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Parasites & Vectors

RESEARCH

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Profiling of differentially expressed genes in sheep T lymphocytes response to an artificial primary *Haemonchus contortus* infection

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Abstract

Background: *Haemonchus contortus* is a common bloodsucking nematode causing widespread economic loss in agriculture. Upon *H. contortus* infection, a series of host responses is elicited, especially those related to T lymphocyte immunity. Existing studies mainly focus on the general immune responses of sheep T lymphocyte to *H. contortus*, lacking investigations at the molecular level. The objective of this study was to obtain a systematic transcriptional profiling of the T lymphocytes in *H. contortus* primary-infected sheep.

Methods: Nematode-free sheep were orally infected once with *H. contortus* L3s. T lymphocyte samples were collected from the peripheral blood of 0, 3, 30 and 60 days post infection (dpi) infected sheep. Microarrays were used to compare gene transcription levels between samples. Quantitative RT-PCR was employed to validate the microarray data. Gene Ontology and KEGG pathway analysis were utilized for the annotation of differentially expressed genes.

Results: Our microarray data was consistent with qPCR results. From microarrays, 853, 242 and 42 differentially expressed genes were obtained in the 3d vs. 0d, 30d vs. 0d and 60d vs. 0d comparison groups, respectively. Gene Ontology and KEGG pathway analysis indicated that these genes were involved in metabolism, signaling, cell growth and immune system processes. Functional analysis of significant differentially expressed genes, such as SLC9A3R2, ABCB9, COMMD4, SUGT1, FCER1G, GSK3A, PAK4 and FCER2, revealed a crucial association with cellular homeostasis maintenance and immune response. Our data suggested that maintaining both effective immunological response and natural cellular activity are important for T lymphocytes in fighting against *H. contortus* infection.

Conclusions: Our results provide a substantial list of candidate genes in sheep T lymphocytes response to *H. contortus* infection, and contribute novel insights into a general immune response upon infection.

Keywords: Sheep T lymphocytes, *Haemonchus contortus*, Microarray, Differentially expressed genes

Background

Haemonchus contortus [illegible] [1]. [illegible] [2], [illegible] [3,4]. [illegible]

[illegible] *H. contortus* [illegible]. [illegible] *H. contortus* [illegible] [5]. [illegible] (L3) [illegible] L4 [illegible]. [illegible] L4 [illegible] 3–5 [illegible] ( ). [illegible] [18] [illegible] [25–30]

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. F a , *H. contortus* a a a aa a g a . T a g , a T , a T 2 (TH2) 6,7 . T TH2- a , a IL-4, IL-5, IL-10, IL-13, IL-25 a IL-31 8 ; B a a g a - , a IgE, IgG1, IgG4 a IgA 9,10 ; a ga a g a a a a 11 . I a , TH2- a T 1 (TH1)- - a a ga a a g , a a a a g a a 12-14 . D g , T a a a a - a a a , g g .

A a g aa T *H. contortus* 15,16 , N a *et al.* a ga a a a a g a - a *H. contortus* a 17 . T , a a a g g - T *H. contortus* . a a g a a a T a / a a a . T a a a g T *H. contortus* a - a g *H. contortus.*

Methods

A a ad a a e

F - - a H a a - a a a a a a g U G a a a aa a (a g U , C JU201308-1-10-072). F a 17,000 *H. contortus* L3 , a a a a . I a a *H. contortus* J a gg g a a . T gg a a g - .

Sa

P a a a a a a 0, 3, 30 a 60 . T aa g - aa (H a g M), g 18-20 a TRI ag (I g). Sa g RNA aa .

RNA e a a

T a RNA T a a g TRI ag (I g) g a - a ' a g RN a M (Qag). RNA a a a - g a I g SSP-3300 a - a a Ag 2100 B a a . T RNA a a a a g a a a a . RNA RNA a a , a C 3a a .

