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14. ABSTRACT
The challenge today is to develop a cytotoxic agent that selectively induces cytotoxicity in prostate cancer cells but avoids significant toxicity to the normal tissues. In this study, we will develop a novel strategy by using TRAIL in combination with amiloride.

15. SUBJECT TERMS
TRAIL; PI3K; Amiloride; Na+/H+; DU-145; apoptosis; Akt; PDK-1

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Introduction:

The long-term goal of our research project is to develop a tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-based therapy for prostate cancer. This translational research project is based on the observation that prostate cancer begins as an androgen-dependent tumor and undergoes clinical regression in response to pharmacological or surgical strategies that reduce testosterone concentration. While this treatment approach is effective initially in controlling the prostate cancer, these tumors ultimately fail to respond to androgen blockade. The failure of androgen ablation therapy leads to a hormone-refractory state of the disease. Androgen receptor mutations (6-10%) and amplifications (20-30%) may explain relapse in some patients (Bartlett et al., 2005). However, HER-2/neu overexpression has been reported in up to 67% of patients with hormone-refractory prostate carcinoma (Osman et al., 2001). Several studies have shown that overexpression of HER-2/neu is correlated with shortened patient survival, increased metastatic potential, and poor prognosis. This is probably because HER-2/neu promotes tumor survival through the PI(3)K-Akt signal transduction pathway. In this final report, we examined whether blockade of HER-2/neu-mediated tumor cell survival signals by quercetin, a common bioflavonoid present in many fruits and vegetables such as onions and apples, can sensitize prostate cancers to TRAIL-induced apoptotic death. The inhibition of HER-2/neu-mediated survival signals results in prevention of regrowth of prostate cancer.

The natural product quercetin (3,5,7,3',4'-pentahydroxyflavone), which is orally bioavailable, is a flavonoid found in many fruits and vegetables. Quercetin and its metabolites are potent antioxidants which have oxygen radical scavenging properties and inhibit xanthine oxidase and lipid peroxidation *in vitro* (Bors et al., 1994; Da Silva et al., 1998; Vulcain et al., 2005). Previous research has also shown that quercetin has anti-tumor, anti-inflammatory, anti-allergic, and anti-viral activities (Middleton, Jr. and Kandaswami, 1993; Kandaswami and Middleton, Jr., 1994; Wang, 2000; Nair et al., 2002; Suzuki et al., 2002). However, the molecular mechanisms underlying the anti-tumor effects are generally unknown. Several researchers have reported that quercetin inhibits PI(3)K with an IC_{50} of 3.8 μM (Matter et al., 1992; Yoshizumi et al., 2001). We examined whether the anti-tumor effects of quercetin, as manifested by its ability to selectively suppress colony formation by prostate cancer cells *in vitro*, are mediated by its ability to inhibit the PI(3)K-Akt signal transduction pathway.

Several researchers have observed a significant increase in HER-2/neu expression after the progression from hormone-dependent to hormone-independent disease (Osman et al., 2001; Signoretti et al., 2000). The expression of HER-2/neu is correlated with increased metastatic potential, poor prognosis in prostate cancer, and resistance to apoptosis (Signoretti et al., 2000). HER-2/neu (also known as ErbB2) is a gene in the epidermal growth factor receptor (EGFR) family (HER-1, HER-2, HER-3, HER-4). In many physiological contexts signaling through the HERs is induced by the formation of HER heterodimers, whose cytoplasmic tails are phosphorylated and coupled to SH2-containing proteins to initiate a cellular signaling pathway (Carraway and Cantley, 1994; Olayioye et al., 1998). The HER-2/neu gene encodes a 185 kDa transmembrane receptor tyrosine kinase. Unlike the other epidermal growth factor receptors (EGFR), HER-2/neu has an intrinsic tyrosine kinase activity that activates PI(3)K in the absence of ligand (Fruman et al., 1998; Figure 1). PI(3)K consists of a regulatory subunit (p85) that binds to an activated growth factor/cytokine receptor and undergoes phosphorylation, which results in the activation of its catalytic subunit (p110) (Rodriguez-Viciana et al., 1996). PI(3)K phosphorylates phosphoinositides at the 3'-position of the inositol ring, and its major lipid product is phosphatidylinositol 3,4,5-triphosphate (PIP_3) (Rameh and Cantley, 1999). PIP_3 facilitates the recruitment of Akt to the plasma membrane through binding with the pleckstrin homology (PH) domain of Akt (Rameh and Cantley, 1999). Akt is activated by phosphoinositide-dependent kinase-1 (PDK1) through phosphorylation at threonine 308 and serine 473 (Alessi et al., 1997). A number of pro-apoptotic proteins have been identified as direct Akt substrates, including BAD, caspase-9, and Forkhead transcription factors (Brunet et al., 1999; Cardone et al., 1998; Cross et al., 1995; Datta et al., 1997; del Peso et al., 1997; Hetman et al., 2000; Zhao et al., 2004). The pro-apoptotic function of these molecules is

