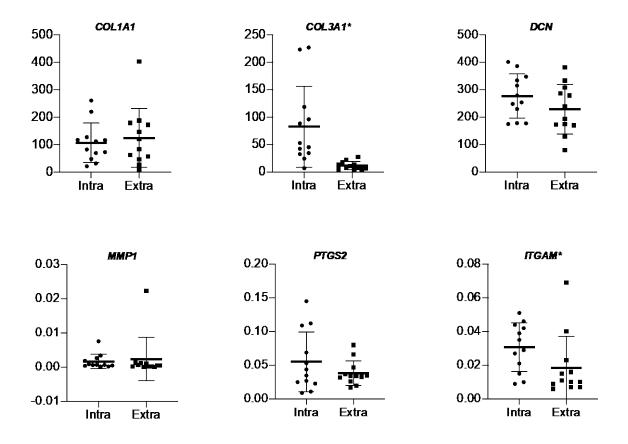
# The following content was supplied by the authors as supporting material and has not been copy-edited or verified by JBJS.

## Supplemental Document

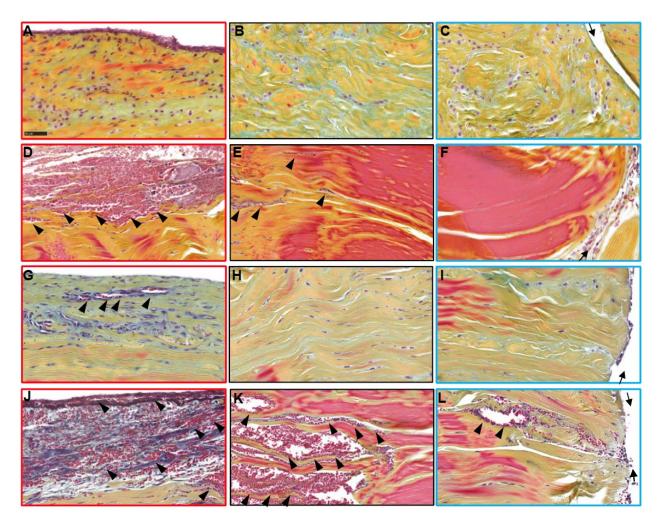


**Figure S1.** Gene expression in intact intrasynovial and extrasynovial tendons (\* p < 0.05 intrasynovial vs. extrasynovial).

Copyright © by The Journal of Bone and Joint Surgery, Incorporated Shen et al. Flexor Tendon Injury and Repair. The Influence of Synovial Environment

FLEXOR TENDON INJURY AND REPAIR. THE INFLUENCE OF SYNOVIAL ENVIRONMENT ON THE EARLY HEALING RESPONSE IN A CANINE MODEL

http://dx.doi.org/10.2106/JBJS.20.01253 Page 2



**Figure S2.** Representative images of pentachrome staining on the longitudinal sections of repaired intrasynovial (A-C and G-I) and extrasynovial (D-F and J-L) flexor tendons at 3 days (A-F) and 7 days (G-L) after repair. Histologic assessment revealed different vascular responses to injury at the tendon surface (A, D, G, and J), 500  $\mu$ m from the laceration site (B, E, H, and K), and immediately next to the laceration site (C, F, I, and L). Scale bar in A = 50  $\mu$ m; applies to all panels. Arrows and arrow heads indicate the sites of blood vessels and laceration site, respectively.

**Table S1.** List of differentially expressed proteins between intact extrasynovial flexor tendons and intrasynovial flexor tendons.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
MMP8	Neutrophil collagenase	Degrades fibrillar type I, II, and III collagens.	-6.8	<0.001
MMP3	Stromelysin-1	Degrade cartilage matrix and activate procollagenase	-3.7	0.002
VIT	Vitrin	Glycosaminoglycan binding	-3.6	<0.001
HAPLN1	Hyaluronan and proteoglycan link protein 1	Stabilize proteoglycan aggregates	-3.3	<0.001
ACAN	Aggrecan	Cartilage matrix	-2.7	0.006
COMP	Cartilage oligomeric matrix protein	Maintain cartilage integrity	-2.0	0.043
TNXB	Tenascin XB	ECM structural constituent-cell adhesion, collagen fibril formation	-2.0	0.006
PRG4	Proteoglycan 4	Boundary lubrication	-1.9	0.002
BGN	Biglycan	ECM structural constituent conferring compression resistance	-1.9	0.036
MATN2	Matrilin 2	Extracellular adaptor protein, matrix assembly	-1.9	0.024
FN1	Fibronectin 1	Cell surface and ECM interaction	-1.8	0.026
NID2	Nidogen-2	Cell and ECM interaction	-1.7	0.005
ITIH1	Inter-alpha-trypsin inhibitor heavy chain 1	Hyaluronan localization and metabolic process	-1.7	0.002
GUSB	Glucuronidase beta	Glycosaminoglycan/ hyaluronan catabolic process	-1.5	0.009
COL5A1	Collagen type V alpha 1 chain	ECM structural constituent conferring tensile strength	-1.5	0.043
LAMA4	laminin subunit alpha 4	Cell and ECM interaction	-1.5	0.011
COL15A1	Collagen type XV alpha 1 chain	ECM structural constituent conferring tensile strength	-1.4	0.046
BSG	Basigin (Ok blood group)	Collagenase stimulatory factor	-1.4	0.045
FBLN1	Fibulin 1	ECM structural constituent, fibrinogen binding	-1.4	0.025
ASPN	Asporin	Inhibitor of chondrogenesis	1.6	0.028
CAPN1	Calpain 1	ECM catabolic process	1.5	0.005

