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

Yi Yang^{1,2}, Qian-Jin Zhou^{1,3}, Xue-Qiu Chen^{1,2}, Bao-Long Yan^{1,4}, Xiao-Lu Guo^{1,2}, Hong-Li Zhang^{1,5} and Ai-Fang Du^{1,2*}

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

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.

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. 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.

* Correspondence: afdu@zju.edu.cn

¹Institute of Preventive Veterinary Medicine, College of Animal Sciences, Zhejiang University, Hangzhou 310058, China

²Zhejiang Provincial Key Laboratory of Preventive Veterinary Medicine, Zhejiang University, Hangzhou 310058, China

Full list of author information is available at the end of the article

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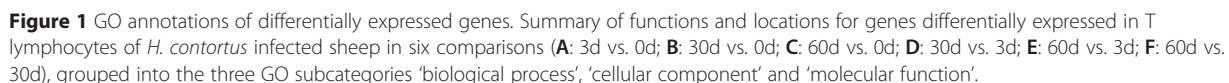
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Database		3d		60d		30d		60d		30d		60d	
Diff genes	Up-regulated	853	99	242	234	42	15	1058	977	805	689	102	2
	Down-regulated		754		8		27		81		116		100
GO annotation		327		71		14		389		320		37	
KEGG Pathway annotation		139		26		9		159		139		11	
PANTHER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

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Gene Symbol	Gene Name	Gene Accession	Locus Coordinates (kb)					
			chr1	chr2	chr3	chr4	chr5	chr6
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			

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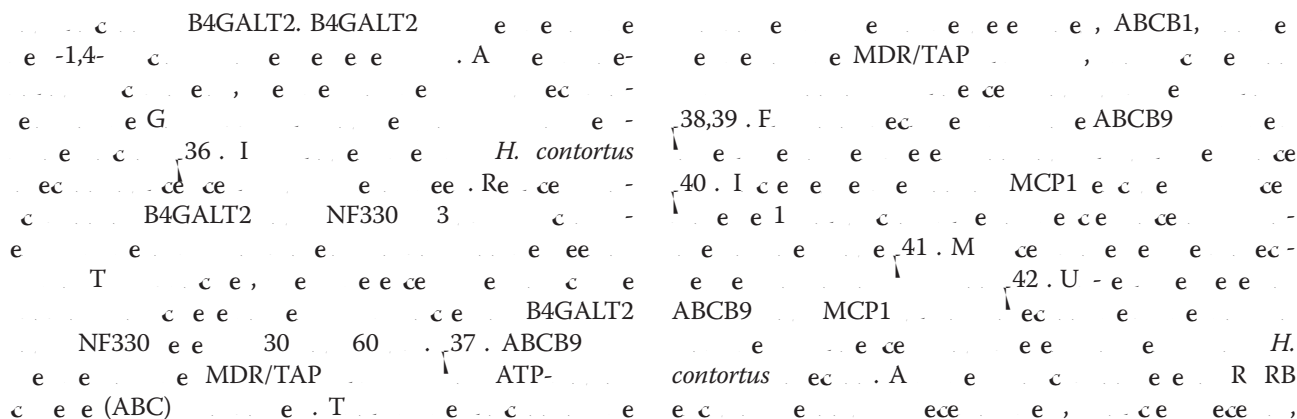


Table 4 The correlative genes involved in the immune-relevant pathways from the results of KEGG pathway analysis in the six comparisons

