Family Matters: The Central Role of the IL-17 Family of Cytokines in Inflammatory Diseases

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- The speaker has been compensated for the presentation of this information

Evolution of the Understanding of the Pathophysiology of Psoriatic Disease

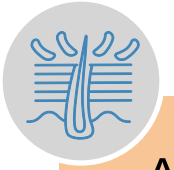
Psoriasis is a skin disease with several clinical manifestations[1-3]

Clinical types of psoriasis include[1,a]

- Plaque
- Scalp and nail disease
- Inverse
- Erythroderma
- Pustular
- Guttate

Plaque psoriasis is the most common type of psoriasis, accounting for 90% of all cases[2]

Characterized by salmon-pink plaques covered in silvery/grey scales[3]

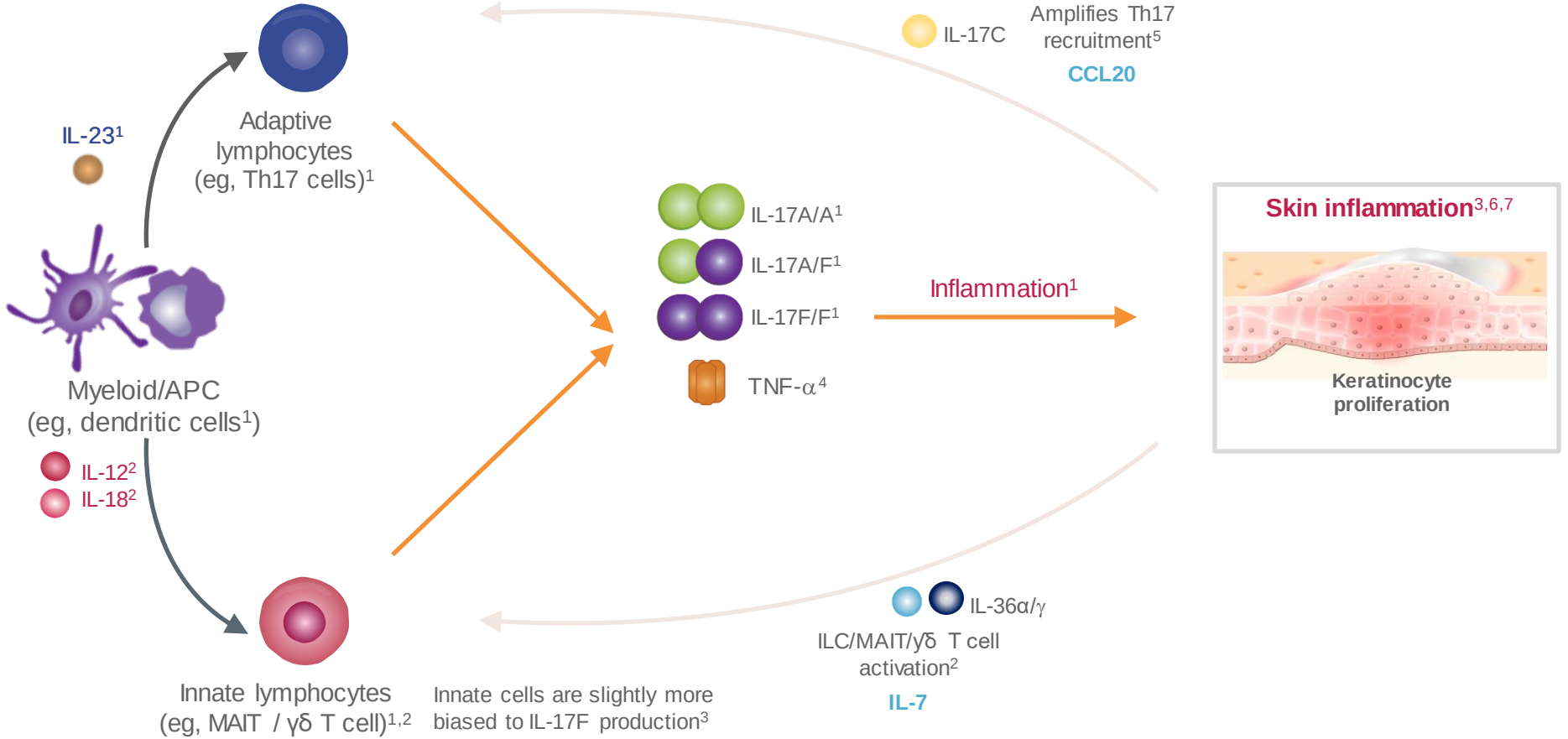


Although the most **common manifestation of psoriasis is at the skin**, recognition of psoriasis as a chronic, multisystem inflammatory disorder is imperative in order to optimize management[4]

[a]List is not exhaustive.

1. Langley RG, et al. *Ann Rheum Dis*. 2005;64 suppl 2(suppl 2):ii18-ii23; discussion ii24-ii25. 2. Griffiths CE, Barker JN. *Lancet*. 2007;370(9583):263-271. 3. Griffiths CEM, et al. *Lancet*. 2021;397(10281):1301-1315. 4. Elmets CA, et al. *J Am Acad Dermatol*. 2019;80(4):1073-1113.

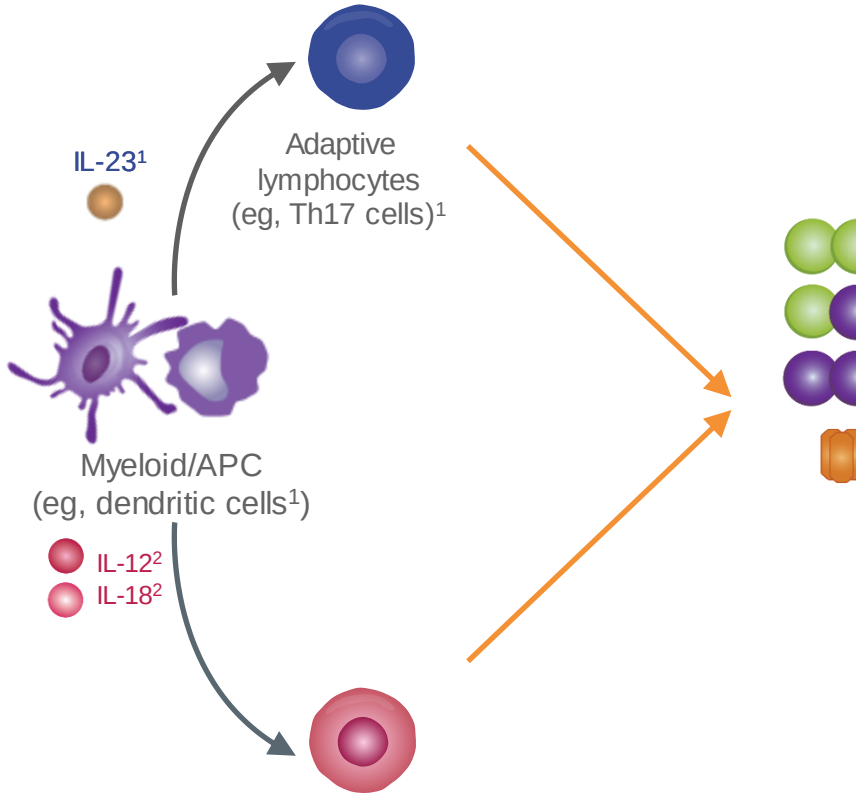
The IL-23/IL-17 Axis: A Central Part of the Pathophysiology of PSO[1-7]

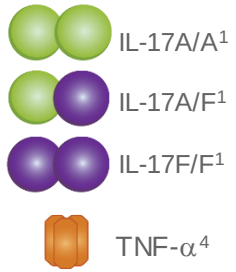


APC, antigen-presenting cell; BMP, bone morphogenetic protein; CCL, C-C motif chemokine ligand; γδ, gamma delta; IL, interleukin; ILC, innate lymphoid cell; MAIT, mucosal-associated invariant T cell; PsA, psoriatic arthritis; RANKL, receptor activator of nuclear factor κB ligand; Th, T helper; TNF, tumor necrosis factor. Example cell types are shown; not an exhaustive list.

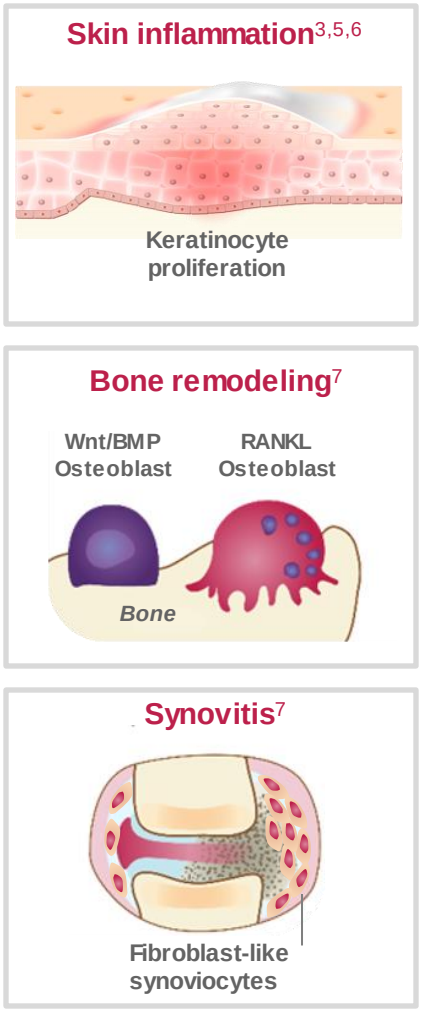
1. Tsukazaki H, Kaito T. *Int J Mol Sci*. 2020;21(17):6401. **2.** Rosine N, Miceli-Richard C. *Front Immunol*. 2021;11:553742. **3.** Cole S, et al. *Front Immunol*. 2020;11:585134. **4.** Blanco P, et al. *Cytokine Growth Factor Rev*. 2008;19(1):41-52. **5.** Russell T, et al. *Cells*. 2021;10(2):341. **6.** Lynde CW, et al. *J Am Acad Dermatol*. 2014;71(1):141-150. **7.** Oliver R, et al. *Br J Dermatol*. 2021;10.1111/bjd.20827.

