RESEARCH ARTICLE

Genes Selectively Expressed in Rat Organs

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Abstract: *Background***:** Understanding organic functions at a molecular level is important for scientists to unveil the disease mechanism and to develop diagnostic or therapeutic methods.

Aims: The present study tried to find genes selectively expressed in 11 rat organs, including the adrenal gland, brain, colon, duodenum, heart, ileum, kidney, liver, lung, spleen, and stomach.

A R T I C L E H I S T O R Y

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*Materials and Methods***:** Three normal male Sprague-Dawley (SD) rats were anesthetized, their organs mentioned above were harvested, and RNA in the fresh organs was extracted. Purified RNA was reversely transcribed and sequenced using the Solexa high-throughput sequencing technique. The abundance of a gene was measured by the expected value of fragments per kilobase of transcript sequence per million base pairs sequenced (FPKM). Genes in organs with the highest expression level were sought out and compared with their median value in organs. If a gene in the highest expressed organ was significantly different ($p < 0.05$) from that in the medianly expressed organ, accompanied by q value 0.05 , and accounted for more than 70% of the total abundance, the gene was assumed as the selective gene in the organ.

*Results & Discussion***:** The Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Ontology (GO) pathways were enriched by the highest expressed genes. Based on the criterion, 1,406 selective genes were screened out, 1,283 of which were described in the gene bank and 123 of which were waiting to be described. KEGG and GO pathways in the organs were partly confirmed by the known understandings and a good portion of the pathways needed further investigation.

*Conclusion***:** The novel selective genes and organic functional pathways are useful for scientists to unveil the mechanisms of the organs at the molecular level, and the selective genes' products are candidate disease markers for organs.

Keywords: High-throughput sequencing, selective expression, organic markers, rat, genetic variations, DNA.

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1. INTRODUCTION

It was once believed that all somatic cells shared the same genome because all of a creature's cells and organs develop from a fertilized egg. The expression of an animal's genome controls the animal's functions, whose functions are executed by its cells. Therefore, cells have different functions depending on different gene expression profiles [1, 2], and so do different tissues and organs. The other gene expression profiles will doom cell differentiation [3], organ development [4], and its functions. Based on the understanding, it can be assumed that some genes as constructive ones must be universally expressed in all the cells with a nucleus, and some could be selectively expressed in cells, tissues, and organs at different developmental stages [5, 6]. At an animal's adulthood, its gene expression profiles could

be relatively stable to maintain its biological functions, and the gene expression profile would reflect its function. Therefore, the products (RNAs and proteins) from the gene selectively expressed in an organ suggest its function(s).

Health and disease are the eternal themes of humans, and are usually related to gene expression profiles. The mechanism study on human health and disease is generally carried on model animals at first, then on humans. Among them, adult rats and mice are model animals most frequently used by scientists, and no animals are studied more deeply than them. Therefore, it is a good strategy to understand humans by investigating gene expression profiles in rats. Identifying molecular targets and disease markers from rats and mice is usually the first step to understanding human health and disease, then to finding therapeutic strategies and methods. The selective gene products released into the blood can be used as damage markers. However, it is a big premise to understand the normal model animal's biological features at the molecular level before scientists comprehensively understand human health and disease [7]. There were much data from animals suggesting that some genes selectively

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expressed in organs, *e.g*. NeuN (Rbfox3) in the brain or neuron [8] though with alternative opinions [9], troponin (Tnnc1, Tnni3) in the heart [10], glutamic pyruvic transaminase (GPT, Gpt) in the liver [11], and neutrophil gelatinaseassociated lipocalin (NGAL) in the kidney [12]. The findings are very useful and even were adopted for clinic diagnosis and treatment. The gene products selectively and originally distributed can be used as molecular organic markers and then make disease diagnosis more accurate or earlier. Nevertheless, in the background of precision medicine [13], the selective gene products in organs are still insufficient for clinical practice, and it is still necessary to systematically screen the genes selectively expressed in organs.

 Proteins and RNAs are the end products of genes and execute their functions. To identify the selective functions at the molecular level, all the selectively distributed proteins in organs should be screened out. However, among them, protein screening is a big economic burden because the study would consume plenty of antibodies. Since proteins and RNAs were transcribed and even then translated from genes, the present study would apply high-throughput sequencing technology to analyze gene expression profiles of 11 organs, including the adrenal gland, brain, colon, duodenum, heart, ileum, kidney, liver, lung, spleen, and stomach, at the RNA level, and then, based on the results, to find the likely organic markers and analyze the functional pathways the selective genes would be involved in.

2. MATERIALS AND METHODS

2.1. Materials

 Adult male Sprague-Dawley (SD) rats (age, 45 days; body weight, 180-220 g) were obtained from Chengdu Dossy Experimental Animal Co. Ltd., Chengdu, China [Certification No. SCXK (Chuan) 2008–24]. TRIzol Plus RNA Purification kit was purchased from Invitrogen (Carlsbad, CA, USA). Ultra-pure water was produced with a Milli Q water purification system manufactured by EMD Millipore Group (Darmstadt, Germany). NanoDrop ND-1000 spectrophotometer was manufactured by PeqLab (Erlangen, Germany). The multimicroplate reader of Infinite 200pro was manufactured by Tecan Group (Mannedorf, Switzerland). Other instruments or reagents used in the present study were made in China if not mentioned.