M c a a e e e

S a g a a - a *Bos taurus* 21 a G Ba a a a a 17 . A Ag a a a g 19,075 U G , 25,865 ag (EST , a aga U G , a > 0.001) a 1,417 (B a G INC., S a g a). T GEO a - a a a GPL16283 22 , a a a GSE42302 23 . T a C 3 a RNA a a a 24 . F - g a a Ag a a 5 μ , PMT 100%.

Da a a c a d a a

F a E a a a a a aa. T a aa g Ag 4 44P a ag a a a a aa (a) a ag B R a a g a g . Ba g a a a , g a a g - aa - g g a a a g g. I - a a - a a a , a a a ag - a a a g a a ag ($P < 0.05$), g a g a 0 g , 3 g , 30 g a 60 g . G a g2 a g g a a 1 ($P < 0.05$) a - a g a a g *H. contortus* .

F a a g a g a a a a Da a a A a , V a a a I g a D (DAVID, :// a a . .g /). G O g (GO), KEGG a a a PANTHER a a DAVID g g 25 .

Q a a e RT-PCR (PCR) a da

F - g PCR 26 - - . P T 1. T DNA RNA . Q - RT-PCR g S BR G (T). R △C , g C g , g 3 , 30 , 60 - 0 .

Results

A a f ba e e e e

S - - - g . T 3 . 0 , 30 . 0 , 60 . 0 , 30 . 3 , 60 . 3 60 . 30 . T 2 - g . A 853 (99 - g), 242 (234 - g), 42 (15 - g), 1058 (977 - g), 805 (689 - g) 102 (2 - g) g 3 . 0 , 30 . 0 , 60 . 0 , 30 . 3 , 60 . 3 60 . 30 , . D g A 1. T - g 3 . 0 , 30 . 0 60 . 0 (T 3), .

GO e c e a a

I g T g *H. contortus* , G O g (GO, . g g 73.7999941 20001T -303.89999(60)

Table 2 General situation of differentially expressed genes in six comparisons

Database		3d vs. 0d		30d vs. 0d		60d vs. 0d		30d vs. 3d		60d vs. 3d		60d vs. 30d	
Diff genes	Up-regulated	853	99	242	234	42	15	1058	977	805	689	102	2
	Down-regulated		754		8		27		81		116		100
GO annotation		327		71		14		389		320		37	
KEGG Pathway annotation		139		26		9		159		139		11	
PANTHER Pathway annotation		41		12		2		60		46		7	

Summary of the amount and annotations of differentially expressed genes (diff genes) in T lymphocytes of sheep infected with *H. contortus* in the six comparisons.

(IL-8, FCER1G, IGLL1, C CL2 OVAR). F . A F g 3, PCR . H , PCR .

Discussion

I , *H. contortus* , , , , , . A , , T *H. contortus* . O *H. contortus* , *H. contortus* . T (FEC) *H. contortus* , FEC 2,400 ( ) , 17,000 L3 . T . T 3 . 0 , 60 . 0 , 60 . 30 . H 30 . 0 , 30 . 3 60 . 3 (Table 2). L3 , , L4 . D ,

27 . T , T , 28 . I , 17,000 . A , . T , 3 . 0 . A 25–30 , *H. contortus* . T 27 . F . , T 7 . T , 30 . 0 30 . 3 . H , , 60 . T O ( ) 60 . T T , GO . A GO . T GO , , . T , T 29 . I

Table 3 Common thirty-five genes differentially expressed in the 3d vs. 0d, 30d vs. 0d and 60d vs. 0d comparisons

