

Review

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Volume 2 : Issue 1

Article Ref. #: 1000CSMMOJ2105

Article History

Received: January 21st, 2015

Accepted: March 3rd, 2015

Published: March 4th, 2015

Citation

McCarty MF. Flavones and flavonols may have clinical potential as CK2 inhibitors in cancer therapy. *Cancer Stud Mol Med Open J*. 2015; 2(1): 39-51. doi: [10.17140/CSMMOJ-2-105](http://dx.doi.org/10.17140/CSMMOJ-2-105)

Flavones and Flavonols may have Clinical Potential as CK2 Inhibitors in Cancer Therapy

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ABSTRACT

The serine-threonine kinase CK2, which targets over 300 cellular proteins, is over expressed in all cancers, presumably reflecting its ability to promote proliferation, spread, and survival through a wide range of complementary mechanisms. *Via* an activating phosphorylation of Cdc373, a co-chaperone which partners with Hsp90, CK2 prolongs the half-life of protein kinases that promote proliferation and survival in many cancers, including Akt, Src, EGFR, Raf-1, and several cyclin-dependent kinases. CK2 works in other ways to boost the activity of signaling pathways that promote cancer aggressiveness and chemoresistance, including those driven by Akt, NF-kappaB, hypoxia-inducible factor-1, beta-catenin, STAT3, hedgehog, Notch1, and the androgen receptor; it also promotes the epidermal-mesenchymal transition and aids efficiency of DNA repair. Several potent and relatively specific inhibitors of CK2 are now being evaluated as potential cancer drugs; CX-4945 has shown impressive activity in cell culture studies and xenograft models, and is now entering clinical trials. Moreover, it has long been recognized that the natural flavone apigenin can inhibit CK2, with a K_i near 1 micromolar; more recent work indicates that a range of flavones and flavonols, characterized by a planar structure and hydroxylations at the 7 and 4' positions - including apigenin, luteolin, keampferol, fisetin, quercetin, and myricetin - can inhibit CK2 with K_i s in the sub-micromolar range. This finding is particularly intriguing in light of the numerous studies demonstrating that *each* of these agents can inhibit the growth of cancer cells lines *in vitro* and of human xenografts in nude mice. These studies attribute the cancer-retardant efficacy of flavones/flavonols to impacts on a bewildering array of cellular targets, including those whose activities are boosted by CK2; it is reasonable to suspect that, at least in physiologically achievable concentrations, these agents may be achieving these effects primarily *via* CK2 inhibition. Inefficient absorption and rapid conjugation limit the bioefficacy of orally administered flavonoids; however, the increased extracellular beta-glucuronidase of many tumors may give tumors privileged access to glucuronidated flavonoids, and nanopartical technology can improve the bioavailability of these agents. Enzymatically modified isoquercitrin has particular promise as a delivery vehicle for quercetin. Hence, it may be worthwhile to explore the clinical potential of flavones/flavonols as CK2 inhibitors for cancer therapy.

KEYWORDS: Cancer; CK2; CX-4945; Hsp90; Flavones; Flavonols; Xenografts; Beta-glucuronidase; HDA6; Sulforaphane.

CK2 IS OVER-EXPRESSED AND UP-REGULATES PROLIFERATION, SPREAD, AND SURVIVAL IN CANCER

CK2, a serine-threonine kinase once known as casein kinase 2, is a ubiquitously expressed tetramer comprised of two catalytic subunits - α and/or α' - and two regulatory β subunits that direct it to specific targets. CK2 is capable of phosphorylating a huge range of cellular

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proteins; over 300 physiological targets have been documented to date (though ironically casein is not one of them!).¹ Its level of expression and its sub-cellular localization determine its activity, as post-translational modifications or allosteric interactions are thought to have little impact in that regard; moreover, no gain-of-function mutants of this kinase are known.

Virtually all cancer cell lines studied to date overexpress CK2 protein, relative to its expression in normal tissues of origin; moreover, they tend to route a higher proportion of this protein to the cell nucleus.² This is not likely to be accidental, as high CK2 activity works in a bewildering number of complementary ways to promote cellular proliferation and spread, while suppressing apoptosis. Hence, cancer cells which overexpress CK2 will tend to be selected for.