2.2. Animal Treatment

 Three rats were normally treated for three days. Then, the animals were intraperitoneally anesthetized with urethane (1.0 g/kg) . The rats' chests and abdomens were opened, and their organs were harvested, including the adrenal gland (Ad), brain (frontal cortex) (Br), colon (Co), duodenum (the first 5 cm) (Du), heart (left ventricle) (He), ileum (the end 5 cm) (Il), kidney (right) (Ki), liver (Li), lung (right) (Lu), spleen (Sp), and stomach (gastric antrum) (St). The tunica and mesentery of the organs were removed clearly. All the organs were frozen with liquid nitrogen and kept at -80°C by dry ice to keep them fresh, and then sent to Sangon Biotech Co. Ltd. (Shanghai China) (https:// www.sangon.com/) immediately for high-throughput sequencing.

 The animal experiments were approved by the Animal Care and Use Committee of Yunnan Provincial Key Laboratory of Molecular Biology for Sinomedicine (Approved No. LL-20171023-01), Yunnan University of Traditional Chinese Medicine.

2.3. High-throughput Sequencing of mRNA

 The fresh organs were frozen with liquid nitrogen and ground to powder. The total RNA in the powder was extracted and purified using the TRIzol Plus RNA Purification kit (Invitrogen, Carlsbad, CA, USA). The quantity and quality of RNA were measured by the NanoDrop ND-1000 spectrophotometer. RNA integrity was assessed by three bands (28S, 18S, and 5S) using formaldehyde denaturing agarose gel electrophoresis RNA as previously described [14, 15].

 Similar to the results of our previous study [16], doublestranded cDNA (ds-cDNA) was reversely transcribed from the total RNA using a SuperScript ds-cDNA synthesis kit (Invitrogen, Carlsbad, USA) in the presence of 100 pmol/L oligo dT primers. Solexa high-throughput sequencing technique was used to sequence the cDNA by Sangon Biotech Co. Ltd. (Shanghai, China). The raw data containing reads of 150 bases of nucleotide in fastq format was transformed to original sequences in fasta format by Seqkit software in the disc operation system (DOS) model [17]. The sequences that matched 27 bp or more to the rat's reference mRNA sequences (https://www.ncbi.nlm.nih.gov/) were screened out by TBtools software (v0.664445552). The expected value of fragments per kilobase of transcript sequence per million base pairs sequenced (FPKM) was used for the normalization of expression level [18].

2.4. Screening Genes Selectively Expressed

 Values of gene's FPKM in every organ were collected. The overall function of the organs at the gene expression level was analyzed by cluster analysis. The distance between organs was calculated by the Vegan package of Bray curtis method [19], and the cluster tree was established by Hcluster [20].

 Based on the assumption that a gene is significantly overexpressed in an organ (statistical consideration), if its expression abundance accounts for the majority of that in all organs, say more than 70%, the gene is considered to be selectively expressed in that organ. The maximum FPKM value of a gene in any organs less than 5 was ignored because the expression level of the gene was supposed to be too low to analyze. Genes with FPKM above 5 were further analyzed. The means of a gene's FPKM in all the organs were sorted. The organ with the median value and those with the biggest value were selected. Then, the expression level of the gene in the two organs (the highest and median organs) was compared with the Student t-test. The q-value, a false-discovery rate alternative to *p*-values, was also calculated as an adjustment for multiple comparisons [21]. If *p*value and q-value were both less than 0.05, the gene was regarded as a candidate gene selectively expressed in the organ.

Fig. (1). Distribution of gene expression and clustering analysis was made from 32,623 genes' transcripts detected. The distribution of gene expression in different organs was similar (Mean \pm SD, n = 3) (A). However, the function of the organs was different based on the clustering analysis of total gene expression from 11 organs (n = 3) (**B**). **Abbreviations:** Ad, adrenal gland; Br, brain; Co, colon; Du, duodenum; He, heart; Il, ileum; Ki, kidney; Li, liver; Lu, lung; Sp, spleen; St, stomach. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

 The means of the gene in all the organs were summed up as "Total". The mean of the gene in the organ highest expressed it was regarded as "max mean". Then, the MT ratio $((max mean)/total)$ was calculated. If the MT ratio was above 0.7, the gene was regarded as a selective gene in the organ. The gene's product in the organ was regarded as an organic marker that may execute the selective function of the organ. The last reports on the relationship between the selective genes and the organs were searched at PubMed (www.pubmed.gov) on June 10, 2023.

 The last report of the selective gene from the PubMed database was sought in the relative organ by searching the gene name and the organ both in the fields of title or abstract.

2.5. KEGG, and GO Analysis

 The values of a gene in all the organs were sorted by its mean, and the organ that expressed the median value and that expressed the biggest value were selected. The expression abundance of the gene in the two organs was compared with the Student t-test. If there was significance $(p < 0.05)$, the gene in the organ was regarded as an interesting gene. Interesting genes expressed in an organ were further analyzed to enrich the selective Kyoto Encyclopedia of Genes and Genomes (KEGG, https://www.kegg.jp/) and Gene Ontology (GO, http://www.geneontology.org/) pathways. KEGG enrichment [22] and KOG enrichment [23, 24] were performed by ClusterProfiler [25]. GO [26, 27] enrichment was performed by TopGO. The *p*-value and q-value were also calculated using the software mentioned above.

3. RESULTS

3.1. Total FPKM Distribution

 In the normal rats, 32,623 genes' transcripts were detected, and most genes were expressed at a very low level $(FPKM < 1)$, only a small portion of genes expressed at a very high level (FPKM > 1000) (Fig. **1A**). The overall FPKM distribution of every organ was similar. However, organs' function is believed to be different, which suggests that the gene most highly expressed in one organ could be different from that in the other. According to the results of cluster analysis at the expression level (Fig. **1B**), the function of the colon is near the ileum, then to the duodenum and stomach, which is easy to be understood. The function of the kidney is near to the adrenal gland, then to the heart and brain; and the spleen's function is near to the lung. To our surprise, the function of the liver was far from that of the other organs.

