A REVIEW OF THE PLEIOTROPIC ACTIONS OF THE IFN-INDUCIBLE CXC CHEMOKINE RECEPTOR 3 LIGANDS IN THE SYNOVIAL MICROENVIRONMENT

Luna Dillemans[1], Lien De Somer[2], Barbara Neerinckx[3], Paul Proost[1]

Affiliations

[1]Laboratory of Molecular Immunology, Department of Microbiology, Immunology and Transplantation, Rega Institute, KU Leuven, Leuven, Belgium

[2]Laboratory of Immunobiology, Department of Microbiology, Immunology and Transplantation, Rega Institute, KU Leuven, Leuven, Belgium

[3]Skeletal Biology and Engineering Research Center, Department of Development and Regeneration, KU Leuven, Leuven, Belgium - Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium

Corresponding author

Paul Proost – paul.proost@kuleuven.be - Department of Microbiology, Immunology and Transplantation, Rega Institute, Katholieke Universiteit Leuven, Leuven

ORCID

Luna Dillemans (0000-0001-5375-8403)
Lien De Somer (0000-0002-8488-5090)
Barbara Neerinckx (0000-0001-9220-9466)
Paul Proost (0000-0002-0133-5545)

SUPPLEMENTARY DATA

SUPPLEMENTARY TABLE 1 | Overview of studies investigating the IFN-inducible CXCR3 ligands in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, septic arthritis and osteoarthritis.

Study	Diseases	Disease: number of included subjects (treatment)	Technique for substrate detection	CXCR3 ligand in serum (S) or plasma (P) (mean ± SD or median with [IQR])	CXCR3 ligand in synovial fluid (SF) or synovial tissue (ST) (mean ± SD or median with [IQR])	Disease vs. control population	Correlation with disease activity markers of arthritis
Patel et al. [1]	RA OA TJI	RA: N = 23, S: N = 16 OA: N = 8 TJI: N = 3 (treatment not mentioned)	ELISA	CXCL9 (S: 4024 ± 1270 pg/ml in seropositive RA) CXCL10 (S: 3109 ± 1181 pg/ml in seropositive RA)	RA SF: CXCL9 (SF, 15.024 ± 6.392 ng/ml), CXCL10 (SF, 32.090 ± 10.489 ng/ml) OA and TJI (considered as one group): CXCL9 (SF, 0.280 ± 0.095 ng/ml), CXCL10 (SF, 0.324 ± 0.106 ng/ml)	S: CXCL10 in seropositive RA > seronegative controls, CXCL9 in seropositive RA = seronegative controls SF: CXCL9 and CXCL10 in RA > OA and TJI	N.D.
Hanaoka et al. [2]	RA OA	RA: N = 32 OA: N = 10 (oral prednisolone or gluco-corticosteroids, < 5 mg)	ELISA	N.D.	RA: CXCL10 (SF, 6.05 ± 0.86 ng/ml) OA: CXCL10 (SF, 2.32 ± 1.28 ng/ml)	SF: CXCL10 in RA > OA	N.D.
Lee et al. [3]	RA OA	RA: N = 18 (on DMARDs [N = 18]) OA: N = 11	ELISA	RA: CXCL10 (S, 363.9 ± 78.9 pg/ml) OA: CXCL10 (S, 87.7 ± 10.8 pg/ml)	RA: CXCL10 (SF, 1502.0 ± 87.1 pg/ml) OA: CXCL10 (SF, 267.3 ± 87.0 pg/ml)	SF: CXCL10 in RA > OA S: CXCL10 in RA > OA RA: CXCL10 in SF > S	N.D.
Kuan et al. [4]	RA	RA : N = 28 (sampled at baseline during active disease and after treatment with DMARDS, prednisolone or biological agents)	Cytometric bead array	CXCL9 (S: 3062.0 pg/ml [IQR: 1245.7 – 4899.0]) CXCL10 (S: 2255.7 pg/ml [IQR: 1430.7 – 4196.1])	N.D.	S: CXCL10, CXCL9 in RA > HC	↓ S [CXCL10] (1713.0 pg/ml) and ↓ S [CXCL9] (1302.9 pg/ml) in patients with improved clinical activity after treatment for 12 weeks with DMARDS or biological agents ↓ S [CXCL10] in patients that achieved EULAR response < patients that achieved no EULAR response (1628.2 pg/ml vs. 1787.8 pg/ml)

Pandya et al. [5]	RA	RA: N = 43 (early, untreated RA)	Flow cytometry bead-based immunoassay	CXCL9, CXCL10 (P), specific mean/median P levels not mentioned)	N.D.	P: CXCL10, CXCL9 in RA > HC	- P [CXCL10] correlated with multiple disease activity parameters: DAS28-CRP, DAS28-ESR, CDAI, SJC in 66 joints, CRP and ESR - P [CXCL10] was negatively associated with symptom duration
Ruschpler et al. [6]	RA OA	RA: N = 20 (treated with DMARDS, NSAIDs, corticosteroids or a combination) OA: N = 10 (treated with NSAIDS [N = 7] or not treated [N = 3])	DNA oligo-nucleotide array, RT-PCR and Western Blot	N.D.	RA vs. OA: ST RNA: CXCR3 (2.3-fold ↑), CXCL9 (9.8-fold ↑) CXCL10 (4.6-fold ↑) (DNA nucleotide microarray) RA vs. OA: ST mRNA: CXCR3 (3.6-fold ↑), CXCL9 (135-fold ↑) CXCL10 (340-fold ↑) (RT-PCR)	ST: mRNA expression of CXCL9, CXCL10 and CXCR3 in RA > OA ST: CXCR3 protein in RA > OA	N.D.
Muhsin et al. [7]	RA JIA	RA: N = 77 (no therapy [N = 17], DMARDS [N = 20], MPS [N= 16] and etanercept [N= 24]) JIA: N = 79 of which oligoJIA (N = 47), polyJIA (N = 26) and other not defined JIA types (N = 6) and of which no therapy [N = 18], DMARDS [N = 37], MPS [N= 13] and etanercept [N= 11]	ELISA	RA: CXCL10 (S: 41.5 pg/ml [IQR: 22.1–78 pg/ml]) JIA: CXCL10 (S: 38.5 pg/ml [IQR: 24.4–97 pg/ml])	N.D.	S: CXCL10 in RA > HC S: CXCL10 in JIA > HC	- S [CXCL10] (cut-off value of 29.2 pg/ml) in JIA had a diagnostic sensitivity and specificity of respectively 91.1% and 91.8% - S [CXCL10] (cut-off value of 20.1 pg/ml) in RA had diagnostic sensitivity and specificity of respectively 100% and 96.2%
Ichikawa et al. [8]	RA	RA: N = 22 (sampled at baseline, after treated for 3 months and 6 months with etanercept)	ELISA	CXCL10 (S: 395 ± 291 pg/ml pre-treatment), (S: 153 ± 213 pg/ml after 3 months), (S: 121 ± 163 pg/ml after 6 months)	N.D.	S: CXCL10 pre-treatment > RA treated with etanercept for 3 months > RA treated with etanercept for 6 months	- S [CXCL10] correlated with DAS28-CRP but not with other clinical disease activity measures (SJC, TJC, CRP and ESR)

Kokkonen et al. [9]	RA	RA: N = 85 (pre-patients before onset of any symptoms of joint disease) of which 69 were also sampled at diagnosis (no treatment mentioned)	ELISA	RA at diagnosis: CXCL9 (P: 707.8 pg/ml [IQR: 431.6 – 1 433.5]), CXCL10 (P : 1 039.2 pg/ml [IQR: 442.1 – 1 961.6 pg/ml] RA pre-patients : CXCL9 (P: 342.0 pg/ml [IQR: 240.0 – 484.4]), CXCL10 (P : 702.8 pg/ml [IQR: 391.5 – 1 077.7 pg/ml]	N.D	P: CXCL9, CXCL10 in early RA > matched pre-patients P : CXCL9, CXCL10 in pre-patients = HC	↑ P [CXCL10] and [CXCL9] in relation to closer to the onset of symptoms
Ueno et al. [10]	RA OA	RA: N = 20 OA: N = 20 Treated with either DMARDS (N = 19), prednisolone (N = 18), NSAIDS (N = not mentioned) Not mentioned which patients were treated of RA and OA group	ELISA RT-PCR	RA: CXCL9 (S: 119 ± 26 pg/ml), CXCL10 (S: 115 ± 18 pg/ml), CXCL11 (S: 115 ± 29 pg/ml)	RA: CXCL9 (SF, 552±125 pg/ml), CXCL10 (SF, 336±35 pg/ml), CXCL11 (SF, 133 ± 34 pg/ml) OA: CXCL9 (SF, 71±26 pg/ml) , CXCL10 (SF, 133±27 pg/ml), CXCL11(SF, 7 ± 4 pg/ml)	SF: CXCL9, CXCL10, CXCL11 in RA > OA ST: mRNA CXCL9, CXCL10, CXCL11 in RA > OA RA: CXCL9 and CXCL10 SF > S	No correlation of S levels of CXCL9 CXCL10 or CXCL11 with CRP, RF, medication or disease duration
Imam et al. [11]	RA	RA: N = 60 Early RA (disease duration < 2y): N = 30 Long-standing RA (disease duration ≥ 2y) : N = 30	ELISA	Early RA: CXCL10 (S: 1448.86 ± 1253.38 pg/ml) Longstanding RA: CXCL10 (S: 726.84 ± 316.27 pg/ml)	N.D.	S: CXCL10 in RA (early and long-standing) > HC S: CXCL10 in early RA > long-standing RA	S [CXCL10] correlated to DAS28-ESR, TJC and SJC but not with disease duration, ESR and CRP S [CXCL10] in early RA (cut-off value of 793.0 pg/ml) had a diagnostic sensitivity and specificity of respectively 65% and 77% S [CXCL10] in long-standing RA (cut-off value of 470.0 pg/ml) had a diagnostic sensitivity and specificity of respectively 88.3% and 90%
Lande et al. [12]	RA OA PsA	RA: N = 19, OA: N = 15 PsA: N = 11	ELISA	N.D.	RA, PsA and OA CXCL10 and CXCL11 (SF, specific mean/median SF levels not mentioned)	SF: CXCL10 in RA > OA, PsA > OA; PsA = RA SF: CXCL11 in RA > OA, PsA = OA	N.D.

