Animal Cells and Systems
Vol. 15, No. 1, March 2011, 1–8

Taylor & Francis
Taylor & Francis Group

Stearoyl-CoA desaturase induces lipogenic gene expression in prostate cancer cells and inhibits ceramide-induced cell death

Seung-Jin Kim and Eungseok Kim*

Department of Biological Sciences, College of Natural Sciences, Chonnam National University, Gwangju, Korea

(Received 9 December 2010; received in revised form 13 January 2011; accepted 13 January 2011)

Perturbation of metabolism with increased expression of lipogenic enzymes is a common characteristic of human cancers, including prostate cancer. In the present work the overexpression of stearoyl-CoA desaturase (SCD) in LNCaP cells led to increased mRNA levels of fatty acid synthase (FAS) and acetyl-CoA-carboxylase-α, whereas micro RNA-mediated silencing of SCD inhibited the expression of these lipogenic genes in LNCaP cells. Treatment with the FAS-specific inhibitor cerulenin inhibited SCD induction of LNCaP cell proliferation. In addition, a transient transfection assay revealed the capability of cerulenin to suppress SCD and dihydrotestosterone induction of androgen receptor transcriptional activity. Furthermore, overexpression of SCD in LNCaP cells produced marked resistance to ceramide-induced cell death with reduced poly(ADP-ribose) polymerase (PARP) cleavage. In contrast, silencing of SCD expression increased Bax protein in LNCaP cells. Furthermore, addition of ceramide to SCD knockdown LNCaP cells increased cell death and caspase-3 activity with drastic increase of PARP cleavage. Together, the data indicate that SCD may provide resistance of prostate cancer cells to ceramide-induced cell death.

Keywords: SCD; FAS; cell death; PARP; prostate cancer

Introduction

Deregulation of lipogenesis has been linked to tumor development and progression (Menendez and Lupu 2007). Overexpression of lipogenic enzymes is common in several human cancers including prostate cancer (Baron et al. 2004; Kuhajda 2000). Expression of stearoyl-CoA desaturase (SCD), fatty acid synthase (FAS) and acetyl-CoA-carboxylase-α (ACC-α) is markedly increased in prostate cancer (Milgraum et al. 1997; Van de Sande et al. 2002; Yahagi et al. 2005). SCD is a key lipogenic enzyme that catalyzes the delta 9-cis desaturation of acyl-CoA species such as palmitoyl-CoA and stearoyl-CoA, to produce palmitoleoyl-CoA and oleoyl-CoA, respectively. Since these monounsaturated fatty acids produced by SCD are phospholipid substrates, the changed expression or activity of SCD is closely correlated with altered membrane fluidity and cell–cell interaction, influencing the progression of cancers and other diseases (Hess et al. 2010). SCD promotes cell proliferation, and inhibition of SCD expression or activity boosts cell death (Scaglia and Igal 2005; Fritz et al. 2010; Hess et al. 2010). Thus, given the phenotype of SCD, deregulation of SCD expression or activity would be expected to affect tumorigenesis and cancer progression.

Increased expression of SCD in prostate cancer patients was recently reported (Fritz et al. 2010). Consistent with this report, we have demonstrated that, among the variety of peptides produced by proteolytic cleavage of SCD, a SCD-derived peptide (amino acids 130–162) enhances the 5α-dihydrotestosterone (DHT)-induced androgen receptor (AR) transcriptional activity by direct interaction with AR, leading to increased proliferation of AR-positive LNCaP prostate cancer cells (Kim et al., in press). Interestingly, SCD-deficient mice showed concomitant reduction of genes involved in the lipogenic pathway, such as FAS in the liver.

FAS is the key enzyme in the synthesis of long-chain fatty acids, in particular palmitic acid from acetyl-CoA, malonyl-CoA and nicotinamide adenine dinucleotide phosphate. Upregulated expression or activity of FAS has been linked to poor prognosis of cancers. Pharmacological inhibition or RNA interference-mediated silencing of FAS inhibits cell proliferation with increased apoptotic cell death, implying that the enhanced expression of these enzymes may play important roles in prostate tumorigenesis and cancer progression (Swinnen et al. 2002; De Schrijver et al. 2003; Brusselmans et al. 2005; Bandyopadhyay et al. 2006; Beckers et al. 2007).

The present study was undertaken to test the hypothesis that downregulation of SCD in prostate cancer cells heightens apoptotic cell death in part by modulation of FAS expression. SCD induced key lipogenic enzymes, FAS and ACC-α, in LNCaP

*Corresponding author. Email: ekim@chonnam.ac.kr

ISSN 1976-8354 print/ISSN 2151-2485 online

DOI: 10.1080/19768354.2011.555188
http://www.informaworld.com

prostate cancer cells and chemical inhibition of FAS suppressed the proliferative effect of SCD on prostate cancer cells. However, SCD overexpression conferred resistance to cell death induced by ceramide, which is known to be increased by FAS inhibition in cancer cells. Concomitantly, micro RNA (miRNA)-mediated silencing of SCD led to increased sensitivity to ceramide induction of cell death with increased caspase-3 activity and poly(ADP-ribose) polymerase (PARP) cleavage. In addition, the level of proapoptotic Bax protein was increased by knockdown of SCD in LNCaP cells. Together, these results emphasize the role of SCD in resistance to cell death stimuli. Modulation of SCD expression or activity might provide a therapeutic approach for metabolic cancers, including prostate cancer.