Fig. (2). Genes selectively expressed in different organs based on their abundance. **Abbreviations:** Ad, adrenal gland; Br, brain; Co, colon; Du, duodenum; He, heart; Il, ileum; Ki, kidney; Li, liver; Lu, lung; Sp, spleen; St, stomach. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.2. Genes with Description Selectively Expressed in Different Organs

 There were 15,922 genes with FPKM in any organ above 5, and 14,115 genes were significantly $(p < 0.05)$ highly expressed in an organ. Among them, there were 12,617 genes accepted with $q < 0.05$. Apart from 123 genes without description, there were 1,283 genes with description selectively expressed in 11 organs (Fig. **2**).

Note: Sorted by q-value. Br, brain; Co, colon; Du, duodenum; He, heart; Ki, kidney; Lu, lung; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

(Table 2) contd….

Note: Sorted by q-value. Ad, adrenal gland; Co, colon; Du, duodenum; He, heart; Il, ileum; Ki, kidney; Lu, lung; Sp, spleen; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; Lu, lung; Sp, spleen; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

From the results from Fig. (**2**), the brain (Br) was the organ with the most complex function because 459 genes were selectively expressed in it. Instead, the gastrointestinal tracts, including the stomach (St), duodenum (Du), ileum (Il), and colon (Co), selectively expressed fewer genes, suggesting that their functions could be relatively simple or similar to other organs.

 The total genes selectively expressed or the top 20 (if more) in 11 organs are listed in Tables **1-11**. Their full lists

can be seen in the supplementary data. According to the description of the gene name, most selective genes were associated with the known specific functions of the organ. For example, Mgarp (mitochondria-localized glutamic acid-rich protein) in the adrenal gland (Table **1**) is associated with steroidogenesis [28]; Scg3 (secretogranin III) in the brain (Table **2**) with neuroendocrine [29]; Reg3g (regenerating islet-derived 3 gamma) in the colon (Table **3**) with intestinal bacterial translocation to the mesenteric lymph nodes [30];

			Median Last Refs.* Organ		FPKM				
No.	Gene Name	Product (Description)			Mean	Total	<i>p</i> -value	q-value	total
1	Gip	Gastric inhibitory polypeptide		Ad	79.2	81.4	7.42E-06	1.11E-03	0.973
\overline{c}	LOC100910259	Liver carboxylesterase-like	\overline{a}	Sp	498.7	699.5	5.32E-05	2.99E-03	0.713
3	Prap1	Proline-rich acidic protein 1	\overline{a}	Br	4433.8	4622.2	9.65E-05	4.04E-03	0.959
4	3'-phosphoadenosine 5'-phosphosulfate Papss2 synthase 2		$\overline{}$	Sp	649.9	779.5	1.20E-04	4.51E-03	0.834
5	Tm4sf5	Transmembrane 4 L six family member 5	\overline{a}	Ad	940.9	1272.0	1.36E-04	4.81E-03	0.740
6	RGD1311933	Similar to RIKEN cDNA 2310057J18	\overline{a}	Ad	221.2	221.9	2.62E-04	6.69E-03	0.997
7	Cyp2c7	Cytochrome P450, family 2, subfamily c, polypeptide 7		Ad	48.0	50.7	3.56E-04	7.82E-03	0.947
8	Aadac	Arylacetamide deacetylase	$\overline{}$	St	96.4	133.8	6.93E-04	1.10E-02	0.720
9	Tmprss15	Transmembrane protease, serine 15	\overline{a}	Sp	138.8	139.2	7.87E-04	1.17E-02	0.997
10	RGD1561551	Similar to Hypothetical protein MGC75664	\overline{a}	Ad	842.1	842.9	1.28E-03	1.50E-02	0.999
11	Alppl2	Alkaline phosphatase, placental-like 2	$\overline{}$	Co	60.3	71.1	1.40E-03	1.57E-02	0.848
12	Akp3	Alkaline phosphatase 3, intestine, not Mn requiring	$[73]$	Ad	2279.3	2280.1	1.67E-03	1.72E-02	1.000
13	Ada	Adenosine deaminase	$[74]$	Ki	1461.9	2071.3	1.74E-03	1.76E-02	0.706
14	Bco1	Beta-carotene oxygenase 1	$[75]$	Ki	160.1	210.3	1.78E-03	1.78E-02	0.761
15	Slc4a7	Solute carrier family 4, sodium bicarbonate cotransporter, member 7	[75, 76]	St	108.5	137.6	1.90E-03	1.79E-02	0.789
16	Alpi	Alkaline phosphatase, intestinal	$[77]$	Br	1098.5	1193.8	1.84E-03	1.81E-02	0.920
17	Treh	Trehalase (brush-border membrane glycoprotein)	$[78]$	Ki	260.7	268.5	2.44E-03	2.09E-02	0.971
18	Trpv6	Transient receptor potential cation channel, subfamily V, member 6	$[79]$	Sp	24.2	32.7	2.45E-03	2.10E-02	0.741
19	Otop3	Otopetrin 3	\overline{a}	Co	69.3	70.2	3.51E-03	2.53E-02	0.987
20	Pdx1	Pancreatic and duodenal homeobox 1	[80]	Ad	58.6	61.7	4.91E-03	3.02E-02	0.950

Table 4. Top 20 of 25 genes with description selectively expressed in the duodenum (Du) based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; Co, colon; Ki, kidney; Sp, spleen; St, stomach

* Last Refs. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

(Table 5) contd….