Immune-relevant pathway	3d vs 0d	30d vs 0d	60d vs 0d	30d vs 3d	60d vs 3d	60d vs 30d
Hematopoietic cell lineage	CD59↓	-	<i>FCER2</i> ↑	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	<i>SUGT1</i> ↓, MAP3K7IP2↓, MAPK9↓	-	-	MAP3K7IP2↑, MAPK9↑, <i>SUGT1</i> ↑	MAPK9↑, <i>SUGT1</i> ↑	-
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	<i>FCER1G</i> ↓, PPP3R1↓	<i>SHC1</i> ↑	-	PPP3R1↑, <i>SHC1</i> ↑, <i>FCER1G</i> ↑	PIK3R2↑, NFATC1↑, PPP3R1↑, <i>FCER1G</i> ↑	<i>SHC1</i> ↓
T cell receptor signaling pathway	PPP3R1↓, NCK2↑, <i>PAK4</i> ↑	<i>PAK4</i> ↑	-	NCK2↓, PPP3R1↑	<i>PAK4</i> ↓, NCK2↓, PIK3R2↑, NFATC1↑, PPP3R1↑	-
B cell receptor signaling pathway	PPP3R1↓	-	-	PPP3R1↑	PIK3R2↑, NFATC1↑, PPP3R1↑	-
Fc epsilon RI signaling pathway	<i>FCER1G</i> ↓, MAPK9↓	-	-	<i>FCER1G</i> ↑, MAPK9↑	PIK3R2↑, MAPK9↑, <i>FCER1G</i> ↑	-
Leukocyte transendothelial migration	CYBA↓, CYBB↑, MSN↓, CTNNA1↓, 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↓, <i>GSK3A</i> ↓	<i>SHC1</i> ↑, <i>GSK3A</i> ↑	<i>GSK3A</i> ↑	CXCR4↓, GNB2↑, FOXO3↑, <i>GSK3A</i> ↑, <i>SHC1</i> ↑	GNG10↓, PIK3R2↑, <i>GSK3A</i> ↑, FOXO3↑, GNB2↑	<i>SHC1</i> ↓
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.

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Additional files

Additional file 1: De a d f f e e a e e e d e 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 f f e e a e e e d 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 e - e a e d a d d - e a e d 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.

C e e e

The authors declare that they have no competing interests.

A c b

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.

A c e d e

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A d e a

¹Institute of Preventive Veterinary Medicine, College of Animal Sciences, Zhejiang University, Hangzhou 310058, China. ²Zhejiang Provincial Key Laboratory of Preventive Veterinary Medicine, Zhejiang University, Hangzhou 310058, China. ³Faculty of Life Science and Biotechnology, Ningbo University, Ningbo 315211, China. ⁴Wenzhou Medical University, Wenzhou 325035, China. ⁵Zhejiang center for animal disease control and prevention, Hangzhou 310000, China.

