Malattia di Still dell'Adulto
Still a Clinical Challenge

Serena Bugatti

Early Arthritis Clinic and b/tsDMARDs Clinic
SC di Reumatologia
Fondazione IRCCS Policlinico San Matteo, Università di Pavia

serena.bugatti@unipv.it
s.bugatti@smatteo.pv.it



Donna, originaria del Perù, 43 anni,

Anamnesi Patologica Remota muta

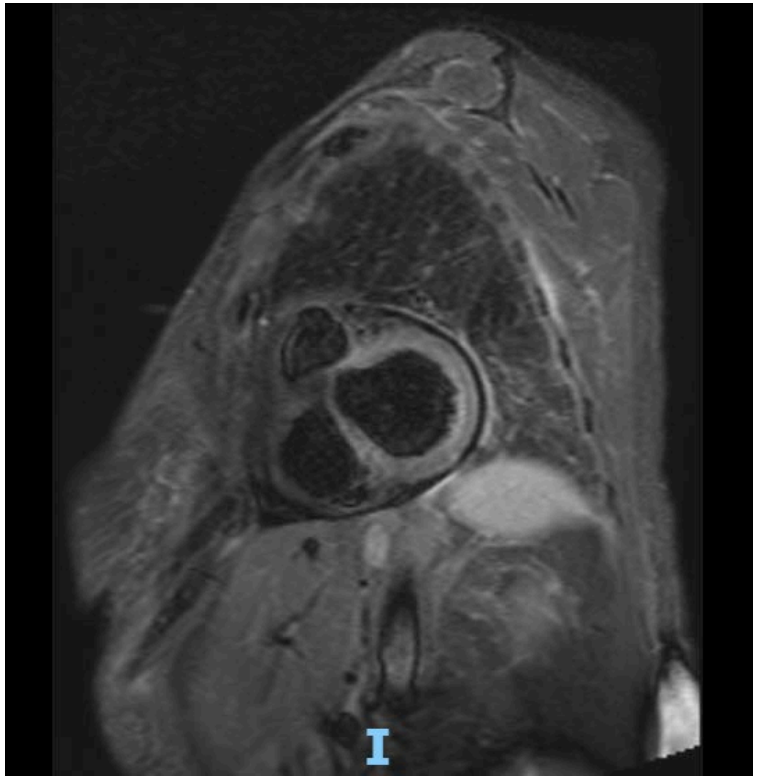
Accesso in PS ad Aprile 2021 per febbre ondulante ma persistente (picco di 39.5°C), faringodinia, artralgie ad anche/caviglie/ginocchia, oppressione toracica

- TNF molecolare SARS-COV2 negativo
- Leucocitosi neutrofila (N 12.000/microL)
- PCR 22.4 mg/dL
- Procalcitonina 1.31 ng/mL
- Hb 11.1 g/dL
- Troponina 958 pg/mL
- BNP 1678 ng/mL
- Elevazione di D-dimero, LDH (788 U/L), fibrinogeno
- Ad ECG riscontro di sovraslivellamento tratto ST diffuso
- Obiettività nei limiti

- Embolia polmonare? → AngioTC torace negativa per TEP

- Ad ecocardiografia lieve falda di versamento pericardico e focale ipocinesia del setto inferiore e parete inferiore medio-apicale con FEvs conservata

→ Ricovero in UTIC per miopericardite , impostata ASA 3g/die e colchicina 1 g/die, terapia antibiotica empirica con piperacillina tazobactam



Eziologia infettiva?

Emocolture e urocolture negative

Sierologia Borrelia, EBV, CMV Parvovirus B19, Coxiella Burnetii, Chlamidia e Mycoplasma Pneumoniae, Echovirus:

negative per infezioni recenti

Eziologia neoplastica?

- Ecografia addominale e TC addome con mdc → solo lieve epatomegalia
- TC torace → nulla di patologico

Durante il ricovero in UTIC

- Normalizzazione indici di danno cardiaco
- Persistenza di febbre, stabilità di PCR (18 mg/dL) e procalcitonina (2.3 ng/mL)
- Peggioramento artralgie arti inferiori
- Comparsa di rash pruriginoso a dorso e arti inferiori

Trasferimento in Reumatologia

All’ingresso in reparto

- ANA, anti-ENA, ANCA, LAC, aPL, RF, aCCP negativi
- HIV, HBV, CMV DNA, HHV8 DNA, amebiasi, tripanosomiasi negativi
- AST 200 mU/mL, ALT 200 mU/mL
- Ferritina 19.181 ng/mL
- Obiettività generale nei limiti (fegato palpabile in arcata), non articolazioni dolorabili né tumefatte

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Table 1. Possible manifestations of AOSD.

Cardinal Manifestations
Skin rash
Fever > 39 °C
Leukocytes > 10,000/mm^3, neutrophils > 80%
Arthritis and arthralgia
Other frequent manifestations
Odynophagia, pharyngitis
Myalgia, myositis
Lymphadenopathy, splenomegaly
Hepatomegaly, hepatitis
Pericarditis, myocarditis, pleuritis, lung disease (interstitial lung infiltrates)
Increased ESR, CRP, fibrinogen
Increased ferritin, decreased glycosylated ferritin

Mitrovic S, Fautrel B. J Clin Med 2021;10:2633. .

