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Transcriptional Features of Cattle Visceral and Subcutaneous Adipose Tissues: A Study of RNA-seq

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Abstract

Visceral and subcutaneous are the two major types of bovine adipose tissues, and they show metabolic and functional differences according to their distribution, exploring the transcriptional features of visceral and subcutaneous adipose tissues is necessary. In the present study, we conducted RNA-seq analysis to compare the transcriptome between visceral (great omental) and subcutaneous (backfat) adipose tissues from Chinese Simmental cattle and validate them by qRT-PCR. We found that 5864 genes were differentially expressed between two tissues, including 2979 up-regulated and 2885 down-regulated in visceral adipose tissue. Functional analysis revealed a variety of differentially expressed genes (DEGs) involved in lipid metabolism and immune response processes. This may provide valuable information to further our understanding of the complexity of gene regulation governing the physiology of different fat depots. This work highlighted potential genes regulating lipid metabolism and immune responses; it may contribute to a better understanding of the metabolic and functional differences between visceral and subcutaneous adipose tissues.

Keywords

Visceral Adipose Tissue, Subcutaneous Adipose Tissue, Transcriptional Features, Cattle

1. Introduction

Adipose tissue is an important organ in the storage and release of energy, and regulates various physiologic and pathologic processes through secretion of adi-

pokines [1] [2]. In the beef cattle industry, the composition of the fat in different adipose tissues is of major interest because of the effect of fatty acids on human health and the quality of the beef [3].

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are the two major types of adipose tissue, according to their distribution in mammals [4]. There are many differences between VAT and SAT including anatomical, cellular, molecular, physiological, clinical, and prognostic [5]. Fat storage and allocation within body depots of farm animals are associated with animal health and meat quality, these differences are caused by a variety of mechanisms such as a different content of immune cells, different sensitivity to lipolytic and anti-lipolytic stimulation, and different metabolic activities [6] [7]. Evidence from recent studies has confirmed the distinct features of VAT and SAT in livestock. Wang *et al.* (2013) [8] identified that DEGs between SAT and VAT are potentially associated with the inflammatory features of VAT in pigs. Ji (2014) [9] found that VAT has a greater capacity for expression of pro-inflammatory cytokines such as interleukin 1B (*IL1B*), *IL6*, and *IL6R* compared with SAT, which may lead to an excessive accumulation of visceral lipid in Holstein cows. In addition, through a 2D LC-MS/MS (two-dimensional liquid chromatography tandem mass spectrometry) analysis, Restelli [10] demonstrated different proteomic profiles between VAT and SAT in goats. Romao *et al.* [11] found that the miRNA may differ among VAT and SAT, suggesting that miRNAs may play a role in the regulation of bovine adipogenesis.

Previous research also reported these differences in cattle, but little research has been undertaken on the molecular differences between VAT and SAT in beef cattle. Thus, we conducted an RNA-seq analysis to detect DEGs between these two tissues in Simmental cattle. We aimed to provide information to support further research into the adipose tissue of cattle and contribute to a better understanding of the metabolic and functional differences between visceral and subcutaneous adipose tissues.

2. Materials and Methods

2.1. Animal Samples

Three female Simmental beef cattle at 20 months of age (from Zhang Jiakou, Hebei Province, China) were used to harvest adipose tissue. All cows were obtained from a same farm, no pregnant, reared under the same conditions. The cattle were weaned at six months of age and then raised on a diet of corn and corn silage. The thickness of backfat was measured right before slaughter (1.07 ± 0.049 cm). Subcutaneous adipose tissue (the hypodermal layer of backfat, namely SAT in this case) and visceral adipose tissue (great omentum, namely VAT in this case) was collected immediately after slaughter, treated with RNAlater (Ambion, NY, USA), and then frozen in liquid nitrogen until RNA extraction.

All animal procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, and were approved by the Ethical Review

Committee on the Welfare of Laboratory Animals of Hebei North University (permit number: 20-0013).

