Quercetin Potentiates UVB-Induced c-Fos Expression: Implications for Its Use as a Chemopreventive Agent

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Abstract

Quercetin (Qu) is currently being investigated as a chemopreventive agent for several cancers, including nonmelanoma skin cancer induced by UV light. We previously reported that Qu degradation has important consequences on signaling and cell biology. In this study, we report that Qu induces c-Fos mRNA and protein expression through activation of p38 and cAMP-responsive element binding protein (CREB), and Qu potentiates UVB-induced c-Fos expression. Inclusion of ascorbic acid (AA) in cell culture medium stabilizes Qu and completely prevents both Qu- and UVB-induced p38 and CREB activation, leading to a blockade of c-fos gene expression through reduced CREB/cAMP-responsive element binding. AA stabilizes c-Fos mRNA, increasing steady-state levels even when c-fos gene expression is suppressed, but this has no effect on c-Fos protein levels in either mock- or UVB-irradiated cells. We report that Qu blocks mammalian target of rapamycin signaling and inhibits c-Fos protein expression directly through this mechanism because cotreatment with Qu and AA resulted in the complete suppression of UVB-induced c-Fos protein expression even in the presence of significantly increased mRNA levels. We further confirmed that this was not due to increased protein turnover because inhibition of proteasome activity with MG-132 did not raise c-Fos protein levels in Qu-AA-treated cells. Together, these data indicate that although Qu has been reported to have some beneficial properties as a chemopreventive agent, it is also capable of inducing c-fos expression, a cellular event important for the promotion phase of tumor development, if it is not stabilized. Cancer Prev Res; 3(7); 876-84. ©2010 AACR.

Introduction

Currently, there is a major focus on the use of natural products as chemopreventive agents for nonmelanoma skin cancer (NMSC) and other types of cancer because of their antioxidant and anti-inflammatory properties in addition to their potential to inhibit numerous signaling pathways involved in cell proliferation, transformation, migration, and survival (1–3). Flavonoids represent one of the most actively studied classes of molecules for their potential to prevent cancer. However, the cellular effects of these compounds are often very complicated due to the general lack of specificity for any particular intracellular target, and the end effect on cell fate is often the combination of multiple cellular activities. In the current study, we investigated some of the cellular effects of quercetin (Qu; 3,3′,4′,5,7-pentahydroxyflavone) on UVB-induced signaling in human keratinocytes. Our original interest in Qu was with regard to the compound’s known phosphatidylinositol 3-kinase (PI3-K) inhibitory activity, and we initially reported that a concentration of 50 μmol/L was required for consistent suppression of UVB-induced PI3-K activation in HaCaT human keratinocytes due to cell-independent rapid degradation of Qu in aqueous cell culture medium (4). At this concentration, we showed that Qu actually displays pro-oxidant activity, an effect that could be inhibited by including 1 mmol/L ascorbic acid (AA) in the growth medium to stabilize Qu. However, this reduced the proapoptotic effect of Qu, leading to the interpretation that the generation of reactive species during Qu degradation, could be a beneficial action through increased killing of initiated cells. On the contrary, our current findings suggest that there are significant cellular consequences to Qu degradation that could lead to elevated promotion of the initiated cells that survive Qu treatment, which raises questions about the chemopreventive efficacy in UV-induced skin cancer.

Chronic exposure to UV light is the primary cause of NMSC, the most common type of cancer in the United States (5). UVB (280-320 nm) comprises between 1% and 10% of the total UV light that reaches the earth’s surface. UVB is known to act as a complete carcinogen, and our laboratory and others have shown that UVB-induced activation of the transcription factor activator protein-1 (AP-1) plays a functional role in UVB-induced tumor promotion (6). AP-1 stimulates cell proliferation through regulation...
of cell cycle protein expression (reviewed in ref. 7) and also controls cellular transformation because inhibition of AP-1 has been shown to block the effect of tumor promoting agents (6, 8–12).