Han et al. [13]	RA	RA: N = 29 (baseline, treated with MTX or other DMARDS) and started with etanercept (N = 7) or adalimumab (N = 32)	ELISA	At baseline in RA: CXCL10 (S: 606 ± 581 pg/ml in responders to TNF inhibitor therapy vs. 283 ± 265 pg/ml in non-responders) At baseline in anti-CCP+ anti-CCP- RA and in RF+ and RF- RA: CXCL10: (S: specific mean/median S levels not mentioned) After TNF inhibitor therapy in RA: CXCL10 (S: 411.1 ± 458.3 pg/ml in responders, 218.4 ± 237.3 pg/ml in non-responders)	N.D.	S: baseline [CXCL10] in RA patient that reach EULAR response criteria at week 14 > RA patients that did not respond to TNF inhibitor therapy S: [CXCL10] after treatment in responders and non-responders < before treatment	Baseline or posttreatment S [CXCL10] did not correlate with DAS28 or ESR Baseline S [CXCL10] in anti-CCP+ RA > anti-CCP- RA Baseline S [CXCL10] in RF+ RA = RF- RA
Schmutz et al. [14]	RA Cartilage damage or degene-ration	RA: N = 8 (treated with NSAIDs, MTX, steroids or auranofin [N = 7], non-treated [N = 1]) Cartilage damage or degeneration: N = 9 (treated with steroids [N= 1] or with NSAIDs [N= 1], non-treated [N = 7])	Microarray technology	N.D.	ST: mRNA CXCL9 in RA ST (ST, 3.6 ± 0.1 fold increased) > ST of patients with cartilage damage or degeneration ST: mRNA CXCL10 in RA ST (1.6 ± 0.1 fold increased but NS) > ST of patients with cartilage damage or degeneration (not significant)	ST: mRNA CXCL9 in RA > cartilage damage or degeneration	N.D.
Jude et al. [15]	RA	Long-standing RA: N = 33 treated with prednisolone and azathioprine (N = 15), MTX (N = 9), leflunomide (N = 6) and sulfasalazine (N = 3)	ELISA	Long-standing RA: CXCL10 (S, specific mean/median S levels not mentioned)	N.D.	S: [CXCL10] in long-standing RA > HC (data not shown in paper)	- S [CXCL10] correlated with S sCD163 levels in long-standing (sCD163 levels in longstanding RA > HC, sCD163 did correlate with CRP and RF+ but did not correlate with ESR, DAS28, TJC and SJC)
Aldridge et al. [16]	RA	RA: N = 8 (blood and SF samples) RA: N = 9 (ST) (no treatment mentioned)	Multiplex assay	CXCL9, CXCL10 and CXCL11 (P, specific mean/median P levels not mentioned)	CXCL9, CXCL10 and CXCL11 (SF, specific mean/median SF levels not mentioned)	P and SF: [CXCL10], [CXCL9] in RA SF > RA blood P P and SF: [CXCL11] in RA SF < RA blood P	N.D.
Tsubaki et al. [17]	RA	Early RA (duration of disease prior to diagnosis less than 1 y): N = 9	RT-PCR	N.D.	ST mRNA CXCL9, CXCL10 and CXCL11 (ST, specific mRNA levels not mentioned)	ST mRNA CXCL9 and CXCL10 in RA is high and co-incidental expression in synovial sublining	N.D.

Nakayama et al. [18]	RA	RA: PB samples of patients with inactive RA (N = 11 of which patients received oral steroids [N=3], synthetic DMARDs [N = 9], or biological DMARDs [N =2]), PB samples of patients with active RA (N = 19 of which patients received oral steroids [N= 11], synthetic DMARDs [N= 15], or biological DMARDs [N= 4]), and SF samples (N = 20 of which patients received oral steroids [N= 8], synthetic DMARDs [N= 12], or biological DMARDs [N= 4])	RT-PCR	Whole blood: CXCL9 and CXCL10 mRNA in B cells isolated by positive selection from whole blood	SF: CXCL9 and CXCL10 mRNA in B cells isolated by positive selection from SF, and in $CD4^+$ T cells and $CD8^+$ T cells isolated from the SF	SF: mRNA of CXCL9 and CXCL10 in B cells of SF > PB of patients with active RA SF: mRNA of CXCL9 and CXCL10 in B cells of SF > $CD4^+$ T cells and $CD8^+$ T cells in SF	N.D.
Hueber et al. [19]	RA PsA AS	Early RA (disease duration < 6 months): N = 56 of which treated with DMARDS (N = 23) PsA and AS (taken together as one group): N = 21 (no treatment mentioned)	Multiplex assay	Early RA, PsA, AS: CXCL10 (S, specific mean/median S levels not mentioned)	N.D.	S: [CXCL10] in early RA > PsA and AS S: [CXCL10] in PsA and AS = HC	N.D.
Proost et al. [20]	RA PsA AS CA	RA: N = 71 PsA: N = 14 AS: N = 18 CA: N = 23 (no treatments mentioned)	ELISA	N.D.	RA, PsA, AS: CXCL10 (SF, median 10 – 20 ng/ml) CA: CXCL10 (SF, median < 1 ng/ml)	SF: [CXCL10] in RA = PsA = AS SF: [CXCL10] in RA > CA SF: [CXCL10] in PsA > CA SF: [CXCL10] in AS > CA	No correlation between S CRP levels and SF [CXCL10] levels
Loos et al. [21]	RA PsA AS CA	RA: N = 75 PsA: N = 14 AS: N = 18 CA: N = 24 (no treatments mentioned)	ELISA	N.D.	AS, PsA, RA, CA: CXCL9 and CXCL11 (SF, specific mean/median levels not mentioned)	SF: [CXCL9] in RA = AS = PsA SF: [CXCL9] in RA > CA SF: [CXCL9] in AS > CA SF: [CXCL9] in PsA > CA SF: [CXCL11] in RA = PsA = CA SF: [CXCL11] in RA > AS	N.D.

Wang et al. [22]	AS	AS: N = 42 All patients were sampled before treatment (N = 42) and some patients were sampled after treatment with etanercept and NSAIDs (N = 15)	ELISA	Untreated AS: CXCL10 (S, 575 ± 261 pg/ml) Etanercept-treated AS: CXCL10 (S, specific mean/median levels not mentioned)	N.D.	S: [CXCL10] in untreated AS > HC S: [CXCL10] in untreated AS > etanercept-treated AS	- S [CXCL10] correlated with ESR, CRP and ASDAS before treatment - S [CXCL10] did not correlate with IgM, IgG and IgA before treatment - S [CXCL10] correlated with TNF-α levels before treatment - S [CXCL10] decreased after etanercept treatment
Duftner et al. [23]	AS	AS: N = 12 Patients were sampled before treatment (N = 12) and after treatment with infliximab (N = 6)	ELISA	Untreated AS: CXCL9 (S, 59.2 pg/ml [IQR: 34.1 – 730.5 pg/ml]), CXCL10 (S, specific mean/median levels not mentioned) Infliximab-treated AS: CXCL9 and CXCL10 (S, specific mean/median levels not mentioned)	N.D.	S: [CXCL9] in untreated AS > HC S: [CXCL10]: untreated AS = HC, untreated AS > infliximab-treated AS	- S [CXCL10] decreased after infliximab treatment
Erdem et al. [24]	OA SpA RA	OA: N = 19 SpA: N = 19 RA: N = 17	ELISA	N.D.	OA: CXCL9 (SF, 501 pg/ml [range: 1468]), CXCL10 (SF, 52 pg/ml [range: 102]) SpA: CXCL9 (SF, 775 pg/ml [range: 957]), CXCL10 (SF, 76 [range: 152]) RA: CXCL9 (SF, 957 pg/ml [range: 5146]), CXCL10 (SF, 119 pg/ml [range: 198])	SF: CXCL9 in RA > OA, SpA > OA, RA = SpA SF: CXCL10 in RA > OA, SpA = OA, RA = SpA	SF [CXCL9] correlated with SF [CXCL10] in patients with RA
Röhner et al. [25]	RA PsA	RA (N is not reported) PsA (N is not reported)	Multiplex assay	N.D.	RA and PsA: CXCL10, IFN-γ (SF, specific mean/median levels not mentioned)	N.D.	N.D.

Abji et al. [26]	PsA CA: gout	PsA: N = 46 of SF samples were obtained (N = 8) Gout (N = 6)	Multiplex assay RT-PCR	PsA: CXCL10 (S, 493 pg/ml [IQR: 356–984])	PsA: SF: CXCL10 mRNA in SF (17.3-fold) > blood SF: CXCL10 mRNA in SF in PsA (44.3-fold) (N = 8) > gout (N = 6)	S: CXCL10 in psoriasis patient with PsA > psoriasis patient that do not develop PsA SF and whole blood cells: CXCL10 mRNA in PsA SF > PsA S SF cells: CXCL10 mRNA: PsA > gout	- S [CXCL10] levels were significantly associated with conversion status to PsA in psoriasis patients (OR 1.3, [95% CI: 1.1-1.5])
Antonelli et al. [27]	PsA	PsA: N = 68 treated with cyclosporine (N =7), MTX (N = 5), salazopyrin (N = 4) and NSAIDs (N = 43) (treatment was not mentioned for other 9 patients)	ELISA	PsA: CXCL10 (S, 269 ± 234 pg/ml)	N.D.	S: CXCL10 in PsA > HC	- S [CXCL10] correlated inversely with disease duration
Muntyanu et al. [28]	PsA OA RA CA	PsA: N = 47 of which S was taken (N = 47) and of which SF was taken (N = 40) (paired samples of SF and S from 11 patients , paired samples of SF cells and blood RNA from 7 patients) OA: N = 14 (only SF) RA: N = 11 (only SF) CA (gout): N = 8 (only SF)	RT-PCR, Multiplex assay	PsA: CXCL10 (S, 0.31 ng/ml [IQR: 0.20 – 0.44 ng/ml])	PsA: CXCL10 (SF, 5.39 ng/ml [IQR: 1.81 – 9.82 ng/ml]) OA: CXCL10 (SF, 0.83 ng/ml [IQR: 0.73 – 3.38 ng/ml]) CA (gout): CXCL10 (SF, 0.97 ng/ml [IQR: 0.80 – 1.48 ng/ml]) PsA: CXCL10 (mRNA of SF cells, 10-fold increased compared to OA, and 36.2-fold increased compared to gout)	S: CXCL10 in PsA > HC SF: CXCL10 in PsA > OA, PsA > gout, PsA = RA PsA: CXCL10 in SF > S in paired samples PsA: CXCL10 mRNA in SF > S in paired samples SF cells: CXCL10 mRNA in PsA = RA, PsA > OA, PsA > CA (gout)	N.D.
Lima et al. [29]	PsA	Active PsA: N = 16 of which patients were treated with systemic therapy (N = 6), MTX (N =1), acitretin (N = 3), prednisolone and leflunomide (N = 2)	ELISA	PsA: CXCL10 (S, 49.8 pg/ml [IQR: 49.2 pg/ml]), CXCL9 (S, 128.1 pg/ml [IQR: 421.9 pg/ml])	N.D.	S: CXCL10 in PsA < HC, PsA < psoriasis without PsA S: CXCL9 in PsA = HC, PsA = psoriasis without PsA	N.D.

Pollock et al. [30]	PsA	Active PsA: N = 20 (discovery cohort, for micro-array and RT-PCR analysis) of which treated with NSAIDs (N = 13), DMARDS (N = 14) and biologics (N = 2) Active PsA: N = 48 (validation cohort, for nCounter analysis) of which treated with NSAIDs (N = 31) and DMARDS (N = 23)	Oligo microarray technology, RT-PCR, nCounter analysis	PsA: CXCL10 (whole-blood, 1.53-fold [micro-array and RT-PCR for discovery cohort] and 1.45-fold [nCounter analysis for validation cohort] increased compared to patients with psoriasis)	N.D.	Whole-blood CXCL10 expression in PsA > psoriasis without PsA	N.D.
König et al. [31]	PsA OA RA	PsA: N = 8 of which untreated (N = 2), treated with solely NSAIDs (N = 3), solely steroids (N = 1), MTX + steroids (N = 1) and NSAIDs + steroids (N = 1) OA: N = 10 (treatment not mentioned) RA: N = 7 of which treated with NSAIDs (N = 1), sulfasalazine (N = 1), sulfasalazine + steroids (N = 1), NSAIDs + steroids (N = 2), NSAIDs + MTX + steroids (N = 1) and NSAIDs + gold + steroids (N = 1)	*In situ* hybridisation with antisense probes	N.D.	PsA: CXCL9 (ST, specific mean/median levels not mentioned) OA: CXCL9 (ST, specific mean/median levels not mentioned) RA: CXCL9 (ST, specific mean/median levels not mentioned)	ST: CXCL9 mRNA in PsA = RA, PsA > OA, RA > OA	N.D.
Antonelli et al. [32]	PsA	PsA: N = 65: PsA with autoimmune thyroid disorder (N = 28) or without autoimmune thyroid disorder (N = 37) Patients were not on immunomodulant treatment	ELISA	PsA with autoimmune thyroid disorder: CXCL10 (S, 351 ± 295 pg/ml) and CXCL9 (S, 117 ± 71 pg/ml) PsA without autoimmune thyroid disorder: CXCL10 (S, 244 ± 168 pg/ml) and CXCL9 (S, 111 ± 65 pg/ml)	N.D.	S: CXCL10 in PsA (with or without autoimmune thyroid disorder) > HC S: CXCL9 in PsA (with or without autoimmune thyroid disorder) = HC	- S [CXCL10] were not associated with any of the clinical features of PsA - S [CXCL10] were not associated with S [CXCL9] - S [CXCL10] was not associated with disease duration

