EAC 2025

Clinical variability of Primary Immune Regulatory Disorders

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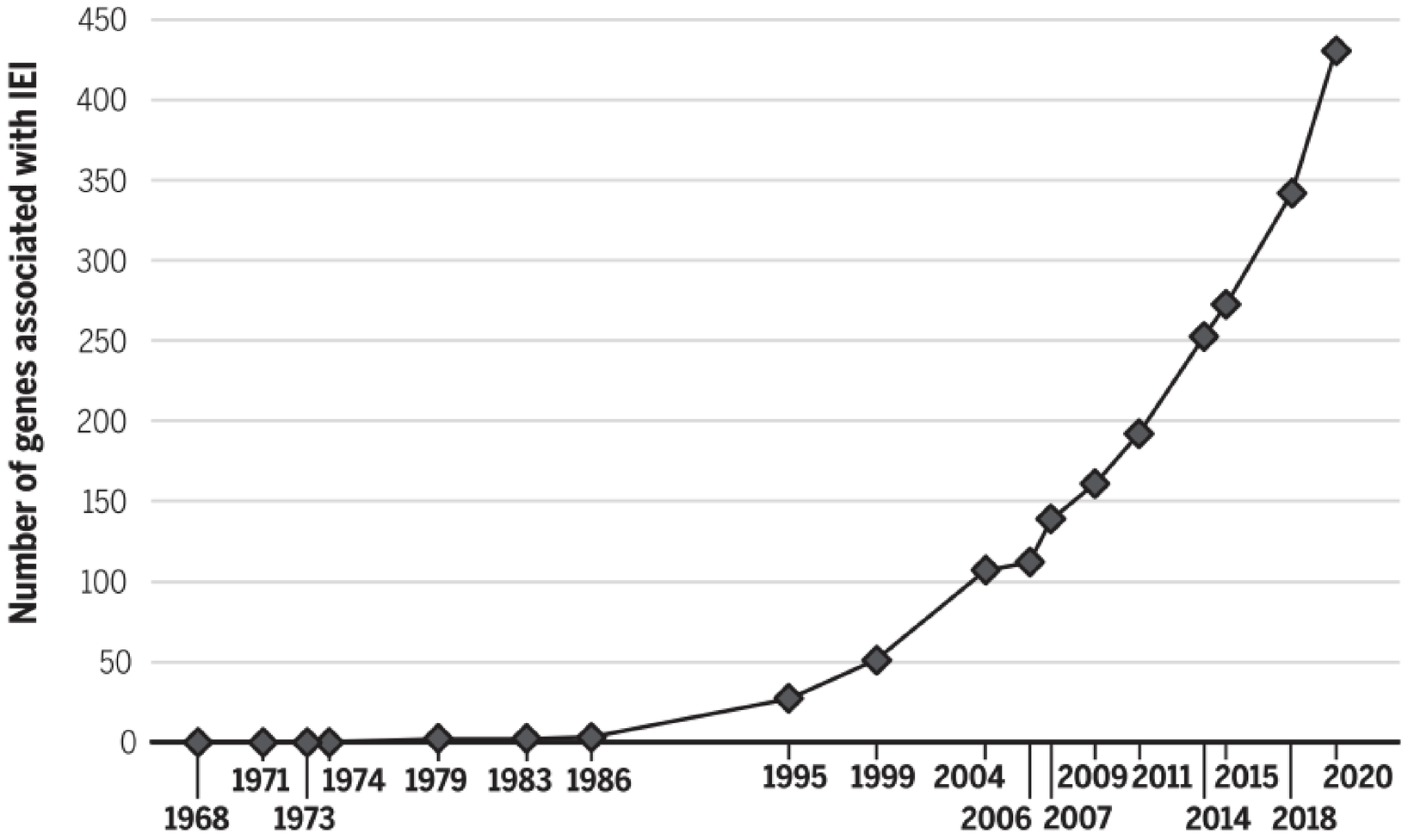
Professor and Division Chief

Today's lecture

1. **Overview** of inborn errors of immunity and PIRDs
2. Focus on **autoimmunity**
3. Focus on **autoinflammatory** diseases
4. Focus on **allergic** disorders

Over 400 IEI disorders were recognized 2020!



Now over 550

Notarangelo et al, Science Immunology, 2020

>40 new genes a year

What phenotype do patients with IEI have?