Gene symbol	Gene name	GenBank number	Log fold change		
			3d vs. 0d	30d vs. 0d	60d vs. 0d
LOC100028054	similar to A kinase (PRKA) anchor protein (yotiao) 9	DY498437.1	−1.8385	2.803	1.744
-	-	CF116320.1	−1.4735	1.6095	1.1825
-	-	EE858261.1	−2.338	1.746	1.2545
-	-	EE823315.1	−1.4945	2.236	2.0075
-	-	EE782465.1	−2.3485	−1.6385	−1.97
-	-	GO684492.1	−1.6265	−1.444	−1.2705
SLC9A3R2	solute carrier family 9 (sodium/hydrogen exchanger), member 3 regulator 2	DY520662.1	−1.1435	2.878	2.3875
SCN8A	sodium channel, voltage-gated, type VIII, alpha	EE862637.1	−2.443	1.2955	1.0355
-	-	GO758506.1	−1.906	−1.005	−1.3805
-	-	DY500374.1	−1.4935	−1.389	−1.316
LOC100057304	similar to Chromosome 1 open reading frame 2	DY491988.1	−2.869	1.2115	1.037
RXRB	retinoid X receptor, beta	EE807201.1	1.5525	2.3845	1.0745
-	-	EE867875.1	−1.7765	−1.206	−1.442
NUDT14	nudix (nucleoside diphosphate linked moiety X)-type motif 14	EE806260.1	−3.048	−3.3985	−3.352
B4GALT2	UDP-Gal: betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 2	DY491344.1	−3.364	1.924	1.649
ABCB9	ATP-binding cassette, sub-family B (MDR/TAP), member 9	EE818298.1	2.149	1.672	1.5765
KLK10	kallikrein related-peptidase 10	GO766063.1	−1.802	−1.3535	−1.302
SLC28A1	Na/nucleoside cotransporter	GO698122.1	−3.4035	−2.886	−3.101
-	-	EE834108.1	−3.603	−1.077	−1.697
C7H5ORF24	chromosome 5 open reading frame 24 ortholog	EE775125.1	1.289	1.301	1.2845
-	-	EE755431.1	−1.564	−1.9835	−2.1185
-	-	EE805398.1	2.4785	1.1985	1.0405
-	-	EE765998.1	−1.1025	1.6255	1.407
-	-	GO773148.1	−2.7225	2.127	2.1205
-	-	EE818179.1	−1.514	1.452	1.161
-	-	DY479153.1	−1.3705	1.4445	1.138
LOC100155914	similar to prion-like protein doppel	EE868622.1	−2.582	−1.266	−1.8615
-	-	DY491124.1	−2.879	−3.3315	−3.5585
-	-	XM_002696802.1	1.096	1.236	1.201
MCP1	mast cell proteinase-1	NM_001009472.1	1.05	2.9485	1.7575
SMAD4	SMAD family member 4	NM_001076209.1	−2.3525	−3.225	−3.2645
ZNF330	zinc finger protein 330	NM_001038157.1	−1.4705	2.286	1.784
SEPT7	septin 7	NM_001001168.1	−2.067	−1.758	−1.2665
COMMD4	COMM domain containing 4	NM_001040597.1	−2.3775	−1.203	−1.5445
-	-	XM_002696814.1	−1.526	−1.228	−1.203

[illegible]