2.2. Library Construction and Sequencing

Three samples from each tissue were used for extracting RNA by using a Fatty Tissue Kit (LC Science, Houston, TX). The integrity of the RNA was confirmed using a 2100 Bioanalyzer (Agilent, USA) and only samples with an RNA integrity number greater than 7 were used in subsequent analyses. After quality control and the removal of ribosomal RNA by using Epicentre ribosomal RNA kit (LC Science, Houston, TX), approximately 20 μg of total RNA was fragmented to 200-nt fragments and was then used as a template for cDNA synthesis. The first strand of cDNA was synthesized with random hexamers, and the second strand was synthesized using a dNTP mix in which dTTP was replaced by dUTP. The double-stranded cDNA was then subjected to end repair, addition of dA to the 3' end, and adaptor ligation; the libraries were further size-selected using a 1:1 volume of AMPure XP beads (Beckman Coulter, Brea, CA). USER enzyme (NEB, USA) was used to degrade the second strand of cDNA, and finally, strand-specific RNA-seq libraries were constructed and sequenced on an Illumina Hiseq 2500 platform at LC Science (Houston, TX).

2.3. RNA-seq Data Analysis

After trimming sequenced reads containing adaptors and reads of low quality (reads with more than 20% bases have a quality value $Q \leq 10$), the valid reads for each sample was aligned to the cattle genome (Bos_taurus; UMD3.1.75) using Tophat (v2.0.4) software [12] with the following parameters: --bowtie -r 0 -mate-std-dev 50-N 3--solexa 1.3-quals. Cufflinks (v2.0.2) [13] was used to assemble the RNA-seq alignments, and then Cuffcompare package is used to compare the transcripts to transcripts in ENSEMBL. The Cuffdiff package is used to compare the expression level of transcripts between tissues. Gene expression level was normalized by considering the "fragments per kilobase of transcript per million mapped reads" (FPKM). The R package edgeR (version 1.6.12) was used to identify DEGs. Genes were considered differentially expressed if they had a Benjamin-Hochberg false discovery rate-corrected *P*-value < 0.05.

The identification of novel transcripts is based on the result of Cuffcompare, transcripts including unknown intergenic transcript, a transfrag falling entirely within a reference intron, and exonic overlap with reference on the opposite strand were considered as novel transcripts.

2.4. Gene Ontology (GO) and Pathway Enrichment Analysis

To identify biological functions, the DEGs were classified into the categories GO cellular component (GO-CC), GO biological processes (GO-BP), and GO molecular function (GO-MF) in the Gene Ontology database (http://www.geneontology.org).

In addition, KEGG Pathway analysis was carried out to identify the main metabolic pathways or signal transduction pathways of the DEGs. In these analyses, the whole genome was considered to be the background, and the calculated *P*-values were corrected using the Bonferroni correction, taking a corrected *P*-value < 0.05 as the threshold for significance.

2.5. Validation of RNA-seq Data

To validate the results from RNA-seq, quantitative reverse-transcription polymerase chain reaction (qRT-PCR) was conducted to measure the expression levels of eight genes that were significantly differentially expressed in different adipose tissues. Total RNA (1 μg) was reverse transcribed to cDNA using a PrimeScript RT reagent kit with gDNA Eraser (Takara, Japan). Primers used for qRT-PCR are shown in Table S1. qRT-PCR was performed on a CFX96 Real Time Detection system (Bio-Rad) using 2× SYBR® Premix ExTaqTM II (Takara). The data were transformed using the formula $2^{-\Delta\Delta Ct}$. Bovine glyceraldehyde 6-phosphate dehydrogenase (*GAPDH*) was used as an endogenous control gene, and its expression patterns in these two tissues are measured before qRT-PCR analysis.

3. Results

3.1. RNA Sequence in Adipose Tissues

A total of 65,702,568 reads for SAT and 76,832,410 reads for VAT were obtained by RNA-seq after quality control. Approximately 60% of the valid reads mapped to the reference genome (Bos_taurus_UMD 3.1.75). After assembly of the cattle adipose transcriptome, 13,905 and 15,943 transcripts were expressed in SAT and VAT, respectively (Table 1).

