SpArking Conversations

Decoding the IL-17 Link: Pathogenic Inflammation in SpA

Tuesday, 14th May 2024

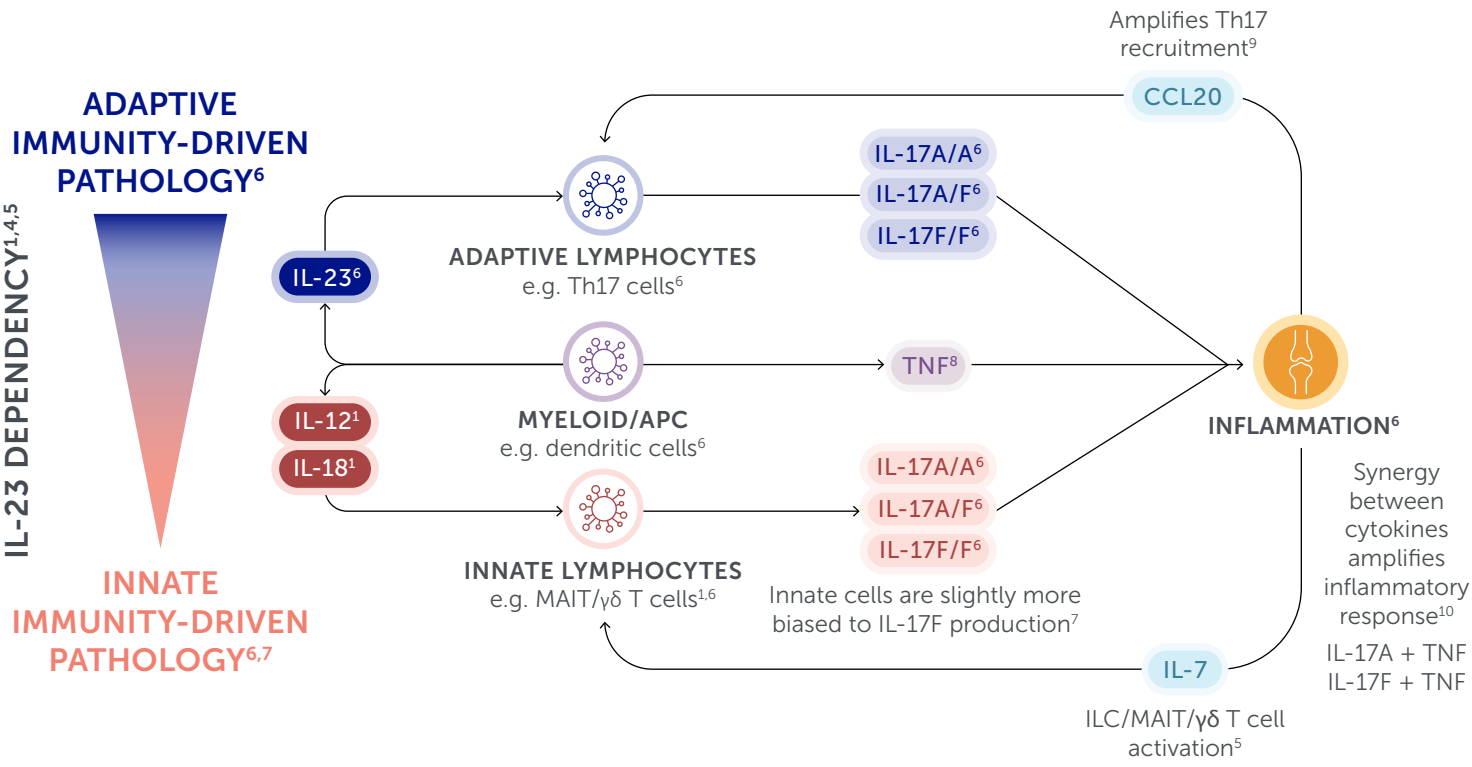
Prof Dennis McGonagle and
Prof Lars Erik Kristensen

SpA Pathobiology is Complex...

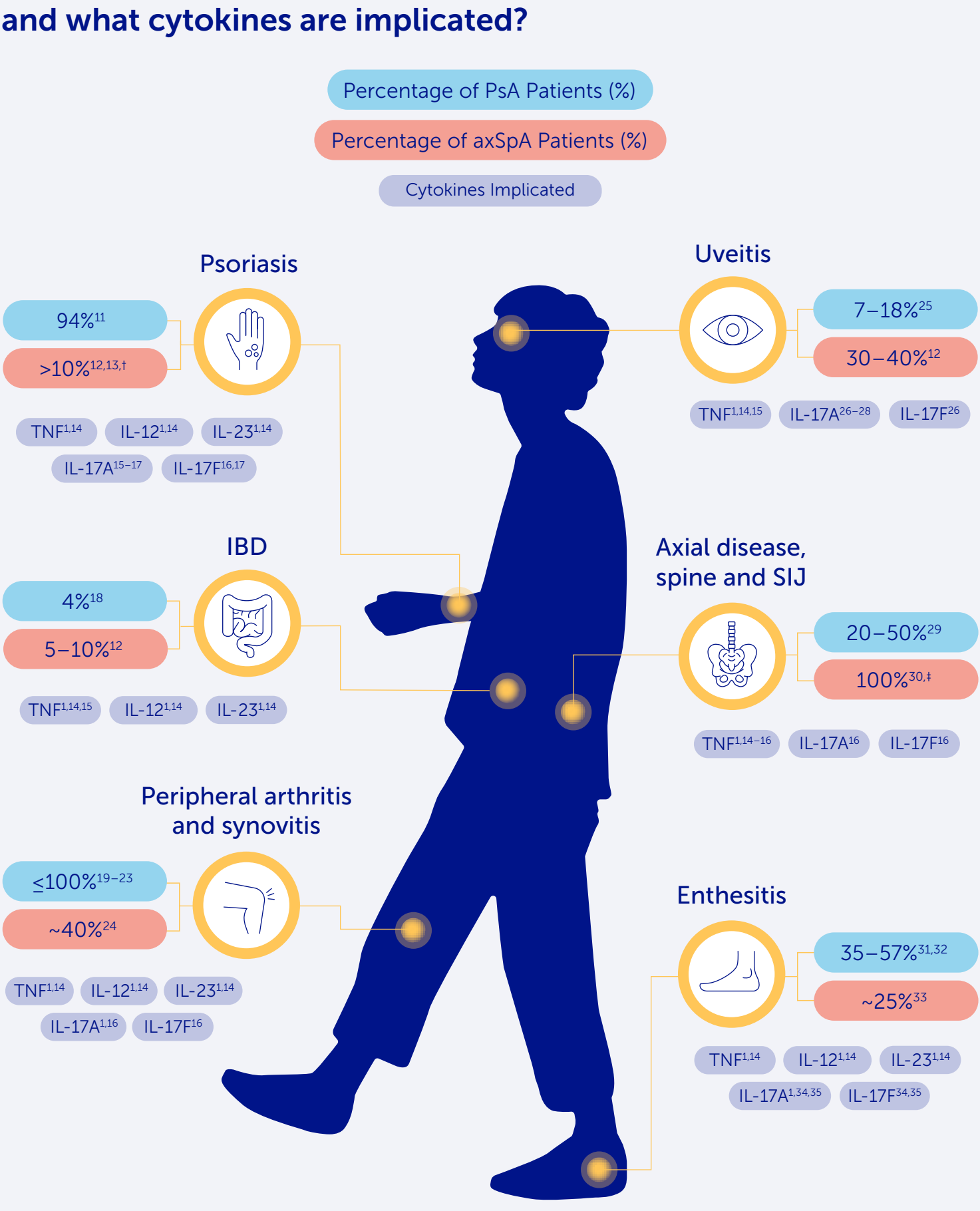
There are **many clinically validated targets** involved in spondyloarthritis pathobiology, including:[1,2]

TNF[1] | IL-12[1,*] | IL-23[1,*] | IL-17[1] | JAK/STAT[2]

Emerging studies are revealing a **new dimension of complexity in the IL-17 pathway** that may help explain its *in vivo* functions[3]



How prevalent are the manifestations associated with SpA, and what cytokines are implicated?



Patients with axSpA and PsA have **overlapping disease manifestations**[11–13,18–25,29–33]

Several clinically validated targets in spondyloarthritis have an important role in the underlying pathobiology of these manifestations, including **IL-17A** and **IL-17F**[1,2,14–17,26–28,34,35]

Abbreviations: APC: antigen-presenting cell; axSpA: axial spondyloarthritis; CCL20: C-C motif chemokine ligand 20; DESIR: DEvenir des Spondylarthropathies Indifférenciées Récentes; IBD: inflammatory bowel disease; IL: interleukin; ILC: innate lymphoid cell; JAK: Janus kinase; MAIT: mucosal-associated invariant T cell; PsA: psoriatic arthritis; SIJ: sacroiliac joint; SpA: spondyloarthritis; STAT: signal transducer and activator of transcription; TNF: tumour necrosis factor; γδ T: gamma delta T cell.

Footnotes: *Validated for PsA but not for axSpA.[1] †The DESIR cohort of 589 adult patients with recent inflammatory back pain suggestive of axSpA reported the prevalence of psoriasis as 26.8% at 6 years from baseline.[13] ‡axSpA is characterised by ectopic bone formation.[30]

References: 1. McGonagle D et al. Front Immunol. 2021;12:614255. 2. Hammitzsch A et al. Front Immunol. 2020;11:591176. 3. Li X et al. Nat Immunol. 2019;20(12):1594–1602. 4. McGonagle DG et al. Ann Rheum Dis. 2019;78(9):1167–1178. 5. Rosine N, Miceli-Richard C. Front Immunol. 2021;11:553742. 6. Tsukazaki H, Kaito T. Int J Mol Sci. 2020;21(17):6401. 7. Cole S et al. Front Immunol. 2020;11:585134. 8. Blanco P et al. Cytokine Growth Factor Rev. 2008;19(1):41–52. 9. Russell T et al. Cells. 2021;10(2):341. 10. Glatt S et al. Ann Rheum Dis. 2018;77(4):523–532. 11. Kane D et al. Rheumatology (Oxford). 2003;42(12):1460–1468. 12. Taurog JD et al. N Engl J Med. 2016;374(26):2563–2574. 13. Lucasson F et al. RMD Open. 2022;8(1):e001986. 14. Coates LC et al. Nat Rev Rheumatol. 2022;18(8):465–479. 15. Ramiro S et al. Ann Rheum Dis. 2023;82(1):19–34. 16. Adapted from Yeremenko N. Curr Opin Rheumatol. 2021;33(4):333–340. 17. Kolbinger F et al. J Allergy Clin Immunol. 2017;139(3):923–932.e8. 18. Williamson L et al. J Rheumatol. 2004;31:1469–1470. 19. Moll JMH and Wright V. Semin Arthritis Rheum. 1973;3(1):55–78. 20. Torre Alonso JC et al. Br J Rheumatol. 1991;30:245–250. 21. Helliwell PS and Taylor WJ. Ann Rheum Dis. 2005;64(Suppl 2):ii3–ii8. 22. Gladman DD. Ann Rheum Dis. 2006;65(Suppl 3):iii22–iii24. 23. Acosta Felquer ML and FitzGerald O. Clin Exp Rheumatol. 2015;33(5 Suppl 93):S26–S30. 24. López-Medina C et al. Arthritis Res Ther. 2019;21(1):139. 25. Chen H and Chou C. Curr Rheumatol Rev. 2008;4:111–114. 26. Huang JC et al. Ocul Immunol Inflamm. 2021;29(3):558–565. 27. Lin P et al. Ophthalmology. 2014;121(1):365–376. 28. Weinstein JE, Pepple KL. Curr Opin Ophthalmol. 2018;29(3):267–274. 29. McGagh D and Coates LC. Rheumatology (Oxford). 2020;59:i29–i36. 30. Klavdianou K et al. Mediterr J Rheumatol. 2022;33(Suppl 1):115–125. 31. Kaeley GS et al. Semin Arthritis Rheum. 2018;48(1):35–43. 32. D'Agostino MA et al. Arthritis Rheum. 2003;48(2):523–533. 33. Mease PJ et al. ACR Open Rheumatol. 2020;2(7):449–456. 34. Mandour M et al. Front Immunol. 2021;12:618581. 35. McDermott N et al. Ann Rheum Dis. 2023;82(Suppl 1):1184. Abstract AB0011.

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Inspired by patients. Driven by science.

Decoding the IL-17 Link: Pathogenic Inflammation in SpA

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SpArking Conversations

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IL: interleukin; SpA: spondyloarthritis.

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IIT: Investigator Initiated Trial.

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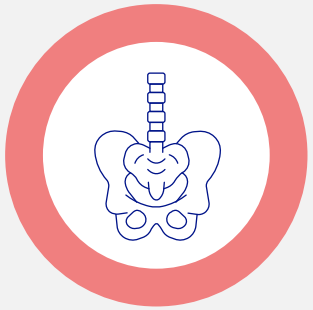
Pathogenic Inflammation in SpA and the IL-17 Family

Professor Lars Erik Kristensen

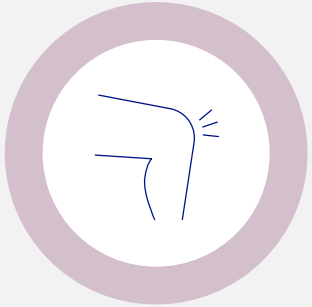
axSpA and PsA Have Overlapping Inflammatory Pathways and Disease Manifestations[1–9]

Musculoskeletal Manifestations

Axial disease



Peripheral arthritis



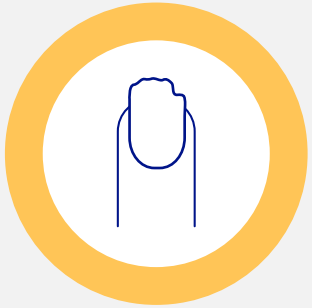
Enthesitis

Joint damage

Dactylitis

Extra-Musculoskeletal Manifestations

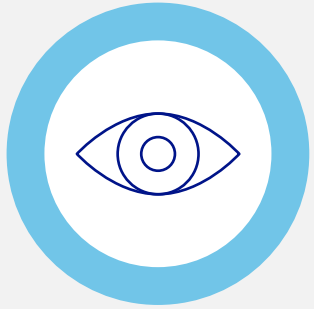
Psoriatic nail disease*



Psoriatic skin lesions

IBD

Uveitis



*Nail disease is a key feature of PsA but is uncommon in axSpA.[8] axSpA: axial spondyloarthritis; IBD: inflammatory bowel disease; PsA: psoriatic arthritis.