## A. Extracellular matrix (ECM) and related proteins.

## B. Cytoskeleton and related proteins.

			Fold change (Extrasynovial	Adjusted
Gene	Protein	Description	/ Intrasynovial)	P value
TAGLN	Transgelin	Actin crosslinking	3.4	<0.001
ADD1	Adducin 1	Membrane-cytoskeleton- associated protein	1.6	0.002
MYH10	Myosin heavy chain 10	Cellular myosin	1.5	0.006
SPTBN1	Spectrin beta, non-erythrocytic 1	Actin-binding protein,	1.5	0.001
SPTAN1	Spectrin alpha, non-erythrocytic 1	Cytoskeleton movement at the membrane	1.4	0.004
DPYSL3	Dihydropyrimidinase like 3	Cytoskeleton remodeling	1.4	0.008
CNN2	Calponin 2	Cytoskeleton organization	1.4	0.031
SEPT9	Septin 9	Filament-forming cytoskeletal GTPase	1.4	0.046
FLNA	Filamin A	Actin filament branching	1.3	0.024
FSCN1	Fascin actin-bundling protein 1	Actin crosslinking	1.3	0.036
RDX	radixin	Actin organization	1.3	0.039
DSTN	destrin, actin depolymerizing factor	Actin depolymerization	-1.3	0.034
VIM	vimentin	Class-III intermediate filaments (mesenchyme)	-2.2	0.003
DES	desmin	Class-III intermediate filaments	-2.9	<0.001

#### C. Proteins involved in inflammation and acute or innate immune response.

Gene CD5L	Protein CD5 molecule like	Description Regulator of inflammation and	Fold change (Extrasynovial / Intrasynovial) 2.2	Adjusted P value 0.004
		lipid synthesis		
FGL2	Fibrinogen like 2	Negative regulator of immune cell response	1.9	0.001
F13A1	Coagulation factor XIII A chain	Procoagulation	1.6	0.001
CD163	Scavenger receptor cysteine-rich type 1 protein M130	Hemoglobin scavenger receptor with a role in anti-inflammatory response	1.5	0.042
CD99	CD99 molecule	Leukocyte extravasation	1.4	0.010
PTGR1	Prostaglandin reductase 1	Negative regulator of leukotriene B4 activity	1.4	0.023
GPX1	Glutathione peroxidase 1	Scavenger of H <sub>2</sub> O <sub>2</sub>	1.4	0.025

Copyright  $\ensuremath{\mathbb{C}}$  by The Journal of Bone and Joint Surgery, Incorporated Shen et al.