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; Co, colon; Du, duodenum; Il, ileum; Ki, kidney; Lu, lung; Sp, spleen; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 20123.

Table 6. Top genes with description selectively expressed in the ileum (Il) based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Ki, kidney; Sp, spleen; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

(Table 7) contd….

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; Co, colon; Du, duodenum; He, heart; Il, ileum; Li, liver; Sp, spleen; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

Table 8. Top 20 of 208 genes with description selectively expressed in the liver (Li) based on their abundance (n = 3).

(Table 8) contd….

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; He, heart; Il, ileum; Ki, kidney; Sp, spleen; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

Table 9. Top 20 of 122 genes with description selectively expressed in rat lung (Lu) based on their abundance (n = 3).

(Table 9) contd….

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; Co, colon; Il, ileum; Ki, kidney; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

Table 10. Top 20 of 102 genes with description selectively expressed in the spleen (Sp) based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; Du, duodenum; He, heart; Il, ileum; Ki, kidney; St, stomach

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

Table 11. Top 20 of 24 genes with description selectively expressed in the stomach (St) based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; Co, colon; Du, duodenum; He, heart; Ki, kidney; Li, liver; Lu, lung; Sp, spleen

* Last Ref. was based on the reports documented in PubMed (www.pubmed.gov) before June 10, 2023.

Gip (gastric inhibitory polypeptide) in the duodenum (Table **4**) with regulation of insulin secretion [31]; Klhl38 (kelchlike family member 38) in the heart (Table **5**), though seldom reported, could be associated with the reversion of striated muscle atrophy [32]; Defa24 (defensin alpha 24) in the ileum (Table 6) with intestinal barrier [33]; Slc3a1 [solute carrier family 3 (amino acid transporter heavy chain), member 1] in the kidney (Table **7**) with the transport of cystine and other amino acids across the membrane [34]; C5 (hemolytic complement) in the liver (Table **8**) was early verified to execute innate immune [35]; Icam1 (intercellular adhesion molecule 1) in the lung (Table **9**) with innate immune [36]; Coch (cochlin) used to highly expressed in the inner ear [37] also highly expressed in the spleen (Table **10**); and Cxcl17 (chemokine (C-X-C motif) ligand 17) in the stomach (Table **11**) with its innate immune [38]. Nevertheless, there were many genes that were not reported in the relative organs (supplementary data).

3.3. KEGG and GO Pathway Enrichment

3.3.1. KEGG Pathway Enrichment

 KEGG is a bioinformatics database resource for understanding high-level functions and utilities of the biological system, which includes the cell, the organism, and the ecosystem, from molecular-level information, especially largescale molecular datasets generated by genome sequencing and other high-throughput experimental technologies. The selective KEGG pathways were enriched based on the abundance of genes most highly expressed in organs. The number of the selective pathway is listed in Fig. (**3**) and the top 20 pathways are listed in Tables **12-22**. Their full lists can be seen in the supplementary data. There were 179 "selective" pathways in 11 rat organs. Among them, 52 pathways were involved in two organs, 7 in three organs, and 1 in four organs. It should be noted that the "selective" pathways engaged in two or more organs were based on enrichment analysis. As can be seen from Fig. (**3**), organs with many selective pathways, like the brain, indicate that they undertake many complex functions. Conversely, organs with few selective pathways, like the adrenal glands and stomach, indicate their relatively simple functions. The results in Fig. (**3**), suggested that the lung could be the top 2 organs with the complex functions of the 11 organs.

Fig. (3). Selective KEGG enrichment in different organs was based on the abundance of genes most highly expressed in organs. **Abbreviations:** Ad, adrenal gland; Br, brain; Co, colon; Du, duodenum; He, heart; Il, ileum; Ki, kidney; Li, liver; Lu, lung; Sp, spleen; St, stomach. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

 The function of some pathways was verified in relative organs based on common understandings, for example, ko04925 (Aldosterone synthesis and secretion) in the adrenal gland (Table **12**), ko04721 (Synaptic vesicle cycle) in the brain (Table **13**), ko04672 (Intestinal immune network for IgA production) in the colon (Table **14**), ko04975 (Fat digestion and absorption) in the duodenum (Table **15**), ko04260 (Cardiac muscle contraction) in the heart (Table **16**), ko00520 (Amino sugar and nucleotide sugar metabolism) in the ileum (Table **17**), ko04964 (Proximal tubule bicarbonate reclamation) in the kidney (Table **18**), ko04976 (Bile secretion) in the liver (Table **19**), ko04151 (PI3K-Akt signaling pathway) in the lung (Table **20**), ko04640 (Hematopoietic cell lineage) in the spleen (Table **21**), and ko04971 (Gastric acid secretion) in the stomach (Table **22**).

3.3.2. GO Pathway Enrichment

 The GO database is the world's largest source of bioinformation on the functions of genes. This knowledge of the genes is a foundation for computational analysis of large-scale molecular biology and genetics experiments in biomedical research. Selective GO pathways were enriched based on the abundance of genes most highly expressed in organs. The number of the selective pathway is listed in Fig. (**4**) and the pathways of the adrenal gland, brain, colon, duodenum, heart, ileum, kidney, liver, lung, spleen, and stomach are listed in Tables **23-33**, respectively. There were 4,432 relatively selective pathways in 11 rat organs. Among them, 971 pathways were involved in two organs, 357 in three organs, 86 in four organs, 21 in five organs, 7 in six organs, and 1 in seven organs. It should be noted that the "selective" pathways are involved in two or more organs based on the enrichment analysis.