Susceptibility to **infection**

Susceptibility to **autoimmunity**

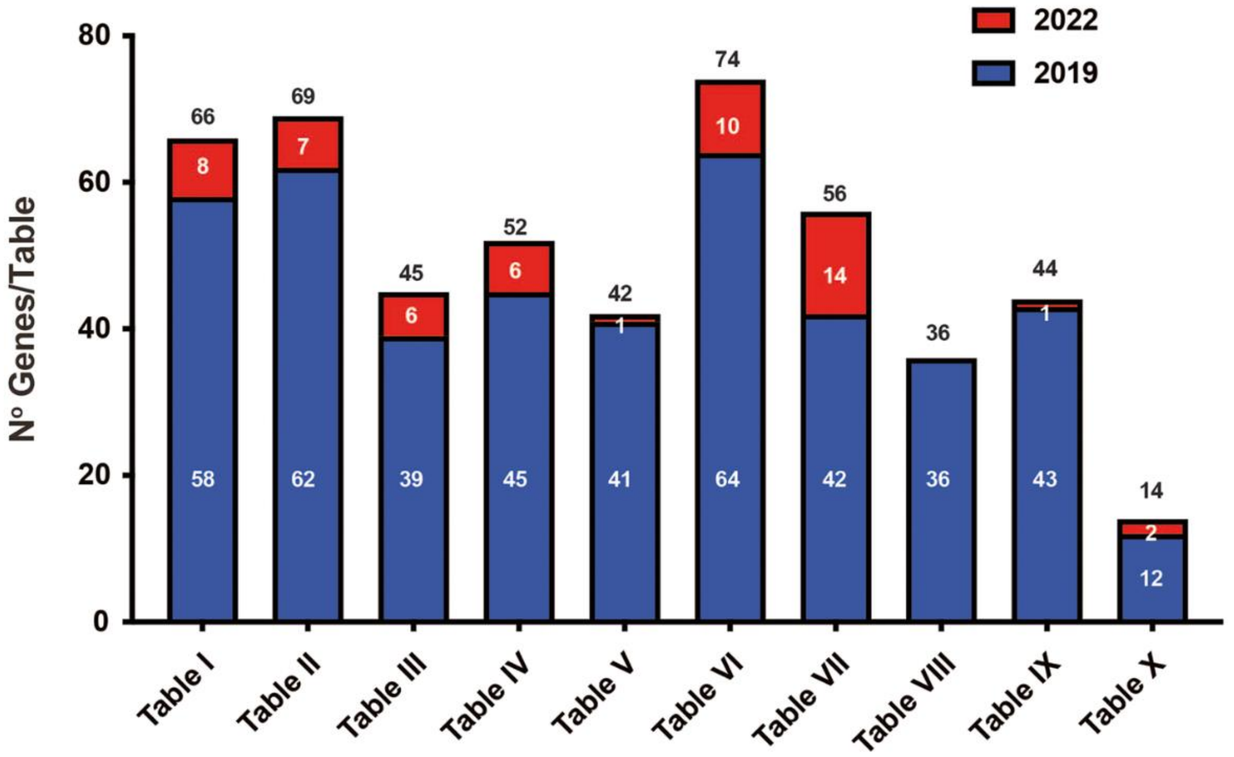
Susceptibility to **inflammation**

Susceptibility to severe **allergies**

Susceptibility to **cancers**

Classification of 500+ IEIs

1. Combined immunodeficiencies (includes SCID)
2. Syndromic immunodeficiencies
3. Antibody deficiencies
4. Primary immune dysregulation
   1. HLH
   2. fHLH with hypo-pigmentation
   3. Regulatory T cell defects
   4. Autoimmunity with or without lymphoproliferation
   5. Immune dysregulation with colitis
   6. Autoimmune lymphoproliferation
   7. Susceptibility to EBV with lymphoproliferation
5. Phagocyte defects
   1. Congenital neutropenia
   2. Defects of motility
   3. CGD and defects of NADPH oxidase
   4. Non-lymphoid defects
6. Innate immunity
   1. MSMD
   2. Epidermodysplasia verruciformis
   3. viral infections
   4. Herpes Simplex encephalitis
   5. Invasive fungal diseases
   6. mucocutaneous candidiasis
   7. TLR defects and bacterial susceptibility
   8. non-hematopoietic tissues
7. Auto-inflammatory disorders
8. Complement deficiencies
9. Bone marrow failure syndromes
10. Phenoocpies



