Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs

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JC - Applied Immunology – WS 22/23

Arge Ankersmit

Immune-mediated inflammatory diseases (IMIDs)

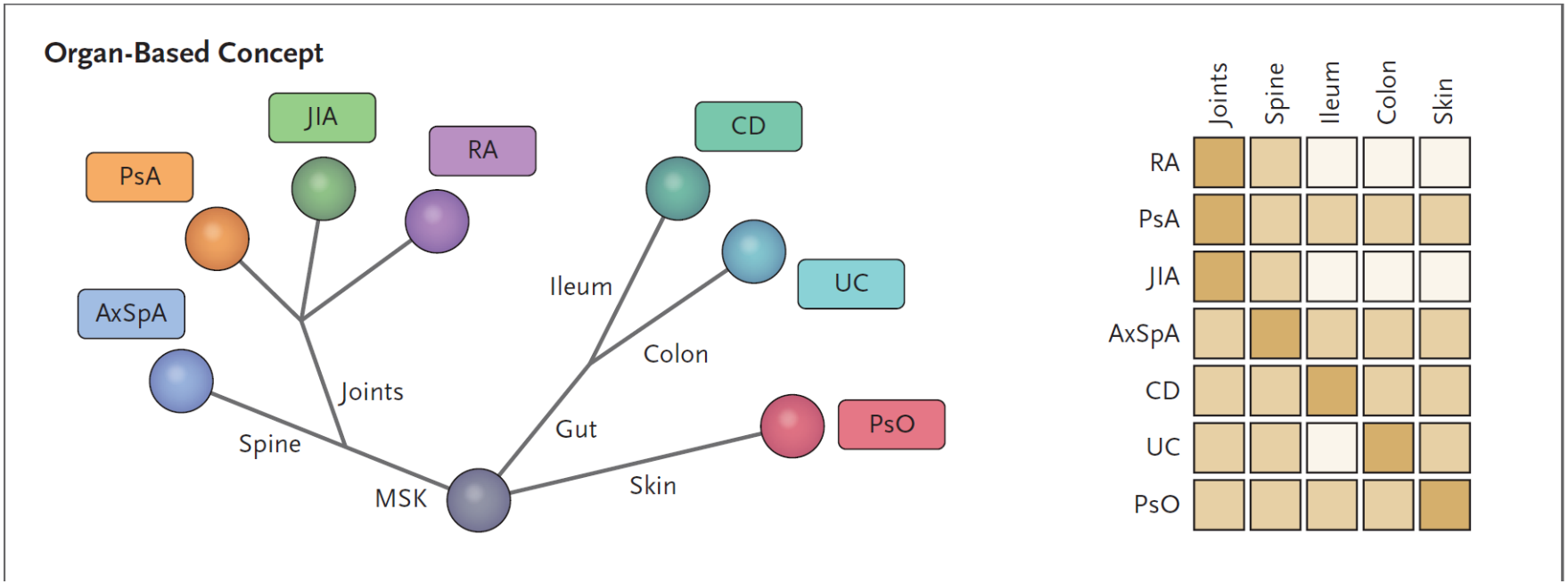
→Inflammatory (but not exclusivley infection associated) syndromes affecting „(inner) surfaces of the body" – the authors focus on:

→Skin

→Gut

→Joints (Synovium)

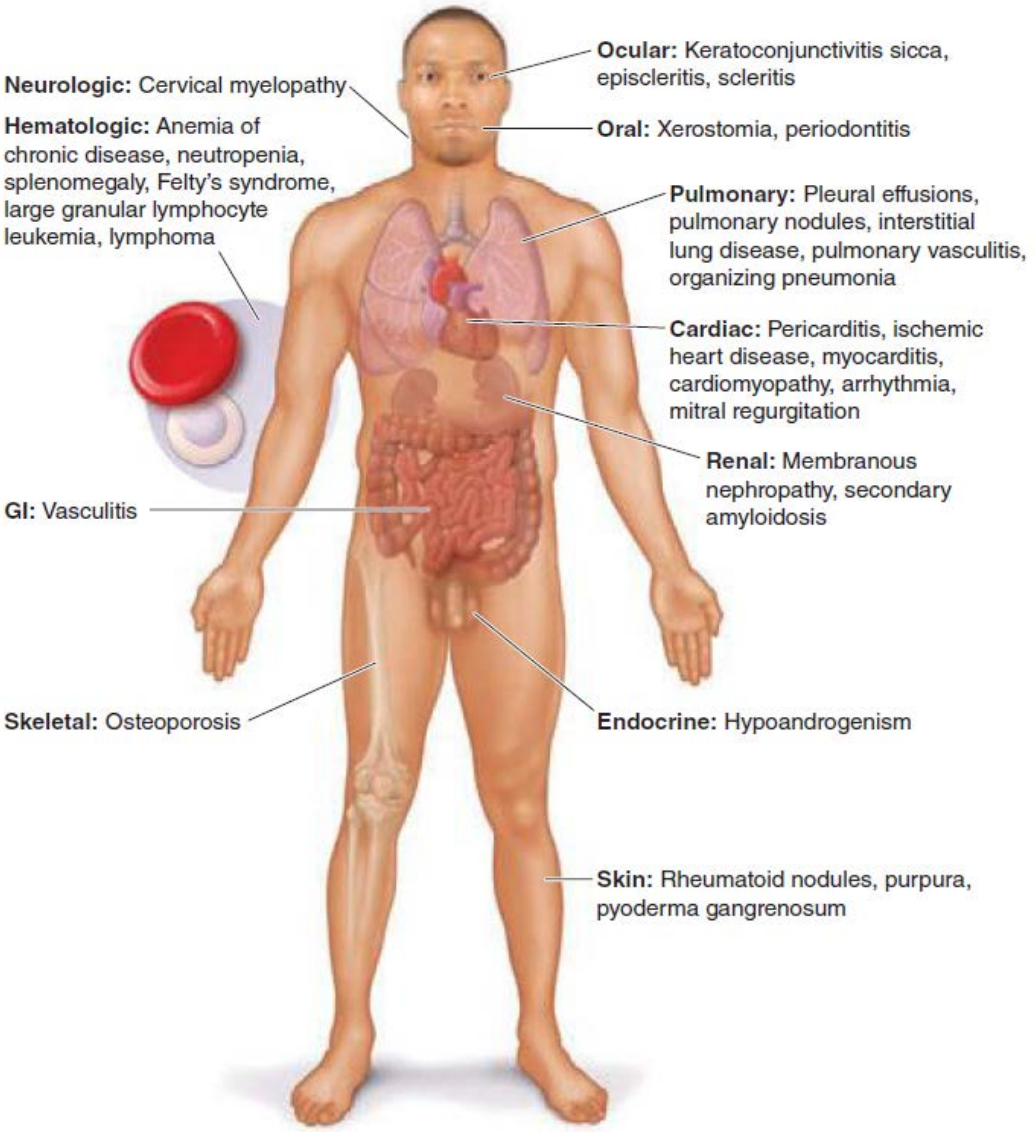
Established Diagnostic Framework of (rheumatic) musculoskeletal disease