1. Coates LC et al. Arthritis Rheumatol. 2016;68(5):1060–1071. 2. Charlton R et al. Ann Rheum Dis. 2018;77(2):277–280. 3. Taurog JD et al. N Engl J Med. 2016;375(13):1303. 4. Mease PJ et al. ACR Open Rheumatol. 2020;2(7):449–456. 5. López-Medina C et al. Arthritis Res Ther. 2019;21(1):139. 6. de Winter JJ et al. Arthritis Res Ther. 2016;18(1):196. 7. Deodhar AA et al. Curr Opin Rheumatol. 2017;29(4):293–297. 8. Ankylosing Spondylitis vs. Psoriatic Arthritis: What's the Difference? Available at: https://creakyjoints.org/symptoms/ankylosing-spondylitis-vs-psoriatic-arthritis/. Accessed April 2024. 9. Tsukazaki H and Kaito T. Int J Mol Sci. 2020;21(17):6401.

SpA Pathobiology is Complex…

There are many clinically validated targets involved in spondyloarthritis pathobiology, including:

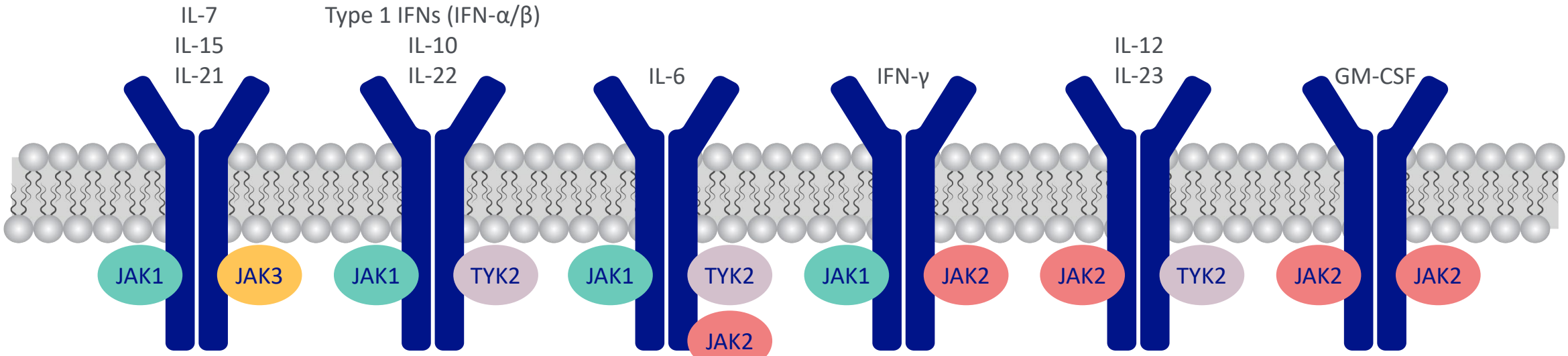
Important distinctions are emerging about which cytokines contribute to the various clinical manifestations and SpA disease phenotypes[2–6]

Emerging studies are revealing a new dimension of complexity in the IL-17 pathway that may help explain its *in vivo* functions[7]

*Validated for PsA but not for axSpA.[1] axSpA: axial spondyloarthritis; IL: interleukin; JAK: Janus kinase; PsA: psoriatic arthritis; SpA: spondyloarthritis; STAT: signal transducer and activator of transcription; TNF: tumour necrosis factor.

1. McGonagle D et al. Front Immunol. 2021;12:614255. 2. Hammitzsch A et al. Front Immunol. 2020;11:591176. 3. McGonagle DG et al. Ann Rheum Dis. 2019;78(9):1167–1178. 4. Rosine N and Miceli-Richard C. Front Immunol. 2021;11:553742. 5. Rezaiemanesh A et al. Biomed Pharmacother. 2018;100:198–204. 6. Siebert S et al. Ann Rheum Dis. 2019;78(8):1015–1018. 7. Li X et al. Nat Immunol. 2019;20(12):1594–1602.

JAK/STAT Pathways Mediate Signalling for Multiple Cytokines Implicated in SpA Pathogenesis[1]



- Growth/maturation of lymphoid cells
- Differentiation/ homeostasis of T and NK cells
- B cell class switching
- Inflammation

- Antiviral
- Inflammation
- Antitumour

- Naïve T cell differentiation
- T cell homeostasis
- Inflammation
- Granulopoiesis

- Antiviral
- Inflammation
- Antimycobacterial

- Innate immunity
- Differentiation/ proliferation of Th1 and Th17 cells
- Inflammation

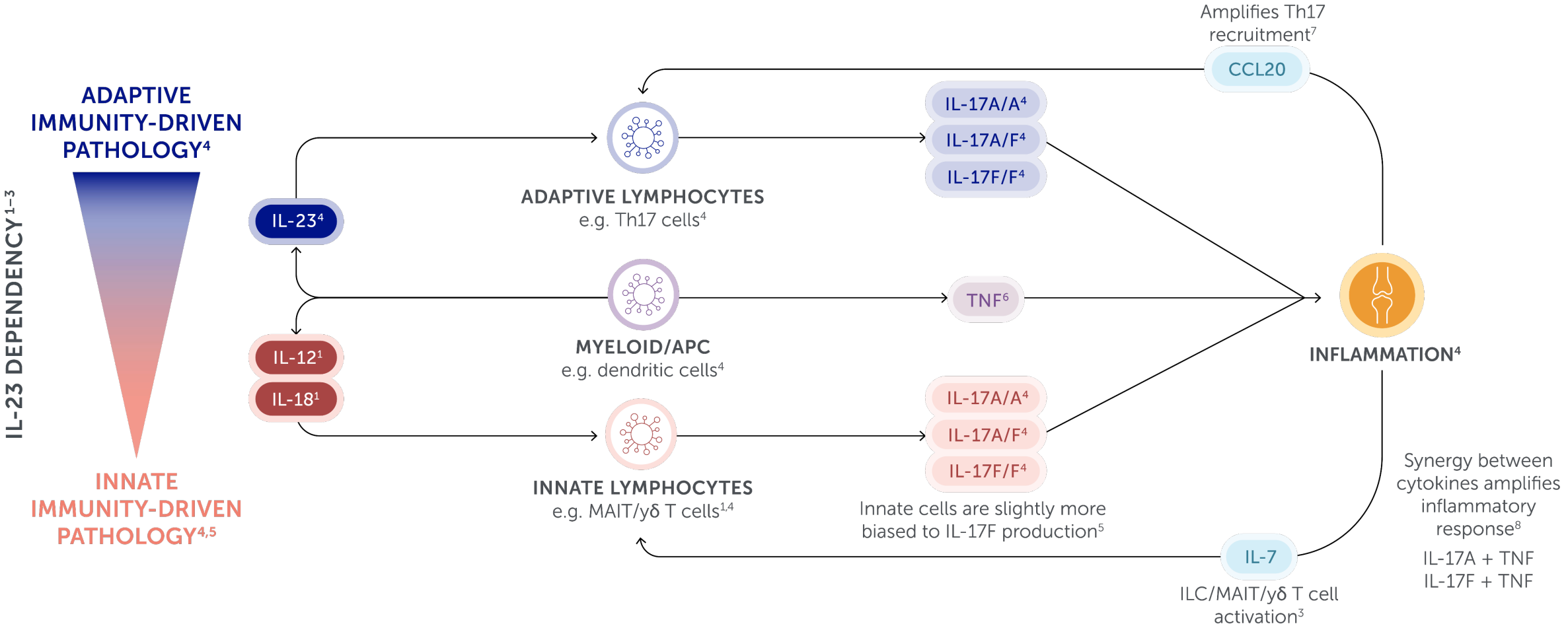
- Erythropoiesis
- Myelopoiesis
- Megakaryocyte/ platelet production
- Growth
- Mammary development

Several cytokines implicated in the pathogenesis of SpA are either **directly** (including IL-12 and IL-23) or **indirectly** (including IL-17 and TNF) **dependent on the JAK/STAT signaling pathway**

GM-CSF: granulocyte-macrophage colony-stimulating factor; IL: interleukin; IFN: interferon; JAK: Janus kinase; SpA: spondyloarthritis; STAT: signal transducer and activator of transcription; NK: natural killer; Th: T helper; TYK: tyrosine kinase.

1. Adapted from McInnes IB et al. Rheumatology (Oxford). 2022;61(5):1783–1794.

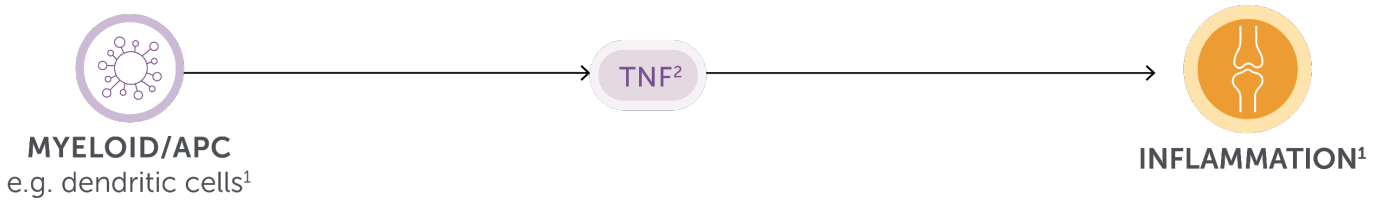
Extracellular Cytokines are Important Drivers of the Inflammation Observed in SpA Pathobiology[1–8]



Example cell types are shown; not an exhaustive list. APC: antigen-presenting cell; CCL20: C-C motif chemokine ligand 20; IL: interleukin; ILC: innate lymphoid cell; MAIT: mucosal-associated invariant T cell; SpA: spondyloarthritis; Th: T helper cell; TNF: tumour necrosis factor; γδ T: gamma delta T cell.

1. McGonagle D et al. Front Immunol. 2021;12:614255. 2. McGonagle DG et al. Ann Rheum Dis. 2019;78(9):1167–1178. 3. Rosine N and Miceli-Richard C. Front Immunol. 2021;11:553742. 4. Tsukazaki H and Kaito T. Int J Mol Sci. 2020;21(17):6401. 5. Cole S et al. Front Immunol. 2020;11:585134. 6. Blanco P et al. Cytokine Growth Factor Rev. 2008;19(1):41–52. 7. Russell T et al. Cells. 2021;10(2):341. 8. Glatt S et al. Ann Rheum Dis. 2018;77(4):523–532.

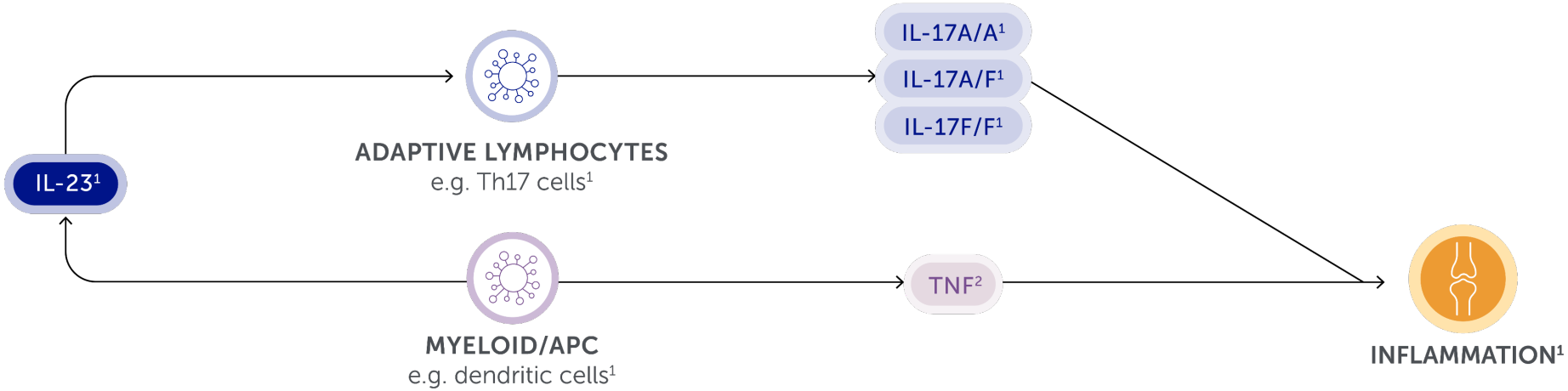
Cells of the Myeloid Lineage Produce TNF to Drive Inflammation[1,2]



Example cell types are shown; not an exhaustive list. APC: antigen-presenting cell; TNF: tumour necrosis factor.

1. Tsukazaki H and Kaito T. Int J Mol Sci. 2020;21(17):6401. 2. Blanco P et al. Cytokine Growth Factor Rev. 2008;19(1):41–52.

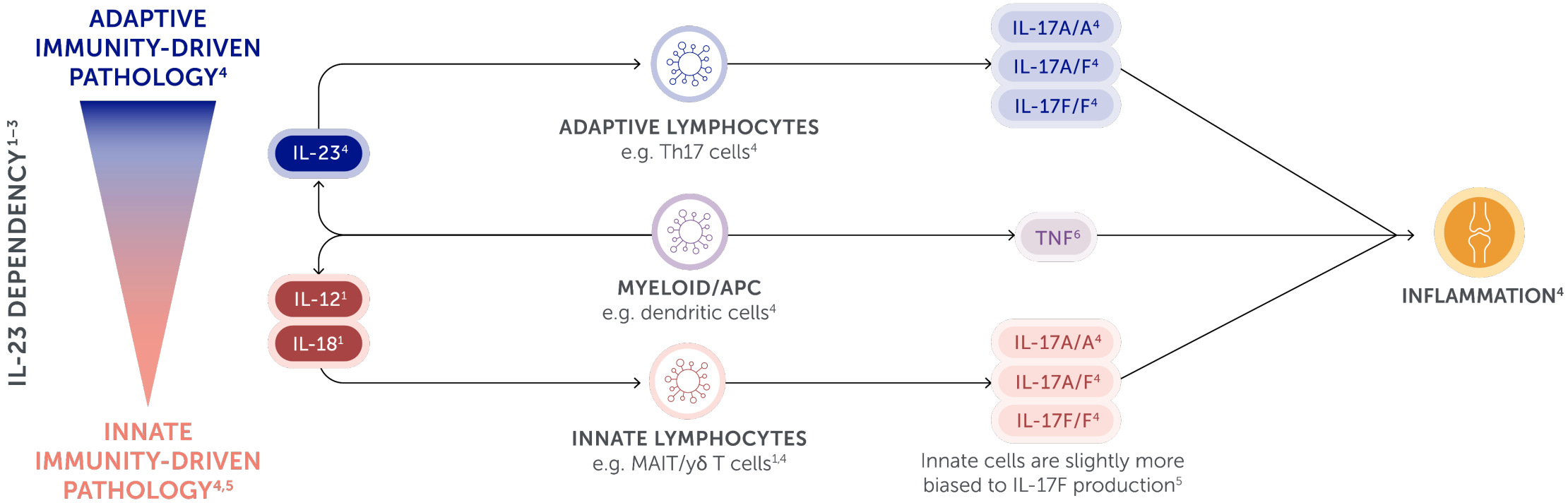
IL-23 Stimulates Adaptive Lymphocytes to Release IL-17 Which Drives the Inflammatory Response[1]



Example cell types are shown; not an exhaustive list. APC: antigen-presenting cell; IL: interleukin; Th17: T helper 17 cell; TNF: tumour necrosis factor.

