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Flavonol Regulation in Tumor Cells

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ABSTRACT

Flavonols comprise a group of flavonoid molecules that are widely distributes in fruits and vegetables. There is epidemiological data to suggest that consumption of flavonols can be accompanied by decreased cancer incidence. The anti-oxidant activity of flavonols may have an important role in preventing carcinogenesis. Therapeutic potential of flavonols is indicated by their growth inhibitory action accompanied by a decrease in several hallmarks of cancer such as resistance to apoptosis. Multiple mechanisms of action have been reported for the action of flavonols on cancer cells. Particular emphasis has been directed to inhibitory effects on several protein kinases and on the potential for prooxidant effects. The diversity of actions presents a problem in trying to elucidate primary and secondary effects but it may be a strength of the therapeutic potential of flavonols that it renders development of resistance more difficult for cancer cells. Cancer chemotherapy is usually characterized by the use of drug combinations. Some additive or synergistic combinations have been identified for flavonols and this is an area of ongoing investigation. As with other polyphenolic molecules there have been questions of cellular uptake and bioavailability. Several investigations have been and are being conducted to modify the structures of flavonols with the goal of increasing bioavailability. At present many investigators are sufficiently encouraged by past observations that they are responding to the challenge to optimize the dietary and therapeutic use of flavonols in cancer prevention and treatment. J. Cell. Biochem. 116: 1190–1194, 2015. © 2015 Wiley Periodicals, Inc.

KEY WORDS: FLAVONOLS; CANCER; CHEMOPREVENTION; CHEMOTHERAPY

Many plant-derived polyphenolic compounds have been identified that have potential cancer preventive or therapeutic effects. This includes a variety of flavonoid molecules and among the flavonoids there are several flavonols that are of interest. Flavonoids have a polyphenolic three-ring structures characterized as a phenyl benzopyrone. Flavonoids generally occur as glycosides in fruits and vegetables. The most widely distributed and the most intensively investigated of the flavonols is quercetin (Fig. 1). An anti-cancer role for flavonoids has been reviewed with varying emphasis on cancer prevention or therapy [Romagnolo and Selmin, 2012; Batra and Sharma, 2013; Ravishankar et al., 2013; Sak, 2014a].

FLAVONOLS AND CANCER PREVENTION

Epidemiological studies of the relationship between flavonoid intake and cancer continue to be conducted. Data from the Nurses' Health Study indicated that participants in the highest quintile of flavonol intake had modestly lower risk of ovarian cancer than did participants in the lowest quintile [Cassidy et al., 2014]. With respect to breast cancer, a meta-analysis of epidemiologic studies concluded that the intake of flavonols and flavones, but not other flavonoid subclasses or total flavonoids, is associated with a decreased risk especially among post-menopausal women [Hui et al., 2013]. In epidemiological studies on the relationship between dietary consumption of flavonoids and cancer incidence there has been a tendency for flavonol intake to show a stronger inverse association than for most flavonoid groups. For example in the NIH-AARP Diet and Health Study, thyroid cancer risk was inversely associated with dietary flavonols but positively associated with flavanones [Xiao et al., 2014]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study has had a particularly large population with wide ranges of intake for different dietary constituents. The data suggested an inverse association between dietary intake of flavonols and the risk of bladder cancer [Zamora-Ros et al., 2014].

ANTICANCER MECHANISMS

Inhibitory effects of flavonols have been noted on the various hallmarks of cancer such as increased rates of cell division, angiogenesis and resistance to apoptosis. At the molecular level,

Conflicts of interest: none.

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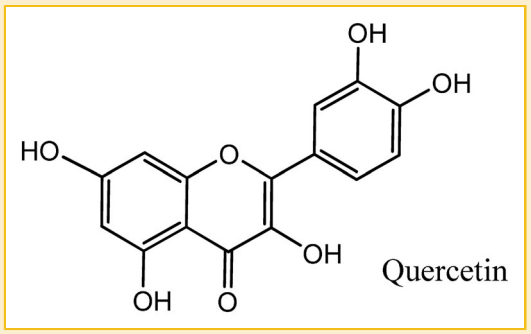

Fig. 1. Structure of quercetin, the most abundant flavonol.