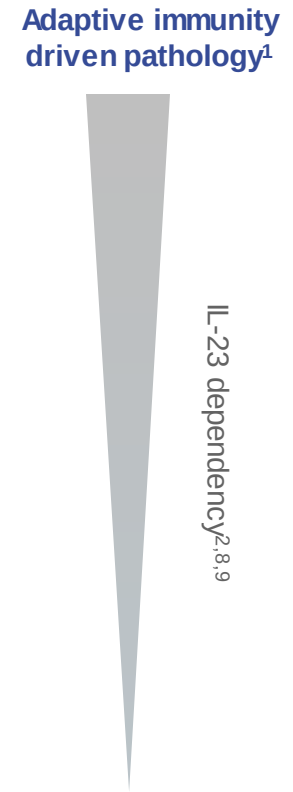
The IL-23/IL-17 Axis: A Central Part of the Pathophysiology of Psoriatic Disease[1-10]





Inflammation[1]





APC, antigen-presenting cell; BMP, bone morphogenetic protein; CCL, C-C motif chemokine ligand; γδ, gamma delta; IL, interleukin; ILC, innate lymphoid cell; MAIT, mucosal-associated invariant T cell; PsA, psoriatic arthritis; RANKL, receptor activator of nuclear factor κB ligand; Th, T helper; TNF, tumor necrosis factor. Example cell types are shown; not an exhaustive list.

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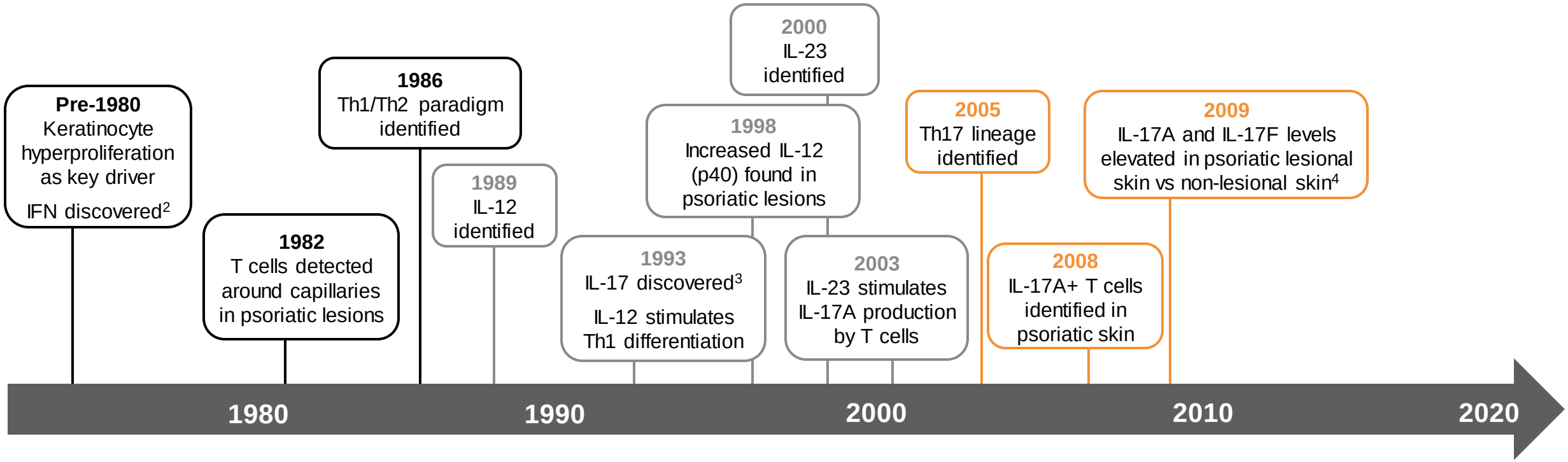
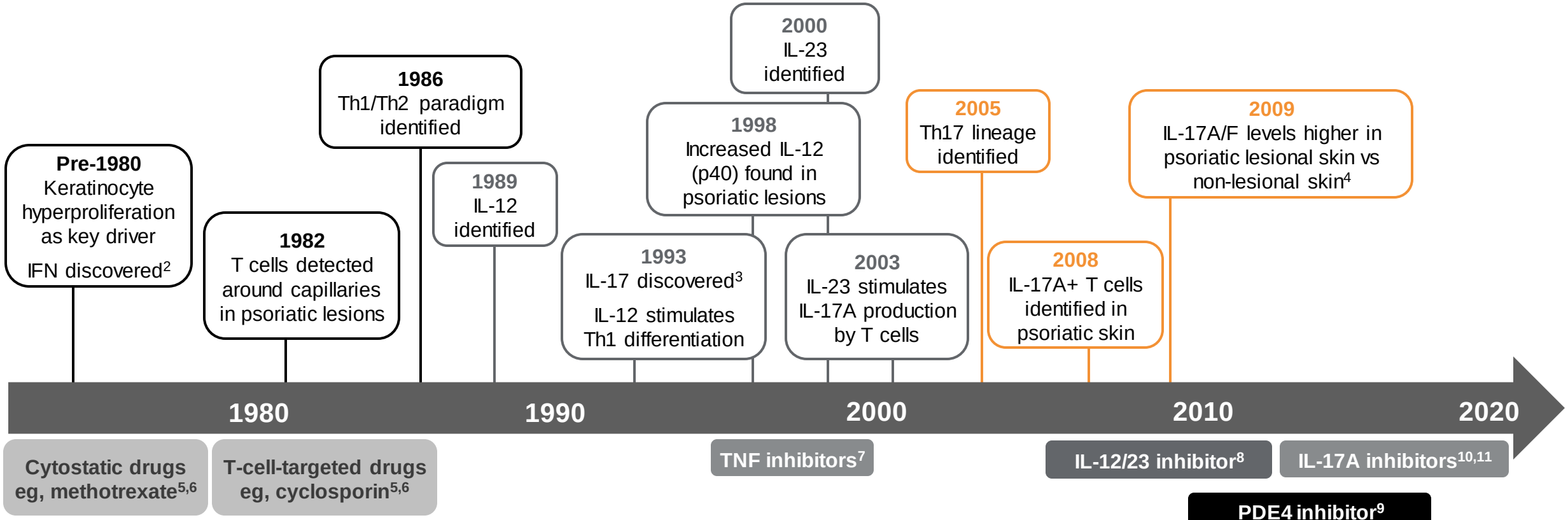
The conceptual understanding of psoriasis pathophysiology has continued to evolve since the 1980s[1]



IFN, interferon; IL, interleukin; Th, T helper.

1. Lynde CW, et al. *J Am Acad Dermatol.* 2014;71(1):141-150. 2. Lindenmann J, et al. *Br J Exp Pathol.* 1957;38(5):551-562.
3. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 4. Johansen C, et al. *Br J Dermatol.* 2009;160(2):319-324.

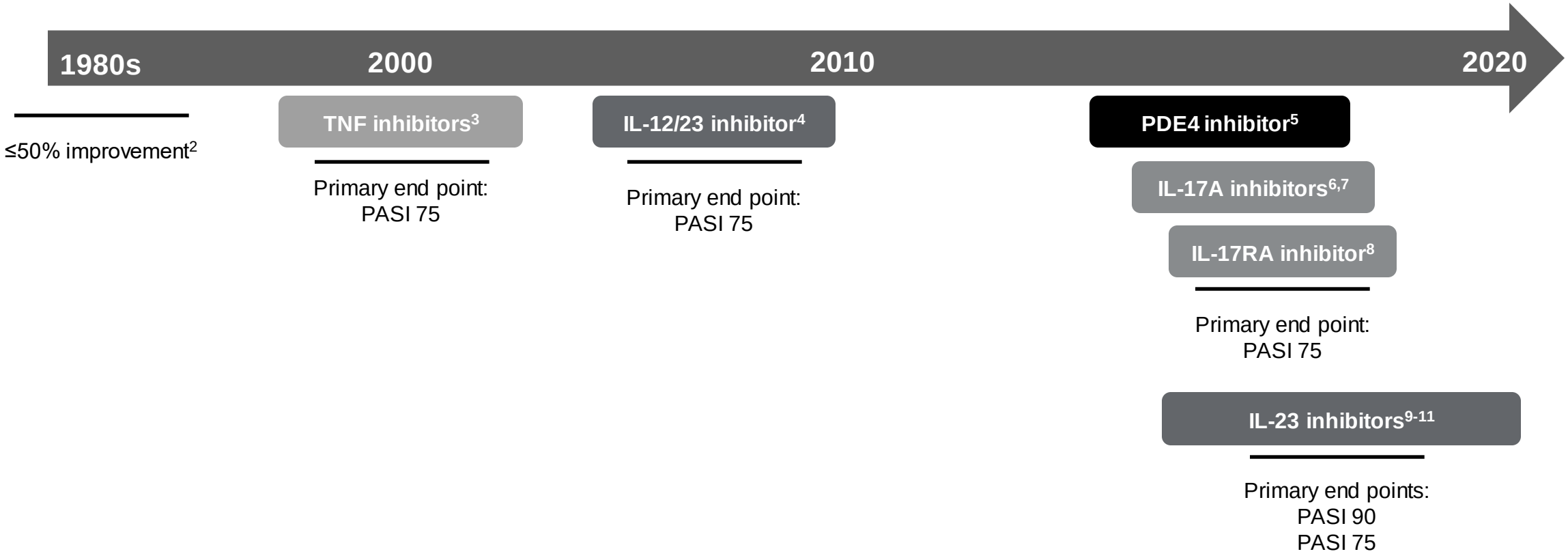
With advancement of conceptual understanding, treatment modalities have continued to evolve as well[1]



IFN, interferon; IL, interleukin; PDE4, phosphodiesterase 4; RA, receptor A; Th, T helper; TNF, tumor necrosis factor.