 As can be seen from Fig. (**4**), organs with many selective pathways, like the lung, spleen and brain, indicate that they undertake many complex functions. Conversely, organs with few selective pathways, like the stomach and adrenal glands, indicate their relative sample functions. The results in Fig. (**3**), is similar to those in Fig. (**4**).

 The top 20 GO pathways are shown in Tables **23-33**, and their full lists can be seen in the supplementary data. As for the top 20 GO pathways, the adrenal gland (Table **23**), colon (Table **25**), and kidney (Table **29**) had no real selective pathways, and the brain had the most selective pathways, suggesting that the brain has specific functions (Table **24**).

Table 14. Selective KEGG pathways in the colon.

Table 15. Selective KEGG pathways in the duodenum.

Note: * also significantly expressed in other organs. Sorted by q-value.

Table 16. Top 20 of 21 Selective KEGG pathways in the heart.

Table 17. Selective KEGG pathways in the ileum.

Note: * also significantly expressed in other organs. Sorted by q-value.

Table 18. Top 20 of 23 selective KEGG pathways in the kidney.

No.	ID	Description	Significant	Annotated	p -value	q-value
1	ko04610	Complement and coagulation cascades	37/265	55/5400	1.98E-36	2.97E-34
2	ko00140	Steroid hormone biosynthesis	15/265	33/5400	7.31E-12	5.46E-10
3	ko00830	Retinol metabolism	14/265	38/5400	1.12E-09	5.59E-08
$\overline{4}$	ko00260*	Glycine, serine and threonine metabolism	11/265	29/5400	5.09E-08	1.90E-06
5	ko03320	PPAR signaling pathway	14/265	56/5400	3.03E-07	9.05E-06
6	ko00120	Primary bile acid biosynthesis	6/265	10/5400	2.35E-06	5.85E-05
7	ko04976	Bile secretion	12/265	51/5400	4.34E-06	9.27E-05
8	ko00220	Arginine biosynthesis	6/265	12/5400	9.50E-06	0.000
9	ko00980	Metabolism of xenobiotics by cytochrome P450	9/265	32/5400	1.49E-05	0.000
10	ko01230*	Biosynthesis of amino acids	12/265	63/5400	4.30E-05	0.001
11	ko00053	Ascorbate and aldarate metabolism	5/265	10/5400	5.64E-05	0.001
12	ko00982	Drug metabolism - cytochrome P450	8/265	31/5400	8.90E-05	0.001
13	ko00340	Histidine metabolism	6/265	17/5400	0.000	0.001
14	ko01040	Biosynthesis of unsaturated fatty acids	6/265	18/5400	0.000	0.002
15	ko00591	Linoleic acid metabolism	6/265	22/5400	0.001	0.005
16	ko01200*	Carbon metabolism	13/265	94/5400	0.001	0.006
17	ko00500	Starch and sucrose metabolism	6/265	24/5400	0.001	0.007
18	ko00983	Drug metabolism - other enzymes	6/265	24/5400	0.001	0.007
19	ko00100	Steroid biosynthesis	4/265	12/5400	0.002	0.016
20	ko00430	Taurine and hypotaurine metabolism	3/265	6/5400	0.002	0.016

Table 19. Top 20 of 34 selective KEGG pathways in the liver.

Table 20. Top 20 of 46 Selective KEGG pathways in the lung.

(Table 20) contd….

Table 21. Top 20 of 33 selective KEGG pathways in the spleen.

Table 22. Selective KEGG pathways in the stomach.

Note: * also significantly expressed in other organs. Sorted by q-value.

Table 23. Top 20 of 122 selective GO pathways in the adrenal gland.

Note: * also significantly expressed in other organs. Sorted by q-value.

According to the results of GO enrichment, the adrenal gland is a hypermetabolic organ because mitochondria in the organ are very active (Table **23**); the brain is a neural organ (Table **24**), which is well-accepted by scientists; the colon is an immune and metabolic organ (Table **25**); the duodenum is mainly an immune organ (Table **26**); the heart is also a hypermetabolic organ (Table **27**); the ileum is primarily an organ associated with protein synthesis, immune, and digestion (Table **28**); the kidney (Table **29**) and liver (Table **30**) are mainly an organ associated with metabolism; the lung is an organ mainly associated with angiogenesis and blood circulation (Table **31**); the spleen is an organ mainly associated with organelle metabolism (Table **32**), and the stomach is an organ mainly associated with digestion and glandular secretion (Table **33**).

Fig. (4). Selective GO enrichment in different organs based on the abundance of genes most highly expressed in organs. **Abbreviations:** Ad, adrenal gland; Br, brain; Co, colon; Du, duodenum; He, heart; Il, ileum; Ki, kidney; Li, liver; Lu, lung; Sp, spleen; St, stomach. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.4. Genes without Description but Selectively Expressed

 Apart from the genes whose function is described, there were 123 genes without a clear description but selectively

Table 24. Top 20 of 897 selective GO pathways in the brain.

expressed in 11 organs (Fig. **5**). From the results of Fig. (**5**), most genes without description were selectively expressed in the adrenal gland and brain. Instead, there were fewer genes without description in rat gastrointestinal tracts, including stomach, duodenum, ileum, and colon. The top 20 genes without description in the adrenal gland, brain, colon, duodenum, heart, ileum, kidney, liver, lung, spleen, and stomach were listed in Tables **34-44**, respectively; and their full lists can be seen in the supplementary data. Because the genes were not described but selectively expressed in the organs, their products and functions need further investigation. Given the low number of genes selectively expressed in the adrenal gland, the high number of undescribed high expression of genes in this organ suggests that the organ may be less studied.