suppressed upon phosphorylation by Akt. Previous studies also show that Akt induces the degradation of IκB by promoting IKKα activity and subsequently stimulating the nuclear translocation of NF-κB (Ozes et al., 1999). Our lab (Nam et al., 2002) and Panka et al. (2001) reported that the PI(3)K-Akt-NF-κB pathway may regulate the expression of FLICE-inhibitory protein (FLIP), an anti-apoptotic molecule. We identified the mechanisms by which HER-2/neu affects TRAIL-induced apoptotic death.

TRAIL is a type II integral membrane protein belonging to the TNF family. TRAIL is a 281-amino acid protein, related most closely to a Fas/APO-1 ligand. Like Fas ligand (FasL) and TNF, the C-terminal extracellular region of TRAIL (amino acids 114-281) exhibits a homotrimeric subunit structure (Pitti et al., 1996). However, unlike FasL and TNF, several studies reveal that TRAIL induces apoptosis in a wide variety of tumor cells, but does not cause toxicity to most normal cells (Ashkenazi and Dixit, 1998). Several studies also reveal that TRAIL, which is constitutively expressed on murine natural killer cells in the liver, plays an important role in surveillance of tumor metastasis (Takeda et al., 2001). The apoptotic signal of TRAIL is transduced by binding to the death receptors TRAIL-R1 (DR4) and TRAIL-R2 (DR5), which are members of the TNF receptor superfamily. Both DR4 and DR5 contain a cytoplasmic death domain that is required for TRAIL receptor-induced apoptosis. TRAIL also binds to TRAIL-R3 (DcR1) and TRAIL-R4 (DcR2), which act as decoy receptors by inhibiting TRAIL signaling (Pan et al., 1997a; Pan et al., 1997b; Sheridan et al., 1997; Walczak et al., 1997; Degli-Esposti et al., 1997a; Degli-Esposti et al., 1997b; Marsters et al., 1997). Unlike DR4 and DR5, DcR1 does not have a cytoplasmic domain and DcR2 retains a cytoplasmic fragment containing a truncated form of the consensus death domain motif (Pan et al., 1997a). Recent studies suggest that DRs and DcRs interact through their extracellular domains to form homometric and/or heterometric complexes (Lee et al., 2005). Differential sensitivity between normal and tumor cells to TRAIL has been explained by the presence of a high concentration of the decoy receptors in normal cells (Gura, 1997; Ashkenazi and Dixit, 1999). However, this hypothesis has been challenged based on the results showing poor correlations between DR4, DR5, and DcR1 expression and sensitivity to TRAIL-induced apoptosis in normal and cancerous breast cell lines (Keane et al., 1999; Leblanc and Ashkenazi, 2003). This discrepancy indicates that other factors such as death inhibitors (FLIP, FAP-1, Bcl-2, Bcl-X_L, or IAP) or pro-apoptotic molecules (Bax, Bad, Bim, or Bid) are also involved in the differential sensitivity to TRAIL. TRAIL binding to death receptors is thought to result in conformational changes that expose a binding surface for Fas-associated death domain (FADD), an adaptor protein (Kischkel et al., 2000; Thomas et al., 2004). TRAIL triggers apoptosis by recruiting the apoptosis initiator procaspase-8 through the adaptor FADD (Bodmer et al., 2000). Caspase-8 can directly activate downstream effector caspases including procaspase-3, -6, and -7 (Cohen, 1997). Caspase-8 also cleaves Bid and triggers mitochondrial damage that in turn leads to cytochrome *c* release (Li et al., 1997). Cytochrome *c* in the cytoplasm binds to Apaf-1, which then permits recruitment of procaspase-9. Caspase-9 cleaves and activates procaspase-3 (Slee et al., 1999). Thus, TRAIL produces apoptosis. On the other hand, the PI(3)K-Akt-NF-κB pathway counteracts this effect, because NF-κB promotes the expression of certain Bcl-2 family, IAP family and FLIP family proteins: (a) The activation of caspases is counteracted by anti-apoptotic molecules of the Bcl-2 family (Bcl-2, Bcl-X_L), because the Bcl-2 family proteins heterodimerize with pro-apoptotic members of the Bcl-2 family (Bax, Bak) and interfere with release of cytochrome *c* by pore-forming proteins (Bid, Bik) (Gross et al., 1999); (b) Members of the inhibitor of apoptosis (IAP) family (c-IAP1, c-IAP2, XIAP) can directly bind and inhibit activation of caspases including caspase-3, -7 and -9 (Roy et al., 1997); (c) Previous studies have shown that several FLIP splice variants exist on the mRNA level, but two endogenous forms, $FLIP_L$ and $FLIP_S$, are detected on the protein level (Shu et al., 1997; Tschopp et al., 1998). Krueger et al. (2001) reported that $FLIP_L$ and $FLIP_S$ prevent caspase-8 activation at different levels of procaspase-8 processing at the DISC (death-inducing signaling complex). Thus, the expression of these Bcl-2 family, IAP family, and FLIP family proteins is promoted by NF-κB, a family of dimeric transcription factors (Chen et al., 2000). The NF-κB family of proteins, including NF-κB1, NF-κB2, RelA, RelB, and c-Rel, can form homo- and heterodimers *in vitro*, except for RelB. In mammals, the most widely distributed NF-κB is a heterodimer composed of p50 and p65 (also called RelA) subunits (Baeuerle and Baltimore, 1989). NF-κB activity is