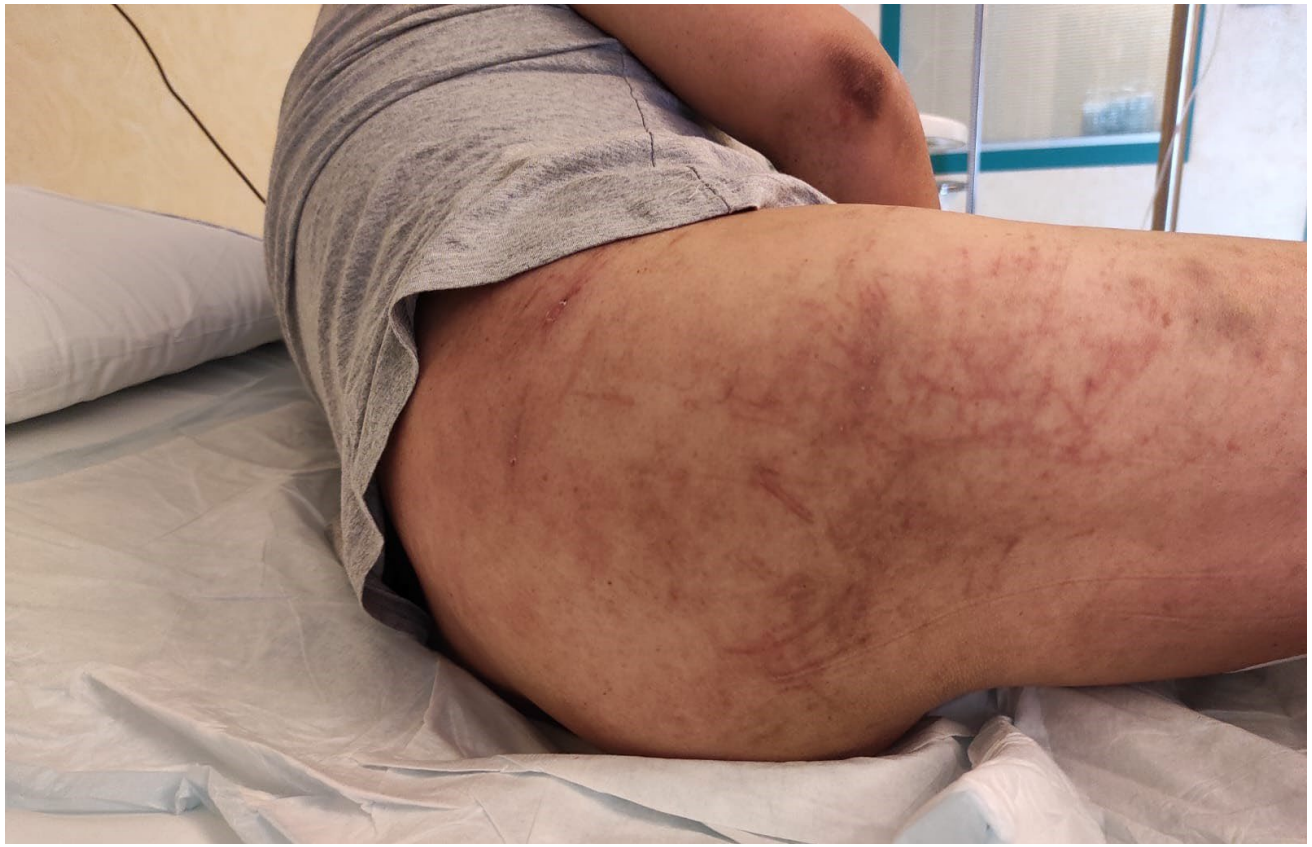
Trasferimento in Reumatologia

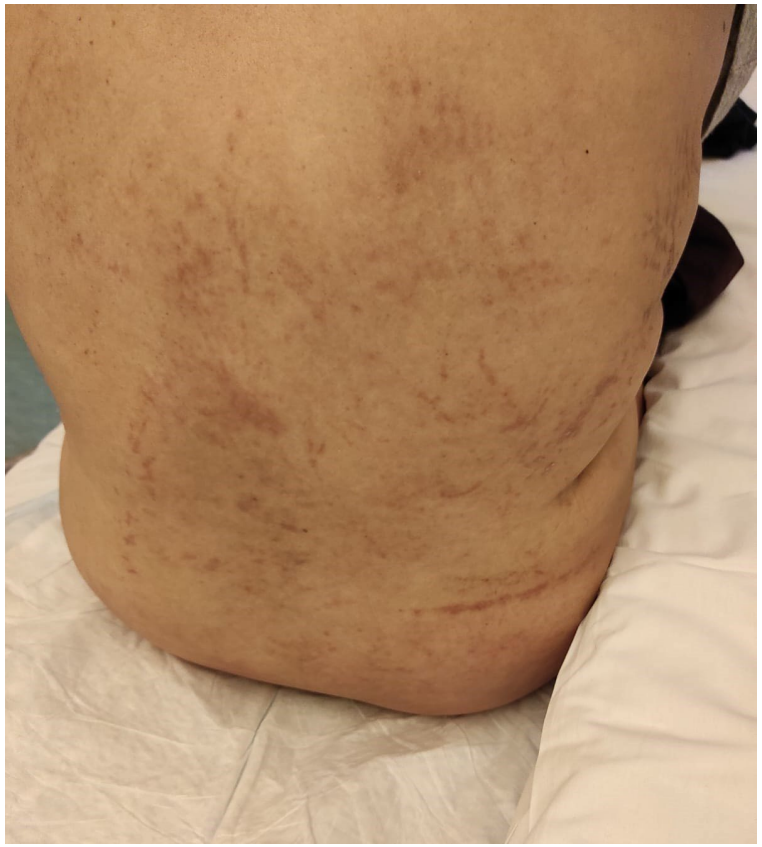
Table 2. Classification criteria for AOSD.

Criteria	Yamaguchi et al. [4]	Fautrel et al. [5]
Major criteria	✓ Fever ≥ 39 °C lasting one week or more ✓ Arthralgia lasting two weeks or more ~~Typical skin rash: maculopapular, non-pruritic, salmon-pink rash with concomitant fever spikes~~ ✓ Leukocytosis ≥ 10,000/mm^3 with neutrophil polymorphonuclear proportion ≥ 80%	✓ Spiking fever ≥ 39 °C ✓ Arthralgia ~~Transient erythema~~ ✓ Pharyngitis ✓ Neutrophil polymorphonuclear proportion ≥ 80% GF proportion ≤ 20%
Minor criteria	✓ Pharyngitis or sore throat ~~Lymphadenopathy and/or splenomegaly~~ ✓ Liver enzyme abnormalities (aminotransferases) ✓ Negative for RF or antinuclear antibodies	~~Typical rash~~ ✓ Leukocytosis ≥ 10,000/mm^3
Exclusion criteria	Absence of infection, especially sepsis and Epstein–Barr viral infection Absence of malignant diseases, especially Lymphomas Absence of inflammatory disease, especially polyarteritis nodosa	None
Criteria requirement	At least five criteria, including two major criteria and no exclusion criteria	Four major criteria or three major criteria and two minor criteria

Mitrovic S, Fautrel B. J Clin Med 2021;10:2633. .

Trasferimento in Reumatologia





Consulenza dermatologica → lesioni flagellate associate a prurito intenso suggestive per AOSD a variante «eruzione pruritica persistente»

Durante il ricovero in Reumatologia

- Diagnosi di Malattia di Still dell'Adulto → metilprednisolone 60 mg/die EV

- Persistenza picchi febbrili 39°C
- Progressiva riduzione di piastrine ($70*10^9/L$), Hb (8 g/dl), neutrofili e fibrinogeno fino a 110 mg/dl
- Ulteriore rialzo di transaminasi >3ULN, LDH, ferritina 25.0000 ng/ml
- Trigliceridi 380 mg/dL

Macrophage Activation Syndrome (MAS)

Classification of macrophage activation syndrome in systemic juvenile idiopathic arthritis

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:

Ferritin >684 ng/ml

and any 2 of the following:

Platelet count $\leq$181 x 10^9/liter

Aspartate aminotransferase >48 units/liter

Triglycerides >156 mg/dl

Fibrinogen $\leq$360 mg/dl

Figure 2 Criteria for the classification of macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. Laboratory abnormalities should not be otherwise explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis or familial hyperlipidaemia.

Ravelli A et al. Ann Rheum Dis 2016 Mar;75(3):481-9.

Sindromi Iperferritinemiche

- adult-onset Still’s disease (AOSD)
- macrophage activation syndrome (MAS)
- catastrophic anti-phospholipid syndrome (CAPS)
- septic shock
- severe coronavirus disease-19 (COVID-19)

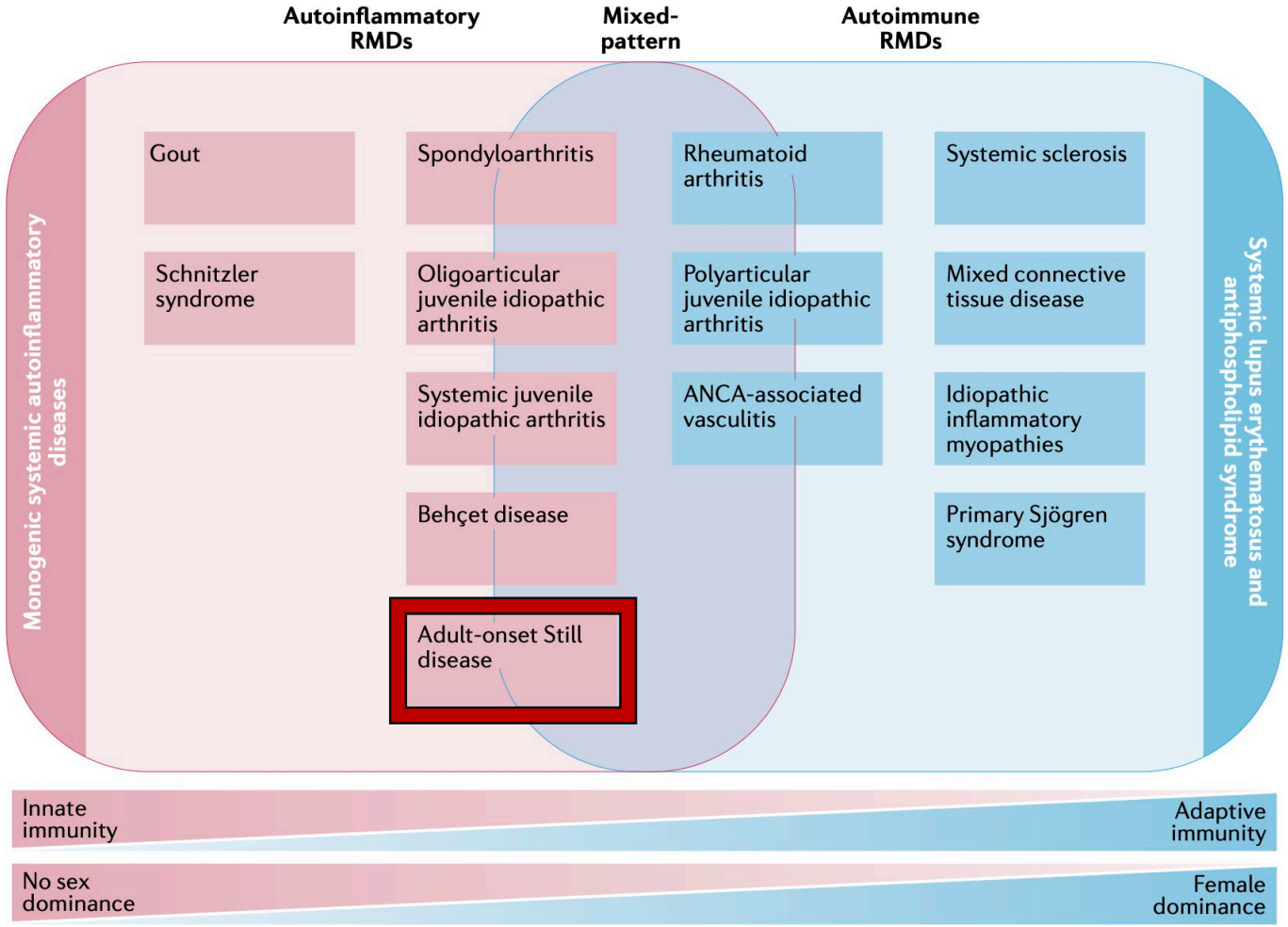
Macrophage Activation Syndrome (MAS)

→ Sindrome da attivazione macrofagica (MAS)
→ Boli metilprednisolone EV 1g/die per tre giorni e ciclosporina 200 mg/die
→ Anakinra (anti-IL1R)

09/2021 ecocardiogramma FE 64%
09/2021 PCR 0.48 mg/dl, ferritina 307 ng/dl
Prednisone ridotto a 7.5 mg/die, prosegue Anakinra

05/2023
Steroid-free, prosegue Anakinra

AOSD Pathogenesis: Auto-Inflammatory or- Immune?