1. Lynde CW, et al. *J Am Acad Dermatol.* 2014;71(1):141-150. 2. Lindenmann J, et al. *Br J Exp Pathol.* 1957;38(5):551-562. 3. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 4. Johansen C, et al. *Br J Dermatol.* 2009;160(2):319-324. 5. Menter A, et al. *J Am Acad Dermatol.* 2009;61(3):451-485. 6. Rønholt K, Iversen L. *Int J Mol Sci.* 2017;18(11):2297. doi:10.3390/ijms18112297 7. Enbrel. Prescribing information. Amgen Inc; 2021. 8. Stelara. Prescribing information. Janssen Biotech Inc; 2020. 9. Otezla. Prescribing information. Amgen Inc; 2020. 10. Cosentyx. Prescribing information. Novartis Pharmaceuticals Corp; 2021. 11. Taltz. Prescribing information. Eli Lilly and Co; 2021. 12. Siliq. Prescribing information. Bausch Health US LLC; 2020. 13. Tremfya. Prescribing information. Janssen Biotech Inc; 2020. 14. Ilumya. Prescribing information. Sun Pharma; 2020. 15. Skyrizi. Prescribing information. AbbVie Inc; 2021.

Evolution in treatment end points with emergence of new treatment modalities[1]



IL, interleukin; PASI 75, ≥75% reduction in the Psoriasis Area and Severity Index; PASI 90, ≥90% reduction in the Psoriasis Area and Severity Index; PDE4, phosphodiesterase 4; RA, receptor A; TNF, tumor necrosis factor.

1. Rønholt K, Iversen L. *Int J Mol Sci*. 2017;18(11):2297. doi:10.3390/ijms18112297. 2. Weinstein GD, et al. *Arch Dermatol*. 1989;125(2):227-230. 3. Enbrel. Prescribing information. Amgen Inc; 2021. 4. Stelara. Prescribing information. Janssen Biotech Inc; 2020. 5. Otezla. Prescribing information. Amgen Inc; 2020. 6. Cosentyx. Prescribing information. Novartis Pharmaceuticals Corp; 2021. 7. Taltz. Prescribing information. Eli Lilly and Co; 2021. 8. Siliq. Prescribing information. Bausch Health US LLC; 2020. 9. Tremfya. Prescribing information. Janssen Biotech Inc; 2020. 10. Ilumya. Prescribing information. Sun Pharma; 2020. 11. Skyrizi. Prescribing information. AbbVie Inc; 2021.

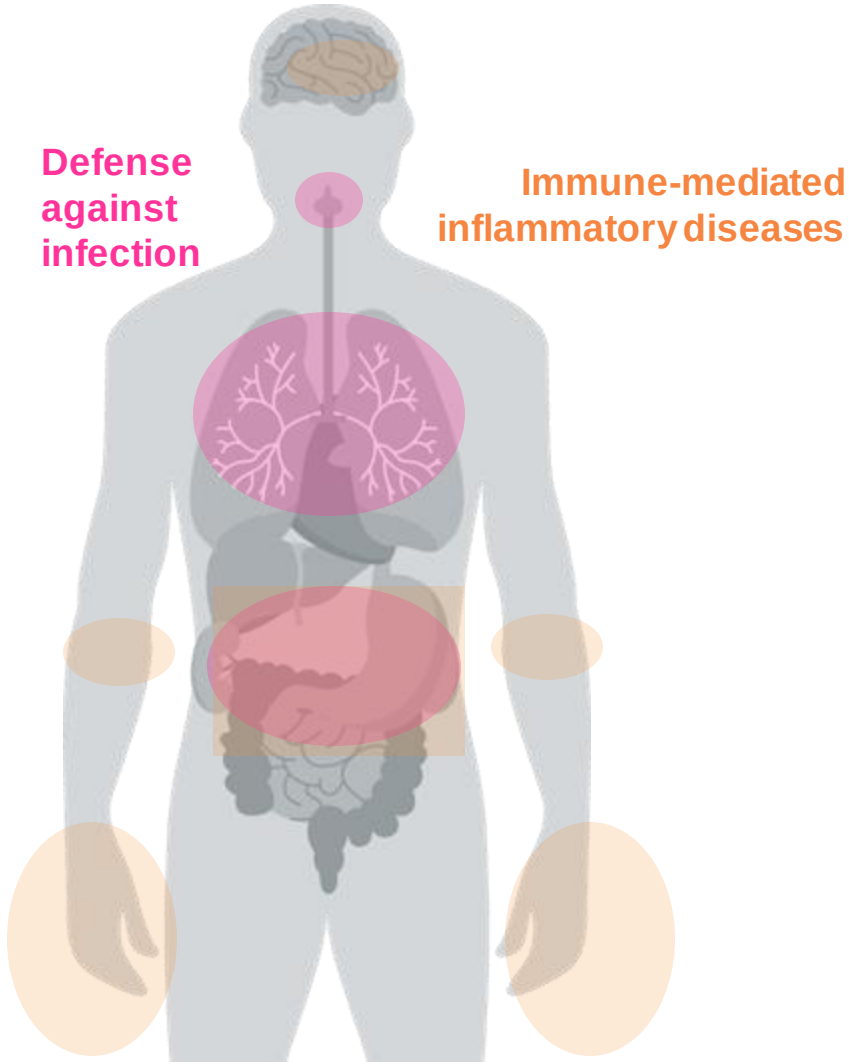
A Closer Look at the IL-17 Family of Cytokines

IL-17 family cytokines are linked to the pathogenesis of inflammatory disease

IL-17 family cytokines were originally discovered in T cells[1]

They are now known to be secreted by macrophages, dendritic cells (DCs), natural killer cells, natural killer T cells, lymphoid tissue inducer cells, and γδ-T cells[1]

IL-17 cytokines play diverse roles in **defense against infection** and in the pathogenesis of diverse **immune-mediated inflammatory diseases**, including psoriasis, rheumatoid arthritis, hidradenitis suppurativa, psoriatic arthritis, inflammatory bowel disease, and systemic lupus erythematosus[1-3]

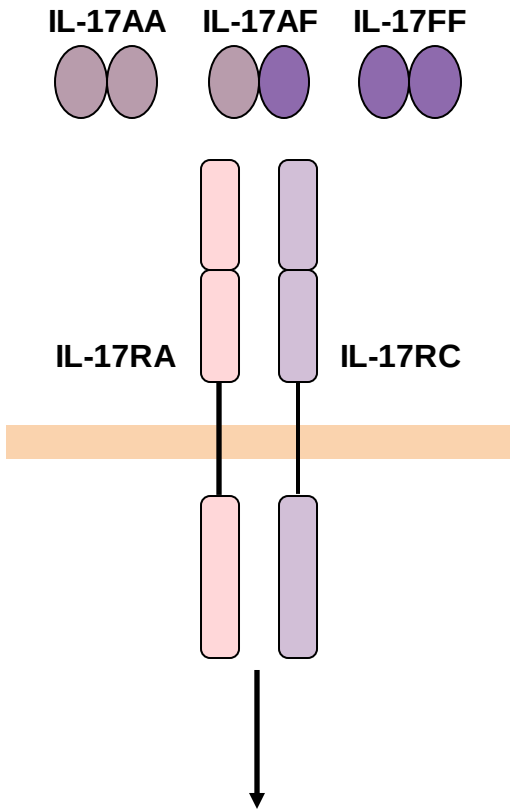


Depositphotos via Getty Images

IL, interleukin.

1. Onishi RM, Gaffen SL. *Immunology*. 2010;129(3):311-321. 2. Fletcher JM, et al. *Clin Exp Immunol*. 2020;201(2):121-134.
3. Blauvelt A, Chiricozzi A. *Clin Rev Allergy Immunol*. 2018;55(3):379-390.

IL-17 family members play key roles in immune-mediated inflammatory diseases and other diseases[1,2]

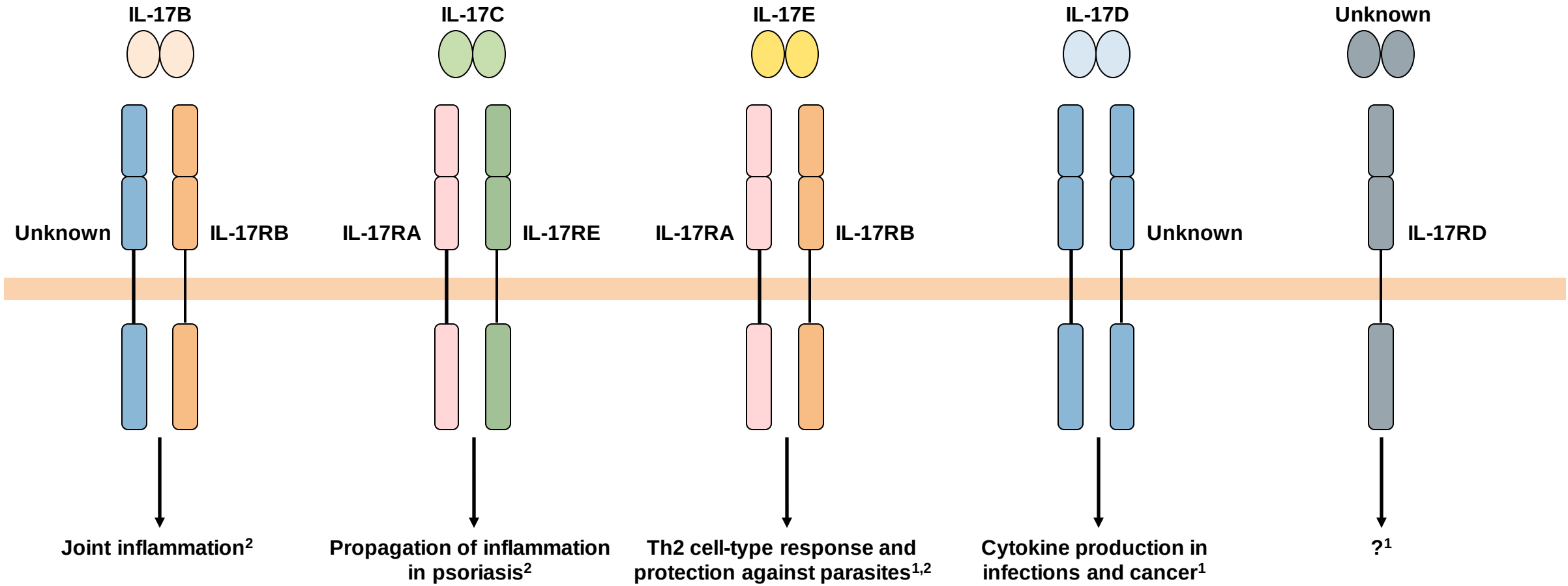


Inflammation in psoriasis and defense against bacterial and fungal infections[1]

IL, interleukin; IL-[x]R, interleukin receptor; Th, T helper.

1. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 2. Brembilla NC, et al. *Front Immunol.* 2018;9:1682.

IL-17 family members play key roles in immune-mediated inflammatory diseases and other diseases[1,2]



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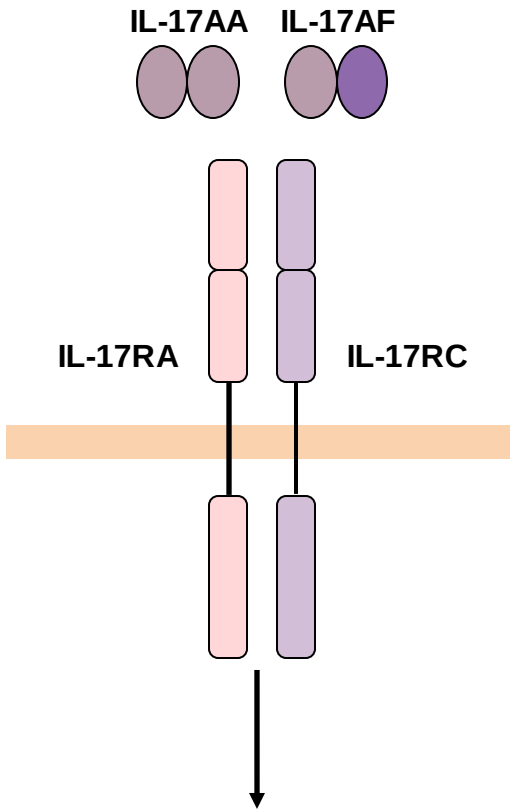
1. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 2. Brembilla NC, et al. *Front Immunol.* 2018;9:1682.

IL-17A binds to the IL-17RA/RC complex[1,2]



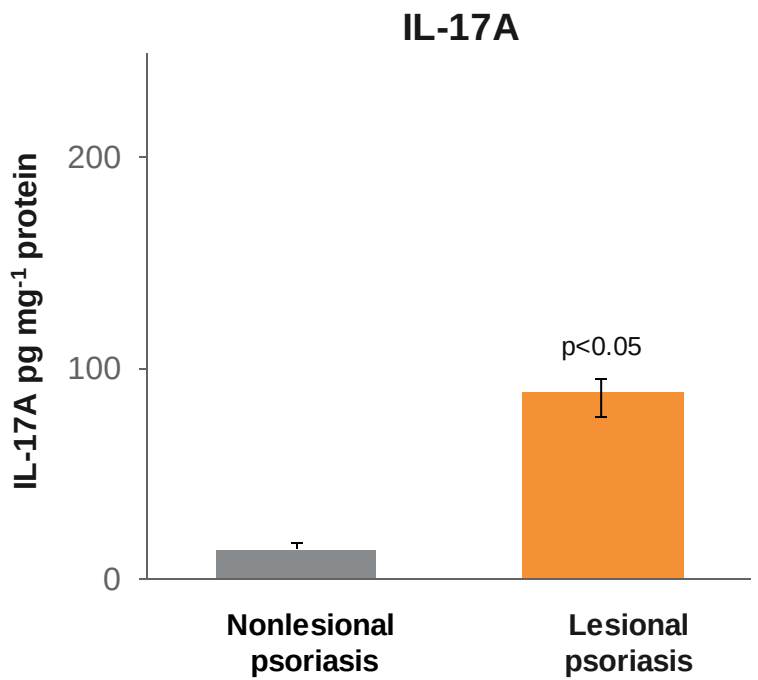
Inflammation in psoriasis and defense against bacterial and fungal infections[1]

IL, interleukin; IL-[x]R, interleukin receptor.

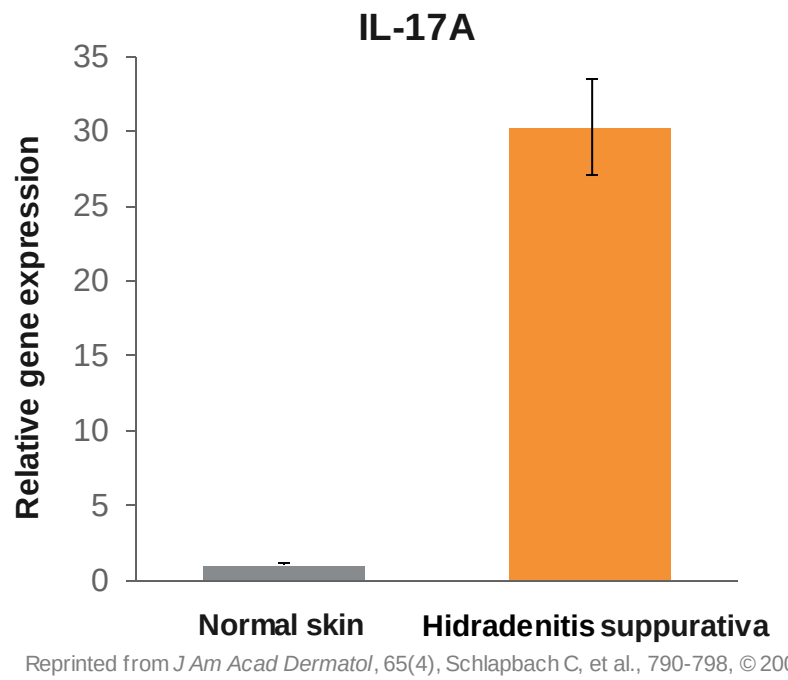
1. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623.

IL-17A is overexpressed in psoriasis and other immune-mediated inflammatory diseases

IL-17A protein expression in patients with psoriasis[1]



IL-17A mRNA levels are increased 30-fold in lesional skin in patients with hidradenitis suppurativa[2]



IL-17A protein levels are elevated in SpA synovial fluid and may also be involved in the pathogenesis of other Immune-mediated inflammatory diseases, including multiple sclerosis and cardiovascular disease[3-5]

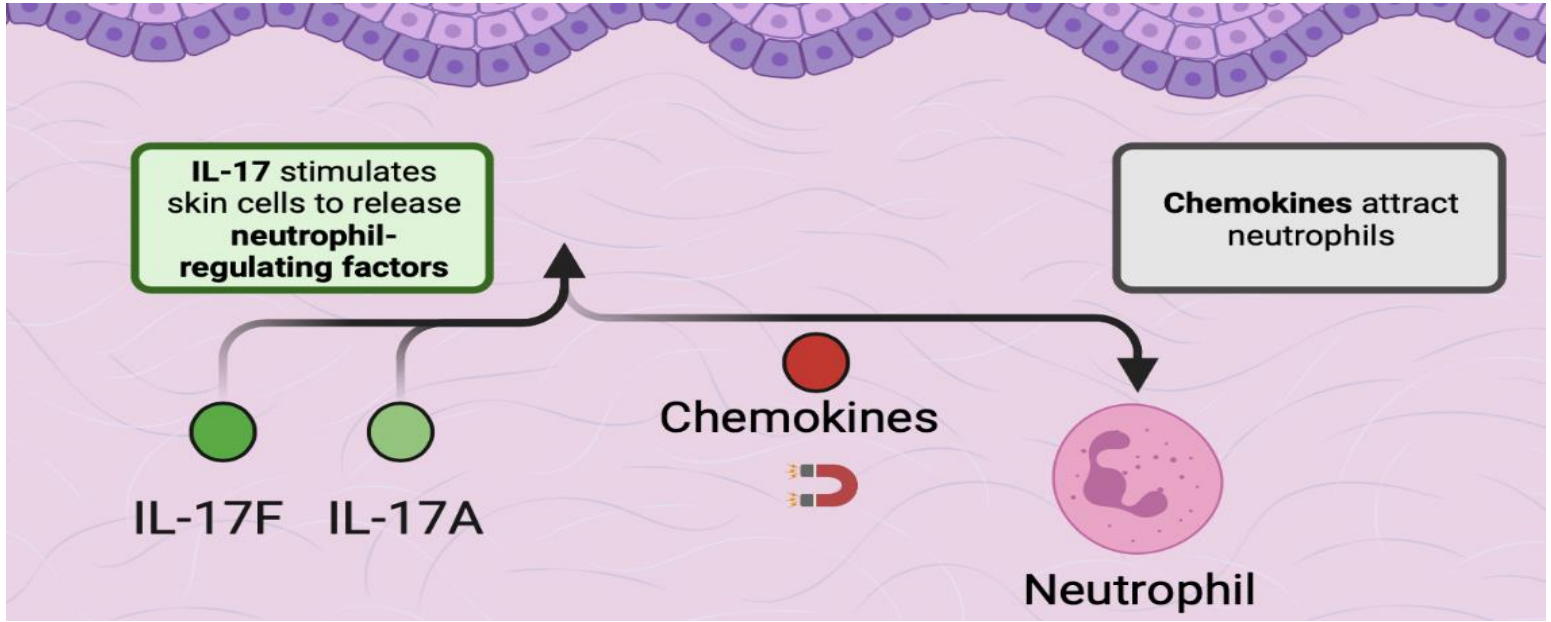
IL, interleukin; mRNA, messenger RNA; SpA, spondyloarthritis.

