Supplementary material

Supplementary material showing: main characteristics of the papers included for search of expression in diseased human tendon tissues; main characteristics of the papers included for search of/for expression in tissues of animal tendon injury or exercise model; main characteristics of the papers included for search of/for cellular responses to cytokine treatment; assessment of study methodology quality; expression of other cytokines in diseased human tendon tissues and animal models of tendon injury or exercise *versus* healthy control tendon; and cellular responses to treatment by other cytokines in tendon cells.

Table i. Main characteristics of the papers included for the search for expression in diseased human tendon tissues

Author	Journal	Tendon	Disease/model	Healthy control?	Quantitative analysis methods	Statistical tests	Investigated genes and proteins/treated cytokines
Millar et al[56]	*Sci Rep*	Rotator cuff	Tear	Yes	PCR, IHC	Yes	IL-17
Chaudhury et al[13]	*J Shoulder Elbow Surg*	Rotator cuff	Tear	Yes	Microarray	Yes	IL-1β, 3, 8, 10, 11, 13, 15, 18, 27; TNF-α
Dakin et al[41]	*Sci Transl Med*	Rotator cuff	Tear/tendinopathy	Yes	PCR	Yes	IL-6, 8, 10, 12, 17; TNF-α
Waugh et al[17]	*Eur Cell Mater*	Achilles/patella	Tendinopathy	Yes	CBA	Yes	IL-1β, 2, 6, 8, 10; IFN-γ
Millar et al[57]	*Nat Commun*	Rotator cuff	Tear	Yes	PCR, IHC	Yes	IL-33
Campbell et al[70]	*Mediators Inflamm*	Rotator cuff	Tear/tendinopathy	Yes	PCR, IHC	Yes	IL-21
Gump et al[44]	*J Appl Physiol*	Achilles	Exercise (1 hr run)	Yes*	ELISA	Yes	IL-6
Pingel et al[14]	*Eur J Appl Physiol*	Achilles	Exercise (1 hr run) in tendinopathy	Yes	PCR	Yes	IL-1β, 6, 10; TNF-α
Ackermann et al[16]	*Knee Surg Sports Traumatol Arthrosc*	Achilles	Tear repair post-op	Yes	CBA	Yes	IL-1β, 6, 8, 10; TNF-α
Pingel et al[63]	*J Appl Physiol*	Patella	Strenuous extension	Yes	ELISA	Yes	IL-6
Gaida et al[50]	*Cells Tissues Organs*	Achilles	Tendinopathy	Yes	ELISA, IHC	Yes	TNF-α
Legerlotz et al[42]	*Rheumatology*	Achilles/tibialis posterior	Tear/tendinopathy	Yes†	PCR	Yes	IL-6; OSM; LIF
Jelinsky et al[62]	*BMC Musculoskelet Disord*	Rotator cuff/ Achilles/patella/ biceps/ECRB/flexor	Tear	Yes*	Microarray	Yes	IL-4, 6, 13, 14, 17; OSM; IFN-γ
Courneya et al[43]	*Fibrogenesis Tissue Repair*	Achilles/tibialis posterior	Tendinopathy	Yes	PCR	Yes	IL-4, 6, 13
Millar et al[40]	*J Bone Joint Surg [Br]*	Rotator cuff	Tear	Yes	PCR, IHC, microarray	Yes	IL-6, 15, 18; TNF-α
Langberg et al[45]	*J Physiol*	Achilles	Exercise (36 km run)	Yes	ELISA	Yes	IL-6
Gotoh et al[15]	*J Orthop Res*	Rotator cuff	Tear	Yes†	IHC	Yes	IL-1β

*studies that sampled control tissues from the healthy region of the same tendon
†studies that sampled control tissues from cadavers
PCR, polymerase chain reaction; IHC, immunohistochemistry; IL, interleukin; TNF, tumour necrosis factor; CBA, cytometric bead array; IFN, interferon; ELISA, enzyme-linked immunosorbent assay; OSM, oncostatin M; LIF, leukemia inhibitory factor; ECRB, extensor carpal radialis brevis

Table ii. Main characteristics of the papers included for the search for expression in tissues of animal tendon injury or exercise model

