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Adipogenesis of bovine perimuscular preadipocytes

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Abstract

In this study, non-transformed progeny adipofibroblasts, derived from mature adipocyte dedifferentiation, was used as a novel *in vitro* model to study adipogenic gene expression in cattle. Adipofibroblasts from dedifferentiated mature perimuscular fat (PMF) tissue were cultured with differentiation stimulants until the cells exhibited morphological differentiation. Treated cells were harvested from day 2 to 16 for RNA extraction, whereas control cells were cultured without addition of stimulants. Results from time course gene expression assays by quantitative real-time PCR revealed that peroxisome proliferator-activated receptor gamma (PPAR-γ), sterol regulatory element binding protein 1 (SREBP-1) and their six down-stream genes were co-expressed at day 2 post-differentiation induction. When compared to other adipogenesis culture systems, the adipogenic gene expression of bovine PMF adipofibroblasts culture was different, especially to the rodent model. Collectively, these results demonstrated PPAR-γ and SREBP-1 cooperatively play a key role to regulate the re-differentiation of bovine adipofibroblasts, during early conversion stages *in vitro*.

Keywords: Adipocyte; Bovine; Differentiation; Fat development; Gene expression; PPAR-γ; SREBP-1; Transcription factor

Understanding mechanisms regulating fat deposition and metabolism in beef cattle is important, since dynamics of adipose physiology is directly associated with both the quality and the value of the meat [1]. Recent attempts to elucidate molecular mechanisms of fat metabolism using advanced molecular biological techniques have provided knowledge regarding molecular markers that are co-expressed with genetic improvement of fat related carcass traits in the beef industry [2,3].

In mice, adipogenesis has been intensively studied using the 3T3-L1 preadipocyte cell line [4]. Studies on differentially expressed gene profiles during differentiation of 3T3-L1 cells have shown that many genes were up- or down-regulated through the course of differentiation; these data identified measurable molecular markers relevant to conversion of proliferative cells into lipid-assimilating adipocytes [5–7]. Gene families like PPAR and SREBP have been reported to play major roles in preadipocyte differentiation [8–10], and these factors regulate down-stream genes typically involved in lipid and fatty acid metabolism. Many of these markers interact functionally to direct several regulatory processes involved in adipogenesis or lipid metabolism [11]. The expression of molecular markers and interactions among genes, during adipogenesis in livestock species, are as yet unclear and not necessarily similar to that of 3T3-L1 cells [12]. Moreover, specific adipose depots in ruminant animals do not respond to regulatory compounds in a similar manner to monogastric animals [12].

Numerous studies in domestic (meat) animals utilize the stromal fraction (S–V) of cells from any given adipose depot to identify alterations of gene expression during adipogenesis, and substantial knowledge has been generated with the S–V cell fraction. However, the S–V cell fraction contains an ill-defined mixture of cells, making absolute identification of cell contribution to adipogenesis difficult [12]. An alternative cell system for adipogenesis studies is

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derived from the mature adipocyte cell fraction. Mature adipocytes have been isolated, semi-purified by centrifugation (removal of S–V cells), cultured in ceiling culture [13] and allowed to dedifferentiate [13–15]. Resultant (non-transformed) progeny cells were used for these studies. These cells are proliferative-competent, but the ability of the cells to undergo the conversion process to become viable lipid-assimilating adipocytes is unclear. The goal of this study, therefore, was to investigate the molecular mechanisms of the conversion process in proliferative-competent bovine perimuscular fat (PMF) adipocytes by analysis of the expression patterns and interactions among particular transcription factors PPAR-γ and SREBP-1 with downstream genes. Understanding of the genetic interaction profile (molecular markers) in these cells will provide knowledge about biochemical pathways involved in adipogenesis of bovine adipocytes.

