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14. ABSTRACT

In this study we investigated the effects of two dietary RXR agonists, phytanic acid, and docohexaenoic acid (DHA), on the cell growth and retinoid metabolism of cultured normal human prostate epithelial cell (PrEC) and human prostate cancer cell lines, PC-3 and LNCaP. Both phytanic acid and DHA inhibited the growth of PC-3 and LNCaP cells and decreased cyclin D1 expression in PC-3 cells. Phytanic acid or DHA altered the metabolism of retinol and generated a novel retinyl ester peak. Mass spectrometry analyses demonstrated the novel retinyl ester peak generated by phytanic acid or DHA was retinyl phytanate or retinyl docosahexaenate, respectively. Real time RT-PCR results showed that both phytanic acid and DHA did not dramatically change LRAT expression level in both cell lines. In addition, LRAT participates in the generation of retinyl phytanate, while the generation of retinyl docosahexaenate by DHA is possibly through another different mechanism other than lecithin:retinol acyltransferase (LRAT) and acyl CoA:retinol acyltransferase (ARAT). These results suggest that both phytantic acid and DHA, natural dietary RXR ligands, may be useful agents for future dietary preventive and therapeutic approaches to human prostate cancer.

15. SUBJECT TERMS
prostate cancer, phytanic acid, docohexaenoic acid, cell proliferation, retinoid metabolism

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Introduction

Retinoids, a group of natural and synthetic small, lipophilic molecules which are vitamin A (retinol) derivatives, regulate cell proliferation and differentiation (Gudas et al., 1994). It is believed that retinoids suppress the process of carcinogenesis by inhibiting cell proliferation, enhancing apoptosis, and inducing cell differentiation (Lotan et al., 1995). Preclinical and clinical research (Kelloff et al., 1999) and epidemiological studies (Hong and Itri, 1994; Lotan, 1996; Niles, 2000) have shown that retinoids have anticarcinogenic effects on many organ sites. Retinoic acid (RA), one of the metabolites of vitamin A, exerts its physiological functions through retinoic acid receptors (RARs) and retinoid X receptors (RXRs) (Chambon, 1996). These receptors are ligand-dependent transcription factors that bind to retinoic acid response DNA elements (RAREs), thereby modulating the expression of specific downstream target genes. There are three subtypes (α, β and γ) of each RAR and RXR, and the expression patterns of every receptor subtype are tissue specific and developmental stage specific (Dollé et al., 1990; Leid et al., 1992). These retinoid receptors function as RAR:RXR heterodimers (Mangelsdorf et al., 1994). Prostate cancer is one of the most common cancers in males (Landis et al., 1998). A large body of epidemiological data indicates that retinoids have actions in the prevention of prostate cancer (Nanus and Gudas, 2000). Our lab observed that the esterification of retinol to retinyl esters, and the levels of LRAT, an enzyme involved in vitamin A esterification and storage, were greatly decreased in human prostate cancer cells (such as PC-3 cells as compared to normal human prostate epithelial cells) and tissues in sections from patient samples (Guo et al., 2002). Recent reports have shown that RXR selective retinoids represent promising agents for the prevention and treatment of prostate cancer (McCormick et al., 1999). Phytanic acid (PA) (3.7.11.15-tetramethylhexadecanoic acid) is a branched-chain, isoprenoid-derived fatty acid, generated by the oxidation of the phytol side chain of chlorophyll in mammals (Jansen et al., 1996). All phytanic acid in the human body comes from dairy products and ruminant fats in the diet (Baxter, 1968). Docosahexaenoic acid (DHA) is a long chain, ω-3 polyunsaturated fatty acid that is present at high levels in fish oils. DHA is an essential nutrient for adequate retina and brain development (de Urquiza et al., 2000; Uauy et al., 2001). Both phytanic acid ((Kitareewan et al., 1996; Lemotte et al., 1996; Radominska-Pandya and Chen, 2002) and DHA are the RXR natural ligands (de Urquiza et al., 2000; Uauy et al., 2001). In this project, we have observed that phytanic acid and DHA, alone and with RAR agonists, suppressed the growth of human prostate cancer cells and decreased the protein level of cyclin D1, a cell cycle regulator. In addition, phytanic acid or DHA enhanced the level of retinyl esters in normal human prostate epithelial cells (PrEC) and human prostate cancer cells (PC-3), and generated a novel retinyl ester peak, which was identified by mass spectrometric analysis as retinyl phytanate or retinyl docosahexaenate, respectively. In addition, LRAT participates in the generation of retinyl phytanate, while the generation of retinyl docosahexaenate by DHA is possibly through another different mechanism other than lecithin:retinol acyltransferase (LRAT) and acyl CoA:retinol acyltransferase (ARAT). These results suggest that both phytantic acid and DHA may be useful agents for future dietary preventive and therapeutic approaches to human prostate cancer.

Body

Results from Jan 2004 to Dec 2004

1. Cell growth analysis

We have conducted several cell growth assays with human prostate cancer cell lines. For these experiments, we used androgen-unresponsive PC-3 cells, which in some respects simulate advanced stage prostate cancer. These cells were plated in 24 well plates in triplicate and were treated with 1 μM *all-trans* retinoic acid (ATRA), different concentrations of phytanic acid (PA), docosahexaenoic acid (DHA), and 5 μM of the synthetic, specific retinoid X receptor (RXR) agonist BMS 188649 (from Bristol-Myers Squibb Company) for 72 and 120 hours. Then cells were trypsinized and counted using a Coulter counter (Figure 1A). After 72 hours and 120 hours treatment, retinoic acid did not have a large effect on the growth of PC-3 cells. The RXR agonist BMS 188649 inhibited the growth of these cells at 72 and 120 hours of treatment. Seventy two and 120 hours treatment of phytanic acid or DHA also caused inhibition of the growth of PC-3 cells (Figure 1B and C) significantly.

2. Studies on cell cycle regulator cyclin D1

Furthermore, we investigated the mechanism of the inhibition of prostate cancer cell growth induced by phytanic acid and DHA. Cyclin D1 is a cell cycle regulator, and we tested in the presence or the absence of retinoic acid, the effects of phytanic acid or DHA on the expression level of cyclin D1 in PC-3 cells by using immunoblotting. We found that 48-hour treatment of phytanic acid (PA) or DHA alone could downregulate the expression of cyclin D1 in PC-3 cells, while retinoic acid alone did not cause significant change However, the combination with retinoic acid increased the inhibitory effect of DHA (not phytanic acid) on the expression of cyclin D1 (Figure 2A and B). In addition, the RXR agonist BMS 188649 reduced the cyclin D1 level in PC-3 cells (Fig 2A). Taken together, the data in figures 1 and 2 demonstrated that as natural ligands of the RXRs, phytanic acid and DHA could be potential agents for the prevention and treatment of prostate cancer.