The AP-1 transcription factor complex is composed of dimers of Jun and Fos protein family members. The exact constituents depend on the stimulus or the physiologic condition, and the different dimer pairs can activate different sets of genes (reviewed in ref. 13). In HaCaT keratinocytes, the UVB-activated AP-1 complex is composed of c-Fos and JunD (14). Although JunD expression is unaffected by UVB irradiation, c-Fos levels have been shown to increase with UVB treatment in a manner that correlates with AP-1 activation, suggesting that alterations in c-Fos protein levels are a major driving factor behind the level of AP-1 activity. In addition, c-Fos expression is required for the malignant progression of skin tumors (15). Increased cellular oxidative stress can lead to p38 activation and ultimately c-fos gene expression by stimulating cyclic AMP response element (CRE) binding (CREB) protein binding to the c-fos promoter (16–18). In the current study, we worked to determine the effect of Qu treatment on c-Fos protein levels in UVB-irradiated HaCaT keratinocytes. We report that Qu actually increased c-Fos protein levels and potentiated the UVB response. This effect could be prevented completely by stabilizing Qu with AA because treatment with Qu+AA completely inhibited the UVB-induced increase in c-fos promoter activity and also inhibited protein synthesis by suppressing mammalian target of rapamycin (mTOR) signaling. These findings show an important cellular effect of Qu resulting from its pro-oxidant activity. Although we previously reported that Qu treatment may be beneficial by killing initiated cells (4), failure to stabilize Qu could have detrimental effects that limit any chemopreventive efficacy of the compound. Even stabilization of Qu with AA was shown to be a transient event, which might not prevent the tumor-promoting event of elevated c-fos expression that occurs as Qu degrades. Importantly, these findings highlight some of the complexities of working with natural products and suggest that some of these compounds may require a significant amount of characterization to validate them as chemopreventive agents and avoid deleterious side effects.

Materials and Methods

Materials

Qu dihydrate and AA were purchased from Sigma-Aldrich. Phospho-specific antibodies for p38 (T180/Y182), CREB (S133), Akt (S473), mTOR (S2448), p70S6K (T389), and 4EBP (S65) were from Cell Signaling Technology. c-Fos antibodies were purchased from Santa Cruz Biotechnology. Real-time PCR probes [c-Fos, HS00170630_m1; glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Hs99999905_m1] and Taqman reagents were purchased from Applied Biosystems. Actinomycin D and MG-132 were from EMD Biosciences/Calbiochem.

Cells

The human keratinocyte cell line, HaCaT, was established from cells obtained from adult sun-damaged skin and have been previously described (19–21). HaCaT cells contain UV signature mutations and express mutant dysfunctional p53 and a defective NF-κB signaling pathway, which are common findings in UV-initiated keratinocytes in human skin. However, these cells maintain p38, PI3-K, and AP-1 signaling pathway functionality compared with normal human keratinocytes and were thus chosen as an appropriate cell line to study UVB-induced c-Fos expression and upstream signaling events. FL-30 cells were developed from HaCaT cells and stably express firefly luciferase driven by a full-length c-fos promoter element (14). The cells were cultured in DMEM with 10% fetal bovine serum and 100 U/mL penicillin/streptomycin at 37°C in 5% CO₂. The cells were cultured to 80% to 90% confluence and maintained in serum-free DMEM for 24 hours before UVB exposure.

UVB irradiation of HaCaT cells

HaCaT cells were pretreated with Qu and/or ascorbate for 1 hour before UVB irradiation. The concentration of 50 μmol/L Qu was chosen based on our previously published study (4) and the fact that this concentration is feasible for chemoprevention studies using topical Qu. After incubation, HaCaTs were washed once in PBS and irradiated with a dose of 250 J/m² using a bank of two SF20 UVB lamps (National Biological Corp.) providing a peak emission of 313 nm. Control cells were treated in the same manner and mock irradiated. Following irradiation, HaCaT cells were again washed with PBS and returned to DMEM containing appropriate drug treatments. In experiments using MG-132, there was no initial pretreatment, and MG-132 was only used following exposure to UVB.