Sucur et al. [33]	RA PsA	RA: N = 129 PsA: N = 53 Patients were treated with NSAIDs, DMARDs, glucocorticoid or biologic treatment A group of RA patients (N = 11) sampled before treatment and 2, 4 and 6 months after treatment with etanercept of adulimumab	Cytometric bead array	RA: CXCL9 and CXCL10 (P; specific mean/median levels not mentioned)	RA: CXCL9 and CXCL10 (SF; specific mean/median levels not mentioned)	P: CXCL10 in RA > HC P: CXCL9 in RA > HC RA: CXCL10 in SF > P	N.D.
Manferdini et al. [34]	OA	OA: N = 20 (treatment was not mentioned)	Multiplex assay	N.D.	OA: CXCL10 (SF, 12239.54 ± 7935.60 pg/ml)	SF: CXCL10 in OA > HC	N.D.
Sohn et al. [35]	OA RA	OA: for which S samples were obtained (N = 24), and for which SF was obtained (N = 12) RA: for which S samples were obtained (N = 23), and for which SF was obtained (N = 14) (treatment not mentioned)	Multiplex assay	OA: CXCL9 (S, 420.13 pg/ml [IQR: 308.4 – 568.6]), CXCL10 (S, 795.55 pg/ml [IQR: 684.7 – 1029.7]) RA: CXCL9 and CXCL10 (S, specific mean/median levels not mentioned)	OA: CXCL9 (SF, 1047.14 pg/ml [IQR: 389.8 – 1925.3]), CXCL10 (S, 2105.40 pg/ml [IQR: 923.2 – 4913.3]) RA: CXCL9 and CXCL10 (SF, specific mean/median levels not mentioned)	S: CXCL9 and CXCL10 in OA > HC OA: CXCL9 and CXCL10 in SF > S	N.D.
Beekhuizen et al. [36]	OA	OA: N = 18 (treatment not mentioned)	Multiplex assay	N.D.	OA: CXCL10: (SF, 710.4 ± 597.1 pg/ml)	SF: CXCL10 in OA > HC	N.D.
Vangsness et al. [37]	OA	OA: N = 12 (treatment not mentioned)	Multiplex assay	N.D.	OA: CXCL10 (SF, specific mean/median levels not mentioned)	N.D.	SF [CXCL10] was increased — but not significantly— in advanced arthritis compared to mild arthritis

Huss et al. [38]	OA	OA undergoing primary TJR (N = 18) and undergoing revision TJR (N = 22) (treatment was not mentioned)	Multiplex	N.D.	OA undergoing primary TJR: CXCL9 (SF, 54 ± 13 pg/ml), CXCL10 (SF, 537 ± 120 pg/ml) OA undergoing revision TJR: CXCL9 (SF, 524 ± 266 pg/ml) and CXCL10 (SF, 4 697 ± 1 990 pg/ml) OA undergoing primary TJR or revision TJR: CXCL9, CXCL10 and CXCL11 (mRNA in synovial NK cells, specific mean/median levels not mentioned)	SF: CXCL10 in OA undergoing primary TJR > OA undergoing revision TJR Synovial NK cells mRNA: CXCL9, CXCL10 and CXCL11 in OA undergoing primary TJR = OA undergoing revision TJR	N.D.
Endres et al. [39]	OA RA	OA: N = 5, which were treated with NSAIDs (N = 3) and not treated (N = 2) RA: N = 5, which were treated with solely DMARDs (N = 1), with solely NSAIDs (N = 1), with DMARDs and steroids (N = 2), and with steroids and NSAIDs (N = 1)	Chemokine antibody membrane array	N.D.	OA: CXCL10 (SF mean intensity, 16.7, ratio OA/RA = 1.0), CXCL9 (SF mean intensity not reported, ratio OA/RA = 1.7), CXCL11 (SF mean intensity not reported, ratio OA/RA = 1.3) RA: CXCL10 (SF mean intensity, 16.2) HC: CXCL10 (SF mean intensity, 21.1)	SF: CXCL10 in OA = RA = HC (moderate expression in OA, RA and HC SF)	N.D.
Yoshida et al. [40]	RA OA	OA: N = 5 RA: N = 11 (treatment was not mentioned)	Laser micro-dissection and cDNA micro-array analysis	N.D.	CXCL9 (ST, 5.924 fold-change increase in RA compared to OA), CXCL10 (ST, 3.388 fold-change increase in RA compare to OA)	ST: CXCL9: RA > OA ST: CXCL10: RA > OA	N.D.
Proost et al. [41]	OA SA	OA: N = 27 SA: N = 13 (treatment was not mentioned)	ELISA	N.D.	SA: CXCL10 (SF, 81 ng/ml) OA: CXCL10 (SF, specific mean/median levels not mentioned)	SF CXCL10 in SA > OA	SF [CXCL10] did not significantly correlated with SF [CXCL8] in OA and SA
Proost et al. [42]	OA SA CA	OA: N = 28 SA: N = 13 CA: N = 27 (treatment was not mentioned)	ELISA	N.D.	OA, SA, CA: CXCL9 and CXCL11 (SF, specific mean/median levels not mentioned)	SF: CXCL9 in SA > OA, SA > CA, OA = CA SF: CXCL11 in SA > OA, SA > CA, OA = CA SF of SA: CXCL9 > CXCL11	N.D.

AS, Ankylosing Spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; CA, crystal-induced arthritis including gout and pseudo-gout; CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; CI, confidence interval; CRP, C-reactive protein; CXCL, CXC chemokine ligand; DAS28, disease activity score in 28 joints; DMARDs, disease-modifying anti-rheumatic drugs; ELISA; enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HC, healthy control; IFN, interferon; Ig, immunoglobulin; IQR, interquartile range; JIA, juvenile idiopathic arthritis; MPS, methylprednisolone; MTX, methotrexate;

N.D., not determined; N.P., not published; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; oligoJIA, oligoarticular JIA; OR, odds ratio; P, plasma; PB, peripheral blood; PBMC, peripheral blood mononuclear cells; polyJIA: polyarticular JIA; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, Rheumatoid factor; RT-PCR, real time polymerase chain reaction; S, serum; SA, septic arthritis; sCD163, soluble CD163; SD, standard deviation; SF, synovial fluid; SJC, swollen joint counts; SpA, spondyloarthritis; ST, synovial tissue; TJC, tender joint counts; TJI, traumatic joint injury; TJR, total joint replacement; TNFα, tumor necrosis factor α; y, years.

SUPPLEMENTARY TABLE 2 | Overview of studies investigating the IFN-inducible CXCR3 ligands in juvenile idiopathic arthritis and adult-onset Still's disease.

Study	Diseases	Disease: number of included subjects (treatment)	Technique for substrate detection	CXCR3 ligand in serum (S) or plasma (P) (mean ± SD or median with [IQR])	CXCR3 ligand in synovial fluid (SF) or synovial tissue (ST) (mean ± SD or median with [IQR])	Disease vs. control population	Correlation with disease activity markers of arthritis
Pharoah et al. [43]	JIA	JIA: N = 50 of which oligoJIA (N = 37) treated with prednisolone (N = 2) , NSAIDs (N = 31), and MTX (N = 11) polyJIA (N = 13) treated with prednisolone (N = 1) , NSAIDs (N = 11), and MTX (N = 8)	RT-PCR, Multiplex assay	JIA: CXCL10 (P, 1297 ± 1148 pg/ml)	JIA: CXCL10 (SF, 6451 ± 3174 pg/ml) [N = 14] JIA: CXCL10 mRNA (SFMC, SF T cells, PBMC, PB T cells, N.P)	P: CXCL10 in JIA P > HC P & SF: CXCL10 in JIA SF > JIA paired P samples mRNA: CXCL10 in JIA T cells of SF > T cells of PB	N.D.
Brescia et al. [44]	JIA	JIA: oligoJIA (N = 10) of which treated with with naproxen (N = 6), MTX and naproxen (N = 1), doxycycline and naproxen (N = 1) or not treated (N = 2) Patients with TJI or hip/skeletal dysplasia having non-arthritic joints undergoing orthopedic procedures (N = 8) and all patients were not treated	Antibody array	N.D.	JIA: CXCL9 and CXCL10 (SF, N.P.) Patients with TJI or dysplasia: CXCL9 and CXCL10 (SF, N.P.)	SF: CXCL9 and CXCL10 in JIA > patients with TJI or dysplasia	N.D.
de Jager et al. [45]	JIA	JIA: N = 65 oligoJIA (N = 30) of which P (N = 30) and SF (N = 19) samples were obtained polyJIA (N = 15) of which P (N = 15) and SF (N = 6) samples were obtained sJIA (N = 20) of which P (N = 20) and SF (N = 9) samples were obtained Patients were treated with NSAIDs, MTX, corticosteroids or anti-TNFα treatment	Multiplex assay	oligoJIA: IFN-γ (P, active disease: 201 ± 100 pg/ml, remission: 102 ± 594 pg/ml), CXCL9 (P, active disease: 127 ± 54 pg/ml, remission: 34 ± 29 pg/ml), CXCL10 (P, active disease: 828 ± 216 pg/ml, remission: 171 ± 65 pg/ml) polyJIA: IFN-γ (P, active disease: 534 ± 242 pg/ml, remission: 89 ± 39 pg/ml), CXCL9 (P, active disease: 102 ± 50 pg/ml, remission: 22 ± 11 pg/ml), CXCL10 (P, active disease: 442 ± 120 pg/ml, remission: 289 ± 119 pg/ml)	oligoJIA: IFN-γ (SF, 176 ± 77 pg/ml), CXCL9 (SF, 2817 ± 844 pg/ml), CXCL10 (SF, 4001 ± 959 pg/ml) polyJIA: IFN-γ (SF, 163 ± 82 pg/ml), CXCL9 (SF, 2266 ± 123.7 pg/ml), CXCL10 (SF, 5128 ± 1759 pg/ml) sJIA: IFN-γ (SF, 171 ± 132 pg/ml), CXCL9 (SF, 85 ± 19 pg/ml), CXCL10 (SF, 2772 ± 1443 pg/ml)	P: CXCL9 & CXCL10 in JIA active disease > JIA remission in sJIA, oligoJIA and polyJIA P: IFN-γ in JIA active disease = JIA remission in sJIA, oligoJIA and polyJIA P: CXCL9 & CXCL10 in JIA active disease in sJIA, oligoJIA and polyJIA > HC	N.D.

de Jager et al. [45]				sJIA: IFN-γ (P, active disease: 101 ± 296 pg/ml, remission: 54 ± 34 pg/ml), CXCL9 (P, active disease: 41 ± 24 pg/ml, remission: 1.8 ± 0.9 pg/ml), CXCL10 (P, active disease: 137 ± 45 pg/ml, remission: 70 ± 29 pg/ml)		P: IFN-γ: JIA active disease in sJIA, oligoJIA and polyJIA = HC P: IFN-γ & CXCL9 & CXCL10 in JIA remission in sJIA, oligoJIA and polyJIA = HC P & SF: CXCL9 & CXCL10 in SF > paired P samples in sJIA, oligoJIA and polyJIA P & SF: IFN-γ in SF = paired P samples in sJIA, oligoJIA and polyJIA P: CXCL9 in oligoJIA = sJIA, CXCL10 in oligoJIA > sJIA	
Hunter et al. [46]	JIA	JIA: OligoJIA (N = 32) with persistent oligoJIA (N = 21) and *extended-to-be** oligoJIA (N = 11) and none of the patients were treated	Microarray	N.D.	SFMC mRNA CXCL9 (3.0-fold increased in extended-to-be oligoJIA compared persistent oligoJIA) SFMC mRNA IFN-γ (1.7-fold increased in extended-to-be oligoJIA compared persistent oligoJIA)	SFMC: mRNA of CXCL9 and IFN-γ in extended-to-be oligoJIA > persistent oligoJIA	N.D.
Schmidt et al. [47]	JIA	JIA: untreated oligoJIA (N = 13)	RT-PCR	Peripheral blood monocytes: CXCL10 and CXCL11 mRNA (specific levels not mentioned)	Synovial monocytes: CXCL10 and CXCL11 mRNA (specific levels not mentioned)	Monocytes: mRNA of CXCL11 and CXCL10 in synovial monocytes (more than 2-fold increased) > PB monocytes	N.D.
Aggarwal et al. [48]	JIA	JIA: polyJIA (N = 12) treated with NSAIDS (N = 12) and ERA (other JIA form; N = 11) treated with NSAIDs (N = 11) and MTX (N = 4) and sJIA (N = 9; treatment not mentioned)	ELISA	ERA: CXCL10 (S, 139 pg/ml) polyJIA: N.D. sJIA: N.D.	ERA: CXCL10 (SF, 2300 pg/ml) polyJIA: N.D. sJIA: N.D.	S: CXCL10 in ERA > HC S & SF: CXCL10 in SF > paired S samples in ERA	N.D.