Szekanecz Z et al. Nat Rev Rheumatol. 2021;17:585-95

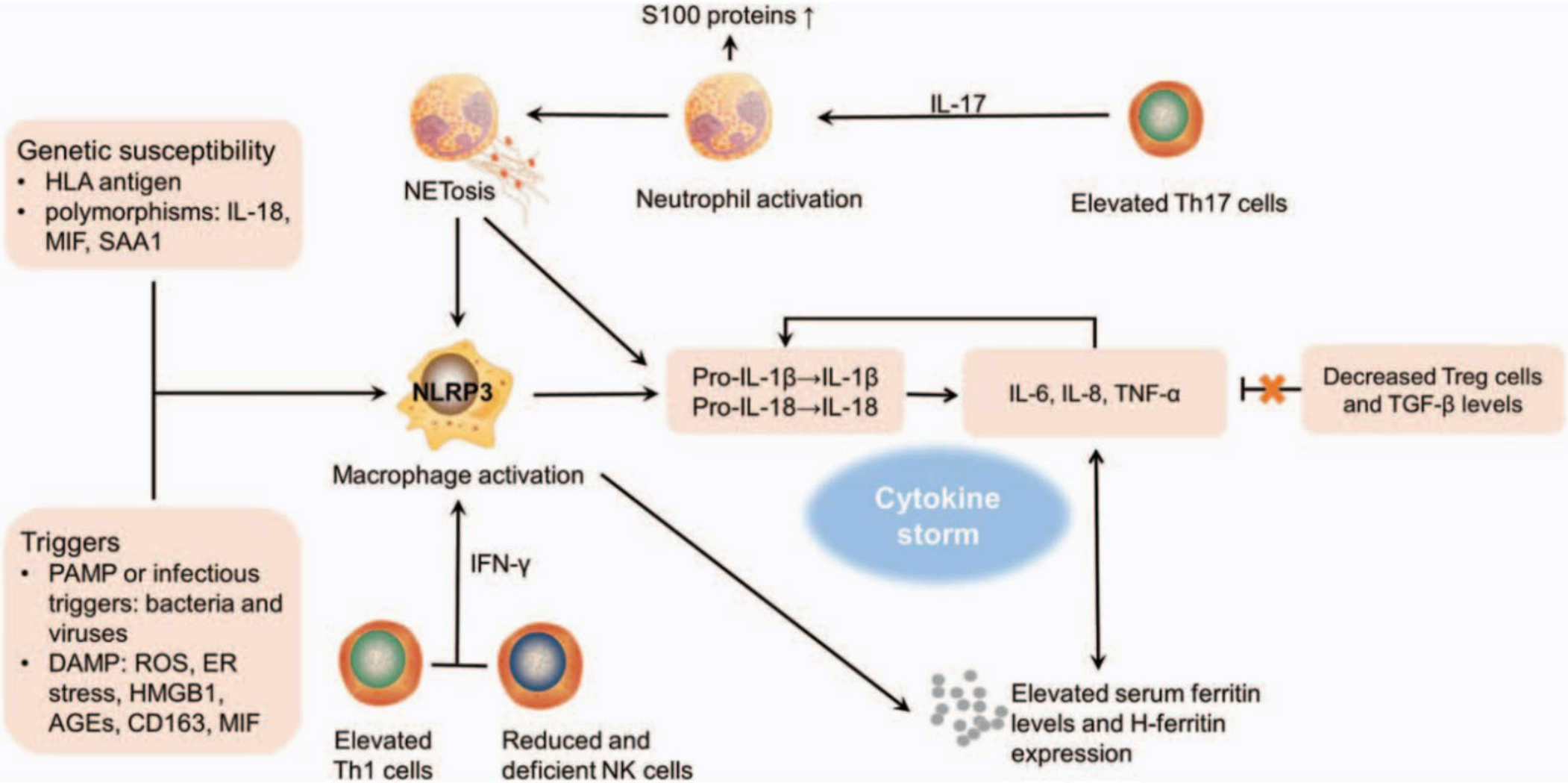
Autoinflammatory diseases

- The definition mainly relies on similarities with monogenic, hereditary periodic fever syndromes
- Innate immunity
- Intense inflammation rate (ESR, CRP)
- Periodic fever
- Macrophages and Neutrophils
- Increased leukocyte and neutrophil counts
- Tissue inflammation
- Pathogenic function of the inflammasome
- Therapeutic response to IL-1 blockade
- No sex dominance

Autoimmune diseases

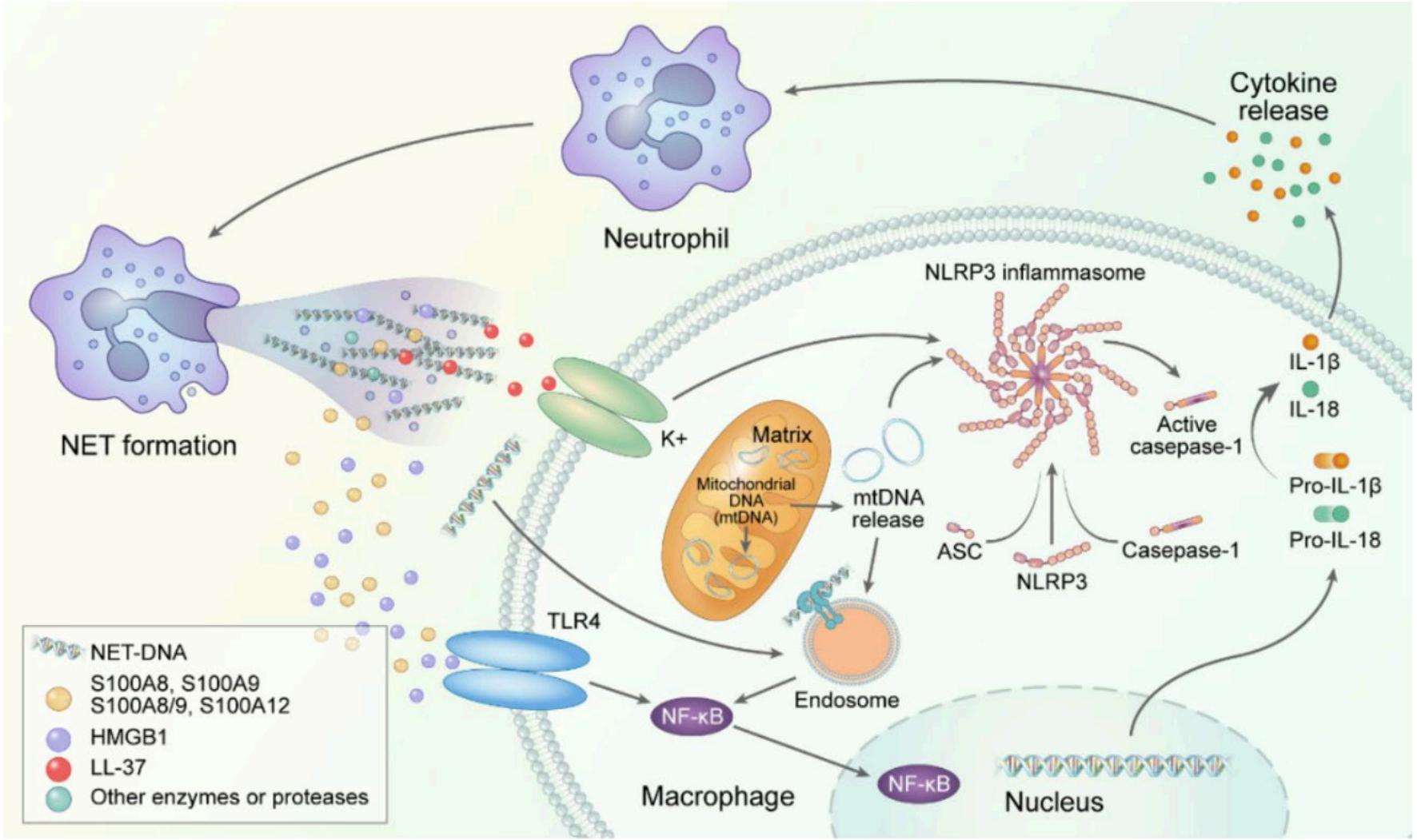
- Adaptive immunity
- Autoantibodies or Autoantigen-specific T and B cells
- Therapeutic response to B-cell suppression
- HLA class II genetic predisposition
- Female dominance