4. DISCUSSION

 Screening selectively expressed genes in organs is not only a tough task but also meaningful work because the results of the work will provide useful clues and even evidence for scientists to unveil the mechanism behind the overall dysfunction and symptoms. At least, we can obtain the putative organic markers for evaluating organic injury.

Table 25. Top 20 of 536 selective GO pathways in the colon.

No.	GO.ID	Term	Ontology	Significant	Annotated	<i>p</i> -value	q-value
1	GO:0002376*	Immune system process	Biological process	153/678	1949/17378	5.70E-18	8.55E-14
2	GO:0031347*	Regulation of defense response	Biological process	52/678	407/17378	4.10E-14	3.07E-10
3	GO:0002682*	Regulation of immune system process	Biological process	89/678	1014/17378	3.80E-13	1.31E-09
4	GO:0019221*	Cytokine-mediated signaling pathway	Biological process	44/678	322/17378	3.80E-13	1.31E-09
5	GO:0045321*	Leukocyte activation	Biological process	70/678	703/17378	4.60E-13	1.31E-09
6	GO:0006952*	Defense response	Biological process	93/678	1091/17378	5.70E-13	1.31E-09
τ	GO:0001775*	Cell activation	Biological process	76/678	804/17378	$6.10E-13$	1.31E-09
8	GO:0042110*	T cell activation	Biological process	46/678	356/17378	8.50E-13	1.50E-09
9	GO:0080134*	Regulation of response to stress	Biological process	83/678	927/17378	9.00E-13	1.50E-09
10	GO:0009607*	Response to biotic stimulus	Biological process	74/678	797/17378	3.10E-12	4.63E-09
11	GO:0009605*	Response to external stimulus	Biological process	132/678	1856/17378	3.40E-12	4.63E-09
12	GO:0006955*	Immune response	Biological process	97/678	1208/17378	5.70E-12	7.12E-09
13	GO:0048518*	Positive regulation of biological process	Biological process	258/678	4587/17378	8.20E-12	9.46E-09
14	GO:0002520*	Immune system development	Biological process	67/678	706/17378	$1.40E-11$	1.32E-08
15	GO:0035556*	Intracellular signal transduction	Biological process	139/678	2034/17378	1.50E-11	1.32E-08
16	GO:0071345*	Cellular response to cytokine stimulus	Biological process	55/678	518/17378	1.50E-11	1.32E-08
17	GO:0043207*	Response to external biotic stimulus	Biological process	70/678	757/17378	1.50E-11	1.32E-08
18	GO:0007159*	Leukocyte cell-cell adhesion	Biological process	37/678	268/17378	2.20E-11	1.83E-08
19	GO:0031349*	Positive regulation of defense response	Biological process	34/678	231/17378	2.40E-11	1.89E-08
20	GO:0046649*	Lymphocyte activation	Biological process	60/678	604/17378	2.70E-11	1.91E-08

Table 26. Top 20 of 171 selective GO pathways in the duodenum.

(Table 26) contd….

Table 27. Top 20 of 554 selective GO pathways in the heart.

Table 28. Top 20 of 141 selective GO pathways in the ileum.

No.	GO.ID	Term	Ontology	Significant	Annotated	p -value	q-value
1	GO:1990904*	Ribonucleoprotein complex	Cellular component	144/1063	1129/18378	5.60E-20	9.98E-17
$\overline{2}$	GO:0030529*	Intracellular ribonucleoprotein complex	Cellular component	143/1063	1128/18378	1.30E-19	1.16E-16
3	GO:0003735*	Structural constituent of ribosome	Molecular function	80/929	507/16814	9.90E-18	4.07E-14
$\overline{4}$	GO:0005840*	Ribosome	Cellular component	86/1063	587/18378	1.10E-15	6.53E-13
5	GO:0005198*	Structural molecule activity	Molecular function	109/929	898/16814	3.30E-15	6.79E-12
6	GO:0042611	MHC protein complex	Cellular component	16/1063	25/18378	1.80E-14	8.02E-12
7	GO:0019882	Antigen processing and presentation	Biological process	27/976	91/17378	3.70E-13	5.55E-09
8	$GO:0043604*$	Amide biosynthetic process	Biological process	103/976	956/17378	9.30E-11	5.00E-07
9	GO:0006412*	Translation	Biological process	97/976	881/17378	1.00E-10	5.00E-07
10	GO:0022626*	Cytosolic ribosome	Cellular component	53/1063	350/18378	1.10E-10	3.92E-08
11	GO:0043603*	Cellular amide metabolic process	Biological process	113/976	1100/17378	1.90E-10	5.50E-07
12	GO:0006518*	Peptide metabolic process	Biological process	104/976	982/17378	2.00E-10	5.50E-07
13	GO:0043043*	Peptide biosynthetic process	Biological process	97/976	893/17378	2.20E-10	5.50E-07
14	GO:0048002	Antigen processing and presentation of peptide antigen	Biological process	17/976	49/17378	5.70E-10	1.22E-06
15	GO:0022627*	Cytosolic small ribosomal subunit	Cellular component	26/1063	121/18378	4.70E-09	1.34E-06
16	GO:0044391*	Ribosomal subunit	Cellular component	58/1063	446/18378	5.80E-09	1.34E-06
17	GO:0015935*	Small ribosomal subunit	Cellular component	30/1063	158/18378	7.00E-09	1.34E-06
18	GO:0044445*	Cytosolic part	Cellular component	59/1063	460/18378	7.20E-09	1.34E-06
19	GO:0005903*	Brush border	Cellular component	23/1063	99/18378	7.50E-09	1.34E-06
20	GO:0019538*	Protein metabolic process	Biological process	372/976	5206/17378	1.20E-08	2.25E-05

Table 29. Top 20 of 206 selective GO pathways in the kidney.