A total of 12,685 transcripts were co-expressed in SAT and VAT. GO analysis indicated that these genes were primarily enriched in the categories of "mitochondrion" (1149 transcripts, P = 3.97E-21), "nucleotide binding" (1277 transcripts, P = 7.11E−17), "metal ion binding" (1605 transcripts, P = 1.39E−11), and "ATP binding" (1037 transcripts, P = 1.55E−11) as shown in Table S2. Notably, some transcripts showed extremely high abundance in both adipose tissues (Table S3), such as *FABP*4 (7406.8 FPKM in VAT and 11559.1 FPKM in SAT) and *SCD* (6039.6 FPKM in VAT and 7334.3 FPKM in SAT) these genes play an important role in lipid metabolism processes and can be regarded as "housekeepers" in adipogenesis. Meanwhile, some transcripts presented specific expression patterns in one tissue, we found 3247 transcripts specific expressed in

Table 1. Summary of RNA-seq alignment.

Samples	Valid reads	Mapped reads	Expressed Transcripts
VAT	76,832,410	45,628,454 (59.39%)	15943
SAT	65,702,568	38,762,747 (59.00%)	13905

VAT while 1214 transcripts specific expressed in SAT (Table S4). However, these transcripts expressed at low level, the mean FPKM is 4.39 in VAT and 6.41 in SAT.

3.2. DEGs in Subcutaneous and Visceral Adipose Tissues

A total of 5864 genes were differentially expressed between SAT and VAT, of which 2979 were up-regulated and 2885 were down-regulated in VAT compared with SAT (Figure 1). The DEGs showed distinct transcriptome features. A total of 329 GO terms and 27 KEGG pathways were significantly enriched among the DEGs (Table S5). The DEGs were involved in various biological processes and molecular functions (Figure S1) including fatty acid metabolism and immune response processes such as fatty acid biosynthesis, the PPAR (peroxisome proliferator activated receptor) signaling pathway, cytokine receptor binding, and the response to stimuli (Figure 2).

3.3. DEGs Involved in Lipid Metabolism

To investigate the function of the DEGs in lipid metabolism, we focused on a

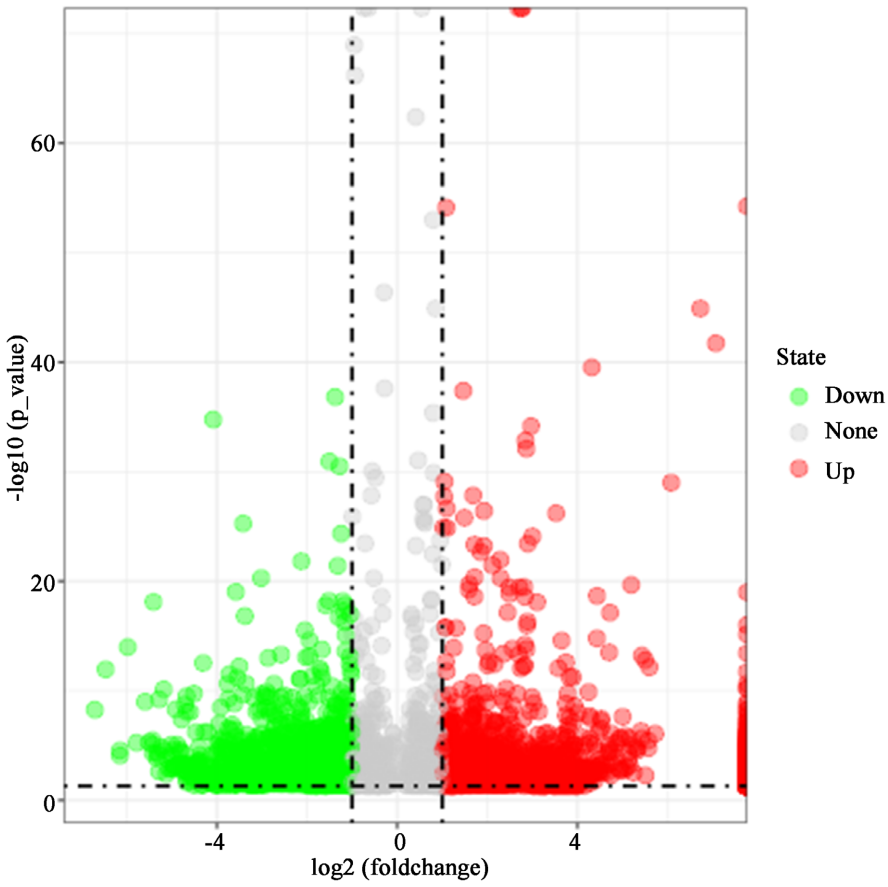

Figure 1. Volcano map of DEGs in two adipose tissues. Note: The red dot represent the over expressed genes and the green dot represented the lower level expression of the genes, the grey dot represented the gene expression were not significant between two tissues.