Pathogenesis: Overview



Wang MY et al. Cmj. 2019;132:2856-64

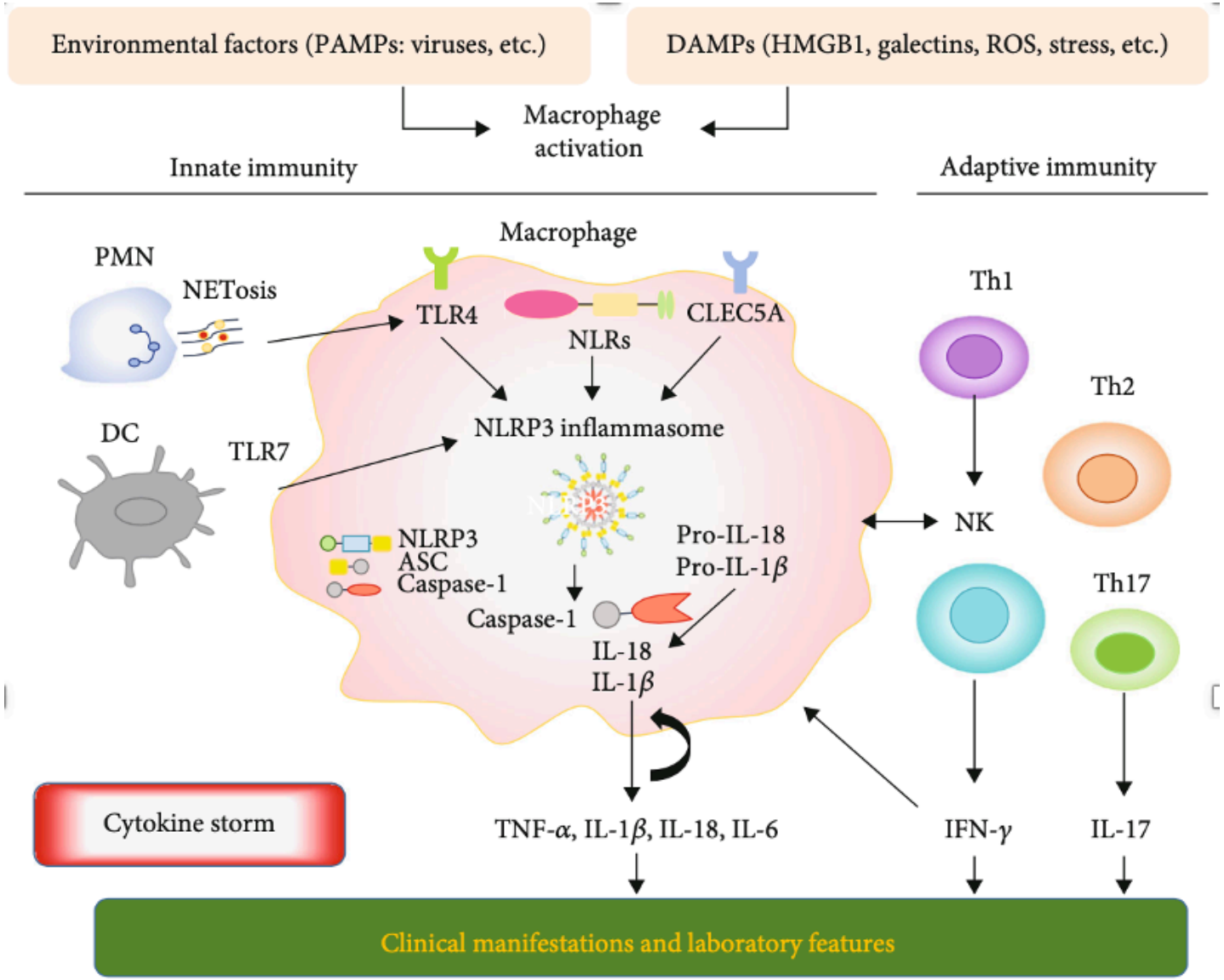
Pathogenesis: Neutrophils



Neutrophil Extracellular Traps

Min JK et al. Scand J Rheumatol. 2003;32:119-21; Bonaventura A et al. Cells 2020;*9:*231; Hu Q et al. Arthritis Research & Therapy 2019;21:9; Kim JW et al. Int. J. Mol. Sci. 2021, 22, 13038

Pathogenesis: Macrophages



The leading actors?

Chen PK et al. J immunol Res. 2021:8998358

Pathogenesis: IL-1

Therapeutic Advances in Musculoskeletal Disease *Systematic Review*

Update on the therapy of adult-onset Still's disease with a focus on IL-1-inhibition: a systematic review

Ther Adv Musculoskel Dis

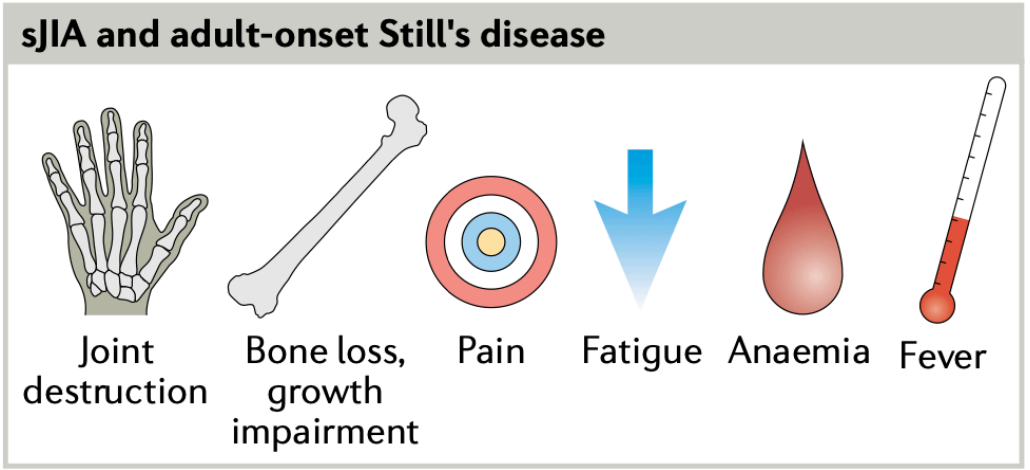
2021, Vol. 13: 1–13

DOI: 10.1177/1759720X211059598

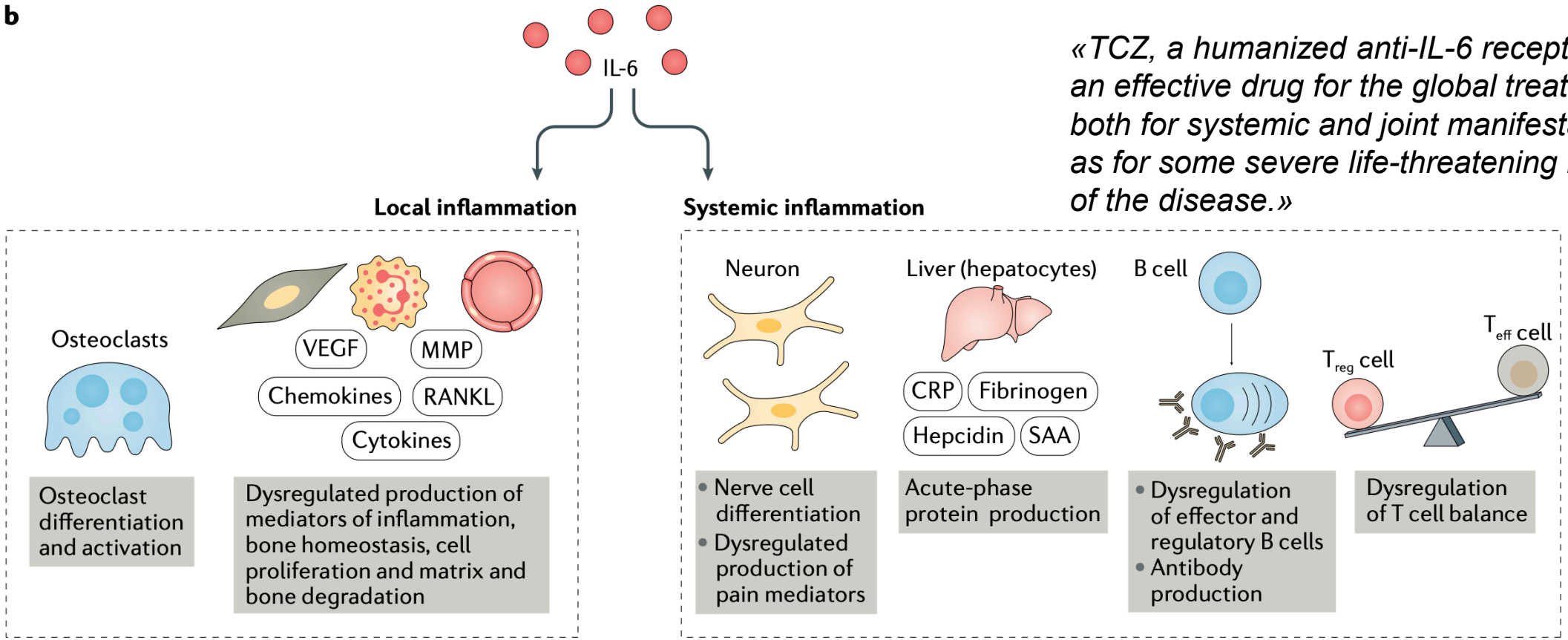
Claudia Kedor, Stylianos Tomaras, Daniel Baeumer and Eugen Feist

Conclusion: The approval of IL-1 inhibitors for AOSD brought us into a new era in the treatment of AOSD. The overall efficacy-safety profile of the IL-1 inhibitors is favorable reflecting a targeted approach as standard of care. We can expect that the successful treatment of AOSD with IL-1 inhibition will facilitate further clinical and basic research with impact on other auto-inflammatory and hyper-inflammatory conditions.

