

Gene expression profiling of skeletal muscles

Supporting information

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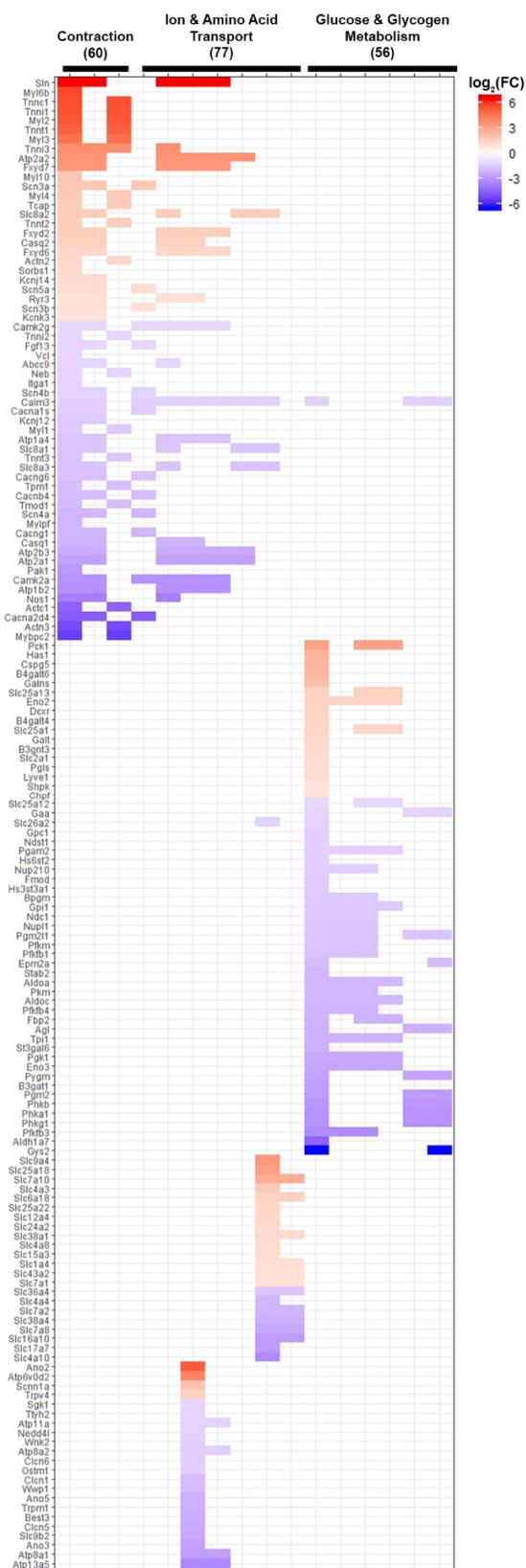


Figure S1. Evaluation of Reactome overrepresented pathway analysis. The statistically significant DE genes were filtered into curated molecular pathways using the *ReactomePA* R package. The Reactome overrepresented pathway analysis tool uses a list of genes and filters the genes into curated molecular pathways. Specific molecular pathways were over-represented based on the input genes exceeding the proportion of genes randomly expected for a particular molecular pathway. Genes with increased expression in So or Ta are labeled in red or blue, respectively. The heat map indicated the log₂(FC) of 160 DE genes associated with the 16 overrepresented pathways identified by the Reactome database before filtering based on the absolute FC being greater than or equal to two. Based on description similarities, the sixteen pathways were combined into three major categories: Contraction, Ion & Amino Acid Transport, and Glucose & Glycogen Metabolism.

Table S1. Differentially Expressed Genes in So and Ta involved in Ion Transport and Glycosaminoglycan biosynthesis pathways.