Authors	Journal	Animal	Tendon	Model	Healthy control?	Quantitative analysis methods	Statistical tests	Investigated genes and proteins
Haslerud et al[21]	*Photomed Laser Surg*	Rat	Achilles	Crush	Yes	ELISA	Yes	IL-1β, 6, 10; TNF-α
Da Ré Guerra et al[20]	*Lasers Med Sci*	Rat	Achilles	Partial transection	Yes	ELISA	Yes	IL-1β, 10; TNF-α
Frara et al[32]	*BMC Musculoskelet Disord*	Rat	FD	Exercise	Yes	ELISA	Yes	IL-1α, β, 10; TNF-α
Tucker et al[60]	*J Orthop Res*	Rat	Rotator cuff	Transection + repair in tendinopathy	Yes	IHC	Yes	IL-1β; TNF-α
Millar et al[59]	*Nat Commun*	Mouse	Patella	Partial transection	Yes	PCR, IHC	Yes	IL-33
Torres-Silva et al[46]	*Lasers Med Sci*	Rat	Achilles	Collagenase	Yes	PCR	Yes	IL-6, 10; TNF-α
de Jesus et al[22]	*Lasers Med Sci*	Rat	Achilles	Crush	Yes	IHC	Yes	IL-1β
Sugg et al[18]	*J Orthop Res*	Rat	Achilles	Transection + repair	Yes	PCR	Yes	IL-1β, 6, 10
Manning et al[25]	*J Orthop Res*	Dog	FD	Transection + repair	Yes	PCR	Yes	IL-1β; TNF-α
Barbe et al[37]	*BMC Musculoskelet Disord*	Rat	FD	Exercise	Yes	ELISA	Yes	IL-1α, β; TNF-α
Gao et al[26]	*PLoS One*	Rat	FD	Exercise	Yes	ELISA	Yes	IL-1α, β, 6, 10, 12; TNF-α
Pingel et al[27]	*Scand J Med Sci Sports*	Rat	Achilles	Exercise	Yes	PCR	Yes	IL-1β, 3, 6
Xavier et al[48]	*Lasers Med Sci*	Rat	Achilles	Collagenase	Yes	PCR	Yes	IL-10
Attia et al[71]	*Am J Sports Med*	Rat	Rotator cuff	Exercise	Yes	Cytokine array	No	IL-1α, β, 2, 4, 6, 10, 13; TNF-α; IFN-γ
Kietrys et al[36]	*PLoS One*	Rat	FD	Exercise	Yes	IHC	No	IL-1β, 6, 10; TNF-α
Casalechi et al[49]	*Lasers Med Sci*	Rat	Achilles	Collagenase	Yes	PCR	Yes	IL-10
Marcos et al[64]	*J Orthop Res*	Rat	Achilles	Collagenase	Yes	PCR	Yes	TNF-α
Dohnert et al[51]	*Int J Nanomedicine*	Rat	Achilles	Crush	Yes	WB	Yes	IL-1β; TNF-α
Eliasson et al[28]	*J Appl Physiol*	Rat	Achilles	Transection + exercise	Yes	Microarray, PCR	Yes	IL-1β
Leumann et al[72]	*Scand J Med Sci Sports*	Rabbit	Patella	Quadriceps weakening	Yes	PCR	Yes	IL-1
Wang et al[73]	*Orthopaedics*	Rat	Achilles	Stress-shielding	Yes	ELISA	Yes	IL-1
Pires et al[19]	*Lasers Med Sci*	Rat	Achilles	Collagenase	Yes	PCR	Yes	IL-1β, 6; TNF-α
Fedorczyk et al[33]	*J Orthop Res*	Rat	FD	Exercise	Yes	ELISA, IHC	Yes	IL-1β
Coq et al[35]	*Exp Neurol*	Rat	FD	Exercise	Yes	ELISA, IHC	Yes	IL-1β; TNF-α
Millar et al[40]	*J Bone Joint Surg Br*	Rat	Rotator cuff	Exercise	Yes	Microarray	Yes	IL-2, 6, 11, 15, 18; TNF-α
Elliott et al[38]	*Neuroscience*	Rat	FD	Exercise	Yes	ELISA	Yes	IL-1α, β, 6, 10; TNF-α
Sun et al[29]	*Clin Orthop Relat Res*	Rat	Patella	Cyclic exercise (surgery)	Yes	WB	Yes	IL-1β
Barbe et al[34]	*J Orthop Res*	Rat	FD	Exercise	Yes	ELISA	Yes	IL-1α, β, 10; TNF-α
Asundi et al[30]	*Eur J Appl Physiol*	Rabbit	FD	Electrical stimulation	Yes	PCR	Yes	IL-1β
Berglund et al[24]	*J Hand Surg Eur*	Rabbit	FD	Transection + repair	Yes	PCR	Yes	IL-1β; TNF-α
Koshima et al[23]	*J Orthop Res*	Rabbit	Rotator cuff	Partial transection	Yes	PCR, ELISA	Yes	IL-1β
Hosaka et al[65]	*J Vet Med Sci*	Horse	FD	Tendinopathy	Yes	PCR, IHC, WB	No	TNF-α
Uchida et al[31]	*J Biomech*	Rat	Patella	Stress-shielding	Yes	IHC	Yes	IL-1β; TNF-α
Hosaka et al[61]	*J Vet Med Sci*	Horse	FD	Tendinopathy	Yes	IHC	No	IL-1α, β; TNF-α; IFN-γ