FLEXOR TENDON INJURY AND REPAIR. THE INFLUENCE OF SYNOVIAL ENVIRONMENT ON THE EARLY HEALING RESPONSE IN A CANINE MODEL

http://dx.doi.org/10.2106/JBJS.20.01253 Page 5

C1QBP	Complement C1q binding protein	Inhibitor of complement C1 and innate immune response	1.4	0.041
GSTP1	Glutathione S-transferase pi 1	Negative regulator of acute inflammatory response	1.3	0.010
MIF	Macrophage migration inhibitory factor	Pro-inflammatory cytokine	-1.8	0.012
CFB	Complement factor B	Component of the alternate pathway of the complement system	-1.7	0.011
CFP	Complement factor properdin	Positive regulator of the alternate pathway of complement system	-1.7	0.048
C1QB	Complement C1q B chain	Component of complement system	-1.6	0.026
C1R	Complement C1r	Component of complement system	-1.5	0.006
C5	Complement C5	Component of complement system	-1.6	0.002
C6	Complement C6	Component of complement system	-1.4	0.013
C8B	Complement C8 beta chain	Component of complement system	-1.4	0.032
C9	Complement C9	Component of complement system	-1.4	0.026
C3	Complement C3	Component of complement system	-1.3	0.035
SERPINA5	serpin family A member 5, Plasma serine protease inhibitor	Inhibition of active Protein C	-1.6	0.004
SERPINA3	Serpin family A member 3	Inhibition of cathepsin G	-1.6	0.004
SERPINA4	Serpin family A member 4	Inhibition of kallikrein	-1.5	0.010
GSTM3	Glutathione S-transferase Mu 3	Cellular detoxification	-1.7	0.004
CD109	Cluster of differentiation 109	Positive regulation of inflammatory response	-1.6	0.002
PLG	Plasminogen	Dissolve blood clot and activate collagenase and complement zymogens	-1.4	0.041

## D. Metabolic enzymes.

			Fold change (Extrasynovial	
				Adjusted
Gene	Protein	Description	, Intrasynovial)	P value
DPYD	Dihydropyrimidine dehydrogenase	Uracil and thymidine catabolic enzyme	2.1	0.010
FH	Fumarate hydratase	Component of Krebs cycle	1.8	0.002

Copyright  $\ensuremath{\mathbb{C}}$  by The Journal of Bone and Joint Surgery, Incorporated Shen et al.

FLEXOR TENDON INJURY AND REPAIR. THE INFLUENCE OF SYNOVIAL ENVIRONMENT ON THE EARLY HEALING RESPONSE IN A CANINE MODEL

http://dx.doi.org/10.2106/JBJS.20.01253 Page 6

SHMT1	Serine hydroxymethyltransferase 1	Amino acid/dTMP metabolic enzyme	1.7	0.006
GOT2	Glutamic-oxaloacetic transaminase 2	Amino acid metabolic enzyme	1.7	<0.001
LDHB	Lactate dehydrogenase B	Pyruvate/lactate metabolic process	1.4	0.012
ACSS1	acyl-CoA synthetase short- chain family member 1	Mitochondrial acetyl-CoA biosynthesis	1.4	0.033
SDHB	Succinate dehydrogenase complex iron sulfur subunit B	Component of Krebs cycle and electron transport chain	1.3	0.024
HADHA	Trifunctional enzyme subunit alpha, mitochondrial	Catalyzes the last three steps of mitochondrial beta-oxidation of long chain fatty acids.	1.3	0.021
AK2	Adenylate kinase 2	ADP biosynthetic enzyme	1.3	0.031
MTHFD1	C-1-tetrahydrofolate synthase, cytoplasmic	Trifunctional enzyme involved in the pathway tetrahydrofolate interconversion	1.2	0.043
IVD	lsovaleryl-CoA dehydrogenase	Amino acid catabolic process	-1.3	0.037
PKM	Pyruvate kinase, muscle	Glycolytic enzyme	-1.4	0.011
MTAP	Methylthioadenosine phosphorylase	metabolism-purine ribonucleoside salvage	-1.4	0.026
PFKP	Phosphofructokinase, platelet	Glycolytic enzyme	-1.4	0.005
GPI	Glucose-6-phosphate isomerase	Glycolytic enzyme	-1.4	0.009
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	Glycolytic enzyme	-1.4	0.028
PGAM1	phosphoglycerate mutase 1	Glycolytic enzyme	-1.7	0.002
F1PCH3_CANLF	Enolase 1	Glycolytic enzyme	-1.8	0.001
LDHA	L-lactate dehydrogenase A chain	Pyruvate/lactate metabolic process	-1.9	0.002
UGP2	UDP-glucose pyrophosphorylase 2	Glucosyl donor in cellular metabolic pathways	-2.0	0.003
ASS1	Argininosuccinate synthase 1	Component of urea cycle and arginine biosythetic process	-2.3	0.041