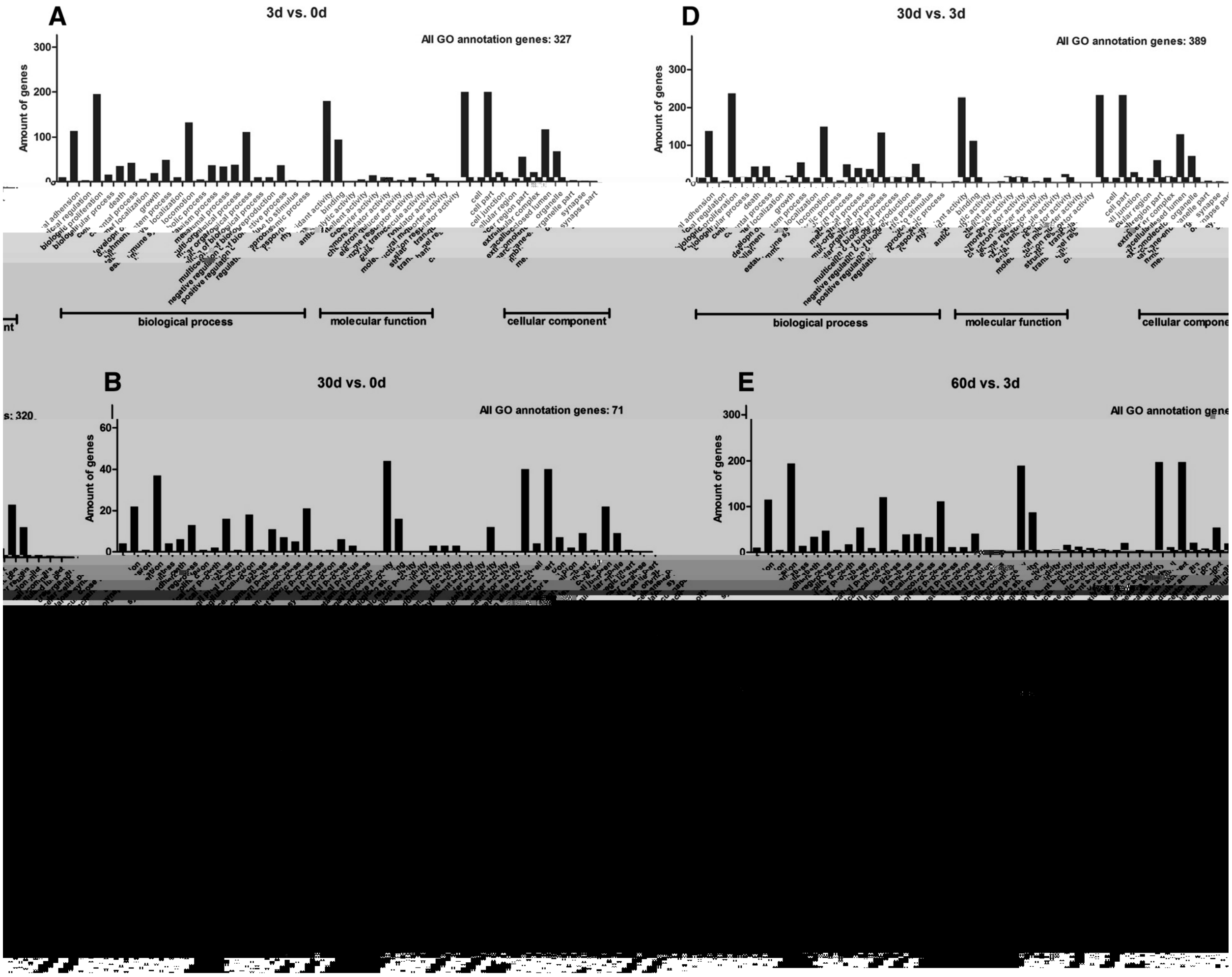

Figure 1 GO annotations of differentially expressed genes. Summary of functions and locations for genes differentially expressed in T lymphocytes of *H. contortus* infected sheep in six comparisons (**A**: 3d vs. 0d; **B**: 30d vs. 0d; **C**: 60d vs. 0d; **D**: 30d vs. 3d; **E**: 60d vs. 3d; **F**: 60d vs. 30d), grouped into the three GO subcategories 'biological process', 'cellular component' and 'molecular function'.

