YES or NO sul ruolo delle IL-23 e -17 nella patogenesi della psoriasi

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1. L’IL-23 è prodotta dalle cellule dendritiche?

1. **Sì**
2. **No**

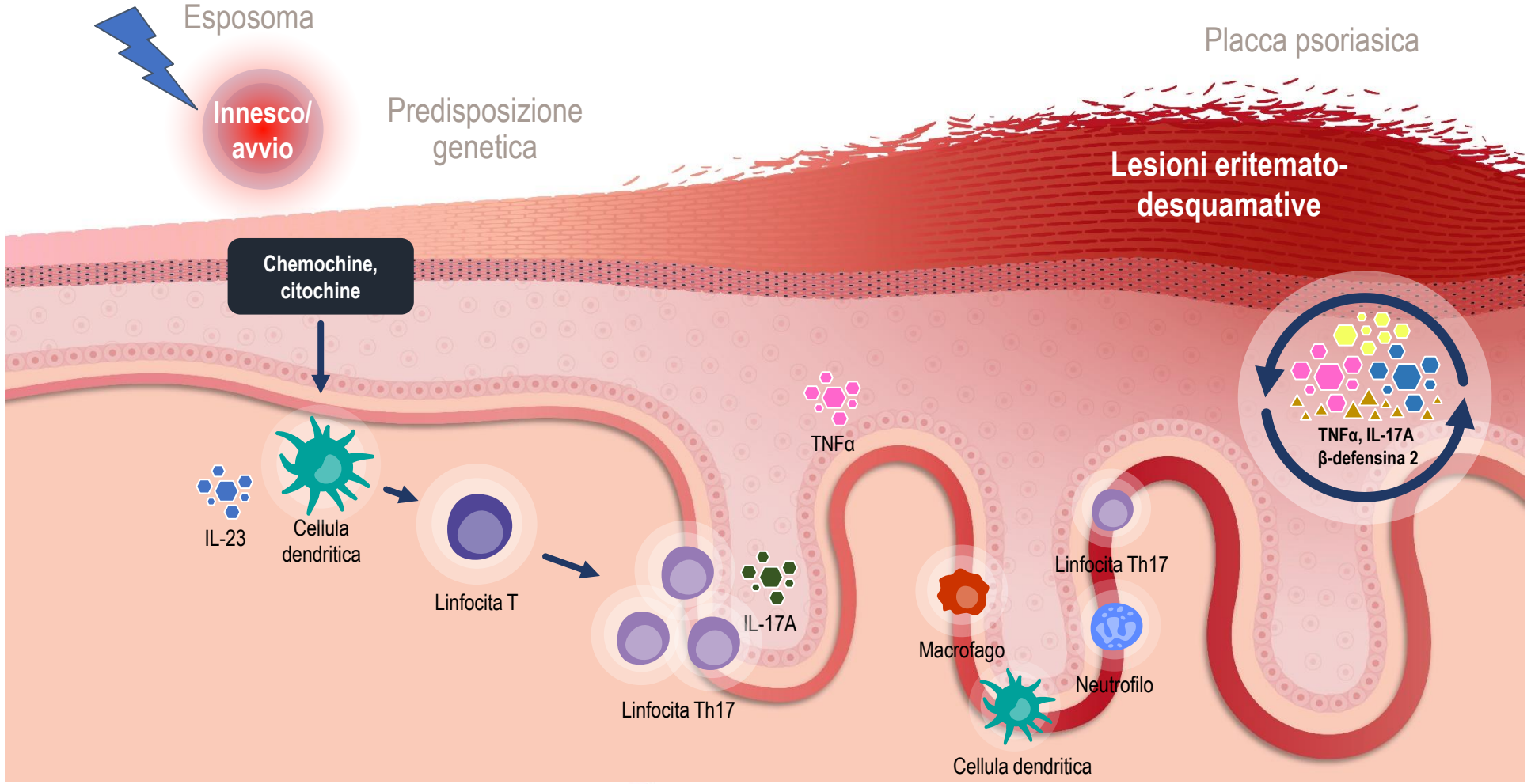
2. Il tildrakizumab blocca il recettore dell'IL-23?

1. **Sì**
2. **No**

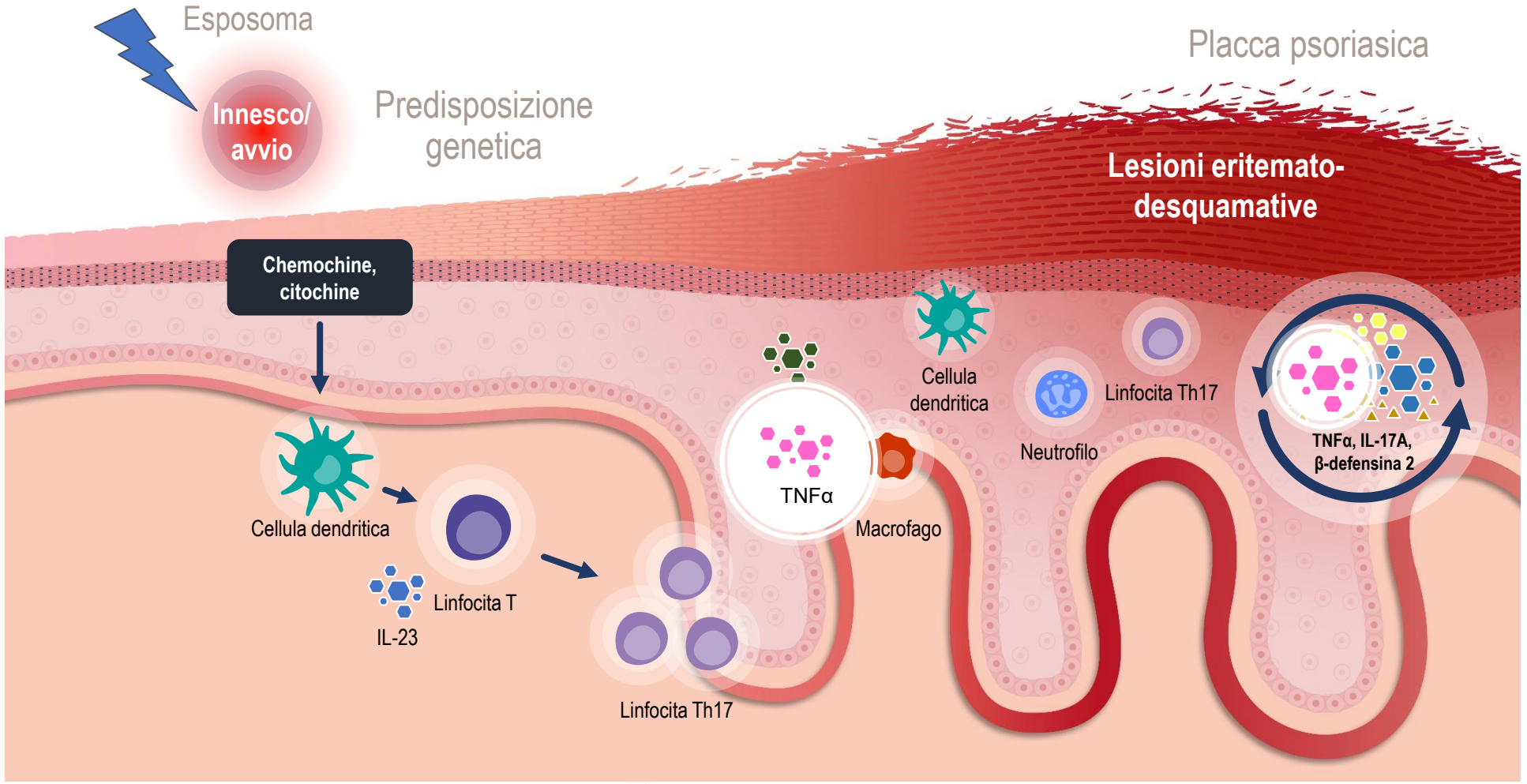
3. L’inibizione della IL-23 riduce il numero di cellule T reg?

1. **Sì**
2. **No**

Cosa causa la psoriasi?