Materials and methods

Plasmids and reagents

Plasmids pSG5-AR, pSG5-PPAR, pSG5-GR, ARE_4-Luc, PPRE-Luc and MMTV-Luc have been described previously (Forman et al. 1995; Yeh and Chang 1996; Heinlein et al. 1999; Hu et al. 2004). pcDNA3-SCD and pcDNA^{TM}6.2-GW/SCDmiR contain human full-length SCD and SCDmiR (Invitrogen), respectively. Cerulenin (Sigma-Aldrich), rosiglitazone (Cayman Chemicals), dexametasone (Sigma-Aldrich) and C2-ceramide (Sigma-Aldrich) were purchased as indicated.

Cell cultures and luciferase assays

Cells were maintained in RPMI-1640 (LNCaP) or DMEM (COS-1) medium supplemented with 10% fetal bovine serum (FBS). RWPE-1 cells were cultured in keratinocyte-SFM (GIBCO) supplemented with Defined Keratinocyte-SFM Growth Supplement (GIBCO). LNCaP cells stably transfected with pcDNA3 (LN-C), pcDNA3-SCD (LN-SCD), pcDNA^{TM}6.2-GW/miR (LN-miR) or pcDNA^{TM}6.2-GW/SCDmiR (LN-SCDmiR) were maintained in RPMI-1640 containing 600 μg/ml geneticin or 3 μg/ml blastacidin. Transient transfection and luciferase assays were performed as previously described (Park et al. 2008). Relative luciferase activity (fold) was expressed based on the induction relative to the transfection of empty vector (set as 1-fold) without ligand; the results are the mean ± standard deviation (SD) of three separate experiments.

Semi-quantitative reverse transcription polymerase chain reaction (semi-Q RT-PCR)

Total RNA was isolated from cells using Trizol reagent (Invitrogen), and cDNA was synthesized using MMLV-RTase (Promega) and oligo dT primers (Invitrogen). The mRNA levels of SCD, FAS, ACC-α and 36B4 were determined by semi-Q RT-PCR as described previously (Park et al. 2008). Abundance of SCD, FAS and ACC-α mRNA was quantified relative to transcript of the internal control, 36B4, using a Gel doc XR system (Bio-Rad). RT-PCR was performed three independent times for each experiment. The sense and antisense strand PCR primer sequences were: SCD (sense; 5′-CGACGTGGCTTTTTCTTCTC-3′) and (antisense; 5′-GGGGGCTAATGTTCTTGT CA-3′), FAS (sense; 5′-AACTCCAGGTTGTCCCTGTG-3′) and (antisense; 5′-CTGGCTCAGCACCTCTATCC-3′), ACC-α (sense; 5′-ACCACCAATGCCAA AGTAGC-3′) and (antisense; 5′-CTGCAGGTTCTCAATGCAAA-3′), 36B4 (sense; 5′-AGATGCAGCAGATCCGCAT-3′) and (antisense; 5′-ATATGAGGCAGCAGTTTCTC CAG-3′).

Cell viability assay

Stably transfected LNCaP cells were seeded in wells of 12-well plates at a density of 15,000 cells/well in medium containing 10% FBS. At the indicated time points, medium was removed and serum-free medium containing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; 0.5 mg/ml; Sigma-Aldrich) was added to each well. Two hours later, cellular formazan product was dissolved with acidic isopropanol, and the absorbance at 570/650 nm was measured (A_{570} nm) by an enzyme-linked immunosorbant assay reader. Value of untreated control cells at 0 h was set as 1; the results are the mean ± SD from three independent experiments.

Western blot analysis

Samples were subjected to 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and the resolved proteins were transferred from the gel to a polyvinylidene fluoride membrane. The membrane was probed with anti-PARP antibody (Cell Signaling Technologies), anti-Bax (Santa-Cruz Biotechnologies) and horseradish peroxidase-conjugated secondary antibody (Santa-Cruz Biotechnologies).

Cell death and caspase-3 activity assays

An assay of cell death was performed using a Trypan Blue dye exclusion assay after 16 h treatment with 20 μM ceramide. Caspase-3 activity was determined by using the CleavaLite™ caspase-3 activity assay kit (Chemicon International). Treated cells were harvested and incubated with lysis buffer on ice for 10 min and centrifuged at 10,000 × *g* for 5 min. Cell lysates were then incubated

with a bioluminescent substrate for caspase-3, which has a Renilla luciferase containing the caspase-3 cleavage site, Asp-Glu-Val-Asp (DEVD). Caspase-3 activities were measured as bioluminescence according to the manufacturers' instructions.