Shared features of inflammaory arthritis and inflammatory bowl disease

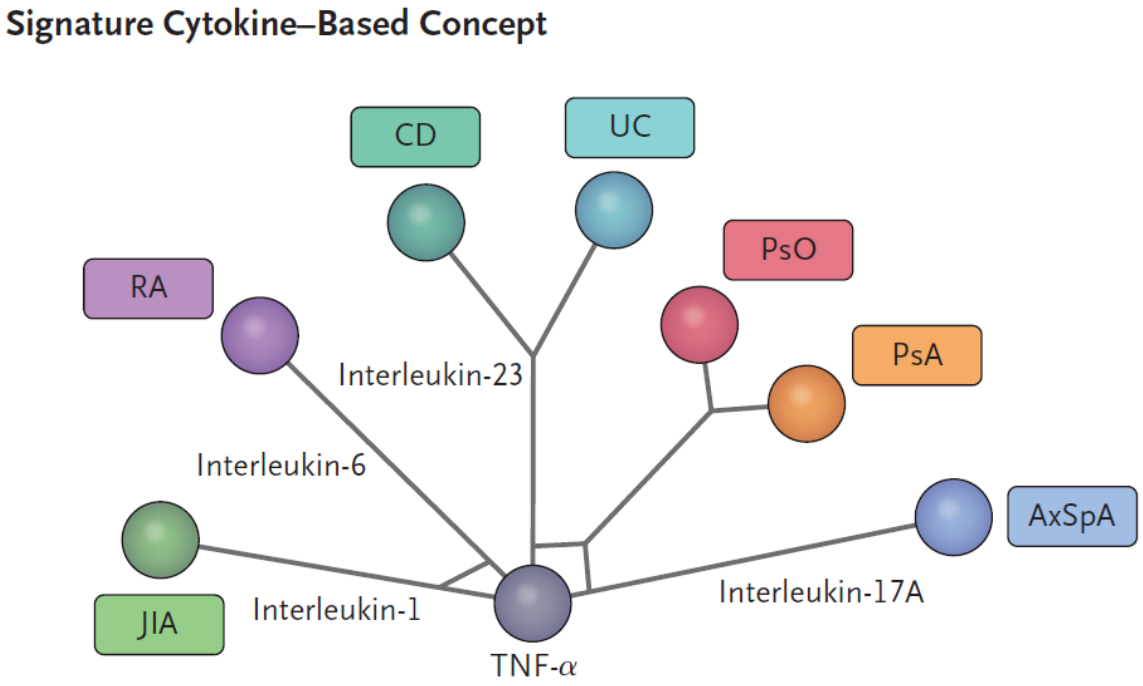
- Shared risk allels (e.g. in MHC related genes) and shared environomental risk factors (e.g. smoking, mechanical stress, or microbiome changes)
- Sustained exuberant immune responses that infiltrate target tissues with activated immune cells
- Chronic clinical course -> sequential disease flares silent phases
- Low potential for spontaneous resolution.

- Common extraarticular and extra-GI manefistations and complications



Extraarticular manifestations of rheumatoid arthritis.

Alternative Classification proposed by the authors:



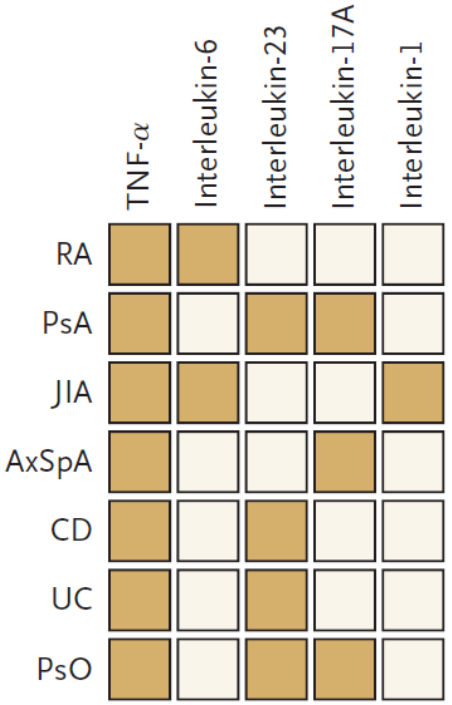


Table 1. Clinical and Pathological Features of Immune-Mediated Inflammatory Diseases and Approved Treatments.*

Variable	Rheumatoid Arthritis	Crohn's Disease	Ulcerative Colitis	Axial Spondyloarthritis	Psoriatic Arthritis
Genetic characteristics	MHC class II (DR4) PTPN22, CTLA4	MHC class II (DRB1) Interleukin-23R, NOD2	MHC class II (DRB1) Interleukin-23R, interleukin-10R	MHC class I (B27) Interleukin-23R, ERAP1	MHC class I (C06) Interleukin-23R, A20
Drivers	Autoimmunity	Microbial dysbiosis and barrier dysfunction	Microbial dysbiosis and barrier dysfunction	Mechanical stress	Mechanical stress and metabolism
Key pathological process	Synovitis	Granuloma formation	Cryptitis and goblet-cell loss	Axial enthesitis	Enthesitis and synovitis
Cellular immune response	B cells, Tph or Tfh cells, macrophages, fibroblasts	Th1/Th17 cells, dendritic cells, macrophages	Th2/Th9/Th17 cells, neutrophils	Th17 cells, T γ/δ cells, ILC3, neutrophils	Th17 cells, T γ/δ cells, ILC3, neutrophils, fibroblasts
Key associated disease	Interstitial lung disease	Erythema nodosum	Primary sclerosing cholangitis	Anterior uveitis	Psoriasis
NSAID responsiveness	Absent	Absent	Absent	High	Moderate
Glucocorticoid responsiveness	High	High	High	Absent	Moderate
Conventional anchor drug	Methotrexate	Azathioprine	Cyclosporine	Sulfasalazine†	Methotrexate
Approved TNF-α inhibitors	Adalimumab, certolizumab, etanercept, golimumab, infliximab	Adalimumab, certolizumab (U.S.), infliximab	Adalimumab, certolizumab (U.S.), golimumab, infliximab	Adalimumab, certolizumab, etanercept, golimumab, infliximab	Adalimumab, certolizumab, etanercept, golimumab, infliximab
Approved cytokine signature drugs (targets)	Tocilizumab (interleukin-6R), sarilumab (interleukin-6R)	Ustekinumab (interleukin-12/23)	Ustekinumab (interleukin-12/23)	Secukinumab (interleukin-17A), ixekizumab (interleukin-17A)	Secukinumab (interleukin-17A), ixekizumab (interleukin-17A), ustekinumab (interleukin-12/23), guselkumab (p19, interleukin-23)
Other approved targeted therapies	Abatacept, rituximab	Vedolizumab	Vedolizumab	None	Apremilast, abatacept
Approved JAK inhibitors	Tofacitinib, baricitinib, upadacitinib, filgotinib (E.U.)	None	Tofacitinib	Upadacitinib (E.U.)	Tofacitinib, upadacitinib (E.U.)

* A20 protein is also known as tumor necrosis factor α (TNF-α)–induced protein 3. CTLA-4 denotes cytotoxic T-lymphocyte–associated protein 4, ERAP1 endoplasmic reticulum aminopeptidase 1, E.U. European Union, ILC3 innate lymphoid cells type 3, interleukin-10R interleukin 10 receptor, interleukin-23R interleukin-23 receptor, JAK Janus kinase, MHC major histocompatibility complex, NOD2 nucleotide-binding oligomerization domain–containing protein 2, NSAID nonsteroidal antiinflammatory drug, PTPN22 protein tyrosine phosphatase nonreceptor type 22, Tfh follicular helper T cell, Th helper T cell, Tph peripheral helper T cell, and U.S. United States.

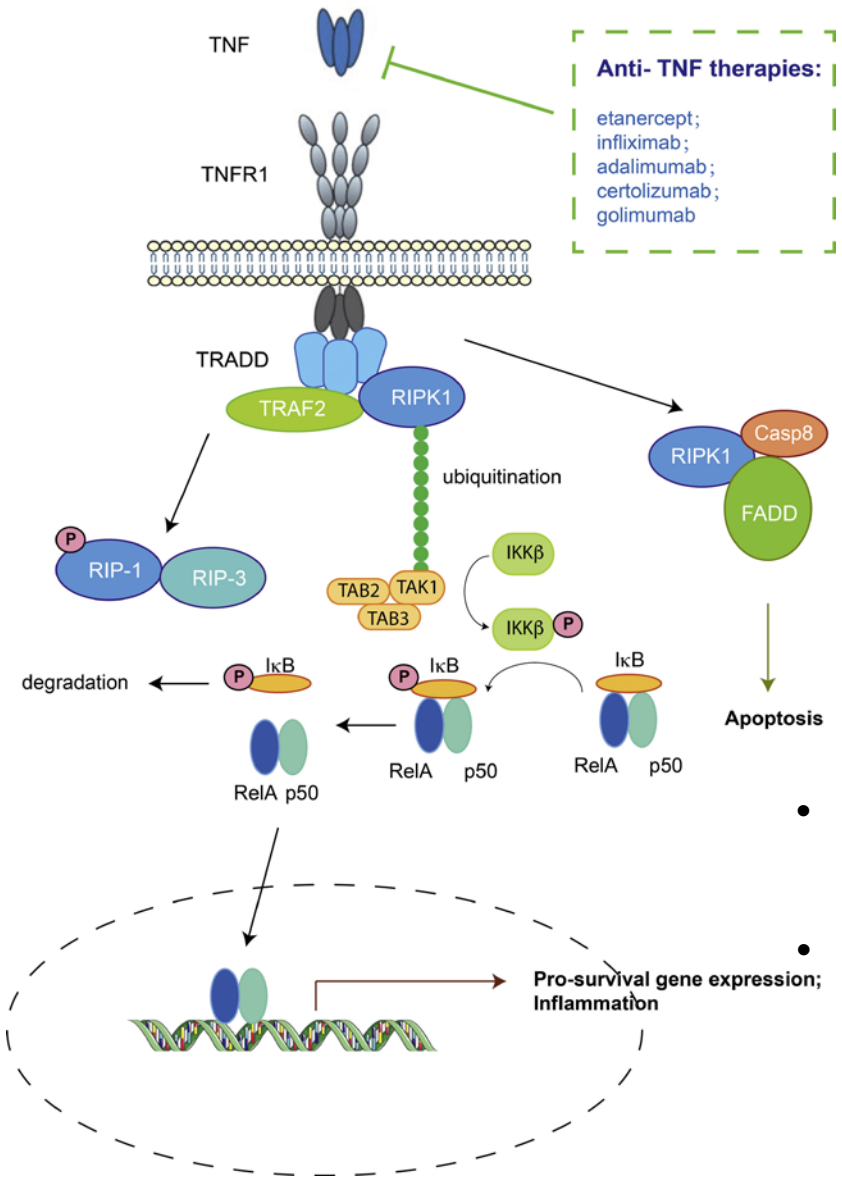
† Sulfasalazine is recommended only for the treatment of peripheral spondyloarthritis.