Materials and methods

Cell establishment, culture and differentiation. The adipofibroblasts were obtained from the dedifferentiation and proliferation of mature bovine adipocytes, derived from perimuscular adipose depot immediately surrounding the sternomandibularis muscle of Angus beef steer during routine slaughter at the Washington State University (WSU) meats laboratory. Details of tissue collection and preadipocyte preparation were previously outlined [13]. The WSU Animal Care and Use Committee screened the use of animals in this research, and the animal use met the standards imposed by both the United States Department of Agriculture and Public Health Service. Cell culture and differentiation were carried out as previously described [16]. In brief, the frozen PMF preadipocytes were thawed and cultured for 2 days in DMEM supplemented with 10% FBS and 1× anitibiotic–antimycotic (Invitrogen) at 37 °C with 5% CO_2. The cell monolayer in each flask was allowed to reach confluence. Two days after confluence (day 0), the cells were separated to two groups: treated and untreated (control). The treated cells were incubated with medium including 1 μg/mL insulin, 0.25 μM dexamethasone (DEX, sigma) and 10 mM acetic acid in DMEM supplemented with 10% FBS and 1× antibiotic–antimycotic. The treatment was continued using the same stimulant-supplemented medium until day 16 when cells were fully differentiated. Control cells were cultured in DMEM supplemented with 10% FBS and 1× antibiotic–antimycotic for 2 days and harvested for RNA extraction. The conversion of preadipocytes into adipocytes was confirmed by the detection of lipid droplets under microscopy using Oil-red O staining on day 16 cells as previously described [17]. Treated cells were harvested on 2, 4, 8, 12, and 16 days for RNA extraction.

Total RNA extraction and complementary DNA (cDNA) synthesis. Total RNA was extracted from cells harvested on each time point by S–V total RNA isolation system (Promega) with RNase-free DNaseI treatment. Quantity and quality of the RNA were checked using RNA nano6000 assay with Bioanalyzer 2100 (Agilent Technologies). The RNA was amplified using MessageAmp™ II aRNA Amplification kit to be able to be utilized for future analysis of microarray hybridization (Ambion). The amplified RNA (aRNA) to produce cDNA, and the cDNA was further used for measurement of RNA abundance by quantitative real-time PCR.

Quantitative real-time PCR (qPCR). The qPCR primers were designed by Primer3 [18] (Table 1). Targeted genes included SREBP-1, PPAR-γ, A-FABP, ACSL1, ELOVL6, FASN, LDLR, SCD, and ribosomal protein, large, P0 (RPLP0). The RPLP0 gene was used as a reference gene in the qPCR analyses, since the gene showed the best stability in the time course assays detected by SYBR Green I in our facility. Standards were generated for each gene by cloning the PCR products into pGEM-T Easy vector (Promega). The plasmid DNA clones were linearized by ScaI restriction enzyme and their concentration was measured by NanoDrop1000 (Labtech International, UK). The standard curve was generated by using the plasmid DNA concentrations range was between 10^7 and 10^{13} molecules/μL using the formula [19]. The qPCR was performed with Quantitect SYBR Green PCR kit (Qiagen) using 20 μL of reaction solution containing 10 μL of 2× Quantitect SYBR Green PCR master mix, 20 ng of cDNA and primers (200 nM). Each reaction was carried out with triplicates and run in ABI PRISM 7700 Sequence Detection System (SDS) with software version 1.7 (Applied Biosystems). The thermal cycling condition was as follows; 95 °C for 5 min, followed by 40 cycles of denaturation at 94 °C for 15 s, annealing at 60 °C for 30 s, and extension at 72 °C for 30 s. For each gene assessment, the SDS software was used to plot standard curves of threshold cycle (C_T) values derived from copy numbers using the linearized plasmid DNA standards. The absolute number of gene copies in each sample was then interpolated from the standard curve by using the average C_T values for each of the replicates for each cDNA sample. And then, relative gene expression for each gene was calculated by ratio of target gene expression to that of reference. Fold change of gene expression was calculated by ratio of expression levels of treated cells to the expression level of control cell. The up-regulated expression fold change was