Results

SCD regulates expression of FAS and ACC-α in LNCaP prostate cancer cells

To understand the possible link between SCD and other lipogenic genes in prostate cancer, the expression profile of SCD, FAS and ACC-α was determined in normal prostate epithelial and prostate cancer cells. Semi-Q RT-PCR analysis showed that mRNA levels of SCD, FAS and ACC-α in LNCaP prostate cancer cells were higher than those of normal prostate epithelial cells (RWPE-1) (Figure 1A). In addition, increased expression of these lipogenic genes was also confirmed in other prostate cancer cells such as PC-3, DU145 and 22Rv1 cells (data not shown). To further confirm SCD regulation of FAS and ACC-α gene expression in LNCaP cells, the effect of SCD on the expression of FAS and ACC-α was evaluated in LNCaP cells stably overexpressing SCD (LN-SCD). Overexpression of SCD in LNCaP cells increased the mRNA levels of FAS and ACC-α genes by 56% and 50%, respectively, as compared to empty vector-transfected LNCaP cells (LN-C) in semi-Q RT-PCR analysis (Figure 1B). In contrast, loss of SCD in LNCaP cells resulted in reduction of FAS and ACC-α mRNA levels by 34% and 35%, respectively (Figure 1C). Together, these data indicate that SCD plays a role as a functional modulator of lipogenic gene expression in prostate cancer cells.

Pharmacological inhibition of FAS activity blocks SCD-induced LNCaP cell proliferation and AR transcriptional activity

Recently, we showed that SCD significantly induced proliferation of LNCaP prostate cancer cells (Kim et al., in press). Since overexpression of SCD resulted in an increase of FAS expression in LNCaP cells, it was appropriate to investigate whether pharmacological inhibition of FAS activity could block SCD-mediated LN-SCD cell proliferation. Consistent with our previous data, SCD significantly increased prostate cancer cell proliferation as compared with control LNCaP cells (LN-C). In addition, treatment with DHT further increased SCD-induced LNCaP cell proliferation. However, when the FAS inhibitor cerulrenin was added (5 μg/ml) to LN-SCD cells, the cell proliferation promoting effect of SCD was completely abolished (Figure 2A), suggesting the requirement of fatty acid supply for SCD-induced proliferation of LNCaP cells.

Other nuclear receptors such as peroxisome proliferator-activated-receptor γ (PPARγ) and glucocorticoid receptor (GR) have been implicated in the proliferation of prostate cancer cells, although AR has an essential role in the proliferation of prostate cancer cells. Since we recently found that SCD enhances DHT-induced AR transactivation, we first performed reporter gene assays to determine whether SCD, a FAS inducer, affected transcriptional activities of PPARγ and GR. However, no significant effect of SCD on PPARγ- and GR-mediated transcriptional activities was evident (Figure 2B), suggesting that SCD may facilitate prostate cancer cell proliferation by specifically modulating AR activity. The next experiment assessed whether fatty acid supply is important for enhancing the effect of SCD on AR transcriptional activity. As shown in Figure 2C, DHT induced AR transactivation and SCD further enhanced DHT-mediated AR transcriptional activity. However, when cerulenin was added together with DHT and SCD into LNCaP cells, the effect of SCD on AR activity was abolished, indicating the importance of FAS activity for both DHT and SCD synergy in AR transcriptional activity.

Effect of SCD on ceramide-induced LNCaP cell death

Chemical inhibition or RNA interference of FAS induces cell apoptosis, in part due to the accumulation of ceramide in tumor cells (Bandyopadhyay et al. 2006). Since overexpression of SCD in the current study led to induction of FAS in LNCaP cells, the cytotoxic effect of ceramide on LNCaP cells stably expressing SCD was investigated. A 16 h treatment with 20 μM ceramide resulted in a marked increase in cell death of control LNCaP cells (LN-C) as compared to vehicle treatment. In contrast, LN-SCD cells were resistant to ceramide-induced cell death (Figure 3A). After ceramide treatment, cleaved PARP fragment, a substrate for pro-apoptotic caspase-3, was markedly increased in LN-C cells. In contrast, LN-SCD cells displayed significantly inhibited PARP cleavage in the presence of ceramide (Figure 3B).