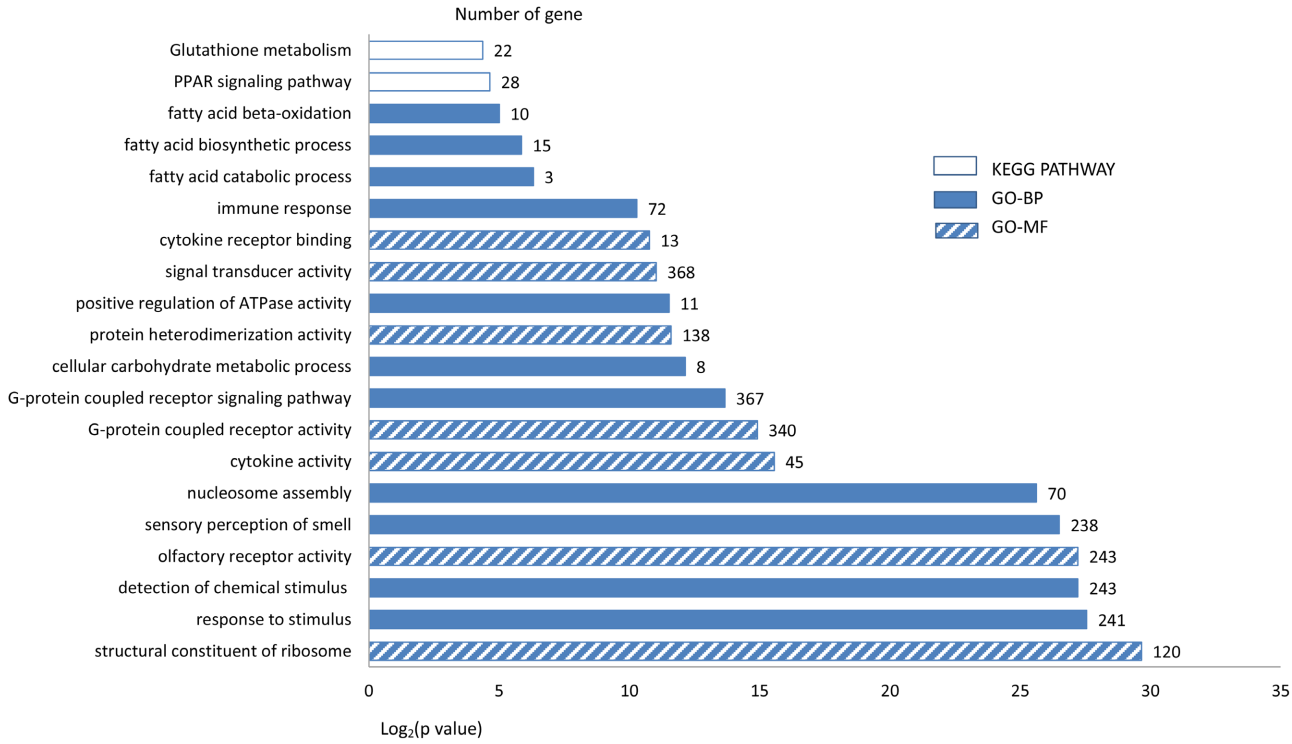

Figure 2. GO (Gene Ontology) and pathway categories enriched for DE transcripts, Gene ontology of DE transcripts. DEGs involved in lipid metabolism and immune response processes.

significantly enriched KEGG category, the PPAR signaling pathway, which has been shown to be important in the regulation of the catabolic and anabolic aspects of lipid metabolism [14] [15]. Twenty-seven DEGs were clustered into this pathway, of which 14 were significantly up-regulated in VAT (**Table 2**, **Figure S2**). To validate the RNA-seq, we examined the expression level of eight up/down-regulated genes using qRT-PCR (**Figure 3(a)**). Five DEGs (*FABP*4, *PCK*1, *CD*36, *ADIPOQ*, and *SCD*) were down-regulated in VAT compared with SAT, and the other three (*LPL*, *EHADH*, and *UBB*) were up-regulated in VAT compared with SAT. There was a significant correlation between the qRT-PCR and RNA-seq results (**Figure 3(c)**), which indicated that the RNA-seq data accurately reflected the transcriptome features of cattle adipose tissue. The well-known regulator *PPARγ* was detected in both adipose tissues with no significant difference in expression level.