Tangye et al JoCI 2022

Inflammation

Celsus
c. 25 BC – c. 50 AD

Tetrad of inflammation

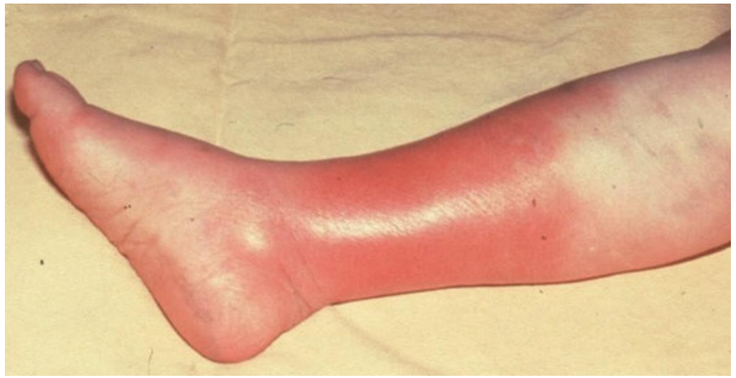
calor (warmth)

dolor (pain)

***tumor* (swelling)**

rubor (redness)

functio laesa (loss of function)

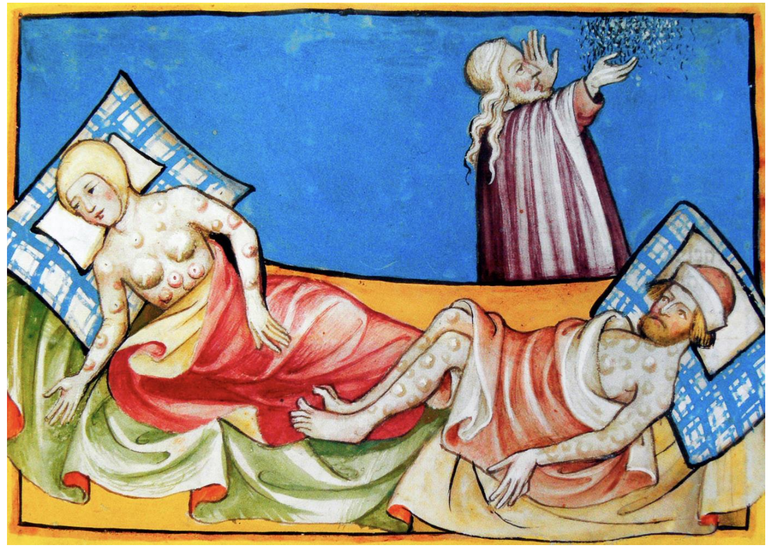


Guy de Chauliac
1301-1368

Lymph nodes swell
during infections

and return to normal after

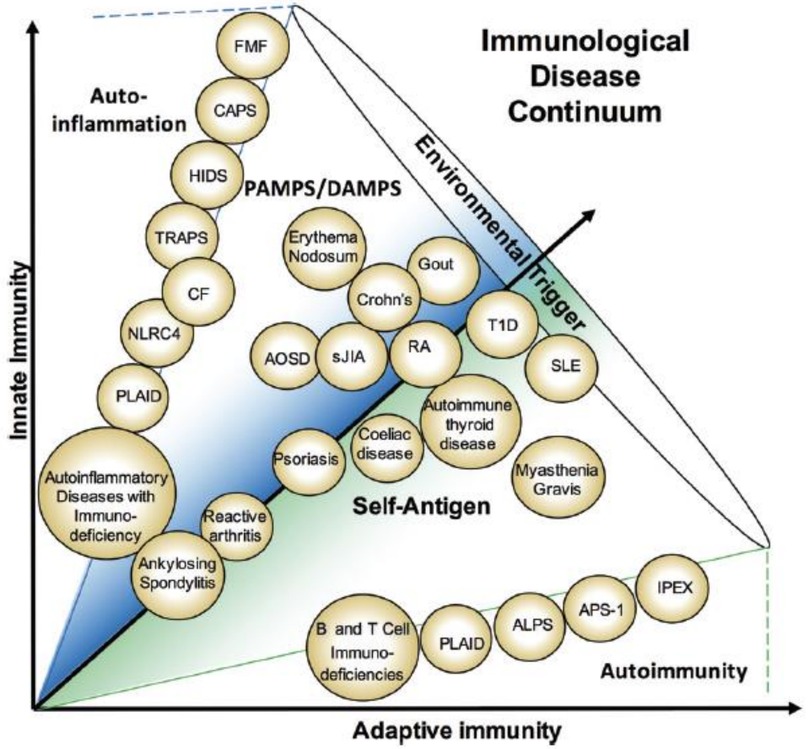
More swelling represents
worse infection