Table 1
Oligonucleotides used for qPCR

Genes	Primers (5′–3′)	Accession No.
SREBP-1	Forward: TACCTGCAGCTTCTCCATCA Reverse: CACCAATGGGTACAGCCTCT	XM_879234
PPAR-γ	Forward: GTGAAGTTCAACGCACTGGA Reverse: ATGTCCTCAATGGGCTTCAC	BC116098
A-FABP	Forward: GGATGGAAAATCAACCACCA Reverse: GCAAACGTCATCCATTTCAA	NM_174314
FASN	Forward: GCATCGCTGGCTACTCCTAC Reverse: GTGTAGGCCATCACGAAGGT	AY343889
LDLR	Forward: TGGACGGATGTTATCAACGA Reverse: TCACACCAGTTCACCCCTCT	K01830
ELOVL6	Forward: CTAAGCAAAGCACCCGAACT Reverse: CCAGCAACCATGTCCTTGTA	BC148954
ACSL1	Forward: TGGCCCATATGTTTGAGAGA Reverse: GGGCCTTGAGATCATCCATA	BC119914
SCD	Forward: CCAGAGGAGGTACTACAAACCTG Reverse: AGCCAGGTGACGTTGAGC	AB075020
RPLP0	Forward: CAGCAGGTGTTTGACAATGG Reverse: TAACCAATCTGCAGGCACAC	NM_001012682

calculated by dividing the results for the treated sample by the control for each of the time point. The down-regulated expression fold change was calculated by dividing the results for the untreated sample by the treated sample within each of the time points, followed by the addition of a negative sign to signify a down regulation.

DNA sequencing. In order for confirmation of the products detected by qPCR, the PCR products were purified, cloned and subjected for sequence analysis with ABI PRISM BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). The sequence reaction was performed in 10 μL of volume containing 0.5 μL of BigDye, 3.2 pmol of M13 Forward (5′-CGCCAGGGTTTTCCCAGTCACGAC-3′) or M13 Reverse (5′-TTCACACAGGAAACAGCTATGAC-3′) primer, 2.0 μL of 5× sequencing buffer, 20 ng of Plasmid DNA as a template. At least two clones for each gene were subjected to sequencing analysis with ABI 3730 genetic analyzer (Applied Biosystems) according to the manufacturer's instruction. Sequences were analyzed with Chromas v1.45 (http://www.technelysium.com.au/chromas.html) and BLASTed against GenBank nucleotide database.

Data analysis. Data on transcript quantification was simply conducted by comparisons between means of treated PMF adipocytes in five time points and untreated PMF preadipocytes from day 2 culture using a *t*-test. Clustering analysis of gene expression changes was performed using PermutMatrix software with which methods for clustering and seriation were based on average linkage criteria and multiple-fragment heuristic, respectively [20].

Results and discussion

Mature adipocytes are traditionally considered to be terminally differentiated cells, operational only in lipid metabolism. However, adipocytes have been reported to dedifferentiate, a process where mature adipocytes lose their characteristics and assume a fibroblast-like appearance, reverting into proliferative-competent preadipocytes [21–23]. Recent studies observed the dedifferentiation of mature adipocytes in cultures derived from bovine adipose tissues [14,15]. Fernyhough et al. [13] established cryopreserved (non-transformed) fractions of the dedifferentiated bovine adipofibroblasts used in this study. Preadipocyte differentiation and conversion into a viable adipocyte is a complex process accompanied by coordinated change in cell morphology, hormone sensitivity, and gene expression [12,24]. In this study, the fibroblast-like bovine PMF preadipocyte (Fig. 1A) was confirmed to proliferate and differentiate to lipid filled adipocytes (Fig. 1B) with similar cell physiology and morphology reported in rodent adipocytes models [9,22]. These changes result from the action of several transcription factors including PPAR-γ and SREBP-1 which play a regulatory role in the process [12,25].