3. Retinol metabolism altered by phytanic acid or DHA treatments in normal prostate epithelial cells and prostate cancer cells

We examined retinol metabolism in cultured normal human prostate epithelial cells (PrEC), LNCaP, and PC-3 cells to determine whether differences in retinol metabolism were present by using HPLC. The normal human prostate epithelial cells (PrEC) showed the esterification of most of the retinol, and no significant production of retinoic acid was observed. Both LNCaP and PC-3 cells showed severely impaired esterification of retinol. PC-3 cells did synthesize some retinoic acid from [^{3}H]retinol, while LNCaP cells only produced a trace amount of [^{3}H]retinoic acid (Figure. 3) (Guo et al., 2002). Therefore, we tested whether the treatment of phytanic acid or DHA could affect retinol metabolism in normal prostate epithelial cells (PrEC) and PC-3 cells. After 48 hours treatment, both phytanic acid and DHA increased the retinyl esters produced in both PrEC and PC-3 cells in the presence of 1 μM retinol (Figure 5).

Results from Jan 2005 to Dec 2005

1. Retinol metabolism altered by phytanic acid or DHA treatment in normal prostate epithelial cells and prostate cancer cells (continued)

In the year 2004 we observed that both phytanic acid and DHA increased the levels of retinyl esters in normal human prostate epithelial cells (PrEC) and human prostate cancer PC-3 cells. In the year 2005 we continued this work, because one marker of human prostate cancer is that compared to the normal human prostate epithelial cells, the esterification of retinol to retinyl esters and the key enzyme involved in this process, LRAT, are greatly decreased.

First we examined the metabolism of [^{3}H] retinol in both cell lines. PrEC cells and PC-3 cells were cultured in medium containing 100 nM [^{3}H] retinol for 12 hours, and retinoids in cells were extracted and separated by HPLC. Before retinoid extraction nonradiolabeled retinoid standards were added to each sample to aid in the identification of radiolabeled retinoids. The PrEC cells displayed a higher level of retinyl esters than the PC-3 cells (Figure 4). In addition, treatment with phytanic acid or DHA increased the [^{3}H] retinyl ester levels in both PrEC and PC-3 cells. Phytanic acid and DHA treatments both resulted in the production of novel retinyl ester peaks (according to their retention times in HPLC diagrams, marked with *) and an increase in retinyl palmitate (Figure 4 and Tables 1 and 2). We obtained similar results after either a 6 or a 24 hour treatment. In contrast, the synthetic RXR agonist BMS 188649 did not have an effect on the retinol metabolism (Figure 4).

We repeated the experiment to examine the effects of phytanic or DHA on the retinol metabolism in these two cell lines in the presence of 1 μM non-radiolabeled retinol for 48 hours**.** The retinyl ester levels in PrEC cells were dramatically higher than those in the PC-3 cells. In the absence of retinol there were almost no retinyl esters detected in either cell line (Figure 5). Similar to the results shown in figure 4, 48 hour treatment with phytanic acid or DHA increased retinyl ester levels in both PC-3 and PrEC cells. In addition, same as in figure 4, both phytanic acid and DHA induced the production of novel retinyl ester peaks in these cells (Figure 5). In addition, the novel retinyl ester peak generated by phytanic acid in PrEC cells was greater than that in PC-3 cells, however, the novel retinyl ester peaks generated by DHA in both cell lines were similar (Figure 5).

2. The effects of phytanic acid or DHA on the mRNA levels of LRAT in both PrEC and PC-3 cells.

To determine if phytanic acid or DHA treatment changed the levels of LRAT mRNA in PrEC or PC-3 cancer cells, we treated cells for 6 or 24 hours with various drugs, followed by the isolation and reverse transcription of RNA (3 μg per sample). The cDNA generated from 30 ng total RNA was used for real time PCR. Real time PCR was performed by using gene specific oligonucleotide primers. These primers were designed to generate cDNA fragments which cross an intron-exon boundary in the genomic DNA. Real time PCR was performed on a DNA Engine Opticon system (MJ Research, Boston, MA) with a SYBR green I Quantitect kit (Qiagen, Valencia, CA). The primer sequences were as follows: human LRAT, forward primer: 5´-TGG AAC AAC TGC GAG CAC TTC GTG-3´; reverse primer: 5'-GCA GGA AGG GTA GTG TAT GAT ACC-3´. Human HPRT (hypoxanthine guanine phosphoribosyl transferase, a constitutively expressed enzyme), forward primer: 5´-TGC TCG AGA TGT GAT GAA GG-3´; reverse primer: 5´-TCC CCT GTT GAC TGG TCA TT-3´.

HPRT was used as a loading control. We found that after either a 6 or a 24 hour treatment, LRAT mRNA levels were not altered significantly in both PrEC or in PC-3 cells (Figure 6 A and B). Therefore, the increase of some retinyl esters such as retinyl palmitate induced by phytanic acid or DHA observed in figure 4 probably was through the increment of LRAT activity.

3. The roles of LRAT in the generation of the novel retinyl ester in the presence of phytanic acid or DHA.

To examine whether LRAT is involved in the synthesis of the new retinyl ester peak observed in the presence of phytanic acid or DHA, we measured the retinyl esters in levels in both the parental PC-3 cell line and in PC-3 cells which express the full length human LRAT cDNA driven by the cytomegalovirus (CMV) promoter. In the presence of retinol only, the amount of retinyl esters in this LRAT engineered PC-3 cell line was much greater than that in parental PC-3 cells (Fig. 7). Forty eight hour culture in the presence of 1 μM retinol and 50 μM phytanic acid resulted in an increase in retinyl esters in the parental PC-3 cell line and the appearance of a novel retinyl ester peak in both parental PC-3 cells and the PC-3 cells which overexpress human LRAT. In addition, the novel retinyl ester peak (marked with *) in PC-3 cells which overexpress human LRAT generated by phytanic acid was much greater than that in the parental PC-3 cells (Fig. 7). However, 48 hour DHA (20 μM) treatment did not significantly increase the level of the novel retinyl ester peak in PC-3 cells which overexpress human LRAT as compared to that in parental PC-3 cells (Fig. 7). These data indicate that LRAT participated in the synthesis of the novel retinyl ester generated by phytanic acid, and it did not play an important role in the synthesis of the novel retinyl ester generated by DHA. The 3D structures of palmitate, phytanic acid, and DHA in figure 8 may explain the different roles of LRAT in the synthesis of the phytanic acid induced novel retinyl ester and the DHA induced novel retinyl ester.

4. Identification of the novel retinyl ester generated by phytanic acid or DHA.

We used mass spectrometry to identify the novel retinyl ester peak generated in PC-3 cells which overexpress human LRAT generated by 50 μM phytanic acid or 20 μM DHA. Using laser desorption ionization-mass spectrometry (LDI-MS) in the positive ion mode, the mass spectra of retinyl esters usually show characteristic fragment molecule ion ($M^{\cdot+}$) at *m/z* 269 u (Wingerath et al., 1997), which fit one known fragmentation pathway of retinyl esters during LDI mass spectrometry: the elimination of the fatty acyl chain (Wingerath et al., 1997). We first performed LDI-MS analysis on the collected HPLC fraction of retinyl palmitate from PC-3 cells which overexpress human LRAT, a known retinyl ester, to demonstrate that this technique was suitable for the identification of new retinyl esters. Three major peaks were detected: *m/z* 269.2 u, *m/z* 524.5 u, and *m/z* 480.5 u (Fig. 9B). The molecular weight of retinyl palmitate is 524.5 (Fig. 9A). The peak at *m/z* 480.5 u was the decarboxylated ion, and it resulted from another known fragmentation pathway: decarboxylation through a cyclic transition state (Wingerath et al., 1997). The peak at m/z 540.5 was the oxidized form of retinyl palmitate. Further, the post source decay (PSD) mass spectrum of the selected molecular ion of the peak at m/z 524.5 is shown in Fig. 9C, and the result fitted the PSD spectra of pattern of retinoids observed in our laboratory (Suh et al, manuscript in preparation). These results show that our mass spectrometry system is suitable for the identification of specific retinyl esters.