Western blotting

Cells were lysed in radioimmunoprecipitation assay buffer, and protein concentration was determined as previously described (4). A total of 40-μg protein was resolved by SDS-PAGE and transferred to a polyvinylidene difluoride membrane. Membranes were blocked in TBS containing 0.1% Tween 20. Antigen-antibody complexes were detected using Amersham Enhanced Chemiluminescence Detection Reagent (GE Healthcare). Densitometric analysis was done using the NIH ImageJ software, and density values were normalized to the non-treated control, which was assigned a value of 1.0.

c-fos-Luciferase assay

FL-30 cells were treated and UVB irradiated in triplicate for each independent experiment. Six hours after exposure to UVB, cells were lysed, and a total of 20 μg protein per
RNA extraction and real-time PCR analysis

For the measurement of steady-state RNA levels, cells were treated as indicated above. In RNA stability assays, cells were pretreated for 30 minutes with 5 μg/mL actinomycin D before treatment with Qu and AA for the indicated times. Cellular RNA was isolated from treated HaCaT cells by phenol-chloroform extraction using the Ambion Total RNA kit (Applied Biosystems) according to the manufacturer’s instructions. Extracted RNA was treated with DNase using the Ambion DNA-free kit and purified using the RNeasy MinElute Cleanup kit from Qiagen. Purified RNA was then reverse transcribed using the High-Capacity cDNA Reverse Transcription kit from Applied Biosystems. Real-time PCR was done using an ABI PRISM 7700 Sequence Detection System and Taqman probes specific for human c-fos and GAPDH. Relative expression was calculated to be $2^{-\Delta\Delta Ct}$, in which $\Delta Ct$ is equal to the difference in cycle number ($Ct$) between c-Fos and GAPDH for each sample, and $\Delta\Delta Ct$ is equal to the difference between $\Delta Ct$ for each treatment and the nontreated control. Each individual assay was done in triplicate for each gene product, and a total of three independent experiments were done.

Electromobility shift assay

After treatment and UVB irradiation, nuclear extracts were isolated from HaCaT cells as previously described (22). The following sequences derived from the human c-fos promoter containing the CRE were used to generate double-stranded oligos for electromobility shift assay analysis: CRE1, 5′-GACCGGCTGACTTTACACT-3′; and CRE2, 5′-TGAGTGTAAACGTCACGG-3′. They were annealed, and 5′-overhangs were labeled with [32P]dCTP (Perkin-Elmer). For gel shift assays, 5 μg of nuclear protein extracts were incubated at room temperature for 20 minutes with a mixture containing 10 mmol/L HEPES (pH 7.9), 0.1 mmol/L EDTA, 50 mmol/L KCl, 2.5 mmol/L DTT, 10% glycerol, 0.5% Triton X-100, and 0.05 mg/mL polydIdC. Labeled probe was added, and the reactions were incubated at room temperature for another 30 minutes. Reactions were then fractionated on a nondenaturing 6% polyacrylamide gel in 0.25 X Tris borate EDTA. The gels were dried and visualized with an MD Storm phosphorimagery (Molecular Dynamics).

Results

Qu induces p38 and CREB phosphorylation leading to c-fos promoter activity unless stabilized by AA

We previously showed that Qu is unstable in DMEM, but can be stabilized for several hours by inclusion of 1 mmol/L AA in the medium (4). Western analysis of protein from HaCaT keratinocytes indicated that 250 J/m² UVB induced p38 phosphorylation (Fig. 1A). Treatment with 50 μmol/L Qu increased p38 phosphorylation in mock-irradiated and UVB-irradiated HaCaT cells compared with the controls. When 1 mmol/L AA was included in the growth medium, Qu-treated cells displayed no increase in phospho-p38 levels, and the response to UVB was completely lost. CREB, a substrate downstream of p38 signaling, displayed a nearly identical response to UVB and Qu as p38, in which there were increases in CREB phosphorylation with both UVB and Qu alone and in combination, and there was a significant reduction in the UVB response when cells were treated in the presence of AA (Fig. 1B). Total p38 and CREB levels were unaffected by Qu, AA, or UVB treatment.