ELISA, enzyme-linked immunosorbent assay; IL, interleukin; TNF, tumour necrosis factor; FD, flexor digitorum; IHC, immunohistochemistry; PCR, polymerase chain reaction; IFN, interferon; WB, Western blotting

Table iii. Main characteristics of the papers included for the search for cellular responses to cytokine treatment

Authors	Journal	Animal	Tendon	Disease/model	Healthy control?	Quantitative analysis methods	Statistical tests	Treated cytokines
Millar et al[56]	*Sci Rep*	Human	Hamstring	Healthy	-	PCR, ELISA	Yes	IL-17
Zhang et al[69]	*Biochem Biophys Res Commun*	Mouse	Achilles	Transection	No	PCR	Yes	IL-1β
Millar et al[57]	*Nat Commun*	Human	Hamstring	Healthy	-	PCR, ELISA	Yes	IL-33
Hosaka et al[52]	*Biomed Res*	Horse	SDFT	Healthy	-	Collagen assay, zymography	Yes	TNF-α
John et al[47]	*J Orthop Res*	Human	Hamstring, patella, finger, Achilles	Healthy	-	PCR, WB, IF	Yes	IL-6, 10; TNF-α
Tohyama et al[39]	*J Bone Joint Surg [Br]*	Rat	Patella	Frozen-thawed	Yes	NB	Yes	IL-1β
Thampatty et al[66]	*Gene*	Human	Patella	Healthy	-	PCR, WB	Yes	IL-1β
Tsuzaki et al[67]	*J Orthop Res*	Human	FDP	Healthy	-	PCR, ELISA	Yes	IL-1β
Corps et al[68]	*Arthritis Rheum*	Human	Not described	Tendinopathy	No	PCR, WB	Yes	IL-1β

PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; IL, interleukin; FDST, flexor digitorum superficialis tendon; TNF, tumour necrosis factor; WB, Western blotting; IF, immunoflorescence microscopy; NB, Northern blotting; FDP, flexor digital profundus

Table iv. Assessment of study methodology quality. The quality of methodology was assessed in the 57 included studies in order to highlight the reports with a high risk of potential bias