Figure 10 shows the mass spectra of the retinoid HPLC fraction of the novel peak generated in the presence of phytanic acid and retinol in the PC-3 cell line which overexpresses human LRAT, and of the retinoid HPLC fraction at the same retention time from the PC-3 cell line which overexpresses human LRAT treated only with retinol. In the presence of retinol and phytanic acid, three new peaks were measured at *m/z* 269.2, 580.5 and 536.5, which were not detected in the spectrum of the sample without phytanic acid treatment (Fig. 10 B and C). The peak of *m/z* 269.2 indicated the presence of retinoids. The molecular weight of retinyl phytanate (Fig. 10A) is 580.5, and the molecular weight of the decarboxylated ion is 536.5. In addition, we performed a post-source decay (PSD) assay on the peak of *m/z* 580.5 (Figure 10D), and the result showed that it was a retinyl derivative. Therefore, these results indicate that the novel retinyl ester peak in HPLC diagram (Fig. 4, 5, and 7) is retinyl phytanate.

In figure 11, there were three new peaks at *m/z* 269.2, 552.5 and 596.5 observed in the mass spectra of DHA generated new retinyl ester peak HPLC fraction (Fig. 11C), as compared to the spectra of the HPLC sample at the same retention time without DHA treatment (Fig. 11B). As described above, the peak of *m/z* 269.2 indicated the presence of retinoids. The molecular weight of retinyl docosahexaenate is 596.5 (Fig. 11A), and the molecular weight of the decarboxylated ion is 552.5. Moreover, we performed a post-source decay (PSD) assay on the peak of *m/z* 596.5, and the result showed that it was a retinyl derivative (Figure 11D), This result suggests that the novel retinyl ester peak generated by culture in the presence of retinol and DHA is retinyl docosahexaenate.

Table 1 Changes in [^{3}H] labeled novel retinyl ester peak and in retinyl palmitate in the presence of 50 uM phytanic acid (PA) and 100 nM [^{3}H] retinol
(same HPLC retention times for each sample)

	Treatments	the [^{3}H] labeled area at the retention time of novel retinyl ester peak caused by phytanic acid	retinyl palmitate
PC-3 cells	Retinol	1	1
	Retinol+PA	8.25 ± 0.73**	2.07 ± 0.23**

	Treatments	the [^{3}H] labeled area at the retention time of novel retinyl ester peak caused by phytanic acid	retinyl palmitate
PrEC cells	retinol	1	1
	retinol+PA	2.24 ± 0.18**	2.18 ± 0.11**

Table 2 Changes in [^{3}H] labeled novel retinyl ester peak and in retinyl palmitate in the presence of 20 uM docosahexaenoic acid (DHA) and 100 nM [^{3}H] retinol
(same HPLC retention times for each sample)

	Treatments	the [^{3}H] labeled area at the retention time of novel retinyl ester peak caused by DHA	retinyl palmitate
PC-3 cells	Retinol	1	1
	Retinol+DHA	15.29 ± 2.94**	2.15 ± 0.56*

	Treatments	the [^{3}H] labeled area at the retention time of novel retinyl ester peak caused by DHA	retinyl palmitate
PrEC cells	Retinol	1	1
	Retinol+DHA	14.22 ± 3.55**	1.87 ± 0.60*

*: $p<0.05$; **: $p<0.01$; each experiment has been done 3 times

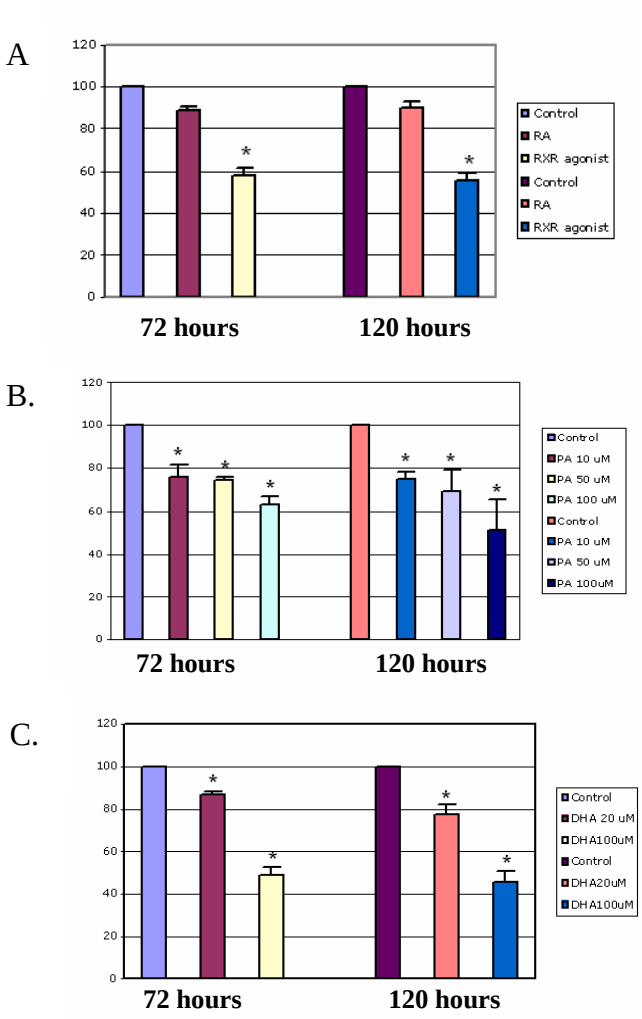
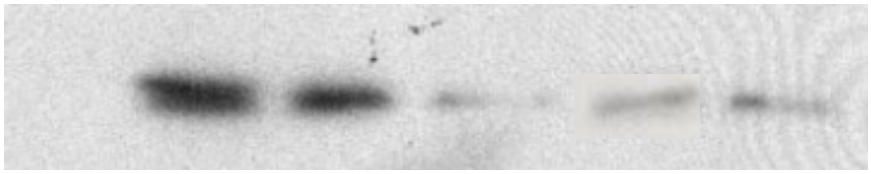


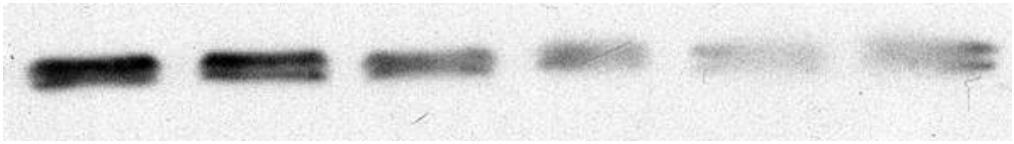
Figure 1. Phytanic acid, DHA, and RXR agonist BMS 188649 inhibited the growth of prostate cancer PC-3 cells. Androgen unresponsive PC-3 cells were seeded in 24 well plates in triplicate at densities of 10,000 cells/ml/well. Then next day, cells were treated with different concentrations of phytanic acid and DHA. Fresh drugs were added every two days. After 72 and 120 hours, cells were counted using a Coulter counter. Mean ± SEM is shown as the results of 3 independent experiments, and the data was analyzed by ANOVA. * indicates a $p<0.05$.