1. Johansen C, et al. *Br J Dermatol.* 2009;160(2):319-324. 2. Schlapbach C, et al. *J Am Acad Dermatol.* 2011;65(4):790-798. 3. Chen S, et al. *J Rheumatol.* 2020;47(11):1606-1613. 4. Tzartos JS, et al. *Am J Pathol.* 2008;172(1):146-155. 5. von Stebut E, et al. *Front Immunol.* 2020;10:3096. doi:10.3389/fimmu.2019.03096.

IL-17A Triggers Neutrophil Responses in PsA and HS

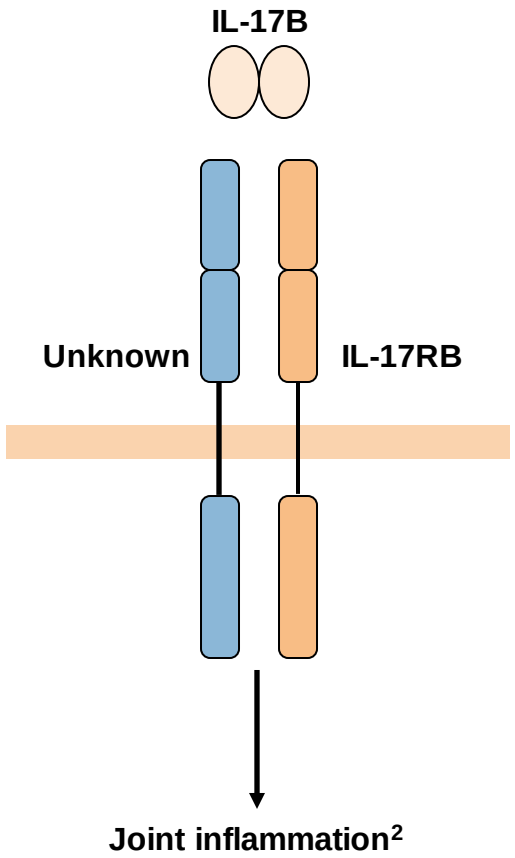
In HS, there is pathogenic activation of the **IL-17–neutrophil axis.**[1-5]

In PsA, neutrophil responses triggered by IL-17A act as a mediator to enhance tendon inflammation leading to enthesitis and tendinitis — typical clinical features of PsA[6]



HS, hidradenitis suppurativa, PsA, psoriatic arthritis. 1. Frew. *J Invest Dermatol*. 2021;doi:10.1016/j.jid.2021.08.400. 2. Giamarellos-Bourboulis et al. *Br J Dermatol*. 2021;185:3. 3. Lima et al. *Br J Dermatol*. 2016;174:514. 4. Byrd et al. *Sci Trans Med*. 2019;11:eaav5908. 5. Glatt et al. *Ann Rheum Dis*. 2018;77:523. 6. Schett G, et al. *Nat Rev Rheumatol*. 2022;18(6):311-325.

IL-17B binds to IL-17RB in complex with an unknown receptor[1,2]



IL, interleukin; IL-[x]R, interleukin receptor.

1. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 2. Brembilla NC, et al. *Front Immunol.* 2018;9:1682.

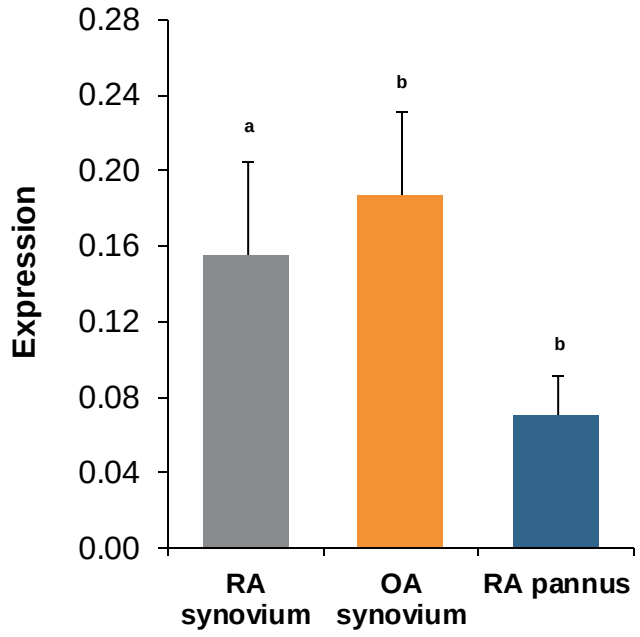
IL-17B may play a role in joint inflammation

IL-17B signals through the IL-17RB receptor[1]

It is expressed by neutrophils, germinal center B cells, neurons, stromal cells, and gut epithelium[1]

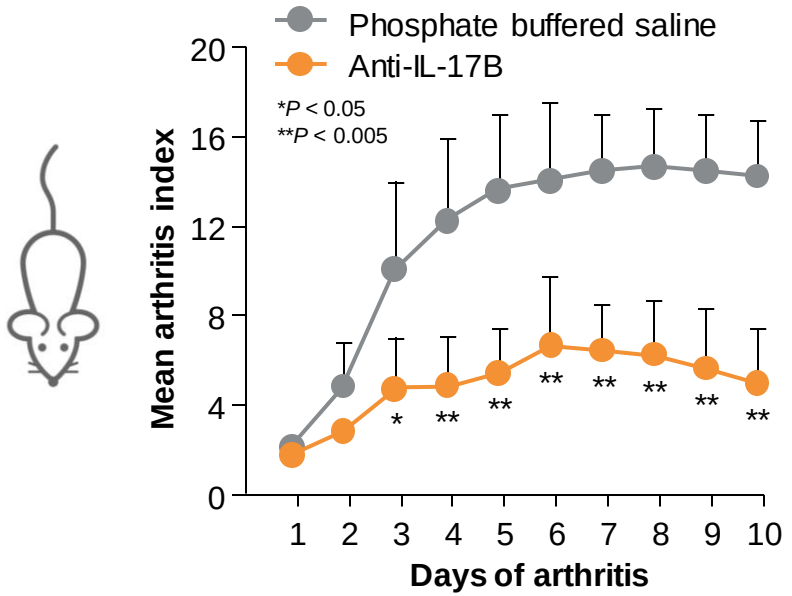
IL-17B is expressed in the synovia and pannus of patients with RA[2,3]

IL-17B Expression[3]



From Kouri VP, et al. *Rheumatology (Oxford)*. 2014;53(1):39-47 by permission of Oxford University Press

IL-17B was upregulated in the arthritic paws of collagen-induced arthritis mice relative to the paws of control mice, and IL-17B neutralization suppressed signs of arthritis[4]



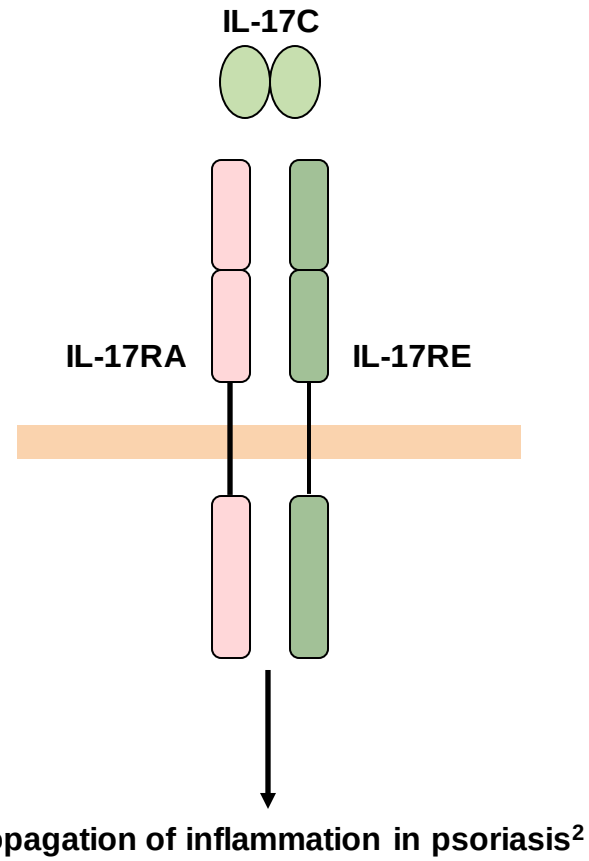
Reprinted from *J Immunol*, 179(10), Yamaguchi Y, et al., 7128-7136, © 2007, with permission from Elsevier. Images courtesy of Getty Images

IL, interleukin; IL-17R, interleukin 17 receptor; OA, osteoarthritis; RA, rheumatoid arthritis.

[a] Significant difference ($P < 0.05$) in expression against IL-17D, IL-17E, and IL-17F in RA. [b] Significant difference ($P < 0.05$) in expression in OA and pannus against all other cytokines tested (IL-17A, IL-17C, IL-17D, IL-17E, and IL-17F).

1. Bie Q, et al. *Mol Immunol.* 2017;90:50-56. 2. Stamp LK, et al. *Arthritis Rheum.* 2008;58(6):1601-1608. 3. Kouri VP, et al. *Rheumatology (Oxford).* 2014;53(1):39-47. 4. Yamaguchi Y, et al. *J Immunol.* 2007;179(10):7128-7136.