## E. Proteins that regulate other biological processes.

	<u> </u>		Fold change (Extrasynovial	
Gene	Protein	Description	/ Intrasynovial)	Adjusted P value
RBMX	RNA binding motif protein, X-linked	pre- and post- transcriptional regulator	2.5	0.010
PCBP1	Poly(rC) binding protein 1	Positive regulation of transcription from RNA polymerase II promoter,	2.1	<0.001
PABPC1	Poly(A) binding protein cytoplasmic 1	Regulation of mRNA stability and metabolism	1.5	0.010
EIF4B	Eukaryotic translation initiation factor 4B	Regulation of translation initiation	1.4	0.045
TUFM	Tu translation elongation factor, mitochondrial	Regulation of translation elongation	1.7	0.008
FKBP11	FK506 binding protein 11, 19 kDa	Regulation of protein folding	1.4	0.028
ERP29	Endoplasmic reticulum protein 29	Processing of secretory protein	1.9	<0.001
PEBP1	Phosphatidylethanolamine binding protein 1	Serine protease inhibitor	1.5	0.004
LAP3	Leucine aminopeptidase 3	Processing and regular turnover of intracellular proteins	1.4	0.015
HSPA9	Heat shock protein family A member 9	Mitochondrial protein import, folding and degradation.	1.7	0.043
RAB2A	RAB2A, member RAS oncogene family	Protein transport	1.5	0.033
ATP13A1	ATPase 13A1	Cellular manganese homeostasis	1.4	0.029
OSTF1	Osteoclast stimulating factor 1	Osteoclast stimulating factor	1.4	0.008
LGALS1	Galectin 1	Regulation of cell apoptosis, proliferation, differentiation, and response to injury	1.5	0.048
PHPT1	Phosphohistidine phosphatase 1	Regulation of phosphohistidine levels of several proteins involved in diverse biological processes	1.3	0.036
MOB1B	MOB kinase activator 1B	Activator of LATS1/2 in the Hippo signaling pathway that controls organ size	1.8	<0.001
GNG12	G protein subunit gamma 12	Regulation or transduction of various transmembrane signals	1.4	0.020

COPYRIGHT © BY THE JOURNAL OF BONE AND JOINT SURGERY, INCORPORATED SHEN ET AL. FLEXOR TENDON INTURY AND REPAIR THE INFLUENCE OF SYNOVIAL ENVIRONMENT

FLEXOR TENDON INJURY AND REPAIR. THE INFLUENCE OF SYNOVIAL ENVIRONMENT ON THE EARLY HEALING RESPONSE IN A CANINE MODEL

http://dx.doi.org/10.2106/JBJS.20.01253 Page 8

EEF1G	Eukaryotic translation elongation factor 1 gamma	Translation elongation factor	-1.7	<0.001
CLU	Clusterin	Extracellular chaperone	-2.1	0.006
PPIAP4	Peptidyl-prolyl cis-trans isomerase	Protein refolding	-1.4	0.043
PSMC6	Proteasome 26S subunit, ATPase 6	Protein folding, turnover, modification	-1.3	0.030
RBP4	Retinol binding protein 4	Retinol transporter	-1.4	0.046
CHAD	Chondroadherin	Regulation of chondrocyte adhesion, growth and proliferation	-2.2	0.043
TGFBI	Transforming growth factor beta induced	RGD-containing protein induced by transforming growth factor-beta and acts to inhibit cell adhesion and may be involved in endochondral bone formation in cartilage	-1.7	0.010
ACIN1	Apoptotic chromatin condensation inducer 1	Positive regulation of apoptosis and monocyte differentiation	-1.4	0.043
CSPG4	Chondroitin sulfate proteoglycan 4	Transmembrane proteoglycan that regulates various biological processes via interaction with extracellular matrices, MMPs, and growth factors and intracellular signaling molecules	-1.3	0.033
FERMT2	Fermitin family member 2	Scaffolding protein that enhances integrin-mediated cell adhesion onto the extracellular matrix and cell spreading	-1.3	0.042

## F. Other proteins.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
RPS19	Ribosomal protein S19	Ribosomal protein	1.7	0.009
RPL7A	Ribosomal protein L7a	Ribosomal protein	1.7	0.039
RAN	RAN, member RAS oncogene family	GTP-binding nuclear protein	1.6	<0.001
AQP1	Aquaporin 1 (Colton blood group)	Formation of water channel	-1.6	0.026

# G. Uncharacterized proteins.

Gene	Protein	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
LOC606860	COX6C domain-containing protein	1.9	<0.001
OLFML1	Olfactomedin like 1	1.7	0.004
LRRC59	Leucine rich repeat containing 59	1.6	0.023
F6Y016	PC4 domain-containing protein	1.5	0.036
LOC611458	alpha-2-Macroglobulin-like	1.5	0.036
PURA	Purine rich element binding protein A	1.4	0.036
CRIP2	Cysteine rich protein 2	1.4	0.048
E2R0S6_CANLF	Annexin	-2.9	<0.001
A1ILJ0	Alpha 1 antitrypsin	-2.2	0.001
LOC478952	Complement factor H	-1.6	0.022
CRIP1	Cysteine rich protein 1	-1.6	0.045
RNH1	Ribonuclease/angiogenin inhibitor 1	-1.5	0.025
FAM129B, NIBAN2	Family with sequence similarity 129 member B	-1.5	0.041
F1P707_CANLF	Complement C3	-1.5	0.018