Gene Symbol	Gene Name	Fold Change (So/Ta)	Localization and Biochemical Properties
Amino Acid and Ion Transport			
P-type 2A ATPases or Sarco-(endo)-plasmic reticulum calcium pumps (SERCA)			
<i>Atp2a2</i>	ATPase, Ca ²⁺ transporting, cardiac muscle, slow twitch 2	13.1	regulates Ca ²⁺ homeostasis and signaling in slow-twitch skeletal myofibers [1]
<i>Atp2a1</i>	ATPase, Ca ²⁺ transporting, cardiac muscle, fast-twitch 1	-6.1	regulates Ca ²⁺ homeostasis and signaling in fast-twitch skeletal myofibers [2]
P-type 2B ATPases or Plasma Membrane Ca²⁺-ATPases (PMCA)			
<i>Atp2b3</i>	ATPase, Ca ²⁺ transporting, plasma membrane 3	-4.9	transports calcium ions [3]
P-type 2C ATPases or Sodium-Potassium Pumps			
<i>Fxyd7</i>	FXYD domain-containing ion transport regulator 7	12	decreases intrinsic K ⁺ affinity without extracellular Na ⁺ competition or effect on membrane potential [4]
<i>Fxyd2</i>	FXYD domain-containing ion transport regulator 2	3.3	membrane potential control based on changing Na ⁺ and K ⁺ affinities [4]
<i>Atp1b2</i>	ATPase, Na ⁺ /K ⁺ transporting, beta 2 polypeptide	-8.3	phosphorylation and ion transport [5]
<i>Atp1a4</i>	ATPase, Na ⁺ /K ⁺ transporting, alpha 4 polypeptide	-2.9	phosphorylation and ion transport [6]
P-type 4 ATPases or Phospholipid Flippases			
<i>Atp8a1</i>	ATPase, amino-phospholipid transporter (APLT), class I, type 8A, member 1	-6.3	mediates amino-phospholipids translocation; dependent on phosphatidylserine for ATPase activity [7]
P-type 5 ATPases or Orphan Transporters			
<i>Atp13a5</i>	ATPase type 13A5	-10	Transports unknown ion in the brain and stomach [8]
V-type ATPase or Plasma membrane H⁺-ATPases			
<i>Atp6v0d2</i>	ATPase, H ⁺ transporting, lysosomal V0 subunit D2	17.4	couples proton transport and ATP hydrolysis
Calcium-activated Chloride Channels			

<i>Ano2</i> *	anoctamin 2	39.7	involved in membrane potential of presynaptic membranes in photoreceptors and olfactory sensory neurons [9]
<i>Ano3</i>	anoctamin 3	-5.8	involved in intracellular calcium-activated anion current [10]
<i>Best3</i>	bestrophin 3	-4.7	regulates calcium release from intracellular calcium storage [11]
<i>Ano5</i>	anoctamin 5	-4.5	involved in sarcolemmal repair and myoblast fusion in skeletal muscle [12]
Voltage-sensitive Chloride Channels			
<i>Clcn5</i>	chloride channel, voltage-sensitive 5	-5.1	Involved in endosomal acidification in skeletal muscles [13]
<i>Clcn1</i>	chloride channel, voltage-sensitive 1	-3.5	involved in membrane potential in skeletal muscles [14]
Calcium Channels			
<i>Cacna2d4</i> *	calcium channel, voltage-dependent, alpha 2/delta subunit 4	-23.6	regulates gating & ligand binding and increases in current amplitude [15]
<i>Cacng1</i>	calcium channel, voltage-dependent, gamma subunit 1	-4.1	decreases Ca ²⁺ entry during stimulation of skeletal muscle [16]
<i>Cacnb4</i>	calcium channel, voltage-dependent, beta 4 subunit	-3.4	increases current amplitude and regulates activation and inactivation kinetics [17]
<i>Cacng6</i>	calcium channel, voltage-dependent, gamma subunit 6	-3.2	reduces the current amplitude [18]
Solute Carrier Family			
<i>Slc22a2</i>	solute carrier family 22 (organic cation transporter), member 2	80.77	removes noxious cationic compounds [19]
<i>Slc9a4</i>	solute carrier family 9 (sodium/hydrogen exchanger), member 4	11.5	involved in cell size and not intracellular pH [20]
<i>Slc25a18</i>	solute carrier family 25 (mitochondrial carrier), member 18	9.9	transports metabolites across inner mitochondrial membrane [21]
<i>Slc7a10</i>	solute carrier family 7 (cationic amino acid transporter, y ⁺ system), member 10	7.1	transports for small neutral amino acids, especially D-serine and glycine
<i>Slc4a3</i>	solute carrier family 4 (anion exchanger), member 3	3.7	lowers the CO ₂ load with the muscle cell [22]
<i>Slc8a2</i>	solute carrier family 8 (sodium/calcium exchanger), member 2	3.4	intracellular calcium concentration regulation; synaptic plasticity [23]