Pathogenesis: IL-6



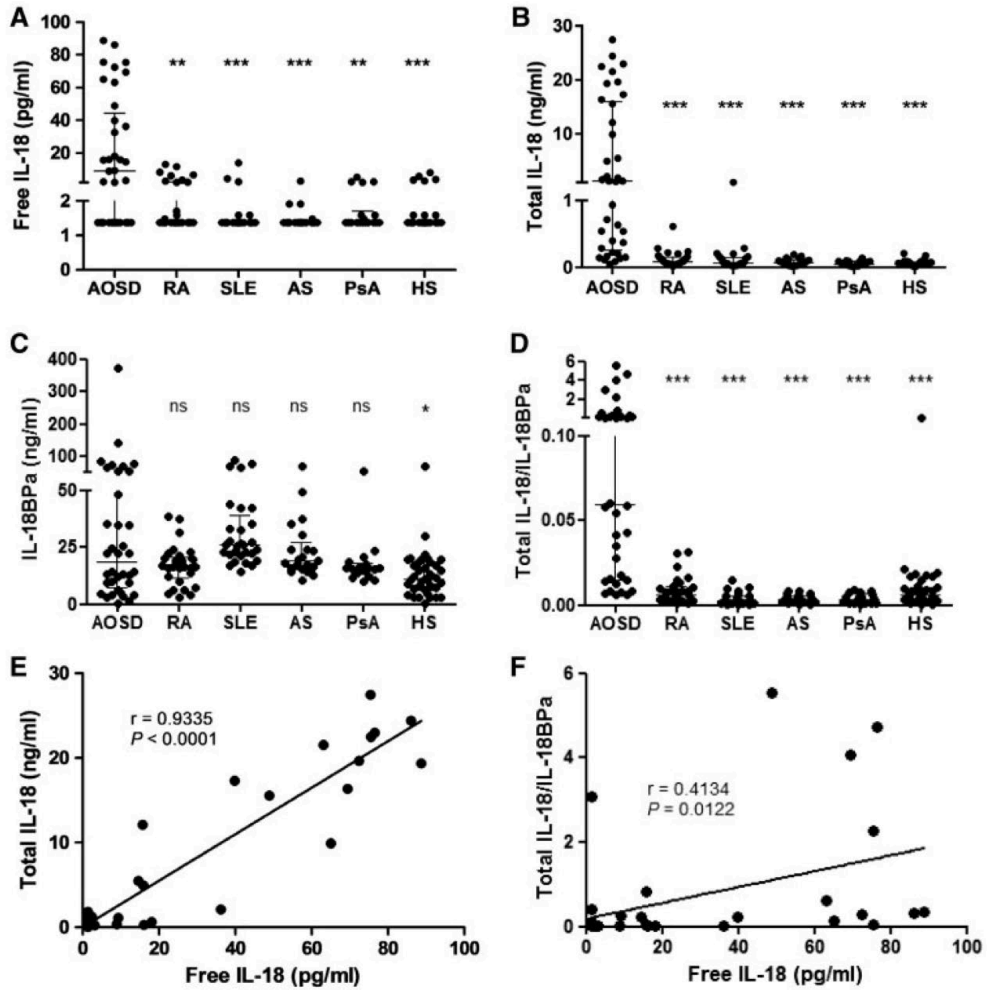
«TCZ, a humanized anti-IL-6 receptor antagonist, is an effective drug for the global treatment of AOSD, both for systemic and joint manifestations, as well as for some severe life-threatening manifestations of the disease.»

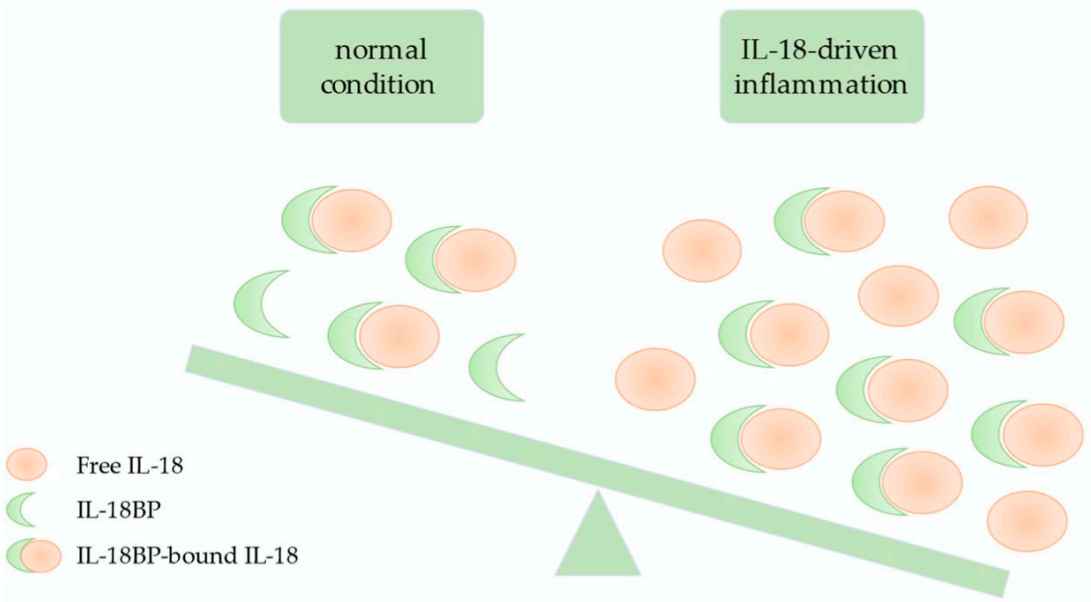


Choy EH et al. Nat Rev Rheumatol. 2020;16:335-45; Castañeda S et al. Expert Opin Biol Ther. 2019;19:273-86

Pathogenesis: IL-18

Fig. 2 Serum levels of IL-18 and IL-18BPa in AOSD and controls





Girard-Guyonvarc'h C et al. J. Clin. Med. 2022;11:430; Girard C et al. Rheumatology 2016;55:2237-47; Ogita A et al. J Nippon Med Sch 2022;1:89:114-8; Kaplanski G. Immunological Reviews. 2018;281:138-53