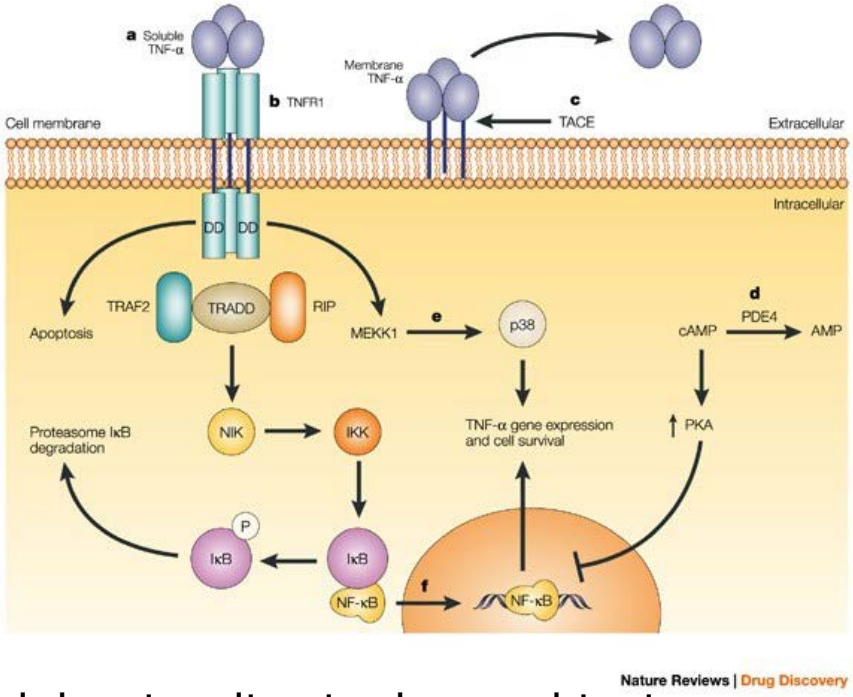
The case for a classification system based on drug response patterns - Notable examples

- Axial spondyloarthritis and psoriatic arthritis but not rheumatoid arthritis respond well to NSAIDs
- Crohn's disease and ulcerative colitis often worsen with NSAID use
- Rheumatoid arthritis responds better to MTX than other IMIDs
- Even IN one diagnostic group (e.g. Rheumatoid arthritis) there are subgroups from non- to excellent responders (limited subgroup)

-> "which suggests that master control pathways in individual diseases are not targeted (by these agents)

TNF-α as a Common Downstream Effector Pathway

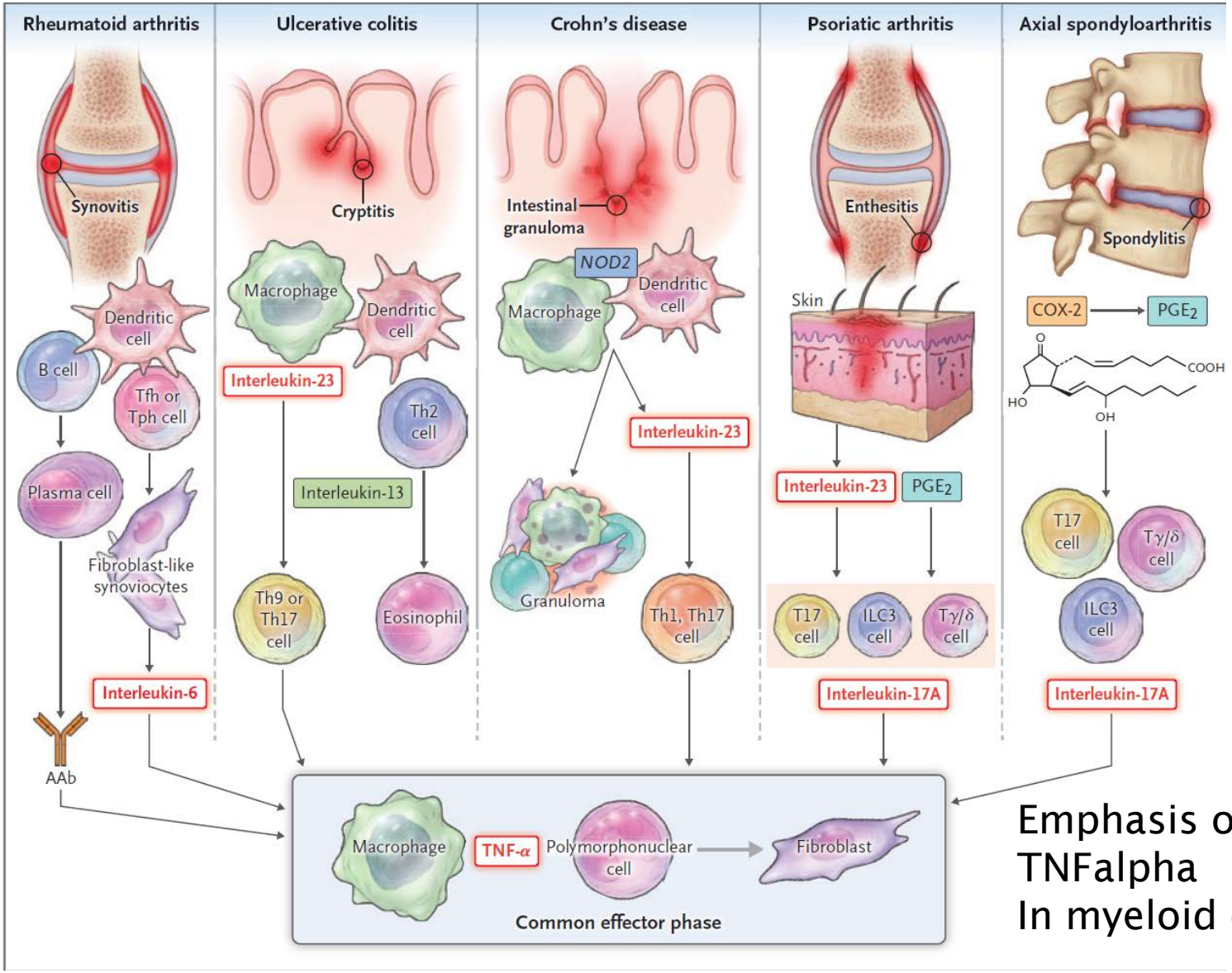




- TNFalpha signaling is almost ubiquitous (TNFR1 is expressed in most cell types).
- Depending on cell type and „context“ different functional outcomes can be triggered (e.g. Stimulation of osteoclasts, upregulation of profinflammatory cytokines in macrophages, programmed cell death in a host of cell lineages)

Zhang H, Shi N, Diao Z, Chen Y, Zhang Y. Therapeutic potential of TNFα inhibitors in chronic inflammatory disorders: Past and future. Genes Dis. 2020 Mar 3;8(1):38-47. doi: 10.1016/j.gendis.2020.02.004. PMID: 33569512; PMCID: PMC7859422.
Palladino MA, Bahjat FR, Theodorakis EA, Moldawer LL. Anti-TNF-alpha therapies: the next generation. Nat Rev Drug Discov. 2003 Sep;2(9):736-46. doi: 10.1038/nrd1175. PMID: 12951580.