. 0 60 . 0 , SLC9A3R2, SCN8A, B4GALT2, NF330, ABCB9, MCP1, R RB, C7H5ORF24, COMMD4, NUDT14, KLK10, SLC28A1, SMAD4, SEPT7. SLC9A3R2 NHE-RF2, / NHE3 30 . D SLC9A3R2 3 , . A 30 60 NF-κB 31 . SCN8A . I , . T 32,33 . L SLC9A3R2, SCN8A 3 . NF330, , 34 . I 35 . NF330

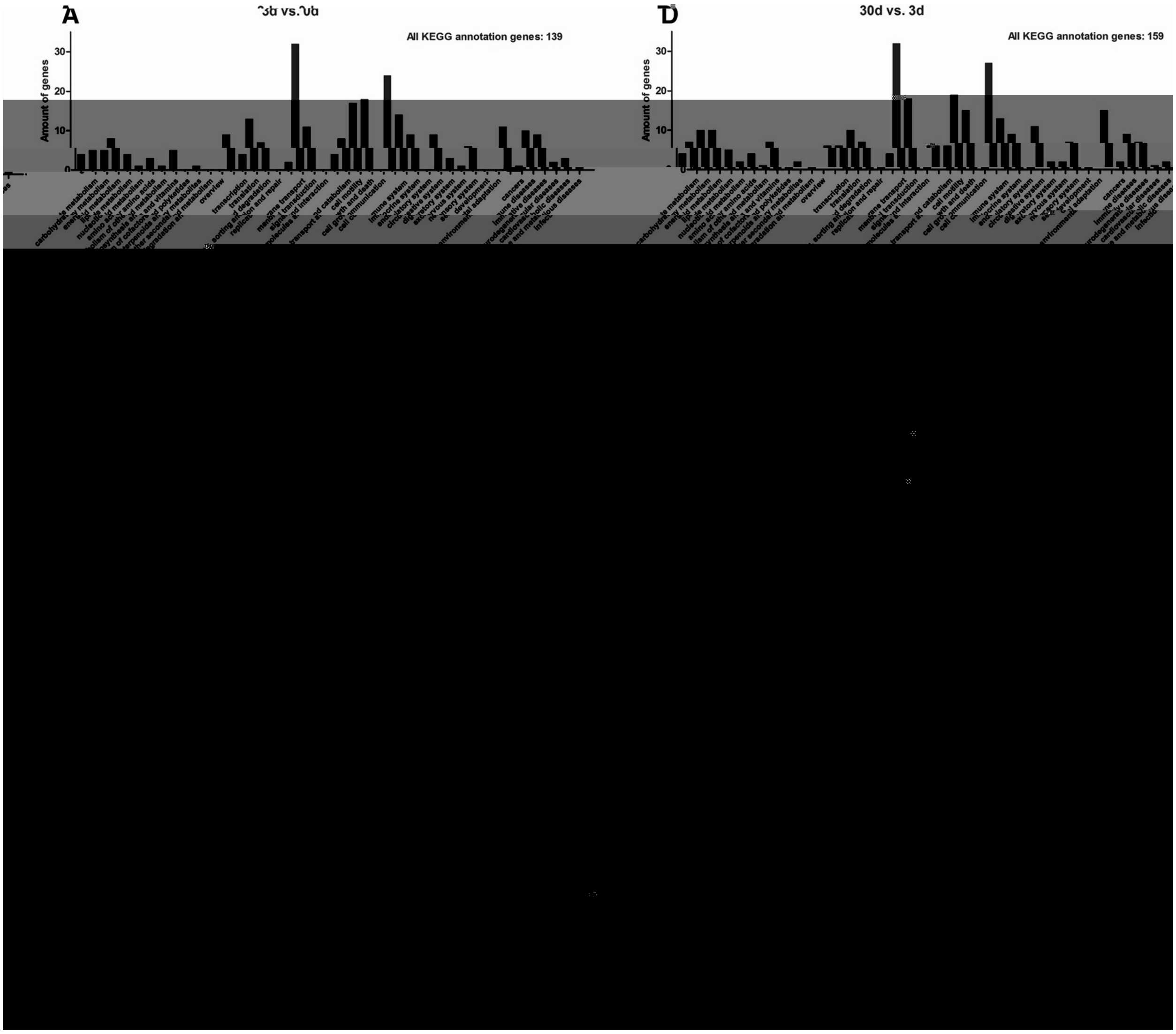

Figure 2 KEGG annotations of differentially expressed genes. All differentially expressed genes in six comparisons (**A**: 3d vs. 0d; **B**: 30d vs. 0d; **C**: 60d vs. 0d; **D**: 30d vs. 3d; **E**: 60d vs. 3d; **F**: 60d vs. 30d) were annotated using the KEGG database for pathway analysis, and were classified according to the six KEGG subcategories ‘metabolism’, ‘GIP (genetic information processing)’, ‘EIP (environmental information processing)’, ‘CP (cellular processes)’, ‘OS (organismal systems)’ and ‘HD (human diseases)’.

[illegible] B4GALT2. B4GALT2 [illegible] -1,4- [illegible] . A [illegible] G [illegible] 36 . I [illegible] *H. contortus* [illegible] . R [illegible] B4GALT2 [illegible] NF330 [illegible] 3 [illegible] T [illegible] , [illegible] B4GALT2 [illegible] NF330 [illegible] 30 [illegible] 60 [illegible] . 37 . ABCB9 [illegible] MDR/TAP [illegible] ATP- [illegible] (ABC) [illegible] . T [illegible]

[illegible] , ABCB1, [illegible] MDR/TAP [illegible] , [illegible] 38,39 . F [illegible] ABCB9 [illegible] 40 . I [illegible] MCP1 [illegible] 1 [illegible] 41 . M [illegible] 42 . U [illegible] ABCB9 [illegible] MCP1 [illegible] *H. contortus* [illegible] . A [illegible] R RB [illegible] ,

Table 4 The correlative genes involved in the immune-relevant pathways from the results of KEGG pathway analysis in the six comparisons