regulated by the IκB family of proteins which interacts with and sequesters the transcription factor in the cytoplasm. IκB proteins become phosphorylated by the multisubunit IκB kinase (IKK) complex, which subsequently targets IκB for ubiquitination and degradation by the 26S proteasome (Zandi and Karin, 1999). We investigated the mechanisms by which the HER-2/neu-PI(3)K-Akt-NF-κB signal counteracts the extent of TRAIL-induced apoptotic death.

Previous studies have revealed a link between HER-2/neu signaling and cyclooxygenase-2 (COX-2) expression (Vadlamudi et al., 1999; Kiguchi et al., 2001). Overexpression of HER-2/neu leads to elevated levels of COX-2 through a MAPK-dependent pathway (Subbaramaiah et al., 2002). COX-2 catalyzes the formation of prostaglandin E_2 (PGE_2) which stimulates CYP19 gene expression (Subbaramaiah et al., 2006). Cytochrome P450 aromatase (aromatase), a product of the CYP19 gene, catalyzes the synthesis of estrogens from androgens (Dubey et al., 2005). Given the significance of estrogen synthesis in hormone-dependent prostate carcinogenesis (Ho et al., 2006), inhibiting aromatase by quercetin results in decreased estrogen biosynthesis and leads to antiestrogenic effects which may be important in prostate cancer.

Body:

HER-2/neu gene expression and TRAIL cytotoxicity

To determine a correlation between HER-2/neu gene expression and TRAIL cytotoxicity, human prostatic adenocarcinoma LNCaP and DU-145 cells were treated with various concentrations of TRAIL (0-1000 ng/ml). Cell survival was analyzed by the trypan blue exclusion assay (Fig. 1B) and the intracellular level of HER-2/neu was measured by western blot analysis (Fig. 1A). Figure 1 shows that LNCaP cells containing a relatively high level of HER-2/neu are resistant to TRAIL. In contrast, DU-145 cells containing a relatively low level of HER-2/neu are sensitive to TRAIL. These results suggest that HER-2/neu protects cells from TRAIL-induced cytotoxicity.