IL-17C binds to the IL-17RA/RE complex[1,2]

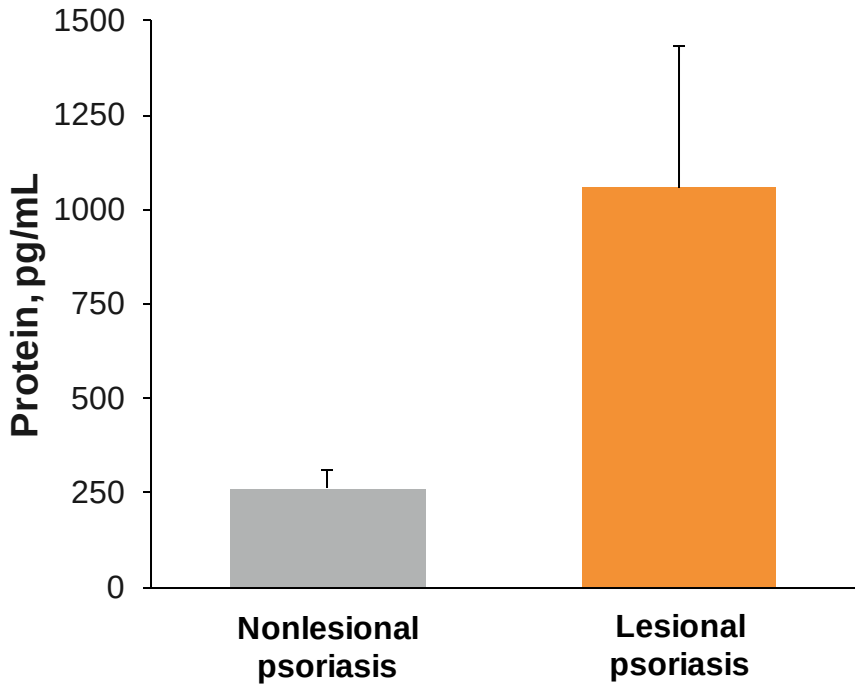


IL, interleukin; IL-[x]R, interleukin receptor.

1. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 2. Brembilla NC, et al. *Front Immunol.* 2018;9:1682.

IL-17C is expressed by activated keratinocytes in psoriatic skin and acts on its receptor on Th17 cells to propagate inflammation

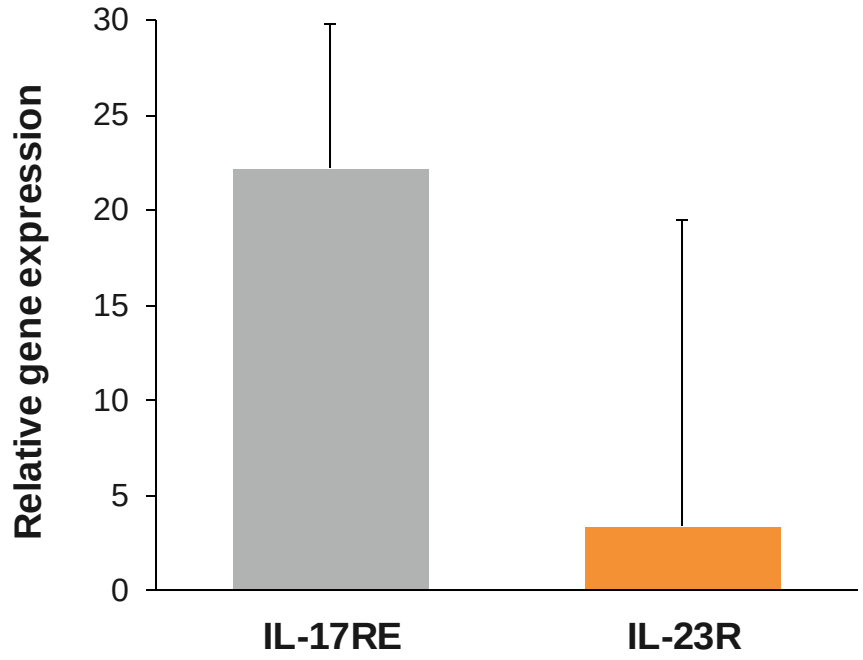
IL-17C protein levels are elevated in lesional vs nonlesional skin in patients with psoriasis[1]



IL-17C protein levels in patient skin biopsies (N = 8)

The IL-17C receptor IL-17RE is present on Th17 cells[2]

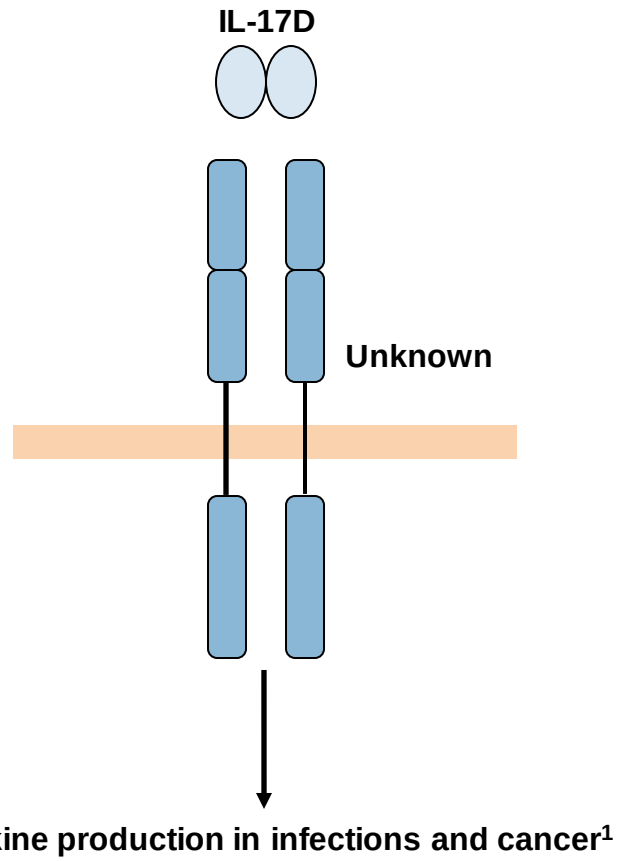
IL-17RE (in a dimer with IL-17RA) is the receptor for IL-17C[3]



IL, interleukin; IL-[x]R, interleukin receptor; Th, T helper.

1. Johnston A, et al. *J Immunol.* 2013;190(5):2252-2262. 2. Maggi L, et al. *Eur J Immunol.* 2012;42(12):3180-3188. 3. Ramirez-Carrozzi V, et al. *Nat Immunol.* 2011;12(12):1159-1166.

IL-17D binds to an unknown receptor complex[1,2]



IL, interleukin; IL-[x]R, interleukin receptor.

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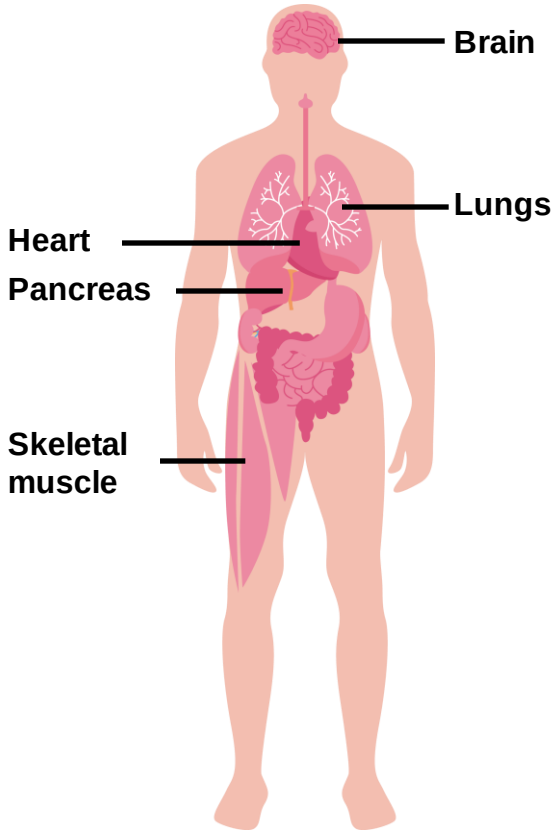
The pathogenic role of IL-17D remains to be elucidated

While its receptor is unknown, IL-17D is expressed in various sites throughout the body[1,2]



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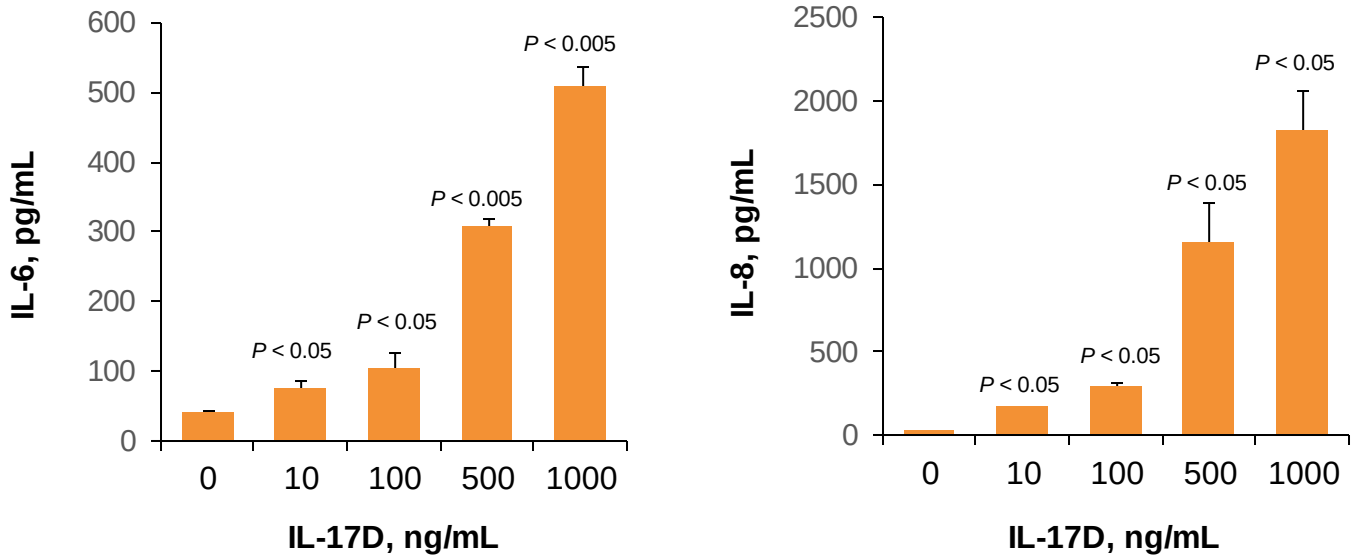
In culture, IL-17D treatment stimulates the production of cytokines, suggesting a potential role in mediating inflammation[2]

