyses were performed to identify genes that are regulated by resveratrol in androgen-sensitive prostate cancer cells (LNCaP), human ovarian cancer cells (PA-1), and renal cell carcinoma cells (RCCS4). The most com-

### Microarray Analyses

Of the chemopreventive agents examined above, several targets are modulated by each of the three, such as NF-κB. Should we conclude that NF-κB is a critical target? Another possibility is there is investigator bias towards examining effects on the NF-κB pathway, and other, possibly undiscovered, targets are not being considered. Perhaps hypothesis-driven research is limiting the ability to discover the unexpected, and we are only discovering mechanisms that we are seeking. One way to limit investigator bias is to perform microarray studies, which have also been used to confirm existing hypotheses. The results from selected microarray experiments involving resveratrol, curcumin, and EGCG are summarized in Table 1. Column three lists how many genes exhibited a greater than two-fold up- or down-regulation, although it should be recognized that lesser-fold changes may also have biological significance. Columns four and five contain a sampling of commonly recognized genes.

<table>
<thead>
<tr>
<th>Chemopreventive Agent</th>
<th>Cell Type, Dose, Time</th>
<th>2×Change</th>
<th>Genes Up-Regulated</th>
<th>Genes Down-Regulated</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resveratrol</td>
<td>LNCaP 100 μM 48 h</td>
<td>555 of 2400</td>
<td>P300 (5.09) Glutathione transferase (2.91) Bak protein (2.14) Pig7 (2.27) CRABP II (2.1)</td>
<td>PSA (0.10) ARA 24 (0.01) Nfxb p65 (0.47) PPAR (0.3)</td>
<td>[10]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>LNCaP 100 μM 24, 48 h</td>
<td>553 of 2400</td>
<td>GADD45 (3.07) CRABP II (3.28) TRAF-1 (1.58) Protein-tyrosine phosphatase (1.4) Rb binding protein 1 (4.7)</td>
<td>NQO-1 (12.4) p21 (4.6)</td>
<td>[39]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>LNCaP 75, 150 μM 0 – 60 h</td>
<td>1,600 of 42,000</td>
<td>Glutathione reductase (2.9) Quinone reductase Phase II enzymes</td>
<td>PSA AR Cyclins D, E, A, B</td>
<td>[38]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>RCCS4 25, 50 μM 24 h</td>
<td>633 of 2059</td>
<td>Hsp27 (2.78) Hsp70 (3.75) Hsp40-like protein (3.21)</td>
<td>MMP14 (0.65) Neuronal cell adhesion molecule (0.54) Integrin α6 (0.67) Integrin β4 (0.63)</td>
<td>[42]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>ECV304 1 μg/mL 24 h</td>
<td>27 of 2400</td>
<td>p21WAF1</td>
<td>CIP1 p53</td>
<td>cyclin B1 cdc2</td>
</tr>
<tr>
<td>Curcumin</td>
<td>CL1–5 10 μM 24 h</td>
<td>152 of 9600</td>
<td>Hsp27 (2.78) Hsp70 (3.75) Hsp40-like protein (3.21)</td>
<td>TRAIL, TNFR, AP13, IGBP3, PKB, IGBP, TRAIL-R2, TNFβ</td>
<td>[43]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>MCF-7 25, 50 μg/mL 24 h</td>
<td>104 of 214</td>
<td>TRAF6, GADD45, BCL2L2, PIG11, PIG3, PCNA, CDC10, JNK1, RBP2</td>
<td>TRAIL, TNFR, AP13, IGBP3, PKB, IGBP, TRAIL-R2, TNFβ</td>
<td>[43]</td>
</tr>
<tr>
<td>EGCG</td>
<td>LNCaP 12 μM 12 h</td>
<td>25 of 250</td>
<td>Protein-tyrosine phosphatase</td>
<td>PKC alpha PI3K homolog</td>
<td>[44]</td>
</tr>
</tbody>
</table>
prehensile of these studies identified 1,600 genes that were up- or down-regulated more than two-fold following a single treat- ment with resveratrol. Changes were reported in genes regulat- ing apoptosis (Bak, Apaf-1), differentiation, signal transduction (CRABP II, TRAF-1), proliferation (protein tyrosine phosphatase), transcription factors, cell adhesion, tumor suppression (Rb bind- ing protein), cell cycle (p300), growth factors (TGFα, GADD45), p53 (PIG7, NQO-1, p65 NF-xB homologue, p21), and GST (gluta- thione transferase). Specifically in prostate cancer cells, resvera- trol induced apoptosis by activating p53 signaling mechanisms and by blocking androgen signaling pathways including prosta- tase-specific antigen (PSA) and the androgen receptor (AR). Col- lectively, these results confirm that resveratrol modulates more than one set of functionally related targets.