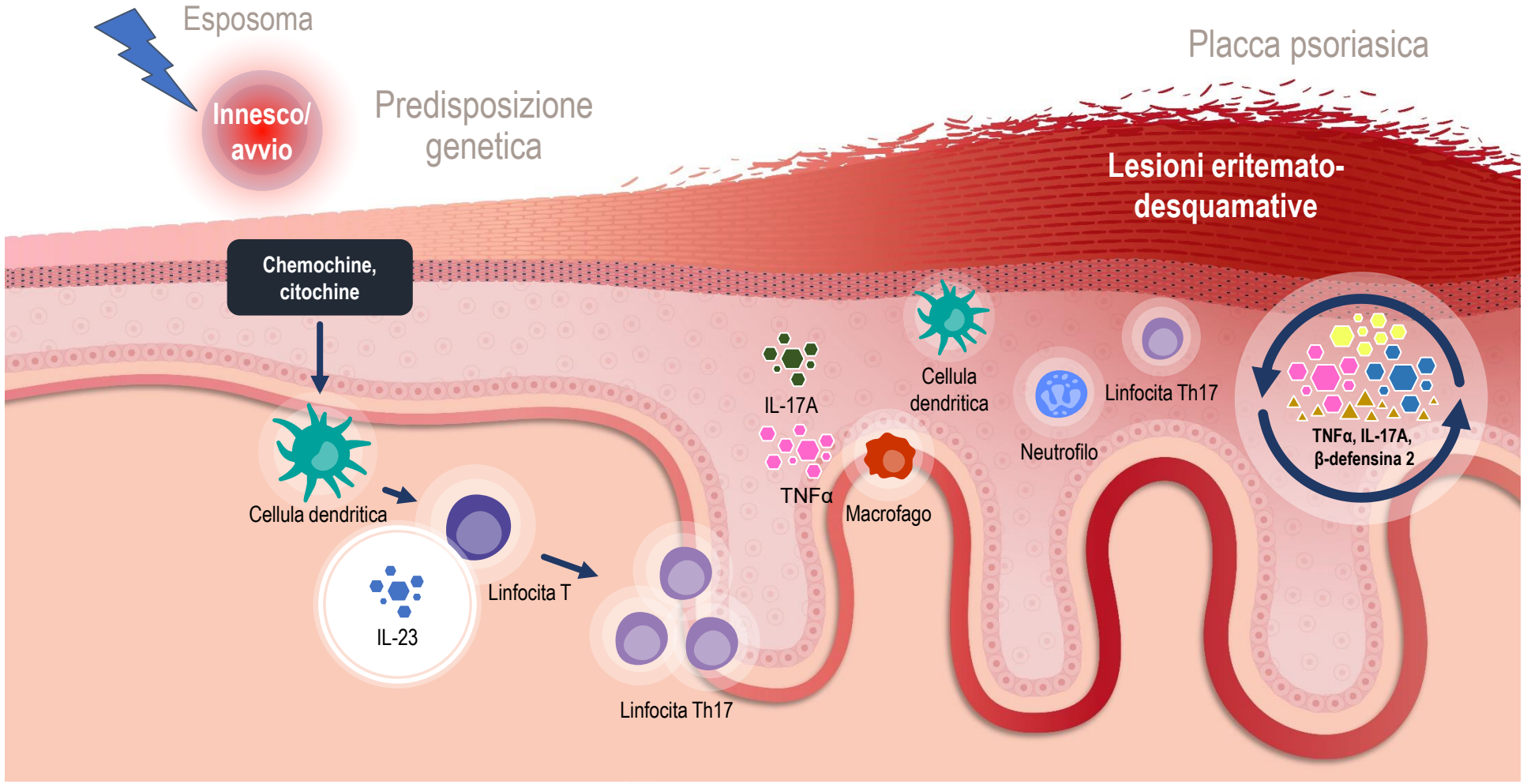


Network delle citochine nella psoriasi: TNFα



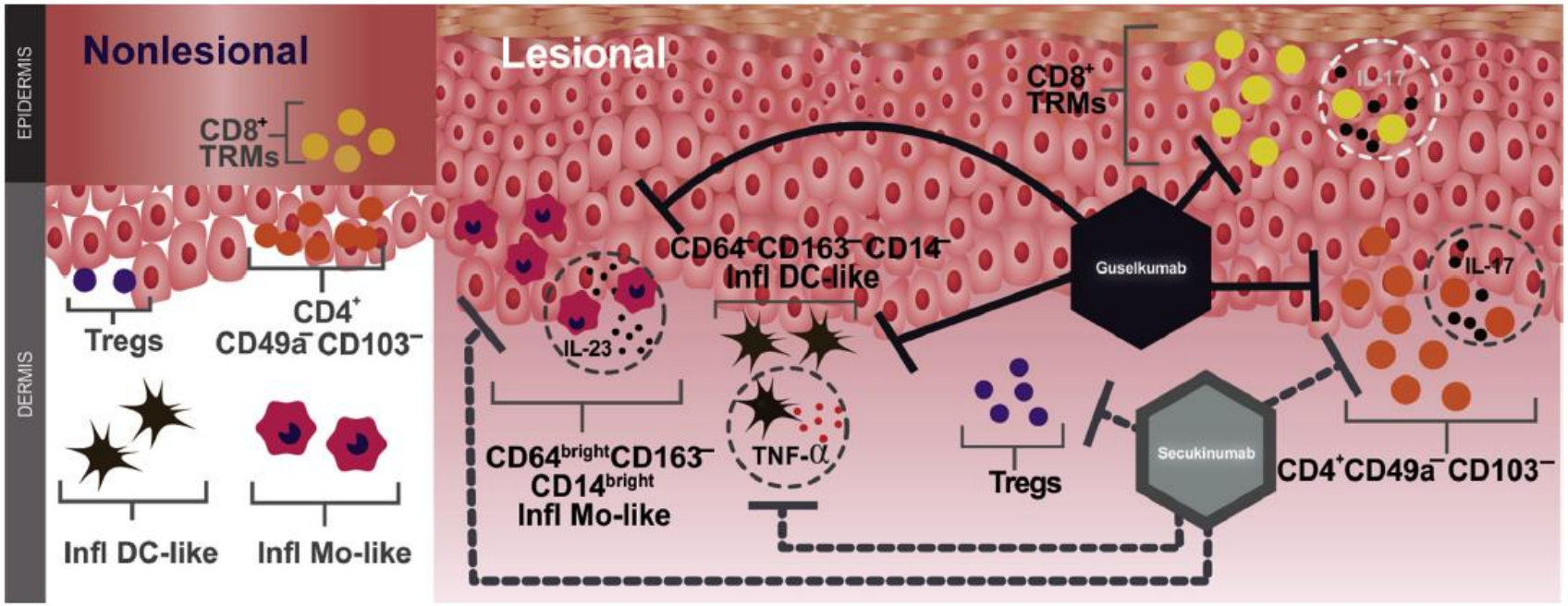
Il interleuchina; Th, T-helper; TNF, fattore di necrosi tumorale; Lowes et al. Annu Rev Immunol 2014

Network delle citochine nella psoriasi: IL-23



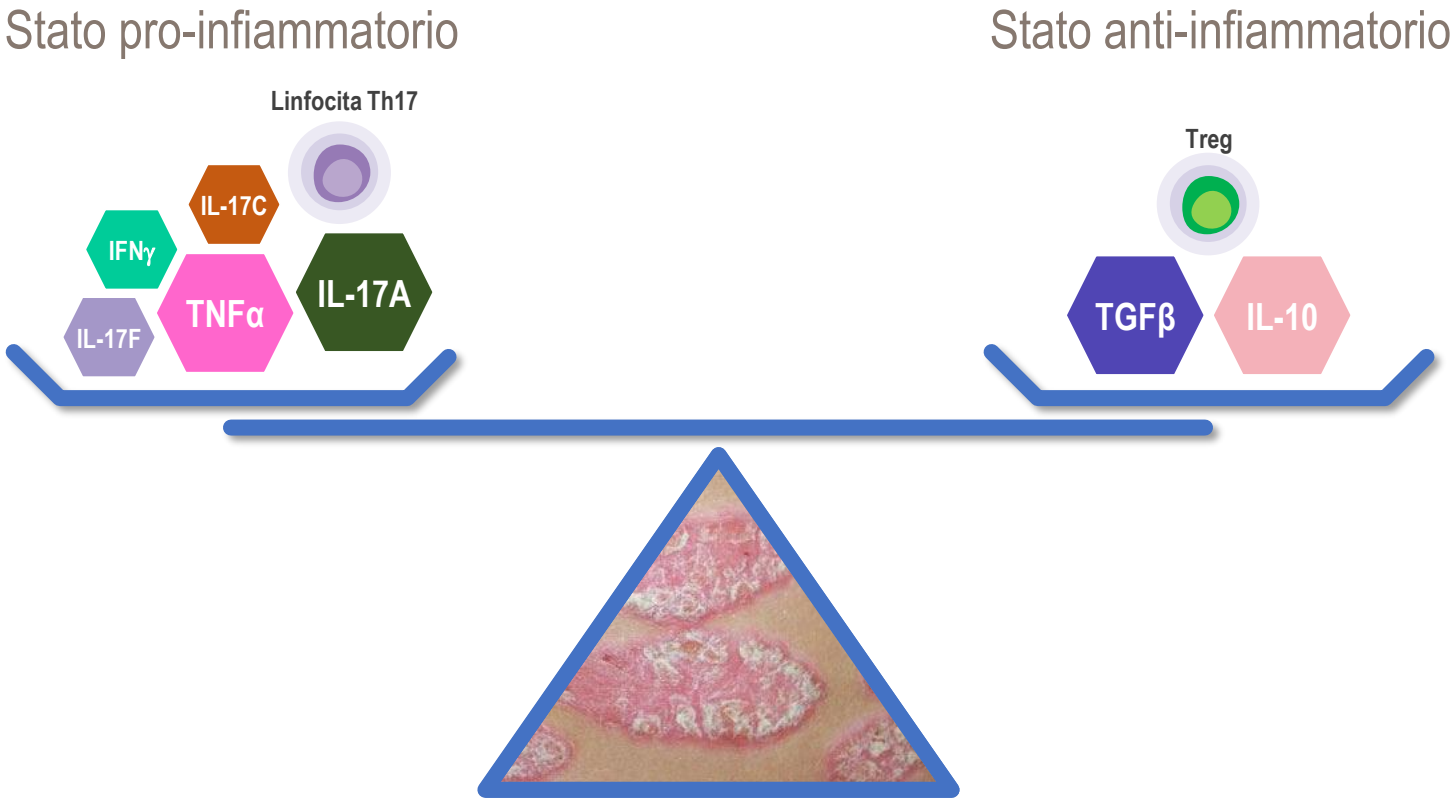
Il, interleuchina; Th, T-helper; TNF, fattore di necrosi tumorale; Lowes et al. Annu Rev Immunol 2014