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Refe e ce

1. Zhou QJ, Zhang HL, Jiang XL, Du AF. The gene structure and promoter region of the vaccine target aminopeptidase H11 from the blood-sucking nematode parasite of ruminants, *Haemonchus contortus*. *Funct Integr Genomics*. 2010;10(4):589–601.
2. Freeman AS, Nghiem C, Li J, Ashton FT, Guerrero J, Shoop WL, et al. Amphidial structure of ivermectin-resistant and susceptible laboratory and field strains of *Haemonchus contortus*. *Vet Parasitol*. 2003;110(3–4):217–26.
3. Sutherland IA, Leathwick DM. Anthelmintic resistance in nematode parasites of cattle: a global issue? *Trends Parasitol*. 2011;27(4):176–81.
4. James CE, Hudson AL, Davey MW. Drug resistance mechanisms in helminths: is it survival of the fittest? *Trends Parasitol*. 2009;25(7):328–35.
5. Nikolaou S, Gasser RB. Prospects for exploring molecular developmental processes in *Haemonchus contortus*. *Int J Parasitol*. 2006;36(8):859–68.
6. Lacroix C, Nguyen TH, Andreoletti O, Prevot F, Grisez C, Bergeaud JP, et al. *Haemonchus contortus* (Nematoda: Trichostrongylidae) infection in lambs elicits an unequivocal Th2 immune response. *Vet Res*. 2006;37(4):607–22.
7. Shakya KP, Miller JE, Horohov DW. A Th2 type of immune response is associated with increased resistance to *Haemonchus contortus* in naturally infected Gulf Coast Native lambs. *Vet Parasitol*. 2009;163(1–2):57–66.
8. Meeusen EN, Balic A, Bowles V. Cells, cytokines and other molecules associated with rejection of gastrointestinal nematode parasites. *Vet Immunol Immunopathol*. 2005;108(1–2):121–5.
9. Bambou JC, De la Chevrotiere C, Varo H, Arquet R, Kooyman FN, Mandonnet N. Serum antibody responses in Creole kids experimentally infected with *Haemonchus contortus*. *Vet Parasitol*. 2008;158(4):311–8.
10. De la Chevrotiere C, Bambou JC, Arquet R, Jacquet P, Mandonnet N. Genetic analysis of the potential role of IgA and IgE responses against *Haemonchus contortus* in parasite resistance of Creole goats. *Vet Parasitol*. 2012;186(3–4):337–43.
11. Terefe G, Lacroix C, Prevot F, Grisez C, Bergeaud JP, Bleuart C, et al. Eosinophils in *Haemonchus contortus*-infected resistant and susceptible breeds of sheep: abomasal tissue recruitment and in vitro functional state. *Vet Parasitol*. 2009;165(1–2):161–4.
12. Fox JG, Beck P, Dangler CA, Whary MT, Wang TC, Shi HN, et al. Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces helicobacter-induced gastric atrophy. *Nat Med*. 2000;6(5):536–42.
13. Zaccane P, Fehervari Z, Jones FM, Sidobre S, Kronenberg M, Dunne DW, et al. *Schistosoma mansoni* antigens modulate the activity of the innate immune response and prevent onset of type 1 diabetes. *Eur J Immunol*. 2003;33(5):1439–49.
14. Chen F, Liu Z, Wu W, Rozo C, Bowdridge S, Millman A, et al. An essential role for TH2-type responses in limiting acute tissue damage during experimental helminth infection. *Nat Med*. 2012;18(2):260–6.
15. Miller JE, Horohov DW. Immunological aspects of nematode parasite control in sheep. *J Anim Sci*. 2006;84(Suppl):E124–32.
16. Shakya KP, Miller JE, Lomax LG, Burnett DD. Evaluation of immune response to artificial infections of *Haemonchus contortus* in Gulf Coast Native compared with Suffolk lambs. *Vet Parasitol*. 2011;181(2–4):239–47.
17. Andronikos N, Hunt P, Windon R. Expression of genes in gastrointestinal and lymphatic tissues during parasite infection in sheep genetically resistant or susceptible to *Trichostrongylus colubriformis* and *Haemonchus contortus*. *Int J Parasitol*. 2010;40(4):417–29.
18. Takeuchi A, Shiota M, Tatsugami K, Yokomizo A, Kuroiwa K, Dejima T, et al. YB-1 suppression induces STAT3 proteolysis and sensitizes renal cancer to interferon-alpha. *Cancer Immunol Immunother*. 2013;62(3):517–27.
19. Kaburaki T, Zhang Q, Jin X, Uchiyama M, Fujino Y, Nakahara H, et al. Effects of Japanese herbal medicine Sairei-to on murine experimental autoimmune uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2013;251(12):2733–9.
20. Trizio D, Cudkovic G. Separation of T and B lymphocytes by nylon wool columns: evaluation of efficacy by functional assays in vivo. *J Immunol*. 1974;113(4):1093–7.
21. Bar-Or C, Czosnek H, Koltai H. Cross-species microarray hybridizations: a developing tool for studying species diversity. *Trends Genet*. 2007;23(4):200–7.
22. Du AF: Gene Expression Omnibus: Agilent-028803 Custom Whole Sheep Genome Oligo Microarray. 2012. <http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE16283>. Accessed 16 Nov 2012.
23. Yang Y, Du AF: Gene Expression Omnibus: Profiling of differentially expressed genes in sheep T lymphocytes response to *Haemonchus contortus* infection. 2012. <http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE42302>. Accessed 16 Nov 2012.
24. Webster LM, Paterson S, Mougeot F, Martinez-Padilla J, Piernney SB. Transcriptomic response of red grouse to gastro-intestinal nematode parasites and testosterone: implications for population dynamics. *Mol Ecol*. 2011;20(5):920–31.
25. Xiang LX, He D, Dong WR, Zhang YW, Shao JZ. Deep sequencing-based transcriptome profiling analysis of bacteria-challenged *Lateolabrax japonicus* reveals insight into the immune-relevant genes in marine fish. *BMC Genomics*. 2010;11:472.
26. Castilho PC, Buckley BA, Somero G, Block BA. Heterologous hybridization to a complementary DNA microarray reveals the effect of thermal acclimation in the endothermic bluefin tuna (*Thunnus orientalis*). *Mol Ecol*. 2009;18(10):2092–102.
27. MacKinnon KM, Burton JL, Zajac AM, Nottter DR. Microarray analysis reveals difference in gene expression profiles of hair and wool sheep infected with *Haemonchus contortus*. *Vet Immunol Immunopathol*. 2009;130(3–4):210–20.