The proapoptotic protein Bax increases cytochrome *c* release from mitochondria and triggers the proapoptotic caspase cascade, leading to induction of cell death (Jurgensmeier et al. 1998). Appropriately, an immunoblot analysis was done to examine whether knockdown of SCD in LNCaP cells increased Bax protein levels. miRNA-mediated silencing of SCD in LNCaP cells (LN-SCDmiR) resulted in an increase of Bax protein (Figure 3C). Consistently, compared to control LNCaP cells (LN-miR), LN-SCDmiR cells displayed a higher

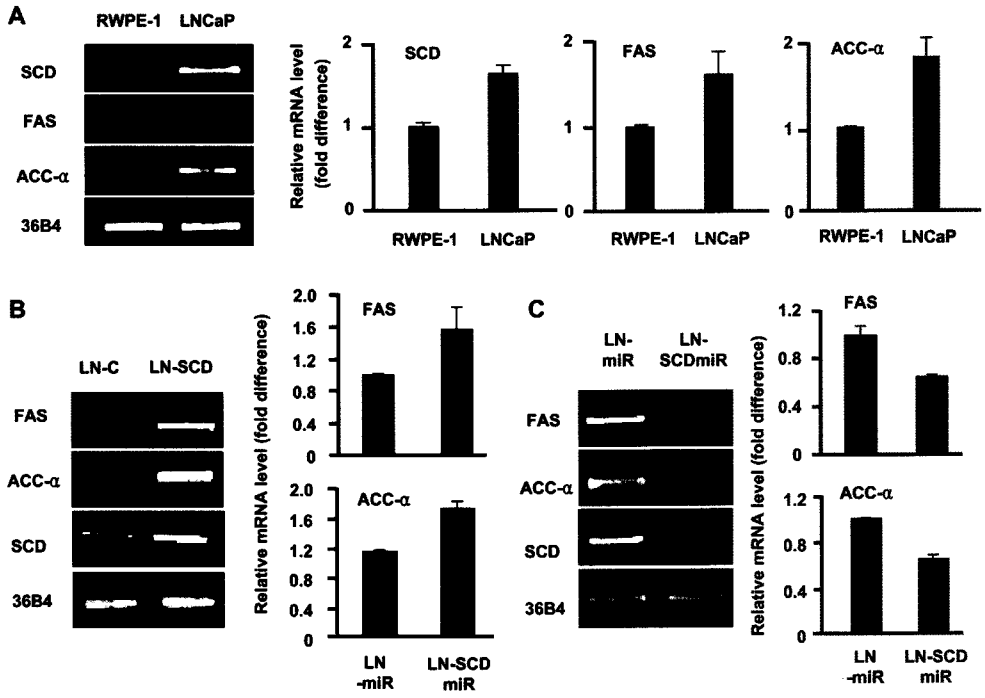

Figure 1. Effect of SCD on expression of lipogenic genes in LNCaP prostate cancer cells. (A) Increased expression of SCD, FAS and ACC-α genes in human prostate cancer cells. The mRNA levels of SCD, FAS and ACC-α were analyzed in nonmalignant (RWPE-1) and malignant prostate cancer cells (LNCaP) by semi-Q RT-PCR analysis. SCD, FAS and ACC-α mRNA levels in RWPE-1 cells were set as 1, and the results are the mean ± SD of three independent experiments. (B) SCD overexpression in LNCaP cells (LN-SCD) resulted in increased FAS and ACC-α expression. (C) Silencing of SCD in LNCaP cells (LN-SCDmiR) inhibited the expression of FAS and ACC-α. Total RNAs prepared from LN-C and LN-SCD cells, or LN-miR and LN-SCDmiR cells were subjected to quantitative RT-PCR to determine FAS and ACC-α mRNA levels. 36B4 fragments were amplified as a loading control. The data shown are representative of three individual experiments and relative mRNA levels of the SCD, FAS and ACC genes are expressed as the mean ± SD of three individual experiments.

death rate even in the absence of ceramide (Figure 3D). Furthermore, knockdown of SCD resulted in increased sensitivity to ceramide, leading to increase of cell death in LNCaP cells. In addition, cleavage of PARP occurred in LN-SCDmiR cells even in the absence of ceramide, and was further induced by ceramide treatment (Figure 3E). The marked increase of PARP cleavage and Bax protein level by the silencing of SCD in LNCaP cells prompted a further analysis of the effect of SCD on ceramide activation of caspase-3 activity using SCD knockdown LNCaP cells. Caspase-3 activity in LN-SCDmiR cells treated with 20 μM ceramide was 1.47-fold higher than control LN-miR cells (Figure 3F).

Discussion

Prostate cancer is the second leading cause of cancer-related deaths in males in the United States (Jemal et al. 2007). Loss of lipid homeostasis by excess intake of a fat-rich diet is considered as a risk factor of development and progression of prostate cancer (Menendez and Lupu 2007). In line with this notion, many genes involved in lipid metabolism, such as FAS and ACC-α, have been reported to have oncogenic roles in prostate cancer (Swinnen et al. 2002; De Schrijver et al. 2003; Brusselmans et al. 2005; Bandyopadhyay et al. 2006; Beckers et al. 2007).