Differential Changes in Inflammatory Mononuclear Phagocyte and T-Cell Profiles within Psoriatic Skin during Treatment with Guselkumab vs. Secukinumab



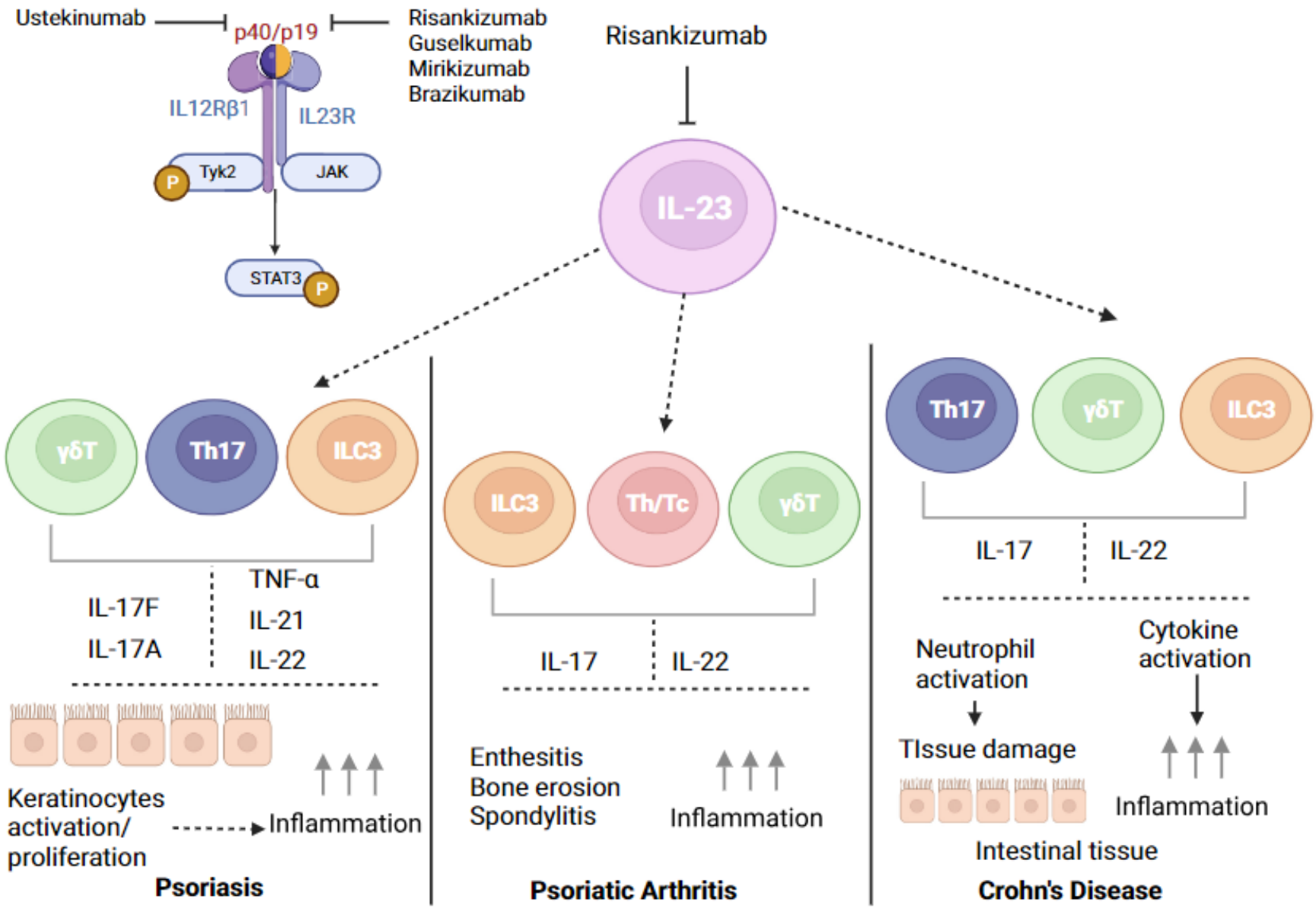
Supplementary Figure S8. Guselkumab and secukinumab differentially alter skin immune profile. Psoriatic skin lesions are infiltrated by IL-23$^+$ Infl Mo–like cells, TNF-α^+ Infl DC–like cells, and IL-17–producing CD4$^+$CD49a$^-$CD103$^-$ T cells and CD8$^+$ TRMs and Tregs. Treatment with either guselkumab (IL-23p19 blocker) or secukinumab (IL-17A blocker) targets IL-23$^+$ Infl Mo–like and TNF-α^+ Infl DC–like cells and CD4$^+$CD49a$^-$CD103$^-$ T cells. Differential effects between guselkumab and secukinumab were seen for CD8$^+$ TRMs and Tregs. Infl DC–like, inflammatory dendritic cell–like; Infl Mo–like, inflammatory monocyte–like; Treg, regulatory T cell; TRM, tissue-resident memory T cell.