Transcriptional activation of c-fos is primarily driven by binding of CREB to CRE in the promoter region (17). We examined the effects of Qu on c-fos promoter activity using FL-30 cells, a HaCaT cell line that has been stably transfected with a firefly luciferase reporter construct in which expression of luciferase is driven by a full-length human c-fos promoter. Irradiation of FL-30 cells with 250 J/m² UVB resulted in a 5.1-fold increase in luciferase expression over control, whereas Qu treatment alone induced a 2.7-fold increase in luciferase expression (Fig. 2A). Qu treatment
Quercetin Modulation of UV-Induced c-Fos Expression

Qu increases c-Fos mRNA, but stabilization with AA prevents UVB-induced c-Fos mRNA expression

Total cellular RNA was isolated from Qu- and UVB-treated HaCaT cells 2 hours after exposure to UVB, and reverse transcribed cDNA was analyzed by real-time PCR with a probe specific for human c-Fos message. UVB-irradiated cells displayed an 8.4-fold increase in c-Fos message compared with mock-irradiated controls (Fig. 3A). Qu treatment also increased the level of c-Fos mRNA by 50-fold over control, a level much greater than that induced by UVB and potentiated the UVB response (126-fold over control). Interestingly, AA supplementation also increased steady-state mRNA levels in mock- and UVB-irradiated HaCaT cells, a finding that differed from the effect of AA on c-fos promoter activity. Although this increase
was not statistically significant compared with control levels, treatment with both Qu+AA did in fact result in a moderate increase.

Since this increase in steady-state c-Fos mRNA caused by supplementation of DMEM with AA could not have been the result of increased transcriptional activity, we next investigated the possibility that AA was increasing the stability of c-Fos mRNA. HaCaT cells were treated with actinomycin D to inhibit mRNA synthesis and subsequently treated with Qu, AA, or both. Through real-time

![Figure 3](https://example.com/image.png)

**Fig. 3.** Qu treatment increases c-Fos mRNA expression and potentiates UVB-induced c-Fos protein production. A, HaCaT cells were pretreated with 50 μmol/L Qu ± 1 mmol/L AA 1 h before irradiation with 250 J/m² UVB and for 2 h post-UVB, at which point RNA was extracted and purified. Real-time reverse transcription-PCR was done using probes specific for c-Fos and GAPDH. The fold increase of steady-state c-Fos mRNA was determined as indicated in Materials and Methods. UVB induced an 8.4-fold increase in c-Fos mRNA, and Qu alone induced a 50-fold increase. Qu treatment in UVB-irradiated cells resulted in a potentiated response, in which the induction of c-Fos mRNA was equal to 126-fold over control cells. AA treatment alone raised steady-state c-Fos mRNA levels by 7.8-fold, and the UVB-induced increase was 28-fold. AA combined with Qu treatment raised steady-state c-Fos levels 47-fold over control, and the UVB response in these cells was completely inhibited, with c-Fos levels remaining at 43-fold over control. These data are means from three independently performed experiments, and statistically significant differences between groups (P < 0.05) are indicated by labels containing different letters. Any two treatment conditions with a label containing the same letter are not significantly different. B, HaCaT cells treated with Qu, AA, or both were concurrently treated with actinomycin D to prevent the synthesis of new mRNA. At the indicated time points, mRNA was extracted and real-time reverse transcription-PCR was performed. Data were analyzed as indicated above. Data were normalized to 0 h, set to 100% for each treatment condition. AA stabilized c-Fos mRNA, which likely contributed to the increase in steady-state c-Fos mRNA detected in the AA-treated samples in A. Qu did not stabilize c-Fos mRNA and reduced the stabilizing effect of AA. These data are a representative sample from two independently performed experiments. C, HaCaT cells were pretreated with 50 μmol/L Qu ± 1 mmol/L AA for 1 h before irradiation with 250 J/m² UVB and following irradiation for 6 h, at which point protein lysates were extracted and Western analysis was done using specific antibodies for c-Fos. Treatment with either Qu or UVB irradiation alone induced c-Fos protein expression over control, but cells treated with both Qu and UVB irradiation displayed a potentiated increase in c-Fos protein. Supplementation with AA had no effect on c-Fos protein levels in mock- and UVB-irradiated HaCaT cells. However, Qu treatment in AA-supplemented cells completely blocked the UVB-induced increase in c-Fos protein levels. Relative band densities are represented numerically immediately below the blot. Data are representative of three independently performed experiments.
PCR analysis, we determined that AA supplementation alone resulted in a marked reduction in the rate of c-fos mRNA decay compared with control (Fig. 3B). Qu treatment had no significant effect on mRNA stabilization alone, but actually reduced the effect of AA.