A.



Control **RA 1 μM** **PA 100 μM** **RA+PA** **BMS 188649 1 uM**

B.



Control **RA 1uM** **DHA 20 uM** **DHA 50 uM** **DHA20uM +RA** **DHA50 uM +RA**

Figure 2. Phytanic acid, DHA, and RXR agonist BMS 188649 inhibited the expression of cyclin D1 in prostate cancer PC-3 cells. PC-3 cells were seeded in 10-cm dishes. Cells were treated with various drugs for 48 hours. Cells were harvested and the whole cell lysate protein was extracted for Western blot.

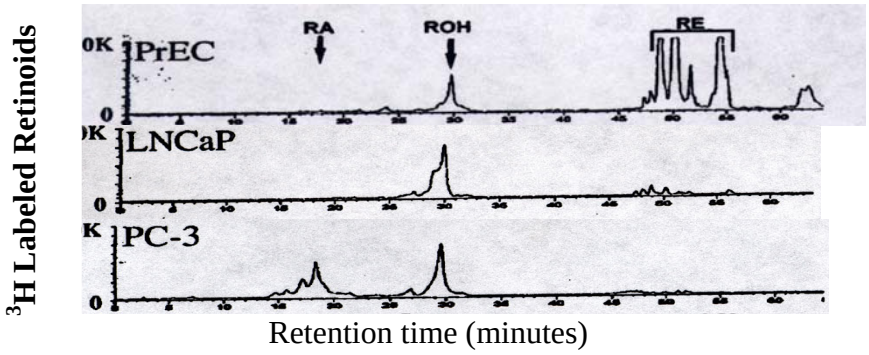


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Figure. 3 The metabolism of [^{3}H]retinol in normal human prostate epithelial cells (PrEC) and in human prostate cancer cells.

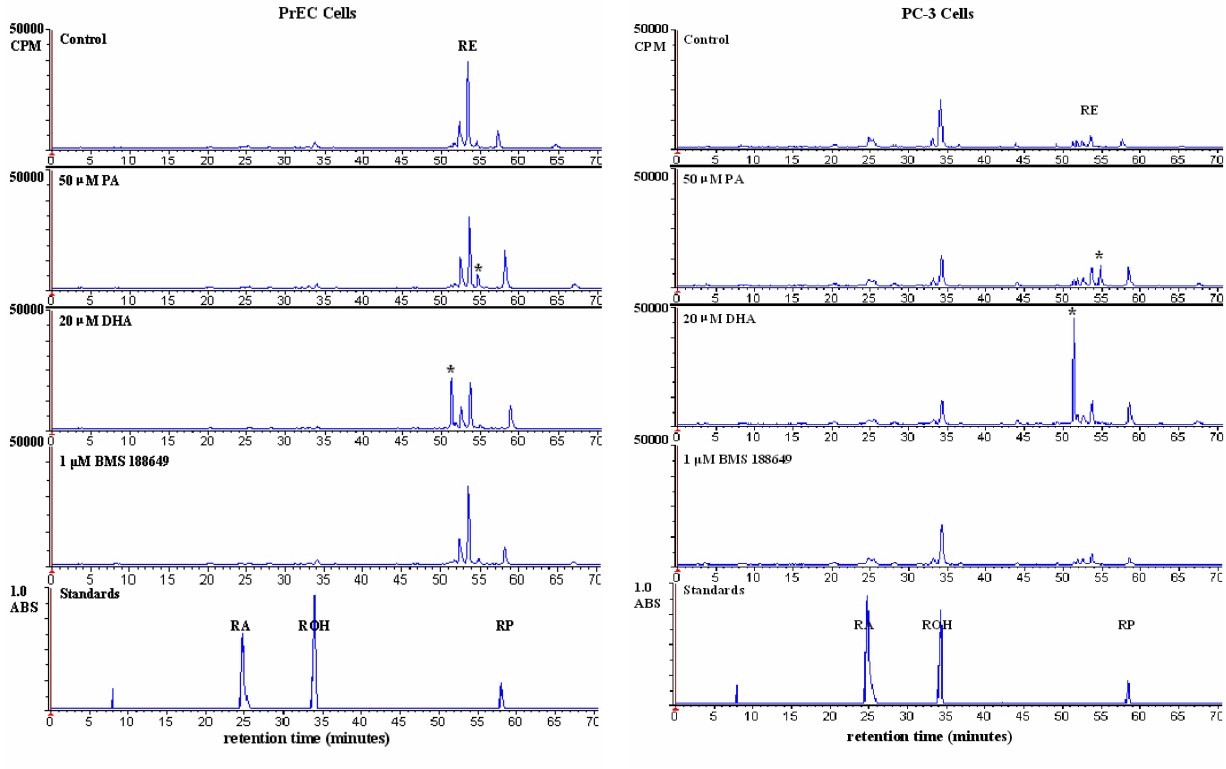


Figure 4. Effects of phytanic acid (PA) and DHA on the metabolism of [^{3}H]retinol in normal human prostate epithelial cells (PrEC) and in human prostate cancer PC-3 cells.

Cells were plated in 60 mm dishes and treated with phytanic acid (50 µM) or DHA (20 µM) for 12 hours in the presence of 100 nM [^{3}H] labeled retinol, and retinoid metabolism was analyzed by HPLC. In A and B respectively, all the Y axis scales are the same. RA, retinoic acid; ROH, retinol; RAc, retinyl acetate; RP, retinyl palmitate. One representative of 3 experiments is shown here.