<i>Slc6a18</i>	solute carrier family 6 (neurotransmitter transporter), member 18	3.1	transports neutral amino acids in the presence of sodium and chloride ions
<i>Slc25a13</i>	solute carrier family 25 (mitochondrial carrier, adenine nucleotide translocator), member 13	3.1	involved a mitochondrial aspartate glutamate carrier and the urea cycle [24]
<i>Slc4a10</i>	solute carrier family 4, sodium bicarbonate cotransporter-like, member 10	-9.3	involved in regulating neuronal pH and excitability [25]
<i>Slc17a7</i> (VGLUT1)	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7	-6.8	transports glutamate and depends on electrogenic and Cl- conditions; distributed in synaptic vesicles [26]
<i>Slc16a10</i>	solute carrier family 16 (monocarboxylic acid transporters), member 10	-6.6	part of net efflux pathway for aromatic amino acids across the sarcolemma [27]
<i>Slc7a8</i>	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	-5.4	exchanges neutral amino acids [28]
<i>Slc9b2</i>	solute carrier family 9, subfamily B (NHA2, cation proton antiporter 2), member 2	-5.1	Part of intracellular and mitochondrial cation/proton antiport system [29]
<i>Slc38a4</i>	solute carrier family 38, member 4	-4.4	UNKNOWN
<i>Slc7a2</i>	solute carrier family 7 (cationic amino acid transporter, y+ system), member 2	-4.1	transports cationic amino acids correlated to nitric oxide production
<i>Slc4a4</i>	solute carrier family 4 (anion exchanger), member 4	-3.9	regulates intracellular pH [30]
<i>Slc8a3</i>	solute carrier family 8 (sodium/calcium exchanger), member 3	-3.1	controls intracellular calcium concentrations at neuromuscular junctions [31]
<i>Slc8a1</i>	solute carrier family 8 (sodium/calcium exchanger), member 1	-3	lowers intracellular calcium concentration during the relaxation in cardiac muscle [32,33]
Nucleotide Sugar Transporter			
<i>Slc35d3</i>	solute carrier family 35, member D3	20.07	orphan sugar nucleotide transporter; regulates platelet-dense granules [34]
Glycosaminoglycan biosynthesis			
<i>Has1</i>	hyaluronan synthase 1	6.1	induces pro-inflammation response
<i>Cspg5</i>	chondroitin sulfate proteoglycan 5	5.9	cell adhesion and growth, receptor binding, or cell migration
<i>B4galtn6</i>	beta 1,4-galactosyltransferase, polypeptide 6	5.4	synthesizes lactosylceramide, a precursor of glycosphingolipids outside a cell [35]