Qu potentiates UVB-induced c-Fos protein expression in HaCaT keratinocytes, and ascorbate-stabilized Qu inhibits increases in c-Fos protein levels

Our laboratory has previously reported that UVB irradiation increases the levels of c-Fos protein (14, 17, 18). We analyzed c-Fos protein levels by Western analysis and confirmed that 250 J/m² UVB did increase expression over the level expressed in mock-irradiated HaCaT cells (Fig. 3C). Treatment with Qu alone also increased c-Fos protein to a level comparable with that induced by UVB, and treatment of cells with both Qu and UVB resulted in a level of c-Fos that was substantially increased over either Qu or UVB treatment alone. These data corroborate our previous finding for the Qu and UVB effects on mRNA expression. Contrary to the effect of AA on steady-state mRNA levels, there was no effect of AA treatment alone on c-Fos protein expression in either mock- or UVB-irradiated cells compared with their respective controls. Interestingly, treatment with Qu+AA showed only a slight increase in c-Fos protein expression in mock-irradiated cells and a complete suppression of c-Fos protein expression even when cells were irradiated with UVB, suggesting that the stabilization of c-fos mRNA did not translate to increased protein.

Qu blocks mTOR signaling and inhibits c-Fos protein translation

One explanation for the apparent disconnect between mRNA and protein levels is that Qu independently affects protein synthesis and mRNA expression. To address this possibility, we investigated the effects of Qu on mTOR signaling because this pathway is known to regulate de novo protein synthesis and because we and others have reported that Qu has inhibitory activity against PI3-K, a kinase upstream of Akt and mTOR activation (4, 23, 24). We determined that mTOR phosphorylation at Ser2448, an activating phosphorylation, was slightly increased with UVB (Fig. 4A), as was phosphorylation of the downstream mTOR effectors 4EBP (S65; Fig. 4B) and p70S6K (T389; Fig. 4C). Qu suppressed the phosphorylation of each of these proteins in mock- and UVB-irradiated cells, and when the cells were treated with Qu in the presence of AA, the level of suppression was increased, a finding that is consistent with our previous report that AA stabilizes Qu in aqueous medium (4).

Lastly, we treated HaCaT cells with Qu+AA in the presence of the proteasome inhibitor MG-132 to prevent c-Fos turnover and more specifically address the effects of stabilized Qu on c-Fos protein synthesis (Fig. 4D). HaCaT cells treated with MG-132 displayed significantly increased c-Fos protein levels due to the inhibition of protein degradation, which resulted in a reduction of the effect of Qu on UVB-induced c-Fos protein levels. However, cells treated with Qu+AA still displayed low levels of c-Fos protein expression in the presence of MG-132 resulting from a sustained reduction of c-Fos translation.

Discussion

NMSC is the most commonly diagnosed of all human malignancies and is the cause of 2,000 deaths annually.
and millions of dollars in health care costs. Clearly, new treatment strategies are needed to prevent the development of precancerous actinic keratoses and squamous cell tumors caused by prolonged exposure to UV light. Qu is currently being evaluated as a potential chemopreventive agent in multiple types of cancer in part because it has established PI3-K and mitogen-activated protein kinase inhibitory activities (for review, see ref. 25). Our initial interest in Qu was specifically due to this activity because it has been shown that the PI3-K and mitogen-activated protein kinase signaling pathways are activated in response to UVB irradiation, and both PI3-K and p38 are upstream of c-Fos expression and AP-1 activation (16, 26, 27). Natural products and small-molecule inhibitors of these pathways would protect against promotion of initiated cells by reducing AP-1 activation and could be potentially useful in cancer prevention.