Pathogenesis: NK cells

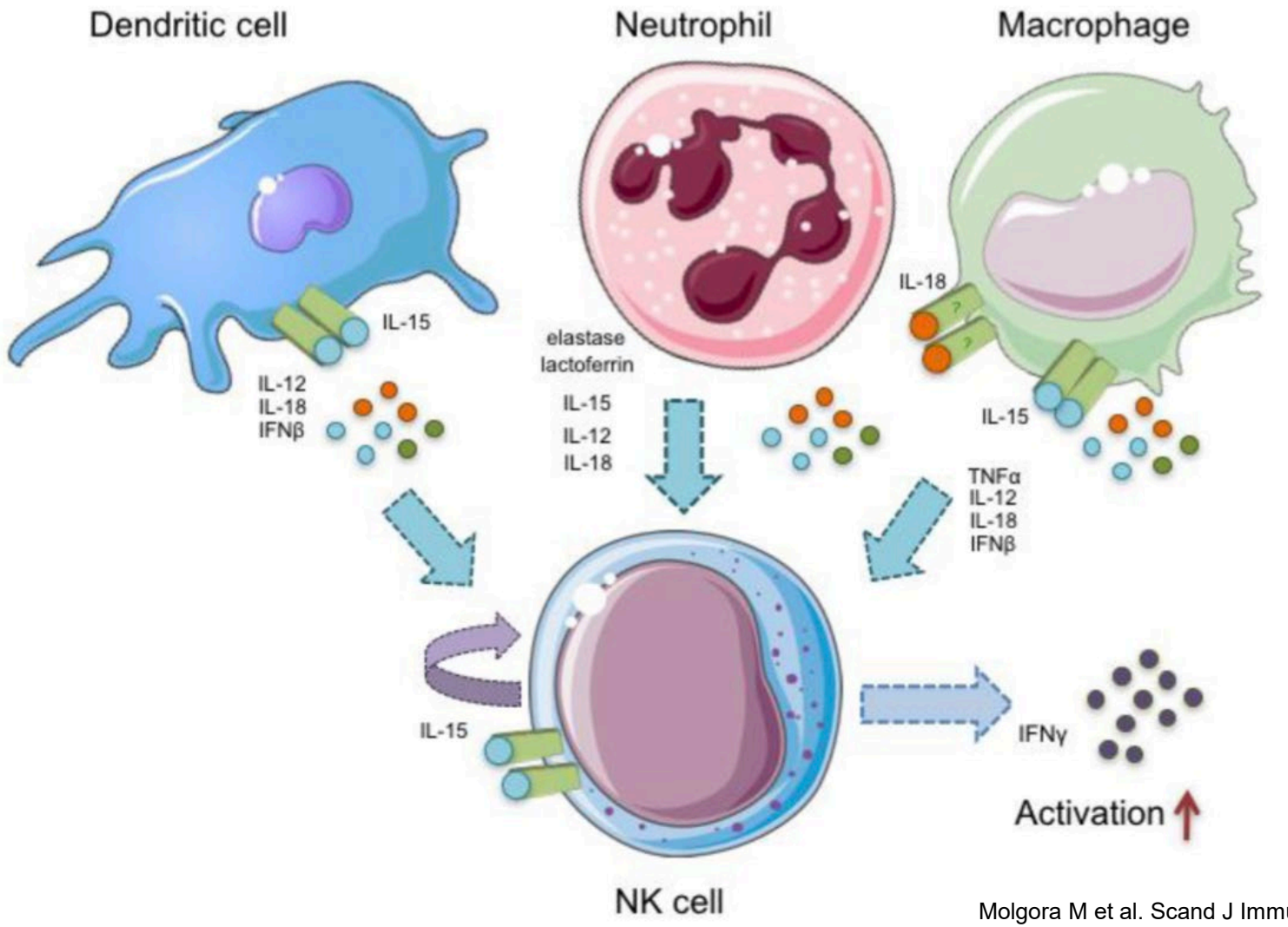


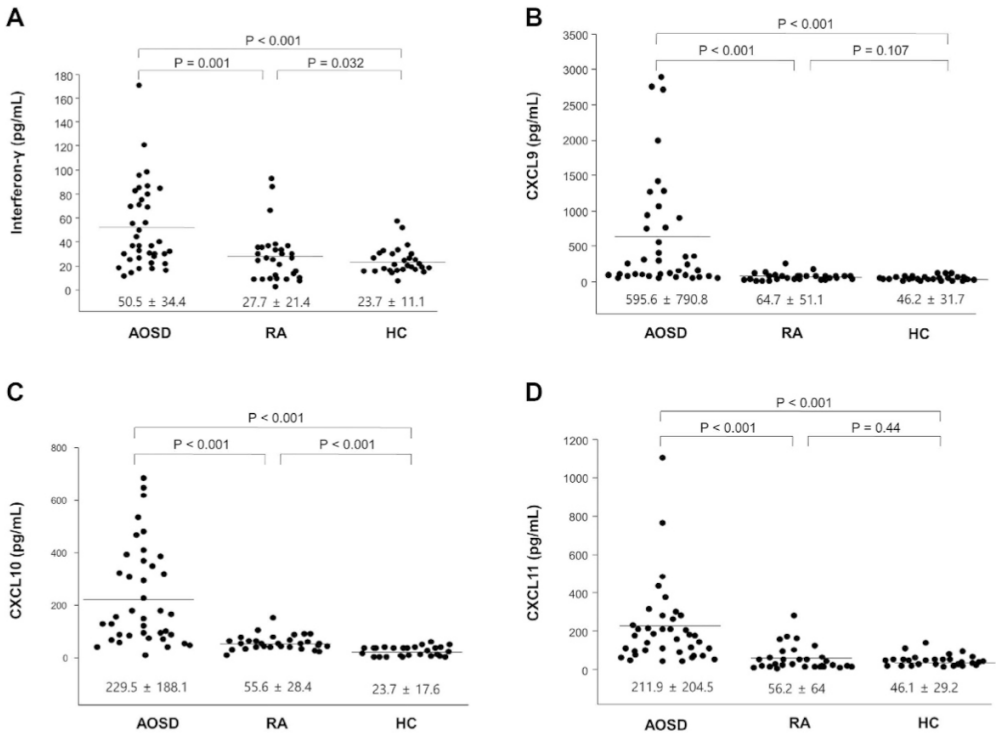
Table 1. Current findings regarding the role of natural killer cells in adult-onset Still disease (AOSD) and systemic juvenile idiopathic arthritis (sJIA).

Disease	Findings	Ref.
AOSD	Lower NK T cell counts Defect in GalCer-mediated NK cytotoxicity	4
AOSD	Lower NK cell counts Lower NK cytolytic function	5
sJIA	Lower NK cytolytic activity Lower circulating CD56^{bright} NK cell levels	9
sJIA	Impaired upregulation of cell-mediated perforin and IFN-γ in NK cells Defect in IL-18 receptor β phosphorylation	16
sJIA	Lower cell counts, cytotoxicity, perforin, and granzyme B expression in NK cells Lower frequency of KIR2DS4	13
sJIA	Increased expression of innate genes and decreased expression of immune-regulating genes of NK cells Alterations in inhibitory and excitatory receptors of NK cells Decreased granzyme K expression in CD56^{bright} NK cells and defective IL-18–induced IFN-γ production	12
sJIA	Impaired NK cell activation by IL-18	21

Molgora M et al. Scand J Immunol. 2018;88:e12705; Jung JY et al. The Journal of Rheumatology 2019; 46:10

Pathogenesis: INF signature

Serum



Lymph nodes

	AOSD	TCL	HNL	TB lymphadenitis	Reactive hyperplasia	*P*-value
CXCL10						**<0.001**
Grade 1	14 (34.1)	9 (90.0)	6 (60.0)	6 (60.0)	10 (100)	
Grade 2	16 (39.0)	1 (10.0)	4 (40.0)	4 (40.0)	0 (00.0)	
Grade 3	11 (26.8)	0 (00.0)	0 (00.0)	0 (00.0)	0 (00.0)	
CXCR 3						**0.002**
Grade 1	10 (24.4)	6 (60.0)	7 (70.0)	4 (40.0)	6 (60.0)	
Grade 2	12 (29.3)	3 (30.0)	3 (30.0)	6 (60.0)	4 (40.0)	
Grade 3	19 (46.3)	1 (10.0)	0 (00.0)	0 (00.0)	0 (00.0)	
CXCL13						**0.004**
Grade 1	24 (58.8)	3 (30.0)	10 (100.0)	10.0 (100.0)	9 (90.0)	
Grade 2	13 (31.7)	4 (40.0)	0 (00.0)	0 (00.0)	1 (10.0)	
Grade 3	4 (9.8)	3 (30.0)	0 (00.0)	0 (00.0)	0 (00.0)	
S100A8/A9						0.273
Grade 1	16 (39.0)	7 (70.0)	7 (70.0)	7 (70.0)	6 (60.0)	
Grade 2	17 (41.5)	2 (20.0)	2 (20.0)	3 (30.0)	4 (40.0)	
Grade 3	8 (19.5)	1 (10.0)	1 (10.0)	0 (00.0)	0 (00.0)	

Skin

	Staining cell percent AOSD	Staining cell percent normal skin	*P*-value (AOSD vs. normal)	Staining cell percent eczema	*P*-value (AOSD vs. eczema)	Staining cell percent psoriasis	*P*-value (AOSD vs. psoriasis)
CXCL9	8.7 ± 10.5	2.2 ± 2.8	0.098	4.8 ± 5.8	0.581	3.0 ± 3.4	0.178
CXCL10	**24.5 ± 21.6**	**4.6 ± 4.9**	**0.012**	**5.2 ± 6.3**	**0.019**	**3.0 ± 2.0**	**0.009**
CXCL11	**27.2 ± 24.3**	23.8 ± 8.4	0.474	**63.2 ± 15.7**	**0.006**	**46.8 ± 17.7**	**0.035**
CXCR3	15.2 ± 17.0	16.2 ± 24.5	0.791	25.2 ± 13.0	0.074	21.2 ± 19.5	0.257

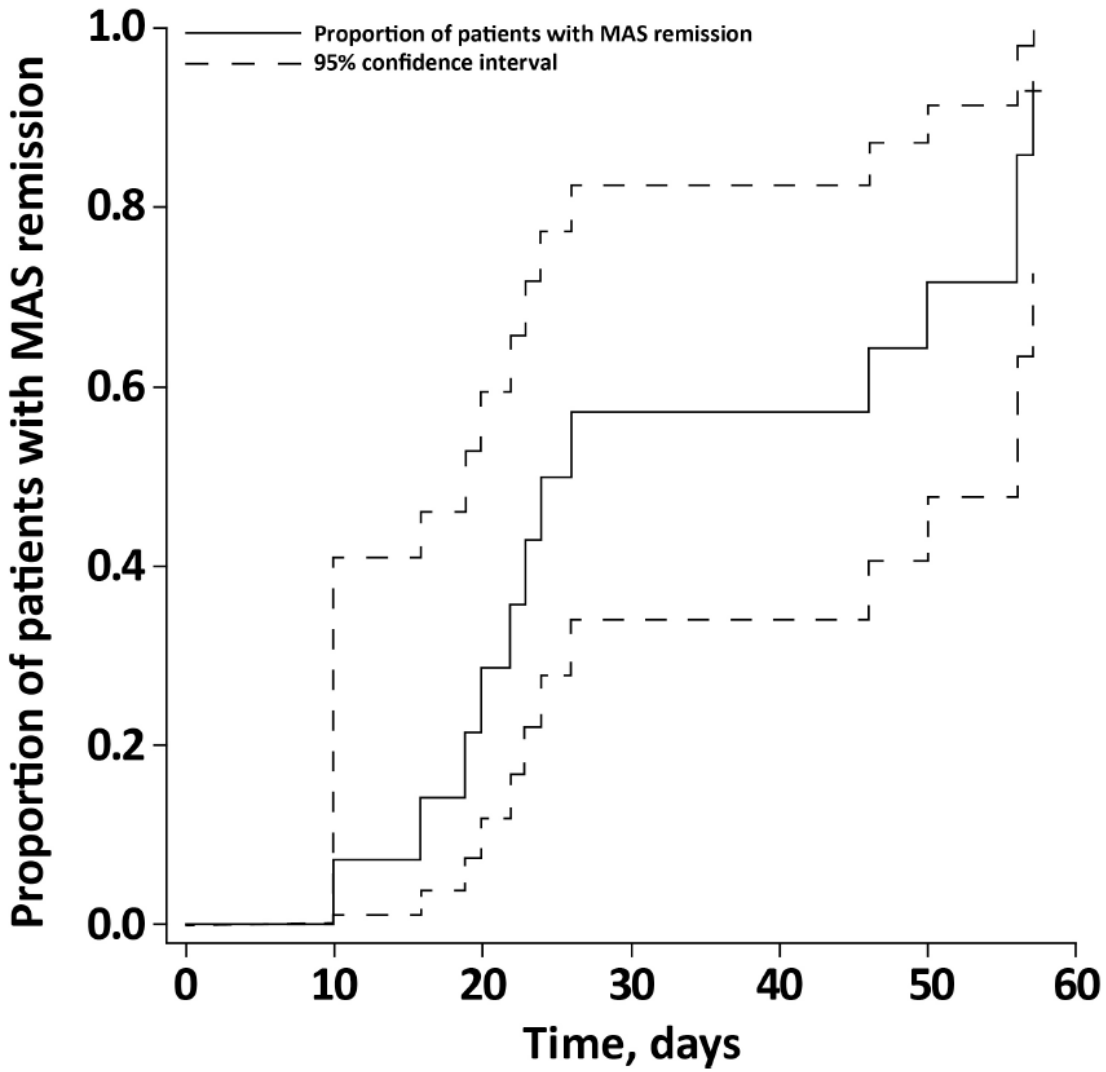
Kim HA et al. Scientific RepoRts. 2019;9:7517; Han JH et al. Scientific RepoRts. 2017;7:46652