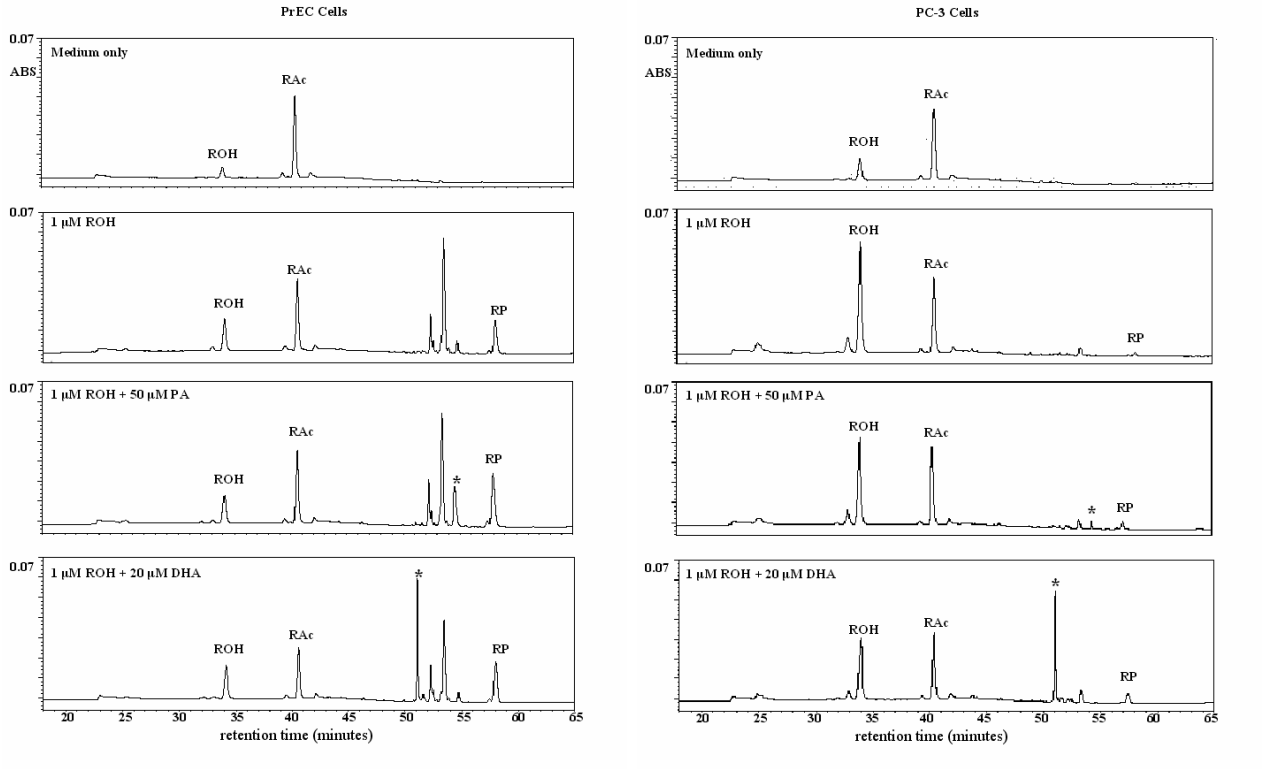
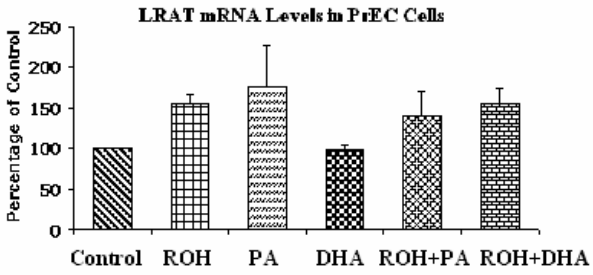
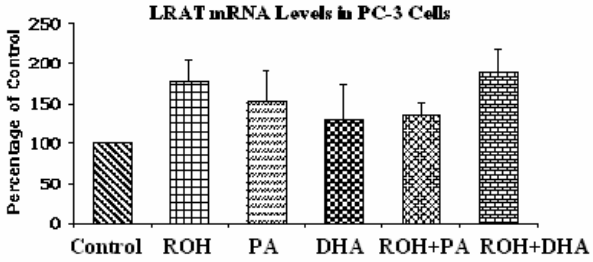


Figure 5. Effects of phytanic acid (PA) and DHA on the metabolism of non-radiolabeled retinol in normal human prostate epithelial cells (PrEC) and in human prostate cancer PC-3 cells. Cells were plated in 15 cm dishes and treated with phytanic acid (50 μM) and DHA (20 μM) in the presence of 1 μM retinol for 48 hours. Before retinoid extraction, retinyl acetate was added into each sample. The metabolism of retinol was determined by HPLC analyses of retinoids extracted from harvested cells. All the Y axis scales are the same. ROH, retinol; RAc, retinyl acetate; RP, retinyl palmitate. One representative of 3 experiments is shown here.

A





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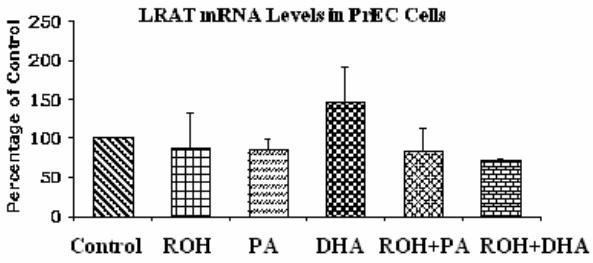

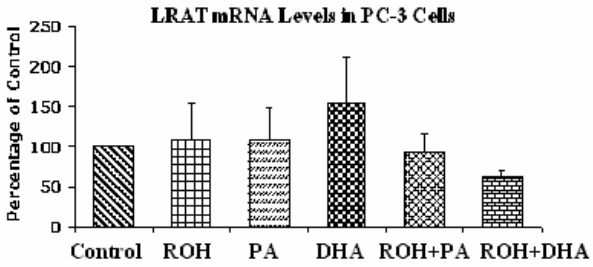

Figure 6. Effects of phytanic acid and DHA on the expression of LRAT in PC-3 and PrEC cells. Cells were treated with various drugs for 6 hours (A) or 24 hours (B), then total RNA was isolated and was used for reverse transcription, then the cDNA from 30 ng total RNA was used for real time PCR. LRAT mRNA levels were normalized to HPRT mRNA. Experiments were repeated 3 times independently. Mean ± SEM is shown as the results of 3 independent experiments. Mean ± SEM is shown as the results of 3 independent experiments, and the data was analyzed by ANOVA.