I e-eea a a	3d . 0d	30d . 0d	60d . 0d	30d . 3d	60d . 3d	60d .30d
Hematopoietic cell lineage	CD59↓	-	*FCER2*↑	IL6R↑	IL1R2↑, CD59↑	-
Complement and coagulation cascades	CD59↓, C5AR1↓	-	-	C5AR1↑, C1R↑, CD59↑	C5AR1↑, CD59↑	-
Toll-like receptor signaling pathway	IRF7↓, MAP3K7IP2↓, MAPK9↓	IRAK1↑	-	IRAK1↑, MAP3K7IP2↑, MAPK9↑, IRF7↑	PIK3R2↑, MAPK9↑, IRF7↑	-
NOD-like receptor signaling pathway	*SUGT1*↓, MAP3K7IP2↓, MAPK9↓	-	-	MAP3K7IP2↑, MAPK9↑, *SUGT1*↑	MAPK9↑, *SUGT1*↑	-
RIG-I-like receptor signaling pathway	IRF7↓, LOC782671↓, MAPK9↓	-	-	LOC782671↑, MAPK9↑, IRF7↑	LOC782671↑, MAPK9↑, IRF7↑	-
Cytosolic DNA-sensing pathway	IRF7↓, LOC782671↓	-	-	LOC782671↑, IRF7↑	LOC782671↑, IRF7↑	-
Natural killer cell mediated cytotoxicity	*FCER1G*↓, PPP3R1↓	*SHC1*↑	-	PPP3R1↑, *SHC1*↑, *FCER1G*↑	PIK3R2↑, NFATC1↑, PPP3R1↑, *FCER1G*↑	*SHC1*↓
T cell receptor signaling pathway	PPP3R1↓, NCK2↑, *PAK4*↑	*PAK4*↑	-	NCK2↓, PPP3R1↑	*PAK4*↓, NCK2↓, PIK3R2↑, NFATC1↑, PPP3R1↑	-
B cell receptor signaling pathway	PPP3R1↓	-	-	PPP3R1↑	PIK3R2↑, NFATC1↑, PPP3R1↑	-
Fc epsilon RI signaling pathway	*FCER1G*↓, MAPK9↓	-	-	*FCER1G*↑, MAPK9↑	PIK3R2↑, MAPK9↑, *FCER1G*↑	-
Leukocyte transendothelial migration	CYBA↓, CYBB↑, MSN↓, CTNNB1↓, MYL9↑	-	-	CXCR4↓, MYL9↓, RHOH↓, CYBB↑	MYL9↓, RHOH↓, PIK3R2↑, CYBB↓, CYBA↑	-
Intestinal immune network for IgA production	TGFB1↓, PIGR↑, TGFB2↑	-	-	CXCR4↓, TGFB2↓, TGFB1↑	TGFB2↓, TGFB1↑	-
Cemokine signaling pathway	FOXO3↓, GNB2↓, *GSK3A*↓	*SHC1*↑, *GSK3A*↑	*GSK3A*↑	CXCR4↓, GNB2↑, FOXO3↑, *GSK3A*↑, *SHC1*↑	GNG10↓, PIK3R2↑, *GSK3A*↑, FOXO3↑, GNB2↑	*SHC1*↓
Fc gamma R-mediated phagocytosis	-	-	-	-	PIK3R2↑	-