CLINICAL SCIENCE

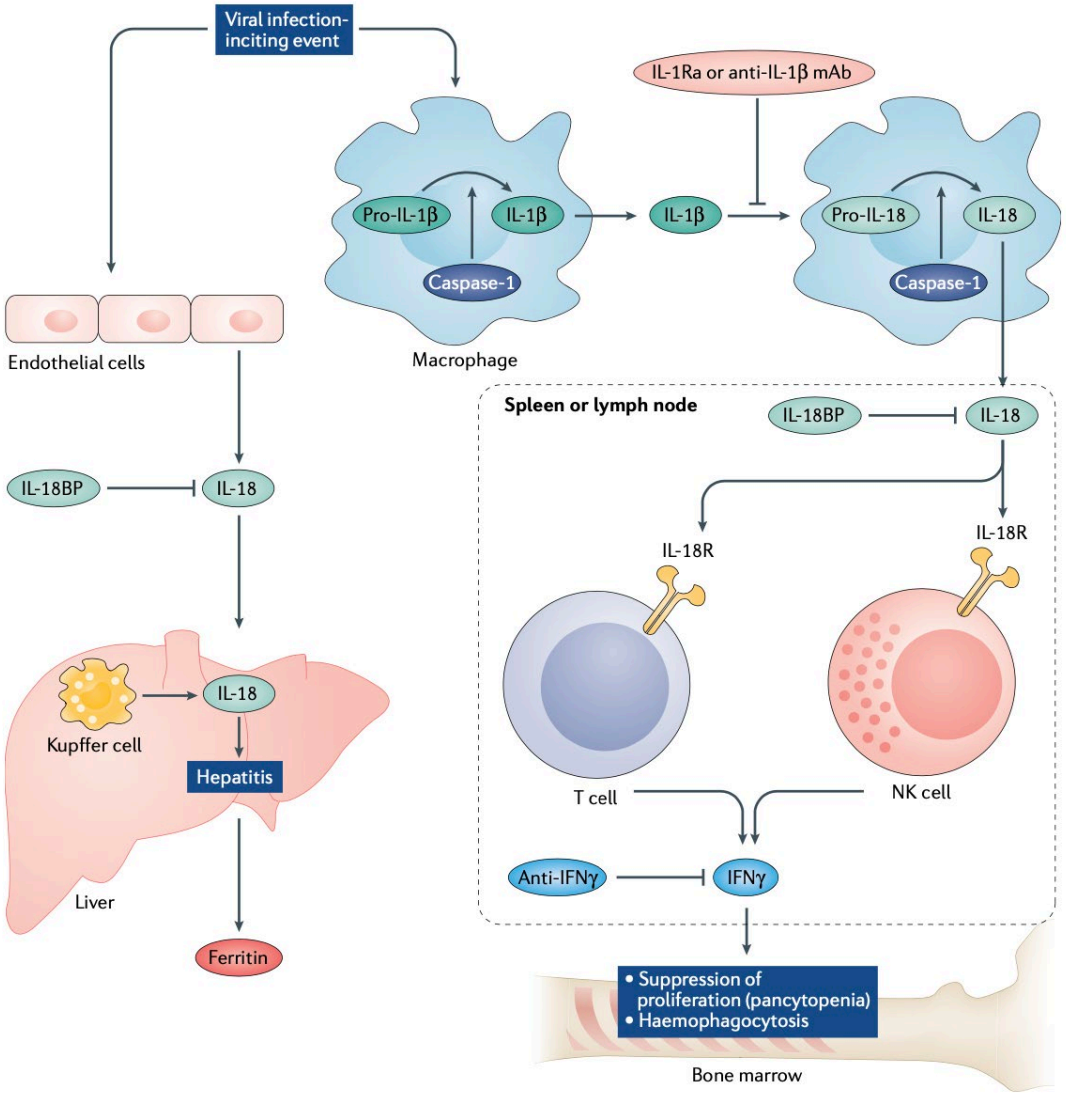
Efficacy and safety of emapalumab in macrophage activation syndrome

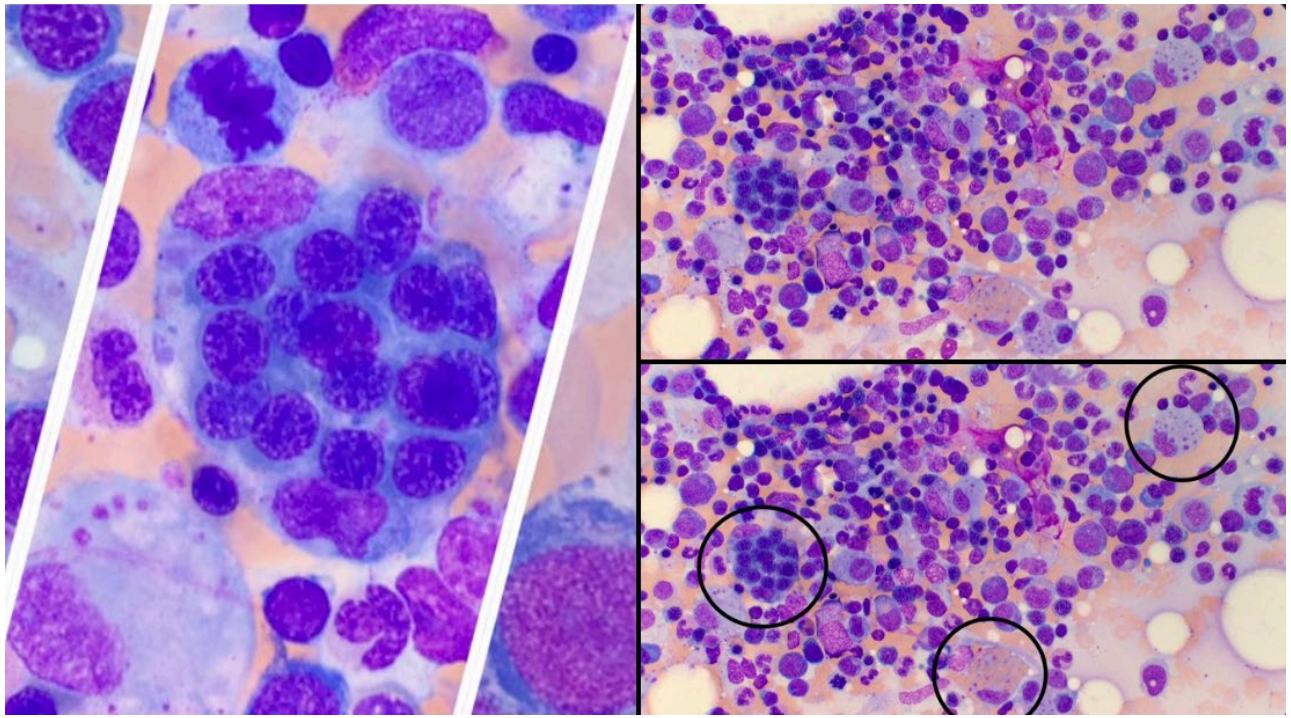
Fabrizio De Benedetti ,[1] Alexei A Grom ,[2,3] Paul A Brogan ,[4] Claudia Bracaglia ,[1] Manuela Pardeo,[1] Giulia Marucci,[1] Despina Eleftheriou,[4] Charalampia Papadopoulou ,[4] Grant S Schulert ,[2,3] Pierre Quartier,[5,6] Jordi Antón ,[7,8] Christian Laveille,[9] Rikke Frederiksen,[10] Veronica Asnaghi,[10] Maria Ballabio,[10] Philippe Jacqmin,[11] Cristina de Min[10]