Several reports point to a linkage between SCD and cancer cell proliferation. SCD expression is increased in various cancers such as prostate, colonic and oesophageal cancers, as well as dichloroacetic acid-induced mouse hepatocellular carcinoma (Lu et al. 1997; Thai et al. 2001; Scaglia and Igal 2005). Although SCD has frequently been linked to cancers and plays a key role in the proliferation of cancer and transformed cells (Scaglia and Igal 2005), whether SCD confers increased survival ability of prostate cancer cells to apoptotic stimuli remains unclear.

Here, we report that increased cell proliferation of LNCaP prostate cancer cells by SCD is, in part, due to induction of FAS, the key enzyme in the synthesis of long-chain fatty aicds. FAS inhibition in LNCaP cells stably expressing SCD abrogated SCD-induced LNCaP

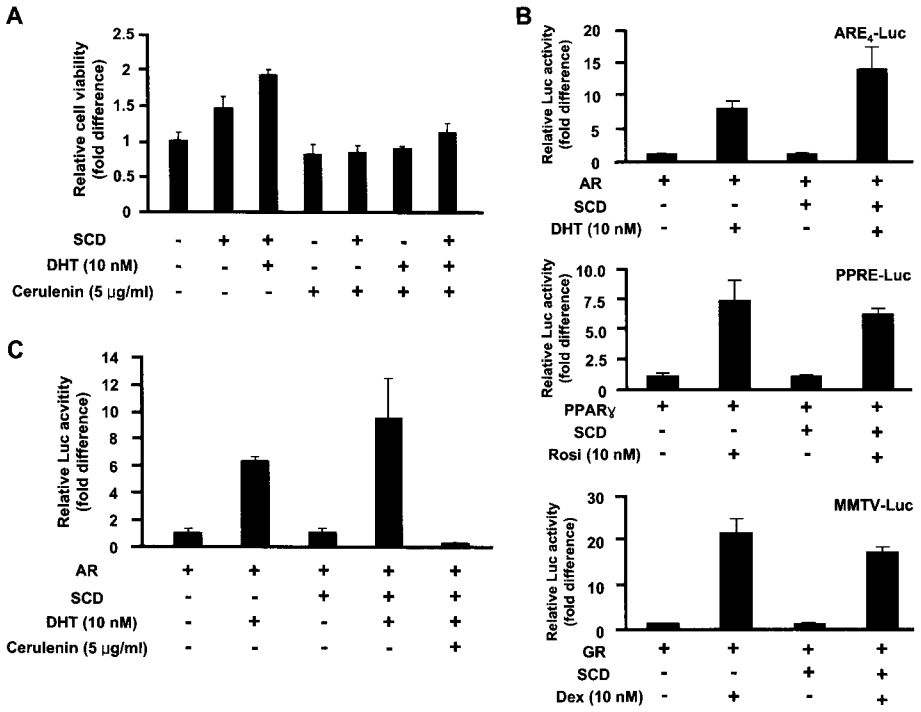

Figure 2. Cerulenin suppresses SCD-mediated LNCaP cell proliferation and AR transcriptional activity. (A) LN-SCD and LN-C cells were treated with vehicle or cerulenin (5 μg/ml) in the presence or absence of DHT (10 nM) for 24 h and cell proliferation was determined by a MTT assay. Data are presented as the mean ± SD of three individual experiments. (B) SCD selectively enhances AR transcriptional activity. COS-1 cells were transfected with expression vectors for the nuclear receptors (pSG5-AR, pSG5-PPARγ or pSG5-GR; 100 ng of each) and the reporter genes containing appropriate response element for corresponding nuclear receptor (ARE_4-Luc, PPRE-Luc or MMTV-Luc; 300 ng of each) in the presence or absence of pcDNA3-SCD as indicated. Cells were treated with 10 nM DHT, 10 nM rosiglitazone or 10 nM dexamethasone for 24 h and assayed for luciferase activity. (C) Cerulenin inhibits the enhancing effect of SCD on DHT-induced AR transactivation. SCD (300 ng) was co-transfected with ARE_4-Luc (300 ng) and pSG5-AR (100 ng) into COS-1 cells. Cells were treated with vehicle or 5 μg/ml cerulenin in the presence or absence of 10 nM DHT for 24 h and harvested for luciferase assay.

cell proliferation. This implies that FAS, together with ACC-α induced by SCD, is required for a constant supply of fatty acids, which are substrates for the synthesis of phospholipids. Since phospholipids are essential components of cell membranes, high levels of FAS may be critical to meet the requirement of fatty acids for membrane biogenesis in rapidly dividing cancer cells. In addition, cerulenin treatment abolished SCD enhancement of AR transcriptional activity, implying that the fatty acid supply by endogenous lipogenesis may be important for SCD-mediated AR transcriptional activity, in addition to coactivation of SCD on AR transactivation through direct interaction with AR. A link between SCD and FAS expression was previously reported in the liver of SCD deficient mice (Ntambi et al. 2002). SCD-induced FAS expression is now further underscored by the present demonstration that overexpression of SCD leads to an increase of FAS in LNCaP prostate cancer cells. How this occurs is not clear. Androgen has been shown to stimulate FAS expression (Swinnen et al. 1997). Furthermore, we recently showed that SCD enhances androgen-induced AR transcriptional activity (Kim et al., in press). Thus, it is possible that SCD may induce FAS expression by enhancing AR transactivation. However, further studies are needed to define the molecular mechanism of SCD-induced FAS expression.