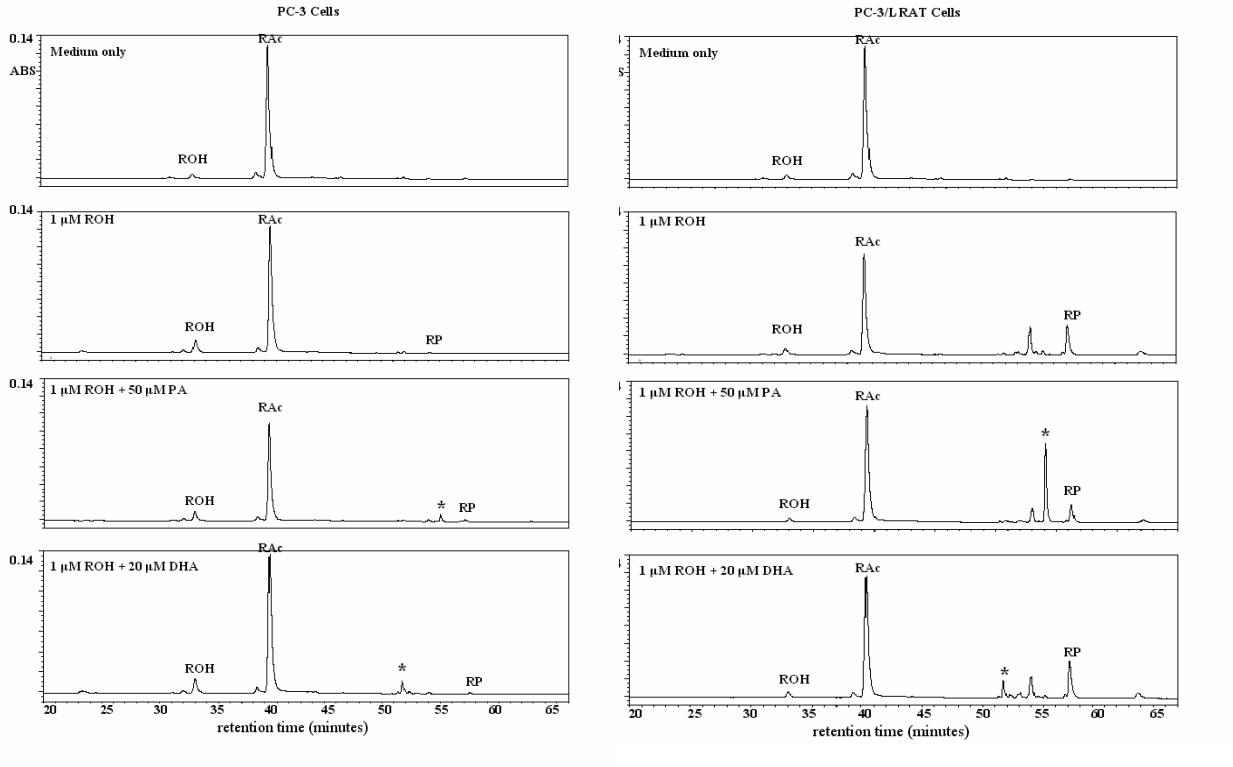

Figure 7. The role of LRAT in the synthesis of the novel retinyl ester peak by PC-3 cells cultured in the presence of phytanic acid or DHA. Parental PC-3 cells and PC-3 cells which overexpress human LRAT (PC-3/LRAT) were cultured in 15 cm dishes for 48 hours. Intracellular retinoids were extracted and analyzed by HPLC. Before retinoid extraction, retinyl acetate was added into each sample. ROH, retinol; RAc, retinyl acetate; RP, retinyl palmitate. This experiment has been performed 4 times with similar results.

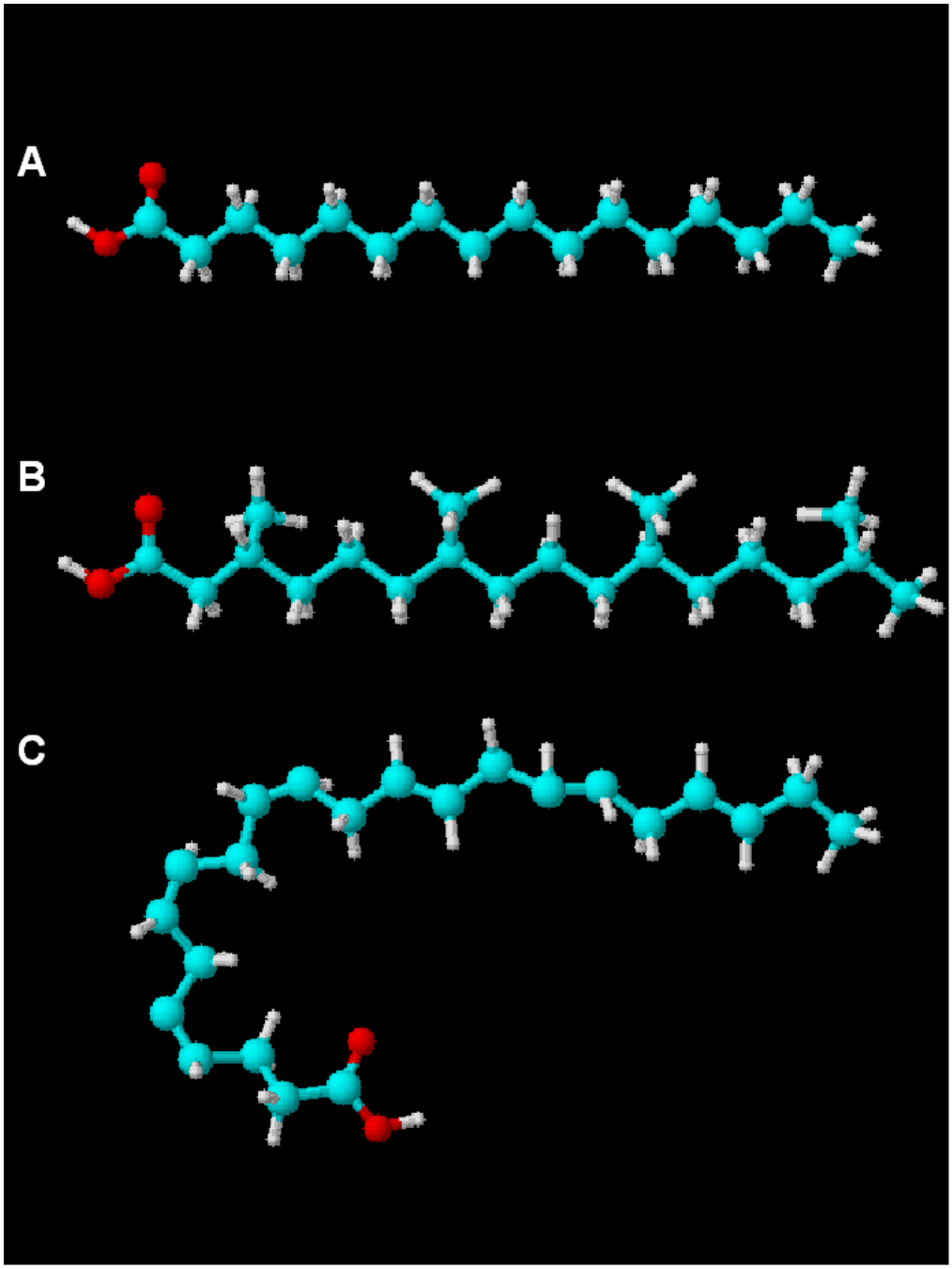

Figure 8. The 3D structures of palmitate (A), phytanic acid (B), and docosahexaenoic acid (C).