TNFalpha as a master regulator?



Emphasis on the role of TNFalpha
In myeloid cells

Table 1 Five approved anti-TNF biologics.

Generic name	Brand name	TNF binding domain	Fc or PEGylation	Indications	Year of FDA approval
Etanercept	Enbrel	human TNFR2	human Fc	rheumatoid arthritis	1998
				polyarticular juvenile idiopathic arthritis	1999
				psoriatic arthritis	2002
				ankylosing spondylitis	2003
				plaque psoriasis	2004
				pediatric plaque psoriasis	2016
Infliximab	Remicade	murine variable region of anti-TNF	human Fc	Crohn's disease	1998
				rheumatoid arthritis (with MTX)	1999
				ankylosing spondylitis	2004
				psoriatic arthritis	2005
				ulcerative colitis	2005
				pediatric Crohn's disease	2006
				plaque psoriasis	2006
				pediatric ulcerative colitis	2011
Adalimumab	Humira	human Fab of anti-TNF	human Fc	rheumatoid arthritis	2002
				psoriatic arthritis	2005
				ankylosing spondylitis	2006
				Crohn's disease	2007
				plaque psoriasis	2008
				polyarticular juvenile idiopathic arthritis	2008
				ulcerative colitis	2012
				pediatric Crohn's disease	2014
				hidradenitis suppurativa	2015
				Non-Infectious Intermediate, Posterior and Panuveitis	2016
				fingernail psoriasis	2017
Certolizumab	Cimzia	humanized Fab of anti-TNF	PEG	Crohn's disease	2008
				rheumatoid arthritis	2009
				psoriatic arthritis	2013
				ankylosing spondylitis	2013
				plaque psoriasis	2018
				axial spondyloarthritis, non-radiographic	2019
Golimumab	Simponi	human Fab of anti-TNF	human Fc	rheumatoid arthritis	2009
				psoriatic arthritis	2009
				ankylosing spondylitis	2009
				ulcerative colitis	2013
				rheumatoid arthritis (infusion)	2013
				psoriatic arthritis (infusion)	2017
				ankylosing spondylitis (infusion)	2017

TNF-α inhibition has demonstrable efficacy in all major forms of arthritis (rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis), as well as in the two main forms of IBD.

Zhang H, Shi N, Diao Z, Chen Y, Zhang Y. Therapeutic potential of TNFα inhibitors in chronic inflammatory disorders: Past and future. Genes Dis. 2020 Mar 3;8(1):38-47. doi: 10.1016/j.gendis.2020.02.004. PMID: 33569512; PMCID: PMC7859422.

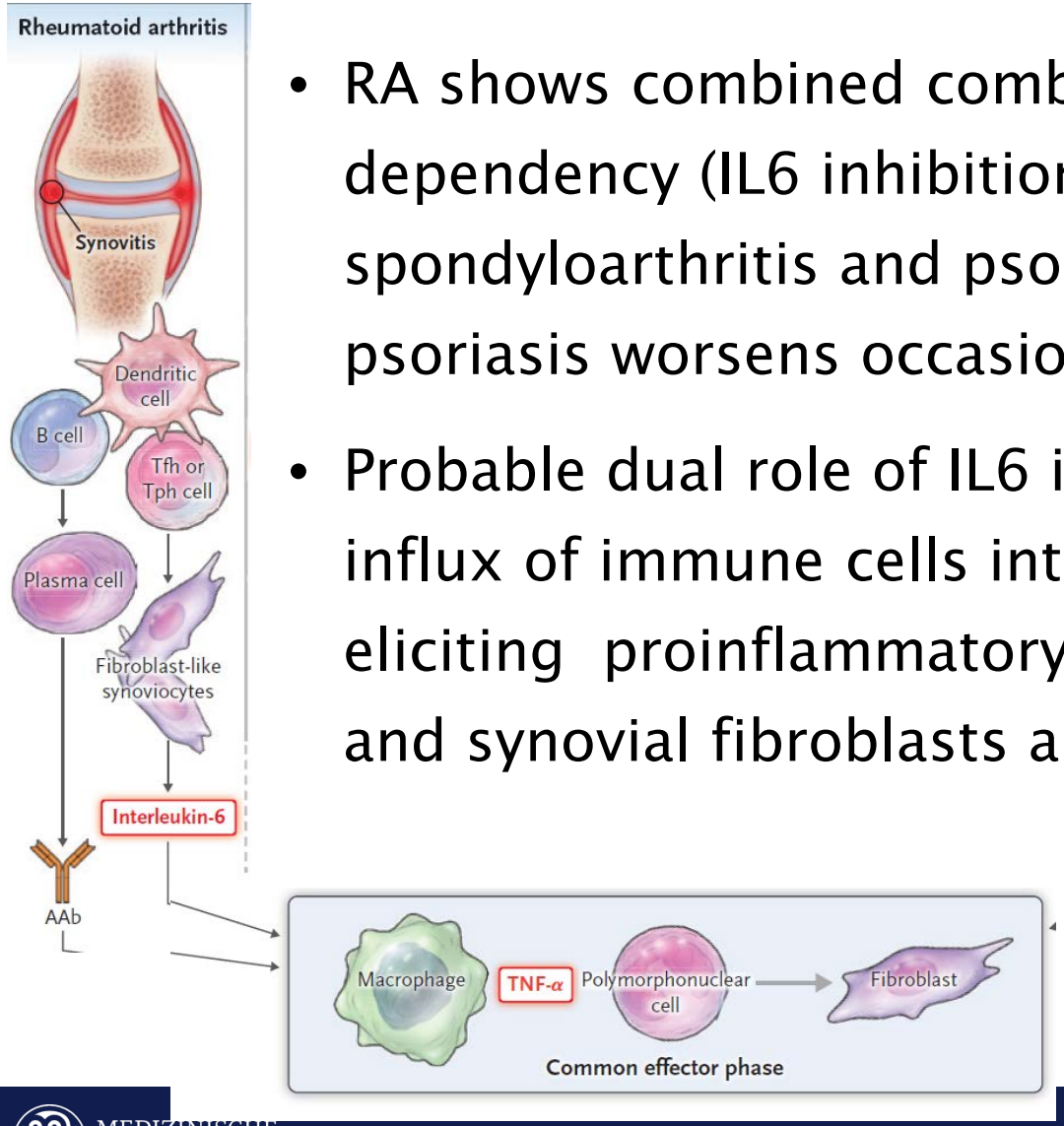
Of note!

- Etanercept, which mainly targets soluble TNF-α, is clinically effective in arthritis rather than in IBD

- Antibodies blocking soluble and membrane-bound TNF-α (infliximab, adalimumab, certolizumab, and golimumab) are effective in both diseases.