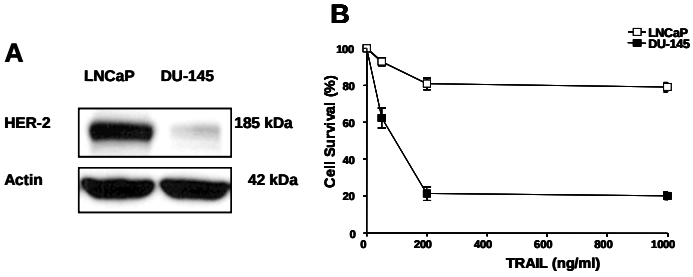

Figure 1. Expression of HER-2/neu and TRAIL sensitivity in LNCaP and DU-145 cells. A: Cells were lysed and subjected to western blot analysis with an anti-HER-2/neu antibody. **B:** LNCaP (□) or DU-145 (■) cells were exposed to TRAIL (0-1000 ng/ml) for 4 hr and survival was analyzed by the trypan blue exclusion assay.

Akt activity and TRAIL-induced apoptotic death

In this grant proposal, we hypothesize that HER-2/neu-enhanced resistance to TRAIL is mediated through the Akt pathway. Previous studies have shown that phosphorylation of Thr-308 and Ser-473 is required for Akt activity. Data from western blot analysis shows that LNCaP cells have relatively high Akt activity (Fig. 2). In contrast, DU-145 cells have relatively low Akt activity (Fig. 2).

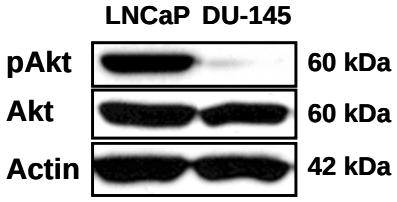

Figure 2. Basal Akt activity in LNCaP and DU-145 cells. Lysates containing equal amounts of protein (20 μg) were separated by SDS-PAGE and immunoblotted with anti-Akt antibody (Akt) or anti-phospho-S473 Akt antibody (pAkt). **Actin**, actin is shown as an internal standard.

We examined whether quercetin, which is known to inhibit the HER-2/neu associated PI(3)K-Akt signal transduction pathway, can sensitize HER-2/neu overexpressing cancers to TRAIL-induced cell death. First, we investigated how quercetin inhibits the HER-2/neu associated PI(3)K-Akt signal transduction pathway. Figure 3 shows that quercetin induced dephosphorylation (inactivation) of Akt, but not PI(3)K.

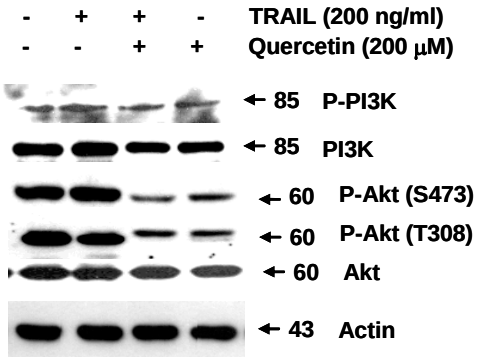

Figure 3. Effect of quercetin on PI(3)K-Akt signal transduction pathway associated kinases. LNCaP cells were treated for 4 h with 200 μM quercetin in the presence or absence of 50 ng/ml TRAIL, and then harvested. Equal amounts of protein (20 μg) were separated by SDS-PAGE and immunoblotted with anti-phospho-PI(3)K, anti-PI(3)K, anti-phospho-PDK-1, anti-PDK-1, anti-phospho(S473)-Akt, anti-phospho(T308)-Akt, or anti-Akt antibody.

Next, we investigated the effect of quercetin on TRAIL-induced cytotoxicity. LNCaP cells were treated with TRAIL in the presence or absence of quercetin. Little or no cytotoxicity was observed with quercetin (10-200 μM) alone (Fig. 4A). TRAIL in combination with quercetin significantly increased TRAIL-induced cytotoxicity (Fig. 4B). TdT-mediated dUTP Nick end labeling (TUNEL) assay showed that apoptotic death was enhanced during combined treatment with TRAIL and quercetin (Fig. 4C).