No.	GO.ID	Term	Ontology	Significant	Annotated	<i>p</i> -value	q-value
	GO:0003824*	Catalytic activity	Molecular function	571/1203	5604/16814	4.10E-26	1.69E-22
2	GO:0044281*	Small molecule metabolic process	Biological process	218/1237	1566/17378	2.20E-23	3.30E-19
3	GO:0005739*	Mitochondrion	Cellular component	210/1275	1536/18378	8.60E-23	1.53E-19
4	GO:0006082*	Organic acid metabolic process	Biological process	136/1237	806/17378	6.90E-22	5.17E-18
5	GO:0019752*	Carboxylic acid metabolic process	Biological process	128/1237	740/17378	1.40E-21	7.00E-18
6	$GO:0044710*$	Single-organism metabolic process	Biological process	378/1237	3483/17378	4.80E-20	1.80E-16
7	$GO:0070062*$	Extracellular exosome	Cellular component	253/1275	2097/18378	7.70E-20	6.86E-17
8	GO:0043436*	Oxoacid metabolic process	Biological process	130/1237	793/17378	8.00E-20	2.40E-16
9	GO:0055114*	Oxidation-reduction process	Biological process	148/1237	967/17378	1.30E-19	3.25E-16
10	GO:1903561*	Extracellular vesicle	Cellular component	253/1275	2110/18378	1.80E-19	$1.02E-16$
11	$GO:0043230*$	Extracellular organelle	Cellular component	253/1275	2114/18378	2.30E-19	$1.02E-16$

(Table 29) contd….

Table 30. Top 20 of 670 selective GO pathways in the liver.

Note: * also significantly expressed in other organs. Sorted by q-value.

There were good examples of some proteins selectively expressed in organs that were used as disease markers [8, 10- 12] or used as therapeutic targets like trastuzumab on HER2 to treat breast cancer [167]. However, many selective genes have still not been revealed.

(Table 32) contd….

Table 33. Top 20 of 21 selective GO pathways in the stomach.

Fig. (5). There were 123 Genes without description but selectively expressed in different organs based on their abundance. **Abbreviations:** Ad, adrenal gland; Br, brain; Co, colon; Du, duodenum; He, heart; Il, ileum; Ki, kidney; Li, liver; Lu, lung; Sp, spleen; St, stomach. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

 The present study screened out 1,406 genes selectively expressed in 11 rat organs, among which, 1,283 genes' function was described, and 123 of which still need to be described in the near future. Some of the genes' function was confirmed in the organs that were noted in Tables **1-11**, but a good portion of them or the relationship between their function and the organs was not addressed. The new findings are useful to unveil the mechanism of their organic functions. Unfortunately, as for the selective genes in organs mentioned in the introduction, only troponin [10] was proved to be selective by the present study, and NeuN in the brain [8], GPT in the liver [11], and NGAL in the kidney [12] were not included in the present list of the selective genes. After consulting the FPKM values, it is exactly that the FPKM of NeuN in the brain was the highest, but not significant. The relative neuronal marker was further proved by recent work [9]. The highest GPT (GPT2) in the liver was significant, but the level of expression was not dominant (only about 45% of the total). Of course, if the criterion of selective genes was lowered, more genes would be included in the selective gene list, namely, in the list of putative organic markers. Phosphodiesterase 5 (PDE5a), an enzyme associated with angiectasis, is another similar example. PDE5a was verified to be the most highly expressed gene in the lung, but not included in the selective gene list (Table **9**), supporting PDE5 inhibitors' pharmacological effect on pulmonary arterial hypertension [168, 169].

Table 34. The top 20/32 genes were not described but selectively expressed in the adrenal glands based on their abundance (n = 3).

		Gene Name	Median		FPKM			Mean
No.	Gene ID		Organ	Mean	Total	p -value	q-value	/total
$\mathbf{1}$	ENSRNOG00000041608	AC123095.1	St	32.5	45.5	2.39E-05	2.00E-03	0.716
$\overline{2}$	ENSRNOG00000055956	AABR07015078.1	St	103.8	141.0	3.62E-05	2.47E-03	0.736
3	ENSRNOG00000030291	Rn50_10_0698.6	St	871.4	1199.5	4.14E-05	2.57E-03	0.727
$\overline{4}$	ENSRNOG00000060657	AABR07000404.1	St	14.2	19.1	1.05E-04	4.21E-03	0.742
5	ENSRNOG00000029145	AY172581.2	St	462.8	594.1	1.68E-04	5.34E-03	0.779
6	ENSRNOG00000057514	AABR07015080.1	St	26.2	35.7	1.79E-04	5.51E-03	0.734
7	ENSRNOG00000057811	AABR07015055.2	St	18.8	25.1	2.46E-04	6.47E-03	0.750
8	ENSRNOG00000055836	AABR07000402.1	St	30.7	42.9	3.34E-04	7.56E-03	0.717
9	ENSRNOG00000046600	AABR07015066.1	St	73.6	100.6	3.88E-04	8.16E-03	0.732
10	ENSRNOG00000055323	AABR07063421.1	St	33.9	47.6	4.49E-04	8.79E-03	0.712
11	ENSRNOG00000046081	AABR07015079.1	St	38.8	55.2	5.83E-04	1.00E-02	0.703
12	ENSRNOG00000047991	AABR07072283.1	St	125.3	143.0	1.02E-03	1.34E-02	0.876
13	ENSRNOG00000053717	Metazoa_SRP	\mathbf{I}	121.7	171.4	1.69E-03	1.68E-02	0.710
14	ENSRNOG00000046768	AC135454.2	St	13.2	14.2	1.62E-03	1.70E-02	0.929
15	ENSRNOG00000056945	LOC102549408	Sp	22.1	26.9	1.97E-03	1.88E-02	0.820
16	ENSRNOG00000049380	Rn50 11 0375.8	Du	55.9	68.7	2.24E-03	1.99E-02	0.814
17	ENSRNOG00000046106	rno-mir-351-1	St	6.4	6.4	2.49E-03	2.11E-02	1.000
18	ENSRNOG00000055947	7SK	Du	24.6	30.8	2.63E-03	2.14E-02	0.800
19	ENSRNOG00000048598	AABR07037925.1	St	84.9	95.4	2.55E-03	2.14E-02	0.889
20	ENSRNOG00000053888	5 8S rRNA	St	11.8	13.7	2.75E-03	2.23E-02	0.858