<i>Galns</i>	galactosamine (N-acetyl)-6-sulfate sulfatase	4.9	breaks down keratan sulfate; present in lysosomes [36]
<i>B3gat1</i>	beta-1,3-glucuronyltransferase 1 (glucuronosyltransferase P)	-6.5	catalyzes biosynthesis of HNK-1 carbohydrate epitope; cell adhesion and neurite outgrowth [37]
<i>St3gal6</i>	ST3 beta-galactoside alpha-2,3-sialyltransferase 6	-4.5	sialylation in selectin ligand biosynthetic pathway[38]
<i>Stab2</i>	stabilin 2	-3.8	endocytosis of metabolic waste products, including hyaluronic acid (HA) and other modified proteins
Amino Acid and Ion Transport Regulators			
<i>Sln[#]</i>	sarcolipin	98.5	regulates sarcoplasmic reticulum Ca ²⁺ - ATPases [39]
<i>Syt6</i>	synaptotagmin VI	25.19	involved in calcium-dependent exocytosis [40]
<i>Adgrv1</i>	adhesion G protein-coupled receptor V1	21.68	binds to calcium in CNS[41]
<i>Casq2</i>	calsequestrin 2	3.1	regulates calcium buffer in sarcoplasmic reticulum [42]
<i>Nos1</i>	nitric oxide synthase 1, neuronal	-12	synthesizes nitric oxide from L-arginine [43]
<i>Camk2a</i>	calcium/calmodulin-dependent protein kinase II alpha	-8.1	mediates second messenger effects of Ca ²⁺ [44]
<i>Casq1</i>	calsequestrin 1	-4.2	Essential for sarcoplasmic reticulum development and Ca ²⁺ storage and release [45]
Cation Channel			
<i>Trpv4</i>	transient receptor potential cation channel, subfamily V, member 4	3.2	regulates osmotic homeostasis [46]
<i>Trpm1</i>	transient receptor potential cation channel, subfamily M, member 1	-4.6	Proposed intracellular metabotropic glutamate receptor-coupled cation channel [47]
Sodium Channel			
<i>Scnn1a</i>	sodium channel, non-voltage-gated 1 alpha	4.4	regulates sodium reabsorption [48]
<i>Scn3a</i>	sodium channel, voltage-gated, type III, alpha	3.9	involved in sodium ion influx in neural tissue [49]
<i>Scn4a</i>	sodium channel, voltage-gated, type IV, alpha	-4	involved in sodium ion influx in skeletal muscle [50]

Positive or negative fold change represents increased gene expression in So or Ta, respectively. All references mentioned in this Table are listed in this supporting information PDF. [#]DE gene both Reactome and 20x fold change

Table S2. Differentially Expressed Genes in So and Ta organized by Immune Response, Signaling, and Cellular function pathways.

Gene Symbol	Gene Name	Fold Change (So/Ta)	Localization and Biochemical Properties
Immune System			
<i>C1rb</i>	complement component 1, r subcomponent B	206.06	part of complement system of innate immune system [51]
<i>C1s2</i>	complement component 1, s subcomponent 2	99.94	part of complement system of innate immune system [51]
<i>Il27</i> (<i>Ebi3 or Il-27p28</i>)	interleukin 27	90.94	Part of specific cell-surface differentiation of T-cells and stimulate T-cells to suppress inflammation [52]
<i>Btn2a2</i>	butyrophilin, subfamily 2, member A2	72.97	inhibits T-cell-mediated immunity [53]
<i>Nccrp1</i> (<i>FBXO50</i>)	non-specific cytotoxic cell receptor protein 1 homolog (zebrafish)	62.98	ubiquitous tissue expression pattern in mice [54]
<i>Orm1</i>	orosomucoid 1	57.38	modulates immunity, binds and carries drugs, mediates sphingolipid metabolism [55]
<i>Klra10</i> (<i>Ly49j</i>)	killer cell lectin-like receptor subfamily A, member 10	55.78	inhibitory intracellular protein lacking a transmembrane domain and has unknown ligand specificity [56]
<i>Pigr</i>	polymeric immunoglobulin receptor	48.6	facilitates transcytosis of soluble immunoglobulin A and immune complexes polymeric isoforms [57]
<i>Vsig8</i>	V-set and immunoglobulin domain containing 8	45.89	interacts with V-Set and transmembrane signaling protein VISTA [58]
<i>Pianp</i>	PILR alpha associated neural protein	35.02	involved in proteolytic processing; ligand for immune inhibitory receptor Pilr α once cleaved [59]
<i>Treml1</i>	triggering receptor expressed on myeloid cells-like 1	29.82	dampens inflammatory response; specific to platelet and megakaryocyte alpha-granules [60]
<i>Klrk1</i>	killer cell lectin-like receptor subfamily K, member 1	24.36	activates natural killer T-cells and macrophages [61]
<i>Ctla4</i>	cytotoxic T-lymphocyte-associated protein 4	24.27	regulates T cell activation; maintains T cell homeostasis [62]
<i>H2-Q10</i>	histocompatibility 2, Q region locus 10	24.1	non-classical major histocompatibility complex class IB molecule that binds to inhibitory Ly49C receptor [63]
<i>Klrd1</i>	killer cell lectin-like receptor, subfamily D, member 1	20.29	expressed on natural killer T-cell surface; cell signaling involvement [64]
<i>Wfdc5</i>	WAP four-disulfide core domain 5	-50.74	pro-inflammation and protease inhibition [65]
<i>Tlr5</i>	toll-like receptor 5	-20.34	inflammatory response initiation [66]
Signaling Pathways			
<i>Derl3</i>	Der1-like domain family, member 3	36.55	involved in endoplasmic reticulum (ER)-associated degradation (ERAD) system [67]
<i>Angpt4</i>	angiopoietin 4	34.42	involved in vascular growth factor Angiopoietin signaling [68]
<i>Rspo3</i>	R-spondin 3	29.82	binds to cell surface receptors and activates Wnt/Beta-catenin signaling [69]