1346 to 1353

Auto-Inflammation

- Auto-inflammation (“Periodic fevers”)
- Severe inflammation after infections



Vasculitis, swelling, unexplained fevers, granulomas, sarcoid/amyloid, arthritis, colitis, rashes…

Fatigue

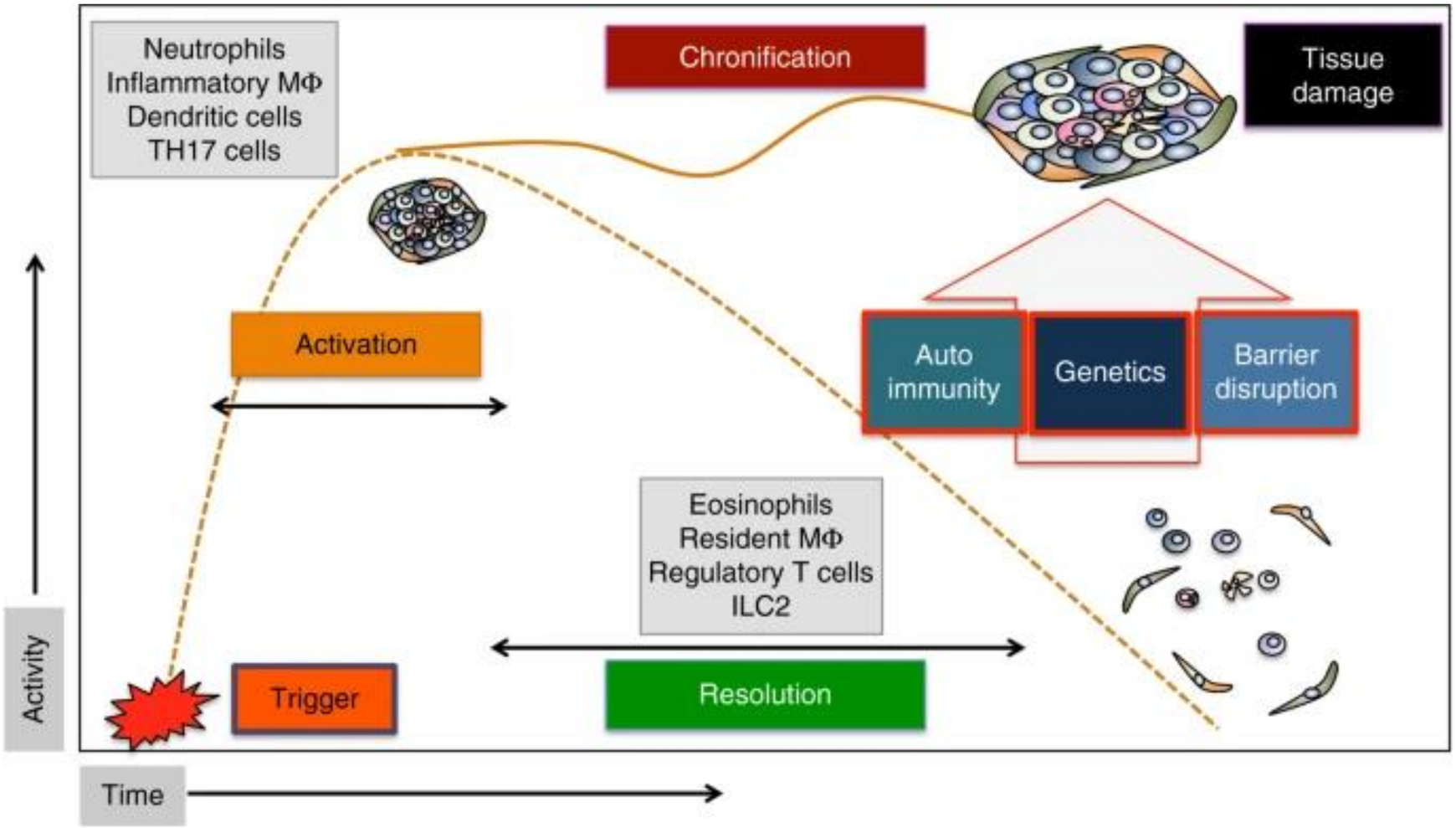
Autoimmunity

- When **specific T and/or B cells** attack one self

- Not the same as auto-inflammation, which is not ***antigen specific***

- Evolution has given us weak mechanisms to prevent attacking oneself
  - these checkpoints are easily thwarted after infections or severe inflammation
  - or in many IEIs

Tempo of inflammation



Georg Schett & Markus F. Neurath , Nat Comm. 2019

VIIa. Auto-inflammatory disorders

Recurrent inflammation

Recurrent fever

Familial Mediterranean Fever (FMF) *
MEFV. AR or AD (Usually M694del variant)

DA: 1–4 days **FA :** Variable.

Polyserositis, Abdominal pain, Arthritis, Amyloidosis. Erysipelas-like erythema. Predisposes to vasculitis and inflammatory bowel disease .

Colchicine-responsive +++.

Mevalonate kinase def* (Hyper IgD sd).
MVK. AR

DA: 3–7 days **FA**: 1–2 monthly.

Cervical adenopathy. Oral aphtosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels.

TNF receptor-associated periodic syndrome; TRAPS. ***TNFRSF1A.*** AD.

DA: 1-4 weeks **FA :** Variable

Prolonged fever. Serositis, rash, Periorbital edema and conjunctivitis.

Amyloidosis. Joint inflammation.

Systemic inflammation with urticaria rash

Familial Cold Autoinflammatory Syndrome (CAPS) * .
NLRP3, NLRP12. AD GOF **DA:** 24-48H

Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure.

Muckle Wells syndrome (CAPS) * ***NLRP3.*** AD GOF.