3.4. DEGs Involved in the Immune Response

Previous research has reported that DEGs in subcutaneous and visceral adipose tissues may be involved in inflammation and immune responses. Our functional analysis revealed that many DEGs were significantly enriched in immune-related categories such as cytokine activity (45 DEGs, $P = 2.07E{-}5$), cytokine receptor binding (13 DEGs, $P = 0.000573$), and immune response (72 DEGs, $P = 0.000803$). Among the DEGs in the immune response category were five members of the major histocompatibility complex gene family: *BoLA-DQA*1 and

Table 2. DEGs involved in PPAR signaling pathway.

Gene	VAT_FPKM	SAT_FPKM	Regulation	P value
FABP4	7406.8	11559.1	down	0
PLTP	54.97	16.87	up	1.33E−05
PCK1	53.82	121.92	down	1.0355E−07
APOA1	2.33	22.88	down	1.92E−05
ANGPTL4	13.54	59.42	down	6.95E−08
SCP2	218.33	264.42	down	0.015666
ACOX2	39.17	14.75	up	0.001583
ACSL1	139.96	240.34	up	6.1E−08
DBI	1384.75	652.096	up	7.82E−55
PCK2	120.48	83.56	up	0.020759
LPL	895.34	645.37	up	6.57E−09
CPT2	17.28	4.71	up	0.012768
PLIN	433.55	619.42	down	6.48E−10
FADS2	3.77	0	up	0.048724
RXRG	25.299	45.57	down	0.0089055
FABP3	6.11	0	up	0.015779
UBB	857.19	647.36	up	1.22E−06
ACSL3	79.27	46.51	up	0.007204
PPARD	6.62	0	up	0.009123
RXRA	33.06	72.91	down	5.43E−05
CD36	1283.4	1884.8	down	9.01E−31
ACAA1	59.50	34.63	up	0.015396
ADIPOQ	2056.9	2572.1	down	9.55E−18
AQP7	180.38	222.37	down	0.01693
EHHADH	35.13	8.68	up	0.000132
PDPK1	9.69	30.674	down	0.00074197
SCD	7038.1	8601.4	down	4.3E−47

BoLA-DQB were up-regulated in VAT while *BoLA-DRB3*, *BoLA-NC*, and *BoLA-DYA* were down-regulated. In addition, several cytokines including *TNFSF18*, *TLR2*, *IL6*, and *IL10* were differentially expressed between VAT and SAT (**Figure 3(b)**).

3.5. Novel Transcripts Involved in Lipid Metabolism

According to the location of sequenced reads and the reference genome, we could identify novel transcripts. A total of 1206 novel transcripts were found to

