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Vol.3, No.2, 156-173 (2012)
doi:10.4236/jbpc.2012.32018

Journal of Biophysical Chemistry

Cancer chemoprevention through the induction of apoptosis by natural compounds

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Received 26 January 2012; revised 28 February 2012; accepted 15 March 2012

ABSTRACT

As cell and tissue homeostasis are mediated by the balance between proliferation and apoptosis, controlling this balance is important for cancer chemoprevention. Cancer chemoprevention can be achieved by the use of natural, synthetic or biologic compounds that reverse, suppress or prevent the development of epithelial malignancies. Natural compounds including flavonoids are able to reduce oxidative stress, which is the most likely mechanism mediating the protective effects against cancer development. In addition, *in vitro* and *in vivo* studies have suggested that flavonoids, such as (-)-epigallocatechin-3-gallete (EGCG), quercetin, and curcumin, act by induction of apoptosis. Several natural compounds inhibit cell proliferation and angiogenesis. Certain natural products have been shown to inhibit the activation of nuclear factor kappa B (NF-κB) and Akt signaling pathways, both of which are known to maintain a homeostatic balance between cell survival and apoptosis. Understanding the mechanism of these natural products will contribute to the development of more specific preventive strategies against cancer development. Here we focus on the ability of natural cancer chemopreventive agents to induce apoptosis, and attempt to provide evidence for the preventive and therapeutic effects of natural compounds, EGCG, quercetin, and curcumin, in a succinct manner highlighting κand Akt signaling pathways *in vivo*.

Keywords: Cancer Chemoprevention; Apoptosis; Natural Compounds

1. INTRODUCTION

Epidemiological studies have shown that diet consisting of a high rich in fruit and vegetable reduces the risk of several types of cancer [1]. Intake of fruit and vegetables has been successfully used in the prevention of chronic diseases associated with oxidative stress conditions, including cancer [2,3]. The cancer preventing properties of fruit and vegetables have been ascribed, at least in part, to their high content of polyphenols [4]. The majority of polyphenols present in food are flavonoids and phenolic acids that are an integral part of the human diet. Laboratory rodent studies have shown that polyphenols have cancer-preventing properties and considered to be potential chemopreventive agents [5-7]. They can influence important cellular and molecular mechanisms associated with multiple carcinogenic steps, such as expression of key proteins in signal transduction pathways (e.g., mitogen activated protein kinases (MAPKs) or activator protein (AP)-1), the transcription factor nuclear factor-kappa B (NF-κB) and its its downstream gene products, modulation of cell-cycle regulation and induction of apoptosis [7], which affect cell differentiation, proliferation and apoptosis, immune responses and metabolism of carcinogens [4].

Apoptosis is conceivably the most potent defense against cancer development since it is the mechanism used by metazoans to eliminate deleterious cells. Many chemopreventive agents have been shown to induce apoptosis in transformed cells both *in vitro* and *in vivo*. Induction of apoptosis appears to be associated with their effectiveness in modulating carcinogenic processes [8]. Since apoptosis provides a physiologic mechanism for eliminating initiated or abnormal cells, dietary factors affecting apoptosis can influence carcinogenesis. In fact, activation of apoptosis in pre-cancerous cells is one of the most important mechanisms of cancer chemoprevention by dietary factors [9].

In this review, we focus on the apoptosis-inducing properties of several natural compounds present in the human diet and describe their beneficial effects against cancer development. Understanding the mechanism of these natural products will contribute to the development of more specific preventive strategies against cancer.

2. CHEMOPREVENTIVE COMPOUNDS IN FOOD

An effective chemopreventive agent should preferably intervene early in the process of carcinogenesis to eliminate pre-malignant cells before they acquire malignant character. Many chemopreventive agents are able to block or delay the promotion and/or progression of pre-malignant or malignant cells by modulating cell proliferation and/or differentiation [8,10] and, therefore, should be chronically administered to individuals with a higher risk of cancer development. However, using this approach, even minor adverse effects would be unacceptable: obstacles to the use of chemoprevention for many cancers include long-term toxicity and the development of chemoresistance [8]. These issues can limit the feasibility and success of conventional forms of chemoprevention for many cancers. Alternative approaches involve the use of agents that eliminate cells expeditiously. Targeted delivery of apoptosis-inducing agents to tumor cells would also prevent the need for chronic exposure, limiting the risk of long term toxicity and/or the development of chemoresistance [8].