**Table S2**. List of differentially expressed proteins between extrasynovial flexor tendons and intrasynovial flexor tendons 3 days after injury and repair.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
MMP8 <sup>a, b</sup>	Neutrophil collagenase	Degrades fibrillar type I, II, and III collagens.	7.6	0.002
TNXBª	Tenascin XB	ECM structural constituent-cell adhesion, collagen fibril formation	2.2	0.026
VITª	Vitrin	Glycosaminoglycan binding	1.9	0.034
MRC2	C-type mannose receptor 2	Endocytotic receptor mediates collagen catabolic process	-1.5	0.031

#### A. ECM and related proteins.

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 7 days after repair.

#### B. Cytoskeleton and related proteins.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
TUBA4A	Tubulin alpha 4a	Major constituent of microtubules	2.3	0.001
ARPC4	Actin-related protein 2/3 complex subunit 4	Actin polymerization	1.6	0.033
TAGLN <sup>a</sup>	Transgelin	Actin crosslinking	-3.2	0.020
FSCN1 <sup>a</sup>	Fascin actin-bundling protein 1	Actin crosslinking	-1.6	0.022
DPYSL3ª	Dihydropyrimidinase like 3	Cytoskeleton remodeling	-1.6	0.023
ACTR1A	Alpha-centractin	A dynactin subunit involved in diverse cellular function, including endoplasmic reticulum to Golgi vesicle- mediated transport	-1.5	0.022
SPTBN1 <sup>a,b</sup>	Spectrin beta, non- erythrocytic 1	Cytoskeleton movement at the membrane	-1.4	0.036
SPTAN1 <sup>a,b</sup>	Spectrin alpha, non- erythrocytic 1	Cytoskeleton movement at the membrane	-1.4	0.031

COPYRIGHT © BY THE JOURNAL OF BONE AND JOINT SURGERY, INCORPORATED SHEN ET AL. FLEXOR TENDON INJURY AND REPAIR. THE INFLUENCE OF SYNOVIAL ENVIRONMENT ON THE EARLY HEALING RESPONSE IN A CANINE MODEL http://dx.doi.org/10.2106/JBJS.20.01253 Page 11 EPB41L2<sup>b</sup> Erythrocyte membrane Cortical actin cytoskeleton -1.4 0.039

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 7 days after repair.

organization. Cell division

#### C. Proteins involved in inflammation and acute or innate immune response.

protein band 4.1 like 2

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
LOC100855540b	GLOBIN domain- containing protein	Iron ion binding and cellular oxidant detoxification	2.9	0.022
HBB	Hemoglobin subunit beta	Involved in oxygen transportation	2.8	0.026
LOC485255 <sup>b</sup>	Hemoglobin subunit epsilon-2	Involved in oxygen transportation	2.3	0.024
PLG <sup>a,b</sup>	Plasminogen	Dissolve blood clot and activate collagenase and complement zymogens	2.8	0.001
PRDX2 <sup>b</sup>	Peroxiredoxin 2	Negative regulator of NF-kB activity, extrinsic apoptotic signaling, and superoxide radicals	2.9	0.001
UBXN1	UBX domain protein 1	Blocking both the NF-kB and RIG-I-like receptors (RLR) pathways	2.7	0.022
S100A9	S100-A9	Proinflammatory calcium- and zinc-binding protein	3.0	0.041
S100A12	S100-A12	Proinflammatory calcium-, zinc-, and copper binding protein	2.4	0.021
MAPK14	Mitogen-activated protein kinase 14	Mediating cellular response to inflammatory stimuli	2.7	0.004
LYZ	Lysozyme	Antimicrobial humoral response	2.1	0.020
CD5L <sup>a</sup>	CD5 molecule like	Regulator of inflammation and lipid synthesis	-2.4	0.031
CD59 <sup>b</sup>	CD59	Potent inhibitor of complement membrane attack complex	-2.4	0.002
FGL2 <sup>a</sup>	Fibrinogen like 2	Negative regulator of immune cell response	-2.1	0.016
CD163ª	Scavenger receptor cysteine- rich type 1 protein M130	Hemoglobin scavenger receptor with a role in anti-inflammatory response	-1.8	0.031

F13A1ª	Coagulation factor XIII A chain	Procoagulation	-1.6	0.026
ANXA5	Annexin A5	Anticoagulant protein	-1.5	0.045
GSTP1 <sup>a,b</sup>	Glutathione S- transferase pi 1	Negative regulator of acute inflammatory response	-1.4	0.031

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 7 days after repair.