the greatest attention has been directed to antioxidant and prooxidant activities and the inhibition of kinase enzymes. Inhibitory effects have been reported on both tyrosine kinases and on serine/threonine kinases. The latter includes cyclin dependent kinases regulating cell division. Furthermore, inhibition of phosphatidyl inositol 3-kinase has been observed. For the various types of kinase inhibition the flavonols are generally among the more active type of flavonoid molecules [Ravishankar et al., 2013]. In reviewing many of the anti-cancer mechanisms that have been proposed for flavonoids, Martinez-Perez et al. [2014] focused on those that would be most applicable to breast cancer. However, flavonols are notable for the diversity of cancer types that are affected. Even for the single flavonol, quercetin, there are many apparent sites for regulation and a wide spectrum of tumor types that can be affected [Sak, 2014b].

Inhibition of proliferation of colon cancer cells by flavonols has been attributed at least in part to a G2/M cell cycle block and a reduction in cyclin D1 expression [Gomez-Alonso et al., 2012]. Suppression of cancer cell growth by flavonols through inhibition of the PI3K-Akt-mTOR signal transduction pathway has also been reported [Jin et al., 2014; Li et al., 2014a]. From work with a chemically induced prostate cancer model in rats it was concluded that quercetin was effective in preventing prostate cancer progression by inhibiting the EGFR signaling pathway and by regulating cell adhesion molecules [Firdous et al., 2014]. In diffuse large B-cell lymphoma cells, quercetin was found to exert inhibitory activity against STAT3 signaling and down regulated the expression of survival genes [Li et al., 2014c]. Effects on other growth regulatory pathways have been noted. After earlier work on cells in culture [Li et al., 2011], studies in a rat bladder carcinogenesis model indicated that fisetin caused induction of p53 and down-regulation of NF-kappa B pathways [Li et al., 2014b].

Pro-apoptotic effects of flavonols have been studied with human colon cancer cells and multiple mechanisms seem possible. Working with HCT-15 cells, Kim et al. [2014] observed that myricetin increased the Bcl-2-associated X protein/B cell lymphoma 2 ratio, but not the cleavage of caspase-3 and -9. In addition they noted the release of apoptosis-inducing factor from mitochondria. Working with HT29 cells, Lee et al. [2014] concluded that kaempferol induced apoptosis via events associated with the activation of cell surface receptors and the mitochondrial pathway. In a study on the action of isorhamnetin on gastric cancer cells, it was concluded that the flavonol inhibited proliferation and invasion and induced apoptosis through binding to the peroxisome proliferator-activated receptor gamma resulting in increased expression of PPAR gamma [Ramachandran et al., 2012].

Flavonols are among a variety of phytochemicals that may have anticancer effects mediated through acting as topoisomerase II poisons [Ketron and Osheroff, 2014]. By disrupting the mechanism of topoisomerase II action these molecules can fragment the genome. Myricetin and quercetin are notably active in this respect while kaempferol and fisetin are less effective. A wide variety of anticancer agents have mutagenic and carcinogenic potential. Flavonols are not exceptional to this tendency. The time line for consideration and a cost–benefit analysis will be important in evaluating this risk. The question becomes one of whether the chance of curing cancer is worth the risk of causing the disease.

EXPERIMENTAL MODELS INCLUDING ANIMAL CELLS IN CULTURE

An advantage of animal models is that they offer a comparison of normal and neoplastic tissues. It is doubtful that there is such a thing as a normal cell in culture. Nevertheless, the simplicity of cultured cell models and the facility for high throughput screening have led to many investigations using such systems. One of the easiest ways to assess proliferation of cells in culture consists of measuring the reduction of tetrazolium salts. Cautionary notes have appeared in the literature over the years warning of the difficulty of using such assays when dealing with redox reagents such as polyphenolic molecules. Forbes et al. [2014] reviewed some of this earlier work and noted that, despite these observations, tetrazolium salt reduction assays had been used in more than a thousand studies on the action of flavonoids on cancer cells. The reduction of dye by flavonoids in the absence of cells is not restricted to tetrazolium salts and was also seen with Alomar Blue. Forbes et al. [2014] selected the trypan blue exclusion assay as a reliable alternative for measuring cell viability. There is a growing popularity of staining with sulforhodamine B as a technique for cytotoxicity screening [Keepers et al., 1991; Vichai and Kirtikara, 2006]. It remains to be established if flavonols present any interference with that procedure.

