Tauroursodeoxycholic Acid Attenuates Lipid Accumulation and Adipogenesis of Adipose-derived Stem Cells

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ABSTRACT SUMMARY

Tauroursodeoxycholic acid (TUDCA)–related research suggests that TUDCA have the ability to decrease ER stress, act as leptin-sensitizing agents in obese mice and human. TUDCA treatment was able to inhibit adipogenic differentiation of human adipose-derived stem cells (hASCs) in the inductive media via decrease in lipid accumulation, while they did not show a significant effect on osteogenic and chondrogenic differentiation. Furthermore, TUDCA treatment was able to inhibit adipogenic differentiation of hASCs by in vivo tissue regeneration.

EXPERIMENTAL METHODS

Human subcutaneous adipose tissue was obtained by liposuction from informed and consenting patients. Only tissues that would have been discarded were used for hASCs isolation with the approval of the Ethics Committee at CHA University.

TUDCA was purchased from Calbiochem. hASCs were incubated for each lineage differentiation times with each lineage induction media in the presence of 50 μM TUDCA. The three inductive medium was changed every two days. Adipogenic differentiation was induced at a cell density of $1\times10^4$ cells/cm² in adipogenic medium (Gibco BRL) for 10 days. The inductive differentiation status of hASCs was estimated by Oil red O staining, extraction assay and RT-PCR. Also ER stress status of adipogenic induced hASCs investigated by western blot. To induce osteogenesis, hASCs were cultured for 21 days in DMEM containing 10% FBS, 1% glutamax (Gibco BRL), 0.2 mM ascorbic acid, 10 mM glycerol 2-phosphate (Sigma), 1% antibiotics, and 0.1 μM dexamethasone (Sigma) for 21 days. The inductive differentiation status of hASCs was estimated by von Kossa staining, Ca$^{2+}$ content assay, RT-PCR, and ALP activity. To induce chondrogenic differentiation, hASCs were cultured for 21 days in DMEM containing 10% FBS, 1% antibiotics, 1% Insulin-Transferrin-Selenium-A Supplement (Gibco BRL), 50 μM
ascorbic acid, 100 nM dexamethasone, and 10 ng/ml TGFβ1 (ProSpec). The inductive differentiation status of hASCs was estimated by alcian blue staining, extraction assay, and RT-PCR.

To confirm the effect of TUDCA on in vivo adipose tissue regeneration, each group of hASCs plus adipose derived ECM with PBS or with TUDCA was injected at 3×10⁶ cells per site into the dorsal subcutaneous spaces of the mice with fibrin gel (Greenplast, Green Cross). Each sample was injected into two sites (right and left) of mice for six weeks.

RESULTS AND DISCUSSION

We examined whether TUDCA affects proliferation and adipogenic differentiation phase of hASCs that were evaluated through Oil red O staining, quantitative analysis, and so on, including ER stress marker (Figure 1). We confirmed that both proliferative and inductive phase in hASCs was associated with the decrease in lipid accumulation with ER stress.

TUDCA significantly decreased adipogenic differentiation of hASCs, while it did not affect osteogenic and chondrogenic differentiation (Figure 2).

We confirmed that tissue weight and sectioned Oil red O staining revealed the decrease in lipid accumulation and regenerated tissue weight in TUDCA treated groups (Figure 3). Therefore, it is possible that attenuation of adipogenesis by TUDCA in mesenchymal stem cells such as hASCs was associated with the decrease in the adipogenic gene expression through decreasing ER stress.

Figure 1. Effect of TUDCA on adipogenic differentiation of hASCs.

Figure 2. Effect of TUDCA on osteogenic and chondrogenic differentiation of hASCs.

Figure 3. Effect of TUDCA on in vivo adipose tissue regeneration by hASCs.

CONCLUSION

These finding suggested that TUDCA treatment on stem cells would be useful as a supplemental strategy for anti-adipogenic differentiation without changing other lineage differentiation. Based on our findings, a better understanding of the relation between chemical chaperone TUDCA and adipogenic differentiation of human mesenchymal stem cells would be a pharmacological and therapeutic approach aimed at reducing the risk of obesity.

REFERENCES


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