Microarray studies performed with cells treated with curcumin or EGCG treatment yielded similarly complex results, confirming these agents modulate gene expression through multiple path- ways involving hundreds of genes or more. Curcumin up-regulat- ed cyclin dependent kinase (CDK) inhibitors, such as p21 and p27, and down-regulated cyclin B1 and cdc2 [41]. A study following curcumin treatment in a lung adenocarcinoma model indicated that several invasion-related genes were suppressed, including matrix metalloproteinase 14 (MMP14), neuronal cell adhesion molecule, and integrins. Additionally, several heat-shock proteins (hsps) were induced. Gene expression was altered up to 14-fold in breast cancer MCF-7 cells as compared to only 1.5-fold in the MCF-10A normal breast cell line following treatment, indicating that curcumin is capable of selectively suppressing the growth of cancer cells. A microarray study of kinases and phosphatases using LNCaP cells indicated that EGCG induced a subset of genes in- volved in cancer cell growth, mostly belonging to the G-protein signaling pathway. The observed anticancer benefits resulting from treatments with combinations of chemopreventive agents indicate that a diet rich in many of these compounds as possible is a reasonable ap- proach. However, this approach may not always be possible, espe- cially in developing countries. It is necessary to determine the most affordable and available combinations that are effective against the broadest range of targets as possible. This needs to be addressed at the mechanistic level. At this time, we are not certain if the observed synergistic responses are due to perceived mecha- nisms or other factors that have not been identified or realized.

**Combination Chemoprevention**

Analyzing the effects of chemopreventive agents using genome- wide or proteome-wide analysis would allow investigators to predict multi-target approaches involving more than one che- mopreventive agent. The combination drug approach was first successful in treating tuberculosis with a cocktail of antibiotics, each with a different mechanism of action. Such an approach is now standard in cancer chemotherapy, where different drugs given in combination reduce the likelihood that a tumor devel- ops resistance to a particular treatment. It is logical to extend this approach to the field of chemoprevention, especially if we consider that dietary chemopreventive agents are naturally present in the diet in combination. Table 2 lists the results from a selection of studies retrieved during a literature search that report the effects of treatment with combinations of che- mopreventive agents.

As a whole, the results indicate that combination treatment is more effective than single-agent treatment. This is presumably due to simultaneously attacking tumor development on multi- ple fronts, which reduces the ability of a tumor cell to develop resistance to a single treatment. Treatment with agents that act synergistically allows for reduced dosing of individual agents, which can reduce single-agent toxic effects and make chemopre- ventive levels more easily attainable in the diet. For example, combination treatment with low doses of cholesterol-lowering statins, celecoxib (COX-2 inhibitor), DFMO (polyamine inhibition), and NSAIDs was successful. Diallyl sulfide, found in garlic, was effective in preventing tumor development when given in combination with either quercetin (anti-inflammatory) or Se- methylselenocysteine (raf/MEK/ERK inhibitor). Combination treatments with agents that exhibit a broad spectrum of chemo- preventive mechanisms, such as curcumin/EGCG or curcumin/ quercetin were also successful. Indole-3-carbinol, found in cruciferous vegetables and having anticarcinogenic, antioxidant, and anti-atherogenic effects, was chemopreventive when paired with putrescine, a polyamine. Combination treatment with all- trans- (4-hydroxyphenyl)retinamide (antiangiogenic/apoptotic) and tamoxifen (modulator of growth factors/hormo- nal activity) targeted multiple mechanisms at once. Other suc- cessful combinations include ellagic acid (antioxidant/proapoptotic) given with selenomethionine (antioxidant), urodeoxycholyte paired with sulindac, DFMO with piroxicam, tomato with garlic, and beta-carotene in combination with vitamin E.

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**Systems Biology**

The individual mechanisms that have been proposed to date as being important in defining the action of chemopreventive agents are important pieces of a yet incomplete puzzle. It has be- come apparent that such mechanisms are too complex to be un- derstood using the classic reductionist approach of identifying linear pathways. Such a narrow approach was historically neces- sitated due to experimental limitations. The evolution of large- scale, high-throughput technologies has led to a paradigm shift away from reductionism in favor of systems biology. In collabo- ration with mathematicians and computer scientists, biologists have created complex algorithms to identify clusters of path- ways, or networks, representing extensive interactions among different components from the subcellular to organism level [58]. Systems biology offers the field of cancer chemoprevention the potential to identify comprehensive mechanisms of action.
involving a multitude of interactions. Both new and preexisting data derived from a broad spectrum of experimental models can be processed in this way to confirm the importance of existing mechanisms as well as to define new mechanistic pathways.