#### D. Metabolic enzymes.

			Fold change (Extrasynovial	Adjusted
Gene	Protein	Description	/ Intrasynovial)	P value
BLVRB⁵	Biliverdin reductase B	Catalyzes the NADPH- dependent reduction of a variety of flavins and contributes to heme catabolism	2.3	0.0055
CA1	Carbonic anhydrase 1	one-carbon metabolic process	2.0	0.034
PGM2	Phosphoglucomutase 2	Carbohydrate metabolism	1.8	0.026
GPIª	Glucose-6-phosphate isomerase	Glycolytic enzyme	1.6	0.020
PFKL	ATP-dependent 6- phosphofructokinase	Catalyzes the first committing step of glycolysis	1.6	0.017
SHMT1 <sup>ª</sup>	Serine hydroxymethyltransferase 1	Ammino acid/dTMP metabolic enzyme	-2.0	0.022
IDH1⁵	lsocitrate dehydrogenase [NADP] cytoplasmic	NADP metabolic process	-1.8	0.038
CYB5R3	NADH-cytochrome b5 reductase 3	Lipid metabolism	-1.7	0.02
GOT2ª	Glutamic-oxaloacetic transaminase 2	Amino acid metabolic enzyme	-1.6	0.020
PNP⁵	Purine nucleoside phosphorylase	Purine metabolism	-1.6	0.027
FH <sup>a</sup>	Fumarate hydratase	Component of Krebs cycle	-1.8	0.031
SDHBª	Succinate dehydrogenase complex iron sulfur subunit B	Component of Krebs cycle and electron transport chain	-1.5	0.042

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 7 days after repair.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
PARK7	Parkinsonism associated deglycase	Positive regulation of cell survival, growth, and transformation	2.4	0.001
GNA11	Guanine nucleotide-binding protein subunit alpha-11	G protein. Activator of phospholipase C	2.2	0.033
PLCB3	Phospholipase C beta 3	Mediated the production of second messenger molecules diacylglycerol and inositol 1,4,5- trisphosphate	1.4	0.039
EIF4A2	Eukaryotic translation initiation factor 4A2	Involved in translation initiation	1.9	0.020
AP1B1	AP-1 complex subunit beta- 1	Protein sorting	1.9	0.034
PSMD2	26S proteasome non- ATPase regulatory subunit 2	Regulates numerous cellular processes by removing misfolded or damaged proteins	1.5	0.020
RBMXª	RNA binding motif protein, X-linked	Pre- and post-transcriptional regulator	-2.9	0.044
LTBP1	Latent transforming growth factor beta binding protein 1	Controls TGF-beta activation	-2.5	0.023
ERP29 <sup>a,b</sup>	endoplasmic reticulum protein 29	Processing of secretory protein	-2.2	0.004
PCBP1 <sup>a,b</sup>	Poly(rC) binding protein 1	Positive regulation of transcription from RNA polymerase II promoter	-2.1	0.001
YIPF5	Yip1 domain family member 5, Protein YIPF5	Regulation of ER to Golgi vesicle-mediated transport	-2.0	0.014
EIF3D⁵	Eukaryotic translation initiation factor 3 subunit D	mRNA cap-binding component of eukaryotic translation initiation factor 3 involved in regulation of cell proliferation	-1.8	0.031
PEBP1 <sup>a,b</sup>	Phosphatidylethanolamine binding protein 1	Serine protease inhibitor	-1.8	0.007
PPP1CC	Serine/threonine-protein phosphatase PP1-gamma catalytic subunit	Protein phosphatase that associates with over 200 regulatory proteins essential for cell division, protein synthesis, and glycogen metabolism	-1.7	0.034
MOB1B <sup>a</sup>	MOB kinase activator 1B	Activates LATS1/2 in the Hippo signaling pathway that controls organ size	-1.6	0.007

# E. Proteins that regulate other biological processes.

Copyright  $\ensuremath{\mathbb{C}}$  by The Journal of Bone and Joint Surgery, Incorporated Shen et al.