In this study, cerulenin, which is a chemical inhibitor of FAS activity, suppressed the effect of SCD on AR transactivation. It has been reported that FAS activity is critical for cancer cell proliferation and survival but not for normal cell proliferation (Kuhajda 2000). A recent study showed that RNA interference-mediated knockdown of SCD in L6 myotube increased the ceramide content and caspase-3 activity, resulting in induction of cell death (Turpin et al. 2006). The same study also reported that saturated, but not unsaturated, fatty acids induced ceramide content with increased caspase-3 activity. In the present study, knockdown of SCD intrinsically increased cell death in LNCaP prostate cancer cells. The past and current observations collectively support

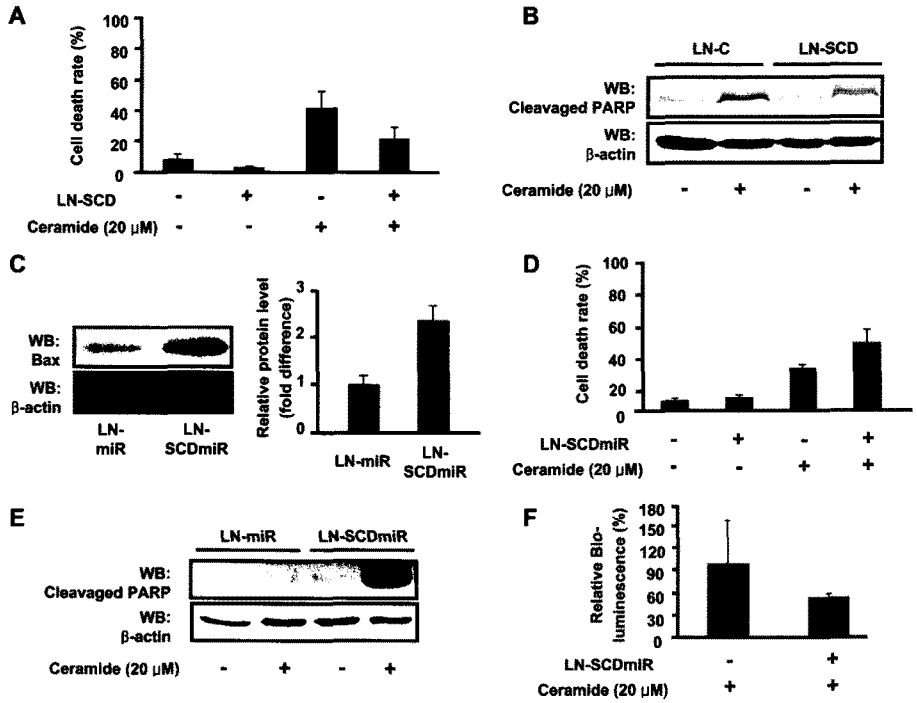

Figure 3. SCD confers resistance to ceramide-induced cell death in LNCaP cells. (A) Overexpression of SCD inhibits ceramide-induced cell death in LNCaP cells. Cells were incubated in the presence or absence of 20 μM ceramide for 16 h and viable cells were counted by the Trypan Blue exclusion assay. Data are presented as the mean ± SD of three individual experiments. (B) Immunoblot analysis of cleaved PARP proteins. LN-C and LN-SCD cells were grown in the presence or absence of ceramide (20 μM) for 16 h and then harvested. Whole cell lysates were subjected to immunoblot analysis using anti-cleaved PARP antibody. β-Actin was used as a loading control. (C) Knockdown of SCD increases Bax protein levels in LNCaP cells. LN-miR and LN-SCDmiR cells were grown for 24 h and then harvested. Whole cell lysates were subjected to immunoblot analysis using anti-Bax antibody. (D) Suppression of SCD expression increases sensitivity to ceramide-induced cell death in LNCaP cells. Cells were incubated in the presence or absence of 20 μM ceramide for 16 h and viable cells were counted by a Trypan Blue exclusion assay. (E) Immunoblot analysis of cleaved PARP protein. LN-miR and LN-SCDmiR cells were grown in the presence or absence of ceramide (20 μM) for 16 h and then harvested for immunoblot analysis to compare the levels of cleaved PARP protein. (F) LN-miR and LN-SCDmiR cells were treated with 20 μM ceramide for 16 h and caspase-3 activity was measured with the CleavaLite™ caspase-3 acitivity assay kit. Data are presented as the mean ± SD of three individual experiments.