Therefore, the molecular mechanisms in the re-differentiating bovine PMF preadipocytes were investigated by elucidating expression profile of the major adipogenic factors, based on previous studies in rodent model and bovine PPAR signaling in KEGG pathway. Moreover, due to a lack of understanding of the specifics of regulation by transcription factors in fat formation in cattle, the gene networks of transcription factors PPAR-γ and SREBP-1 and their down-stream genes in the process of the preadipocyte differentiation were also explored. Fig. 2 shows that relative expression level of the eight adipogenic genes to RPLP0 reference gene expression in treated cells was compared to control cells in time course, since RNA abundance of RPLP0 was stable from day 2 to 16 of the culture in the qPCR assay for each gene (data not shown). It appears that all genes showed significantly higher expression level in treated PMF adipocytes at day 2 than that of the control cells. Furthermore, most of the genes indicated the highest gene expression level on day 2, whereas SREBP-1 gene showed the highest expression at day 8. After day 12, most of the genes showed down-regulations or silent, although only PPAR-γ gene showed up-regulation on day 16 (Fig. 2).

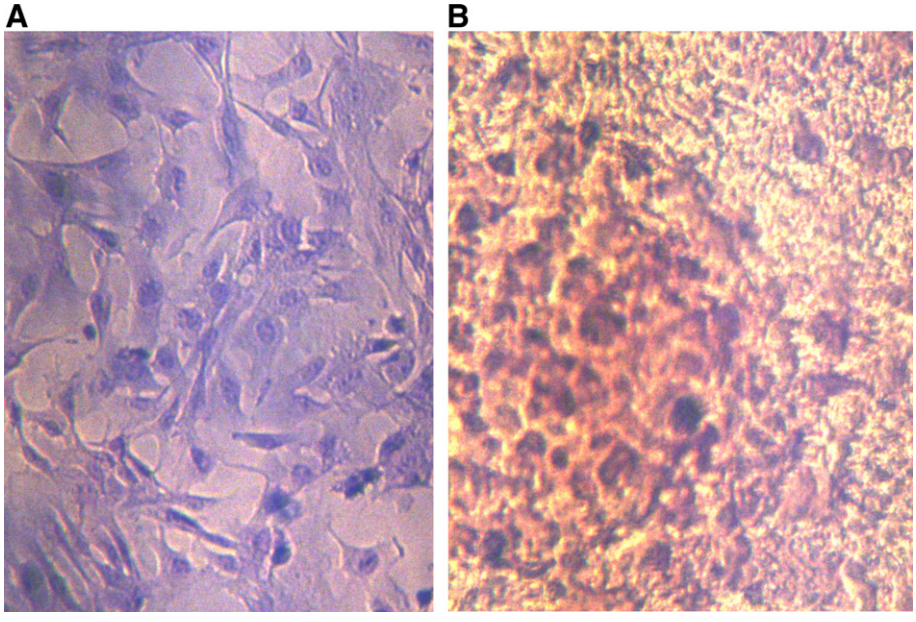

Fig. 1. Differentiation of the bovine PMF preadipocytes. (A) PMF preadipocytes at confluent (0 days). (B) Differentiated PMF adipocytes with lipid droplets on 16 days of culture stained by Oil-red O. Magnifications for each picture are 100×.