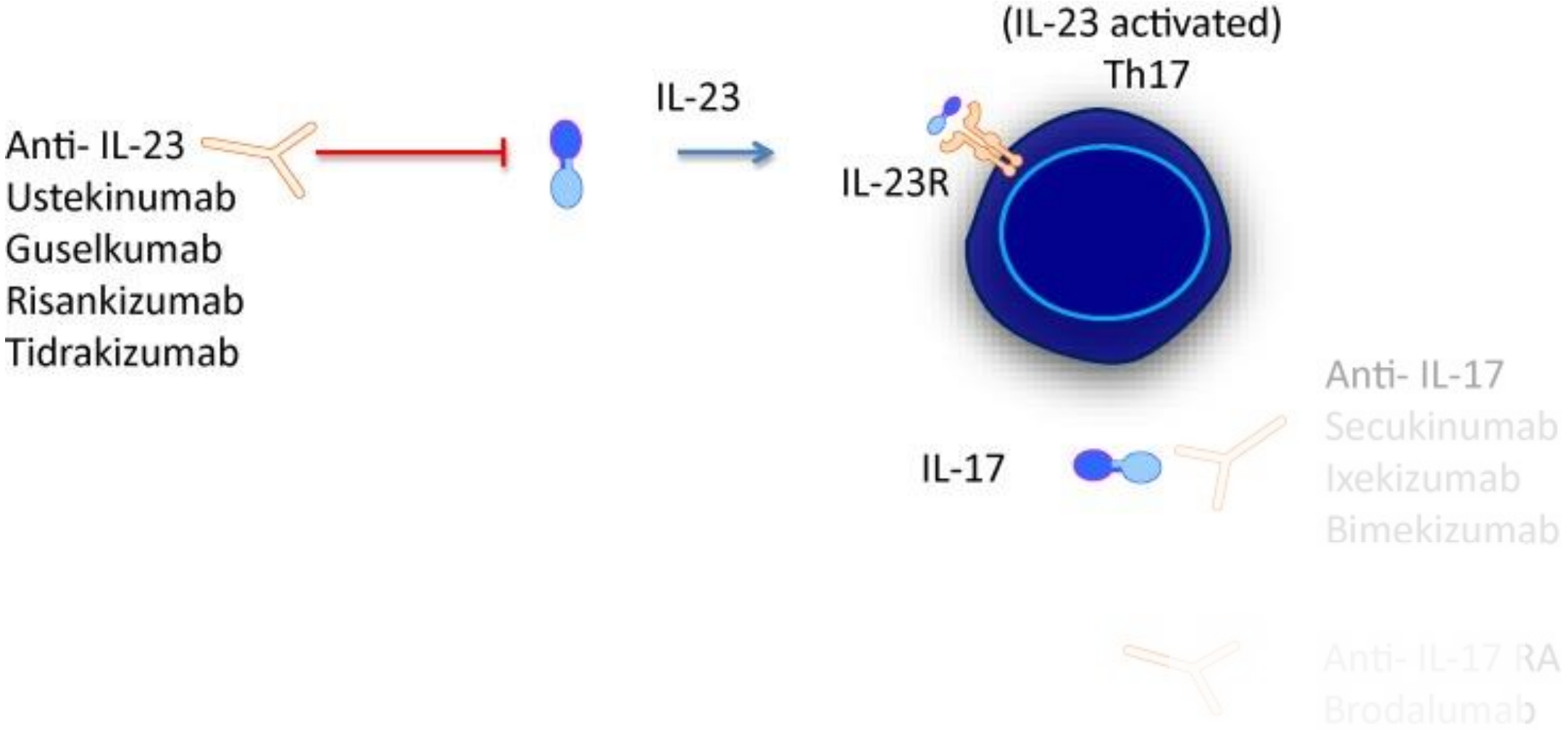
Psoriasi



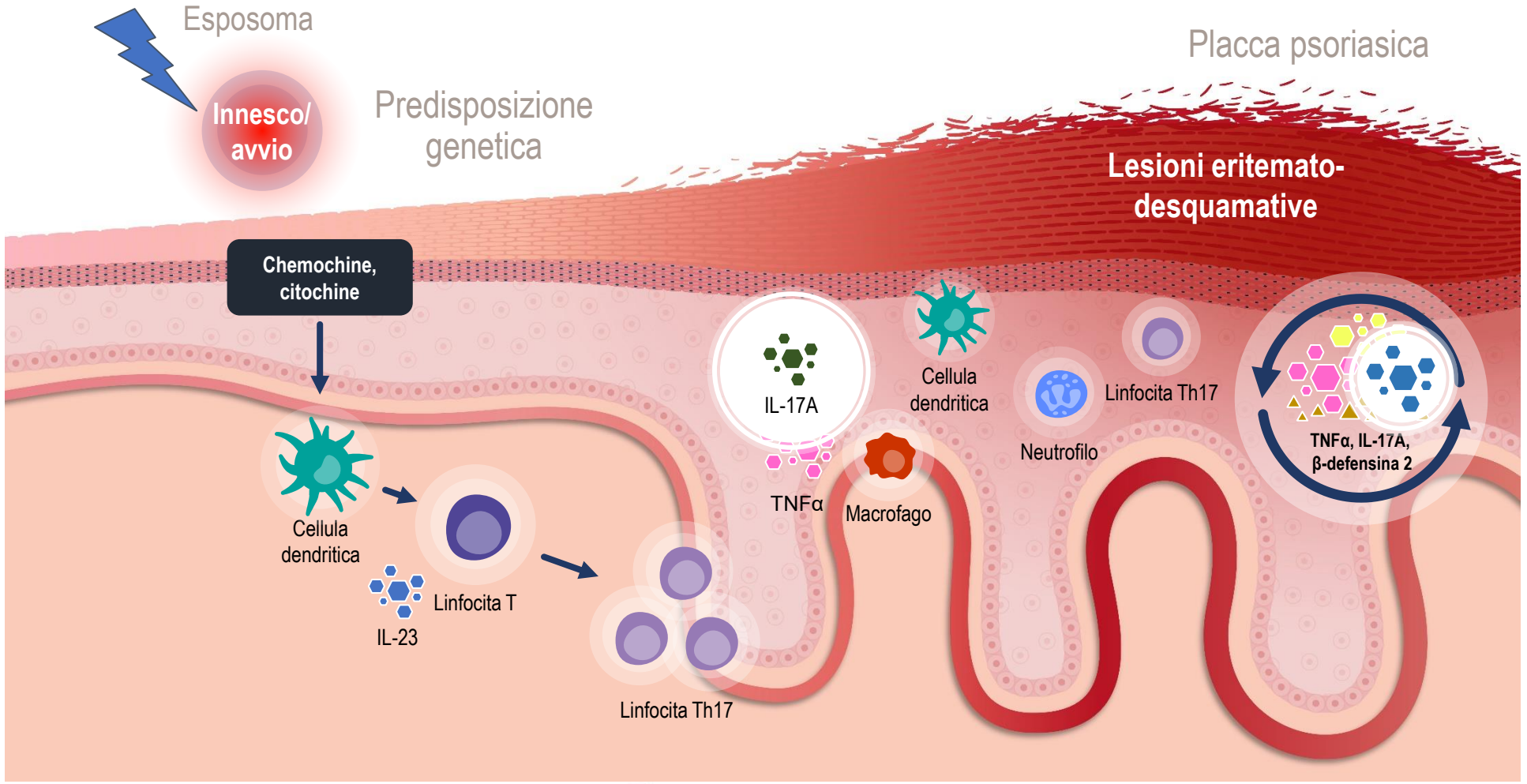
IL, interleuchina; TGF, fattore di crescita trasformante; Th, T-helper; TNF, fattore di necrosi tumorale; Treg, linfocita T-regolatorio

Lowes et al. Annu Rev Immunol 2014





Network delle citochine nella psoriasi: IL-17A



IL, interleuchina; Th, T-helper; TNF, fattore di necrosi tumorale; Lowes et al. Annu Rev Immunol 2014

4. Le T cells possono produrre IL-17 indipendentemente dalla presenza di IL-23?

1. **Sì**
2. **No**

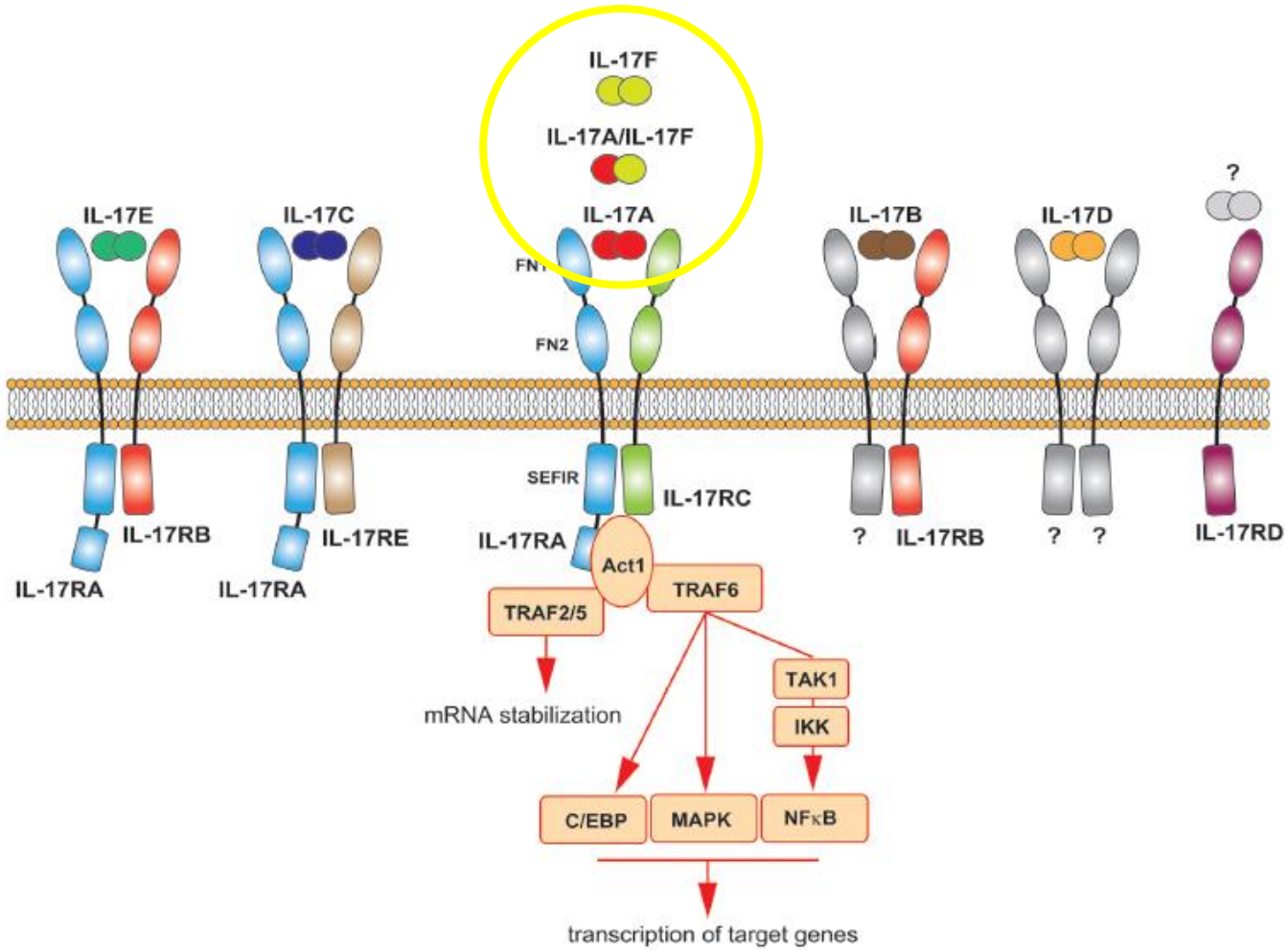
5. Il brodalumab è un anticorpo monoclonale diretto contro la IL-17F?