the suggestion that SCD may be essential not only for cancer physiology, but also for normal physiology such as skeletal muscle myotubes. Increased cell death of SCD knockdown L6 myotubes is due to increased content of ceramide by accumulated saturated fatty acids (Turpin et al. 2006). However, when we tested whether the SCD effect on LNCaP cell survival could be abrogated by exogenous ceramide, SCD overexpressing cells were more resistant to ceramide-induced cell death. This suggests that SCD-induced cell survival may not be primarily due to the reduced content of ceramide, which has been reported to be produced by accumulated saturated fatty acids (Turpin et al. 2006). Considering that SCD catalyzes the conversion of saturated fatty acids to monounsaturated fatty acids (MUFAs), it is possible that in addition to supplying new lipid components for membrane biogenesis in proliferating cancer cells, MUFAs produced by SCD may independently induce signal transduction pathways important for cell survival and proliferation. MUFAs are able to activate the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K)/Akt pathways, which are important for cell growth and survival (Lu et al. 1996; Paine et al. 2000; Askari et al. 2002; Werz et al. 2002). Furthermore, inhibition of PI3K/Akt and MAPK results in activation of caspase-3 activity (Turpin et al. 2006; Gao et al. 2008). In agreement with these reports, reduced levels of SCD in LNCaP cells in the present study resulted in higher caspase-3 activity with increased cleavage of PARP. However, further studies are required to fully understand the molecular pathway by which SCD confers resistance to ceramide-induced cell death.

In summary, SCD-mediated LNCaP cell proliferation occurs, in part, because of increased FAS expression, and SCD overexpression in LNCaP cells confers

resistance to cell death induced by ceramide. Thus, SCD is an important therapeutic target for the treatment of prostate cancer.

Acknowledgements

This work was supported by Grant R01-2006-000-10378-0 from the Basic Research Program of the Korea Science and Engineering Foundation.

References

Askari B, Carroll MA, Capparelli M, Kramer F, Gerrity RG, Bornfeldt KE. 2002. Oleate and linoleate enhance the growth-promoting effects of insulin-like growth factor-I through a phospholipase D-dependent pathway in arterial smooth muscle cells. J Biol Chem. 277:36338–36344.

Bandyopadhyay S, Zhan R, Wang Y, Pai SK, Hirota S, Hosobe S, Takano Y, Saito K, Furuta E, Iiizumi M, et al. 2006. Mechanism of apoptosis induced by the inhibition of fatty acid synthase in breast cancer cells. Cancer Res. 66:5934–5940.

Baron A, Migita T, Tang D, Loda M. 2004. Fatty acid synthase: a metabolic oncogene in prostate cancer? J Cell Biochem. 91:47–53.

Beckers A, Organe S, Timmermans L, Scheys K, Peeters A, Brusselmans K, Verhoeven G, Swinnen JV. 2007. Chemical inhibition of acetyl-CoA carboxylase induces growth arrest and cytotoxicity selectively in cancer cells. Cancer Res. 67:8180–8187.

Brusselmans K, De Schrijver E, Verhoeven G, Swinnen JV. 2005. RNA interference-mediated silencing of the Acetyl-CoA-Carboxylase-alpha gene induces growth inhibition and apoptosis of prostate cancer cells. Cancer Research. 65:6719–6725.

De Schrijver E, Brusselmans K, Heyns W, Verhoeven G, Swinnen JV. 2003. RNA interference-mediated silencing of the fatty acid synthase gene attenuates growth and induces morphological changes and apoptosis of LNCaP prostate cancer cells. Cancer Research. 63:3799–3804.

Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 1995. 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. Cell. 83:803–812.

Fritz V, Benfodda Z, Rodier G, Henriquet C, Iborra F, Avances C, Allory Y, de la Taille A, Culine S, Blancou H, et al. 2010. Abrogation of de novo lipogenesis by stearoyl-CoA desaturase 1 inhibition interferes with oncogenic signaling and blocks prostate cancer progression in mice. Mol Cancer Ther. 9:1740–1754.

Gao Y, Ordas R, Klein JD, Price SR. 2008. Regulation of caspase-3 activity by insulin in skeletal muscle cells involves both PI3-kinase and MEK-1/2. J Appl Physiol. 105:1772–1778.

Heinlein CA, Ting HJ, Yeh S, Chang C. 1999. Identification of ARA70 as a ligand-enhanced coactivator for the peroxisome proliferator-activated receptor gamma. J Biol Chem. 274:16147–16152.

Hess D, Chisholm JW, Igal RA. 2010. Inhibition of stearoylCoA desaturase activity blocks cell cycle progression and induces programmed cell death in lung cancer cells. PLoS One. 5:e11394.

Hu YC, Yeh S, Yeh SD, Sampson ER, Huang J, Li P, Hsu CL, Ting HJ, Lin HK, Wang L, et al. 2004. Functional domain and motif analyses of androgen receptor coregulator ARA70 and its differential expression in prostate cancer. J Biol Chem. 279:33438–33446.