Ethnic group : North European

Continuous fever. Often worse in the evenings.
Urticaria, Deafness (SNHL), Conjunctivitis, Amyloidosis.

Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) *. ***NLRP3.*** AD GOF.

Neonatal onset rash, with continuous fever and inflammation. Aseptic and chronic meningitis, chronic arthropathy. Mental retardation, Sensorineural deafness. and Visual loss in some patients.

A20 haploinsufficiency ***TNFAIP3***. AD LOF. Arthralgia,

mucosal ulcers, ocular inflammation.

PLAID (PLCg2 associated antibody deficiency and immune dysregulation), or APLAID*. ***PLC2G.*** AD GOF.

Cold Urticaria. Impaired humoral immunity.
Hypogammaglobulinemia, autoinflammation.

NLRP1 deficiency*. ***NLRP1.*** AR.
Dyskeratosis, autoimmunity and arthritis.

Others

CANDLE sd (chronic atypical neutrophilic dermatitis with lipodystrophy).
PSMB8, AR and AD. Contractures, panniculitis, ICC, fevers.
PSMG2, AR. Panniculitis, lipodystrophy, AIHA.
*(Variants in **PSMB4, PSMB9, PSMA3,** and **POMP** have been proposed to cause a similar CANDLE phenotype in compound heterozygous monogenic , digenic,and AD monogenic models).*

COPA defect. *COPA. AD*
Autoimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production

NLRC4-MAS (macrophage activating syndrome)*. ***NLRC4.***
AD GOF. Severe enterocolitis and macrophage activation syndrome (HLH). Triggered by cold exposure.

NLRP1 GOF. ***NLRP1.*** AD GOF.
Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis. Increased IL1β.

ALPI deficiency*. ***ALP1.*** AR.
TRIM22 def*. ***TRIM22***. AR
Inflammatory bowel disease.