1. Tsukazaki H and Kaito T. Int J Mol Sci. 2020;21(17):6401. 2. Blanco P et al. Cytokine Growth Factor Rev. 2008;19(1):41–52.

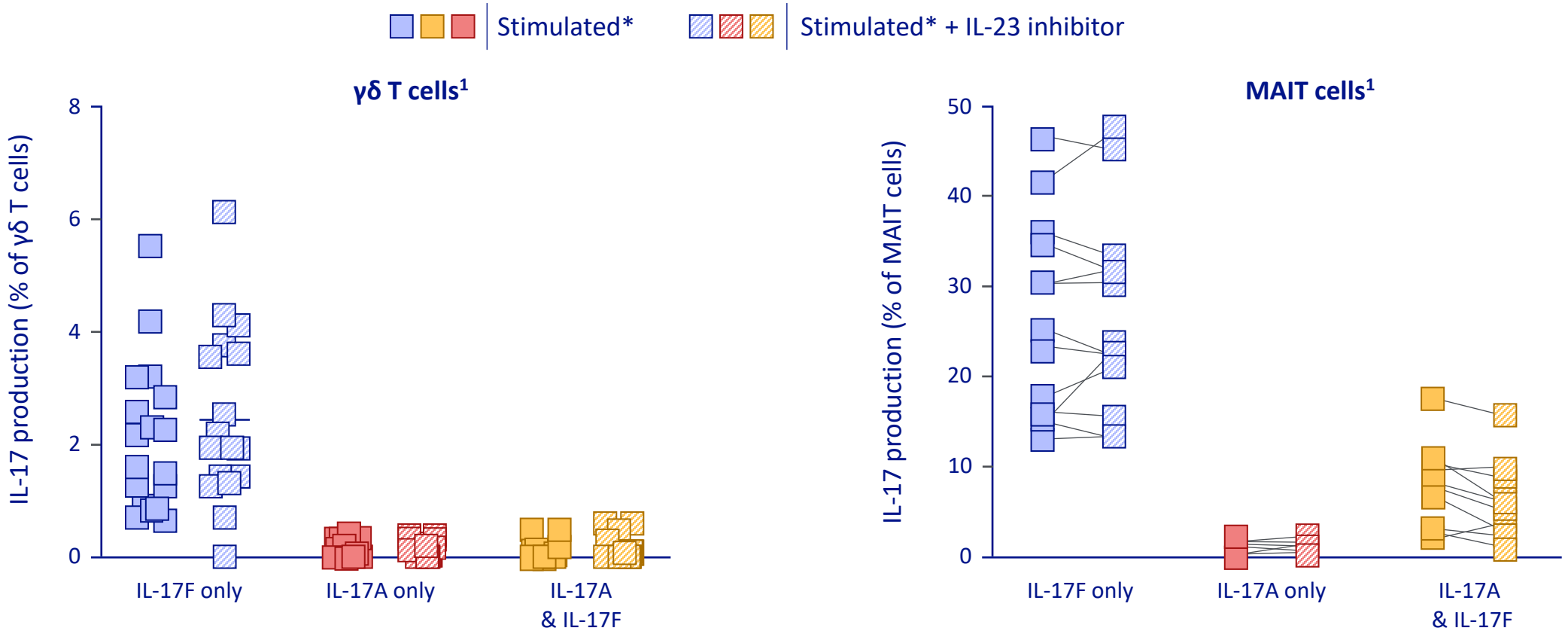
Cells of the Innate Immune System Can Produce IL-17 Independently of IL-23 Stimulation[1–5]



Example cell types are shown; not an exhaustive list. APC: antigen-presenting cell; IL: interleukin; MAIT: mucosal-associated invariant T cell; Th17: T helper 17 cell; TNF: tumour necrosis factor; γδ T: gamma delta T cell.

1. McGonagle D et al. Front Immunol. 2021;12:614255. 2. McGonagle DG et al. Ann Rheum Dis. 2019;78(9):1167–1178. 3. Rosine N and Miceli-Richard C. Front Immunol. 2021;11:553742.
4. Tsukazaki H and Kaito T. Int J Mol Sci. 2020;21(17):6401. 5. Cole S et al. Front Immunol. 2020;11:585134. 6. Blanco P et al. Cytokine Growth Factor Rev. 2008;19(1):41–52.

IL-23–Independent IL-17A and IL-17F Production By Innate Cells Can Contribute to IL-17-Mediated Inflammation[1,2]

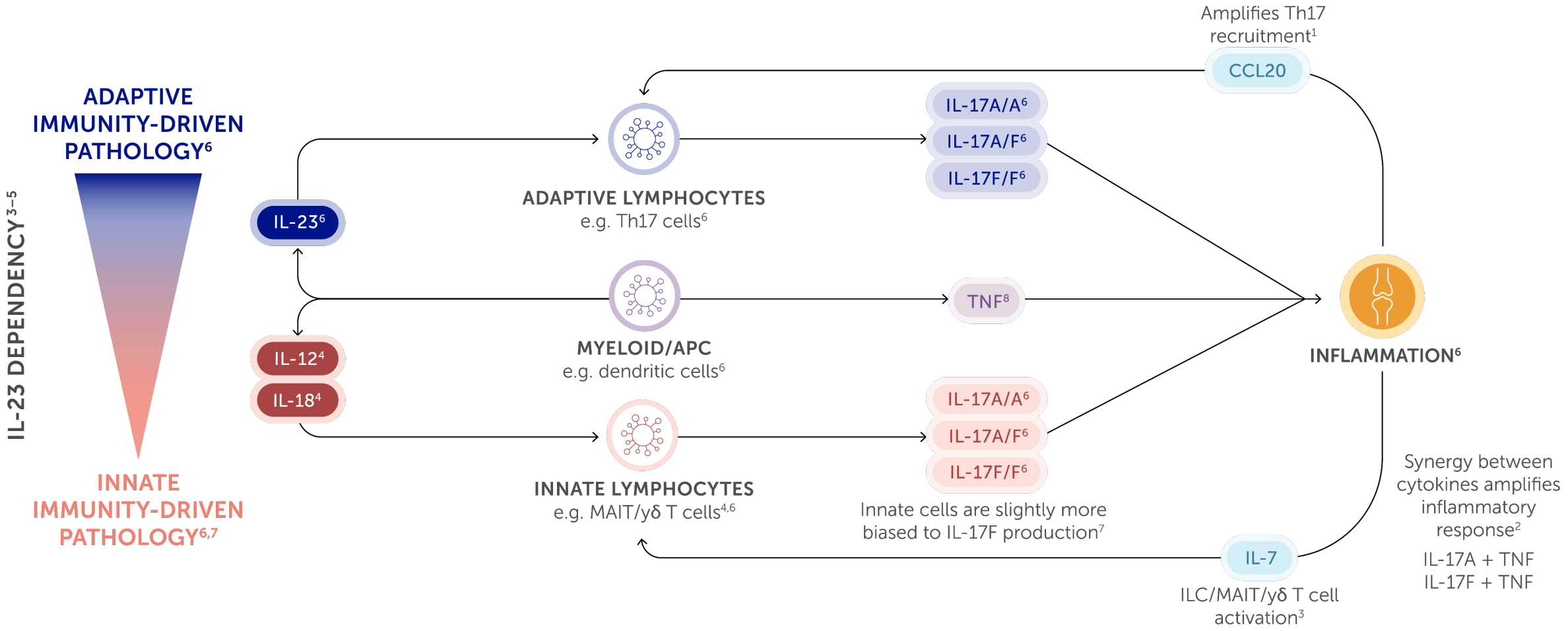


Innate lymphocytes produce IL-17A and IL-17F **independently of IL-23 signalling**,[1,2] with IL-17F predominantly produced[1]

*Stimulated with IL-12/IL-18. Each of the points shown represent data for an individual donor. PBMCs were stimulated with anti-CD3, anti-CD28 and cytokines; after 72 hours, flow cytometry gating followed by intracellular staining was conducted.[1] CD: cluster of differentiation; IL: interleukin; MAIT: mucosal-associated invariant T cells; PBMC: peripheral blood mononuclear cell; γδ T: gamma delta T cells.

1. Adapted from Cole S et al. Front Immunol. 2020;11:585134. 2. Łukasik Z et al. Rheumatology (Oxford). 2021;60(Suppl 4):iv16–iv27.

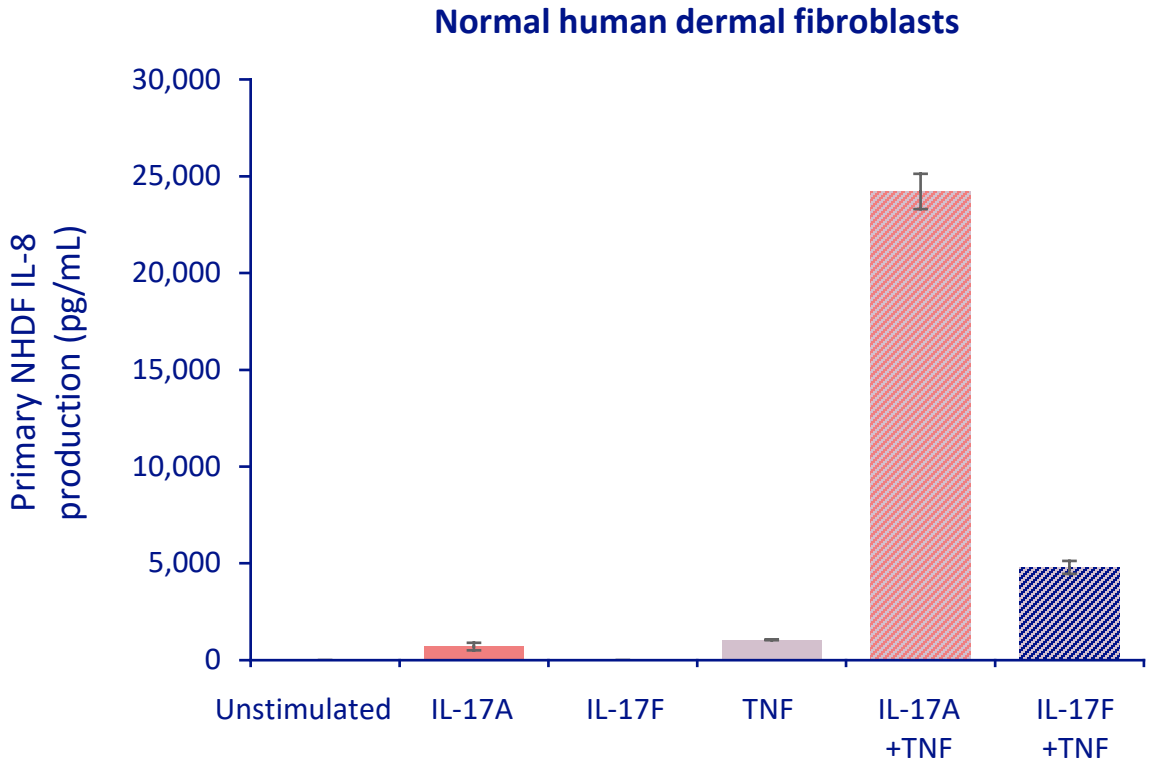
Synergy Between Cytokines and Additional Feedback Loops Amplify the Inflammatory Response[1–3]

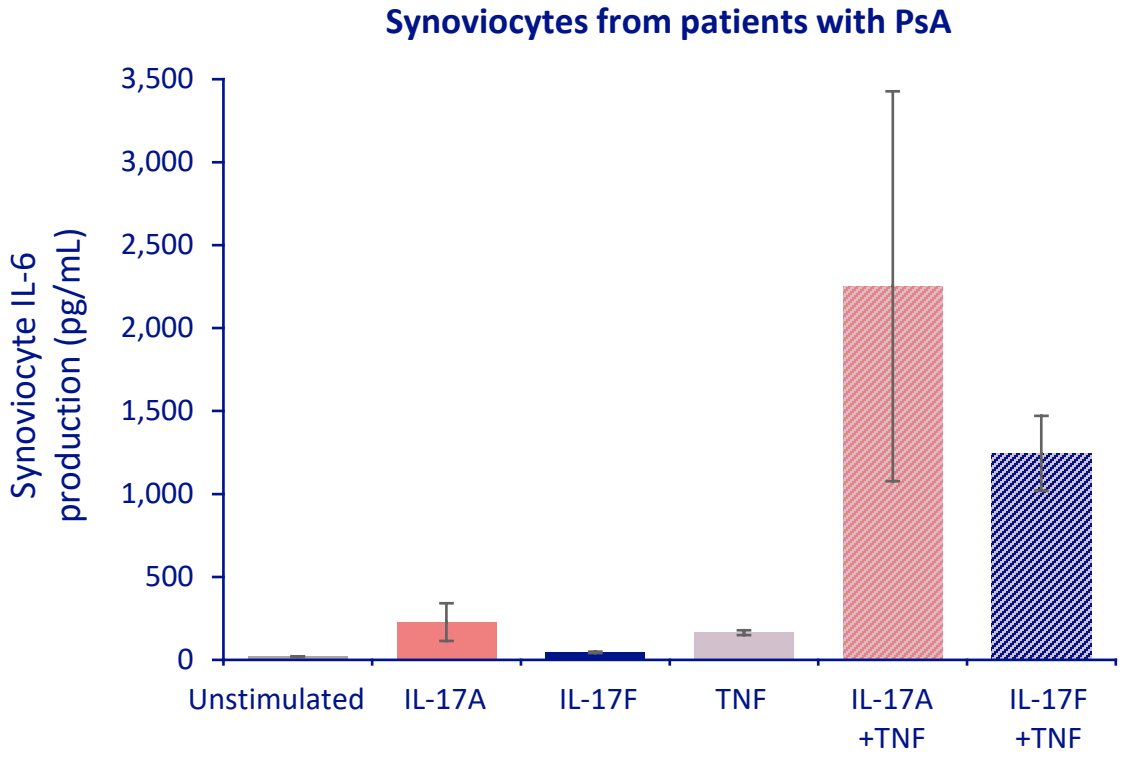


Example cell types are shown; not an exhaustive list. APC: antigen-presenting cell; CCL20: C-C motif chemokine ligand 20; ILC: innate lymphoid cell; MAIT: mucosal-associated invariant T cell; Th17: T helper 17 cell; TNF: tumour necrosis factor; γδ T: gamma delta T cell.