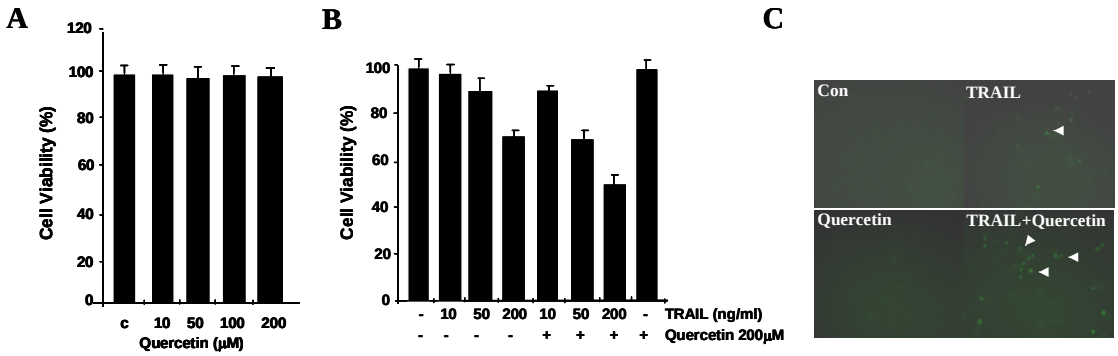

Figure 4. Effect of quercetin on TRAIL-induced cytotoxicity in human prostate adenocarcinoma LNCaP cells. (**A**) Cells were treated for 4 h with various concentrations of quercetin (10-200 μM). (**B**) Cells were treated with various concentrations of TRAIL (10-200 ng/ml) in the presence or absence of 200 μM quercetin. Cell survival was determined by the trypan blue exclusion assay. Error bars represent standard error of the mean (SEM) from three separate experiments. (**C**) Cells were treated for 4 h with TRAIL (200 ng/ml) in the presence or absence of 200 μM quercetin. After treatment, apoptosis was detected by the TUNEL assay. Apoptotic cells are indicated by arrows. Con, untreated control; TRAIL, 200 ng/ml TRAIL; Quercetin, 200 μM quercetin; TRAIL + Quercetin, 200 ng/ml TRAIL in the presence of 200 μM quercetin.

Effect of quercetin on TRAIL-induced proteolytic cleavage of PARP and activation of caspases

Additional studies were designed to examine whether the combination of quercetin and TRAIL treatment in LNCaP cells enhances poly (ADP-ribose) polymerase (PARP) cleavage, the hallmark feature of apoptosis. Previous studies show that PARP (116 kDa) is cleaved yielding a characteristic 85 kDa fragment in the presence of TRAIL alone in human prostate adenocarcinoma DU-145 cells (Lee et al., 2004). Figure 5 shows that the cleavage of PARP was not observed during treatment with either

quercetin (200 μM) or TRAIL (10-200 ng/ml) alone in LNCaP cells. The cleavage of PARP was observed by combined treatment with TRAIL and quercetin. The cleavage of PARP was increased by increasing concentrations of quercetin (Fig. 5). Also, Figure 5 demonstrates that TRAIL in combination with quercetin promoted activation of caspases. Quercetin alone did not activate caspases. Western blot analysis shows that procaspase-8 (57 kDa) was cleaved to the intermediate form (43 kDa) and active form (18 kDa, data not shown) by treatment with TRAIL. The combined treatment with TRAIL and quercetin enhanced the cleavage (activation) of caspase-8. The combined treatment of TRAIL and quercetin also resulted in facilitation of caspase-9 activation (Fig. 5). TRAIL in combination with quercetin enhanced proteolytic processing of procaspase-9 (46 kDa) into its active form (34 kDa). The combined treatment with TRAIL and quercetin also promoted caspase-3 activation. Western blot analysis shows that procaspase-3 (32 kDa), the precursor form of caspase-3, was cleaved in the presence of TRAIL and quercetin.