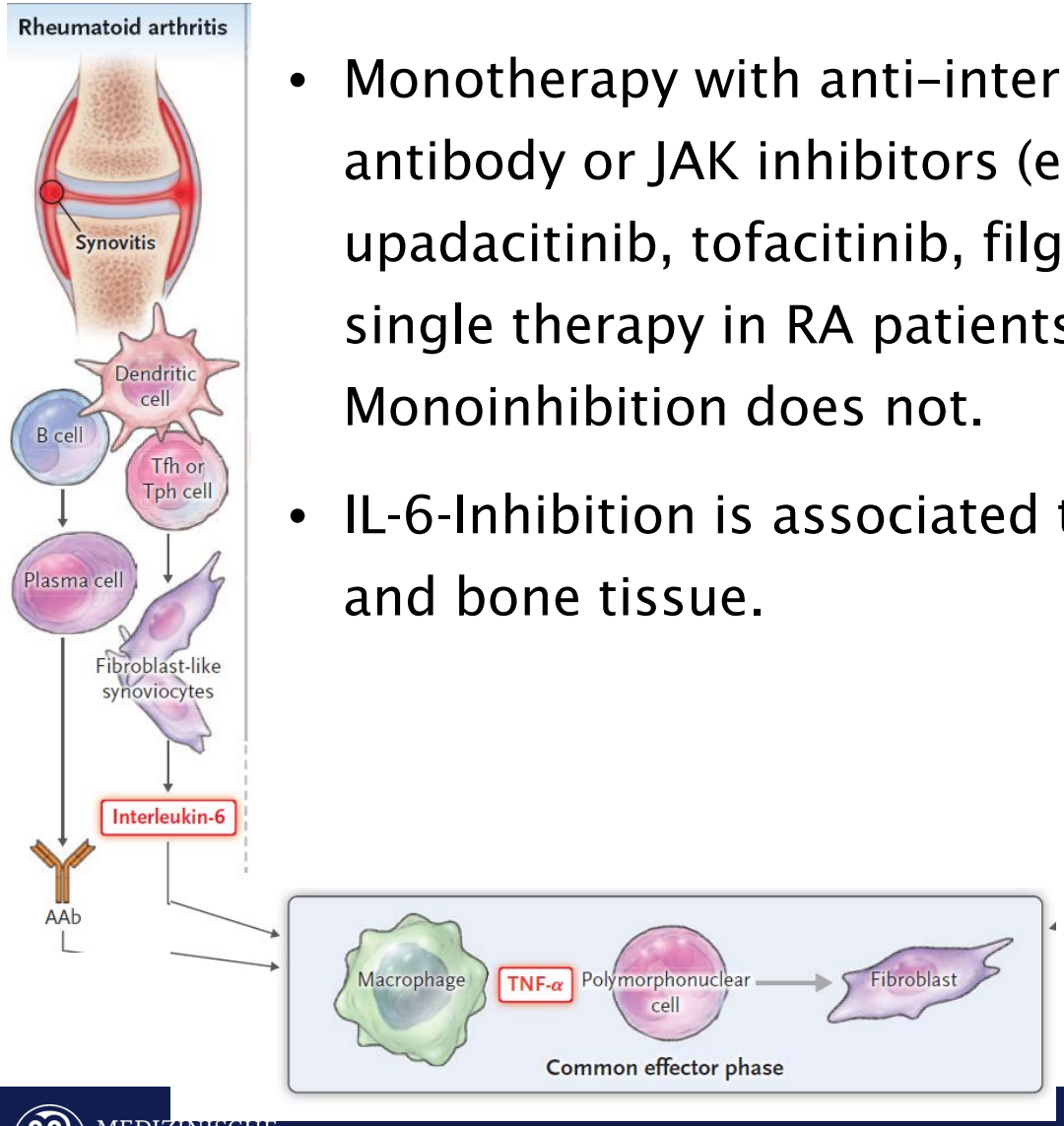
- Membrane-bound TNF-α on macrophages as a trigger for T-cell cytokine production and T-cell survival in IBD?

Interleukin-6: The main cytokine hub in Rheumatoid Arthritis?



- RA shows combined combined TNF-α and IL6 dependency (IL6 inhibition is ineffective in axial spondyloarthritis and psoriatic arthritis, psoriasis worsens occasionally).
- Probable dual role of IL6 in RA in fostering influx of immune cells into the joint and eliciting proinflammatory phenotype -> PBMCs and synovial fibroblasts as major IL6 producers.

Interleukin-6: The main cytokine hub in Rheumatoid Arthritis?



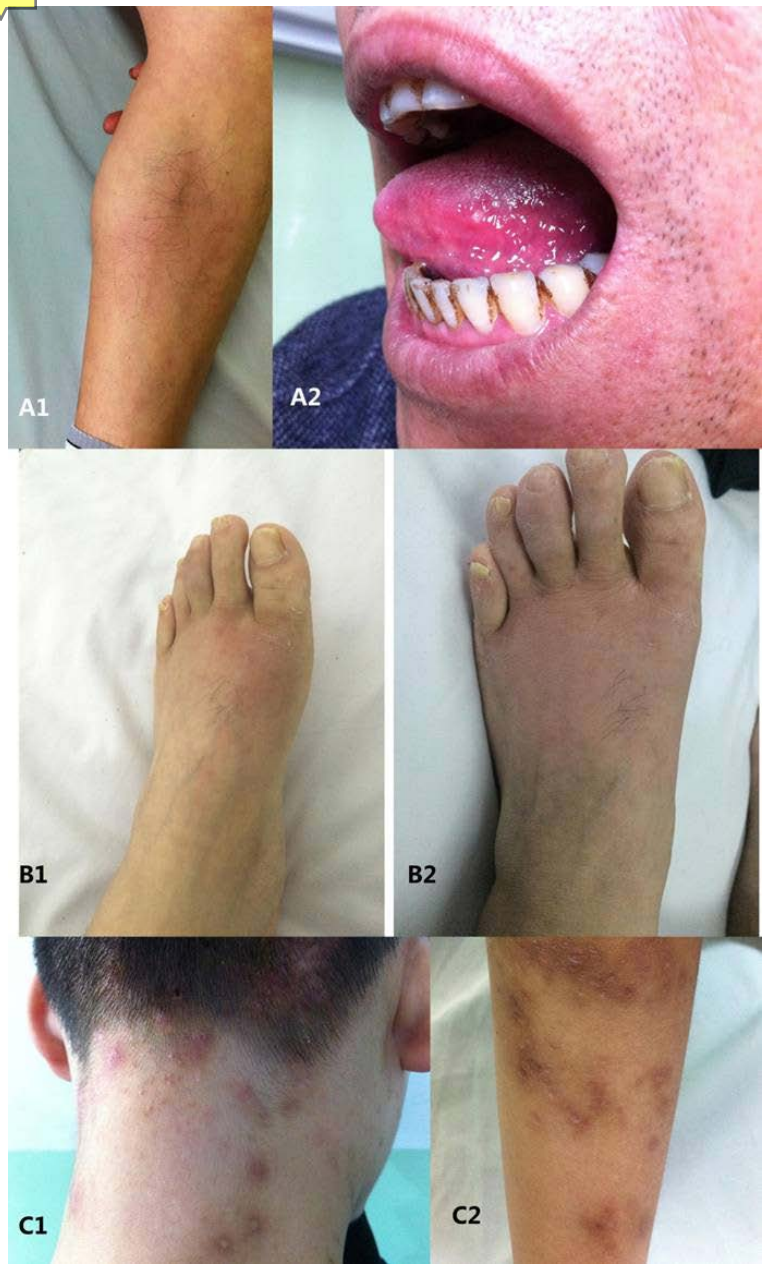
- Monotherapy with anti-interleukin-6 receptor antibody or JAK inhibitors (e.g. baricitinib, upadacitinib, tofacitinib, filgotinib) outperforms MTX single therapy in RA patients, TNF-alpha Monoinhibition does not.
- IL-6-Inhibition is associated to regeneration of joint and bone tissue.

Interleukin-1: The main cytokine hub in Systemic Juvenile Idiopathic Arthritis ?

- IL-1 inhibition is approved for RA but not psoriatic and axial spondyloarthritis or IBD and in RA only effective in a subpopulation.
- Interleukin-1 inhibition (monoclonal antibody **canakinumab** or soluble receptor antagonist **anakinra**) highly effective in

  -> **systemic juvenile idiopathic arthritis**

  -> **adult-onset Still's disease**
- Presumed hyperresponsiveness of macrophages to alarmins such as S100A8 and S100A9, leading to deregulated production of interleukin-1β, interleukin- 6, and interleukin-18.

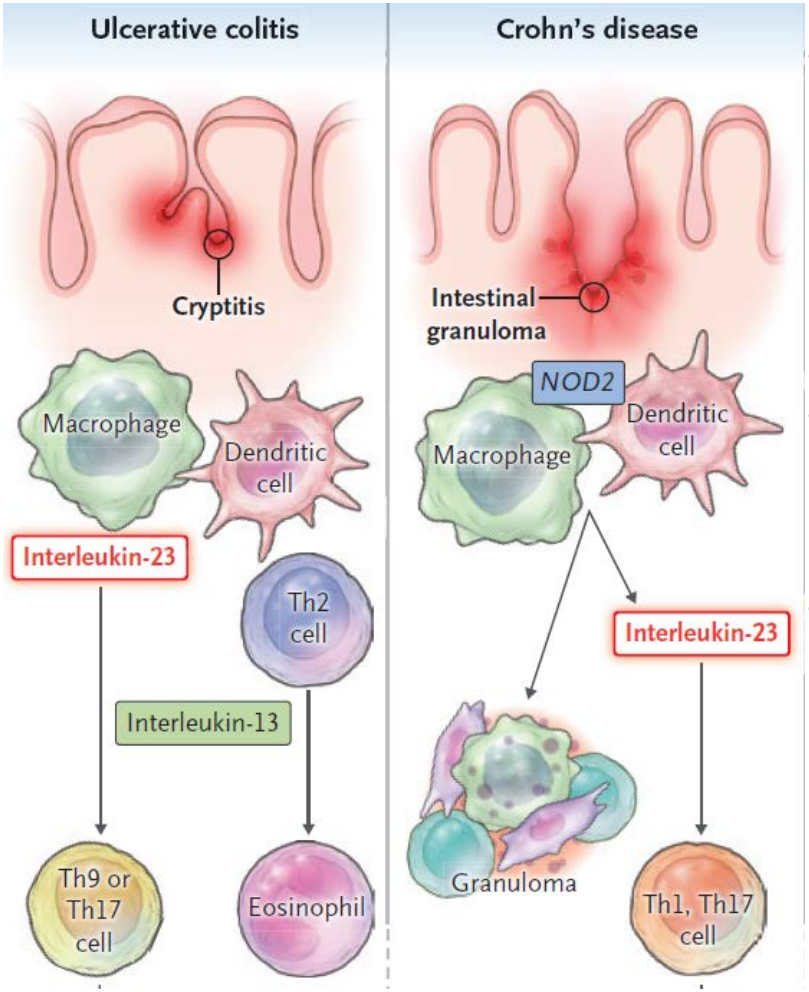


Muckle-Wells syndrome (MWS)