Sikora et al. [49]	JIA	JIA: active sJIA without MAS (N = 12) and active extended oligoJIA (N = 9) (treatment was not mentioned)	RT-PCR	N.D.	ST mRNA CXCL9 (15.8-fold less in sJIA compared to extended oligoJIA) ST mRNA CXCL10 (4.5-fold less in sJIA compared to extended oligoJIA) ST mRNA CXCL11 (3.6-fold less in sJIA compared to extended oligoJIA)	ST: mRNA of CXCL9, CXCL10 and CXCL11 in sJIA < extended oligoJIA	N.D.
Bracaglia et al. [50]	JIA HLH	JIA: sJIA (N = 83) of which sJIA with MAS (N = 20; N = 7 were not treated and N = 13 were treated with glucocorticoids, cyclosporin A, anakinra or cyclophosphamide) and active sJIA without MAS (N = 28; treatment not specified) and inactive sJIA (N = 35; treatment not specified) HLH: secondary HLH (N = 11) of which patients received glucocorticoids, cyclosporin A, anakinra or cyclophosphamide treatment (N =5) and were not treated (N = 6)	Multiplex assay	sJIA with MAS: IFN-γ (S, 15.4 pg/ml [IQR: 5.1 – 52.6]), CXCL9 (S, 13392 pg/ml [IQR: 2163 – 35452]), CXCL10 (S, 1612 pg/ml [IQR: 425 – 4309]) and CXCL11 (S, 565 pg/ml [IQR: 198 – 1007]) active sJIA without MAS: IFN-γ (S, 4.9 pg/ml [IQR: 3.2 – 8.6]), CXCL9 (S, 837 pg/ml [IQR: 471 – 2505]), CXCL10 (S, 307 pg/ml [IQR: 199 – 694]) and CXCL11 (S, 122 pg/ml [IQR: 62 – 197]) inactive sJIA: IFN-γ (S, 4.2 pg/ml [IQR: 3.2 – 9.3]), CXCL9 (S, 901 pg/ml [IQR: 466 – 1213]), CXCL10 (S, 235 [IQR: 172 – 407]) and CXCL11 (S, 111 pg/ml [IQR: 63 – 187])	N.D.	S: IFN-γ, CXCL9, CXCL10 and CXCL11 in sJIA with MAS > active sJIA without MAS S: IFN-γ, CXCL9, CXCL10 and CXCL11 in active sJIA without MAS = inactive sJIA	- ↓ S [IFN-γ], [CXCL9], [CXCL10] and [CXCL11] upon resolution of MAS in active sJIA - S [IFN-γ] and [CXCL9] correlated with S [ferritin] levels, neutrophil count, platelet count, S [ALT] levels and S [LDH] levels in MAS - S [CXCL10] correlated with S [ferritin] levels, neutrophil count, platelet count, S [ALT] levels and S [LDH] levels in MAS - S [CXCL11] correlated with S [ferritin] levels and S [LDH] levels in MAS - S [IFN-γ] correlated with S [CXCL9] and S [CXCL10]

Put et al. [51]	JIA HLH	JIA: sJIA (N = 23) inactive sJIA (N = 10; all 10 patients were treated with NSAIDS, canakinumab, tocilizumab, cyclosporine or MTX), active sJIA without MAS (N= 10; N = 3 were not treated, N = 7 were treated with NSAIDS, canakinumab, cyclosporine, MTX), active sJIA with MAS (N = 3) which were all treated with tocilizumab, NSAID, MTX HLH (N = 2) of which EBV-associated HLH (N = 1) and primary HLH (N = 1) and both were not treated	ELISA	inactive sJIA: CXCL10 and IFN-γ (P, specific mean/median levels not mentioned) active sJIA with MAS: CXCL10 (P, specific mean/median levels not mentioned) sJIA with MAS or patients with another HLH form: CXCL10 and IFN-γ (P, specific mean/median levels not mentioned)	N.D.	P: IFN-γ, CXCL10 in MAS or other HLH form > inactive sJIA P: IFN-γ, CXCL10 in MAS or other HLH form > HC	N.D.
Gattorno et al. [52]	JIA	JIA: active sJIA without MAS (N = 16) which were treated (N = 16) with corticosteroids, etanercept, infliximab, NSAIDS, MTX, azathioprine, cyclosporine A or thalidomide (prior to treatment with anakinra)	Multiplex assay	Active sJIA: CXCL10 and IFN-γ (S, specific mean/median levels not mentioned)	N.D.	S: CXCL10 and IFN-γ in active sJIA > HC	N.D.
Quartier et al. [53]	JIA	JIA: active sJIA (N = 24) sampled before anakinra treatment (N = 24; patient were on corticosteroids and NSAIDS but not on immunosuppressive drugs or DMARDs), 1 month treated with anakinra (N = 12) and 6 months treated with anakinra (N = 24)	Multiplex NGS for gene expression profiling using Illumina	Active sJIA before and after 6 months of treatment with anakinra: CXCL10 (S, specific mean/median levels not mentioned) Active sJIA before and after 1 and 6 months of treatment with anakinra: CXCL10 (gene expression in PBMCs)	N.D.	S: CXCL10 in anakinra-treated sJIA patients for 6 months > paired S samples of active sJIA patients before treatment with anakinra Gene expression in PBMCs in CXCL10: anakinra-treated patients for 1 month or 6 months > before treatment (irrespective of clinical response to anakinra)	N.D.

Qu et al. [54]	JIA	JIA: sJIA (N = 21) of which active sJIA without MAS (N = 14; of which not treated [N = 3]) and inactive sJIA (N = 16; of which not treated [N = 3]) [9 paired samples sampled at active and inactive disease] Other patients (N = 11 of active sJIA group and N = 13 of inactive sJIA group) were treated with canakinumab, adalimumab, tocilizumab, MTX, corticosteroids, etanercept or anakinra	Multiplex assay	Active sJIA and inactive sJIA: CXCL9, CXCL10 and CXCL11 (P, specific mean/median levels not mentioned)	N.D.	P: CXCL11 in active sJIA > HC P: CXCL11 in active sJIA > inactive sJIA	N.D.
Hinze et al. [55]	JIA	JIA: active sJIA without MAS at initial sampling (N = 54) of which treated with MTX (N = 23), glucocorticoids (N = 32), and biologicals: adalimumab (N = 6), anakinra (N = 21), etanercept (N = 8), tocilizumab (N = 12) at initial sampling	Bead array assay	Active sJIA without MAS at initial sampling: CXCL9, CXCL10 (S, specific mean/median levels not mentioned) Active sJIA that developed MAS during study of 21.1 months: CXCL9 (S, 286 pg/ml [IQR: 2.74 - 292]) Active sJIA that did not develop MAS during study of 21.1 month: CXCL9 (S, 11 pg/ml [IQR: 1.64 – 217])	N.D.	S: [CXCL9] in active sJIA without MAS > HC S: [CXCL10] in active sJIA without MAS > HC S: [CXCL9] in active sJIA that developed MAS during study of 21.1 months > active sJIA that did not develop MAS S: [CXCL10] in active sJIA without MAS after 3 days of treatment with canakinumab < active sJIA without MAS before treatment with canakinumab	N.D.

Han et al. [56]	RA AOSD	RA: N = 32: all treated with glucocorticoids and MTX (N = 21) or sulfasalazine (N = 4) or leflunomide (N = 6) or adalimumab (N = 1) Active AOSD: N = 39: initial stage, untreated (N = 30) and treated but in disease flare (N = 9) of which treated with MTX and glucocorticosteroids (N = 5), with azathioprine and glucocorticosteroids (N = 1) or discontinued with medication (N = 3) The patients with active AOSD had arthritis (N = 24) and MAS (N = 5)	ELISA	RA: CXCL10 (S, 146.3 ± 91.4 pg/ml) Active AOSD: CXCL10 (S, 1031.3 ± 2019.6 pg/ml)	N.D.	S : [CXCL10] in active AOSD > RA S : [CXCL10] in RA > HC S: CXCL10: active AOSD > HC S: CXCL10 in active AOSD with MAS = active AOSD without MAS	- S [CXCL10] in active AOSD corelated with S [ferritin] levels , systemic disease scores, S [CXCL13] levels and S [AST] levels - S [CXCL10] ↓ in AOSD patients upon reduction of the disease activity during follow-up (after 9.6 months ± 9.2 months) - change in S [CXCL10] during follow-up was positively correlated with the change in systemic score
Han et al. [57]	RA AOSD	RA: N = 30 (treatment not mentioned) Active AOSD sampled at an initial untreated stage (N = 39) and samples after treatment with corticosteroids and immunosuppressive agents (N = 16) Patients with active AOSD and MAS (N = 4) and patients with active AOSD and arthritis (N = 21)	ELISA	RA: IFN-γ (S, 27.7 ± 21.4 pg/ml), CXCL9 (S, 64.7 ± 51.5 pg/ml), CXCL10 (S, 55.6 ± 28.4 pg/ml), CXCL11 (S, 56.2 ± 64.0 pg/ml) Active AOSD: IFN-γ (S, 50.5 ± 34.4 pg/ml), CXCL9 (S, 595.6 ± 790.8 pg/mL), CXCL10 (S, 229.5 ± 188.1 pg/ml), CXCL11 (S, 211.9 ± 204.5 pg/ml)	N.D.	S : IFN-γ in AOSD > RA, AOSD > HC, RA > HC S : CXCL9 in AOSD > RA, AOSD > HC, RA = HC S : CXCL10 in AOSD > RA, AOSD > HC, RA > HC S : CXCL11 in AOSD > RA, AOSD > HC, RA = HC	- ↓ S [CXCL9], [CXCL10], [CXCL11] in AOSD after treatment with corticosteroids and immunosuppressive drugs compared to before treatment - S [CXCL9] in AOSD correlated with S levels of CRP, ferritin, LDH, systemic scores - S [CXCL10] in AOSD correlated with S levels of ESR, CRP, ferritin, LDH, systemic scores - S [CXCL11] in AOSD correlated with S levels of CRP, ferritin and systemic scores