1. **Sì**
2. **No**

6. L’IL-17F è meno potente ma più abbondante della IL-17A nella cute psoriasica?

1. **Sì**
2. **No**

The IL-17 family of cytokines[1]



SEFIR: IL-17Rs are categorized by a conserved cytoplasmic motif known as the 'similar expression of fibroblast growth factor and IL-17 receptor' or SEFIR domain, which is similar in structure to the toll/interleukin-1 receptor (TIR) domain found in Toll-like receptors (TLRs) and IL-1 receptors

In the early 2000s, genomic sequencing led to the identification of several proteins structurally related to IL-17A or IL-17 or CTLA-8 (6 isoforms):

- IL-17B
- IL-17C
- IL-17D
- IL-17E (also called IL-25)
- IL-17F

Together, these cytokines are known as the IL-17 family.

IL-17F shares the highest homology with IL-17A (55%) and is often co-expressed with IL-17A.

Homodimers or heterodimers of IL-17A and IL-17F bind to a receptor composed of the RA and RC subunits, albeit with differing affinities.

IL-17RA and IL-17RC interact, via **SEFIR domains**, with the ***adaptor protein*** **Act1,** which contains two tumour necrosis factor (TNF) receptor-associated factor (TRAF)-binding motifs.

The pathway involving **TRAF6** leads to activation of the canonical *nuclear factor-kB (NF-kB*) and *mitogen activated protein kinase (MAPK)* pathways, and the *CCAAT/enhancer binding protein (C/EBP) transcription factors* resulting in pro-inflammatory gene expression.

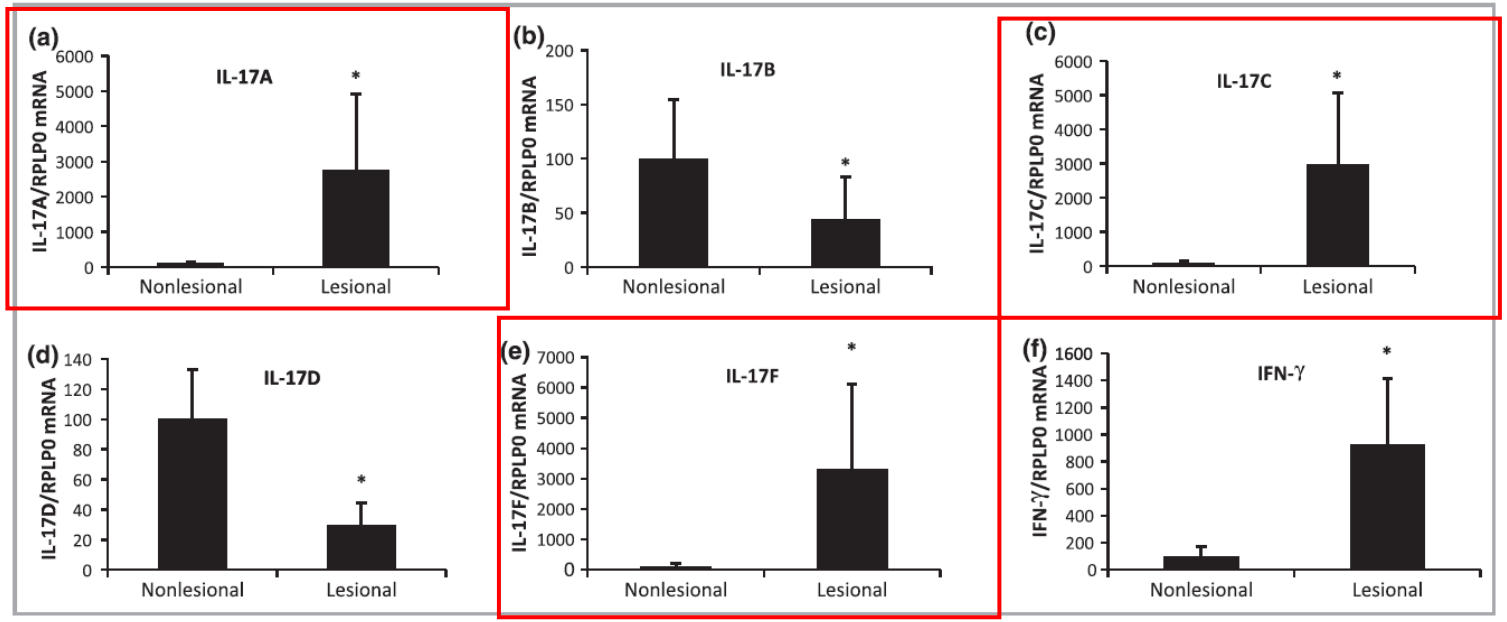
A TRAF6-independent, **TRAF2/5** signalling complex associated with IL-17Rs has also been identified that results in enhanced mRNA stability for the chemokine CXCL1.

Disruption of the relative balance of these two signalling pathways has been hypothesized to underlie autoimmune pathogenesis in certain cases.

1.Brembilla NC, et al., Front Immunol. 2018 Aug 2;9:1682; 2. Wang X, et al. Immunity 2012; 36: 23–31

IL-17 cytokines do not signal through the JAK–STAT pathway like signature TH1 or TH2 cytokines in the adaptive immune system.

mRNA expression profile of the interleukin-17 family members in psoriatic skin



To investigate the mRNA expression profile of the IL-17 family members in psoriatic skin, RNA from punch **biopsies obtained from lesional and nonlesional psoriatic skin from 9 patients with PsO** was isolated and analysed by quantitative RT-PCR.

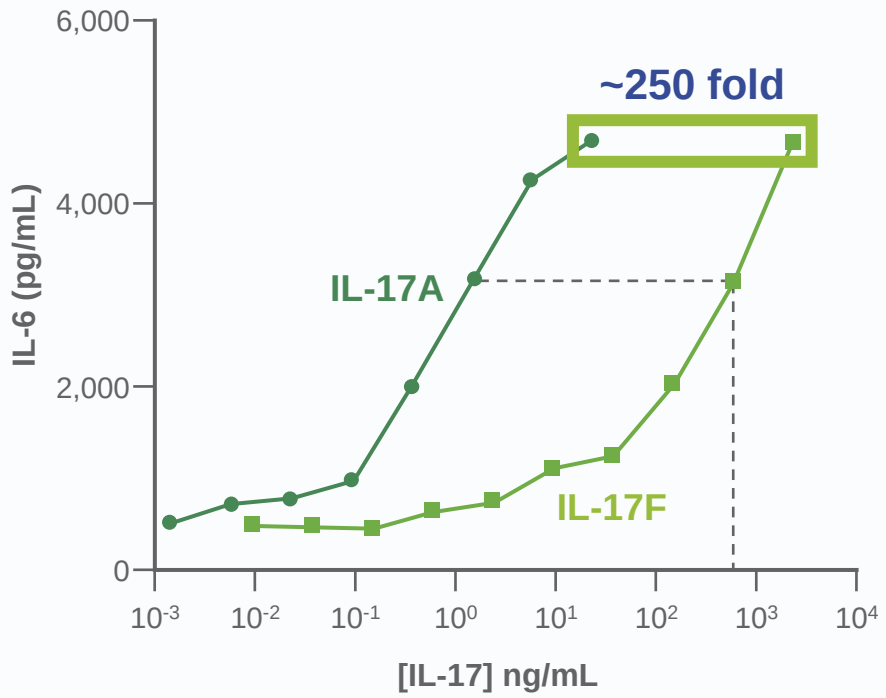
*P < 0.01compared with nonlesional psoriatic skin.