Study	Study population clearly described (age/gender)	Control group clearly described	Sampling method clearly described	Sampling method consistent and unbiased	Quantitative/ semi-quantitative analysis method and statistical comparison	Analysis method representative of whole sample and unbiased	Reliability and/or validity of methods described	Study limitations mentioned/ addressed	Statistical level of significance stated	Check for normal distribution	Total
Haslerud et al[21]	0	1	1	1	1	1	1	1	1	1	9
Millar et al[56]	0	1	1	1	1	1	1	1	1	0	8
Chaudhury et al[13]	0	1	1	1	1	1	1	1	1	0	8
Da Ré Guerra et al[20]	0	1	1	1	1	1	0	0	0	0	5
Frara et al[32]	1	1	1	1	1	1	0	0	1	0	7
Dakin et al[41]	0	1	1	1	1	1	1	1	1	1	9
Tucker et al[60]	1	1	1	1	1	1	0	1	1	0	8
Zhang et al[69]	0	1	1	1	1	1	1	0	1	0	7
Waugh et al[17]	1	1	1	1	1	1	1	1	1	1	10
Millar et al[57]	0	1	1	1	1	1	1	1	1	1	9
Torres-Silva et al[46]	1	1	1	1	1	1	1	0	1	0	8
de Jesus et al[22]	1	1	1	1	1	1	0	1	1	1	9
Campbell et al[70]	0	1	1	1	1	1	1	1	0	0	7
Sugg et al[18]	1	1	1	1	1	1	0	1	1	0	8
Manning et al[25]	0	1	1	1	1	1	0	1	1	0	7
Barbe et al[37]	1	1	1	1	1	1	1	1	1	0	9
Gao et al[26]	1	1	1	1	1	1	0	0	1	1	8
Pingel et al[27]	1	1	1	1	1	1	1	1	1	0	9
Gump et al[44]	1	1	1	1	1	1	1	1	1	0	9
Pingel et al[14]	1	1	1	1	1	0	1	1	1	0	8
Xavier et al[48]	1	1	1	1	1	1	1	0	1	0	8
Attia et al[71]	1	1	1	1	0	1	1	0	1	0	7
Kietrys et al[36]	1	1	1	1	1	1	1	1	1	0	9
Ackermann et al[16]	1	1	1	1	1	1	1	1	1	0	9
Casalechi et al[49]	1	1	1	1	1	1	0	0	1	0	7
Pingel et al[63]	1	1	1	1	1	1	0	1	1	1	9
Marcos et al[64]	1	1	1	1	1	1	0	0	1	0	7
Dohnert et al[51]	1	1	1	1	1	1	1	0	1	0	8
Gaida et al[50]	1	1	1	1	1	1	1	0	1	0	8
Legerlotz et al[42]	1	1	0	1	1	1	0	1	1	0	7
Eliasson et al[28]	0	1	1	1	1	1	0	1	0	0	6
Jelinsky et al[62]	1	1	1	0	1	1	0	1	1	0	7
Leumann et al[72]	1	1	1	1	1	1	1	1	1	0	9
Wang et al[73]	1	1	1	1	1	1	0	1	1	0	8
Pires et al[19]	1	1	1	1	1	1	1	0	1	0	8
Courneya et al[43]	0	1	0	0	0	0	0	0	0	0	1
Hosaka et al[52]	0	1	1	1	1	1	0	1	1	0	7
John et al[47]	0	1	1	1	1	1	0	0	1	0	6
Fedorczyk et al[33]	1	1	1	1	1	1	1	0	1	0	8
Coq et al[35]	1	1	1	1	1	1	1	0	0	0	7
Millar et al[40]	0	1	0	1	1	1	0	1	1	0	6
Millar et al[40]	1	1	1	1	1	1	1	1	1	0	9
Elliott et al[38]	1	1	1	1	1	1	0	1	1	0	8
Sun et al[29]	1	1	1	1	1	1	1	1	0	0	8

(Continued)

Table iv. (Continued)

Study	Study population clearly described (age/gender)	Control group clearly described	Sampling method clearly described	Sampling method consistent and unbiased	Quantitative/ semi-quantitative analysis method and statistical comparison	Analysis method representative of whole sample and unbiased	Reliability and/or validity of methods described	Study limitations mentioned/ addressed	Statistical level of significance stated	Check for normal distribution	Total
Barbe et al[34]	1	1	1	1	1	1	0	0	0	0	6
Berglund et al[24]	1	1	1	1	1	1	0	1	1	0	8
Asundi et al[30]	0	1	1	1	1	1	1	1	0	0	7
Tohyama et al[39]	1	1	1	1	1	1	1	1	1	0	9
Thampatty et al[66]	0	1	1	1	0	1	0	1	0	0	5
Koshima et al[23]	1	1	1	1	1	1	1	1	1	0	9
Hosaka et al[65]	1	1	1	1	0	1	0	0	0	0	5
Uchida et al[31]	1	1	1	1	1	1	1	1	1	0	9
Tsuzaki et al[67]	1	1	1	1	1	1	1	0	1	0	8
Corps et al[68]	0	1	1	1	0	1	1	0	0	0	5
Hosaka et al[61]	1	1	1	1	0	1	0	0	0	0	5
Langberg et al[45]	1	1	1	1	1	1	0	1	1	0	8
Gotoh et al[15]	0	1	0	0	0	0	0	1	0	0	2