T-cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency). ***HAVCR2.***
AR. Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma

VIIb. Auto-inflammatory disorders

Sterile inflammation (skin / bone / joints)

Predominant on the bone / joints

Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia and hyper-calprotectinemia. ***PSTPIP1*** *(C2BP1).* AD

DA: 5 days **FA:** Fixed interval : 4-6 weeks

Destructive arthritis, Pyoderma gangrenosum, inflammatory skin rash, Myositis. Acute-phase response during attacks

Chronic recurrent multifocal osteomyelitis and congenital dyserythropoieticanemia (Majeed syndrome). ***LPIN2.*** AR

DA : Few days **FA :** 1-3 / month

Chronic recurrent multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia, cutaneous inflammatory disorders

DIRA (Deficiency of the Interleukin 1 Receptor Antagonist) ***IL1RN.*** AR
Continuous inflammation.
Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis.

Cherubism. ***SH3BP2.***

AR.

Bone degeneration in jaws

Predominant on the skin

Blau syndrome. ***NOD2*** (CARD15). AD.
Continuous inflammation.

Uveitis, Granulomatous synovitis, Camptodactyly, Rash, Cranial neuropathies, 30% develop Crohn colitis. Sustained modest acute-phase response.

CAMPS ***CARD14***. AD. Psoriasis.

DITRA. (Deficiency of IL-36 receptor antagonist). ***IL-36RN.*** AR .

Life-threatening, multisystemic inflammatory disease characterized by episodic widespread, pustular psoriasis, malaise, and leukocytosis.

ADAM17 deficiency*. ***ADAM17 .*** AR.

Early onset diarrhea and skin lesions. Severe bacteremia.
Defective TNFα production.

SLC29A3 mutation. ***SLC29A3*** . AR.

Hyperpigmentation hypertrichosis, histiocytosis-lymphadenopathy plus syndrome

Otulipenia/ORAS*. ***OTULIN***. AR.
Neonatal onset of recurrent fever, Arthralgia, lipodystrophy. Dermatitis, diarrhea, Neutrophilia

AP1S3 deficiency*. ***AP1S3***. AR.

Pustular psoriasis

Type 1 Interferonopathies

Progressive encephalopathy, ICC, Cerebral atrophy, HSMG, leukodystrophy , Thrombocytopenia, Elevated hepatic transaminases . Chronic cerebrospinal fluid (CSF) lymphocytosis

Aicardi-Goutieres Syndromes :
TREX1 AR-AD (+SLE, FCL), ***RNASEH2A, RNASEH2B*** (+SP), ***RNASEH2C, SAMHD1*** (+ FCL), ***ADAR1*** (+BSN, SP), ***IFIH1*** **GOF** AD (+ SLE, SP, SMS), ***DNASE2***

Spondyloenchondro-dysplasia with immune dysregulation (SPENCDI). ***ACP5.***
Short stature, SP, ICC, SLE-like auto-immunity (Sjögren's syndrome, hypothyroidism, inflammatory myositis, Raynaud's disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, possibly recurrent bacterial and viral infections.

STING-associated vasculopathy, infantile-onset. ***TMEM173***.
Early-onset inflammatory disease, Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICC, FCL.