- ↑ in the **mRNA expression of IL-17A and IL-17F in psoriatic skin** of approximately **28-fold and 33-fold**, respectively, compared with nonlesional psoriatic skin.
- mRNA expression of **IL-17C** significantly ↑ in psoriatic skin (P = 0.0036) with a mean increase in the mRNA expression of approximately 30-fold compared with nonlesional psoriatic skin.
- In contrast, the mRNA expression of **IL-17B and IL-17D** significantly ↓ in psoriatic skin lesions (P = 0.0095 and P = 0.0003, respectively), with a mean decrease of approximately 2.3-fold and 3.4-fold, respectively.
- mRNA expression of **IFN-γ**, a Th1-derived cytokine known to be upregulated in psoriasis, significantly ↑ (P = 0.001) in psoriatic skin with a 9-fold induction compared with nonlesional psoriatic skin.

Johansen C, et al. Br J Dermatol 2009

IL-17F is less potent, but more abundant, than IL-17A in psoriasis

Potency in skin[1]
Dermal fibroblasts



IL-17A is 250-fold more potent than IL-17F

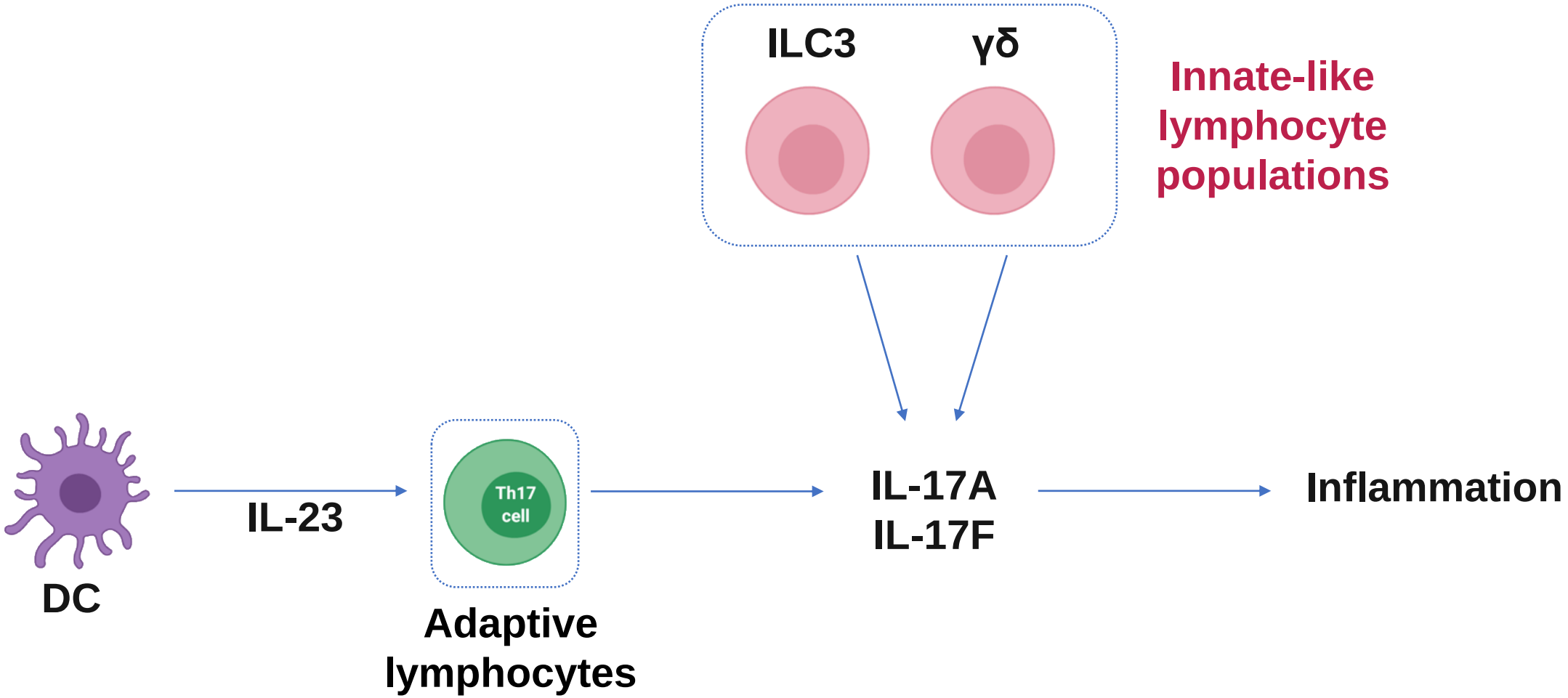
Hypothesis:
IL-17F also contributes to chronic tissue inflammation in lesional skin from patients with psoriatic arthritis (PsA).

Immunostaining was performed on lesional skin from patients with PsA to probe for IL-17F protein.

Primary normal human dermal fibroblasts (NHDFs) were stimulated with recombinant IL-17A and IL-17F, with/without TNF, to assess the effect on inflammatory cytokine production.
IL-17F protein was detected in lesional skin from patients with PsA. Stimulation of primary NHDFs with recombinant IL-17F, in the presence of TNF, induced production of pro-inflammatory mediators (e.g. IL-8 & IL-6), though to a lesser extent than with recombinant IL-17A.

1.Maroof et al. 47th Annual ESDR meeting, September 27-30, 2017;Salzburg, Austria;426.

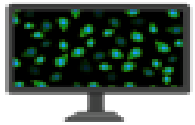
Cellular sources of IL-17A and IL-17F include both adaptive and innate-like lymphocyte populations[1]



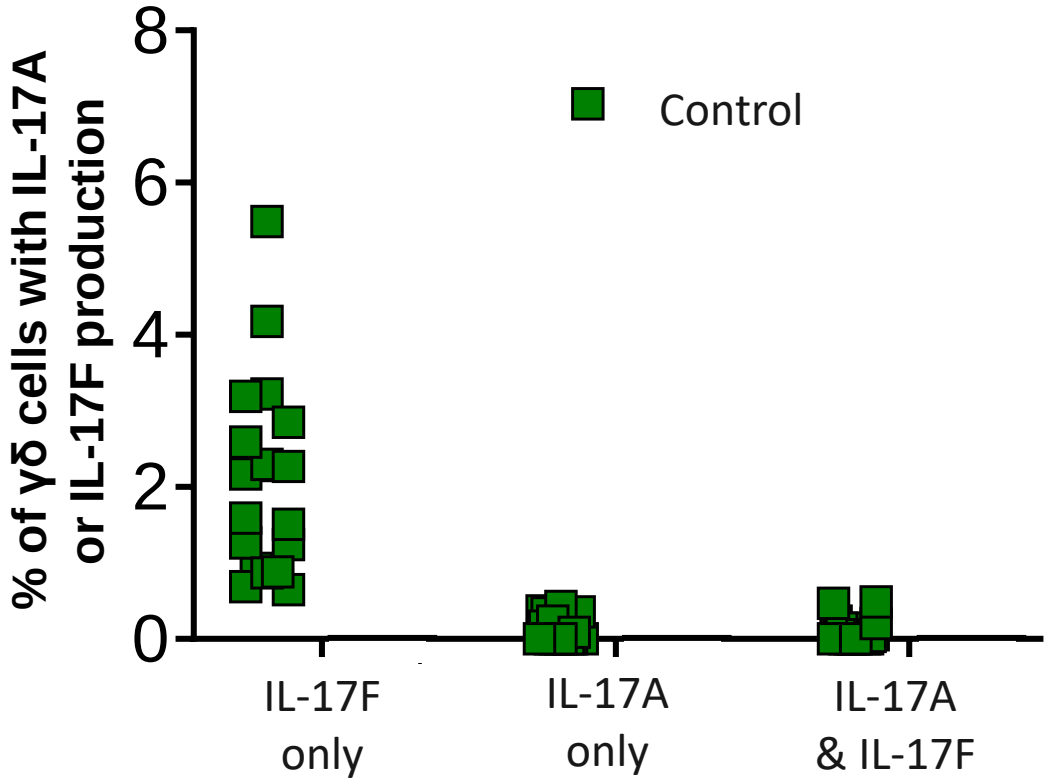
DC, dendritic cell. 1. Cole et al. IGAS 2019;oral presentation.