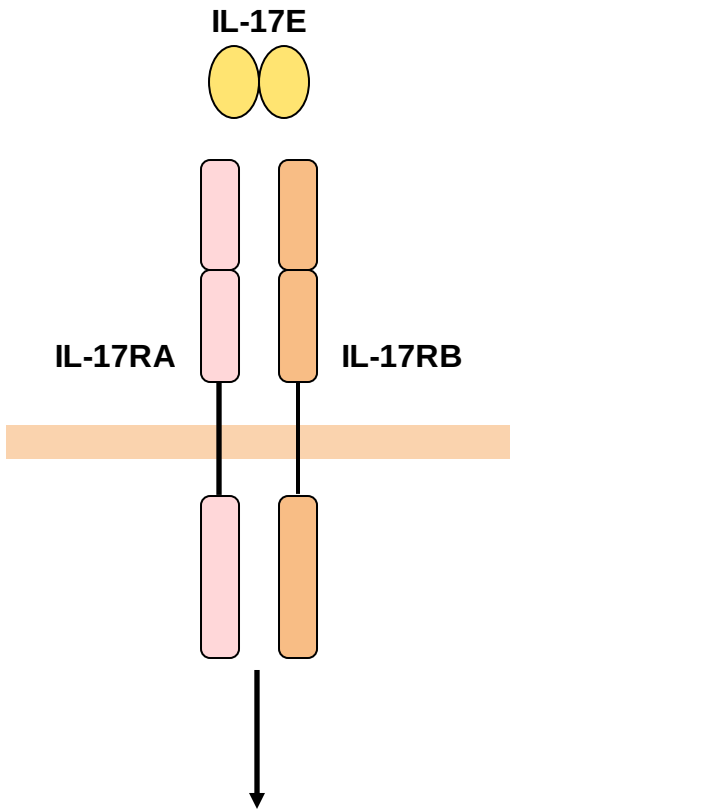


While its function remains unknown, IL-17D has been implicated to potentially play a pathogenic role in rheumatoid nodules and cancer[1,3]

IL, interleukin.

1. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 2. Starnes T, et al. *J Immunol.* 2002;169(2):642-646. 3. Stamp LK, et al. *Arthritis Rheum.* 2008;58(6):1601-1608.

IL-17E binds to the IL-17RA/RB complex[1,2]



Th2 cell-type response and protection against parasites[1,2]

IL, interleukin; IL-[x]R, interleukin receptor; Th, T helper.

1. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 2. Brembilla NC, et al. *Front Immunol.* 2018;9:1682.

IL-17E plays a proinflammatory role in Th2-mediated diseases and an anti-inflammatory role in other diseases

IL-17E (also known as IL-25) acts through the IL-17RA/RB receptor complex[1]

It is expressed by adaptive and innate immune cells and epithelial cells[1]

IL-17E can exert **dual inflammatory functions**[1]

PRO-INFLAMMATORY

IL-17E signaling on epithelial cells and type 2 lymphocytes **promotes Th2-type immune responses**[1,2]

Allergic responses, asthma[1]

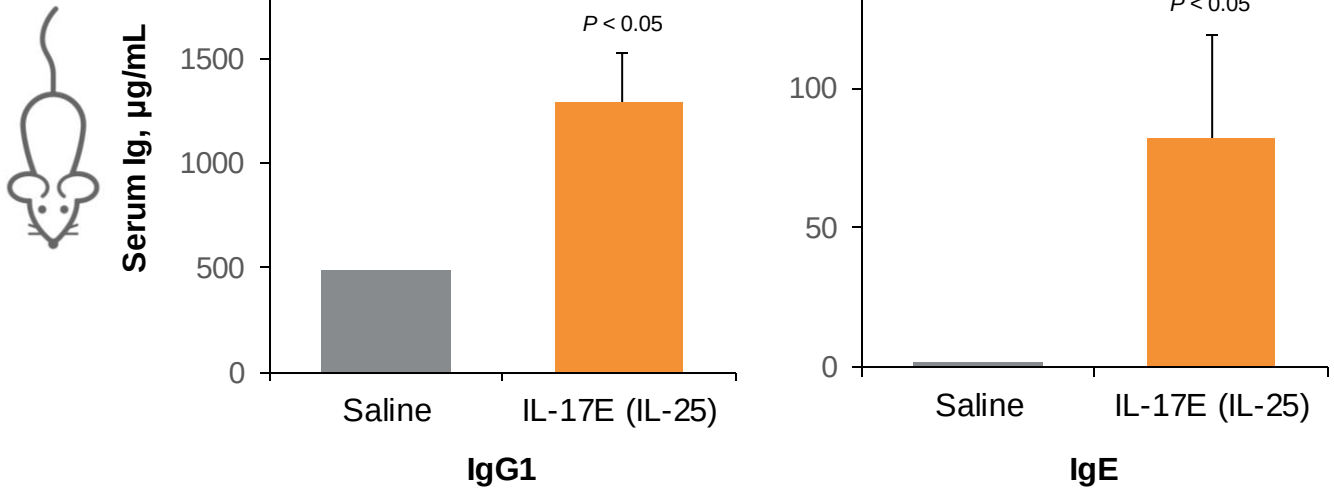
ANTI-INFLAMMATORY

IL-17E **inhibits Th1 or Th17 differentiation** through production of Th2 cytokines[1]

IBD, RA, MS, SLE[1]

*Although IL-17E has been implicated in **psoriasis**, its exact role remains to be elucidated*[1]

IL-17E (IL-25) treatment increases serum levels of IgG1 and IgE in vivo, characteristic of Th2-type inflammation[2]

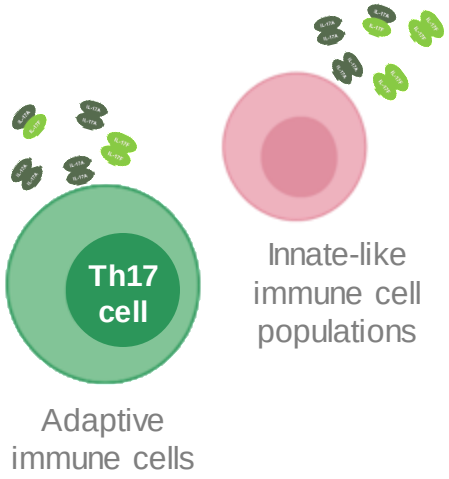


IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; IL-[x]R, interleukin receptor; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; Th, T helper.

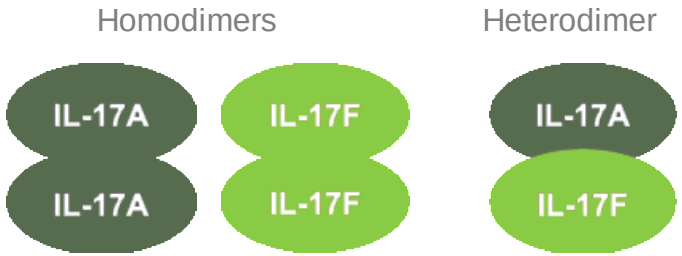
1. Deng C, et al. *Front Immunol.* 2021;12:691559. doi:10.3389/fimmu.2021.691559. 2. Fort MM, et al. *Immunity*. 2001;15(6):985-995.

IL-17A and IL-17F share overlapping biology and are central drivers of inflammation in psoriasis

IL-17A and IL-17F are **produced** by various **adaptive** and **innate-like lymphocyte** populations[1]



IL-17A and IL-17F can occur as either **homodimers** or **heterodimers**[2]

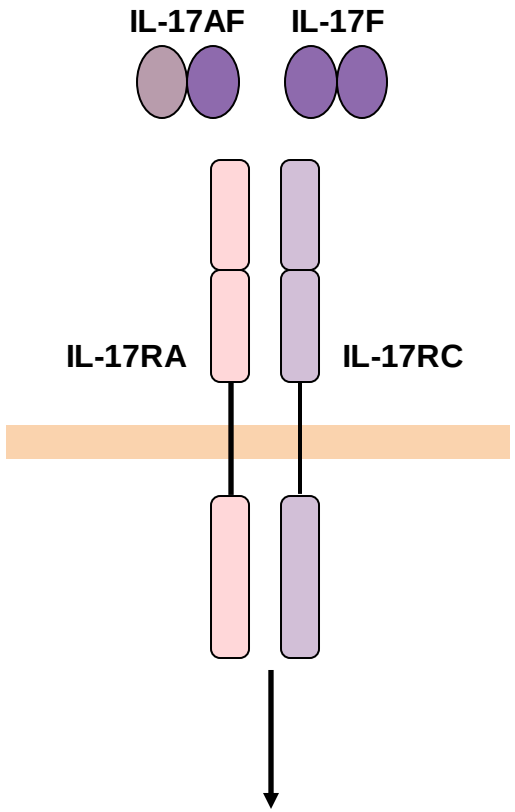


IL-17A and IL-17F signal through the same receptor complex[1,2]

IL, interleukin; IL-17R, interleukin receptor.