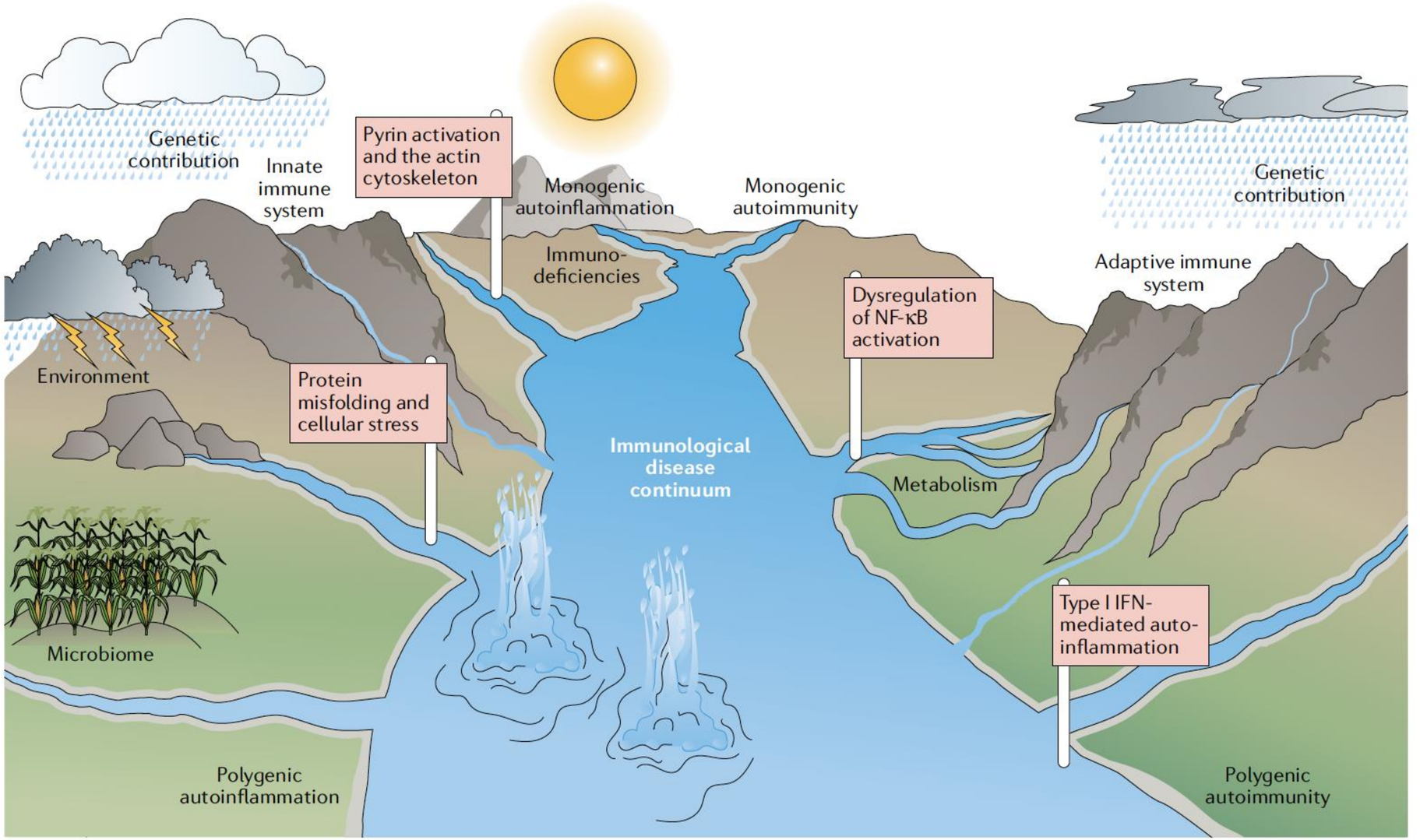
ADA2 deficiency. ***CECR1.*** Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever, Livedo racemosa, some patients develop hypogammaglobulinemia

XL reticulate pigmentary disorder. ***POLA1***. Hyper-pigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies

USP18 def *. ***USP18.*** TORCH like syndrome.

Pediatric systemic lupus erythematosus. ***DNASE1L3.*** Very early onset SLE, reduced complement levels, autoantibodies (dsDNA, ANCA), lupus nephritis, hypocomplementemic urticarial vasculitis syndrome.

OAS1 def*. ***OAS1.*** AD GOF. Pulmonary alveolar proteinosis, skin rash.



Savic et al, Nat Rev Rheum 2020

What to ask in your **History** for auto-inflammation

- Systemic or localized
  - which systems
- Early onset or late
- Periodic or continuous (attack free duration)
- Triggers
- Disease attack/flare duration

- Consanguinity
- Family history

- Treatment response (empirical)

Age of onset

Common age of onset	Disease
Neonatal	NOMID, DIRA, FCAS, SAVI, TRAPS11
Infancy/first year of life	MKD, FCAS, NLRP12, other interferonopathies, Very early-onset IBD, DADA2, NLRP1
Toddler	PFAPA, Blau/Early-onset sarcoidosis
Late childhood	PAPA
Adolescence/Adulthood	Schnitzler, Gout, Recurrent pericarditis, Behçet
Most common of primarily childhood syndromes to have onset in adulthood	TRAPS, DITRA, some forms of AGS
Variable (mostly in childhood)	All others

Triggers

Classic triggers	
Vaccines	MKD
Cold exposure	FCAS, NLRP12, NLRC4, PLAID, SAVI (worsening of lesions)
Menses	FMF
Minor Trauma	PAPA, TRAPS, MKD, Behçet (skin)
Exercise	FMF, TRAPS
Pregnancy	DITRA
Infections	All, especially DITRA
Stress	All

Duration of attack

Less than 24 h	FCAS, FMF, NLRP12
One to three days	FMF, MWS, DITRA (fever)
Three to seven days	MKD, PFAPA, PFIT
Longer than 7 days	TRAPS, PAPA, PAAND
Months	CNO
Chronic	NOMID, DIRA, interferonopathies, systemic JIA, Schnitzler syndrome

Flares are critical for understanding auto-inflammatory diseases.