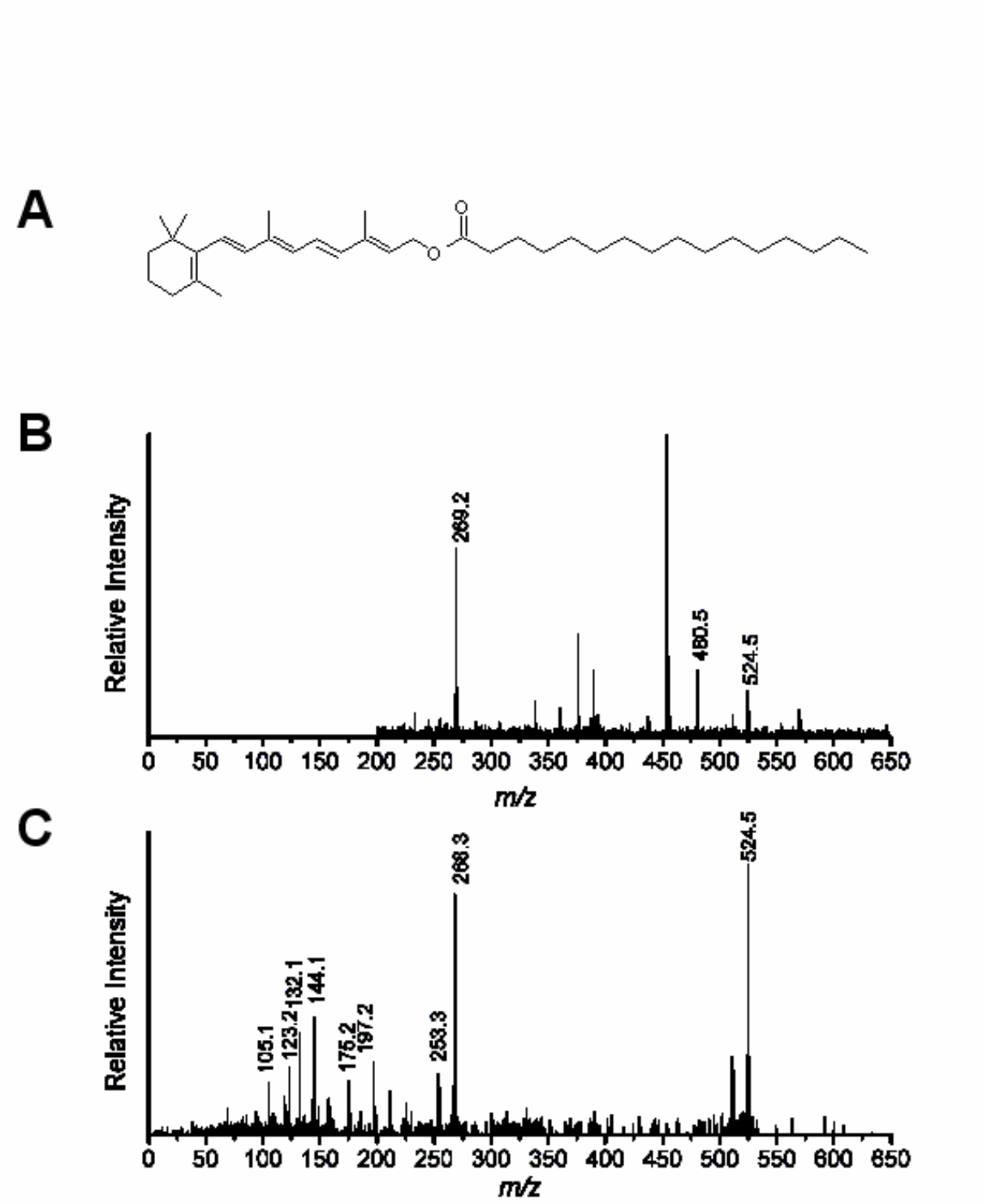

Figure 9. Identification of retinyl palmitate peak of HPLC diagram. PC-3 cells which overexpress LRAT were cultured with 1 μM retinol for 48 hours. The HPLC fraction of extracted retinoids at the retention time of retinyl palmitate was analyzed by using mass spectrometry. A. Molecular formula of retinyl palmitate; B. The mass spectrum of the HPLC fraction at the retention time of retinyl palmitate; C. Post source decay (PSD) structural analysis of the peak of *m/z* 524.5 in panel B.

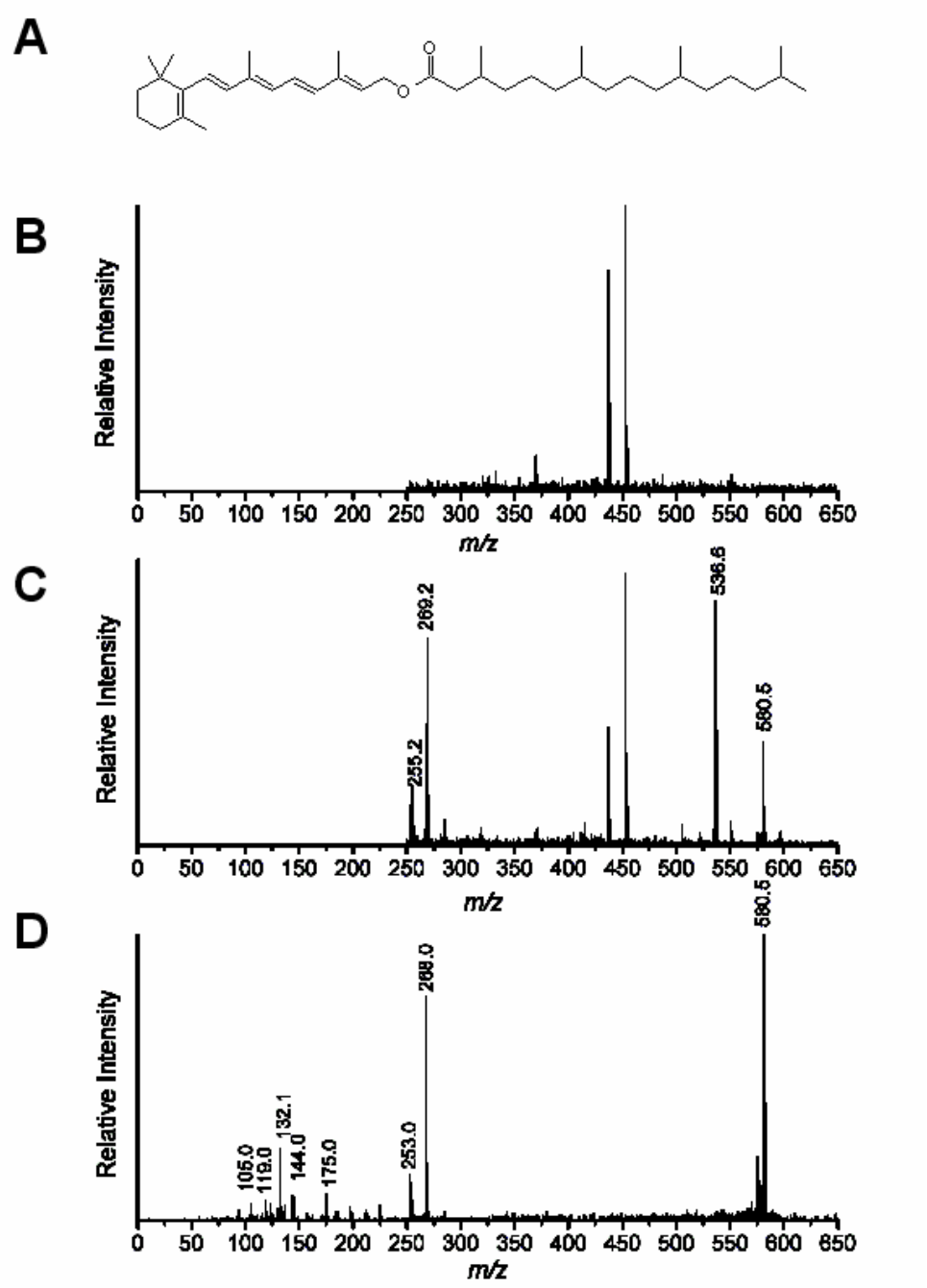

Figure 10. Indentification of the novel retinyl ester peak generated by phytanic acid. PC-3 cells which overexpress LRAT were cultured with 1 μM retinol, or 1 μM retinol and 50 μM phytanic acid, for 48 hours. Then the HPLC fractions of extracted retinoids at the retention time of the novel retinyl ester peak were collected and analyzed by using mass spectrometry. A. Molecular formula of retinyl phytanate; The mass spectrum of the HPLC fraction from cells treated with retinol only (B) or retinol and phytanic acid (C) at the retention time of the novel retinyl ester peak; D. Post source decay (PSD) structural analysis of the peak of *m/z* 580.5 in panel C.