1. Russell T et al. Cells. 2021;10(2):341. 2. Glatt S et al. Ann Rheum Dis. 2018;77(4):523–532. 3. Rosine N and Miceli-Richard C. Front Immunol. 2021;11:553742. 4. McGonagle D et al. Front Immunol. 2021;12:614255. 5. McGonagle DG et al. Ann Rheum Dis. 2019;78(9):1167–1178. 6. Tsukazaki H and Kaito T. Int J Mol Sci. 2020;21(17):6401. 7. Cole S et al. Front Immunol. 2020;11:585134. 8. Blanco P et al. Cytokine Growth Factor Rev. 2008;19(1):41–52.

IL-17A and IL-17F are Drivers of Inflammation in *in Vitro* Models of PsA





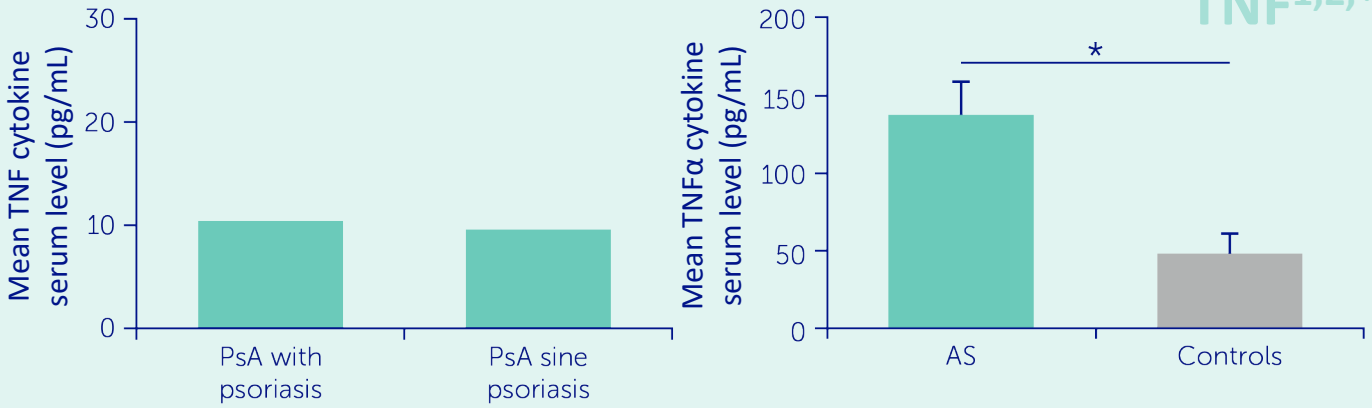
IL-17A and IL-17F independently cooperate with TNF to amplify production of IL-8 and IL-6

NHDFs and synoviocytes from patients with PsA. Data are mean ±SEM. TNF at 1 ng/ml. IL-17A and IL-17F at 100 ng/ml. IL: interleukin; NHDF: normal human dermal fibroblasts; SEM: standard error of mean; PsA: psoriatic arthritis; TNF: tumour necrosis factor.

Adapted from Glatt S et al. Ann Rheum Dis. 2018;77(4):523–532.

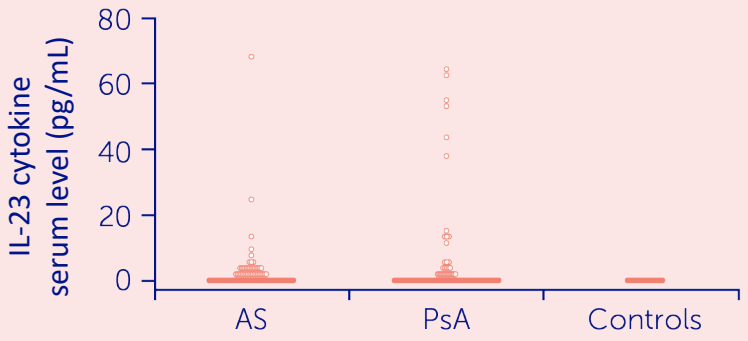
Serum Levels of Extracellular Cytokines in Patients with SpA

TNF[1,2,†]



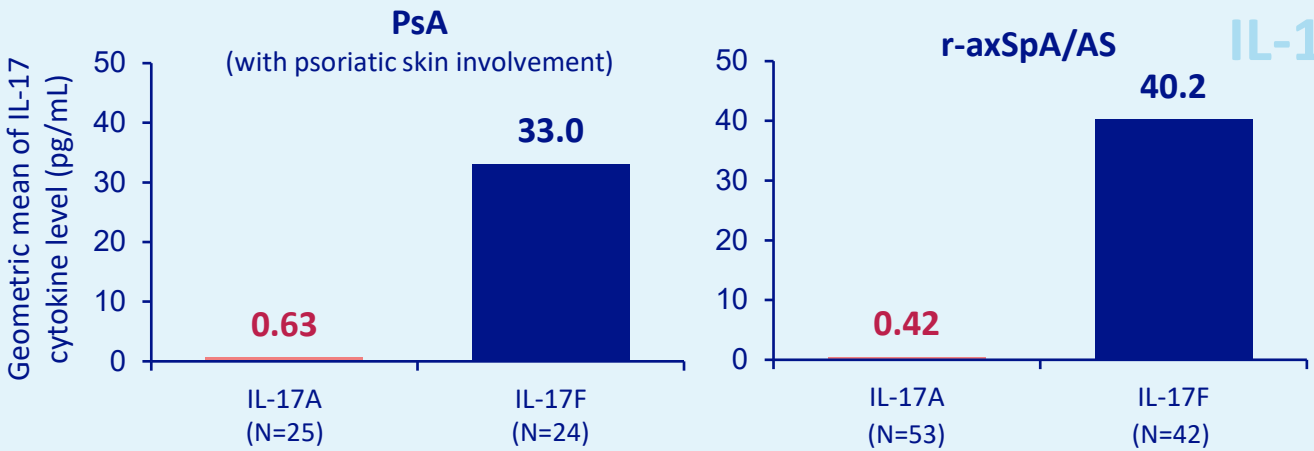
In one study, TNF is **present in serum** from patients with PsA with and sine psoriasis.[1,‡]
In another, serum levels of TNFα were **significantly increased in AS patients** compared to controls[2,§]

IL-23[3,†]



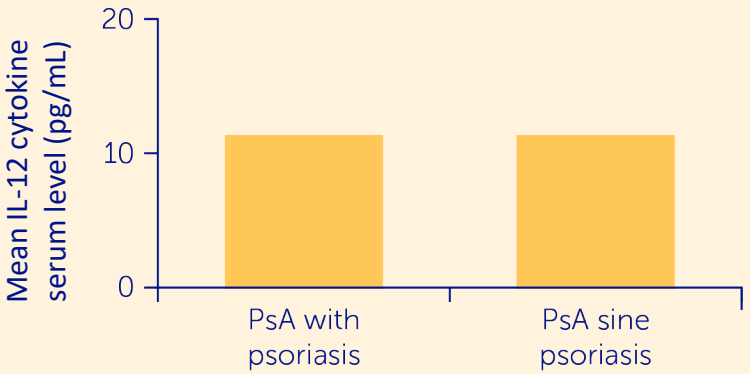
Serum IL-23 levels were significantly higher in patients with SpA compared to controls**

IL-17[4]



IL-17F levels were more than 50-fold higher vs IL-17A levels in serum[††] from patients with SpA

IL-12[1,†]



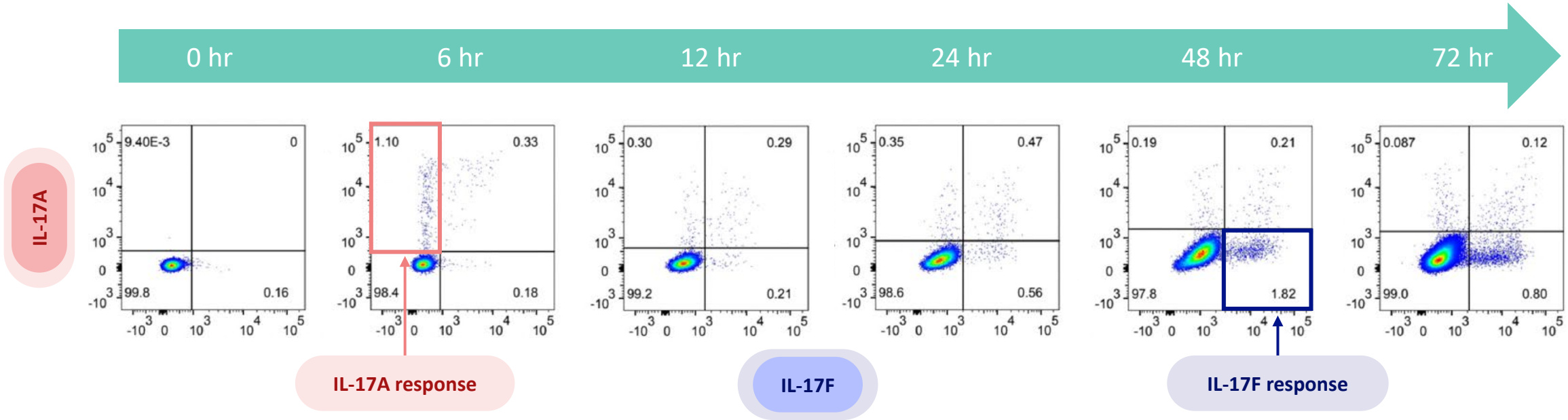
IL-12p70 is **present in serum** from patients with PsA with and sine psoriasis[‡]

*p<0.0001.[2] †Estimated plotting based on graph visualiser software. ‡Group consisted of 41 patients with PsA and psoriasis and 20 patients with PsA sine psoriasis. Biomolecules were assessed by multiplex technology. PsA sine psoriasis refers to patients without clinically evident psoriasis but with suggestive family history.[1] §Group consisted of 140 Iranian patients with AS and 140 control patients. ELISA was used to measure serum cytokine levels.[2] **p=0.0004 for SpA patients versus control group. Group consisted of 69 patients with PsA, 61 patients with AS and 29 healthy volunteers (controls). A sensitive sandwich ELISA was used to measure serum cytokine levels.[2] ††Systemic biomarkers of inflammation. Data obtained from free levels of IL-17A and IL-17F in the serum of PsA patients with psoriasis and in r-axSpA/AS patients.[4] AS: ankylosing spondylitis; ELISA: enzyme linked immunosorbent assay; IL: interleukin; PsA: psoriatic arthritis; r-axSpA: radiographic axial spondyloarthritis; SpA: spondyloarthritis; TNF: tumour necrosis factor.

1. Adapted from Ruscitti P et al. Front Immunol. 2023;14:1229516. 2. Adapted from Mohammadi H et al. Iran J Allergy Asthma Immunol. 2018;17(5):464–476. 3. Adapted from Przepiera-Będzak H et al. Mediators Inflamm. 2015;2015:785705. 4. Adapted from Kolbinger F et al. J Allergy Clin Immunol. 2017;139(3):923–932.e8.

IL-17F Cells Predominate Following Chronic Stimulation of Peripheral Blood Mononuclear Cells

Kinetics of IL-17A and IL-17F expression over time in response to stimulation

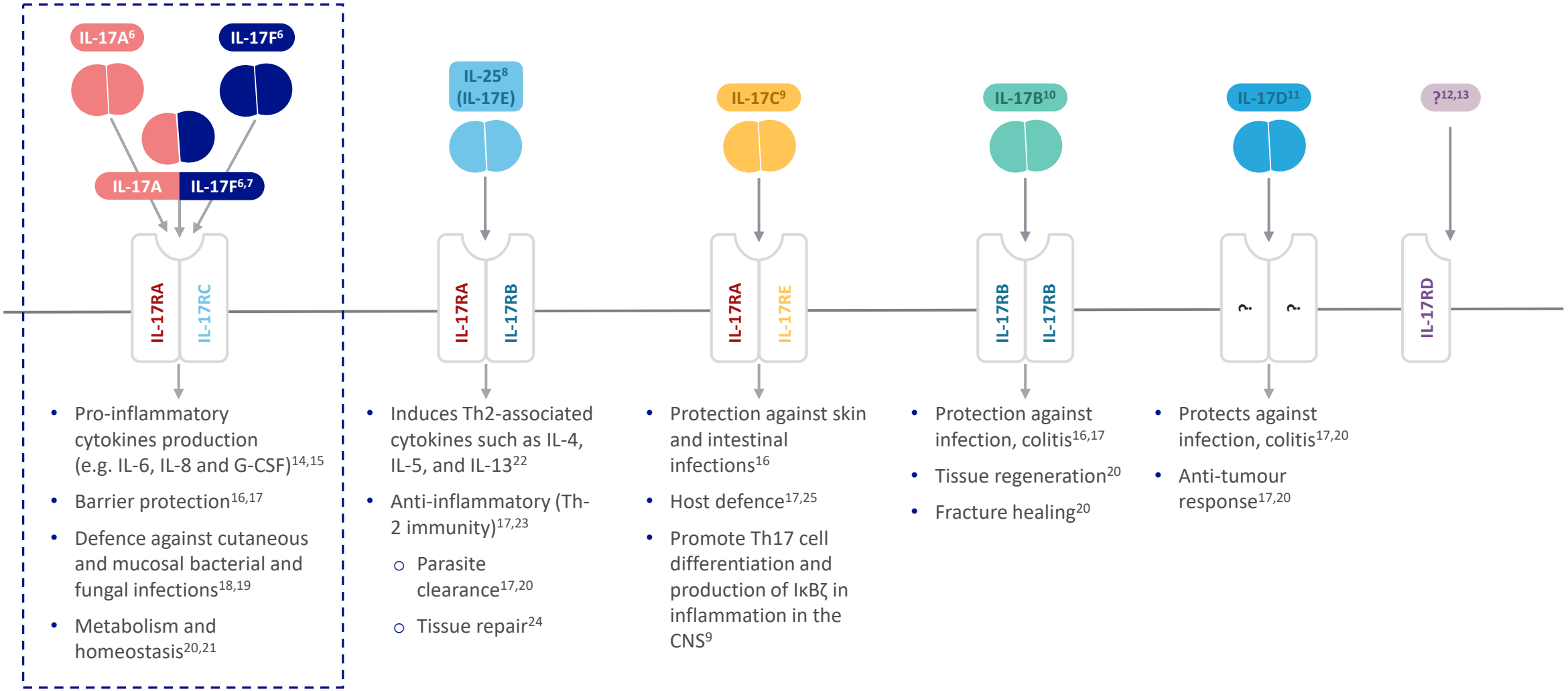


Kinetic analysis using activated PBMCs demonstrated that **IL-17A and IL-17F expression differed over time** in response to stimulation, namely **IL-17A was initially expressed** by Th17 cells, **then switched to an IL-17F-dominated response**

Kinetics of IL-17A and IL-17F production from CD4+ T cells stimulated *in vitro* with anti-CD3 and anti-CD28 in addition to brefeldin A, shown as representative biaxial flow cytometry plots. Fluorochrome-conjugated surface and intracellular antibodies used were: Comp-PE-A (IL-17A) and Comp-PerCP-Cy5-5-A (IL-17F). Numbers in quadrants represent percentage of events in the plot (data representative of 10 donors). CD: cluster of differentiation; IL: interleukin; PBMC: peripheral blood mononuclear cells; Th: T helper cell.