An ideal chemopreventive agent should be selective for damaged or transformed cells, display a significant bioavailability in the target lesion and have more than one mechanism of action. Moreover, it should be highly effective, easy to administer, and inexpensive. Dietary compounds are particularly attractive because of long-standing exposure to them by humans, their relative lack of toxicity, and encouraging indications from epidemiological studies [11]. Indeed, numerous dietary compounds and micronutrients are emerging that have considerable potential for hindering *in vivo* deleterious oxidative processes and inducing apoptosis in cancer cells. One potentially important drawback of dietary compounds is their possible low bioavailability after ingestion [12,13].

Food contains several promising chemopreventive compounds [14-16]. Plant polyphenols, ubiquitous in a diet rich in fruit and vegetables, are thought to be responsible for the cancer protective effects ascribed to this type of diet [4,5,13]. In fact, numerous phenolic compounds have been shown to display anti-proliferative and cytotoxic effects towards several tumor cells, presenting toxic effects that specifically target cancer cells rather than normal cells [17-20]. Dietary polyphenols are predominantly consumed through fruit and beverages (juice, wine, tea, coffee, chocolate and beer), with the exception of vegetables, cereals and olive derivatives that are mainly associated with the Mediterranean diet [21-23]. Their average daily intake has been reported to be approximately 1 g [13,24], which is much greater than the intake of all other classes of dietary anti-oxidants. For example, this value is approximately 10-times higher than vitamin C intake and 100-times greater than the intake of both vitamin E and carotenoids [24].

In addition to the anti-oxidant properties, polyphenols exert interesting biological abilities in animal experiments and *in vitro* systems. The compounds are able to trap and scavenge free radicals, decrease leukocyte immobilization, induce apoptosis, inhibit cell proliferation and angiogenesis, and exhibit phytoestrogenic activity [25-27]. Dietary polyphenols interfere with signal transduction pathways related to the carcinogenesis process, thereby acting as chemopreventive agents. They include the suppression of NF-κB and activating protein (AP-1) activation, inhibition of the mitogen-activated proteins (MAPKs)-, protein kinases- and growth-factor receptor-mediated pathways, cell cycle arrest, induction of apoptosis, anti-oxidant and anti-inflammatory effects, and suppression of angiogenesis [7].

The chemopreventive properties of a variety of compounds can be directly related to their pro-apoptotic properties, most probably exerted via the intrinsic (mitochondrial) apoptotic pathway [8,10] (**Table 1**).

Pro-apoptotic diet-derived compounds can conceivably protect against cancer by enhancing elimination of initiated, precancerous cells. Polyphenols have been shown to induce pro-apoptotic responses in malignant or pre-malignant cells. Many studies have described the pro-apoptotic properties of dietary polyphenols in a varietry of human cancer cell lines derived from colon, prostate, lung, breast cancers, and leukemia [28]. A major catechin, EGCG, among green tea catechins is the most potent polyphenolic compound with respect to inducing apoptosis and inhibiting proliferation in cancer cells: it induces apoptosis in and suppresses growth of human cancer cell lines, such as breast adenocarcinoma (MCF-7 and MDA-MB-231 cells) [29], oral squamous carcinoma [30], leukemia [31], breast [32], lung [33], prostate [34] and colon [35] cancers.

Several studies have indicated that phenolic concentrations leading to apoptosis are within the micromolar range. For example, quercetin reportedly induces apoptosis at concentrations ranging from 29 M to 150 M [36,37]. In general, the effective concentrations required for induction of apoptosis are higher than those leading to growth inhibition. However, some studies have reported the induction of apoptosis without inhibition of cell proliferation (e.g. EGCG effect on H661 lung cancer cells) [38]. Further increases in polyphenol concentration may cause necrosis of all cell lines tested [39].

Recent studies have proposed that different dietary phenolic compounds may act synergistically, together with established anti-cancer agents and act as enhancers of anti-carcer drugs [40,41] (**Table 2**). For example, the synergistic effects of EGCG and curcumin in pre-malignant and malignant human oral epithelial cells [42], resveratrol and quercetin in human pancreatic cancer cells [36], quercetin and cisplatin in human laryngeal Hep2 cells [43] and HeLa cells [44], and EGCG and sulindac or tamoxifen against human PC-9 lung cancer cells [45] have been described. This recognized synergy among dietary phenolics and conventional synthetic drugs provides an interesting approach to combination therapy as well as for the pre-treatment of neoplastic cells with polyphenolic agents. This strategy has been able, in some cases, to even overcome chemoresistance [46].