CK2 MODULATES A PLETHORA OF SIGNALING PATHWAYS

One of CK2's most intriguing and ramified effects is to phosphorylate, and thereby activate, the co-chaperone Cdc37.^{3,4} Activated Cdc37 interacts with Hsp90 to provide chaperoning activity for a broad range of protein kinases, many of which play a role in promoting cell proliferation and survival. These include Akt, Src, EGFR, PDGFR, Raf-1, IKK, RIP1, Cdc2, Cdk2, Cdk4, and Cdk6. This chaperoning activity tends to slow the proteolytic degradation of these kinases, prolonging their effective half-lives; this activity is particularly crucial for the survival of certain mutant constitutively active forms of these kinases often found in cancers. To date, CK2 is the only upstream kinase known to confer activation on Cdc37 - for which reason assessment of Cdc37 phosphorylation at Ser13 has been proposed as a strategy for determining CK2 activity *in vivo*.⁵

But CK2 works in a number of additional ways to boost the activity of signaling pathways that make cancer more aggressive and harder to kill:

Akt

While CK2 boosts Akt expression *via* Hsp90-cdc37-mediated stabilization, it can also work in various complementary ways to increase the phosphorylation and activation of this key kinase, which promotes cellular proliferation while acting in a number of ways to inhibit apoptosis. CK2 phosphorylates Akt directly at Ser129; this up-regulates the activation of Akt mediated by PDK1 and mTORC2, and facilitates its association with Hsp90.^{6,7} And CK2 inhibits phosphatase activities that target Akt; it phosphorylates and thereby reduces the activity of the crucial cancer suppressor PTEN, and also promotes proteasomal degradation of PML, a protein which is an obligate component of a nuclear complex that dephosphorylates Akt within the nucleus.⁸⁻¹¹ CK2 also has the potential to work upstream from Akt, enhancing its activation by up-regulating certain tyrosine kinase signaling pathways.

NF-kappaB

Numerous studies show that CK2 inhibition suppresses NF-kappaB activity in cancer cell lines, whereas overexpression of this kinase boosts NF-kappaB activity.¹²⁻²⁷ CK2 promotes degradation of IkappaB; this can reflect an activating phosphorylation of IKKbeta, as well as a direct phosphorylation of IkappaB that renders it more sensitive to proteolytic cleavage by calpain.^{13,14,19,24} CK2 activity also has been reported to somehow boost the expression of IKK-i/IKKepsilon, an alternative IkappaB kinase complex capable of promoting IkappaB degradation.¹⁷ And the transcriptional activity of p65 is enhanced by a phosphorylation of Ser529 conferred by CK2.²⁰

Hypoxia-inducible factor-1 (HIF-1)

CK2 enhances the transcriptional activity of HIF-1, even though it doesn't increase the protein expression or nuclear binding of this factor.²⁸⁻³⁰ Some evidence suggests that this reflects a reduction of p53 levels; nuclear p53 somehow antagonizes the transcriptional activity of HIF-1.²⁹ CK2's impact on p53 level, in turn, may reflect phosphorylations of MDM2 that enhance its ability to promote proteasomal degradation of p53.

Beta-Catenin

Many studies show that CK2 inhibition decreases Wnt-beta-catenin signaling.^{22,31-39} Down-regulation of Akt, which stabilizes beta-catenin through inhibition of glycogen synthase kinase-3 and also *via* a direct phosphorylation on Ser552, evidently can contribute to this effect.^{37,38} However, CK2 also phosphorylates beta-catenin directly on Thr393, an effect which likewise prolongs the half-life and promotes the transcriptional activity of this factor.^{32,33}

STAT3

There are several reports that inhibition of CK2 suppresses STAT3 phosphorylation and activation in cancer cell lines.⁴⁰⁻⁴² The basis of this effect is not yet clear. In some cell lines, suppression of IL-6 expression may contribute to this effect.

Hedgehog

In human lung cancer cells, CK2 activity has been shown to boost the mRNA and protein expression of Gli1, and to enhance the half-life and transcriptional activity of this key mediator of hedgehog signaling.⁴³ CK2 can directly phosphorylate Gli1, and it has been suggested that this may be responsible for the positive impact of CK2 on hedgehog signaling.

Notch1

In human lung cancer cell lines expressing Notch1, in-

hibition of CK2 activity suppresses Notch1-driven transcription, whereas forced overexpression of CK2 has the opposite effect.⁴⁴ This may reflect the fact that CK2 activity increases the half-life of Notch1 protein.