FLEXOR TENDON INJURY AND REPAIR. THE INFLUENCE OF SYNOVIAL ENVIRONMENT ON THE EARLY HEALING RESPONSE IN A CANINE MODEL

http://dx.doi.org/10.2106/JBJS.20.01253 Page 14

GNG12ª	G protein subunit gamma 12	Regulation or transduction of various transmembrane signals	-1.6	0.026
CAPN2	Calpain 2	Proteolysis of substrates involved cytoskeleton remodeling and signal transduction, including myoc	-1.6	0.009
CAST	Calpastatin	Specific inhibition of calpain	-1.5	0.031
FUBP1	Far upstream element- binding protein 1	Regulates MYC expression	-1.6	0.031
ARL6IP5	ADP ribosylation factor like GTPase 6 interacting protein 5	Positive regulation of apoptotic process	-1.6	0.022
SPCS2	Signal peptidase complex subunit 2	Signal peptide processing	-1.6	0.044
LAP3 <sup>a,b</sup>	Leucine aminopeptidase 3	Involved in processing and regular turnover of intracellular proteins	-1.5	0.027
TMED2	Transmembrane p24 trafficking protein 2	Vesicular protein trafficking	-1.5	0.047
PHPT1 <sup>a</sup>	Phosphohistidine phosphatase 1	Regulation of phosphohistidine levels of several proteins involved in diverse biological processes	-1.5	0.049
PGRMC1	Membrane-associated progesterone receptor component 1	Regulates drug, hormone and lipid metabolism via binding and activating P450	-1.5	0.044
LMAN2	Vesicular integral- membrane protein VIP36	Transport and sorting of glycoproteins	-1.5	0.031
RPN1	Dolichyl- diphosphooligosaccharide protein glycosyltransferase subunit 1	Protein glycosylation	-1.5	0.035

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 7 days after repair.

## F. Other proteins.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
SPR	Sepiapterin reductase	Tetrahydrobiopterin biosynthetic process	2.9	0.020
LOC100684574	Histone H3	Histone	2.2	0.036

ATP6V1B2	ATPase H+ transporting V1 subunit B2	Proton pump	1.8	0.027
RPS19	Ribosomal protein S19	Ribosomal protein	-2.0	0.022
RPL30	Ribosomal_L7Ae domain-containing protein	Structural constituent of ribosome	-1.5	0.022
HNRNPA2B1	Heterogeneous nuclear ribonucleoprotein A2/B1	mRNA processing and transport	-1.4	0.046
DARS	Aspartyl-tRNA synthetase	Aspartate-tRNA ligase activity	-1.3	0.041

# G. Uncharacterized proteins.

Gene PSMC5	Protein Proteasome 26S subunit	Fold change (Extrasynovial / Intrasynovial) 2.1	Adjusted P value 0.027
HNRNPUL1	Heterogeneous nuclear ribonucleoprotein U like 1	1.9	0.005
A1ILJ0	Alpha 1 antitrypsin	2.2	0.026
OLFML1	Olfactomedin like 1	-1.9	0.022
PURA	Purine rich element binding protein A	-1.9	0.007
CRIP2	Cysteine rich protein 2	-1.8	0.020
RCN1	Reticulocalbin 1	-1.8	0.033
LOC606860	COX6C domain-containing protein	-1.6	0.031
AHNAK	AHNAK nucleoprotein	-1.4	0.026

**Table S3.** List of differentially expressed proteins between extrasynovial flexor tendons and intrasynovial flexor tendons 7 days after injury and repair.

## A. ECM proteins

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
MMP8 <sup>a,b</sup>	Neutrophil collagenase	Degrades fibrillar type I, II, and III collagens.	8.5	0.001
ITIH1ª	Inter-alpha-trypsin inhibitor heavy chain 1	Hyaluronan localization and metabolic process	1.9	0.012

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 3 days after repair.

#### B. Cytoskeletal and related proteins.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
SEPT9ª	Septin 9	Filament-forming cytoskeletal GTPase	-1.7	0.043
MYH10 <sup>a</sup>	Myosin heavy chain 10	Cellular myosin	-1.6	0.046
CORO1B	Coronin-1B	Actin-binding protein that regulates leading edge dynamics and cell motility in fibroblasts	-1.6	0.043
SPTBN1 <sup>ab</sup>	Spectrin beta, non- erythrocytic 1	Cytoskeleton movement at the membrane	-1.5	0.028
SPTAN1 <sup>ab</sup>	Spectrin alpha, non- erythrocytic 1	Cytoskeleton movement at the membrane	-1.5	0.028
EPB41L2 <sup>b</sup>	Erythrocyte membrane protein band 4.1 like 2	Cortical actin cytoskeleton organization. Cell division	-1.5	0.043