The anti-carcinogenic and cytotoxic activities of polyphenols are largely determined by structural parameters, as much as their anti-oxidant potencies [20,47-50]. Despite their close resemblance, their bioactivity varies considerably upon minor structural modifications, since such modifications often induce significant conformational changes [7,51,52]. This implies an important drawback in the understanding of the effects of polyphenols in human health, when considering the huge number of different compounds (>8000) [12].

3. APOPTOSIS

Although the term apoptosis was first used in 1972 [53] to describe a morphologically distinct form of cell death, several components of this concept have only recently been described in detail. The process of programmed cell death is characterized by distinct morphological characteristics and energy-dependent biochemical mechanisms. Apoptotic cells show morphological changes such as cell shrinkage, pyknosis and extensive plasma membrane blebbing leading to the formation of apoptotic bodies,

Table 1. Anticancer effect and mechanisms of natural compounds through NF-κB or PI3K/Akt pathway *in vivo*.

Compounds	Plant	Target organs	Carcinogens/cell line	Animal	Effects/molecular targets	Ref no.
(-)-Epigallocatechin gallete (EGCG)	Green tea	Intestine	None	$Apc^{Min+/-}$ mice	Attenuates aberrant nuclear β-catenin and activated Akt and ERK signaling	115
		Intestine	Azoxymethane	c57bl/ksj-*db/db* mice	Overcomes the activation of the IGF/IGF-IR axis, improving hyperlipidemia, hyperinsulinemia, and hyperleptinemia	116
		Liver	Diethylnitrosamine	c57bl/ksj-*db/db* mice	Inhibits IGF/IGF-1R axis, improving hyperinsulinemia, and attenuating chronic inflammation	117
		Tumor-associated endothelial cells and endothelial progenitor cells	A375SM (melanoma), xenograft	Nude mice	Selective anti-angiogenic effects, inhibits the phosphorylation of Akt in tumor-associated endothelial cells, MMP-9 mRNA expression level and vascular endothelial growth factor in endothelial progenitor cells	118
		Urinary bladder	UM-UC-3, xenograft	Nude mice	Down-regulates N-cadherin and inactivation of Akt signaling	119
Curcumin	*Curcuma longa*	Head and neck	CAL27 (squamous cell carcinoma), xenograft	Nude mice	Suppresses the activation of NF-κB without affecting the expression of pAKT	124
		Breast	MDA-MB23 (adenocarcinoma), xenograft	Nude mice	Inhibits survivin, NF-κB and its downstream effectors cyclin D1 and Bcl-2, and strongly up-regulated p21WAF1	125
		Head and neck	SCC40 (squamous cell carcinoma), xenograft	Nude mice	Blocks nicotine-induced activation of the AKT/MTOR pathway in HNSCC, which retards cell migration, reduced MMP-9 expression	128
			4-Nitroquinoline 1-oxide	CBA/CaJ mice		
		Colon	HCT-116 (adenocarcinoma), xenograft	Nude mice	Decreases COX-2, IL-8, and VEGF mRNA and protein expression, decreased AKT and extracellular signal-regulated kinase activation	133
		Brain	B16F10 (mouse melanoma), xenograft	c57bl mice	Suppresses Cyclin D1, p-NF-κB, BclXL, p-Akt, and VEGF	134
Quecetin	Vegetable and fruits	Salivary gland	ACC-2 and ACC-M (adenoid cystic carcinoma), xenograft	Nude mice	Down-regulates the PI3K/Akt/IKK-α/NF-κB signaling pathway	147

Table 2. Synergistic induction of apoptosis by combining natural compounds and anticancer drugs/radiation through NF-κB or PI3K/Akt pathway *in vivo*.