The findings from the current study are summarized in Fig. 5. We determined that Qu potentiated the UVB-induced c-fos gene expression, a direct result of increased p38 and CREB phosphorylation. The inhibitory effect of Qu on PI3-K was not sufficient to prevent the elevation of c-Fos protein levels that directly resulted from increased gene expression. These effects of Qu could be prevented by stabilizing the compound with AA, which resulted in a complete inhibition of UVB-induced c-fos mRNA and protein expression, and all upstream signaling. These findings exemplify the difficulties that can arise when working with natural products.

We previously reported that Qu could potentially act as a chemopreventive agent due to its ability to kill initiated cells through PI3-K inhibition and pro-oxidant effects (4). However, considering the results of the current study, Qu degradation could potentially have the consequence of increasing AP-1 activity and negating the chemopreventive effect. Dietary Qu is effective in preventing cancer in animal models in colon (28–33), breast (34), and lung tissues (35), as well as squamous cell carcinoma of the
tongue (36). In NMSC models, the effects of Qu are unclear. In one study, dietary Qu had no effect on UV-induced squamous cell carcinoma (37), whereas topically applied Qu decreased papilloma formation in a chemically induced skin cancer mouse model (38). We have tested topical Qu in a UVB-induced skin cancer model and found no significant reduction of squamous cell carcinoma incidence, tumor multiplicity, or tumor burden compared with vehicle-treated controls (data not shown). There are several possible explanations for the differences in these reported results. First, orally administered Qu may not adequately distribute to the skin to elicit any preventative effect. Second, it is possible that Qu is more effective against chemically induced skin cancer, although Kato et al. (38) used a topical dose that was five times more concentrated than the dose we used (5% versus 1%, respectively). Interestingly, a recent study evaluating myricetin, a flavonol with great structural similarity to Qu, showed significant efficacy in preventing UVB-induced skin tumor formation when much lower amounts were used (0.001-0.003% myricetin/treatment versus 1% Qu/treatment in our study; ref. 39). There have been no reports describing myricetin stability, but we have evidence that myricetin does not induce c-Fos expression in cultured HaCat cells when used at the same concentration as Qu in the current study (data not shown). Lastly, the formulation used to deliver Qu topically may affect the long-term stability of Qu in the skin, and as shown in the current study, Qu degradation can affect cell signaling and the cellular response to UVB. Overall, these studies suggest that the effectiveness of Qu is dependent on the specific type of cancer and the method of administration. Furthermore, our findings suggest that any aqueous-based topical formulation of Qu developed for human use would have to contain a Qu-stabilizing agent that significantly slowed Qu degradation to prevent the detrimental effects of Qu degradation. If Qu is to be pursued as a topical chemopreventive agent for NMSC, further studies are needed to determine if there are optimal conditions under which Qu can be effective.

Our findings, combined with the large number of reported cellular effects of various natural products, highlight the complexities and the careful considerations required to properly evaluate these compounds for their chemopreventive potential, particularly with regard to the proper dosing required to achieve desired experimental or clinical outcomes. Some of these studies highlight an important conflict in the reports of in vitro and in vivo effects of Qu. For example, pioneering studies by Nagao et al. (40) identified numerous flavonoids, including Qu, with mutagenic potential. However, oral Qu has been shown to display no carcinogenic effect in rats (41), despite the known relationship between mutagenicity and carcinogenicity. In addition, other studies using different in vitro models show conflicting findings to our own. Ying et al. (42) recently published a study showing that 10 μmol/L Qu blocks intercellular adhesion molecule expression in part through the inhibition of c-fos induction. As previously stated, we had determined that this dose was ineffective at preventing UVB-induced PI3-K activity, our primary goal, but raising the concentration to an effective level caused increased sensitization to UVB-induced c-fos expression. This property may be detrimental to the chemopreventive effect of Qu, but might be useful for other purposes, such as increasing the sensitivity of tumor cells to agents such as cisplatin as reported by Sharma et al. (43). These facts all indicate that Qu is capable of eliciting different effects that need to be well characterized to fully understand how the compound might be useful in preventing or treating cancer. Qu is an excellent example of how natural products need to be thoroughly examined before drawing premature conclusions about their preventive or therapeutic efficacy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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