Table v. Expression of other cytokines in tissues of diseased human tendon, animal models of tendon injury or exercise *versus* healthy control tendon. Arrows indicate increased (↑), unchanged (→), or decreased (↓) expression of cytokines in tissues of diseased human tendon, animal models of tendon injury or exercise versus healthy control tendon

Cytokine	Animal	Disease model	Increased, unchanged, decreased in diseased *versus* control	
			Gene	**Protein**
IL-1	Rat	Achilles, stress shield		↑ (3 wks)[73]
	Rabbit	Patella, quad weakening	→ (6 mths)[72]	
IL-1α	Rat	Flexor digitorum, exercise		↑ (3 wks) → (6, 8 wks)[32,34] →/↑ (12 wks)[37,38] ↑ (18 wks)[26]
	Horse	Flexor digitorum superficialis, tendinopathy		↑ (descriptive)[61]
IL-2	Human	Achilles, tendinopathy		↓*[17]
	Rat	Rotator cuff, exercise	↓ (4 wks)[40]	
IL-3	Human	Rotator cuff, tear	↑ [13]	
	Rat	Achilles, exercise	→ (7 wks)[27]	
IL-4	Human	Rotator cuff/Achilles/patella/biceps/ECRB/flexor, tear	↑ (IL-4R)[62]	
		Achilles/tibialis posterior, tendinopathy	→ (IL-4Rα)[43]	
IL-8	Human	Rotator cuff, tear	↓[13] →[41]	
		Rotator cuff/Achilles, tendinopathy	→[41]	→*[17]
		Achilles, tear, post-operative (2 wks)		↑*[16]
IL-11	Human	Rotator cuff, tear	↓[13]	
	Rat	Rotator cuff, exercise	↑ (4 wks)[40]	
IL-12	Human	Rotator cuff, tear/ tendinopathy	→[41]	
	Rat	Flexor, exercise		→ (training, 18, 24 wks)[26]
IL-13	Human	Rotator cuff, tear	↑[13]	
		Achilles/tibialis posterior, tendinopathy	↑ (IL-13Rα2)[43]	
IL-14	Human	Rotator cuff/Achilles/patella/biceps/ECRB/flexor, tear	↑[62]	
IL-15	Human	Rotator cuff, tear	↑[13,40]	↑[40]
	Rat	Rotator cuff, exercise	↑ (4 wks)[40]	
IL-17	Human	Rotator cuff, tear	→ (IL-17A)[56] → (IL-17RB)[41]	
		Rotator cuff/Achilles/patella/biceps/ECRB/flexor, tear	↓ (IL-17D)[62]	
		Rotator cuff, tendinopathy	↑ (IL-17A)[56] → (IL-17RB)[41]	
IL-18	Human	Rotator cuff, tear	↓[13] ↑[40]	↑[40]
	Rat	Rotator cuff, exercise	↑(4 wks)[40]	
IL-21	Human	Rotator cuff, tear/tendinopathy	→[70]	→[70]
			↑ (IL-21R, tendinopathy > tear > control)[70]	↑ (IL-21R, tendinopathy > tear > control)[70]
IL-27	Human	Rotator cuff, tear	↓[13]	
IL-33	Human	Rotator cuff, tear	→[57]	→[57]
	Mouse	Patella, partial transection (defect)	→ (1, 3 days)[57]	→ (1 day)[57]
IFN-γ	Human	Achilles, tendinopathy		↑ (descriptive)*[17]
	Horse	Flexor digitorum superficialis, tendinopathy		↑ (descriptive)[61]

*studies that sampled control tissues from the healthy region of the same tendon
ECRB, extensor carpal radialis brevis; IL, interleukin; IL-4R, interleukin-4 receptor; IL-13R, interleukin-13 receptor; IL-17R, interleukin-17 receptor; IL-21R, interleukin-21 receptor; IFN, interferon

Table vi. Cellular responses to treatment by other cytokines in tendon cells

Treatment	Cells	Increased, unchanged, decreased in response to treatment *versus* control	
		Gene	**Protein**
IL-17	Human, hamstring, normal	Collagen I ↑/→ Collagen III ↑[56]	Total collagen ↑ (Collagen I → Collagen III ↑)[56]
IL-33	Human, hamstring, normal	Collagen I ↑ Collagen III ↑[57]	Collagen I → Collagen III ↑[57]

IL, interleukin