Note: Sorted by q-value. Du, duodenum; Il, ileum; Sp, spleen; St, stomach

Note: Sorted by q-value. Ad, adrenal gland; Co, colon; Du, duodenum; Il, ileum; Ki, kidney; Li, liver; Lu, lung; Sp, spleen; St, stomach

Table 36. Genes were not described but selectively expressed in the colon based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; St, stomach

Table 37. Genes were not described but selectively expressed in the duodenum based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; Ki, kidney

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Table 38. Genes were not described but selectively expressed in the heart based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Co, colon; Du, duodenum; Il, ileum; Ki, kidney; Li, liver; St, stomach

Table 39. Genes were not described but selectively expressed in the ileum based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Lu, lung

Table 40. Genes were not described but selectively expressed in the kidney based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Br, brain; He, heart; Lu, lung; Sp, spleen; St, stomach

Table 41. Genes were not described but selectively expressed in the liver based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Du, duodenum

Table 42. Genes were not described but selectively expressed in the lung based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; He, heart; Ki, kidney; St, stomach

Table 43. Genes were not described but selectively expressed in the spleen based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Du, duodenum; Ki, kidney; Lu, lung; St, stomach

Table 44. Genes were not described but selectively expressed in the stomach based on their abundance (n = 3).

Note: Sorted by q-value. Ad, adrenal gland; Du, duodenum

 The selective genes and their products can be used as physiological or disease markers. If a cell is injured, the selective gene's product normally existing in its cytoplasm will be released to the blood. Based on the principle, some injury markers like serum Myl3 protein for heart injury [170] were screened out and verified by the present study. Theoretically, products from selective genes can be used as disease markers. However, it should be noted that because of some genes expressed in rats (*e.g*., Uox in the liver) [171], but not in humans, the fact that the products from the selective genes used as disease markers are only advisory, needing further verification.

 The functional pathways of an organ enriched by the highest-expressed genes were largely supported by the known understanding. However, there are still some interesting functions that were not focused on. For example, KEGG pathways (Tables **12-22**) like ko00061 (fatty acid biosynthesis) in the adrenal gland, ko04911 (insulin secretion) in the brain, ko00280 (Valine, leucine, and isoleucine degradation) in the heart and kidney, and ko04360 (axon guidance) in the lung were seldom paid attention to by scientists. Similar results would be obtained in the results of GO pathways (Table **23-33**). The unpopular organic functional pathways enriched by the present study would open a new window to make insight into their mechanism. Especially the adrenal glands may be an organ with few basic researches.

 Though the selective genes and the interesting genes only existed in one organ, the organic pathways including KEGG (Tables **12-22**) and GO (Tables **23-33**) pathways, enriched by them could exist in two or more organs. Since a pathway often involves many proteins, it is theoretically different for the real functions of the same selective pathway enriched by different selective genes. The same pathway is enriched in different organs with different profiles. Anyway, the functions are different from organ to organ, although they share some similarities at pathway levels.

CONCLUSION

 In the end, because there were no standard criteria ready to evaluate a gene's selectivity, the present study used the dominant portion of FPKM value and statistical analysis. If the FPKM value of a gene in an organ accounted for 70% of the total values of all the organs concerned, the gene was assumed as the selective gene in the organ after excluding genes with low abundance. If the criterion were lowered, the list of the selective genes would be lengthened. On the other hand, the selective genes screened out by the present study were only based on the results of 11 organs in male rats, and some selective genes in other organs or female rats were

neglected or missed. Moreover, the weights of the organs were not taken into account in the present study. Considering that the genome of rats has approximately 85% similarity with that of humans, this study provides a useful exploration of human organic markers and organ function, though the selective genes, the putative markers, and the functional pathways suggested are only advisory and worthy of further investigation.

AUTHORS' CONTRIBUTIONS

 It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

ETHICS APPROVAL AND CONSENT TO PARTICI-PATE

 The animal experiments were approved by the Animal Care and Use Committee of Yunnan Provincial Key Laboratory of Molecular Biology for Sinomedicine (Approved No. LL-20171023-01), Yunnan University of Traditional Chinese Medicine, Kunming, Yunnan, China.

HUMAN AND ANIMAL RIGHTS

 All the animal experimentation was performed according to the Guide for the CARE and USE of Laboratory Animals and ARRIVE guidelines.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

 The raw data were uploaded as supplemental materials on the journal's web.

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CONFLICT OF INTEREST

 The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

 Supplementary material is available on the publisher's website along with the published article. The raw data were uploaded on July 19, 2023 (Link: https://pan.baidu.com/s/1uOpvEIU_dRYgGmEIWc0SjA?p wd=DWG1 Password: DWG1)

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