Androgen Receptor

CK2 inhibitors suppress androgen receptor-mediated transcription in prostate cancer cell lines, at least in part by blocking androgen-induced nuclear translocation of the receptor.⁴⁵⁻⁴⁷ The direct target of CK2 in this effect has not been identified.

DNA Repair

CK2-mediated phosphorylations of XRCC1 and MDC1, nuclear proteins which play a key role in the repair of DNA single-strand and double-strand breaks, respectively, are required for their proper activity.⁴⁸⁻⁵³ Hence, inhibition of CK2 can boost the killing activity of DNA-damaging cytotoxins not only by up-regulating mechanisms of apoptosis, but also by impeding the efficiency of DNA repair.

Epidermal-Mesenchymal Transition

Studies with CK2 inhibitors demonstrate that CK2 activity can promote the epidermal-mesenchymal transition necessary for invasive behavior by boosting expression of vimentin, snail, and smad2/3, while suppressing that of E-cadherin.⁵⁴⁻⁵⁸ For some reason this effect is most prominent in cancer cells which overexpress CK2 alpha catalytic subunits, relative to CK2 beta regulatory subunits.^{59,60}

NEW DRUGS FOR INHIBITION OF CK2 - CX-4945

These considerations make it abundantly clear that well tolerated and effective pharmaceutical inhibitors of CK2 may have a bright future in oncology - both as agents for slowing cancer growth and spread, and as adjuvants to chemo- or radiotherapy. Some pharmaceutical companies are moving aggressively to evaluate the potential of this approach, and the highly potent and orally active CK2 inhibitor CX-4945 has shown impressive anti-cancer activity in mouse xenograft models, in doses which the animals appear to tolerate well.^{61,62} Moreover, in doses that don't greatly retard tumor growth, CX-4945 considerably amplifies response of an ovarian cancer xenograft to gemcitabine and cisplatin - though the somewhat greater weight loss in the mice receiving combination therapy suggests that toxicity might also be increased to a degree.⁶³ This agent is now entering clinical trials, and its progress should be followed with the greatest interest.

FLAVONES/FLAVONOLS AS NATURAL INHIBITORS OF CK2

However, there are other known inhibitors of CK2, one being the dietary flavone apigenin. Indeed, long before the development of the more potent pharmaceutical inhibitors of CK2,

this agent was employed as a relatively specific inhibitor of CK2 in cell culture studies, with a K_i near 1 μM .⁶⁴ There are indeed a number of studies, both in cancer cell culture and in mouse xenograft models, showing that apigenin can exert cancer-retardant and chemo-potentiating effects. In xenograft models, apigenin has shown activity whether administered parenterally or orally, alone or as an adjuvant to chemotherapy.⁶⁵⁻⁸¹ Intriguingly, many of the effects of apigenin on signaling pathways reported in cell culture or xenograft studies are parallel to those of CK2 inhibition, including down-regulated activity of Akt,^{4,74,82-86} HIF-1,^{65,67,87-91} NF-kappaB,^{4,17,21,28,92-95} STAT3,^{4,94,96} beta-catenin,^{97,98} Gli1,⁹⁹ AR,^{100,101} and Cdc37,⁴ and up-regulated p53.^{94,102-109} Indeed, Zhao and colleagues have recently proposed that inhibition of CK2 is a key mediator of apigenin's anti-cancer activity in multiple myeloma cells.⁴ A survey of the burgeoning cancer research literature involving apigenin - 476 citations on Pubmed at present - reveals apigenin can influence a truly dizzying array of molecular targets in cancer cells; it is reasonable to suspect that, rather than directly inhibiting dozens of separate targets, it must be influencing one or more signaling factors that have a remarkably broad impact on the molecular biology of cancer cells. CK2 may be the crucial target in this regard. However, none of the studies in which apigenin has been administered in cancer-retardant doses to xenograft-bearing mice have assessed the impact of apigenin on tumor CK2 activity. A study assessing this - perhaps by measuring Ser13 phosphorylation of Cdc37 in tumors - would be worthwhile; and it would also be intriguing to see whether apigenin administration has any significant additional impact on cancer growth in animals that are already receiving potent doses of CX-4945; if CK2 is apigenin's key target, little additional benefit might be seen.