Kasama et al. [58]	AOSD	AOSD: active AOSD (N = 17) which were sampled before treatment and after treatment with glucocorticosteroids, immunosuppressants (cyclosporin A, MTX, cyclophosphamide) or intravenous immunoglobin Some patients had MAS (N = 4)	ELISA	AOSD: CXCL10 (S, 2032.2 ± 2500.8 pg/ml)	N.D.	S: CXCL10 in active AOSD > HC	S [CXCL10] in active AOSD after treatment did not significantly ↓
Kim et al. [59]	AOSD	AOSD: active AOSD (N = 48) but S samples were obtained from 8 patients (treatment was not mentioned)	ELISA	Active AOSD: CXCL10 (S, 920.3 ± 1463.9 pg/ml)	N.D.	N.D.	- S [CXCL10] in AOSD did not correlate with percentage of inflammatory cells expressing CXCL10 in the lymph node

*_extended-to-be_ oligoarticular JIA: children who were studied at a time when the disease was still limited to ≤ 4 joints but whose oligoarthritis extended to a more severe phenotype by 1 year of follow-up

ALT, alanine aminotransferase; AOSD, adult-onset Still's disease; AST, aspartate aminotransferase; CRP, C-reactive protein; CXCL, CXC chemokine ligand; EBV, Epstein-Barr virus; ELISA; enzyme-linked immunosorbent assay; ERA; enthesitis-related arthritis; ESR, erythrocyte sedimentation rate; HC, healthy control; HLH, haemophagocytic lymphohistiocytosis; IFN, interferon; IQR, interquartile range; JIA, juvenile idiopathic arthritis; LDH, lactate dehydrogenase; MAS, Macrophage Activation Syndrome; MTX, methotrexate; N.D., not determined; NGS, Next-Generation Sequencing; N.P., not published; NSAIDs, non-steroidal anti-inflammatory drugs; oligoJIA, oligoarticular JIA; P, plasma; PB, peripheral blood; PBMC, peripheral blood mononuclear cells; polyJIA, polyarticular JIA; RA, rheumatoid arthritis; RT-PCR, real time polymerase chain reaction; S, serum; SD, standard deviation; SF, synovial fluid; SFMC, synovial fluid mononuclear cells; sJIA, systemic JIA; ST, synovial tissue; TJI, traumatic joint injury; TNFα, tumor necrosis factor α.

SUPPLEMENTARY TABLE 3 | Studies investigating targeted knock-out of CXCR3 in rodent models of arthritis.

Model	Animal + injection	Intervention	Outcome	Reference
CAIA	C57BL/6 mice + IV injection of type II collagen Ab (5 mg) + IP injection of LPS (100 µg) 3 days after	$CXCR3^{-/-}$	↓ arthritis score ↓ paw swelling ↓ eroded surface per total bone surface in joints ↓ histologic scores of joint damage and inflammation ↓ synovial infiltration of $F4/80^{+}$ macrophages and $CD4^{+}$ T cells ↓ serum osteoclastogenic cytokines: RANKL, TNF-α, IL-6 ↓ mRNA expression of RANKL, TNF-α, IL-6 in spleens No mRNA expression of CXCL10 in serum and spleen ↓ bone destruction: ↓ serum CTX levels ↓ cartilage damage: ↑ safranin O-stained cartilage proteoglycan ↓ activation of osteoclasts (↓ number of $TRAP^{+}$ cells) *compared to WT animals	[60]
CIA	C57BL/6 mouse + s.c. injection of chicken type II collagen and CFA and boosted after 21 days	$CXCR3^{-/-}$	↓ incidence of CIA development ↓ clinical score by 43-51% at day 28-33 post-immunization	[61]
		IV injection of Cr^{51}-labeled T_{H1} cells from $CXCR3^{-/-}$ mice and WT mice into WT mice with CIA (1 - 4 × 10^6 cells, IV injection)	= recruitment to the joints of T_{H1} cells from $CXCR3^{-/-}$ mice as those of WT mice ↓ recruitment to LNs of T_{H1} cells of $CXCR3^{-/-}$ mice compared to those of WT mice	
K/BxN serum transfer arthritis	C57BL/6 mice + IP injection of 150 µl serum of K/BxN mice on day 0 and day 2	$CXCR3^{-/-}$	= ankle thickening compared to WT mice	[62]
AA	Lewis rat + s.c. injection of 0.5 mg of killed *M. butyricum* in 50 µl mineral oil	IV injection of Cr^{51}-labeled $CXCR3^{+}$ T cells or $CXCR3^{-}$ T cells (isolated from spleen of Lewis rats and separated using positive selection via magnetic beads separation into $CXCR3^{+}$ and $CXCR3^{-}$ T cells)	↑ recruitment of $CXCR3^{+}$ T cells to inflamed joints > $CXCR3^{-}$ T cells	[63]
CIOA	Ly5.1 ($CD45.1^{+}$) and Ly5.2 ($CD45.2^{+}$) C57BL/6 mice + intra-articular injection of 10 U/ 10 µl of bacterial collagenase of *Clostridium histolyticum*	$CXCR3^{-/-}$ (B6.129P2-Cxcr3tm1Dgen/J)	↓ cell numbers of NK cells and macrophages in the synovial fluid ↓ relative proportions of NK cells and macrophages in synovial fluid ↓ histological joint score ↓ CD69 expression of synovial NK cells ↑ safranin O-stained cartilage proteoglycan No accumulation of activated $TRAP^{+}$ osteoclasts (instead activated osteoblast were present) ↓ cartilage abnormalities (positive for Alizarin S red stain) *compared to WT mice	[64]

AA, rat adjuvant arthritis; Ab, antibodies; CAIA, type II collagen antibody-induced arthritis; CIA, type II collagen-induced arthritis; CIOA, collagenase-induced osteoarthritis; CFA, Complete Freund's adjuvant; CTX, C-terminal telopeptides of type I collagen; IL, interleukin; IP, intraperitoneal; IV, intravenous; LNs, lymph nodes; LPS, lipopolysaccharides; NK, natural killer; RANKL, Receptor activator of nuclear factor kappa-B ligand; s.c., subcutaneous; TNF-α, tumor necrosis factor α; TRAP, Tartrate-resistant acid phosphatase; WT, wild-type.

SUPPLEMENTARY TABLE 4 | Studies investigating selective CXCR3 antagonists, CXCR3 agonists and CXCR3 targeting antibodies in rodent models of arthritis.

Model	Animal + injection	Drug administered (name molecule [dose]; administration route and dosing regimen)	Outcome	Reference
CIA	DBA/1 mice + intradermal injection of chicken type II collagen (2 mg/ml) in CFA containing 2 mg/ml *M. tuberculosis*	Small-molecule CXCR3 antagonist (JN-2 [8 mg/kg]; IP injection twice every week after boosting)	↓ clinical disease score from week 3 onwards ↓ paw swelling ↓ bone erosion ↓ histopathological scores of joint inflammation, pannus formation and cartilage damage ↓ mRNA expression of TNF-α, IL-6, TNFSF11 in spleen ↓ serum RANKL, TNF-α, IL-6 *compared to untreated mice	[65]
CIA	B10.RIII mice + intradermal injection of bovine type II collagen (300 µg) in 0.5 mg/ml CFA containing *M. tuberculosis*	Small-molecule non-competitive CXCR3 antagonist (SCH 546738 [at 40 mg/kg BW or 10 mg/kg BW]; oral administered, twice daily)	↓ disease score at 40 mg/kg BW and 10 mg/kg BW doses of SCH 546738 at day 7 and 9 after boost with bovine collagen type II ↓ leukocyte infiltration in joint at 40 mg/kg BW ↓ structural damage to the bone and cartilage at 40 mg/kg BW ↓ total histopathological scores at 40 mg/kg BW	[66]
CIA	DBA/1 J mice + intradermal injection of bovine type II collagen (100 µg) in 2 mg/ml CFA	Small-molecule non-competitive CXCR3 antagonist (AMG 487 [5 mg/kg]; IP injection every 48h for 20 days)	↓ clinical arthritis scores ↓ paw edema ↓ histological joint inflammation and damage ↓ % of $CXCR3^+$ $T\text{-}bet^+$ splenic cells ↓ % of IL-17 producing $CXCR3^+$ and $CD4^+$ splenic cells ↓ % of $ROR\gamma T^+$ $CXCR3^+$ and $CD4^+$ splenic cells ↓ % of $STAT3^+$ $CD4^+$ splenic cells ↓ % of IL-22 producing $CXCR3^+$ splenic cells ↑ % of IL-10 producing $CXCR3^+$ and $CD4^+$ splenic cells ↑ % of $Foxp3^+$ $CXCR3^+$ and $CD4^+$ splenic cells ↓ mRNA and protein levels of CXCR3, T-bet, IL-17A, RORγT and IL-22 in knee tissue ↓ mRNA expression of STAT3 in knee tissue ↑ mRNA and protein levels of Foxp3 and IL-10 in knee tissue	[67]
			↓ % of NFκB p65-, NOS2-, MCP-1-, IFN-γ- and TNF-α- producing $CD19^+$ B cells in spleen ↑ % of IL-4- and IL-27-producing $CD19^+$ B cells in spleen ↓ mRNA and protein expression of NFκB p65, NOS2, IFN-γ and TNF-α in knee tissue ↑ mRNA and protein expression IL-4 and IL-27 in knee tissue	[68]
			↓ % of $GITR^+$ $CD25^+$, $GITR^+$ $CD45^+$, $GITR^+$ $IL\text{-}9^+$ and $GITR^+$ $NFκB^+$ splenic lymphocytes ↓ % of $CD45^+$ $CD4^+$ and $CD45^+$ $CCR6^+$ splenic lymphocytes ↓ % of $CD45^+$ $IL\text{-}6^+$, $CD45^+$ $IL\text{-}17A^+$ and $CD45^+$ $IL\text{-}21^+$ splenic lymphocytes ↑ % of $GITR^+$ $Foxp3^+$ cells and $GITR^+$ $STAT6^+$ cells ↓ mRNA and protein expression of CD4, CCR6, IL-6, IL-9, IL-21 and GITR in knee tissue	[69]

CIA	DBA/1 mice + intradermal injection of bovine type II collagen (200 µg) in CFA containing *M. tuberculosis*	Small molecule CXCR3/CCR5/CCR2 antagonist (TAK-779 [150 µg TAK-779 in 100 µl of a 5% mannitol solution]; s.c. injection every 48h)	↓ incidence of CIA development ↓ arthritic index ↓ leukocyte infiltration in the joint = plasma levels of anti-collagen Ab = levels of CCR5 mRNA in splenic and LN T cells *compared to vehicle-treated mice	[70]
Humanized mouse air-pouch model	NSG mice + IP injection of 10^7 human PBMC in 0.5 ml PBS	Small-molecule CXCR3 agonist (PS372424 [1 µM in blood]; IV injection, administered once 24h before cell migration to the pouch was evaluated)	↓ migration of human $CD45^+$ cells towards the pouch filled with 1 ml PBS containing 5 µg of CXCL11 or CCL5 or CXCL12 compared to vehicle-treated mice ↓ migration of human $CD45^+$ cells towards the pouch filled with 1 ml PBS containing 5 µg of SF compared to vehicle-treated mice ↓ MFI CXCR3 and CCR5 on splenic human T cells	[71]
		Small-molecule CXCR3 antagonist (NBI-74330 [100 mg/kg]; IV injection, administered once 24h before cell migration to the pouch was evaluated)	= migration of human $CD45^+$ cells towards the pouch filled with 1 ml PBS containing 5 µg of CCL5 compared to vehicle-treated mice = migration of human $CD45^+$ cells towards the pouch filled with 1 ml PBS containing 5 µg of SF compared to vehicle-treated mice	
		CXCR3 neutralizing antibody [25 µg] (IV injection, administered once 24h before cell migration to the pouch was evaluated)	= migration of human $CD45^+$ cells towards the pouch filled with 1 ml PBS containing 5 µg of SF compared to vehicle-treated mice	
AA	Lewis rat + s.c. injection of 0.5 mg of killed *M. butyricum* in 50 µl mineral oil	IV injection of Cr^{51}-labeled $CXCR3^+$ T cells or $CXCR3^-$ T cells (isolated from spleen of Lewis rats and separated using positive selection via magnetic beads separation into $CXCR3^+$ and $CXCR3^-$ T cells)	↑ recruitment of $CXCR3^+$ T cells to inflamed joints > $CXCR3^-$ T cells	[63]
		IV injection of T lymphoblasts ($1\text{-}2 \times 10^7$ cells) from *in vivo* Ag-stimulated LNs labeled with Ci of $Na_2{}^{51}CrO_4$ or Ci ^{111}In-oxine in rats treated CXCR3 mAb (XR3.2 [2 mg]; IV injected immediately before injection of labeled T cells)	↓ recruitment of T cells to inflamed joints by 42%-87% (dependent on the respective joint) compared to untreated rats	
		IV injection of *in vitro mycobacterial* Ag-activated LN T cells ($1\text{-}2 \times 10^7$ cells) labeled with Ci of $Na_2{}^{51}CrO_4$ or Ci ^{111}In-oxine in rats treated CXCR3 mAb (XR3.2 [2 mg]; IV injected immediately before injection of labeled T cells)	↓ recruitment of T cells to synovial tissue by 66% compared to untreated rats	