<i>Dab1</i>	disabled 1	28.93	binds to phospholipids and un-phosphorylated low-density lipoprotein receptor (LDLR) amino sequence [70]
<i>Garem1</i> (<i>Garem2</i>)	GRB2 associated regulator of MAPK1 subtype 2	28.86	adaptor in EGF-mediated signaling pathway [71]
Calcium Signaling			
<i>Itpka</i>	inositol 1,4,5-trisphosphate 3-kinase A	27.77	calcium signaling; facilitates phospho-group transfer in inositol phosphate metabolism [72]
<i>Casr</i>	calcium-sensing receptor	-33.21	maintains extracellular calcium levels [73]
<i>Pvalb</i>	parvalbumin	-23.46	regulates Ca ²⁺ ions to sarcoplasmic reticulum to mediate relaxation in type II myofibers [74]
Secretory Pathway involvement			
<i>Dmkn</i>	dermokine	77.5	involved in wound healing [75]
<i>Pcsk1n</i>	proprotein convertase subtilisin/kexin type 1 inhibitor	59.69	Expressed in endocrine cells and neurons possessing a regulated secretory pathway [76]
<i>Pmel</i>	premelanosome protein	35.1	transmembrane glycoprotein modified in the secretory pathway [77]
G-protein-coupled receptors			
<i>Olf1033</i>	olfactory receptor 1033	69.06	G-protein-coupled receptors (GPCR) with an unknown ligand [78]
<i>Mrap2</i>	melanocortin 2 receptor accessory protein 2	23.35	traffics melanocortin receptors to a cell surface [79]
Insulin Release			
<i>Gipr</i>	gastric inhibitory polypeptide receptor	38.18	stimulated insulin secretion [80]
<i>Ghrl</i>	ghrelin	32.57	binds to growth hormone secretagogue receptor; regulates glucose-induced insulin release [81]
<i>Igf2bp1</i>	insulin-like growth factor 2 mRNA binding protein 1	21.77	binds to 5' UTR of insulin-like growth factor 2 (IGF2) mRNA and regulates its translation [82]
Cell Motility			
<i>Tspan8</i>	tetraspanin 8	-54.85	involved in protease expression, body-weight regulation in males, and cell migration [83]
Cell proliferation			
<i>Tmem45b</i>	transmembrane protein 45b	27.86	Potential cell proliferation involvement [84]
<i>Mstn</i> (<i>Gdf8</i>)	myostatin	-30.58	inhibited myoblast proliferation [85]
Cell Apoptosis			
<i>Fank1</i>	fibronectin type 3 and ankyrin repeat domains 1	32.46	regulates cell apoptosis via the AP-1 pathway [86]
Transcription			
<i>Tmem233</i>	transmembrane protein 233	-46.35	potential epigenetic control of skeletal muscle-associated genes [87]
Protein binding, aggregation, and ubiquitination			
<i>Hspa1a</i>	heat shock protein 1A	44.75	protein refolding, endocytosis, and chromosome stability [88]