Innate-like lymphocyte populations produce IL-17F and IL-17A independently of IL-23 signaling[1]

In vitro



γδ T cells
Intracellular cytokine staining



- In the graph shown here, PBMCs were differentiated into γδ T cells, which were then sorted by flow cytometry
  - Cells were sorted according to whether they produced IL-17F only, IL-17A only, are both IL-17A and IL-17F
- To assess whether the production IL-17A and IL-17F by γδ T cells is dependent on IL-23, an anti-IL-23 antibody was added to the experiment
  - **Addition of the anti-IL-23 antibody did not affect the production of IL-17A and IL-17F, suggesting that these cytokines are produced by γδ T cells independently of IL-23**
- Similar findings have **also been observed in other innate-like lymphocyte lineages, including ILC3 cells and MAIT cells**
- These data suggest that some innate-like lymphocyte populations are sources of IL-23-independent IL-17A and IL-17F

PBMCs: Peripheral Blood Mononuclear Cells
ILC3: Type 3 innate lymphoid cells
MAIT: Mucosal associated invariant T cells

Cells stimulated with IL-12 and IL-18. 1. Cole S, et al. IGAS 2019;oral presentation.

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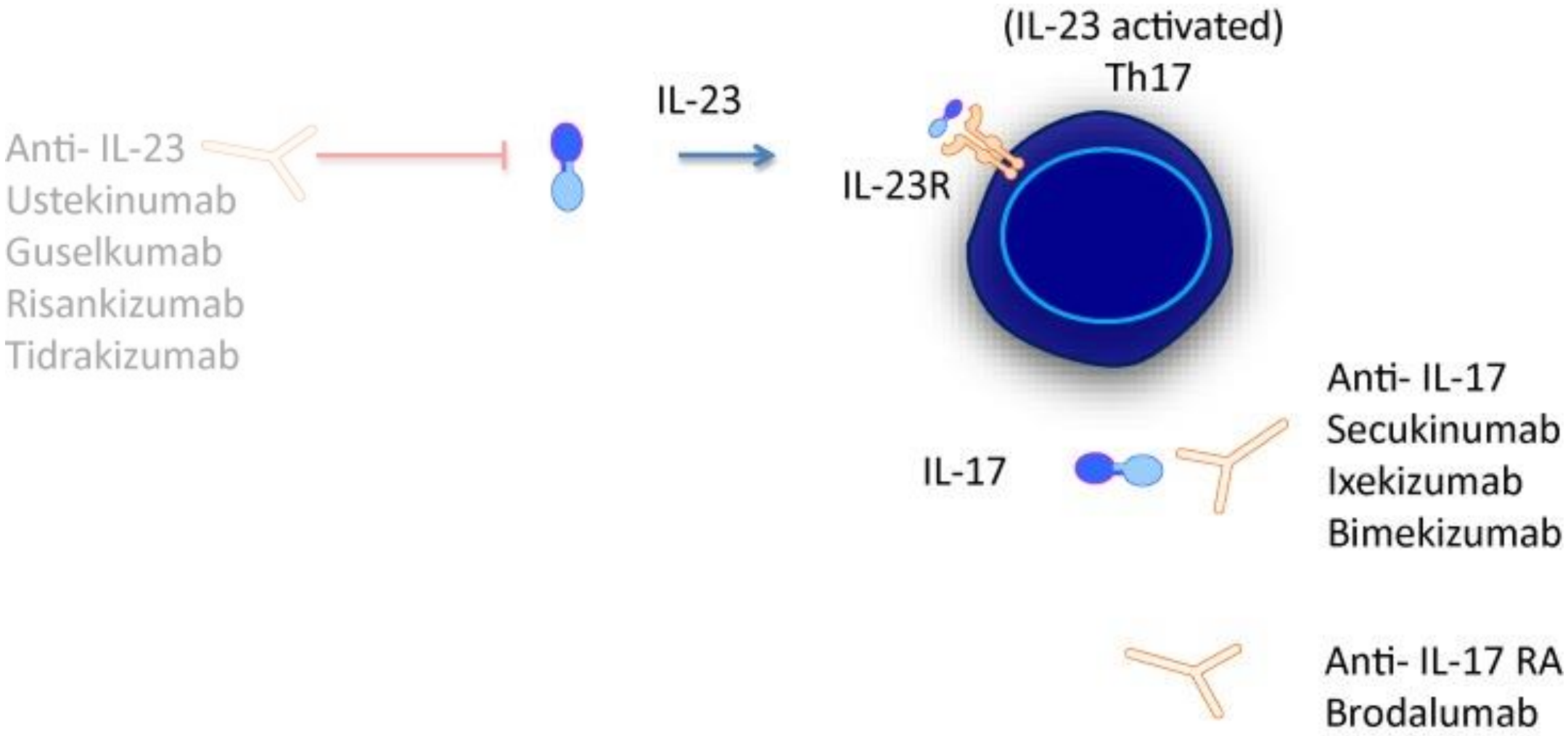
The paradigm of IL-23-independent production of IL-17F and IL-17A and their role in chronic inflammatory diseases

Victoria Navarro-Compán[1†], Luis Puig[2†], Silvia Vidal[3], Julio Ramírez[4], Mar Llamas-Velasco[5], Cristina Fernández-Carballido[6], Raquel Almodóvar[7], José Antonio Pinto[8], Eva Galíndez-Aguirregoikoa[9], Pedro Zarco[7], Beatriz Joven[10], Jordi Gratacós[11], Xavier Juanola[12], Ricardo Blanco[13], Salvador Arias-Santiago[14,15,16], Jesús Sanz Sanz[17], Rubén Queiro[18*‡] and Juan D. Cañete[4*‡]

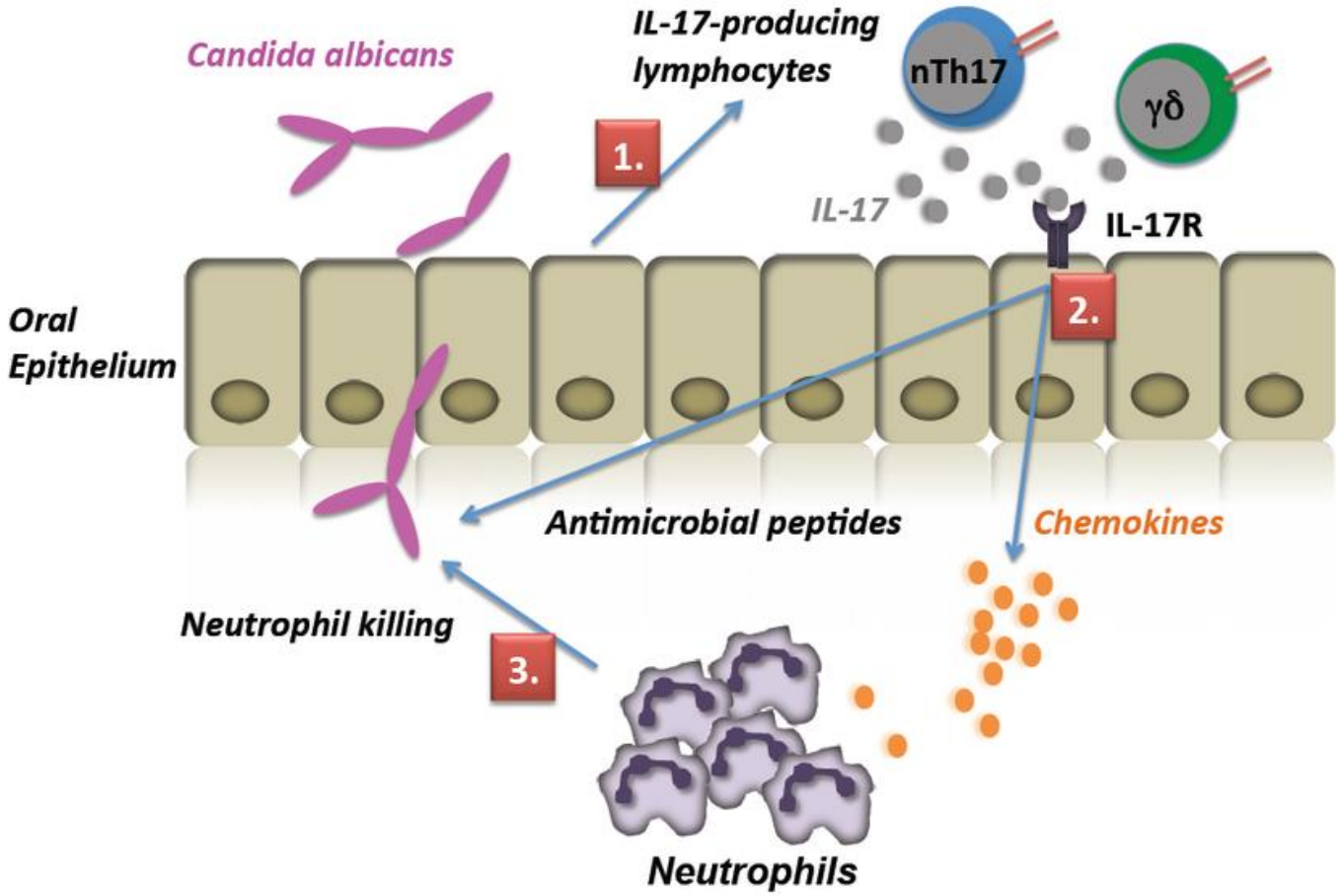
TABLE 1 Available therapies targeting IL-17 and IL-23 in IMIDs.