1. Jin W, Dong C. *Emerg Microbes Infect*. 2013;2(9):e60. doi:10.1038/emi.2013.58. 2. Brembilla NC, et al. *Front Immunol.* 2018;9:1682. doi:10.3389/fimmu.2018.01682.

IL-17F binds to the IL-17RA/RC complex[1,2]



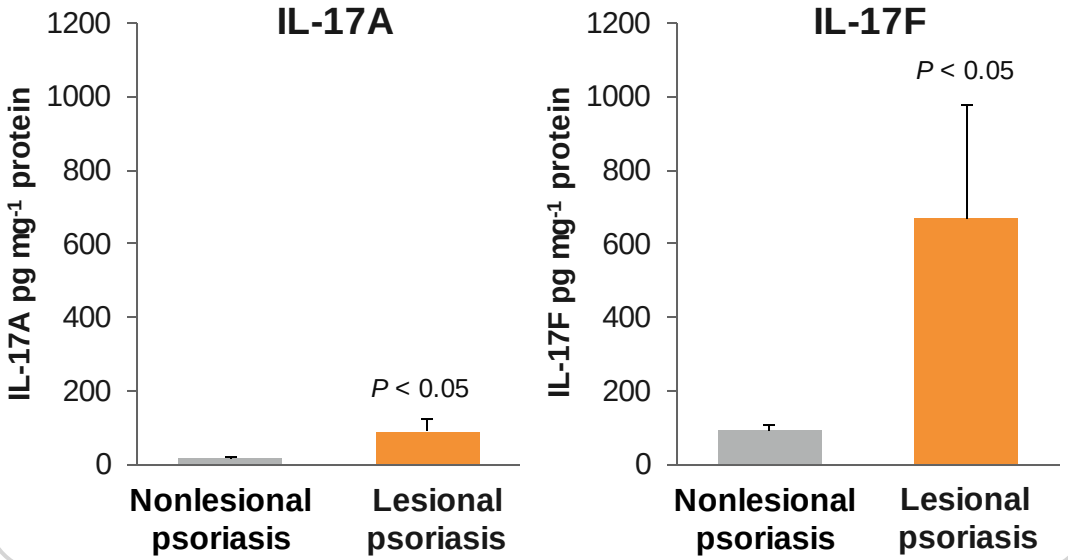
Inflammation in psoriasis and defense against bacterial and fungal infections[1]

IL, interleukin; IL-[x]R, interleukin receptor.

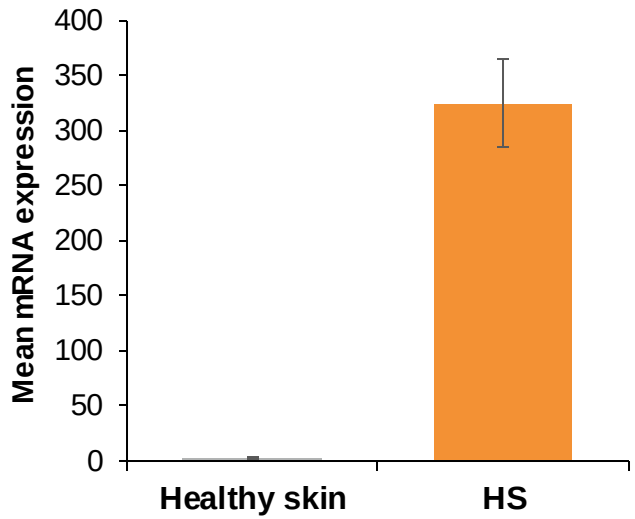
1. Liu X, et al. *Int Arch Allergy Immunol.* 2020;181(8):618-623. 2. Brembilla NC, et al. *Front Immunol.* 2018;9:1682.

IL-17F is overexpressed in psoriasis and other immune-mediated inflammatory diseases

IL-17F, in addition to IL-17A, protein expression is elevated in patients with psoriasis[1]



IL-17F is significantly (~154-fold) elevated in hidradenitis suppurativa lesions compared with healthy skin[2]



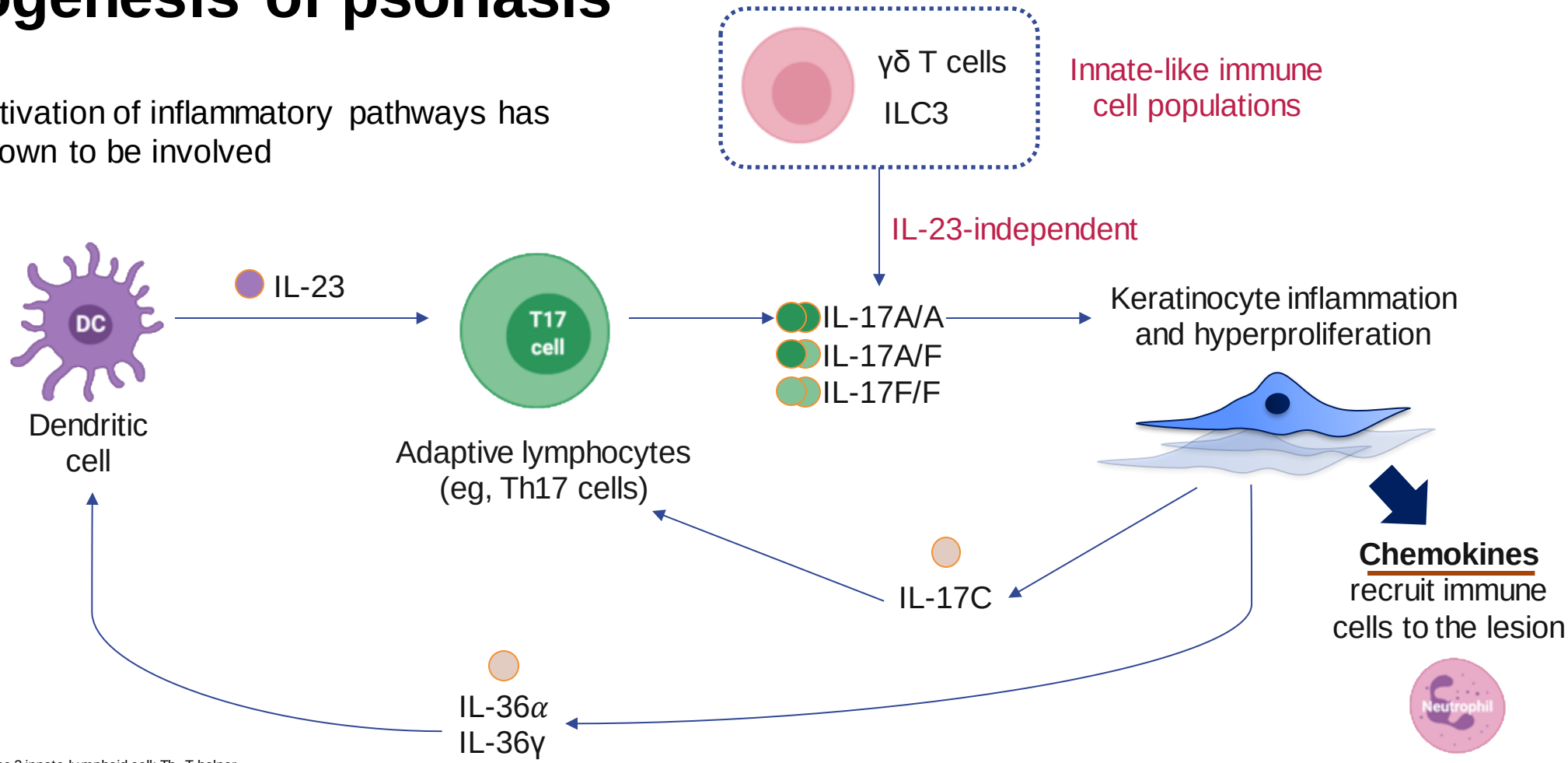
IL-17F may also be implicated in other immune-mediated inflammatory diseases, as it is significantly elevated in inflamed colonic lesions in Crohn's disease (4.4x higher) compared with uninflamed regions, as well as in the serum of patients with atopic dermatitis (1.9x higher) compared with controls.[3,4] Further, it may play an additive role in the proinflammatory cytokine response in psoriatic arthritis[5]

HS, hidradenitis suppurativa; IL, interleukin; mRNA, messenger RNA.

1. Johansen C, et al. *Br J Dermatol.* 2009;160(2):319-324. 2. Rumberger BE, et al. *Inflamm Res.* 2020;69(10):967-973. 3. Seiderer J, et al. *Inflamm Bowel Dis.* 2008;14(4):437-445. 4. Park YA, et al. *Pediatr Allergy Immunol Pulmonol.* 2015;28(2):112-116. 5. Schett G, et al. *Nat Rev Rheumatol.* 2022;18(6):311-325.

Our current understanding of key cytokines that drive the pathogenesis of psoriasis[1-3]

Over-activation of inflammatory pathways has been shown to be involved



IL, interleukin; ILC3, type 3 innate lymphoid cell; Th, T helper.

Example cell types are shown; not an exhaustive list. Adapted from Refs 2 and 3.

1. Lynde CW, et al. *J Am Acad Dermatol.* 2014;71(1):141-150. 2. Krueger J, et al. Genome Informatics 2020;poster presentation. 3. Cole S, et al. *Front Immunol.* 2020;11:585134.

Summary

Summary

Plaque psoriasis is the most common form of psoriasis, and patients experience both cutaneous as well as systemic manifestations

The understanding of the complex pathophysiology of psoriasis and its treatment modalities continues to evolve, and the efficacy standards of treatments keep improving

IL-17A and IL-17F have emerged as key drivers of psoriasis and belong to a larger family of cytokines that include IL-17B, IL-17C, IL-17D, and IL-17E (IL-25)

While the precise functions of many IL-17 family members are yet to be elucidated, they appear to play diverse roles in defense against infection and the pathogenesis of various Immune-mediated inflammatory diseases, including psoriasis

IL, interleukin.