Cole S et al. J Allergy Clin Immunol. 2023;152(3):783–798.

IL-17A and IL-17F Play an Important Role in Driving Inflammation in SpA[1–5]



- Pro-inflammatory cytokines production (e.g. IL-6, IL-8 and G-CSF)[14,15]
- Barrier protection[16,17]
- Defence against cutaneous and mucosal bacterial and fungal infections[18,19]
- Metabolism and homeostasis[20,21]

- Induces Th2-associated cytokines such as IL-4, IL-5, and IL-13[22]
- Anti-inflammatory (Th-2 immunity)[17,23]
  - Parasite clearance[17,20]
  - Tissue repair[24]

- Protection against skin and intestinal infections[16]
- Host defence[17,25]
- Promote Th17 cell differentiation and production of IκBζ in inflammation in the CNS[9]

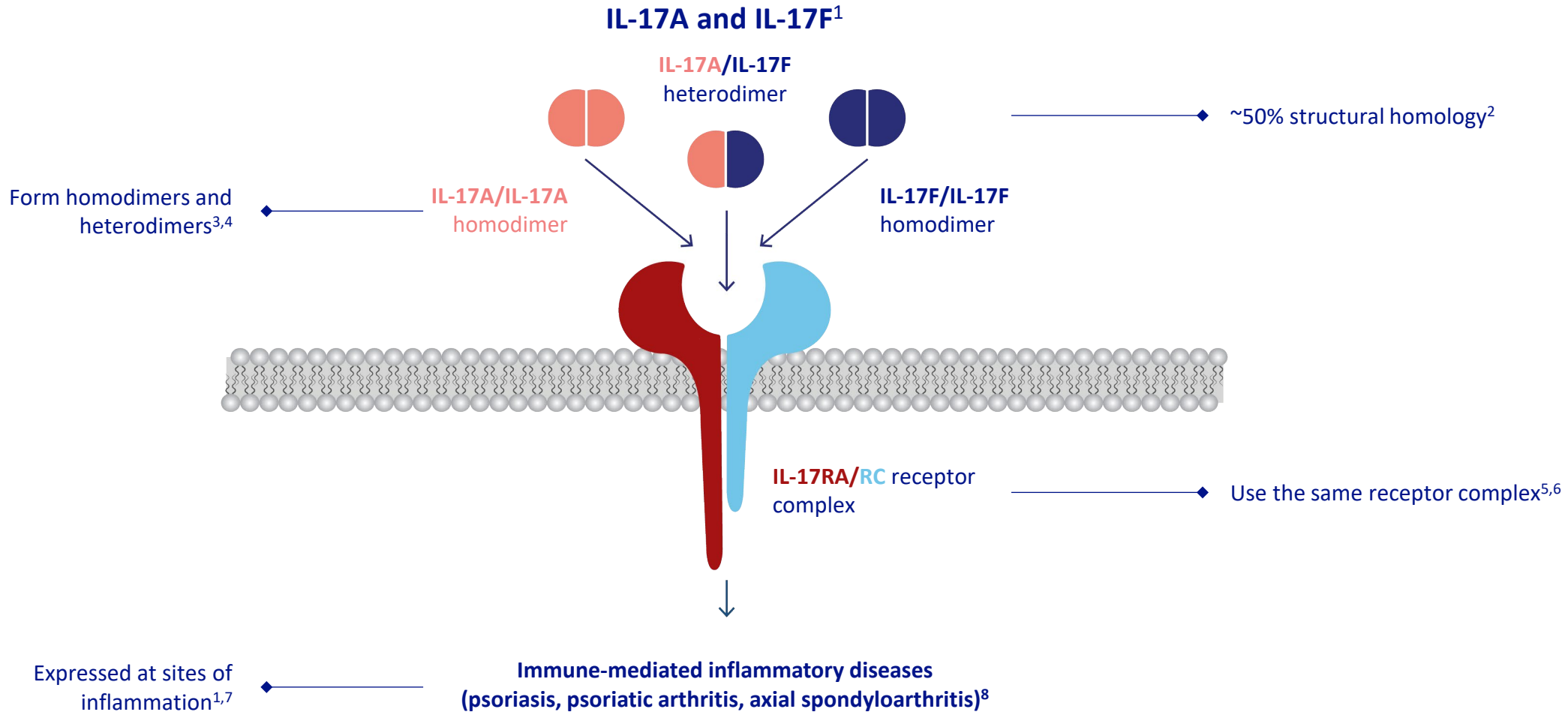
- Protection against infection, colitis[16,17]
- Tissue regeneration[20]
- Fracture healing[20]

- Protects against infection, colitis[17,20]
- Anti-tumour response[17,20]

CNS: central nervous system; G-CSF: granulocyte colony-stimulating factor; IL: interleukin; SpA: spondyloarthritis; Th17: T helper 17 cell.

1. Glatt S et al. Ann Rheum Dis. 2018;77(4):523–532. 2. Yang XO et al. J Exp Med. 2008;205(5):1063–1075. 3. Goepfert A et al. Immunity. 2020;52(3):499–512. 4. Jadon DR et al. Nat Rev Rheumatol. 2020;16(11):609–627. 5. Shah M et al. RMD Open. 2020;6(2):e001306. 6. Toy D et al. J Immunol. 2006;177(1):36–39. 7. Wright JF et al. J Immunol. 2008;181(4):2799–2805. 8. Rickel EA et al. J Immunol. 2008;181:4299–4310. 9. Chang SH et al. Immunity. 2011;35(4):611–621. 10. Shi Y et al. J Biol Chem. 2000;275(25):19167–19176. 11. Starnes T et al. J Immunol. 2002;169(2):642–646. 12. Yang RB et al. J Biol Chem. 2003;278(35):33232–33238. 13. Monin L et al. Cold Spring Harb Perspect Biol. 2018;10(4)a028522. 14. Fossiez F et al. J Exp Med. 1996;183:2593–2603. 15. Hymowitz SG et al. EMBO J. 2001;20(19):5332–5341. 16. Navarro-Compán V et al. Front Immunol. 2023;14:1191782. 17. Meehan EV and Wang K. Genes 2022;13:1643. 18. Puel A et al. Curr Opin Immunol. 2010;22(4):467–474. 19. Ishigame H et al. Immunity. 2009;30(1):108–119. 20. Davydova A et al. Biomedicines. 2023;11(5):1328. 21. Bechara R et al. J Exp Med. 2021;218(5):e20202191. 22. Fort MM et al. Immunity. 2001;15:985–995. 23. Deng C et al. Front Immunol. 2021;12:691559. 24. Allen JE and Sutherland TE. Semin Immunol. 2014;26(4):329–340. 25. Nies JF and Panzer U. Front Immunol. 2020;11:341.

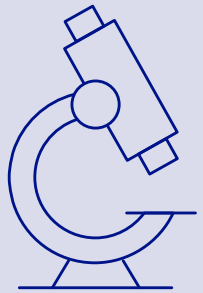
IL-17A and IL-17F Share Overlapping Biology



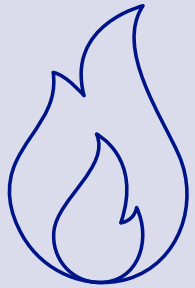
IL: interleukin; IL-17R: interleukin-17 receptor; RC: receptor chain; TNF: tumour necrosis factor.

1. Yang XO et al. J Exp Med. 2008;1063–1075. 2. Hymowitz SG et al. EMBO J. 2001;20:5332–5341. 3. Chang SH and Dong C. Cell Res. 2007;17:435–440. 4. Wright JF et al. J Biol Chem. 2007;282(18):13447–13455. 5. McAllister F et al. J Immunol. 2005;175(1):404–412. 6. Kuestner RE et al. J Immunol. 2007;179(8):5462–5473. 7. van Baarsen LGM et al. Arthritis Res Ther. 2014;16:426. 8. Glatt S et al. Ann Rheum Dis. 2018;77(4):523–532.

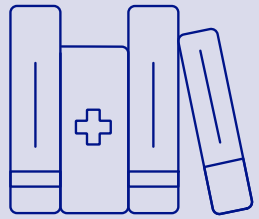
Summary



Spondyloarthritis pathobiology is complex; there are many clinically validated targets involved, including TNF, IL-12, IL-23, IL-17 and JAK/STAT[1,2]



IL-17A and **IL-17F** both play an important role in driving pathogenic inflammation in SpA, via **IL-23-dependent** (adaptive) and **IL-23-independent** (innate) inflammatory pathways, and can **synergistically amplify inflammatory responses** in the presence of TNF[3–9]



Whilst evidence to date has largely focused on the role of IL-17A in SpA, **recent studies support the important role of IL-17F in pathogenic inflammation in SpA**[9–11]

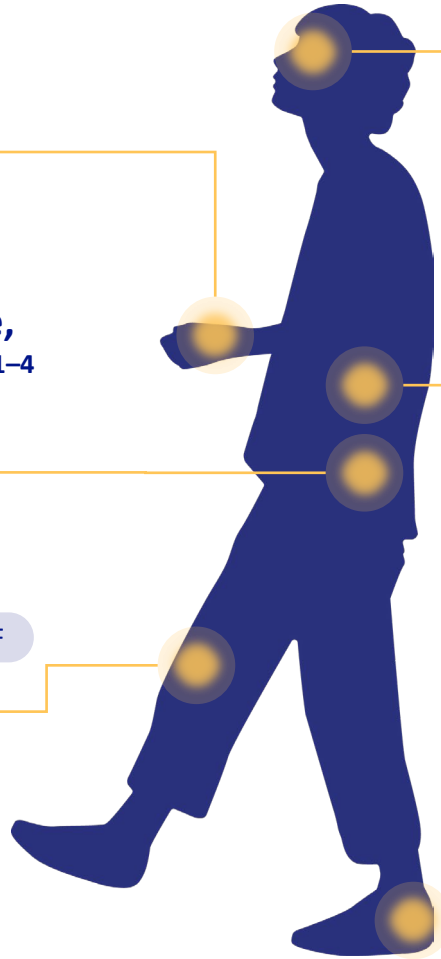
axSpA: axial spondyloarthritis; IL: interleukin; JAK: Janus kinase; PsA: psoriatic arthritis; SpA: spondyloarthritis; STAT: signal transducer and activator of transcription; TNF: tumour necrosis factor.

1. McGonagle D et al. Front Immunol. 2021;12:614255. 2. Hammitzsch A et al. Front Immunol. 2020;11:591176. 3. Yang XO et al. J Exp Med. 2008;205(5):1063–1075. 4. Jadon DR et al. Nat Rev Rheumatol. 2020;16(11):609–627. 5. Shah M et al. RMD Open. 2020;6(2):e001306. 6. Goepfert A et al. Immunity. 2020;52(3):499–512. 7. Tsukazaki H and Kaito T. Int J Mol Sci. 2020;21(17):6401. 8. Cole S et al. Front Immunol. 2020;11:585134. 9. Glatt S et al. Ann Rheum Dis. 2018;77(4):523–532. 10. Kolbinger F et al. J Allergy Clin Immunol. 2017;139(3):923–932.e8. 11. Cole S et al. J Allergy Clin Immunol. 2023;152(3):783–798.

IL-17A and IL-17F in Tissues of Interest in SpA

Professor Dennis McGonagle

Inflammatory Cytokines Implicated in SpA Disease Manifestations



Psoriasis[1–5]

TNF
IL-12 IL-23
IL-17A IL-17F

Axial disease, spine and SIJ[1–4]

TNF
IL-17A IL-17F

Peripheral arthritis and synovitis[1,2,4]

TNF
IL-12 IL-23
IL-17A IL-17F

Uveitis[1,3,4,6–8]

TNF
IL-17A IL-17F

IBD[1,3,4]

TNF
IL-12 IL-23

Enthesitis[1,4,9,10]

TNF
IL-12 IL-23
IL-17A IL-17F

axSpA: axial spondyloarthritis; IBD: inflammatory bowel disease; IL: interleukin; PsA: psoriatic arthritis; SIJ: sacroiliac joint; SpA: spondyloarthritis; TNF: tumour necrosis factor.

1. Adapted from McGonagle D et al. Front Immunol. 2021;12:614255. 2. Adapted from Yeremenko N. Curr Opin Rheumatol.2021;33(4):333–340. 3. Ramiro S et al. Ann Rheum Dis. 2023;82(1):19–34. 4. Coates LC et al. Nat Rev Rheumatol. 2022;18(8):465–479. 5. Kolbinger F et al. J Allergy Clin Immunol. 2017;139(3):923–932.e8. 6. Huang JC et al. Ocul Immunol Inflamm. 2021;29(3):558–565. 7. Lin P et al. Ophthalmology. 2014;121(1):365–376. 8. Weinstein JE and Pepple KL. Curr Opin Ophthalmol. 2018;29(3):267–274. 9. Mandour M et al. Front Immunol. 2021;12:618581. 10. McDermott N et al. Ann Rheum Dis. 2023;82(Suppl 1):1184. Abstract AB0011.