Compounds	Combination agent	Target organ	Carcinogen / cell line	Animal	Effects/molecular targets	Ref. no.
EGCG	Tamoxifen	Breast	Xenograft, MDA-MB-231 (estrogen receptor-negative breast cancer)	Nude mice	Decreases the tumor protein expression of mTOR and decreases of the expression of EGFR, NF-κB, b-Raf, p-MEK, S6K, 4EBP1, Akt, vascular EGFR-1 (VEGFR-1) and VEGF	148
Quercetin	Sulforaphane	Pancreas	Xenograft, MIA-PaCa2 (pancreatic cancer)	Nude mice	Affects the self-renewal potential, ALDH1activity, apoptosis induction, inhibition of angiogenesis, NF-κB and epithelial-mesenchymal transition processes	153
	trans-Pterostilbene (trans-3, 5-dimethoxy-4'-hydroxystilbene, t-PTER),FOLFOX6, radiation	Colo-rectum	Xenograft, HT-29 (colorectal cancer)	Nude mice	Over-expresses superoxide dismutase 2 and down-regulates of bcl-2 expression by inhibiting NF-κB activation	155
Curcumin	Radiation	Colo-rectum	Xenograft, HCT-116 (colorectal cancer)	Nude mice	Potentiates the anti-tumor effects of adiation therapy by suppressing NF-κB and NF-κB-regulated gene products, leading to inhibition of proliferation and angiogenesis	123
	EGCG	Breast	Xenograft, MDA-MB-231 (breast cancer)	Nude mice	Decreases the level of VEGFR-1 protein expression, decreases the tumor protein levels of EGFR and Akt	150
	Gemcitabine	Pancreas	xenograft, MIA PaCa2 (pancreas cancer)	Nude mice	Potentiates the anti-tumor effects of gemcitabine by suppressing proliferation, angiogenesis, NF-κB, and NF-κB-regulated gene products	151
			xenograft, Pa03C (pancreas cancer)	Nude mice	Reduces the activation of NF-κB as well as the expression of matrix metalloproteinase-9 and cyclin D1	152
	resveratrol	Prostate	None	Prostate-specific PTEN knockout mice	Negatively regulates of the activated p-Akt, cyclin D1, AR and mTOR	154
	Paclitaxel	Uterine cervix	Xenograft, HeLa cells (uterine cervical cancer), 3-methylcholanthrene	NOD-SCID mice	Augments the anti-tumor action of paclitaxel by down-regulating the activation and down-stream signaling of anti-apoptotic factors and survival signals such as NF-κB, Akt and mitogen-activated protein kinases	156
	Cisplatin	Head and neck	Xenograft, CAL27 (SCC)	Nude mice	Inhibites cytoplasmic and nuclear IKKβ, resulting in inhibition of NF-κB activity	157
	Dasatinib	Colo-rectum	None	$Apc^{Min+/-}$ mice	Suppresses EFGRs, IGF-R and c-Src signaling pathway, decreases the activation of down-stream signaling pathways, Akt and Erk(s), associated with decreased NF-κB activity	158

which are subsequently phagocytosed by macrophages, parenchymal or neoplastic cells. Apoptosis rarely causes an inflammatory response, since 1) apoptotic cells do not release their constituents into the surrounding interstitial tissue; 2) apoptotic cells are quickly phagocytosed by cells in the surrounding tissue, preventing secondary necrosis, and 3) the engulfing cells do not produce inflammatory cytokines [54].

Apoptosis can be initiated by receiving extracellular or intracellular signals including growth factor withdrawal, UV- or gamma-irradiation, chemotherapeutic agents, heat shock, nutrient deprivation, and by a family of transmembrane proteins called death receptors. These signals are transduced to adapter proteins and transmitted to specific cysteine proteases called "initiator caspases". At this point the cell is committed to undergo apoptosis, followed by "execution of cells" (mediated by sequential activetion of the so-called "executioner caspases"), systematic disintegration of cell structure and phagocytosis of the cell corpses [55].

Caspases (cysteine-dependent aspartate-specific proteases) are typically activated iduring the early stages of apoptosis. This family of proteins is synthesized as inactive zymogens but, once activated, can begin a proteolytic cascade, which results in the cleavage of key cellular components required for normal cellular function, including structural proteins in the cytoskeleton and nuclear proteins such as DNA repair enzymes. Caspases can also activate other degradative enzymes such as DNAases, which begin to cleave the DNA in the nucleus. To date, 14 different members of the caspase-family (**Table 3**) have been described in mammals [55-57]. The ten major pro-apoptotic caspases can be classified as initiators (caspase-2, -8, -9, -10), effectors or executioners (caspase-3, -6, -7) and inflammatory caspases (caspase-1, -4, -5) [55,58]. Other caspases that have been identified to date (caspase-11, -12, -13 and -14) are involved in specific apoptotic processes or expressed solely in specific types of tissue [55].