ANTIOXIDANT AND PROOXIDANT ACTION

The antioxidant actions of flavonols lend themselves to a defensive role in cancer chemoprevention. The structural requirements for antioxidant activity have been reviewed by Singh et al. [2014, Fig. 3]. These authors have also summarized the structural requirements for anti-cancer activity based on studies with many flavonoid derivatives [Singh et al., 2014, Fig. 7]. Features common to both antioxidant and anticancer activity included oxy-groups at C-3, C-5, C-3′ and C-4′. One might desire antioxidant activity for chemoprevention and prooxidant activity for cancer therapy. Making that distinction may prove difficult in practice and will be influenced by other factors such as the concentrations of metal ions. The antioxidant action of flavonols can arise from both the scavenging of reactive oxygen species and the chelation of metal ions [Chobot and Hadacek, 2011].

Maroziene et al. [2012] found a correlation between the cytotoxicity of flavonoids, including several flavonols, and the redox potential of the phenoxyl radical/phenol couple. The cytotoxicity could be decreased by antioxidants and could be modified by inhibitors of enzymes acting on flavonols. Inhibitors of cytochrome P450 decreased cytotoxicity while cytotoxicity was increased by inhibition of catechol-o-methyltransferase.

COMBINATION STUDIES

Combined treatment of cancer with flavonols together with other anticancer agents offers the possibility of synergistic action. In their excellent review of the pleiotropic effects of quercetin, Russo et al. [2014] noted that cotreatment with quercetin has been studied with cisplatin, carboxyamidotriazole, tiazofurin and cytosine arabinoside in a variety of cancer cell types.

There is evidence for additive effects of flavonols and histone deacetylase inhibitors in causing growth inhibition and increased differentiation of colon cancer cells as judged by the induction of alkaline phosphatase and dipeptidyl peptidase [Lea et al., 2010a,b; Lea, 2011]. For example, there were additive effects of valproate and quercetin 3-glucoside on growth inhibition and the activity of alkaline phosphatase in Caco-2 human colon cancer cells [Lea, 2011]. These observations could provide encouragement for clinical studies of combination treatment with flavonols and approved histone deacetylase inhibitors such as vorinostat.

Additive effects of quercetin with other naturally occurring polyphenolics have been reported. Quercetin was reported to increase the inhibition of proliferation in some cancer cell lines by epigallocatechin gallate [Wang et al., 2012]. In both in vivo and in vitro models, quercetin increased the bioavailability and decreased methylation of green tea polyphenols. Even combination of quercetin with other flavonols may merit attention because Jaramillo-Carmona et al. [2014] found combination of quercetin and kaempferol enhanced cytotoxicity in HCT-116 human colon cancer cells. Considering that there can be qualitative as well as quantitative differences between the action of different flavonols, there can be a rationale for examining combinations.

The anti-oxidant action of flavonols might be expected to counter the activity of some chemotherapeutic agents that exert cytotoxic effects through the formation of free radicals or reactive oxygen species. However, if there are tissue selective effects there may be reduced toxicity in normal tissues. Thus it has been observed that isorhamnetin can protect against doxorubicin-induced cardiotoxicity in vitro and in vivo [Sun et al., 2013].

Quercetin was observed to enhance retuximab-induced growth inhibition and apoptosis in diffuse large B-cell lymphoma cell lines [Li et al., 2014c].

The inhibition of multiple drug resistance by quercetin suggests that flavones may be useful agents in combination chemotherapy against cancer with a number of current drugs [Batra and Sharma, 2013]. Multiple drug resistance can arise from over-expression of ATP-binding cassette proteins. Yuan et al. [2012] synthesized a series of methylated quercetin derivatives and they identified compounds with enhanced inhibitory action on P-glycoprotein and breast cancer resistance protein. Such compounds have potential use in combination with established cancer chemotherapeutic agents.