- Broader class: Cryopyrin-associated periodic syndromes (CAPS)
- Commonly recurrent episodes of fever, rash and joint pain
- Sequalae include: Renal amyloidosis, neurological complications (e.g. chronic meningitis, seizures, hydrocephalus)
- Underlying mutations in **CIAS1/NLRP3**
- Increased activity of the protein cryopyrin, or DAMP– mediated activation of the **inflammasome**
- **IL-1 is a signature drugable target in this disease**

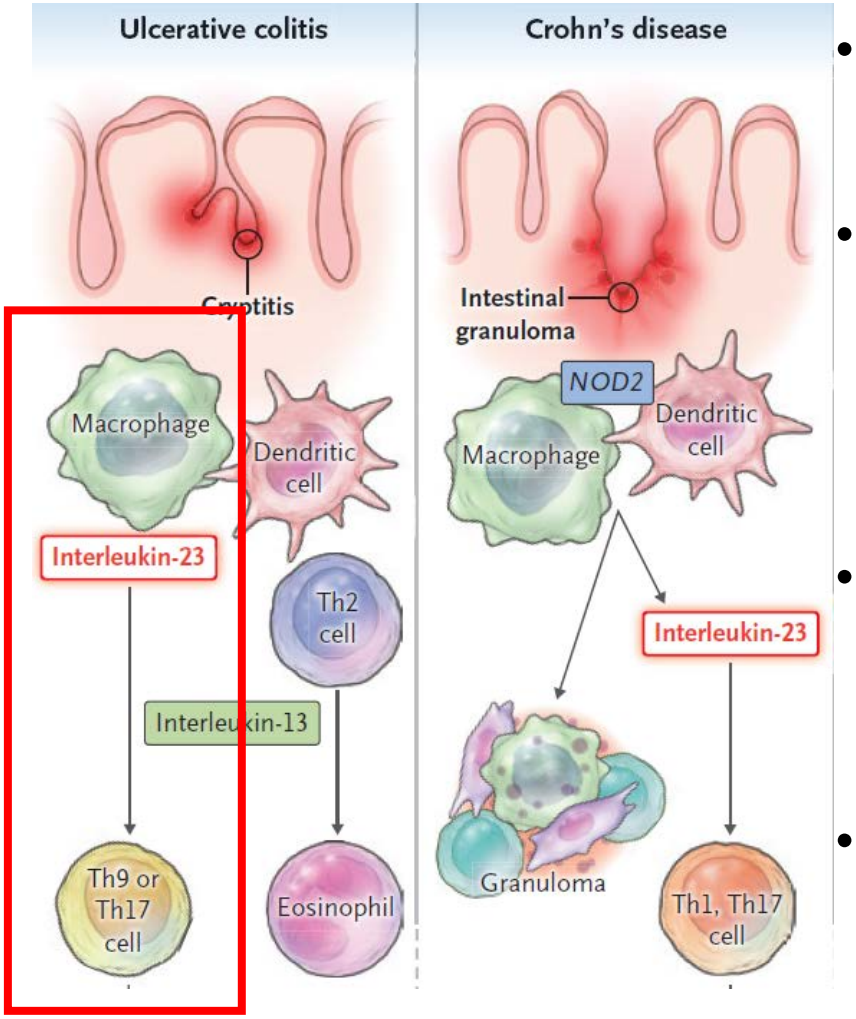
Wu D, Shen M. Muckle-Wells syndrome in Chinese patients: a single center case series. Clin Rheumatol. 2017 Apr;36(4):965-969. doi: 10.1007/s10067-016-3523-3. Epub 2016 Dec 27. PMID: 28028683.

Interleukin-23 in Crohn's Disease and Ulcerative Colitis



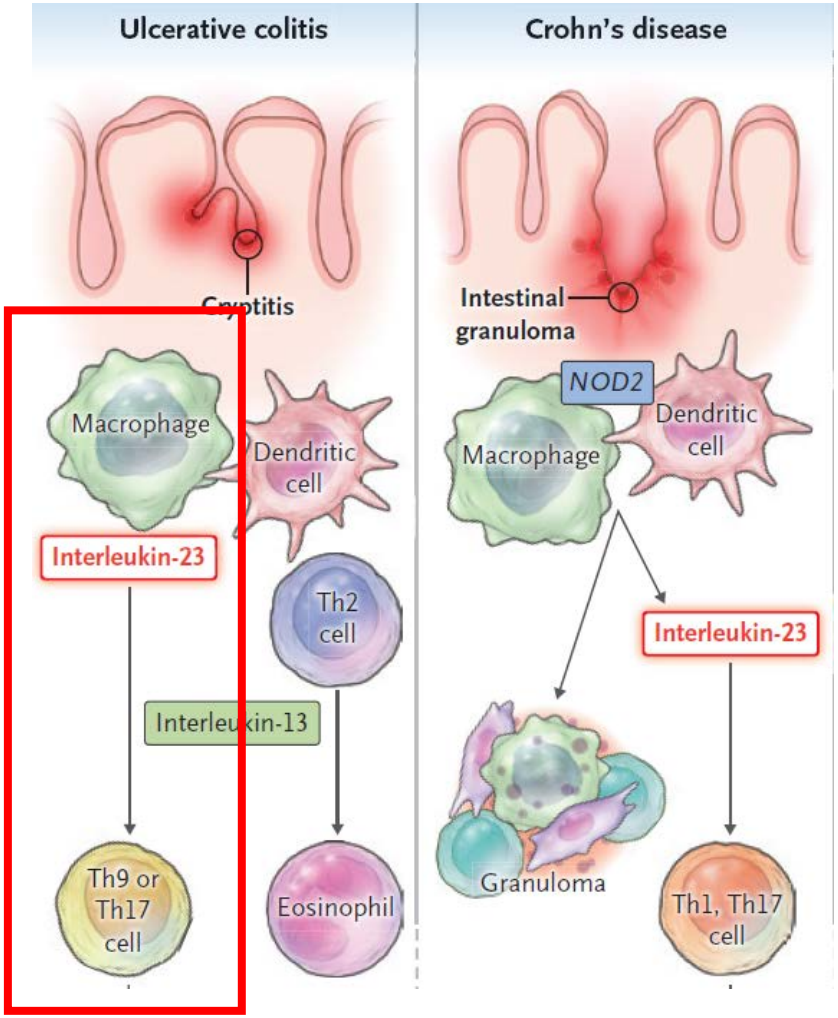
- Both diseases respond to interleukin-12 and interleukin-23 inhibitor ustekinumab (targets p40 the common subunit of IL12 and 23)
- Targeting p19 subunit (risankizumab or guselkumab) on IL23 is as effective
- Both diseases share common IL23 signalling related risk allels

Interleukin-23 in Crohn's Disease and Ulcerative Colitis



- Primary source of IL23: Dendritic cells and macrophages,
- IL23 promotes differentiation and activation of classical type 17 helper T (Th17) cells, T γ/δ cells, and innate lymphoid cells type 3 (ILC3).
- IL23 -> Activation of T cells with markers for both type 1 helper T (Th1) and Th17
- IL23 -> Inhibition of Foxp3 positive Treg differentiation and IL10 production

Interleukin-23 in Crohn's Disease and Ulcerative Colitis



IL 23 inhibition is beneficial in these disorders, IL17A inhibition may exacerbate intestinal inflammation.