Although apigenin is considered the prototype flavone inhibitor of CK2, recent studies show that other naturally-occurring flavones and flavonols have similar or slightly more potent inhibitory activity. Working *in vitro* with human recombinant CK2, Lolli and colleagues have recently reported that apigenin, luteolin, kaempferol, fisetin, quercetin, and myricetin can inhibit CK2 with K_i s of 0.8, 0.5, 0.4, 0.35, 0.55, and 0.92 μM , respectively.¹¹⁰ This inhibition is competitive with respect to the phosphodonor substrate ATP. All effective compounds are planar and are hydroxylated at the 7 and 4' positions. Hydroxylations at 5, 3, and 3' positions do not greatly add to or detract from activity.

These findings may help to explain the curious fact that *every one* of these flavones or flavonols has been reported to exert anti-cancer effects, both in cancer cell cultures, and in xenografted mice. Here are citations for the xenograft studies: apigenin,⁶⁵⁻⁸¹ luteolin,¹¹¹⁻¹²² kaempferol,¹²³ fisetin,¹²⁴⁻¹²⁶ quercetin,¹²⁷⁻¹⁴⁵ myricetin.¹⁴⁶ There are at least 53 published studies in which flavones or flavonols have decreased the growth of human xenografts in nude mice.

It seems likely that, ultimately, a drug such as CX-4945 will offer the most convenient and effective way to address the CK2 activity of clinical cancer. However, this or comparable

drugs will not be available for several years, and when available will initially only be approved for use in a limited number of cancers - and will doubtless be staggeringly expensive to use for off-label purposes. For this reason, it would be prudent to give serious attention to the possibility that apigenin or related flavones/flavonols might be clinically useful for suppressing CK2 activity in some sufficiently high dosage schedule. This might be assessed by pharmacokinetic studies in which a marker for CK2 activity, such as phosphorylation of Cdc37 - or Thr145 phosphorylation of p21, employed as a marker in studies with CX-4549⁶¹ - is determined in leukocytes or some other accessible cell type. The efficacy of a given agent will presumably reflect its absorbability, the rapidity with which it is conjugated once absorbed (glucuronidation or sulfation), and its capacity to pass through cell walls. Pharmaceutical innovations which optimize absorbability might make this approach more feasible.¹⁴¹ With respect to quercetin, the approved food additive enzymatically-modified isoquercitrin (EMIQ), unlike quercetin, is highly soluble, but is metabolized to yield free quercetin at the intestinal brush border; a human pharmacokinetic study found that when equimolar amounts of quercetin and EMIQ were administered orally, the plasma levels of quercetin achieved were twenty-fold higher with EMIQ.¹⁴⁷⁻¹⁵¹ This agent apparently has not yet been tested in rodent tumor models.

Rapid conjugation of absorbed flavonoids limits their capacity to exert intracellular effects.¹⁵² It is therefore fortunate that some tumors may have privileged access to flavone/flavonol glucuronide conjugates, owing to the fact that extracellular beta-glucuronidase activity tends to be elevated in tumors, particularly in their hypoxic/necrotic regions.^{153,154} Infiltrating immune cells may be the chief source of this activity. Moreover, the tendency of extracellular pH to be acidic in such regions can be expected to amplify their beta-glucuronidase activity.¹⁵⁵⁻¹⁵⁷ Many investigators have proposed or presented evidence that glucuronide-masked anti-cancer agents - including flavonoids - can be selectively activated within tumors.^{154,157-165} Hence, the rapid glucuronidation of flavones and flavonols may not be an insuperable obstacle to the capacity of these compounds to inhibit CK2 *in vivo*. Perhaps this mechanism contributes to the demonstrable efficacy of flavones/flavonols in mouse xenograft studies; co-administration of a beta-glucuronidase inhibitor might clarify this. A corollary of this consideration, however, is that measurement of CK2 activity in healthy tissues following oral administration of flavones/flavonols may underestimate the capacity of these agents to inhibit CK2 within tumors.