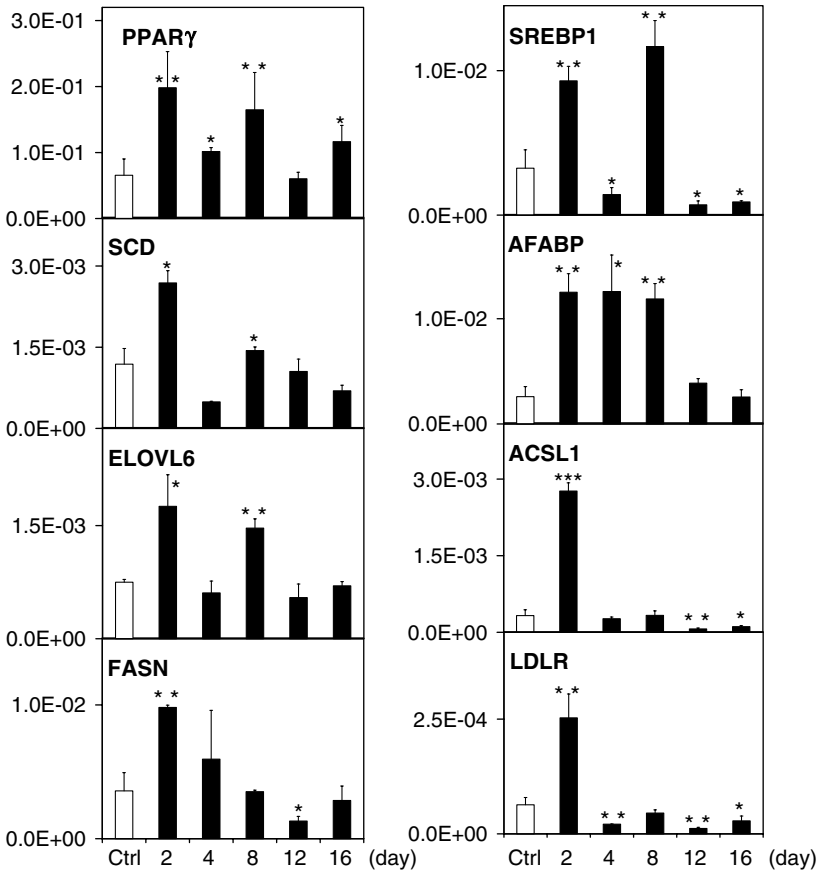

Fig. 2. Expression levels of adipogenic genes in differentiating bovine PMF preadipocyte. In each graph, *y*-axis indicates relative expression level of targeted genes to the RPLP0 gene expression. Bars indicate standard deviations. Comparisons of gene expression levels by *t*-test between control and treated cells from five time points are significantly different when asterisks $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ are indicated.

As one of the molecular makers of adipogenesis, RNA abundance of A-FABP was measured to assess the extent of the preadipocyte differentiation and development since it plays an important role in fatty acid transportation [3]. High RNA abundance of A-FABP from the day 2 of the culture suggests that the progeny preadipocytes from dedifferentiated mature adipocytes may potentially have an ability to re-differentiate at early time point due to inherited characteristics of molecular components in the cytoplasm of progeny cells derived from the mature adipocytes (Fig. 2), although shape of the cells remains fibroblast-like form (Fig. 1A).

Clustering analysis was performed to elucidate patterns of expression of the eight genes during the PMF pre-adipocyte differentiation, according to the gene expression fold change in the differentiating PMF preadipocytes (Fig. 3). There were three clusters observed by the patterns of their gene expression. Cluster 1 including A-FABP and PPAR-γ genes showed that these genes were highly up-regulated from day 2 to 8 and moderately degraded on day 12 and day 16. Cluster 2 including FASN, ELOVL6, SCD, and SREBP-1 genes interestingly showed expression fold changes for the genes revealed repetition of up- and down-regulation from day 2 to 12. Cluster 3 including LDLR and ACSL1 genes indicated up-regulation on day 2 and down-regulation from day 4 to the end of the culture (Fig. 3). The expression patterns of transcription factors PPAR-γ and SREBP-1 and their down-stream genes in the cluster 1 and 2 demonstrated that those factors were co-expressed from day 2 of the culture, suggesting adipogenesis in the preadipocytes was induced at early stage.

In terms of transcriptional activation initiated with SREBP-1, it is known that genes containing SRE (sterol regulatory element) sites on their 5′-promoter region are regulated by SREBP-1, which are classified in two isoforms SREPB-1 (1a and 1c) in human [26]. Expression abundance of SREBP-1c is usually tenfold SREBP-1a in most animal tissue [27,28]. Hence, the SREBP-1 detected in this study is considered to be SREBP-1c identified from other species. Interestingly, genes including ACSL1, ELOVL6, FASN, LDLR, PPAR-γ, SCD, and SREBP-1 itself are reported to contain SRE site in their promoter sequences [10,29–32]. In fact, the genes categorized in cluster 2 showed co-expression with a trend of cross of up- and down-regulation from day 2 to 12. Additionally, genes in cluster 3 are co-expressed with SREBP-1 on day 2 (Fig. 3). The possible reason for the repetition in cluster 2 is because SREBP-1 involves a negative feedback system which is regulated by levels of its derivatives such as poly-unsaturated fatty acids (PUFA) brought by down-stream gene activities [10]. Thus,