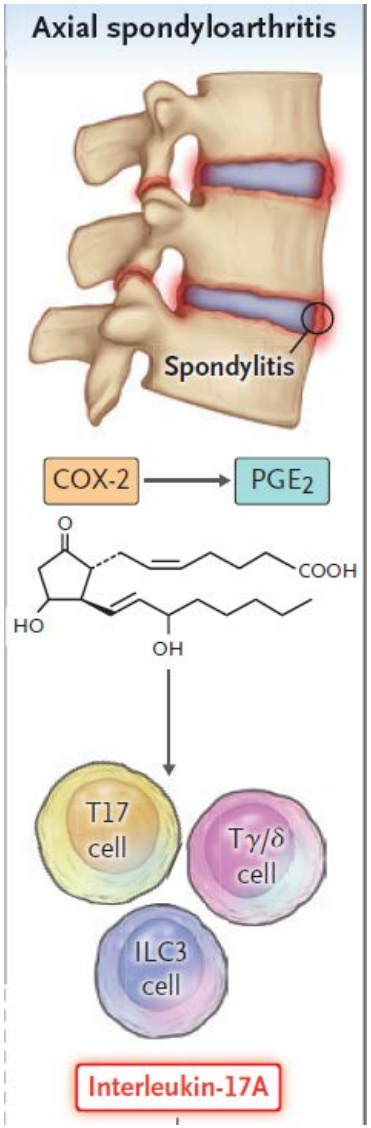
IL 17A may promote epithelial integrity and antimicrobial defense in both the gut and the skin.

IL17A inhibition is beneficial in psoriasis .

Exacerbation of experimental colitis by IL-17A inhibition was associated with impaired intestinal barrier function.

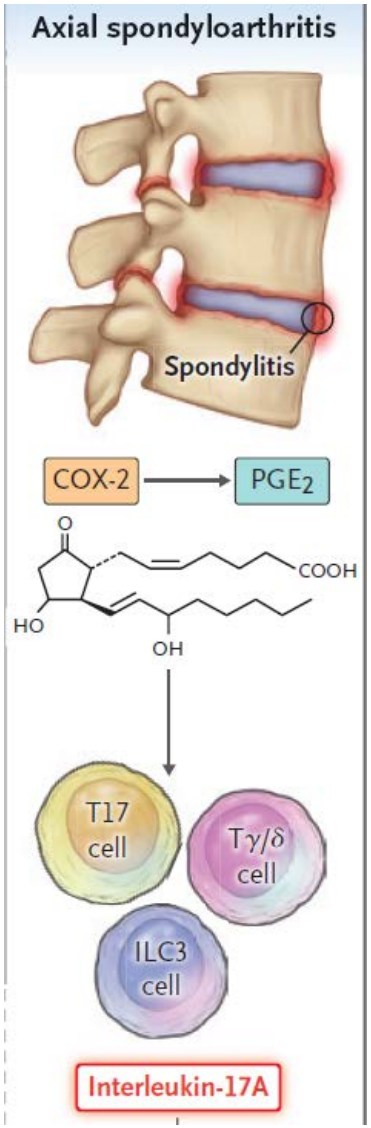
IL23 is not essential for interleukin-17A–mediated maintenance of intestinal barrier function

Interleukin-17A in Axial Spondyloarthritis



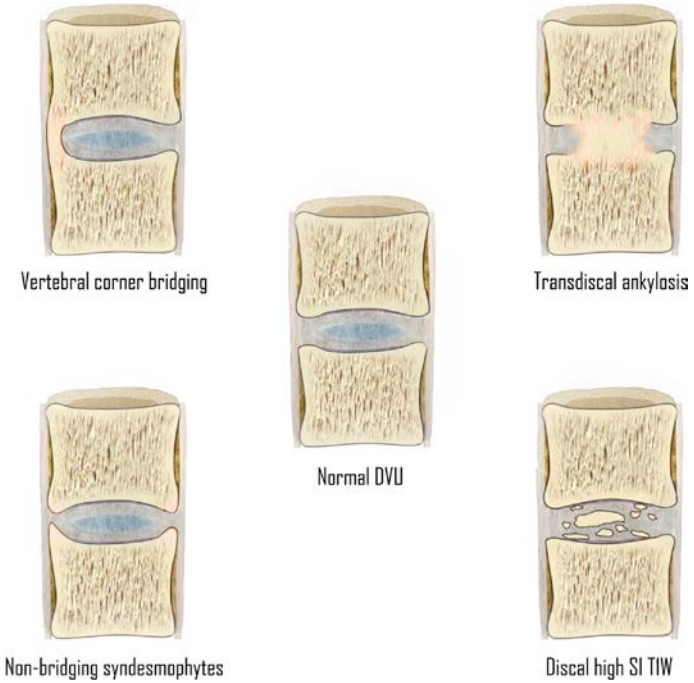
- About 5% of patients with axial spondyloarthritis have concomitant clinical IBD, and 3% of patients with IBD have concomitant axial spondyloarthritis
- But Inhibition of interleukin-17A (with secukinumab or ixekizumab) has remarkable efficacy in axial spondyloarthritis but not IBD symptoms
- Tissue micromilieu specific roles of different cytokine hubs.

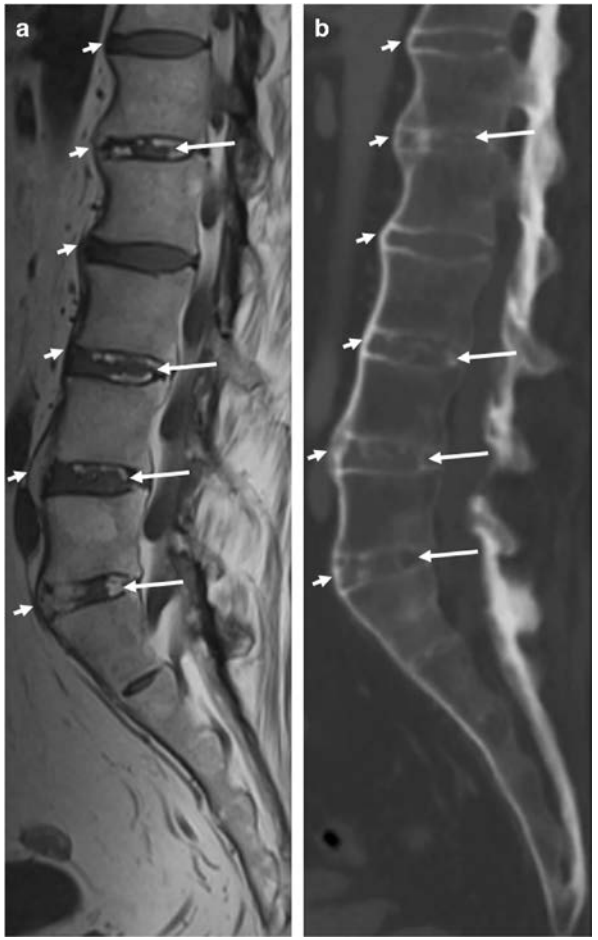
Interleukin-17A in Axial Spondyloarthritis



- Sources of IL17a: T17 cells (CD4+Th17 and CD8+ cytotoxic T17 [Tc17] cells), T γ/δ cells, and ILC3,
- Sides of inflammation: tendons and their insertions (entheses): Prime role of IL17a in inflammation at this side, in absence of IL23
- Mechanistically: IL17a production appears to be linked to asustained production of prostaglandin E2 through cyclooxygenase 2 (COX-2) activation.
- Associated to vasodilatation and neutrophil attraction to tissues.
- COX2 activation and PGE2 secretion loops back positivles to IL17a production
- Both PGE2 and IL17a sensitize pain sensation in dorsal root ganglia

Interleukin-17A in Axial Spondyloarthritis

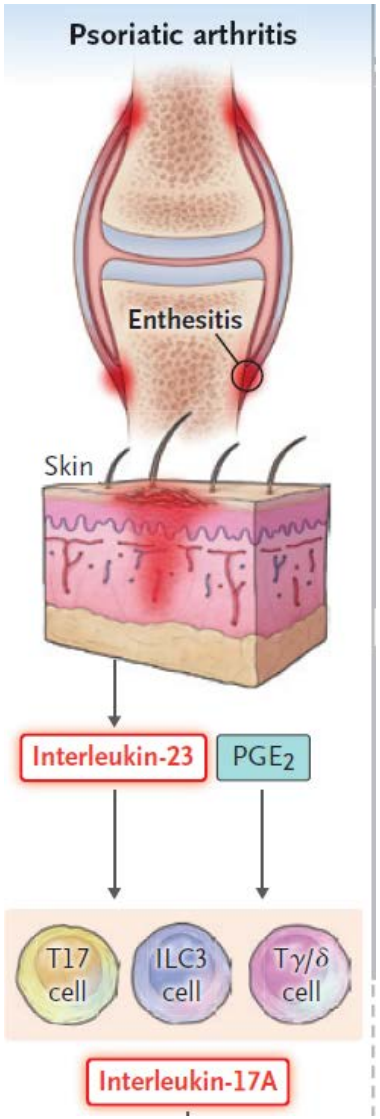




- Common final endpoint: Osteoblast activation -> bone spur formation and ankylosis in axial spondyloarthritis