De Benedetti F, *et al*. *Ann Rheum Dis* 2023;**82**:857–865. doi:10.1136/ard-2022-223739



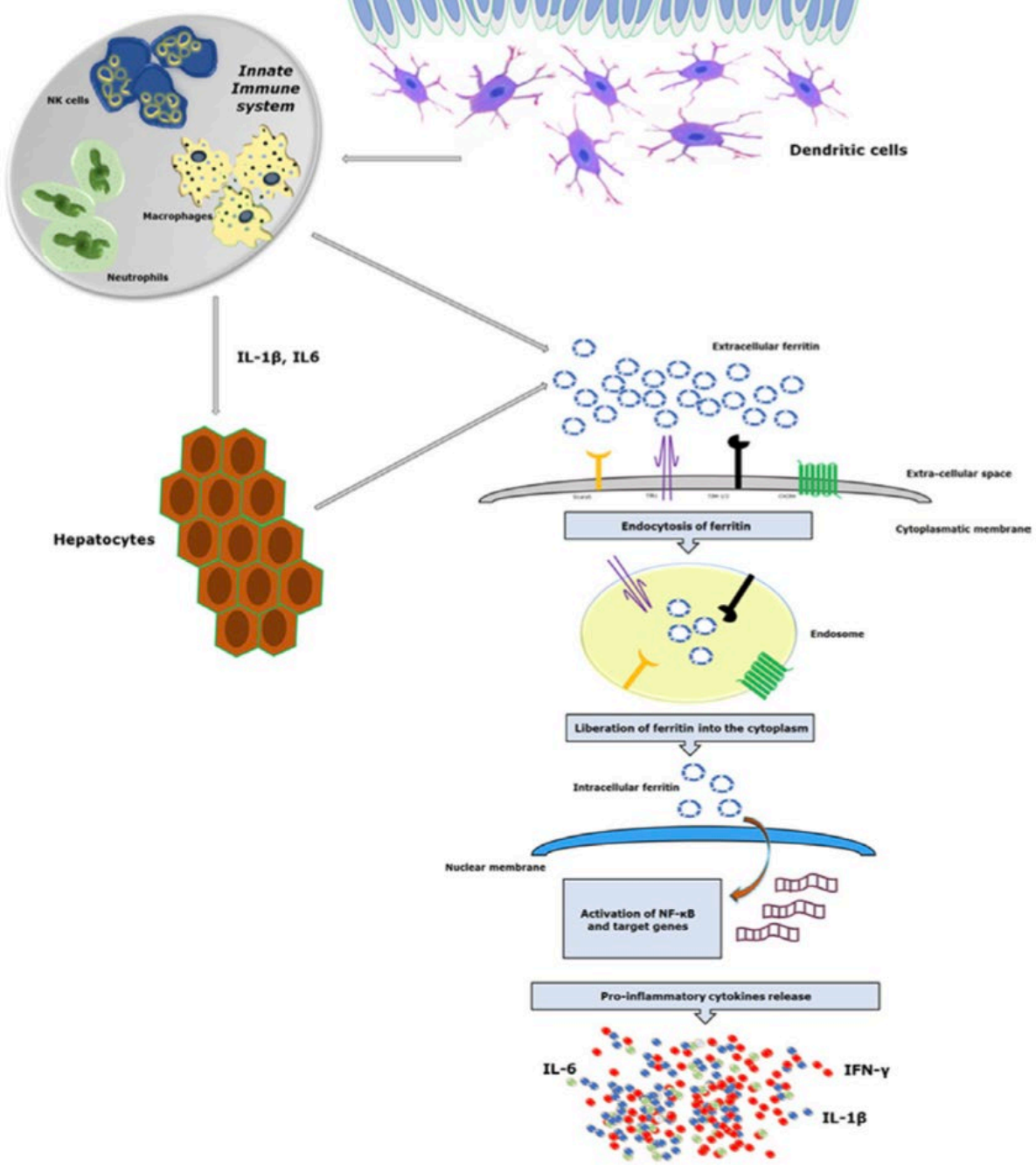
Macrophage Activation Syndrome





Dinarello CA et al. Nature Reviews Rheumatolgy 2019;15:61

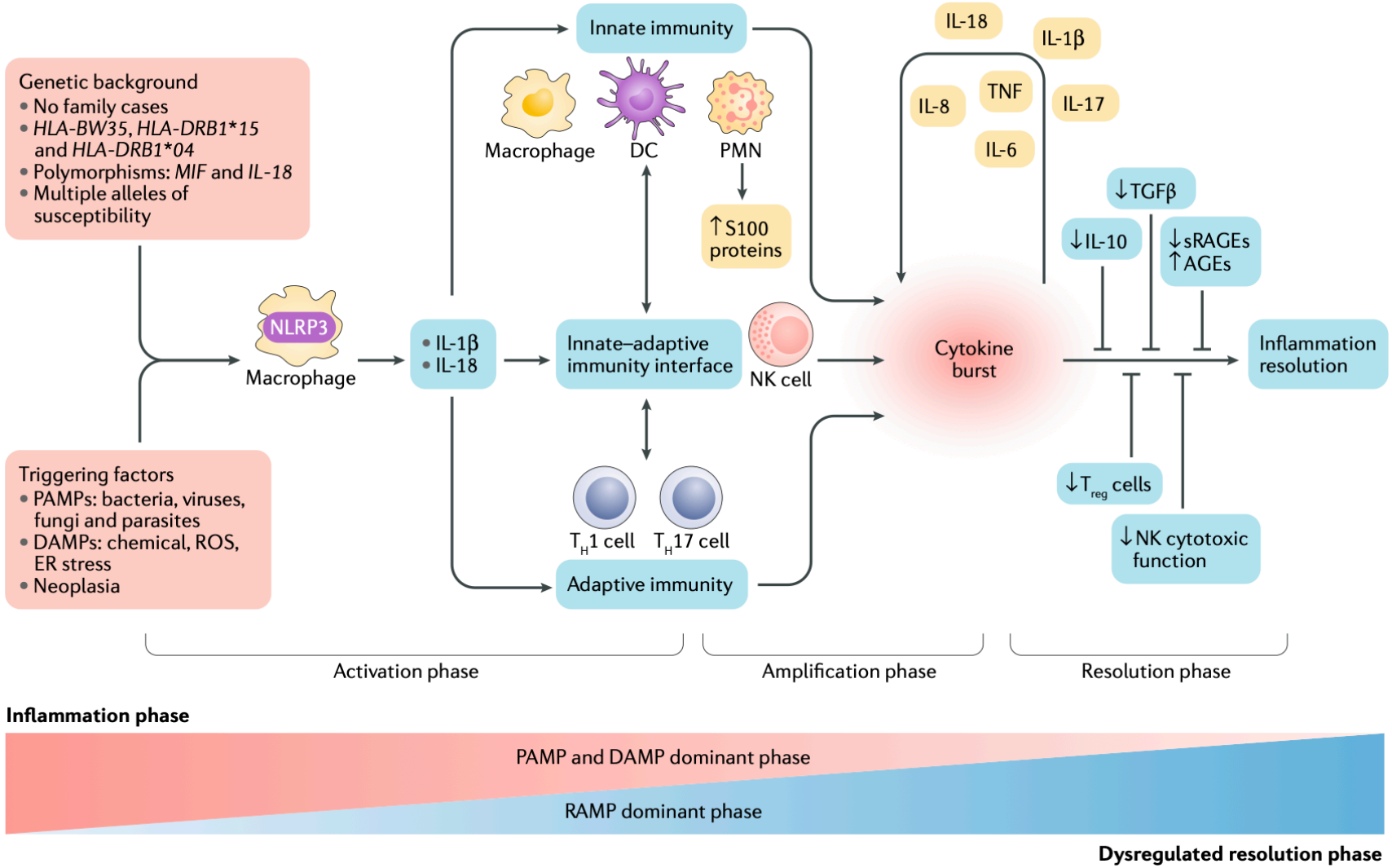
Pathogenesis: Ferritin



The Hyperferritinemic Syndrome?

Ruscitti P et al. Ann Rheum Dis 2020;79:1515–1516; Rosário C et al. BMC Medicine 2013, 11:185

Pathogenesis



Feist E et al. Nat Rev Rheumatol. 2018;14:603-618

Conclusions

- Rare - Non-hereditary - Young disease
- Increased mortality
- Multifactorial etiology:

- **polygenetic susceptibility** (innate and adaptive immune systems)
- **DAMPs**, **PAMPs** and activation of **Toll-Like Receptors**

- Mainly Autoiflammatory
- Cells involved: **Macrophages**, **Neutrophils**$_{(NETs)}$, **Dendritic cells**, **NK cells**, **T$_{regs}$**
- Cytokines involved: **IL-1$_b$**, **IL-18$_b$**, **IL-6**, **INF$_g$**, **TNF$_a$**, **TGF$_b$**, **IL-17**, **IL-4**, **IL-10**
- The hyperferritinemic Syndrome
- No Autoantibodies or Autoantigen-specific T and B cells found yet