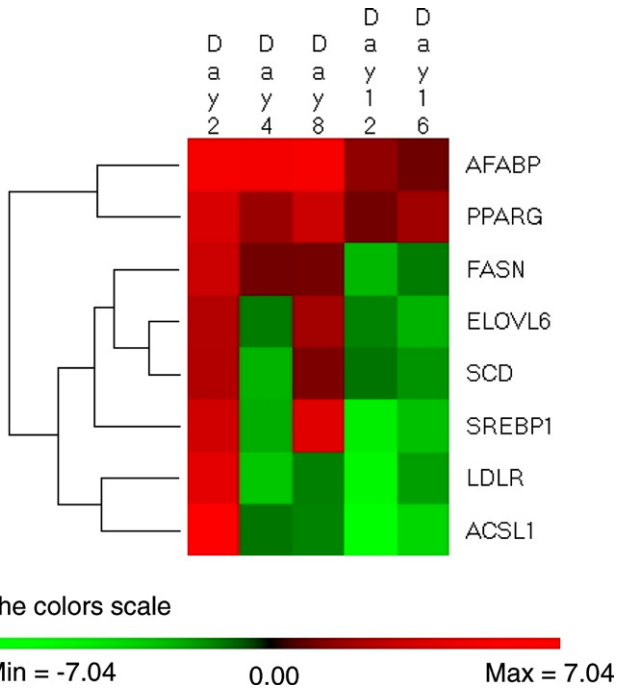

Fig. 3. Expression pattern of adipogenic genes by clustering analysis. Data measurements were examined by qPCR and the results were shown as fold change over the expression level of control. As shown by the color scale bar, increasing green and red signal intensities indicate genes that decrease and increase in expression of treated PMF adipocytes during the time course.

it seems that the genes in cluster 2 were up-regulated on the first day to produce PUFA by co-expression of SREBP-1, FASN, EVOLV6, and SCD, while the same genes were down-regulated at the following time point, when increased PUFA blocked transcription activity of SREBP-1. Unlike the genes in cluster 2, transcription activation of two genes (LDLR and ACSL1) in cluster 3 may be repressed by the other effect.

As shown in the PPAR signaling pathway in *bos taurus* from KEGG (http://www.genome.jp/dbget-bin/get_pathway?org_name=bta&mapno=03320), fatty acid binding proteins trigger interactions mediated by PPAR-γ to induce various biological pathways including lipid metabolism, adipocyte differentiation and gluconeogenesis. In the molecular pathway map, PPAR-γ stimulates transcription of A-FABP, ACSL1, FASN, and SCD genes. In addition to the PPAR signaling indicated in the KEGG, previous results demonstrated in rodent models support that the gene interaction shown in this study was regulated by transcription activation of SREBP-1 and PPAR-γ [10,33]. However, the timing of the transactivation was earlier than that of the other *in vitro* models [24].

Although CCAAT/enhancer binding protein alpha (C/EBP-α) has been also known as another important transcription factor in regulation of adipocyte differentiation in various species [34–36], the expression of this gene was under detectable level in the bovine PMF system (data not shown). Tan et al. [37] also reported that C/EBP-α gene was not expressed in an *in vitro* study of differentiation using bovine bone marrow-derived preadipocytes. These suggest the transcriptional regulation of adipogenic genes in bovine preadipocytes is different from that of porcine and rodent preadipocytes [35,36,38], although the results showed PPAR-γ played a pivotal role in the regulation of gene transcription and cellular differentiation as indicated in the other animal species [39].

In summary, our results suggest that the bovine adipofibroblast cell culture system is viable for use in adipogenesis studies, that there are specific regulatory genes expressed during the adipogenesis process of these cells, and that genetic interactions exist among specific adipogenic factors evaluated. This information is lacking in the bovine. Global gene expression profiling during adipogenesis in these bovine preadipocytes using high-throughput technology such as DNA microarray, is on-going, and will supply detailed molecular biochemical pathway underlying bovine preadipocyte differentiation.

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