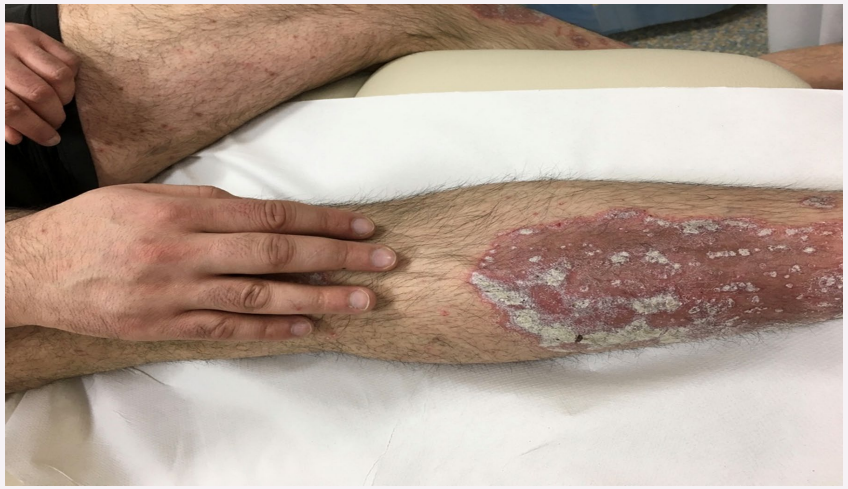
Patients with More Active Psoriasis Typically Experience Greater PsA Disease Burden and Reduced Quality of Life[1]

>10%* of patients with axSpA have psoriasis[2,3]

94% of patients with PsA have psoriasis[4]

More severe psoriasis (**BSA >3%**) has a significant[†] impact on patients, including:[1,‡]

- **Greater pain** (mean pain VAS)[§]
- **Greater fatigue** (mean fatigue VAS)[§]
- **Greater functional impairment** (HAQ)**
- **Less likely to achieve MDA** (modified MDA)**



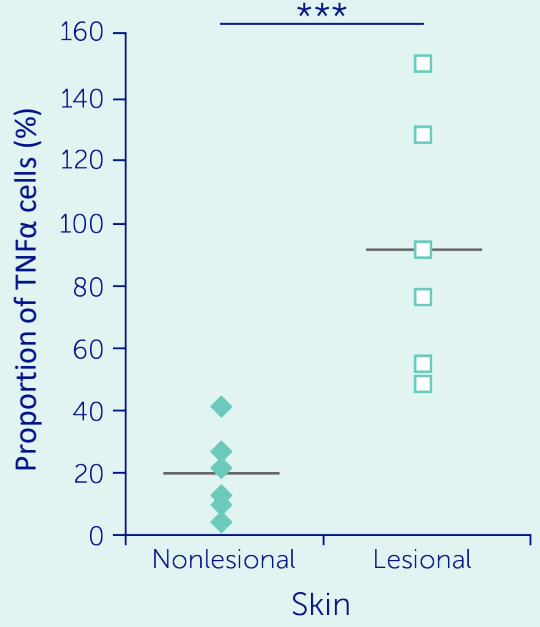
In PsA, the **EULAR 2023 recommendations** newly advise that mode of action choice should include the consideration of clinically relevant[††] skin involvement[5]

Image courtesy of Professor Dennis McGonagle. *The DESIR cohort of 589 adult patients with recent inflammatory back pain suggestive of axSpA reported the prevalence of psoriasis as 26.8% at 6 years from baseline.[3] [†]p<0.05.[1] [‡]Retrospective cross-sectional analysis of patients with PsA aged ≥18 years who had data on BSA affected by psoriasis and were enrolled in the Corrona PsA/Spondyloarthritis Registry from 1st March 2013 to 1st June 2015.[1] [§]Adjusted model for estimated differences in mean patient-reported pain or fatigue between patients with BSA >3% vs ≤3%.[1] **Association of BSA level with modified MDA status (risk of not being in modified MDA) or functional status measured by the HAQ. Modified MDA was defined as fulfilment of 5/6 criteria, with removal of the criterion for BSA.[1] [††]Body surface area involvement >10%, or skin involvement that negatively impacts the patients' quality of life (such as face or genital involvement).[5] axSpA: axial spondyloarthritis; BSA: body surface area; DESIR: DEvenir des Spondylarthropathies Indifférenciées Récentes; HAQ: health assessment questionnaire; MDA: minimal disease activity; PsA: psoriatic arthritis; VAS: visual analogue scale.

1. Mease PJ et al. J Rheumatol. 2017;44(8):1151–1158. 2. Taurog JD et al. N Engl J Med. 2016;374(26):2563–2574. 3. Lucasson F et al. RMD Open. 2022;8(1):e001986. 4. Kane D et al. Rheumatology (Oxford). 2003;42(12):1460–1468. 5. Gossec L et al. Ann Rheum Dis. 2024;0:1–14. doi:10.1136/ard-2024-225531.

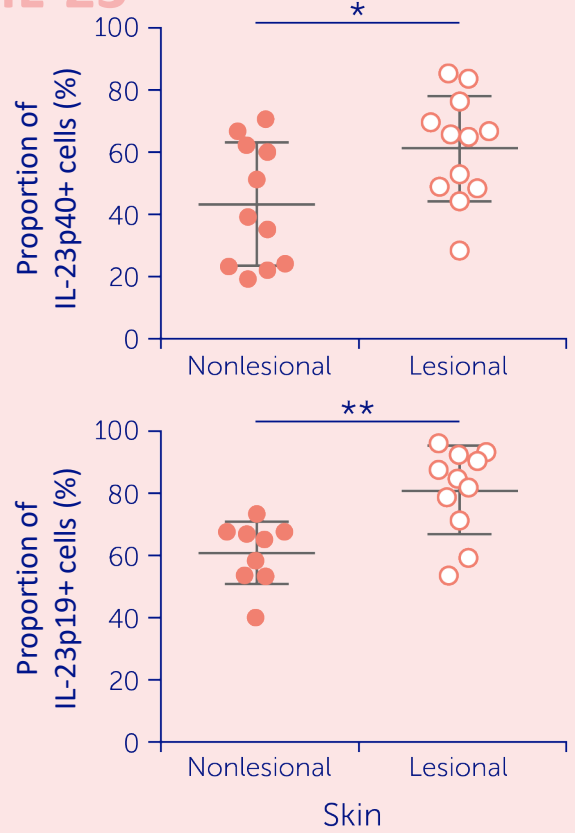
Extracellular Cytokines in Psoriasis (1/3)

TNF[1,†]



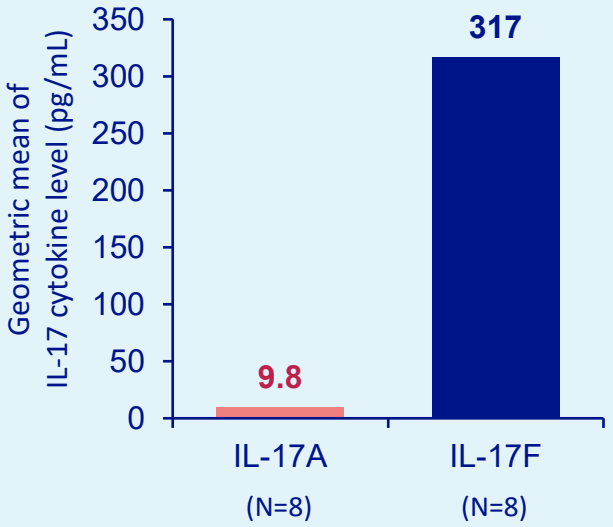
TNFα protein level was significantly increased in lesional psoriatic skin compared with nonlesional psoriatic skin[‡]

IL-23[2,†]



The percentage of **IL-23p40- and IL-23p19-positive cells was significantly higher** in lesional skin from patients with PsA compared to paired nonlesional skin[§]

IL-17[3]



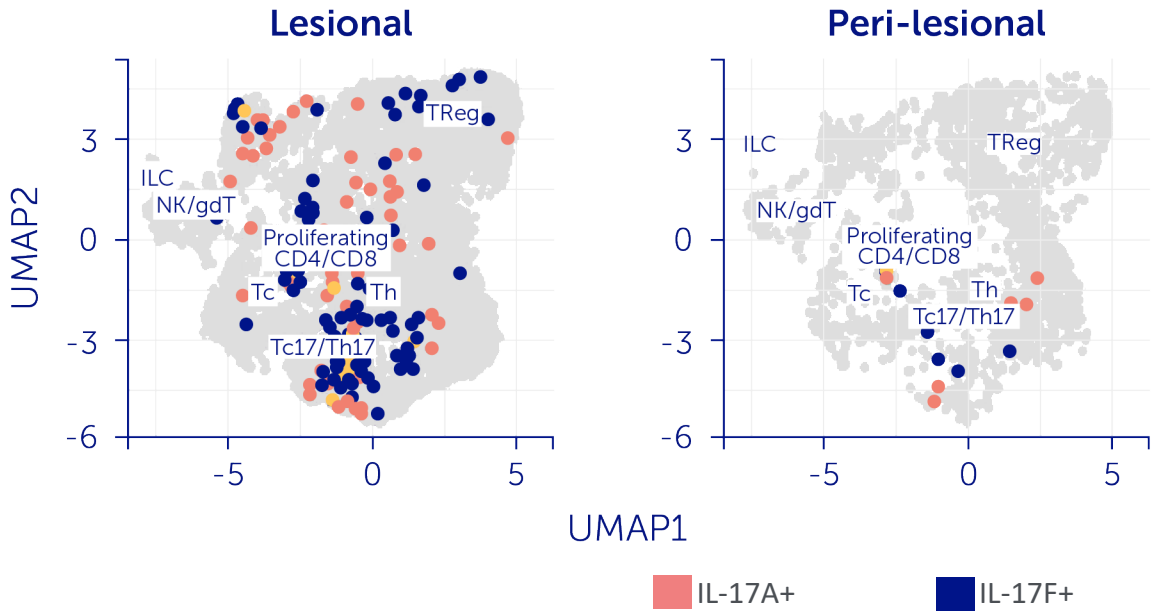
In patients with psoriasis, both **IL-17A and IL-17F cytokines** were expressed in skin[††]

*p<0.05.[2] **p<0.01.[2] ***p=0.0099.[1] [†]Estimated plotting based on graph visualiser software. [‡]TNFα ELISA was performed on cell extracts from keratome biopsies from nonlesional and lesional psoriatic skin (n=6). Each value was determined twice.[1] [§]Digital image analysis was performed on non-lesional and lesional skin (n=11–12). IL-23p40- and Il-23p19-positive cells were determined using QuPath software. Results are shown as mean±SD.[2] [††]Data obtained from lesional skin dermis samples of patients with psoriasis at baseline. IL-17A and IL-17F levels were quantified by using microparticle-based fluorescent sandwich immunoassays, validated in human serum.[3] IL: interleukin; PsA: psoriatic arthritis; TNF: tumour necrosis factor.

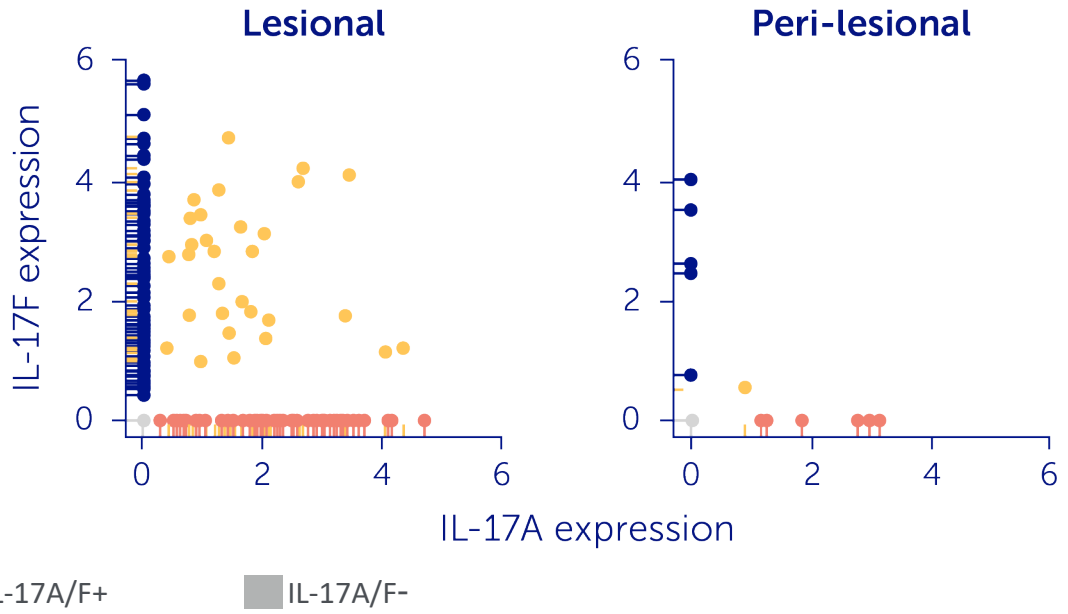
1. Adapted from Johansen C et al. J Immunol. 2006;176(3):1431–1438. 2. Adapted from Nerviani A et al. Ann Rheum Dis. 2021;80(5):591–597. 3. Adapted from Kolbinger F et al. J Allergy Clin Immunol. 2017;139(3):923–932.e8.

Extracellular Cytokines in Psoriasis (2/3)

Single-cell expression of IL-17 isoforms by T lymphocytes



IL-17A vs IL-17F RNA expression in IL-17+ lymphocytes



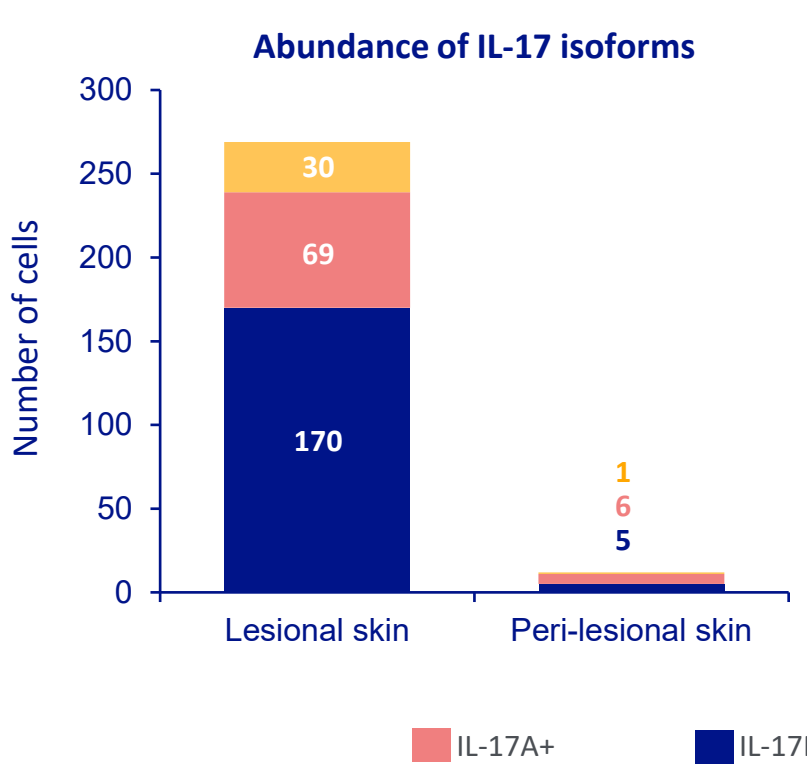
IL-17A+ IL-17F+ IL-17A/F+ IL-17A/F-

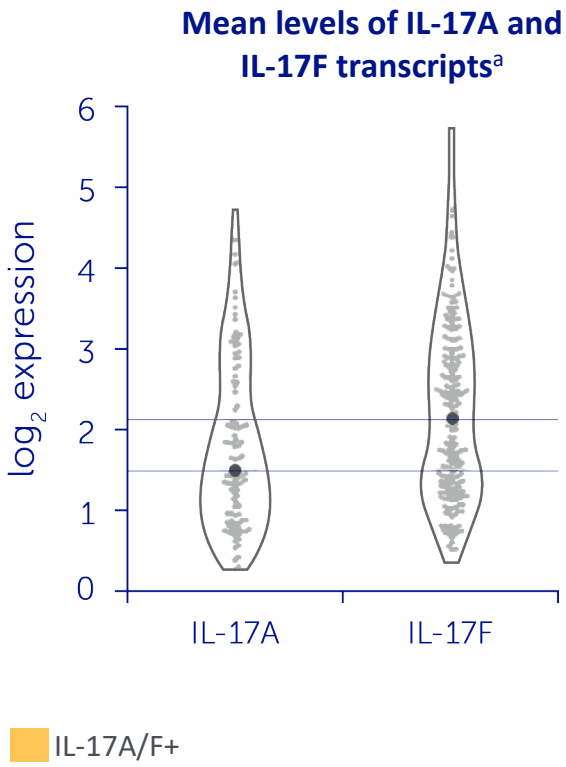
IL-17F+ Tc17/Th17 lymphocytes were markedly expanded in psoriatic lesions compared with peri-lesional samples. IL-17A+ cells and IL-17F+ cells were more frequent than IL-17A/F+ cells

Single-cell RNA-Seq was performed on lesional and peri-lesional skin samples from 6 patients with moderate-to-severe psoriasis. CD: cluster of differentiation; gdT: gamma delta T cell; IL: interleukin; ILC: innate lymphoid cell; NK: natural killer cell; RNA: ribonucleic acid; RNA-Seq: RNA sequencing; Tc: cytotoxic T cell; Th: T helper cell; TReg: regulatory T cell; UMAP: uniform manifold approximation and projection.