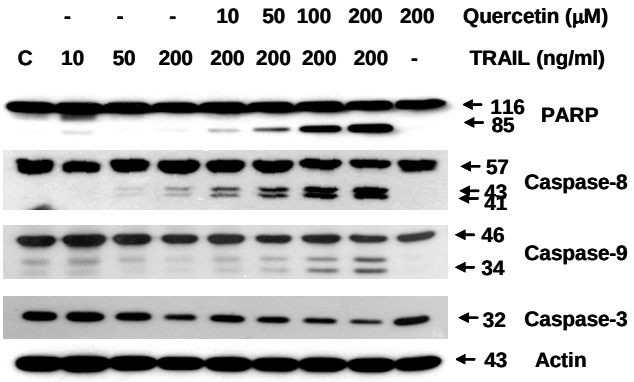

Figure 5. Effect of quercetin on TRAIL-induced proteolytic cleavage of PARP and activation of caspases in LNCaP cells. Cells were treated for 4 h with various concentrations of quercetin (10-200 μM) in the presence or absence of TRAIL (10-200 ng/ml). Cell lysates were subjected to immunoblotting for PARP, caspase-8, caspase-9, or caspase-3. Antibody against caspase-8 detects inactive form (57 kDa) and cleaved intermediate (43 kDa). Anti-caspase-9 antibody detects both inactive form (46 kDa) and cleaved intermediate (34 kDa). Anti-caspase-3 antibody detects inactive form (32 kDa). Immunoblots of PARP show the 116 kDa PARP and the 85 kDa apoptosis-related cleavage fragment. Actin was used to confirm the amount of protein loaded in each lane.

We further examined whether the inhibition of Akt alone is responsible for the enhancing effect of quercetin on TRAIL cytotoxicity, or whether other parts of the HER-2/neu associated PI(3)K-Akt signal pathway are involved. The effect of quercetin on Akt was compared with the effects of LY294002 and wortmannin, inhibitors of PI3K. Figures 6A and 6B show that all these drugs induced dephosphorylation of Akt. These drugs also promoted TRAIL-induced cytotoxicity (Fig. 6C). These results suggest that Akt inactivation (dephosphorylation) is responsible for the quercetin-induced enhancement of TRAIL cytotoxicity.

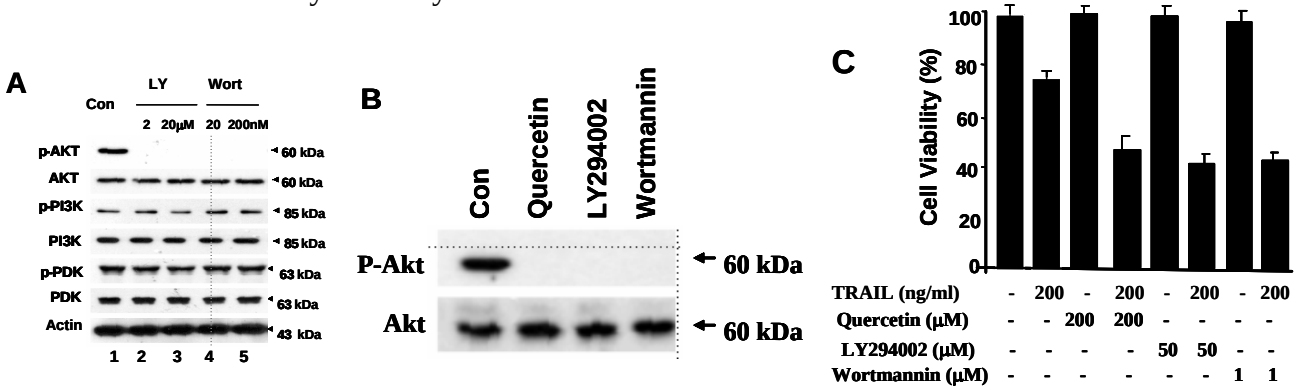

Figure 6 Effect of quercetin, LY294002, or wortmannin on kinases (A & B), and TRAIL-induced cytotoxicity (C) in LNCaP cells. (**A & B**) Cells were treated for 1 h with LY294002 (LY; 2-20 μM), wortmannin (Wort; 20-200 nM), or 200 μM quercetin. Equal amounts of protein (20 μg) were separated by SDS-PAGE and immunoblotted as described in Materials and Methods. Actin is shown as an internal standard. Con, untreated control cells. (**C**) Cells were pretreated with 200 μM quercetin, 50 μM LY294002, or 1 μM wortmannin for 30 min and then treated with TRAIL (200 ng/ml) for 4 h. Cell survival was determined by the trypan blue exclusion assay. Error bars represent standard error of the mean (SEM) from three separate experiments.