It is currently accepted that apoptosis can occur via two main pathways: the extrinsic or death receptor (**Figure 1**) and intrinsic or mitochondrial (**Figure 2**) pathways [59]. The extrinsic pathway initiated extracellularly via activation of cell surface receptors by specific molecules known as pro-apoptotic ligands including CD95L/FasL (receptor CD95/FasR), and Apo2L/TRAIL (receptors DR4, DR5) [53]. The Apo2 ligand has sparked growing interest within the oncology field due to its reported ability to selectively trigger cancer cell death [60,61]. Once activated, the death domains of these receptors, bind to the adaptor protein Fas-associated death domain (FADD), resulting in the assembly of the death-inducing signaling complex (DISC), and recruitment and assembly of the initiator caspase-8 and -10 [62]. Once activated, caspase-8 directly activates caspase-3 to initiate degradation of the cell. Active caspase-8 can also cleave Bid (pro-apoptotic) to tBid, which binds to the mitochondrial membrane to facilitate the release of cytochrome c and initiate the intrinsic pathways. This allows "cross-talk" between the two main pathways and amplifies the apoptotic signaling from death receptors.

The extrinsic and intrinsic pathways both end at the point of the execution phase. Execution caspases activate a cytoplasmic endonuclease, which degrades nuclear material, and proteases that degrade nuclear and cytoskeletal proteins. Such executioners including caspase-3 (considered to be the most important executioner caspase) can be activated by any of the initiator caspases (caspase-8, -9 or -10).

In addition to p53, the extrinsic and intrinsic pathways are also regulated by NF-κB, the ubiquitin proteosome system and the phosphatidylinositol-3-kinase (PI3K) pathway [63]. NF-κB is one of the most studied transcription factors in mammalian cells. Its function has been implicated in inflammation, cell proliferation, differentiation, apoptosis, cell survival and tumorigenesis [64]. NF-κB describes a ubiquitously expressed family of five proteins: p65 (RelA), p50, p52, c-Rel and RelB. Many stimuli produce survival responses in cells that are mediated by NF-κB. Indeed, overall reduction in NF-κB activity has been associated with an increased apoptotic index in many cell types [65]. Inactive NF-κB is bound to IKB

Table 3. Caspases[a] involved in apoptosis or programmed cell death.

Type	Name	Synonyms
Initiator or apical	Caspase-2	ICH1, Nedd2
	Caspase-8	FLICE, MACH1, MCH5, FADD-like Ice
	Caspase-9	MCH6, ICELAP6
	Caspase-10	FLICE2, MCH4
Effectors or executioner	Caspase -3	CPP32, YAMA
	Caspase -6	MCH2
	Caspase -7	MCH3, CMH, ICELAP3
Inflammatory	Caspase -1	ICE
	Caspase -4	ICH2, TX, ICErII
	Caspase -5	ICErIII, TY
	Caspase -11	-
	Caspase -12	-
	Caspase -13	ERICE
	Caspase -14	MICE

a: Caspase = cysteinyl aspartic acid-protease

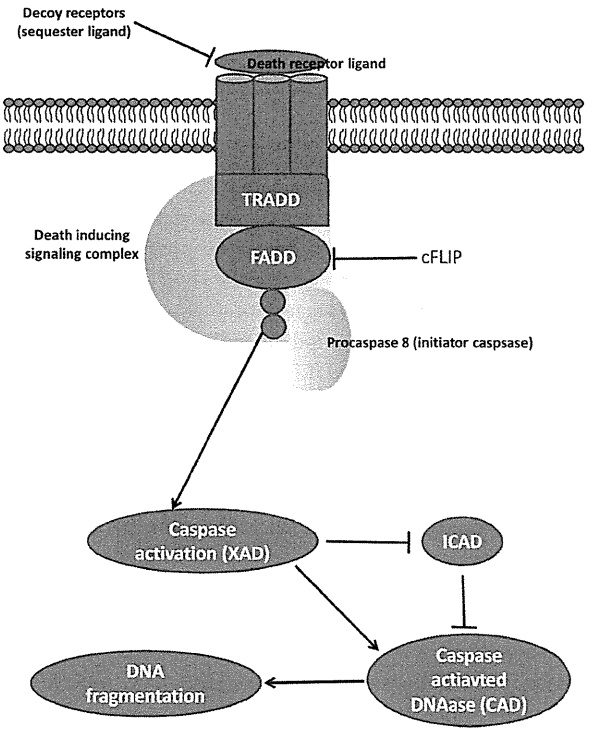

Figure 1. Extrinsic pathway.