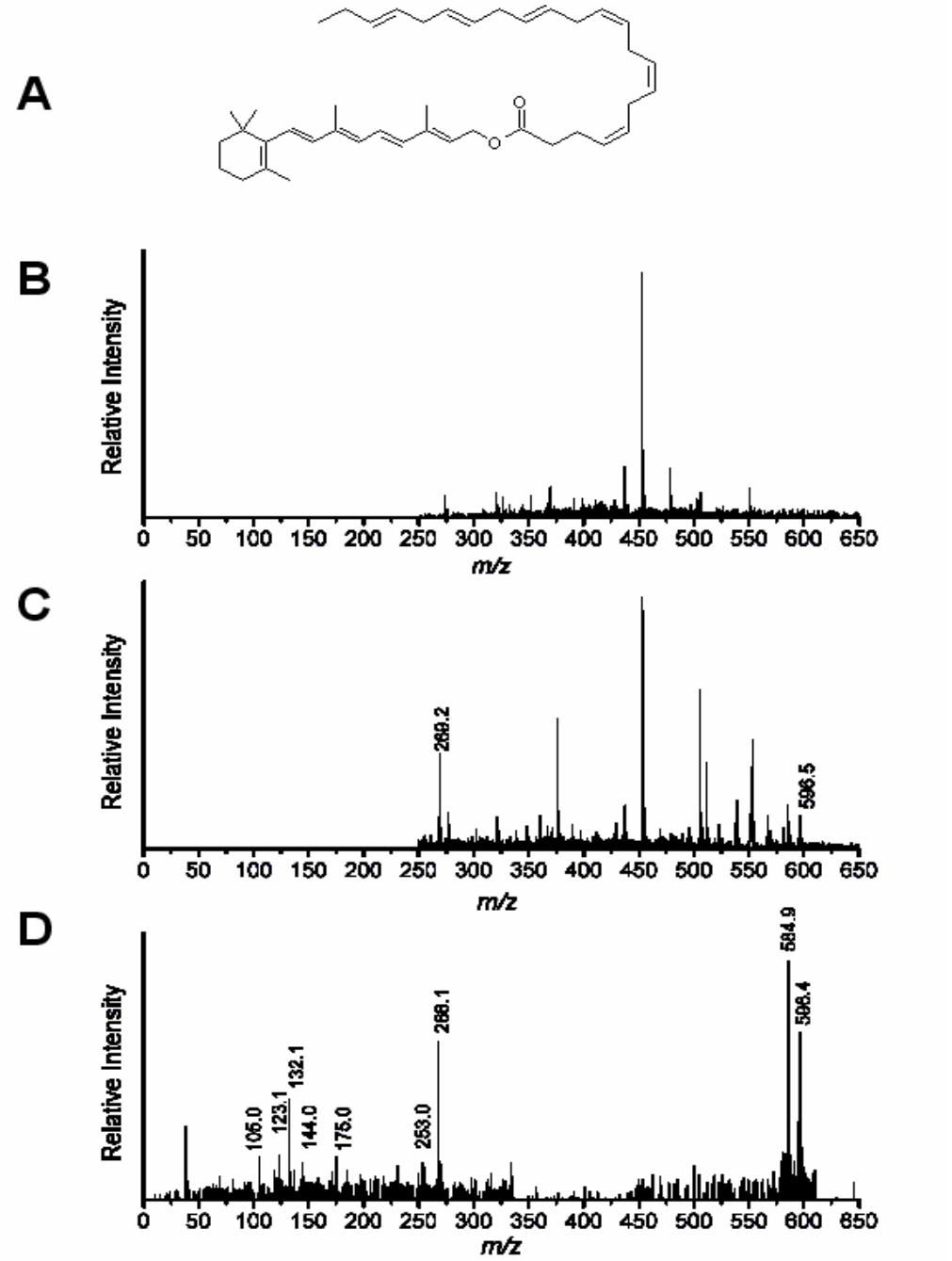

Figure 11. Indentification of the novel retinyl ester peak generated by DHA. PC-3 cells which overexpress LRAT were cultured with 1 μM retinol, or 1 μM retinol and 20 μM DHA, for 48 hours. Then the HPLC fraction corresponding to the novel retinyl ester peak were collected and analyzed by using mass spectrometry. A. Chemical structure of retinyl docosahexaenate; The mass spectrum of the HPLC fraction from cells treated with retinol only (B) or retinol and acid and DHA (C) at the retention time of the novel retinyl ester peak; D. Post source decay (PSD) mass spectrum of the selected molecular ion of the peak of *m/z* 596.5 in panel C.

Key research accomplishments

We observed that phytanic acid (PA) and docosahexaenoic acid (DHA) did decrease the growth of advanced prostate cancer PC-3 cells. In addition, the RXR agonist BMS 188649 also inhibited Pc-3 cell growth.

We found that phytanic acid, DHA, as well as the RXR agonist BMS 188649, decreased the expression level of cyclin D1 in prostate cancer PC-3 cells.

We found that phytanic acid and DHA enhanced the retinyl esters produced in both PrEC and PC-3 cells. In addition, both phytanic acid and DHA generated a novel retinyl ester in these two cell lines, respectively.

We examined the effects of phytanic acid and DHA on the mRNA levels of LRAT in both PrEC and PC-3 cell lines. We found that both drugs did not alter LRAT gene expression significantly.

By using the PC-3 cells which overexpress human LRAT, we found that LRAT participated in the synthesis of phytanic acid generated novel retinyl ester, however, the mechanism of the production of DHA induced novel retinyl ester was through some mechanism other than LRAT.

By using mass spectrometry, we identified the novel retinyl ester generated by phytanic acid is retinyl phytanate, and the novel retinyl ester generated by DHA is retinyl docosahexaenate.

Reportable outcomes

Abstracts

Tang XH and Gudas LJ (2003) Cell growth inhibition and alteration of retinoid metabolism: multiple functions of phytanic acid and docosahexaenoic acid in human prostate cancer cells. (Frontiers in Cancer Prevention Research Meeting, 2003)

Tang XH, Suh MJ, Li R, Gudas LJ (2005) Cell Proliferation Inhibition and Alterations of Retinol Esterification Induced by Phytanic Acid and Docosahexaenoic Acid in Normal Human Prostate Epithelial Cells and in Prostate Cancer Cells--Identification of Novel Retinyl Esters by Mass Spectrometry (manuscript in preparation).

Conclusions

Phytanic acid and DHA suppressed the growth of human prostate cancer PC-3 cells, and downregulated the protein level of cyclin D1 in these cells. These effects are probably mediated through the activation of RXRs. In addition, phytanic acid and DHA increased the retinyl esters produced in both PrEC and PC-3 cells. These results indicate that as natural ligands of the RXRs, the dietary compounds, phytanic acid and DHA could be potential agents for the prevention and treatment of prostate cancer.

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