Effect of combined treatment with TRAIL and quercetin on the level of TRAIL receptor family and anti-apoptotic proteins

Previous studies demonstrate that increased DR5 levels induced by genotoxic agents (Sheikh et al., 1998; Chinnaiyan et al., 2000) or decreased FLIP expression induced by glucose deprivation (Nam et al., 2002) is responsible for increasing TRAIL cytotoxicity. Thus we examined whether changes in the amounts of TRAIL receptors and anti-apoptotic proteins are associated with the promotion of apoptosis by TRAIL in combination with quercetin. LNCaP cells were treated with TRAIL (50 ng/ml) in the presence of quercetin (10-200 μM) for 4 hr. Data from western blot analysis reveal that the combined treatment did not significantly alter the levels of DR4, DR5, DcR2, $FLIP_L$, $FLIP_S$, Bcl-2, Bcl-xL, cIAP-1, and cIAP-2 (Fig. 7). Quercetin alone also did not significantly change the levels of TRAIL receptors and anti-apoptotic proteins (Fig. 7).

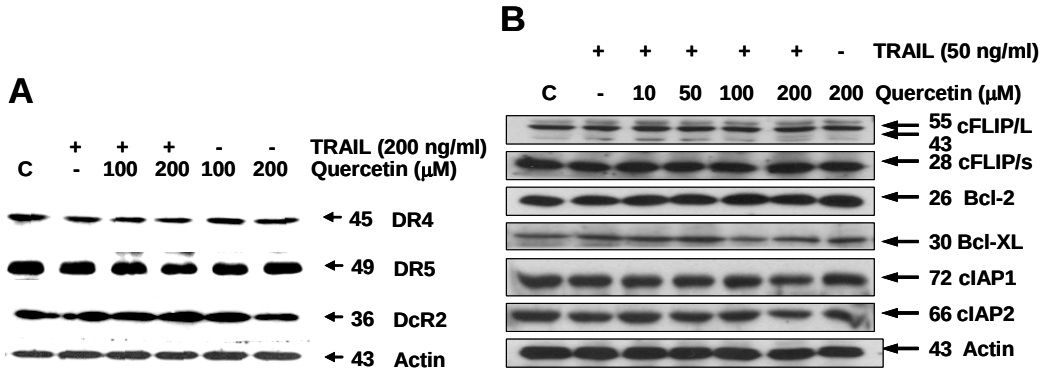

Figure 7. Intracellular levels of TRAIL receptors (A) or anti-apoptotic proteins (B) during treatment with TRAIL in the presence or absence of quercetin. LNCaP cells were treated for 4 hr with 50 or 200 ng/ml TRAIL in the presence or absence of various concentrations of quercetin (10-200 μM). Equal amounts of protein (20 μg) were separated by SDS-PAGE and immunoblotted with anti-DR4, anti-DR5, anti-DcR2, anti-$FLIP_L$, anti-$FLIP_S$, anti-Bcl-2, anti-Bcl-xL, anti-cIAP-1, or anti-cIAP-2. Actin was used to confirm the amount of protein loaded in each lane.

Key research accomplishments:

Our experimental results revealed that quercetin effectively promotes TRAIL-induced apoptosis. Western blot analysis showed that combined treatment with TRAIL and quercetin did not change the levels of TRAIL receptors (DR4, DR5, and DcR2) or anti-apoptotic proteins (FLIP, IAP, and Bcl-2). However, quercetin promotes the dephosphorylation of Akt. Thus, our data reveals that quercetin enhances TRAIL-induced cytotoxcity by activating caspases and inhibiting phosphorylation of Akt.

Reportable Outcomes and Conclusions:

We conclude that quercetin enhances TRAIL-induced cytotoxicity by inhibiting phosphorylation of the PI3K-Akt pathway-associated kinases and phosphatases. We believe that the outcome of these studies provides information to support the development and clinical application of TRAIL in combination with quercetin for the treatment of prostate cancer patients.

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