30. Bhattacharya R, Wang E, Dutta SK, Vohra PK EG, Prakash YS, Mukhopadhyay D. NHERF-2 maintains endothelial homeostasis. *Blood*. 2012;119(20):4798–806.
31. Subramanian H, Gupta K, Ali H. Roles for NHERF1 and NHERF2 on the regulation of C3a receptor signaling in human mast cells. *PLoS One*. 2012;7(12), e51355.
32. Isom LL. Sodium channel beta subunits: anything but auxiliary. *Neuroscientist*. 2001;7(1):42–54.
33. Calhoun JD, Isom LL. The role of non-pore-forming beta subunits in physiology and pathophysiology of voltage-gated sodium channels. *Handb Exp Pharmacol*. 2014;221:51–89.
34. Bolivar J, Garcia-Cozar FJ, Astola A, Iglesias C, Pendon C, Valdivia MM. Genomic structure and chromosome location of the human gene encoding the zinc finger autoantigen ZNF330. *Cytogenet Cell Genet*. 2001;93(3–4):234–8.
35. De Melo IS, Iglesias C, Benitez-Rondan A, Medina F, Martinez-Barbera JP, Bolivar J. NOA36/ZNF330 is a conserved cystein-rich protein with proapoptotic activity in human cells. *Biochim Biophys Acta*. 2009;1793(12):1876–85.
36. Hennet T. The galactosyltransferase family. *Cell Mol Life Sci*. 2002;59(7):1081–95.
37. Sato T, Furukawa K. Expression and Transcriptional Regulation of β 4-Galactosyltransferase Genes in Cancer. In: Endo T, Seeberger PH, Hart GW, Wong C-H, Taniguchi N, editors. *Glycoscience: Biology and Medicine*. Japan: Springer; 2014. p. 1–5.
38. Bangert I, Tumulka F, Abele R. The lysosomal polypeptide transporter TAPL: more than a housekeeping factor? *Biol Chem*. 2011;392(1–2):61–6.
39. Pohl A, Devaux PF, Herrmann A. Function of prokaryotic and eukaryotic ABC proteins in lipid transport. *Biochim Biophys Acta*. 2005;1733(1):29–52.
40. Fujimoto Y, Kamakura A, Motohashi Y, Ohashi-Kobayashi A, Maeda M. **Transcript 3999341299-600A** **Advt 71 (Pharm)-983999639** stably expressed in Chinese hamster ovary-K1 cells is sorted to the microdomains of lysosomal membranes. *Biol Pharm Bull*. 2011;34(1):36–40.
41. Lawrence CE, Paterson YY, Wright SH, Knight PA, Miller HR. Mouse mast cell