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 3 days after repair.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
LOC100855540 <sup>b</sup>	GLOBIN domain- containing protein	Iron ion binding and cellular oxidant detoxification	5.1	0.001
HBA	Hemoglobin subunit alpha	Oxygen transportation	4.9	0.017
LOC485255 <sup>b</sup>	Hemoglobin subunit epsilon-2	Oxygen transportation	3.3	0.002
PLG <sup>ab</sup>	Plasminogen	Dissolve blood clot and activate collagenase and complement zymogens	4.1	<0.001
PRDX2 <sup>b</sup>	Peroxiredoxin 2	Negative regulator of NF- kB activity, extrinsic apoptotic signaling, and superoxide radicals	3.3	<0.001
C5ª	Complement C5	Component of complement system	1.8	0.017
CD59 <sup>b</sup>	CD59	Potent inhibitor of complement membrane attack complex	-2.0	0.008
FGL2 <sup>ab</sup>	Fibrinogen like 2	Negative regulator of immune cell response	-2.8	0.001
CD163 <sup>ab</sup>	Scavenger receptor cysteine-rich type 1 protein M130	Hemoglobin scavenger receptor with a role in anti- inflammatory response	-1.9	0.028
GSTP1 <sup>ab</sup>	Glutathione S- transferase pi 1	Negative regulator of acute inflammatory response	-1.5	0.017

#### C. Proteins involved in inflammation and acute or innate immune response.

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 3 days after repair.

## D. Metabolic enzymes.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
BLVRB⁵	Biliverdin reductase B	Catalyzes the NADPH- dependent reduction of a variety of flavins and contributes to heme catabolism	2.2	0.007

PNP <sup>b</sup>	Purine nucleoside phosphorylase	Purine metabolism	-1.7	0.030
IDH1⁵	Isocitrate dehydrogenase [NADP] cytoplasmic	NADP metabolic process	-1.8	0.043
FH <sup>ab</sup>	Fumarate hydratase	Component of Krebs cycle	-1.9	0.035
GOT2 <sup>ab</sup>	Glutamic-oxaloacetic transaminase 2	Amino acid metabolic enzyme	-1.9	0.003

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 3 days after repair.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
CLUª	Clusterin	Extracellular chaperone	2.6	0.028
CA2	Carbonic anhydrase 2	Carbonate dehydratase activity. positive regulation of bone resorption and cellular pH reduction	2.3	0.035
CA1⁵	carbonic anhydrase 1	one-carbon metabolic process	2.1	0.043
EEF1G <sup>a</sup>	Eukaryotic translation elongation factor 1 gamma	Translation elongation factor	1.7	0.012
PSMC6 <sup>a</sup>	proteasome 26S subunit, ATPase 6	Maintenance of protein homeostasis by removing misfolded or damaged proteins	1.6	0.017
STAT3	signal transducer and activator of transcription 3	Signal transducer and transcription activator that mediates cellular responses to interleukins, KITLG/SCF, LEP and other growth factors	1.6	0.046

E. Proteins that regulate other biological processes.

PCBP1 <sup>ab</sup>	Poly(rC) binding protein 1	Positive regulation of transcription from RNA polymerase II promoter	-1.9	0.003
ERP29 <sup>ab</sup>	Endoplasmic reticulum protein 29	Processing of secretory protein	-2.2	0.002
LAP3 <sup>ab</sup>	Leucine aminopeptidase 3	Processing and regular turnover of intracellular proteins	-1.6	0.028
PEBP1 <sup>ab</sup>	Phosphatidylethanolamine binding protein 1	Serine protease inhibitor	-1.7	0.014
MOB1B <sup>ab</sup>	MOB kinase activator 1B	Activator of LATS1/2 in the Hippo signaling pathway that controls organ size	-1.9	0.001

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 3 days after repair.

## F. Other proteins.

Gene	Protein	Description	Fold change (Extrasynovial / Intrasynovial)	Adjusted P value
SPR⁵	Sepiapterin reductase	Tetrahydrobiopterin biosynthetic process	3.3	0.012
RBM22	Pre-mRNA-splicing factor RBM22	Required for pre-mRNA splicing	2.9	0.017
PSMD5	26S proteasome non-ATPase regulatory subunit 5	involved in 26S proteasome assembly	2.0	0.046
SNX9	Sorting nexin 9	Involved in endocytosis and intracellular vesicle trafficking	-1.6	0.046

<sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 3 days after repair.

G. Uncharacterized proteins.

Gene	Protein	Fold change	Adjusted P
		(Extrasynovial /	value
		Intrasynovial)	

CYP2C18	cytochrome P450 2C21	3.4	0.043
F1PWR2_CANLF		1.6	0.028
LOC606860ª	COX6C domain- containing protein	-2.0	0.003
OLFML1 <sup>ab</sup>	Olfactomedin like 1	-2.3	0.004
CRIP2 <sup>ab</sup>	Cysteine rich protein 2	-1.7	0.048

<sup>a</sup>, exhibits opposite difference between intrasynovial tendons and extrasynovial tendons in intact tissue. <sup>b</sup>, differentially expressed between intrasynovial tendons and extrasynovial tendons 3 days after repair.