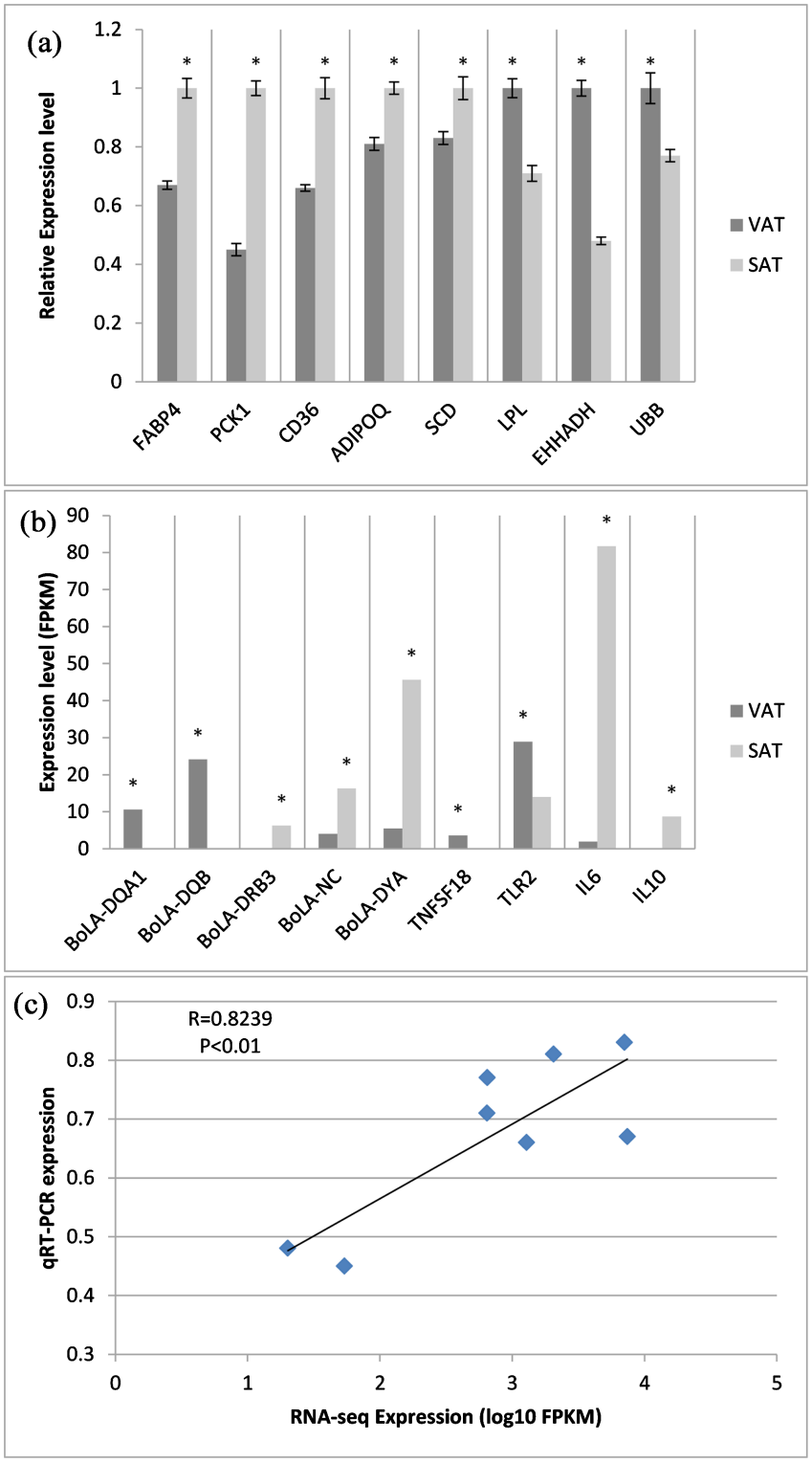

Figure 3. Gene expression patterns in visceral and subcutaneous adipose tissues. (a) Relative expression level of eight DEGs in PPAR signaling pathway, data are expressed as mean ± SD, expression level is normalized by GAPDH (consistent expressed in both adipose tissue, $P > 0.05$, T test); within genes, *indicate differential expression among adipose sites ($P < 0.05$). (b) Expression of DEGs involved in immune response. (c) Correlation of qRT-PCR and RNA-seq analysis.

have protein coding ability but could not be mapped to a known mRNA of the reference genome (**Table S6**). Among these, 541 were differentially expressed between the two adipose tissues (244 down-regulated and 297 up-regulated). GO analysis showed these transcripts participated in various biological processes.

4. Discussion

The structure and function of adipose tissue varies according to its distribution [16]. Visceral and subcutaneous are two major types of adipose tissue and play different roles in metabolic processes, such as in insulin action, the regulation of lipolysis, and cytokine production [17]. In our RNA-seq analysis, plenty of genes were found expressed in visceral and subcutaneous adipose tissues which may reveal the transcriptional complexity of different fat depots, more the 1/3 genes were differential expressed between these two tissues, suggested distinct transcriptional features of cattle adipose tissue.

Among the identified DEGs were many well-known regulators of lipid metabolism. For instance, 27 DEGs were enriched in the PPAR signaling pathway, which is important in glucose homeostasis and lipid metabolism in adipose tissue. Lipoprotein lipase (LPL) is a key regulator of fat accumulation in various adipose areas, which, together with acylation stimulating protein, participates in the regulation of in vivo triglyceride uptake in adipose tissue [18] [19]. We found that *LPL* mRNA was significantly more highly expressed in VAT than in SAT; this may result in higher LPL activity in VAT, and thus influence fat deposition.