AA adoptive T cell transfer (IV injection of 4×10^7 splenic or LN lymphocytes per 100 g of BW) to naïve animals	CXCR3 mAb (XR3.2 [2 mg]; IP injected every 48h on the day of the lymphocyte transfer up to 6 or 10 days after cell transfer [plasma concentration 35-70 µg/ml])	delayed onset of arthritis ↓ carpal, talar and tail joint clinical disease score ↓ of > 50% in total clinical score ↓ weight loss ↓ average weight of joint tissues ↑ safranin O-stained cartilage proteoglycan ↓ observed joint infiltration of leukocytes via histology ↓ synovial infiltration of ^{111}In-oxine-labeled IV injected neutrophils (injected on day 9 post transfer) by 50-60% *compared to untreated animals	[63]

AA, rat adjuvant arthritis; Ab, antibodies; BW, body weight; CCR, CC chemokine receptor; CFA, Complete Freund's adjuvant; CIA, type II collagen-induced arthritis; CXCR, CXC chemokine receptor; Foxp3, forkhead box P3; GITR, glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein; IFN, interferon; IL, interleukin;In^{111}-oxine, indium oxine; IP, intraperitoneal; IV, intravenous; LNs, lymph nodes; mAb, monoclonal antibody; MCP-1/CCL2, monocyte chemotactic protein-1; *M. butyricum, Mycobacterium butyricum*; *M. tuberculosis*, *Mycobacterium tuberculosis*; NFκB, nuclear factor kappa B; NOS2, nitric oxide synthase 2; NSG mice; NOD *scid* gamma mice (NOD.Cg-$Prkdc^{scid}$ $Il2rgtm1^{Wjl/SzJ}$ strain) bearing two mutations on the NOD/ShiLtJ background: severe combined immune deficiency (*scid*) and a null allele of the IL-2 receptor common gamma chain ($IL2rg^{null}$); PBMC, peripheral blood mononuclear cells; RANKL, Receptor activator of nulear factor kappa-B ligand; RORγT, retinoic acid-related orphan receptor γT; s.c., subcutaneous; STAT, signal transducer and activator; T-bet, T-box transcription factor; TNF-α, tumor necrosis factor α; TNFSF11, Tumor necrosis factor ligand superfamily member 11 which encodes for RANKL; WT, wild-type.

SUPPLEMENTARY TABLE 5 | Studies investigating CXCL10-targeting therapies in rodent models of arthritis.

Model	Animal + injection	Intervention	Outcome	Reference
AA	Lewis rat + s.c. injection of CFA (1 mg *M. tuberculosis* H37Ra in 0.1 ml oil)	Naked DNA vaccine encoding for rat CXCL10 (100 µg in PBS, injected in tibia's anterior muscle, administered every 7 days, 1 month before induction of active AA)	↑ titer of anti-CXCL10 Ab before onset of disease ↓ clinical disease score during acute and early chronic phase ↓ paw swelling ↓ histological joint damage: ↓ synovial mononuclear cell infiltrate, ↓ thickness of synovial lining, ↓ joint space narrowing, ↓ periosteal new bone formation	[72]
		Self-specific anti-CXCL10 Ab isolated from DNA-vaccinated rats with AA (administered 2 days after the onset of AA, given every 48h [dose and route of administration not mentioned])	↓ clinical disease score *In vivo* polarization of LN $CD4^+$ T cells into low IFN-γ and TNF-α and high IL-4 producing cells	
		Naked DNA vaccine encoding for rat CXCL10 (500 µg in PBS, injected in tibia's anterior muscle, administered every 7 days, on day 2, 4 and 7 after the onset of disease)	↓ clinical disease score ↑ titer of anti-CXCL10 Ab No histological joint damage: no cartilage loss, bone erosion or periosteal new bone formation	
CIA	DBA/1 mice + intradermal injection of type II collagen in CFA containing 2 mg/ml *M. tuberculosis*	Anti-CXCL10 mAb (200 µg, IV injection into the tail vein, once at day 14 after the first immunization, at the same time as the booster injection of type II collagen was given)	↓ synovial infiltration of $F4/80^+$ macrophages and $CD4^+$ T cells ↓ bone destruction determined by histology and micro-CT scans ↓ serum cytokines: RANKL, TNF-α *compared to untreated animals	[73]
None (healthy mice)	ICR mice	Retrovirus encoding CXCL10 (50 µl [dose not mentioned], injected in the tibial metaphyses, once a week for 6 weeks)	↑ bone erosion compared to mice injected with control retrovirus	
CAIA	C57BL/6 mice + IV injection of type II collagen Ab (5 mg) + IP injection of LPS (100 µg) 3 days after	$CXCL10^{-/-}$	↓ arthritis score ↓ paw swelling ↓ eroded surface per total bone surface in joints ↓ histologic scores of joint damage and inflammation ↓ synovial infiltration of $F4/80^+$ macrophages and $CD4^+$ T cells ↓ serum osteoclastogenic cytokines: RANKL, TNF-α, IL-6 ↓ mRNA expression of RANKL, TNF-α, IL-6 in spleens ↓ bone destruction: ↓ serum CTX levels ↓ cartilage damage: ↑ safranin O-stained cartilage proteoglycan ↓ activation of osteoclasts (↓ number of $TRAP^+$ cells) *compared to WT animals	[60]

hTNF-Tg	Tg197 hTNF-Tg mouse	TNF-α and CXCL10 targeting BsAb which was generated by conjugating a single-chain variable fragment of anti-CXCL10 mAb [E10] to the Fc region of adalimumab (6.9 μM, supracalvarial injection, treated daily for 5 days)	↓ arthritis score and histopathological score compared to untreated animals = arthritis and histopathological compared to adalimumab-treated animals ↓ human TNF-α, mouse IL-1β and mouse IL-10 compared to adalimumab-treated animals	[74]
LPS-induced bone erosion	C57BL/6 mice + calvarial injection of 12.5 mg/kg LPS		↓ bone resorption compared to vehicle-treated group (similar bone resorption in adalimumab-treated group compared to vehicle-treated group)	
K/BxN serum transfer	C57BL/6 mice + serum transfer of K/BxN mice on day 0 and day 2		↓ ankle swelling ↓ leukocyte infiltration in the synovium ↓ cartilage damage and bone destruction ↓ activation of osteoclasts (↓ number of $TRAP^+$ cells) compared to vehicle-treated group = ankle swelling = leukocyte infiltration in the synovium = cartilage damage and bone destruction = activation of osteoclasts (= number of $TRAP^+$ cells) compared to adalimumab-treated group	
PTA	C57BL/6 mice + received moderate fractures of the left tibial plateau	None	↑ mRNA of CXCL10 in synovial tissue post-fracture compared to pre-fracture ↑ mRNA of CXCL10 in synovial tissue post-fracture compared to MRL/MpJ mice who are protected from PTA	[75]
DIO that develop posttraumatic arthritis	Sprague Dawley rats + high fat/high sucrose diet	None	↑ serum CXCL10 compared to mice on low-fat diet CXCL10 SF levels in collateral limbs were associated with arthritis score (Modified Mankin score)	[76]

AA, rat adjuvant arthritis; Ab, antibodies; BsAb, bispecific antibody; CAIA, type II collagen antibody-induced arthritis; CFA, Complete Freund's adjuvant; CIA, type II collagen-induced arthritis; CTX, C-terminal telopeptides of type I collagen; DIO, Diet-induced obesity; hTNF-Tg, transgenic mouse that overexpresses human TNF-α; ICR, Institute of Cancer Research; IFN, interferon; IL, interleukin; IP, intraperitoneal; IV, intravenous; LNs, lymph nodes; LPS, lipopolysaccharides; mAb, monoclonal antibody;,micro-CT, microfocal computed tomography; MRL/MpJ, Murphy Roths Large; *M. tuberculosis*, *Mycobacterium tuberculosis*; PTA, post-traumatic arthritis; RANKL, Receptor activator of nuclear factor kappa-B ligand; s.c., subcutaneous; SF, synovial fluid; Tg, transgenic; TNF-α, tumor necrosis factor α; TRAP, Tartrate-resistant acid phosphatase; WT, wild-type.