<i>Plekhd1</i>	pleckstrin homology domain containing, family D (with coiled-coil domains) member 1	35.05	membrane binding and protein localization [89]
<i>Btbd16</i>	BTB (POZ) domain-containing protein 16	32.6	potential zinc-finger transcription factor [90]
<i>Fam159b</i> (<i>Shisal2b</i>)	shisa like 2B	20.26	does not target proteins for ubiquitination and degradation, unlike most Shisa proteins [91]
<i>Hspa1b</i>	heat shock protein 1B	20.04	mediates protein aggregation and folding; ubiquitin-proteasome pathway [88]
Photoreceptor Focus			
<i>Opn1mw</i>	opsin 1 (cone pigments), medium-wave-sensitive (color blindness, deutan)	63.04	detects green wavelength [92]
<i>Rp1</i>	Retinitis pigmentosa 1	23.61	involved in photoreceptor development, organization of photoreceptor outer segments, and regulation of photoreceptor microtubules [93]
Gamete			
<i>Spats1</i> (<i>Srsp1</i>)	spermatogenesis associated, serine-rich 1	65.66	involved in establishing first male meiotic division [94]
<i>Ces5a</i>	carboxylesterase 5A	53.31	catalyzes carboxylic ester and water to produce an alcohol and carboxylate [95]
<i>Meig1</i>	meiosis expressed gene 1	41.05	involved in microtubular organelle for sperm head and flagellar formation [96]
<i>Ell3</i>	elongation factor RNA polymerase II-like 3	37.97	Testis-specific RNA polymerase II elongation factor [97]
<i>Als2cr12</i> (<i>Flacc1</i>)	flagellum associated containing coiled-coil domains 1	30.37	stiffens sperm tail while allowing elastic bending [98]
<i>Zp2</i>	zona pellucida glycoprotein 2	29.06	involved in oocyte-sperm recognition; preventing penetration of many sperm through zona pellucida [99]
<i>Gng13</i>	guanine nucleotide binding protein (G protein), gamma 13	27.74	potential involvement in ovary development [100]
<i>Ccdc169</i>	coiled-coil domain containing 169	20.33	associate with an upstream transcription factor, SOHLH2, which is involved in differentiation during spermatogenesis and oogenesis [101]
<i>Catsperd</i>	cation channel sperm associated auxiliary subunit delta	-20.3	Involved in proper channel assembly and/or ion transport [102]
Miscellaneous			
<i>Csn1s2b</i>	casein alpha s2-like B	241.61	calcium-sensitivity casein protein [103]
<i>Gpr75</i>	G protein-coupled receptor 75	72.96	triggers stimulation of insulin secretion[104]
<i>Mansc4</i>	MANSC domain containing protein 4	56.75	UNKNOWN
<i>Fam216b</i>	family with sequence similarity 216, member B	44.84	UNKNOWN
<i>Selenbp2</i>	selenium binding protein 2	39.51	binds to acetaminophen intermediate[105]
<i>Sbk3</i>	SH3 domain binding kinase family, member 3	37.63	UNKNOWN

<i>Serpib7</i>	serine (or cysteine) peptidase inhibitor, clade B, member 7	28.13	UNKNOWN
<i>Tmem45a2</i>	transmembrane protein 45A2	27.42	UNKNOWN
<i>Tmem151b</i>	transmembrane protein 151B	22.96	UNKNOWN
<i>Hist1h2ak</i>	H2A clustered histone 15	21.88	one of core chromatin histones [106]
<i>Fam227b</i>	family with sequence similarity 227, member B	20.34	UNKNOWN
<i>Tmem56</i> (or <i>Tlcd4</i>)	TLC domain-containing protein 4 (TRAM/Lag1/CLN8 Domain)	-25.19	UNKNOWN
<i>Pld5</i>	phospholipase D family, member 5	-21.16	UNKNOWN

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