JOINT INHIBITION OF HDAC6 AND CK2 TO TARGET HSP90 FUNCTION

In light of the fact that inhibition of the chaperoning function of Hsp90-Cdc37 plays a key role in the cancer-retardant efficacy of CK2 inhibitors, it is pertinent to note that acetylation of Hsp90 notably reduces its chaperoning activity.¹⁶⁶⁻¹⁷⁰ The cytosolic deacetylase HDAC6 targets these acetylations of Hsp90,

restoring its activity. Hence, type II histone deacetylase inhibitors have the potential to complement the impact of CK2 inhibitors on the chaperoning of many pro-oncogenic kinases. Moreover, it has recently emerged that sulforaphane can function as an inhibitor of HDAC6 within cells;¹⁷¹ this phenomenon may be clinically relevant, as acute ingestion of 68 g of broccoli sprouts has been reported to suppress global histone deacetylase activity in peripheral blood mononuclear cells.¹⁶⁶ This finding may be of particular interest, in light of the fact that HDAC6, rather like CK2, works in multifarious ways to sustain malignant cellular behavior, and is emerging as a key target for cancer therapy.^{172,173} It would be of interest to determine whether flavones/flavonols and sulforaphane might complement each other's efficacy in integrative cancer therapy.

A POTENTIAL COUNTERVAILING EFFECT - NRF2 ACTIVATION

Although the great majority of reports examining quercetin's impact on cancer, *in vitro* or *in vivo*, with or without concurrent chemotherapy, conclude that quercetin has cancer suppressive activity, one recent study found that, in low micromolar concentrations, quercetin protected a human ovarian cancer cell line from a range of cytotoxic drugs; concurrent quercetin administration decreased the cancer-retardant efficacy of cisplatin in a xenograft model. This effect was traced to quercetin's ability to activate nrf2 and thereby increase the expression of antioxidant enzymes, glutathione, and glutathione-dependent detoxicant enzymes. The ability of phase 2 induction *via* nrf2 activation to promote chemoresistance in some cancers has been demonstrated. Hence, while a number of studies describe a chemosensitizing effect for quercetin in cancer models^{135,136,174-176} including a report that low concentrations of quercetin sensitize some ovarian cancer cell lines to cisplatin - the possibility remains that quercetin (and presumably other phase 2-inductive flavonols) may promote chemoresistance in some cancers. (The "flip side" of this observation is that quercetin has potential for protecting healthy tissues from chemotherapy drugs, as demonstrated in mice.¹⁷⁷⁻¹⁸¹ These considerations, in any case, do not speak to quercetin's potential utility as an adjuvant for slowing cancer growth.

EVALUATING THE HYPOTHESIS

As noted above, EMIQ may be the most appropriate agent to study in pre-clinical and clinical trials, owing to its ability to promote absorption of quercetin. In cancer xenograft models, the impact of EMIQ administration on Ser13 phosphorylation of Cdc37 in the tumor could be determined to assess this agent's ability to suppress CK2 activity *in vivo*. Positive results in such studies could then encourage clinical cancer trials with EMIQ. Rather than expecting objective response, it would be more realistic to hope that flavonol administration will slow the growth and spread of cancer, as it does in rodent models. A placebo-controlled design might thus be required to establish clinical efficacy. The extent of Ser13 phosphorylation of Cdc37 in

leukocytes could be measured as a surrogate for CK2 inhibition in the cancer - bearing in mind, however, that quercetin metabolites might have greater activity within inflamed tumor tissue.

In regard to toxicity considerations, it should be noted that knockout of the alpha subunits of CK2 results in embryonic lethality.^{182,183} However, flavonols *in vivo* would achieve at best only partial inhibition of CK2. In rodent studies with CX-4945, cancer control is noted with doses that are not overtly toxic to the animals. Phase I clinical trials with this agent have not yet been reported, so it is not clear what the dose-limiting toxicities of CK2 inhibitors will be. Flavonols are of course prominent phytochemicals in natural diets. The toxicological evaluation of EMIQ in rodents has been described by Valentova and colleagues;¹⁴⁷ when fed at up to 2.5% of diet to rats for 13 weeks, yellowish discoloration of bones and urine was noted, and weight gain was slightly decreased at the highest doses. At 5% of diet, isoquercetin feeding to male rats was associated with significant declines in body weight, hemoglobin, triglycerides, bilirubin, and phosphorus, with small increases in the relative weights of the lungs and testes.¹⁸⁴ EMIQ has been accorded GRAS status for use as a food additive. These considerations suggest that it would be reasonably safe to test EMIQ in doses of several grams daily in Phase I cancer trials.

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