REFERENCES

1. Patel DD, Zachariah JP, Whichard LP. CXCR3 and CCR5 Ligands in Rheumatoid Arthritis Synovium. Clin Immunol. 2001;98(1):39–45. doi: https://doi.org/10.1006/clim.2000.4957
2. Hanaoka R, Kasama T, Muramatsu M, Yajima N, Shiozawa F, Miwa Y, et al. A novel mechanism for the regulation of IFN-γ inducible protein-10 expression in rheumatoid arthritis. Arthritis Res Ther. 2003;5(2):74–81. doi: https://doi.org/10.1186/ar616
3. Lee EY, Seo MR, Juhnn YS, Kim JY, Hong YJ, Lee YJ, et al. Potential role and mechanism of IFN-gamma inducible protein-10 on receptor activator of nuclear factor kappa-B ligand (RANKL) expression in rheumatoid arthritis. Arthritis Res Ther. 2011;13(3):R104. doi: https://doi.org/10.1186/ar3385
4. Kuan WP, Tam L shan, Wong C kwok, Ko FWS, Li T, Zhu T, et al. CXCL9 and CXCL10 as Sensitive Markers of Disease Activity in Patients with Rheumatoid Arthritis. J Rheumatol. 2010;37(2):257–64. doi: https://doi.org/10.3899/jrheum.090769
5. Pandya JM, Lundell AC, Andersson K, Nordström I, Theander E, Rudin A. Blood chemokine profile in untreated early rheumatoid arthritis: CXCL10 as a disease activity marker. Arthritis Res Ther. 2017;19(1):20. doi: https://doi.org/10.1186/s13075-017-1224-1
6. Ruschpler P, Lorenz P, Eichler W, Koczan D, Hänel C, Scholz R, et al. High CXCR3 expression in synovial mast cells associated with CXCL9 and CXCL10 expression in inflammatory synovial tissues of patients with rheumatoid arthritis. Arthritis Res Ther. 2003;5(5):241–52. doi: https://doi.org/10.1186/ar783
7. Muhsin HY, Kadri ZHM, Ad'hiah AH, Mayouf KZ. Predictive significance of CXCL8, CXCL10 and CXCL16 in juvenile idiopathic and rheumatoid arthritis Iraqi patients. Egypt Rheumatol. 2020;42(2):153–7. doi: https://doi.org/10.1016/j.ejr.2019.06.002
8. Ichikawa T, Kageyama Y, Kobayashi H, Kato N, Tsujimura K, Koide Y. Etanercept treatment reduces the serum levels of interleukin-15 and interferon-gamma inducible protein-10 in patients with rheumatoid arthritis. Rheumatol Int. 2010;30(6):725–30. doi: https://doi.org/10.1007/s00296-009-1356-y
9. Kokkonen H, Söderström I, Rocklöv J, Hallmans G, Lejon K, Dahlqvist SR. Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. Arthritis Rheum. 2010;62(2):383–91. doi: https://doi.org/10.1002/art.27186
10. Ueno A, Yamamura M, Iwahashi M, Okamoto A, Aita T, Ogawa N, et al. The production of CXCR3-agonistic chemokines by synovial fibroblasts from patients with rheumatoid arthritis. Rheumatol Int. 2005;25(5):361–7. doi: https://doi.org/10.1007/s00296-004-0449-x
11. Imam AM, Hamed AM, Nasef SI, Hassan AM, Omar HH. Biochemical Analysis of C-X-C Motif Chemokine Ligand 10 (CXCL10) as a Biomarker in Patients with Rheumatoid Arthritis. Egypt J Immunol. 2019;26(2):79–86.
12. Lande R, Giacomini E, Serafini B, Rosicarelli B, Sebastiani GD, Minisola G, et al. Characterization and Recruitment of Plasmacytoid Dendritic Cells in Synovial Fluid and Tissue of Patients with Chronic Inflammatory Arthritis. J Immunol. 2004;173(4):2815–24. doi: https://doi.org/10.4049/jimmunol.173.4.2815
13. Han BK, Kuzin I, Gaughan JP, Olsen NJ, Bottaro A. Baseline CXCL10 and CXCL13 levels are predictive biomarkers for tumor necrosis factor inhibitor therapy in patients with moderate to severe rheumatoid arthritis: A pilot, prospective study. Arthritis Res Ther. 2016;18(93). doi: https://doi.org/10.1186/s13075-016-0995-0
14. Schmutz C, Hulme A, Burman A, Salmon M, Ashton B, Buckley C, et al. Chemokine receptors in the rheumatoid synovium: upregulation of CXCR5. Arthritis Res Ther. 2005;7(2):217–29. doi: https://doi.org/10.1186/ar1475
15. Jude C, Dejica D, Samasca G, Balacescu L, Balacescu O. Soluble CD163 serum levels are elevated and correlated with IL-12 and CXCL10 in patients with long-standing rheumatoid arthritis. Rheumatol Int. 2013;33(4):1031–7. doi: https://doi.org/10.1007/s00296-012-2459-4
16. Aldridge J, Ekwall AKH, Mark L, Bergström B, Andersson K, Gjertsson I, et al. T helper cells in synovial fluid of patients with rheumatoid arthritis primarily have a Th1 and a CXCR3+ Th2 phenotype. Arthritis Res Ther. 2020;22(1):245. doi: https://doi.org/10.1186/s13075-020-02349-y
17. Tsubaki T, Takegawa S, Hanamoto H, Arita N, Kamogawa J, Yamamoto H, et al. Accumulation of plasma cells expressing CXCR3 in the synovial sublining regions of early rheumatoid arthritis in association with production of Mig/CXCL9 by synovial fibroblasts. Clin Exp Immunol. 2005;141(2):363–71. doi: https://doi.org/10.1111/j.1365-2249.2005.02850.x
18. Nakayama T, Yoshimura M, Higashioka K, Miyawaki K, Ota Y, Ayano M, et al. Type 1 helper T cells generate CXCL9/10-producing T-bet+ effector B cells potentially involved in the pathogenesis of rheumatoid arthritis. Cell Immunol. 2021;360:104263. doi: https://doi.org/10.1016/j.cellimm.2020.104263
19. Hueber W, Tomooka BH, Zhao X, Kidd BA, Drijfhout JW, Fries JF, et al. Proteomic analysis of secreted proteins in early rheumatoid arthritis: anti-citrulline autoreactivity is associated with upregulation of proinflammatory cytokines. Ann Rheum Dis. 2007;66(6):712–9. doi: https://doi.org/10.1136/ard.2006.054924
20. Proost P, Struyf S, Loos T, Gouwy M, Schutyser E, Conings R, et al. Coexpression and interaction of CXCL10 and CD26 in mesenchymal cells by synergising inflammatory cytokines: CXCL8 and CXCL10 are discriminative markers for autoimmune arthropathies. Arthritis Res Ther. 2006;8(4):R107. doi: https://doi.org/10.1186/ar1997
21. Loos T, Dekeyzer L, Struyf S, Schutyser E, Gijsbers K, Gouwy M, et al. TLR ligands and cytokines induce CXCR3 ligands in endothelial cells: Enhanced CXCL9 in autoimmune arthritis. Lab Investig. 2006;86(9):902–16. doi: https://doi.org/10.1038/labinvest.3700453
22. Wang J, Zhao Q, Wang G, Yang C, Xu Y, Li Y, et al. Circulating levels of Th1 and Th2 chemokines in patients with ankylosing spondylitis. Cytokine. 2016;81:10–4. doi: https://doi.org/10.1016/j.cyto.2016.01.012
23. Duftner C, Dejaco C, Kullich W, Klauser A, Goldberger C, Falkenbach A, et al. Preferential type 1 chemokine receptors and cytokine production of CD28- T cells in ankylosing spondylitis. Ann Rheum Dis. 2006;65(5):647–53. doi: https://doi.org/10.1136/ard.2005.042085

24. Erdem H, Pay S, Musabak U, Simsek I, Dinc A, Pekel A, et al. Synovial angiostatic non-ELR CXC chemokines in inflammatory arthritides: Does CXCL4 designate chronicity of synovitis? Rheumatol Int. 2007;27(10):969–73. doi: https://doi.org/10.1007/s00296-007-0317-6
25. Röhner E, Matziolis G, Perka C, Füchtmeier B, Gaber T, Gerd-Rüdiger Burmester FB, et al. Inflammatory synovial fluid microenvironment drives primary human chondrocytes to actively take part in inflammatory joint diseases. Immunol Res. 2012;52(3):169–75. doi: https://doi.org/10.1007/s12026-011-8247-5
26. Abji F, Pollock RA, Liang K, Chandran V, Gladman DD. Brief Report: CXCL10 Is a Possible Biomarker for the Development of Psoriatic Arthritis Among Patients With Psoriasis. Arthritis Rheumatol. 2016;68(12):2911–6. doi: https://doi.org/10.1002/art.39800
27. Antonelli A, Fallahi P, Sedie AD, Ferrari SM, Maccheroni M, Bombardieri S, et al. High values of Th1 (CXCL10) and Th2 (CCL2) chemokines in patients with psoriatic arthtritis. Clin Exp Rheumatol. 2009;27(1):22–7.
28. Muntyanu A, Abji F, Liang K, Pollock RA, Chandran V, Gladman DD. Differential gene and protein expression of chemokines and cytokines in synovial fluid of patients with arthritis. Arthritis Res Ther. 2016;18(1):296. doi: https://doi.org/10.1186/s13075-016-1196-6
29. Lima XT, Oliveira RTD, Braga FG, Magalhães RF, Mamoni RL, Blotta MHSL. Circulating levels of chemokines in psoriasis. Autoimmunity. 2015;48(1):57–60. doi: https://doi.org/10.3109/08916934.2014.947476
30. Pollock RA, Abji F, Liang K, Chandran V, Pellett FJ, Virtanen C, et al. Gene expression differences between psoriasis patients with and without inflammatory arthritis. J Invest Dermatol. 2015;135(2):620–3. doi: https://doi.org/10.1038/jid.2014.414
31. König A, Krenn V, Toksoy A, Gerhard N, Gillitzer R. Mig, GROα and RANTES messenger RNA expression in lining layer, infiltrates and different leucocyte populations of synovial tissue from patients with rheumatoid arthritis, psoriatic arthritis and osteoarthritis. Virchows Arch. 2000;436(5):449–58. doi: https://doi.org/10.1007/s004280050472
32. Antonelli A, Fallahi P, Sedie AD, Ferrari SM, Maccheroni M, Bombardieri S, et al. High values of alpha (CXCL10) and beta (CCL2) circulating chemokines in patients with psoriatic arthritis, in presence or absence of autoimmune thyroiditis. Autoimmunity. 2008;41(7):537–42. doi: https://doi.org/10.1080/08916930802170401
33. Sucur A, Jajic Z, Artukovic M, Matijasevic MI, Anic B, Flegar D, et al. Chemokine signals are crucial for enhanced homing and differentiation of circulating osteoclast progenitor cells. Arthritis Res Ther. 2017;19(1):142. doi: https://doi.org/10.1186/s13075-017-1337-6
34. Manferdini C, Paolella F, Gabusi E, Cattini L, Rojewski M, Schrezenmeier H, et al. Osteoarthritic Milieu Affects Adipose-Derived Mesenchymal Stromal Cells. J Orthop Res. 2020;38(2):336–47. doi: https://doi.org/10.1002/jor.24446
35. Sohn DH, Sokolove J, Sharpe O, Erhart JC, Chandra PE, Lahey LJ, et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. Arthritis Res Ther. 2012;14(1):R7. doi: https://doi.org/10.1186/ar3555
36. Beekhuizen M, Gierman LM, van Spil WE, Van Osch GJVM, Huizinga TWJ, Saris DBF, et al. An explorative study comparing levels of soluble mediators in control and osteoarthritic synovial fluid. Osteoarthr Cartil. 2013;21(7):918–22. doi: https://doi.org/10.1016/j.joca.2013.04.002
37. Thomas Vangsness J, Burke WS, Narvy SJ, MacPhee RD, Fedenko AN. Human knee synovial fluid cytokines correlated with grade of knee osteoarthritis - a pilot study. Bull NYU Hosp Jt Dis. 2011;69(2):122–7.
38. Huss RS, Huddleston JI, Goodman SB, Butcher EC, Zabel BA. Synovial tissue-infiltrating natural killer cells in osteoarthritis and periprosthetic inflammation. Arthritis Rheum. 2010;62(12):3799–805. doi: https://doi.org/10.1002/art.27751.
39. Endres M, Andreas K, Kalwitz G, Freymann U, Neumann K, Ringe J, et al. Chemokine profile of synovial fluid from normal, osteoarthritis and rheumatoid arthritis patients: CCL25, CXCL10 and XCL1 recruit human subchondral mesenchymal progenitor cells. Osteoarthr Cartil. 2010;18(11):1458–66. doi: https://doi.org/10.1016/j.joca.2010.08.003
40. Yoshida S, Arakawa F, Higuchi F, Ishibashi Y, Goto M, Sugita Y, et al. Gene expression analysis of rheumatoid arthritis synovial lining regions by cDNA microarray combined with laser microdissection: Up-regulation of inflammation-associated STAT1, IRF1, CXCL9, CXCL10, and CCL5. Scand J Rheumatol. 2012;41(3):170–9. doi: https://doi.org/10.3109/03009742.2011.623137
41. Proost P, Vynckier AK, Mahieu F, Put W, Grillet B, Struyf S, et al. Microbial Toll-like receptor ligands differentially regulate CXCL10/IP-10 expression in fibroblasts and mononuclear leukocytes in synergy with IFN-γ and provide a mechanism for enhanced synovial chemokine levels in septic arthritis. Eur J Immunol. 2003;33(11):3146–53. doi: https://doi.org/10.1002/eji.200324136
42. Proost P, Verpoest S, De Borne K Van, Schutyser E, Struyf S, Put W, et al. Synergistic induction of CXCL9 and CXCL11 by Toll-like receptor ligands and interferon-γ in fibroblasts correlates with elevated levels of CXCR3 ligands in septic arthritis synovial fluids. J Leukoc Biol. 2004;75(5):777–84. doi: https://doi.org/10.1189/jlb.1003524
43. Pharoah DS, Varsani H, Tatham RW, Newton KR, Jager W De, Prakken BJ, et al. Expression of the inflammatory chemokines CCL5, CCL3 and CXCL10 in juvenile idiopathic arthritis, and demonstration of CCL5 production by an atypical subset of CD8+ T cells. Arthritis Res Ther. 2006;8(2):R50. doi: https://doi.org/10.1186/ar1913
44. Brescia AMC, Simonds MM, Sullivan KE, Rose CD. Secretion of pro-inflammatory cytokines and chemokines and loss of regulatory signals by fibroblast-like synoviocytes in juvenile idiopathic arthritis. Proteomics Clin Appl. 2017;11(5–6):1600088. doi: https://doi.org/10.1002/prca.201600088
45. De Jager W, Hoppenreijs EPAH, Wulffraat NM, Wedderburn LR, Kuis W, Prakken BJ. Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study. Ann Rheum Dis. 2007;66(5):589–98. doi: https://doi.org/10.1136/ard.2006.061853
46. Hunter PJ, Nistala K, Jina N, Eddaoudi A, Thomson W, Hubank M, et al. Biologic predictors of extension of oligoarticular juvenile idiopathic arthritis as determined from synovial fluid cellular composition and gene expression. Arthritis Rheum. 2010;62(3):896–907. doi: https://doi.org/10.1002/art.27284
47. Schmidt T, Berthold E, Arve-Butler S, Gullstrand B, Mossberg A, Kahn F, et al. Children with oligoarticular juvenile