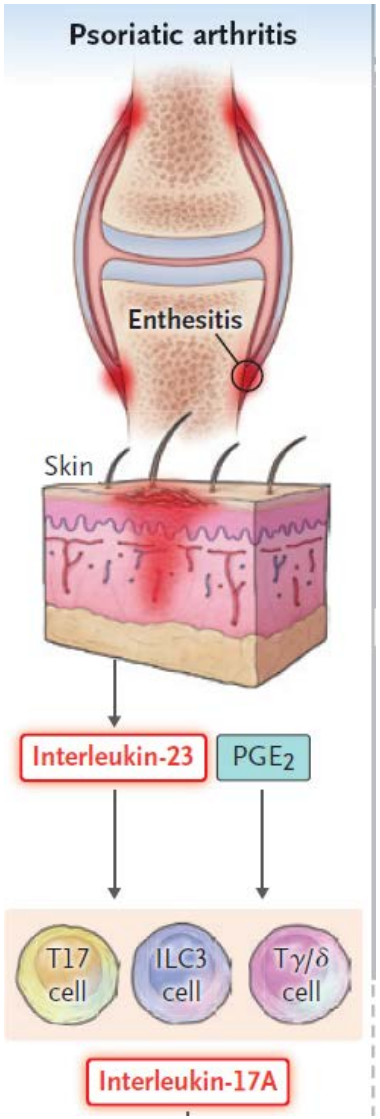
https://insightsimaging.springeropen.com/articles/10.1186/s13244-019-0752-4

Combined Interleukin-17A and Interleukin-23 in Psoriatic Arthritis



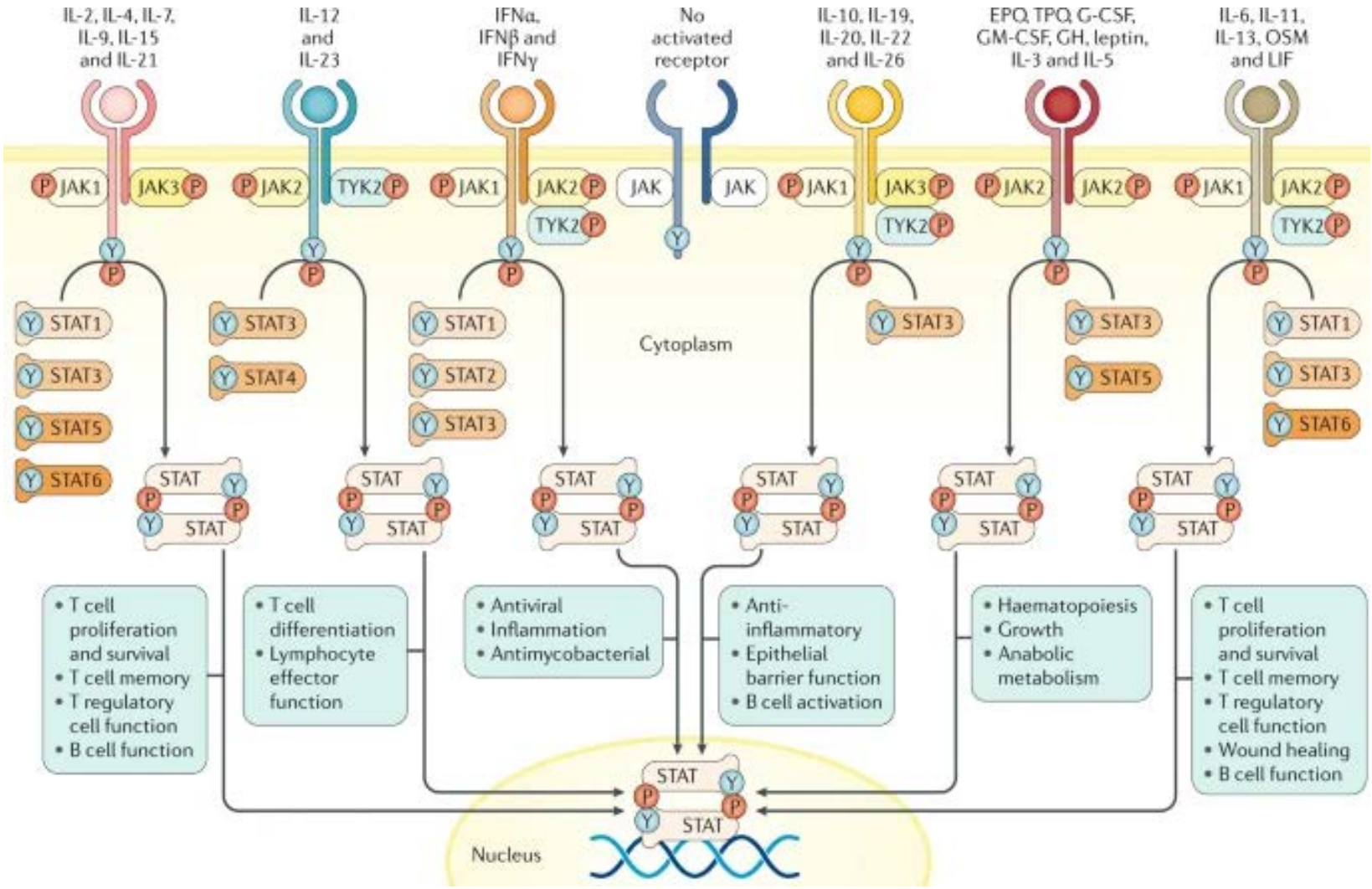
- Approximately 30% of patients with psoriasis have psoriatic arthritis
- Psoriatic arthritis differs fundamentally from rheumatoid arthritis : Genetic link with the interleukin-23 receptor and MHC class I (e.g., C06) alleles; essentially lacks the autoimmune background of RA, no signs of autoantibody formation or B-cell dependency
- Clinically distinct phenotype: Asymmetric arthritis (mostly oligoarthritis), Enthesitis, bony spurs and ankylosis.

Combined Interleukin-17A and Interleukin-23 in Psoriatic Arthritis



- Good response to IL17A and IL23 inhibition (in Skin AND Joints!)
- Excessive T-cell activation, neutrophil influx, and resident tissue responses to mechanical stress in psoriatic skin and joint disease.
- Inhibition of IL17A and interleukin-23 provides more robust control of the skin disease than TNF-α, but not in joints.
- IL17A and IL23 as key hubs of “mechano inflammation”.
- Hypothesis: IL23 might be released systemically from other tissues (e.g. skin or gut) secondarily triggering joint inflammation.

Single- versus Multiple-Cytokine Inhibition in IMIDs



Salas, A., Hernandez-Rocha, C., Duijvestein, M. et al. JAK–STAT pathway targeting for the treatment of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 17, 323–337 (2020). https://doi.org/10.1038/s41575-020-0273-0

Single- versus Multiple-Cytokine Inhibition in IMIDs

- JAK inhibitors block the signaling of several cytokines and are effective in a wide range of IMIDs,
- Several but not all cytokine hubs that signal through JAKs, including JAK1/2 (e.g., interleukin-6) and tyrosine kinase 2 (e.g., interleukin-6 and interleukin-23),
- JAK inhibitors are also effective in axial spondyloarthritis, which involves TNF-α and interleukin-17A, cytokines that do not require JAK signaling.
- Other cytokines that are sensitive to JAK inhibition not yet recognized as hubs?

Discussion

- A cytokine hub driven mechanism-based understanding of IMIDs instead of an organ based one?
- Lead cytokine hubs or cytokines a proxys for conserved cell-cell interactions?
- The paramount role of the tissue micromillieu in governing the effect of cytokine mediated signaling
- Systemic inter-organ cytokine driven communication
- Is the focus on cytokines and even protein mediators to narrow (e.g. miRNA and lipids in inflammtion and resolution and tissue regeneration)?

References (in order of appearance)

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