Jemal A, Siegel R, Ward E, Murray T, Xu JQ, Thun MJ. 2007. Cancer statistics, 2007. Ca-Cancer J Clin. 57:43–66.

Jurgensmeier JM, Xie Z, Deveraux Q, Ellerby L, Bredesen D, Reed JC. 1998. Bax directly induces release of cytochrome c from isolated mitochondria. Proc Natl Acad Sci U S A. 95:4997–5002.

Kim SJ, Choi H, Park SS, Chang C, Kim E. 2011. Stearoyl CoA Desaturase (SCD) Facilities Proliferations of Prostate Cancer Cells through Enhancement of Androgen Receptor Transactivation. Mol Cells. 31 (in press) DOI: 10.1007/s10059-011-0043-5.

Kuhajda FP. 2000. Fatty-acid synthase and human cancer: New perspectives on its role in tumor biology. Nutrition. 16:202–208.

Lu G, Morinelli TA, Meier KE, Rosenzweig SA, Egan BM. 1996. Oleic acid-induced mitogenic signaling in vascular smooth muscle cells. A role for protein kinase C. Circ Res. 79:611–618.

Lu JX, Pei HY, Kaeck M, Thompson HJ. 1997. Gene expression changes associated with chemically induced rat mammary carcinogenesis. Mol Carcinogen. 20:204–215.

Menendez JA, Lupu R. 2007. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat Rev Cancer. 7:763–777.

Milgraum LZ, Witters LA, Pasternack GR, Kuhajda FP. 1997. Enzymes of the fatty acid synthesis pathway are highly expressed in in situ breast carcinoma. *Clin* Cancer Res. 3:2115–2120.

Ntambi JM, Miyazaki M, Stoehr JP, Lan H, Kendziorski CM, Yandell BS, Song Y, Cohen P, Friedman JM, Attie AD. 2002. Loss of stearoyl-CoA desaturase-1 function protects mice against adiposity. Proc Natl Acad Sci U S A. 99:11482–11486.

Paine E, Palmantier R, Akiyama SK, Olden K, Roberts JD. 2000. Arachidonic acid activates mitogen-activated protein (MAP) kinase-activated protein kinase 2 and mediates adhesion of a human breast carcinoma cell line to collagen type IV through a p38 MAP kinase-dependent pathway. J Biol Chem. 275:11284–11290.

Park SS, Choi H, Kim SJ, Kim OJ, Chae KS, Kim E. 2008. FXR alpha down-regulates LXR alpha signaling at the CETP promoter via a common element. Mol Cells. 26:409–414.

Scaglia N, Igal RA. 2005. Stearoyl-CoA desaturase is involved in the control of proliferation, anchorage-independent growth, and survival in human transformed cells. J Biol Chem. 280:25339–25349.

Swinnen JV, Esquenet M, Goossens K, Heyns W, Verhoeven G. 1997. Androgens stimulate fatty acid synthase in the human prostate cancer cell line LNCaP. Cancer Res. 57:1086–1090.

Swinnen JV, Roskams T, Joniau S, Van Poppel H, Oyen R, Baert L, Heyns W, Verhoeven G. 2002. Overexpression of fatty acid synthase is an early and common event in the development of prostate cancer. Int J Cancer. 98:19–22.

Thai SF, Allen JW, DeAngelo AB, George MH, Fuscoe JC. 2001. Detection of early gene expression changes by differential display in the livers of mice exposed to dichloroacetic acid. Carcinogenesis. 22:1317–1322.

Turpin SM, Lancaster GI, Darby I, Febbraio MA, Watt MJ. 2006. Apoptosis in skeletal muscle myotubes is induced

by ceramides and is positively related to insulin resistance. Am J Physiol Endocrinol Metab. 291:E1341–1350.

Van de Sande T, De Schrijver E, Heyns W, Verhoeven G, Swinnen JV. 2002. Role of the phosphatidylinositol 3′-kinase/PTEN/Akt kinase pathway in the overexpression of fatty acid synthase in LNCaP prostate cancer cells. Cancer Res. 62:642–646.

Werz O, Szellas D, Steinhilber D, Radmark O. 2002. Arachidonic acid promotes phosphorylation of 5-lipoxygenase at Ser-271 by MAPK-activated protein kinase 2 (MK2). J Biol Chem. 277:14793–14800.

Yahagi N, Shimano H, Hasegawa K, Ohashi K, Matsuzaka T, Najima Y, Sekiya M, Tomita S, Okazaki H, Tamura Y, et al. 2005. Co-ordinate activation of lipogenic enzymes in hepatocellular carcinoma. Eur J Cancer. 41:1316–1322.

Yeh S, Chang C. 1996. Cloning and characterization of a specific coactivator, ARA70, for the androgen receptor in human prostate cells. Proc Natl Acad Sci U S A. 93:5517–5521.