idiopathic arthritis have skewed synovial monocyte polarization pattern with functional impairment - a distinct inflammatory pattern for oligoarticular juvenile arthritis. Arthritis Res Ther. 2020;22(1):186. doi: https://doi.org/10.1186/s13075-020-02279-9
48. Aggarwal A, Agarwal S, Misra R. Chemokine and chemokine receptor analysis reveals elevated interferon-inducible protein-10 (IP)-10/CXCL10 levels and increased number of CCR5+ and CXCR3+ CD4 T cells in synovial fluid of patients with enthesitis-related arthritis (ERA). Clin Exp Immunol. 2007;148(3):515–9. doi: https://doi.org/10.1111/j.1365-2249.2007.03377.x
49. Sikora KA, Fall N, Thornton S, Grom AA. The Limited Role of Interferon-γ in Systemic Juvenile Idiopathic Arthritis Cannot Be Explained by Cellular Hyporesponsiveness. Arthritis Rheum. 2012;64(11):3799–808. doi: https://doi.org/10.1002/art.34604.
50. Bracaglia C, Graaf K De, Marafon DP, Guilhot F, Ferlin W, Prencipe G, et al. Elevated circulating levels of interferon-γ and interferon-γ-induced chemokines characterise patients with macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Ann Rheum Dis. 2017;76(1):166–72. doi: https://doi.org/10.1136/annrheumdis-2015-209020
51. Put K, Avau A, Brisse E, Mitera T, Proost P, Bader-meunier B, et al. Cytokines in systemic juvenile idiopathic arthritis and haemophagocytic lymphohistiocytosis: tipping the balance between interleukin-18 and interferon-γ. Rheumatology. 2015;54(8):1507–17. doi: https://doi.org/10.1093/rheumatology/keu524
52. Gattorno M, Piccini A, Lasiglië D, Tassi S, Brisca G, Carta S, et al. The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2008;58(5):1505–15. doi: https://doi.org/10.1002/art.23437
53. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011;70(5):747–54. doi: https://doi.org/10.1136/ard.2010.134254
54. Qu H, Sundberg E, Aulin C, Neog M, Palmblad K, Horne AC, et al. Immunoprofiling of active and inactive systemic juvenile idiopathic arthritis reveals distinct biomarkers: a single-center study. Pediatr Rheumatol. 2021;19(1):173. doi: https://doi.org/10.1186/s12969-021-00660-9.
55. Hinze T, Kessel C, Hinze CH, Seibert J, Gram H, Foell D. A dysregulated interleukin-18-interferon-γ-CXCL9 axis impacts treatment response to canakinumab in systemic juvenile idiopathic arthritis. Rheumatol. 2021;60(11):5165–74. doi: https://doi.org/10.1093/rheumatology/keab113
56. Han JH, Suh C hee, Jung J yang, Nam J young, Kwon JE, Yim H, et al. Association of CXCL10 and CXCL13 levels with disease activity and cutaneous manifestation in active adult-onset Still's disease. Arthritis Res Ther. 2015;17(1):260. doi: https://doi.org/10.1186/s13075-015-0773-4
57. Han JH, Suh C hee, Jung J yang, Ahn M hyun, Han MH, Kwon JE. Elevated circulating levels of the interferon-γ-induced chemokines are associated with disease activity and cutaneous manifestations in adult-onset Still's disease. Sci Rep. 2017;7(46652). doi: https://doi.org/10.1038/srep46652
58. Kasama T, Furuya H, Yanai R. Correlation of serum CX3CL1 level with disease activity in adult-onset Still's disease and significant involvement in hemophagocytic syndrome. Clin Rheumatol. 2012;31(5):853–60. doi: https://doi.org/10.1007/s10067-012-1952-1
59. Kim HA, Kim YH, Jeon YK, Yang WI, Kwon JE, Han JH. Histopathology and expression of the chemokines CXCL10, CXCL13, and CXCR3 and the endogenous TLR-4 ligand S100A8/A9 in lymph nodes of patients with adult-onset Still's disease. Sci Rep. 2019;9(1):7517. doi: https://doi.org/10.1038/s41598-019-44032-6
60. Lee JH, Kim B, Jin WJ, Kim HH, Ha H, Lee ZH. Pathogenic roles of CXCL10 signaling through CXCR3 and TLR4 in macrophages and T cells: relevance for arthritis. Arthritis Res Ther. 2017;19(1):163. doi: https://doi.org/10.1186/s13075-017-1353-6
61. Al-Banna NA, Vaci M, Slauenwhite D, Johnston B, Issekutz TB. CCR4 and CXCR3 play different roles in the migration of T cells to inflammation in skin, arthritic joints, and lymph nodes. Eur J Immunol. 2014;44(6):1633–43. doi: https://doi.org/10.1002/eji.201343995
62. Jacobs JP, Ortiz-Lopez A, Campbell JJ, Gerard CJ, Mathis D, Christophe B. Deficiency of CXCR2, but not of other chemokine receptors attenuates a murine model of autoantibody-mediated arthritis. Arthritis Rheum. 2010;62(7):1921–32. doi: https://doi.org/10.1002/art.27470.
63. Mohan K, Issekutz TB. Blockade of Chemokine Receptor CXCR3 Inhibits T Cell Recruitment to Inflamed Joints and Decreases the Severity of Adjuvant Arthritis. J Immunol. 2007;179(12):8463–9. doi: https://doi.org/10.4049/jimmunol.179.12.8463
64. Benigni G, Dimitrova P, Antonangeli F, Sanseviero E, Milanova V, Blom A, et al. CXCR3/CXCL10 Axis Regulates Neutrophil–NK Cell Cross-Talk Determining the Severity of Experimental Osteoarthritis. J Immunol. 2017;198(5):2115–24. doi: https://doi.org/10.4049/jimmunol.1601359
65. Kim B, Lee JH, Jin WJ, Kim HH, Ha H, Lee ZH. JN-2, a C-X-C motif chemokine receptor 3 antagonist, ameliorates arthritis progression in an animal model. Eur J Pharmacol. 2018;823:1–10. doi: https://doi.org/10.1016/j.ejphar.2018.01.037
66. Jenh CH, Cox MA, Cui L, Reich EP, Sullivan L, Chen SC, et al. A selective and potent CXCR3 antagonist SCH 546738 attenuates the development of autoimmune diseases and delays graft rejection. BMC Immunol. 2012;13(1):2. doi: https://doi.org/10.1186/1471-2172-13-2
67. Bakheet SA, Ansari MA, Nadeem A, Attia SM, Alhoshani AR, Gul G, et al. CXCR3 antagonist AMG487 suppresses rheumatoid arthritis pathogenesis and progression by shifting the Th17/Treg cell balance. Cell Signal. 2019;64:109395. doi: https://doi.org/10.1016/j.cellsig.2019.109395
68. Bakheet SA, Alrwashied BS, Ansari MA, Nadeem A, Attia SM, Alanazi MM, et al. CXC chemokine receptor 3 antagonist AMG487 shows potent anti-arthritic effects on collagen-induced arthritis by modifying B cell inflammatory profile. Immunol Lett. 2020;225:74–81. doi: https://doi.org/10.1016/j.imlet.2020.06.014
69. Bakheet SA, Alrwashied BS, Ansari MA, Nadeem A, Attia SM, Assiri MA, et al. CXCR3 antagonist AMG487 inhibits

glucocorticoid-induced tumor necrosis factor-receptor-related protein and inflammatory mediators in CD45 expressing cells in collagen-induced arthritis mouse model. Int Immunopharmacol. 2020;84:106494. doi: https://doi.org/10.1016/j.intimp.2020.106494
70. Yang YF, Mukai T, Gao P, Yamaguchi N, Ono S, Iwaki H, et al. A non-peptide CCR5 antagonist inhibits collagen-induced arthritis by modulating T cell migration without affecting anti-collagen T cell responses. Eur J Immunol. 2002;32(8):2124–32. doi: https://doi.org/10.1002/1521-4141(200208)32:8<2124::AID-IMMU2124>3.0.CO;2-S
71. O'Boyle G, Fox CRJ, Walden HR, Willet JDP, Mavin ER, Hine DW, et al. Chemokine receptor CXCR3 agonist prevents human T-cell migration in a humanized model of arthritic inflammation. Proc Natl Acad Sci U S A. 2012;109(12):4598–603. doi: https://doi.org/10.1073/pnas.1118104109
72. Salomon I, Netzer N, Wildbaum G, Schif-Zuck S, Maor G, Karin N. Targeting the Function of IFN-γ-Inducible Protein 10 Suppresses Ongoing Adjuvant Arthritis. J Immunol. 2002;169(5):2685–93. doi: https://doi.org/10.4049/jimmunol.169.5.2685
73. Kwak HB, Ha H, Kim HN, Lee JH, Hun SK, Lee S, et al. Reciprocal cross-talk between RANKL and interferon-γ-inducible protein 10 is responsible for bone-erosive experimental arthritis. Arthritis Rheum. 2008;58(5):1332–42. doi: https://doi.org/10.1002/art.23372
74. Kang SE, Park JK, Yoo HJ, Kang H soo, Park YW, Park BC, et al. Efficacy of novel bispecific antibody targeting TNF-α/CXCL10 in the treatment of experimental arthritis. Transl Res. 2021;232:75–87. doi: https://doi.org/10.1016/j.trsl.2021.01.004
75. Furman BD, Kent CL, Huebner JL, Kraus VB, McNulty AL, Farshid G, et al. CXCL10 is Upregulated in Synovium and Cartilage following Articular Fracture. J orthop. 2018;36(4):1220–7. doi: https://doi.org/10.1002/jor.23735.CXCL10
76. Collins KH, Reimer RA, Seerattan RA, Leonard TR, Herzog W. Using diet-induced obesity to understand a metabolic subtype of osteoarthritis in rats. Osteoarthr Cartil. 2015;23(6):957–65. doi: https://doi.org/10.1016/j.joca.2015.01.015