Adapted from Cole S et al. J Allergy Clin Immunol. 2023;152(3):783–798.

Extracellular Cytokines in Psoriasis (3/3)





IL-17F+ cells were more frequent than IL-17A+ cells. The average transcript level per cell was significantly higher for IL-17F than IL-17A

Single-cell RNA-Seq was performed on lesional and peri-lesional skin samples from 6 patients with moderate-to-severe psoriasis. [a]In single cells isolated from lesional skin.
IL: interleukin; RNA-Seq: RNA sequencing.

Adapted from Cole S et al. J Allergy Clin Immunol. 2023;152(3):783–798.

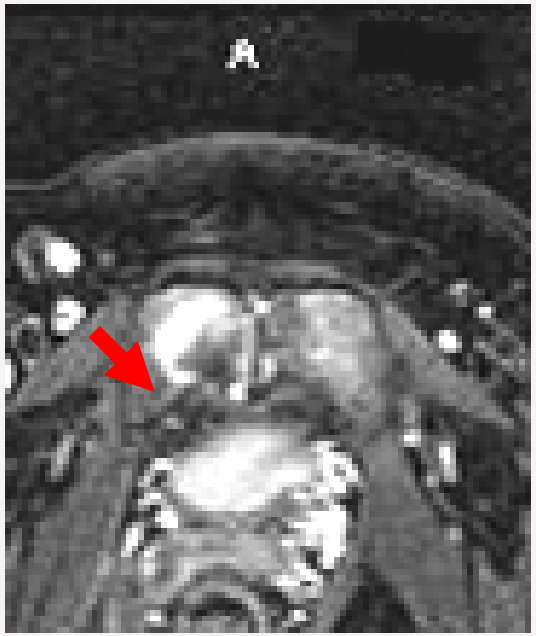
Enthesitis May Lead to Functional Impairment in SpA Patients[1,2]

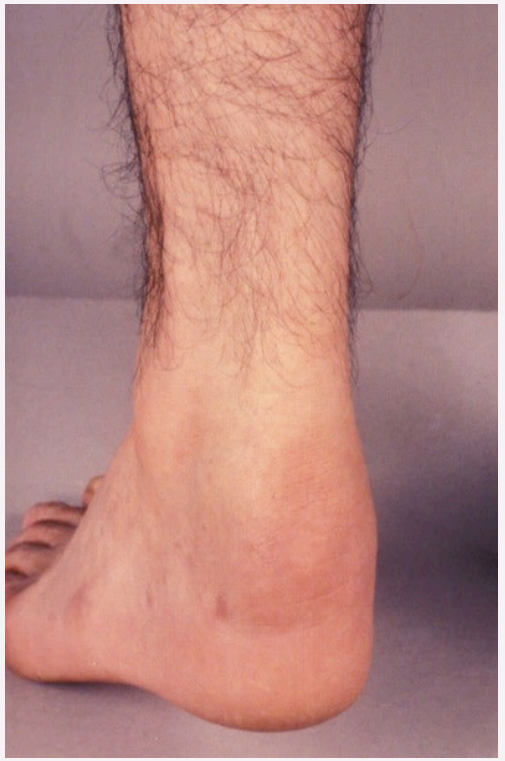
~25% of patients with axSpA have enthesitis[3]

35–57% of patients with PsA have enthesitis[4,5]

Persistent enthesitis can lead to structural damage, including tendon injuries and bone erosions that, if untreated, may lead to **functional impairment** and **reduced quality of life**[1,2]

In PsA, the **EULAR 2023 recommendations** maintain that physicians should avoid overtreatment of entheseal pain by ensuring enthesitis is PsA-related. Confirmation of definite entheseal inflammation should be established, which may require additional diagnostic imaging[6,*]

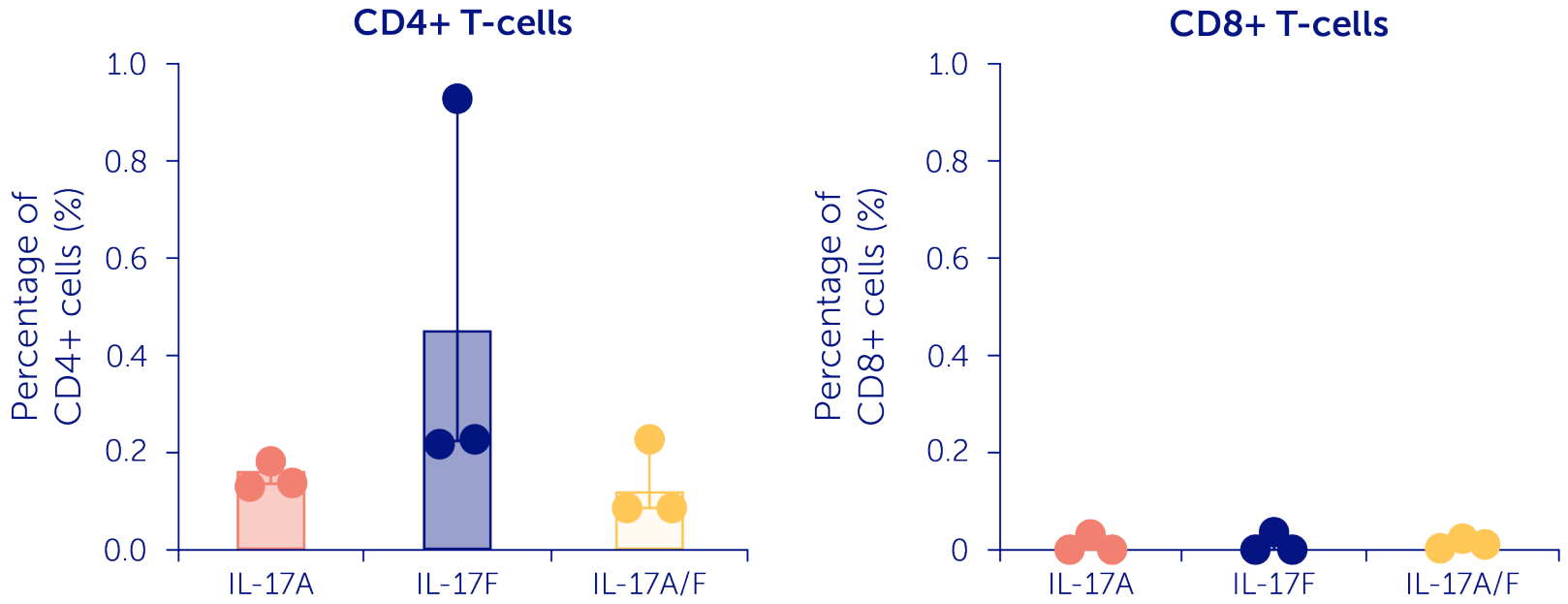




Images courtesy of Professor Dennis McGonagle. *Unequivocal enthesitis was defined as definite entheseal inflammation (which might need additional diagnostic imaging).[6] axSpA: axial spondyloarthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis.

1. Wu X et al. Front Immunol. 2022;13:978504. 2. McGonagle D et al. Semin Arthritis Rheum. 2021;51(6):1147–1161. 3. Mease PJ et al. ACR Open Rheumatol. 2020;2(7):449–456. 4. Kaeley GS et al. Semin Arthritis Rheum. 2018;48(1):35–43. 5. D'Agostino MA et al. Arthritis Rheum. 2003;48(2):523–533. 6. Gossec L et al. Ann Rheum Dis. 2024;0:1–14. doi:10.1136/ard-2024-225531.

IL-17A and IL-17F in Enthesitis in SpA



IL-17A and IL-17F were expressed in CD4+ in **peri-entheseal bone samples** following stimulation for 72 hours *in vitro*

Estimated plotting based on graph visualiser software. N=3. IL-17 expression by CD4 and CD8 T-cells in peri-entheseal bone was measured following 72 hours of stimulation with anti-CD3 and CD28 (100 ng/ml). Error bars representative of the mean with range. CD: cluster of differentiation; IL: interleukin; SpA: spondyloarthritis.

Adapted from McDermott N et al. Ann Rheum Dis. 2023;82(Suppl 1):1184. Abstract AB0011.

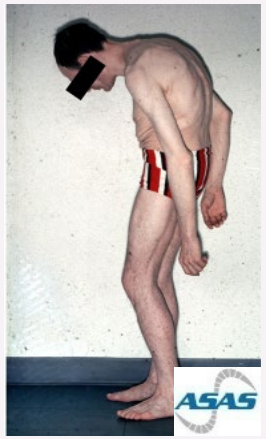
Bone Formation in SpA Leads to Functional Impairment and a Reduced Quality of Life[1–3]

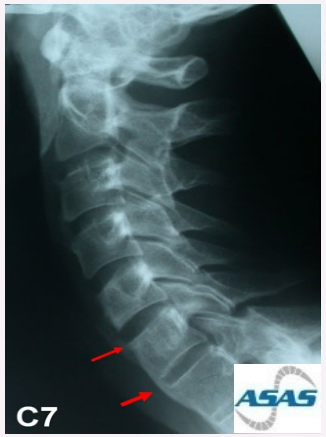
axSpA is characterised by **ectopic bone formation**[3]

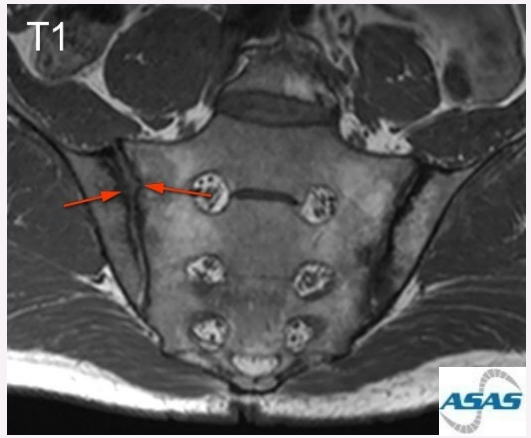
- This results in reduced range of motion and stiffness, spinal ankylosis and reduced quality of life[2,3]

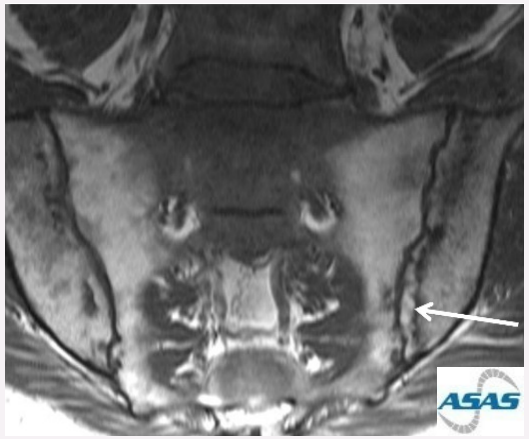
20–50% of patients with PsA have axial involvement[4]

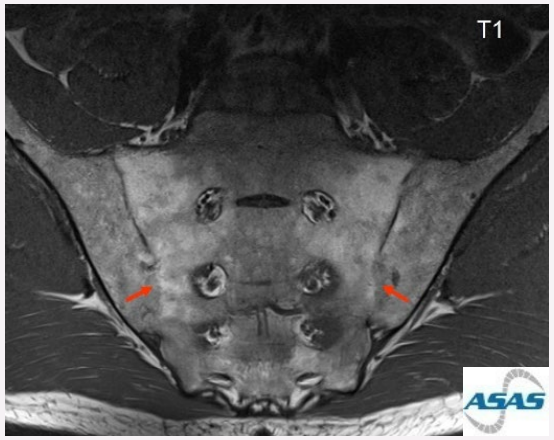
- New bone formation can occur in the **axial skeleton or in peripheral joints**, resulting in chronic pain, functional impairment and decreased quality of life[1]







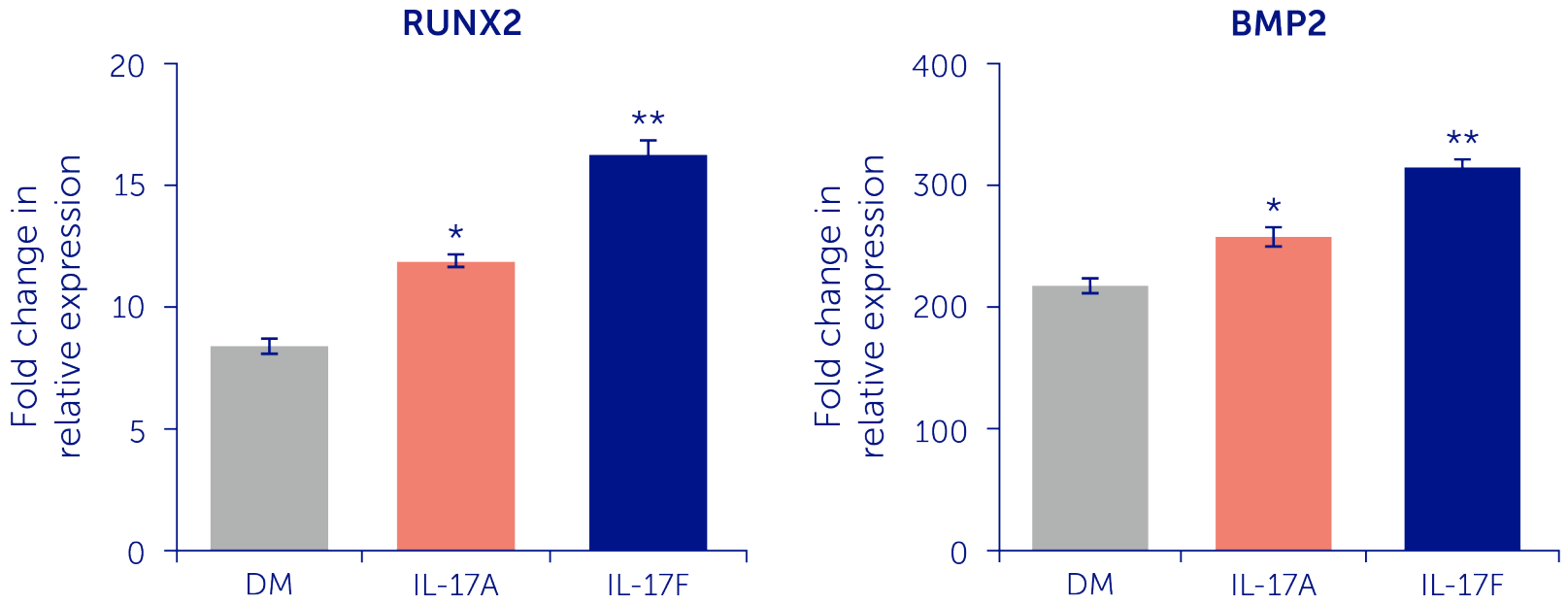




Images adapted from ASAS Educational Slide Kits. 2013. Available at: https://www.asas-group.org/education/asas-slide-library/. Accessed April 2024. axSpA: axial spondyloarthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis.