Conclusions

At the present time, we submit that the key mechanism by which any known chemopreventive agent mediates a reduction in tumorigenesis remains ill-defined. The situation is even more confounded in combination chemopreventive work. Most studies performed to date have examined in vitro activities. Results from in vivo studies often show much more modest benefits, stemming from problems of bioavailability, toxicity, and physiological dosing limitations. In a typical case, irrespective of perceived mechanism, the biological and physiological complexity of a mammal is required to establish efficacy. Moreover, even animal models are not sufficient to predict efficacy in human beings. The failure of β-carotene in clinical trials [59] well exemplifies this point. As illustrated with resveratrol, curcumin and EGCG, a great deal can be learned about the mode of action of a chemopreventive agent. It may be, however, that a critical, straightforward pathway leading to the chemoprevention of cancer will never be known. It may be necessary to finally accept a superb therapeutic response as being empirical in nature and due to a fortuitous sequence of events leading to a good outcome. Of utmost importance is the ability to facilitate a predictable clinical response in the absence of toxicity.

Nonetheless, it is clear that many contemporary basic and clinical scientists, as well as health authorities and regulatory agents, will not find the proposition of empiricism to be sufficiently satisfying. In order to realistically approach a true definition of critical mechanism, we suggest the greatest hope lies in exploring modern-day science is not capable of simply disregarding the molecular mechanism leading to a favorable therapeutic outcome and then proceeding with confidence. This is fundamentally equivalent to accepting the untenable philosophy of ignorance is bliss. Certainly, a great deal of work remains to be done for the accurate definition of chemopreventive mode of action, but we should be willing to forge ahead on a semi-empirical basis in our fight against this dreadful disease.

Acknowledgement

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References

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Table 2 Combination treatments involving chemopreventive agents

<table>
<thead>
<tr>
<th>Agents</th>
<th>Model</th>
<th>Findings</th>
<th>Reference</th>
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<tr>
<td>Celecoxib</td>
<td>Colon cancer</td>
<td>Combinations at low dosages inhibit carcinogenesis more effectively and with less toxicity than if given alone</td>
<td>[47]</td>
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<tr>
<td>DFMO</td>
<td></td>
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<td>Statins</td>
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<td>NSAIDs</td>
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<td>EGCG</td>
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<tr>
<td>Curcumin</td>
<td>Normal, premalignant and malignant human oral epithelial cells</td>
<td>Synergistically inhibit cell growth</td>
<td>[48]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Adenomas in familial adenomatous polyposis SW480 colon tumor cell line</td>
<td>Decreased number and size of polyps</td>
<td>[49]</td>
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<tr>
<td>Indole-3-carbinol</td>
<td></td>
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<tr>
<td>Putrescine</td>
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<td></td>
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<tr>
<td>Ursodeoxycholate</td>
<td>Mouse model of polyposis</td>
<td>Prevents intestinal adenomas at lower doses than with sulindac alone, less toxicity</td>
<td>[50]</td>
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<tr>
<td>Sulindac</td>
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<tr>
<td>All-trans-N-(4-hydroxyphenyl)retinamide</td>
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<td>Tamoxifen</td>
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<td>DFMO</td>
<td>Azoxy methane-induced colonic neoplasias</td>
<td>Synergistically reduces the number, size, and incidence of colon tumors</td>
<td>[51]</td>
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<td>Piroxicam</td>
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<tr>
<td>Dialyl sulfide</td>
<td>DMBA-induced mammary tumor</td>
<td>Combination regimen more effective than single-agent</td>
<td>[52]</td>
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<td>Se-methylselenocysteine</td>
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<td>Ellagic acid</td>
<td>DMBA-induced mammary tumor</td>
<td>Combination regimen more effective than single-agent</td>
<td>[53]</td>
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<tr>
<td>Selenomethionine</td>
<td>DMBA-induced mammary tumor</td>
<td>Combination regimen more effective than single-agent</td>
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<td>Tomato</td>
<td>Male Swiss albino mice</td>
<td>Combination regimen more effective than the single-agent in inhibiting DMBA-induced genotoxicity and oxidative stress</td>
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<td>Garlic</td>
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<td>S-Alllylcysteine</td>
<td>Gastric cancer</td>
<td>Modulatory effects on glutathione redox cycle antioxidants</td>
<td>[56]</td>
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<td>Lycopene</td>
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<tr>
<td>Beta-carotene</td>
<td>Oral cancer</td>
<td>Combination treatment results in regression of oral leukoplakia</td>
<td>[57]</td>
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<td>Vitamin E</td>
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