An up or down arrow beside each gene indicates up- or down- regulated. Italic genes are also amongst top ten differentially expressed genes.

DNA 43 . T
MHC II 44 . C7H5ORF24,
5
DNA
45,46 . T - R RB
C7H5ORF24
T -
. COMMD4, -
,
NF-κB
47-49 . NF-κ

T

H. contortus .

D

KEGG

. I

, KEGG

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. O

SUGT1, PAK4, FCER1G, GSK3A,

SHC1 FCER2. T

. PAK4

/ 21

. A PAK4 3 30

T

56,57 .

PAK

. PAK4

R GTP

. F ,

T

. T SUGT1 NOD-

58 . T NOD-

IL-1 NF-κB ,

. D

SUGT1

N 1 , N 1

. H

SUGT1 ,

59 . S T

30 SUGT1 PAK4

0 . GSK3A

3-

(PIK3CG, NK

)

60,61 . T

. H

, GSK3A

. T SHC1

. T

, . A

SHC1

62-64 . SHC1

,

. T

. GSK3A SHC1

30 60 . T

. T

T . FCER1G

F IgE. U

FCER1G

65-67 . A IgE, FCER2 (CD23),

,

. CD23 IgE ,

IgE B

68 . U *H. contortus*

,

IgE. T

CD23+ B CD4+ T

CD11 + ,

69 . FCER1G FCER2

,

30 60 .

A

IL-13

60 . 30 . M

IL-13 RNA

3 , 7

30 . IL-13, T 2-

, IgE ,

70 .

IL-13

RNA 60 .

“ ”

H. contortus .

E ca a a

T

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JU201308-1-10-072.

Conclusions

I ,

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H. contortus

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H. contortus

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H. contortus .

Additional files

Additional file 1: De a d ffe e a e e ed e e e c a . Detail information of all modulated genes was listed according to probe ID, log2 fold change, p value, gene description, gene symbol and so on.

Additional file 2: I e- e e a e e f KEGG a a a a f d ffe e a e e ed e e e c a . Symbol, name, GenBank No. and log fold change of immune-relevant genes were listed.

Additional file 3: T e - e a ed a d d - e a ed e e e c a . Symbol, name, GenBank No. and log fold change of top ten genes were listed. About half genes were yet to be identified.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
DAF built and guided the team. ZQJ and DAF designed the experiments, with input from YY. YY, ZHL and CXQ cultured the *H. contortus* L3s from eggs and raised sheep. YY and CXQ collected T lymphocytes from peripheral blood samples. YBL extracted RNA. YY and GXL performed the quantitative RT-PCR validation. YY dealt with the microarray data and wrote the manuscript. All authors read and approved the final version of the manuscript.

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