1. Paine A and Ritchlin C. Calcif Tissue Int. 2018;102(5):559–574. 2. Lories RJU et al. Arthritis Res Ther. 2009;11:221. 3. Klavdianou K et al. Mediterr J Rheumatol. 2022;33(Suppl 1):115–125. 4. McGagh D and Coates LC. Rheumatology (Oxford). 2020;59:i29–i36.

IL-17A and IL-17F in Bone Formation in SpA



IL-17A and IL-17F enhanced *in vitro* osteogenic differentiation and bone formation

Stimulation of hPDCs with IL-17A or IL-17F for 9 days resulted in a **significant increase in the expression of the osteogenic markers RUNX2† and BMP2** compared to differentiation medium

Estimated plotting based on graph visualiser software. *p<0.01; **p<0.001. †RUNX2 is a transcriptional regulator of osteogenesis. Results are expressed as the mean fold change in expression compared to day 0 GM±SEM. hPDCs were isolated from biopsies obtained from 6 patients undergoing orthopedic surgery and cultured under DM or supplemented with 50 ng/mL rhIL-17A or 50 ng/mL IL-17F for 9 days. Target gene quantification was achieved using 2-ΔΔCT method relative to *HPRT1* as the housekeeping gene. BMP2: bone morphogenetic protein 2; DM: differentiation medium; GM: growth medium; hPDCs: human periosteum-derived cells; HPRT1: hypoxanthine phosphoribosyltransferase 1; IL: interleukin; rhIL-17A: recombinant human interleukin-17A; RUNX2: runt-related transcription factor 2; SEM: standard error of mean; SpA: spondyloarthritis.

Adapted from Shah M et al. RMD Open. 2020;6(2):e001306.

Peripheral Joint Damage in Patients with SpA Can Negatively Impact Functionality[1,2]

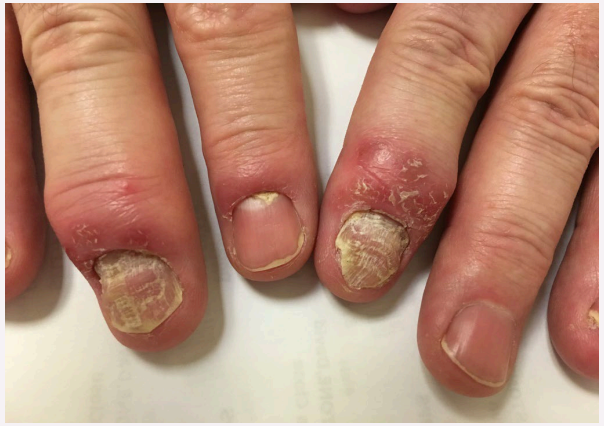
~40% of patients with axSpA have **peripheral arthritis** and **~6%** have **dactylitis**[2,3]

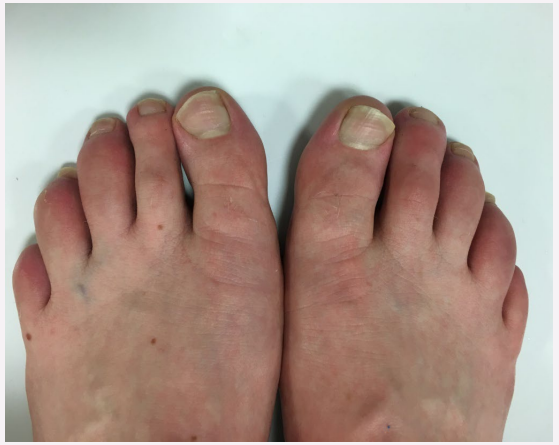
≤100% of patients with PsA have **peripheral arthritis** and **16–50%** have **dactylitis**[4–9]

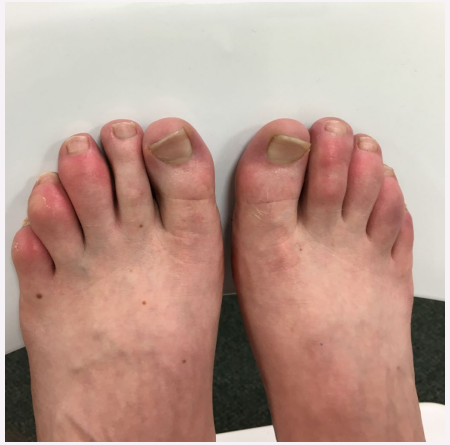
Manifestations of inflammation in the peripheral joints can range from **dactylitis** of the digits to **arthritides** in the large joints of the lower body[3,10,11]

Such manifestations can negatively impact functionality, productivity and overall **quality of life**[1,2]

In PsA, the **EULAR 2023 recommendations** provide updated stringent guidance on the sequencing of treatments for patients with PsA and peripheral arthritis[12]





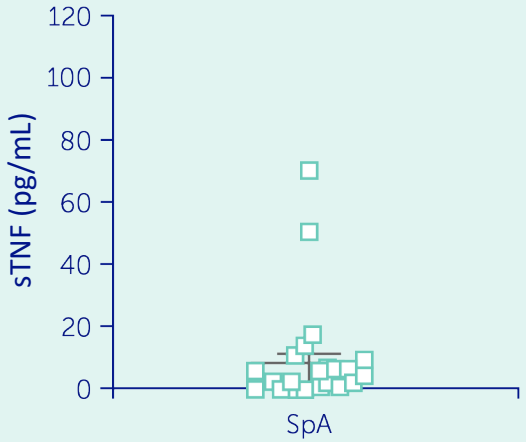


Images courtesy of Professor Dennis McGonagle. axSpA: axial spondyloarthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis.

1. Bagel J and Schwartzman S. Am J Clin Dermatol. 2018;19(6):839–852. 2. López-Medina C et al. Arthritis Res Ther. 2019;21(1):139. 3. de Winter JJ et al. Arthritis Res Ther. 2016;18(1):196. 4. Moll JMH and Wright V. Semin Arthritis Rheum. 1973;3(1):55–78. 5. Torre Alonso JC et al. Br J Rheumatol. 1991;30:245–250. 6. Helliwell PS and Taylor WJ. Ann Rheum Dis. 2005;64(Suppl 2):ii3–ii8. 7. Gladman DD. Ann Rheum Dis. 2006;65(Suppl 3):iii22–iii24. 8. Acosta Felquer ML and FitzGerald O. Clin Exp Rheumatol. 2015;33(5 Suppl 93):S26–S30. 9. Helliwell PS et al. J Rheumatol. 2005;32:1745–1750. 10. Kaeley GS et al. Semin Arthritis Rheum. 2018;48(2):263–273. 11. Alpay-Kanıtez N et al. Eur J Rheumatol. 2018;6(4):167–173. 12. Gossec L et al. Ann Rheum Dis. 2024;0:1–14. doi:10.1136/ard-2024-225531.

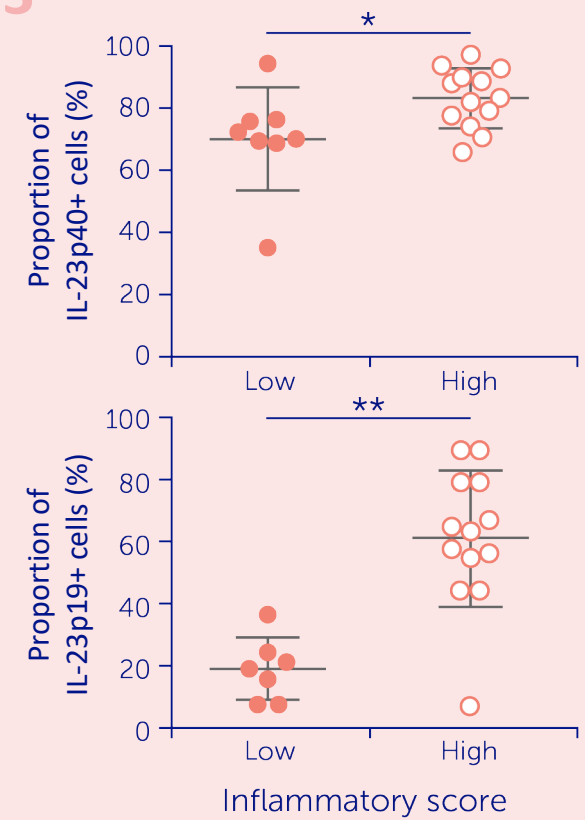
Extracellular Cytokines in Peripheral Joints in SpA

TNF[1]



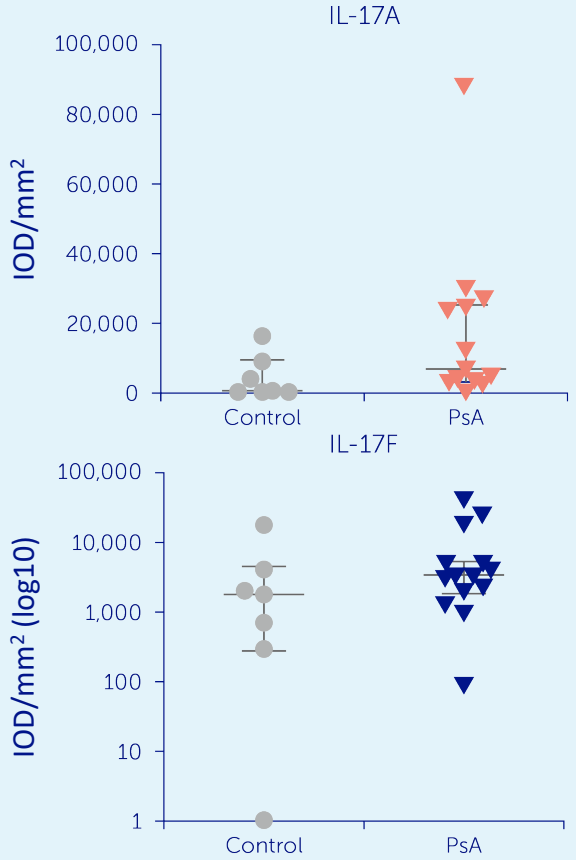
Soluble TNF protein was present in synovial fluid samples from patients with SpA[1,†]

IL-23[2]



The proportions of **IL-23p40- and IL-23p19-positive cells were significantly higher** in synovial tissue from patients with PsA with a high inflammatory score compared with synovial tissue with a low inflammatory score[2,‡]

IL-17[3]



In PsA **synovial tissue, IL-17A and IL-17F were abundantly expressed**[3,§]

Estimated plotting based on graph visualiser software. *p<0.05.[2] **p<0.01.[2] †Soluble TNF expression was measured by ELISA in 20 patients with SpA.[1] ‡IL-23p40- and IL-23p19-positive cells were determined using QuPath software and are presented as a percentage of total number of cells (n=4–8 for low inflammatory score; n=13–14 for high inflammatory score). Data are presented as mean±SD.[2] §IL-17A data presented on a linear scale, IL-17F data presented on a logarithmic scale,. Synovial biopsies were obtained from 15 patients diagnosed with PsA, as defined by the CASPAR criteria, and 7 non-inflammatory control patients. Expression of IL-17A and IL-17F was determined by immunohistochemistry using monoclonal antibodies. The intensity of staining was analysed using digital image analysis.[3] CASPAR: ClASsification Criteria for Psoriatic Arthritis; ELISA: enzyme-linked immunosorbent assay; IL: interleukin; IOD: integrated optical density; PsA: psoriatic arthritis; SD: standard deviation; SpA: spondyloarthritis; (s)TNF: (soluble) tumour necrosis factor.

1. Adapted from Kaaij MH et al. J Exp Med. 2020;217(10):e20200288. 2. Adapted from Nerviani A et al. Ann Rheum Dis. 2021;80(5):591–597. 3. Adapted from van Baarsen LGM et al. Arthritis Res Ther. 2014;16(4):426.

Summary

There are many inflammatory cytokines implicated in SpA disease manifestations, including TNF, IL-12, IL-23 and IL-17[1–10]

Within the IL-17 family, **IL-17A** and **IL-17F have been shown to play a role in SpA disease manifestations** including psoriasis,[5] enthesitis,[10] bone formation[11] and peripheral arthritis and synovitis[12]

IL: interleukin; PsA: psoriatic arthritis; SIJ: sacroiliac joint; SpA: spondyloarthritis; TNF: tumour necrosis factor.

1. Adapted from McGonagle D et al. Front Immunol. 2021;12:614255. 2. Adapted from Yeremenko N. Curr Opin Rheumatol. 2021;33(4):333–340. 3. Ramiro S et al. Ann Rheum Dis. 2023;82(1):19–34.
4. Coates LC et al. Nat Rev Rheumatol. 2022;18(8):465–479. 5. Kolbinger F et al. J Allergy Clin Immunol. 2017;139(3):923–932.e8. 6. Huang JC et al. Ocul Immunol Inflamm. 2021;29(3):558–565.
7. Lin P et al. Ophthalmology. 2014;121(1):365–376. 8. Weinstein JE and Pepple KL. Curr Opin Ophthalmol. 2018;29(3):267–274. 9. Mandour M et al. Front Immunol. 2021;12:618581. 10. McDermott N et al. Ann Rheum Dis. 2023;82(Suppl 1):1184. Abstract AB0011. 11. Shah M et al. RMD Open. 2020;6(2):e001306. 12. van Baarsen LGM et al. Arthritis Res Ther. 2014;16(4):426.