Mechanism of action	Therapy	Approved indications*	PsO	PsA	axSpA	HS	IBD	Uveitis
Anti-IL-17A	Ixekizumab	Plaque psoriasis, psoriatic arthritis, axial spondylarthritis						
	Secukinumab	Plaque psoriasis, psoriatic arthritis, axial spondylarthritis, juvenile idiopathic arthritis						
Anti-IL-17RA	Brodalumab	Plaque psoriasis						
Anti IL-17A and IL-17F	Bimekizumab	Plaque psoriasis, psoriatic arthritis, and axial spondyloarthritis. Phase 3 clinical development completed for hidradenitis suppurativa, EMA approval pending						
Anti-IL12/23	Ustekinumab	Plaque psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis						
Anti-IL23p19	Guselkumab	Plaque psoriasis, psoriatic arthritis. In phase 3 clinical development for Crohn's disease and ulcerative colitis						
	Risankizumab	Plaque psoriasis, psoriatic arthritis, Crohn's disease. In phase 3 clinical development for ulcerative colitis						
	Tildrakizumab	Plaque psoriasis. In phase 3 clinical development for psoriatic arthritis						

axSpA, axial spondyloarthritis; HS, hidradenitis suppurativa; IBD, inflammatory bowel disease; IL, interleukin; PsA, psoriasis arthritis; PsO, psoriasis.
*The table only includes therapies that have been approved by the European Medicines Agency (EMA) or that have published phase 3 clinical development.
Green: approved or shown efficacy in phase 3 clinical trials. Red: Lack of efficacy. Yellow: Insufficient or unclear evidence.


(IL-23 activated)
Th17
IL-23
Anti- IL-23
Ustekinumab
Guselkumab
Risankizumab
Tidrakizumab
IL-23R
Anti- IL-17
Secukinumab
Ixekizumab
Bimekizumab
IL-17
Anti- IL-17 RA
Brodalumab

IL17 e Candida



International Journal of
Molecular Sciences

MDPI

Review

Psoriasis and Cardiometabolic Diseases: Shared Genetic and Molecular Pathways

Stefano Piaserico *, Gloria Orlando and Francesco Messina

Table 1. List of the shared genetic and molecular pathways between psoriasis and CV events or CV risk factors.

	Atherosclerosis	Hypertension	Diabetes	Hyperlipidemia	Obesity	NAFLD
Shared genetic background with psoriasis	IL-23R and IL-23	- eNOS - LNPEP - AGT	- PSORS2, PSORS3, PSORS4 - CDKAL1 - JAZF1 - ST6GAL1 - IL-12B, IL-23R, IL-23A	- HLA gene region - ApoE $^{+}$ - Paraoxonase 1 - LXR-α $^{++}$ - PPAR-α $^{++}$	- FTO * - MC4R $^{\wedge}$	
Shared molecular pathways with psoriasis	IL-12 * IL-17 *§	- Endothelin-1 - Upregulated ACE signaling † - TNFα, IL-17	- TNF-α, IL-23, IL17 - adipokines	- TNFα, IL-6 and IL-1β - Dysfunctional HDL and anti-HDL antibodies - Vitamin D deficiency	- Free fatty acids - Adipokines - TNFα, IL-6, and IL-1 - Gut microbiota dysregulation	TNF-α IL-17 *°

° IL-17 may promote the progression of NAFLD to NASH; $^{+}$ both protective and detrimental effects on psoriasis severity depending on the polymorphism; $^{++}$ downregulated in psoriatic skin; $^{\wedge}$ associated with psoriatic arthritis; † increased expression of the renin gene in psoriatic skin indicates a hormone-like action of plaque products; * in patients with higher PASI; § contradicting findings have been reported in different experimental animal models

IL17 e IL23 e tumori

Table 2. Major interleukins involved in CRC progression and studied as biomarkers.

Cytokine	Functional Effect in CRC	Expression Patterns	Reference
IL-1α	Promotes metastasis and the chemosensitivity	↑	[136,137]
IL-1β	Promotes the proliferation of colon cancer cells, tumorigenesis, and alters the tumor microenvironment	↑	[137–139]
IL-18	Antitumorigenic properties and release of other signals	↓	[140,141]
IL-2, IL-7, IL-9, IL-15	Antitumor activity, promote EMT, proliferation, invasion, and metastasis	IL-4, IL-7 upregulated, IL-9 downregulated, IL-2 in between	[142–147]
IL-21	Activation of immune response biomarkers	↑ (Potential for biomarker)	[148–150]
IL-6	Promotes mitosis, proliferation, metastasis, migration, and angiogenesis	↑	[151–154]
IL-11	Facilitates the proliferation of CRC	↑	[155–157]
IL-8	Promotes cell proliferation, angiogenesis, cancer metastasis, chemoresistance, antianoikis, maintains CCSC properties	↑	[158–160]
IL-10	Pathogenesis and progression	↑	[141,161–1
IL-22	Dominant role in CRC tumorigenesis, antiapoptosis, and cell proliferation	↑	[164–166]
IL-17a	Promotes cell cycle progression and angiogenesis	↑	[167]
IL-17b	Promotes tumor	↑	[168–171]
IL-4	Overexpressed in early CRC, tumor development	↑	[172]
IL-23	Overexpressed in CRC tissue and predictive for CRC metastasis	↑	[173–176]

Upwards arrow just showed upregulation of the genes while downwards show suppression or downregulation.

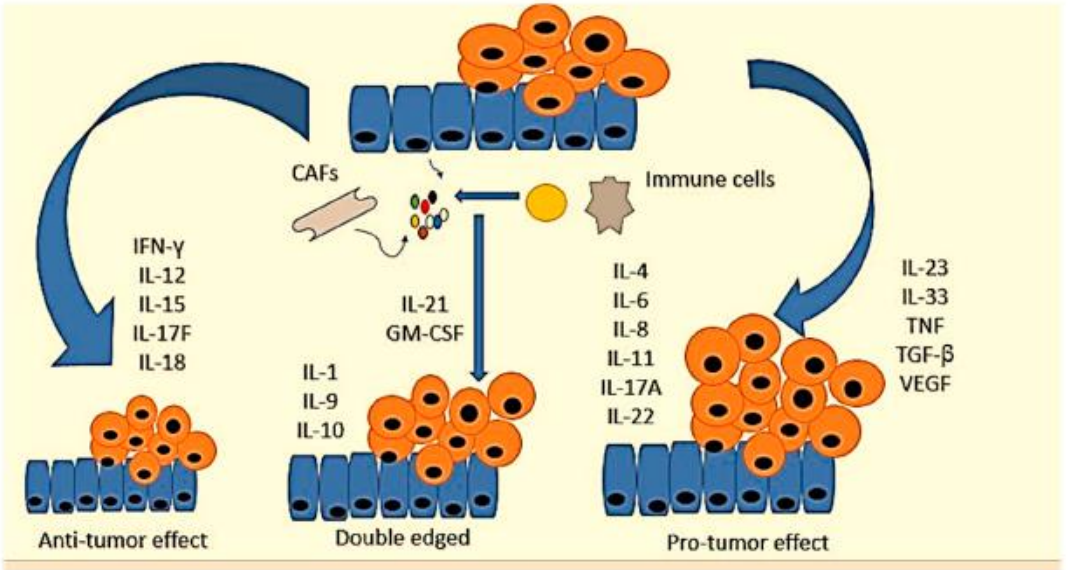


Figure 3. Cytokine networks in the pathogenesis of colorectal cancer. Cytokines expressed by tumor and/or stromal cells cluster to form networks with antitumor, pro-tumor, or bivalent properties. IFN-γ, interleukin-12 (IL-12), IL-15, IL-17F, and IL-18 inhibit CRC development. IL-4, IL-6, IL-8, IL-11, IL-17A, IL-22, IL-23, IL-33, TNF, TGF-β, and VEGF are pro-tumorigenic. The contribution of IL-1, IL-9 IL-10, IL-21, and GM-CSF to intestinal cancer remains unclear.

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