In contrast, *CD*36 was preferentially expressed in SAT. Studies have reported that changes in *CD*36 expression and subcellular distribution are linked to fatty acid uptake, especially of long-chain fatty acids [20] [21] [22]. Interestingly, another three genes (*FABP*4, *PCK*1, and *SCD*) have also been reported to be involved in fatty acid transport (F*ABP*4), gluconeogenesis (*PCK*1), and desaturation (*SCD*) [23] [24] which may affect de novo synthesis of fatty acid. In our study, these four genes were all down-regulated in VAT compared with SAT, which suggests that bovine VAT has lower fatty acid metabolic activity than SAT.

Interestingly, we also observed distinct expression patterns of some lipid metabolism-related genes between our result and previous researches. *ADIPOQ* and *SCD* are found more abundant in visceral adipose tissue than in subcutaneous adipose tissue of Holstein cows. These differential expression genes suggested distinct transcriptional features between beef cattle and dairy cattle. Combine analysis of RNA-seq analysis in different cattle breeds will be useful in understanding of gene regulated mechanisms of cattle.

Furthermore, we also detected novel transcripts that are likely to participate in lipid metabolism. For example, ENSBTAT00000043749 on chr15 was expressed in VAT and was classified into the GO categories "lipid metabolic process" and "fatty acid biosynthetic process".

Adipose tissue is not only an energy storage organ, but is also highly active in expressing and releasing cytokines and initiating an inflammatory or immune response [25] [26]. We found many DEGs that are involved in immune response-related processes. *BoLA-DQA*1 and *BoLA-DQB* are two BoLA (bovine leukocyte antigen) class II molecules, which can present antigen to bovine $CD4^+$ T cell lymphocytes and play an important role in immune responses to infectious pathogens [27] [28]. Both *BoLA-DQA*1 and *BoLA-DQB* were up-regulated in VAT in our study, together with other pro-inflammatory cytokines and genes such as *TNFSF*18 and *TLR*2 [29] [30]. This suggests that VAT can produce more pro-inflammatory cytokines than SAT, and indicates that the former is more sensitive to immune responses. In contrast, we also found several down-regulated cytokines in VAT, such as *IL*6 and *IL*10, which may reveal distinct immune characteristics between VAT and SAT and further confirm the transcriptional complexity of bovine adipose tissue.

5. Conclusion

In conclusion, through an RNA-seq analysis between the visceral and subcutaneous adipose tissues of cattle, we detected a large number of DEGs and novel transcripts. Our findings support the complexity of gene regulation governing the physiology of different fat depots, especially relating to lipid metabolism and immune responses.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Figures and Tables

(https://pan.baidu.com/s/1HSPLpTfGq10tKVdfabqU9Q, Password: 0fae)

Supplementary Figure S1. GO analysis of differential expressed genes.

(https://pan.baidu.com/s/1HSPLpTfGq10tKVdfabqU9Q, Password: 0fae)

Supplementary Figure S2. igure S1 DEGs involved in PPAR signaling pathway.

Supplementary Table S1. Primers used for qRT-PCR analysis of mRNA levels.

(https://pan.baidu.com/s/1HSPLpTfGq10tKVdfabqU9Q, Password: 0fae)

Supplementary **Table S2.** Co-expression of transcripts between VAT and SAT_GO_enrichment.

(https://pan.baidu.com/s/1HSPLpTfGq10tKVdfabqU9Q, Password: 0fae)

Supplementary Table S3. Top ten transcripts with high abundance in both adipose tissues.

(https://pan.baidu.com/s/1HSPLpTfGq10tKVdfabqU9Q, Password: 0fae)

Supplementary Table S4. Specific expressed genes in different adipose tissues.

(https://pan.baidu.com/s/1HSPLpTfGq10tKVdfabqU9Q, Password: 0fae)

Supplementary Table S5. Significantly enriched GO and KEGG.

(https://pan.baidu.com/s/1HSPLpTfGq10tKVdfabqU9Q, Password: 0fae)

Supplementary Table S6. Novel Transcripts.

(https://pan.baidu.com/s/1HSPLpTfGq10tKVdfabqU9Q, Password: 0fae)