ABSORPTION AND BIOAVAILABILITY

It is often stated that flavonol glycosides require hydrolysis to form the aglycone before uptake by intestinal cells. However, quercetin-3-glucoside can be transferred by a sodium–glucose transporter SGLT1 [Olthof et al., 2000; Wolffram et al., 2002]. Enhanced uptake relative to quercetin may be a factor in the greater inhibition of colon cancer cell proliferation by quercetin-3-glucoside observed by Lea et al. [2010a]. α-Oligoglucosylation of quercetin glucosides has been shown to enhance bioavailability in humans [Murota et al., 2010]. On the other hand, some investigators have described circumstances where quercetin glucosides appear to be completely hydrolyzed before absorption [Walle et al., 2000]; so this is a topic that merits further investigation. This view is reinforced by the lack of an antiproliferative effect by quercetin 3-glucoside on three cancer cell lines reported by Delgado et al. [2014]. Quercetin glycosides are widely distributed. When considering dietary sources, onions seem a good source as regards quantity and bioavailability [Lee and Mitchell, 2012]. In view of the low bioavailability arising from low aqueous solubility and intestinal absorption, one of the approaches that is being explored to improve flavonol bioavailabilty is delivery in a nanoparticle form [Men et al., 2014; Tran et al., 2014].

Flavonols are subject to modification by phase II drug metabolizing enzymes most notably to form glucuronides, sulfates and methylated derivatives [Rodriguez-Mateos et al., 2014]. The literature is not always consistent but some of these metabolites may retain regulatory activities either directly or after being converted back to the original flavonol. Characterization of these effects presents an additional degree of complexity in assessing the regulatory role of flavonols.

NEW DERIVATIVES

Poor uptake of flavonols and metabolism to inactive compounds present a challenge for the use of flavonols as cancer preventive or therapeutic agents. Such considerations have led many investigators to synthesize structural analogs that might possess superior pharmacodynamic properties.

Dias et al. [2013] prepared halogenated derivatives of flavonols and found that antiproliferative activity against HCT116 human colon cancer cells was greatest with 4′-substituted derivatives and the activity was greater than that of quercetin, used as a positive control. Antiprolifereative activity increased going from F to Cl to Br. Antiproliferative activity against human leukemic cells was also increased when a flavonol was substituted with Br at the 4′ position [Burmistrova et al., 2014]. Forbes et al. [2014] found that increasing the hydrophobicity and lipophilicity of a flavonol significantly lowered the effective concentration of several analogs (4′-iodo, 3′-phenyl, and 4′-phenyl flavonol) into the desired low micromolar range thus enhancing their therapeutic potential.

Synthesis of modified flavonols has permitted structure-activity relationships to be identified. Work with prostate cancer cells

indicated that the 3′, 4′, and 5′ arrangement on the B ring of either hydroxy or methoxy residues is important for growth arrest and that methoxy analogs may be superior to their hydroxy counterparts [Britton et al., 2012]. In this study the inclusion of fluorine in the A ring failed to significantly alter the growth inhibition potency for most compounds. However, two compounds were found to be exceptions in that their growth-inhibitory action was lower than that of their non-fluorinated counterparts. Of the naturally occurring flavonols, myricetin is notable for having hydroxyl groups at the 3′, 4′, and 5′ positions and tends to have lower IC_{50} values for growth inhibition than other naturally occurring flavonols such as quercetin, kaempferol, and fisetin that do not have hydroxyls at all three of those positions.

The replacement of OH groups of flavones with O-methylated derivatives has been suggested to reduce the degree of metabolic removal of flavones while retaining their anti-proliferative activity. Shi et al. [2014] synthesized O-alkylated derivatives of quercetin and screened for anti-proliferative activity against 16 mainly lung cancer cell lines. They found that anticancer activity was enhanced when the OH groups at C-3′ and C-4′ were replaced with methoxy moieties. Longer alkyl chains were also examined and they found that 3-propyloxyquercetin was more potent than the 3-methoxyquercetin and was the most inhibitory compound of those investigated.

CONCLUSIONS

In view of the difficulty of documenting safety in lifetime exposure, chemoprevention of cancer in the near future is only likely to occur with flavonols that are naturally occurring. Dietary guidelines will be aided by further characterization of the influence of individual flavonols and their various glycosides. Determination of the influence of flavonol combinations is an immense task but may prove worthwhile in view of evidence for complementary effects of different flavonols.

Work should continue on chemical modification of flavonols that can increase bioavailability and make for more effective chemotherapeutic agents. A beginning has been made in studying combinations with other chemotherapeutic agents. In screening the action of new compounds it is to be hoped that there will be less use of assays that are affected by redox active molecules such as flavonols. Past work suggests that flavonols with their multiple cellular targets offer the prospect of identifying new drugs that will challenge the ability of cancer cells to develop resistance.

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