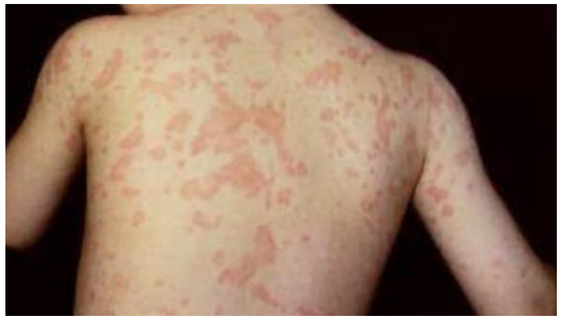
We need to measure cytokines and interferons *during* the flares

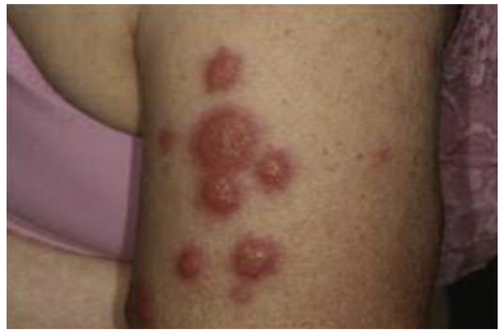
Interval between attacks

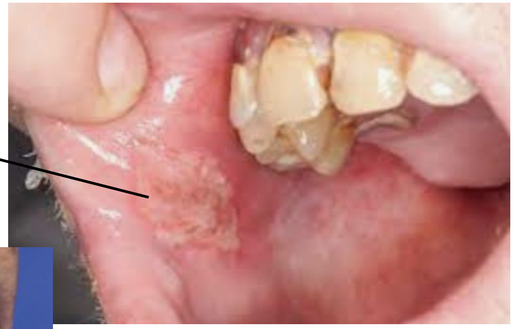
Three to six weeks	PFAPA, MKD
More than six weeks	TRAPS
Mostly unpredictable	All others
Truly periodic	PFAPA, cyclic neutropenia

Dermatological manifestations

Urticarial-like rash	FCAS, MWS, NOMID, sJIA (occasional), MKD (occasional), Schnitzler, NLRP-12, PLAID, NLRC4
Fasciitis/plaque	FMF (“erysipelas-like”), TRAPS (painful, centrifugal, migratory fasciitis), APLAID (cellulitis)
Neutrophilic dermatosis	PAAND, Majeed, Otulipenia, Behçet, SAPHO
Maculopapular	sJIA, MAS, MKD, TRAPS11, NLRC4
Nodular	Gout (tophi), DADA2
Multiforme/mobiliform	MKD
Granulomatous (waxy) rash	Blau/Early-onset sarcoidosis, PLAID
Pustular rash	Behçet, CNO, DIRA, DITRA, AP1S3, Majeed, HA20, SAVI, APLAID, CARD14, Otulipenia
Pathergy	Behçet, PAPA, HA20
“Abscesses”	Behçet, PAPA, PAAND
Blister	APLAID
Psoriatic	CNO, PAPA, DITRA, CARD14, AP1S3
Acneiform	Behçet, CNO (SAPHO), PAPA, PAAND
Panniculitis	Behçet, Interferonopathies, Blau/Early-onset sarcoidosis, Otulipenia
Lipodystrophy	PRAAS/CANDLE, Very early-onset IBD, Otulipenia
Ulcerative (including pyoderma)	Behçet, PAPA, Very early-onset IBD, HA20, PAAND, NLRP1
Livedo-like	DADA2, Interferonopathies
Pernio/chilblains	Interferonopathies, DADA2
Vasculitis	FMF, Behçet, DADA2, MKD, PAPA, SAVI, PAAND, Otulipenia
Atopy	PLAID
Other	CARD14 (pityriasis rubra piliaris), NLRP1 (dyskeratosis, self-healing palmoplantar carcinoma), SAVI (nail dystrophy)







Broad categories

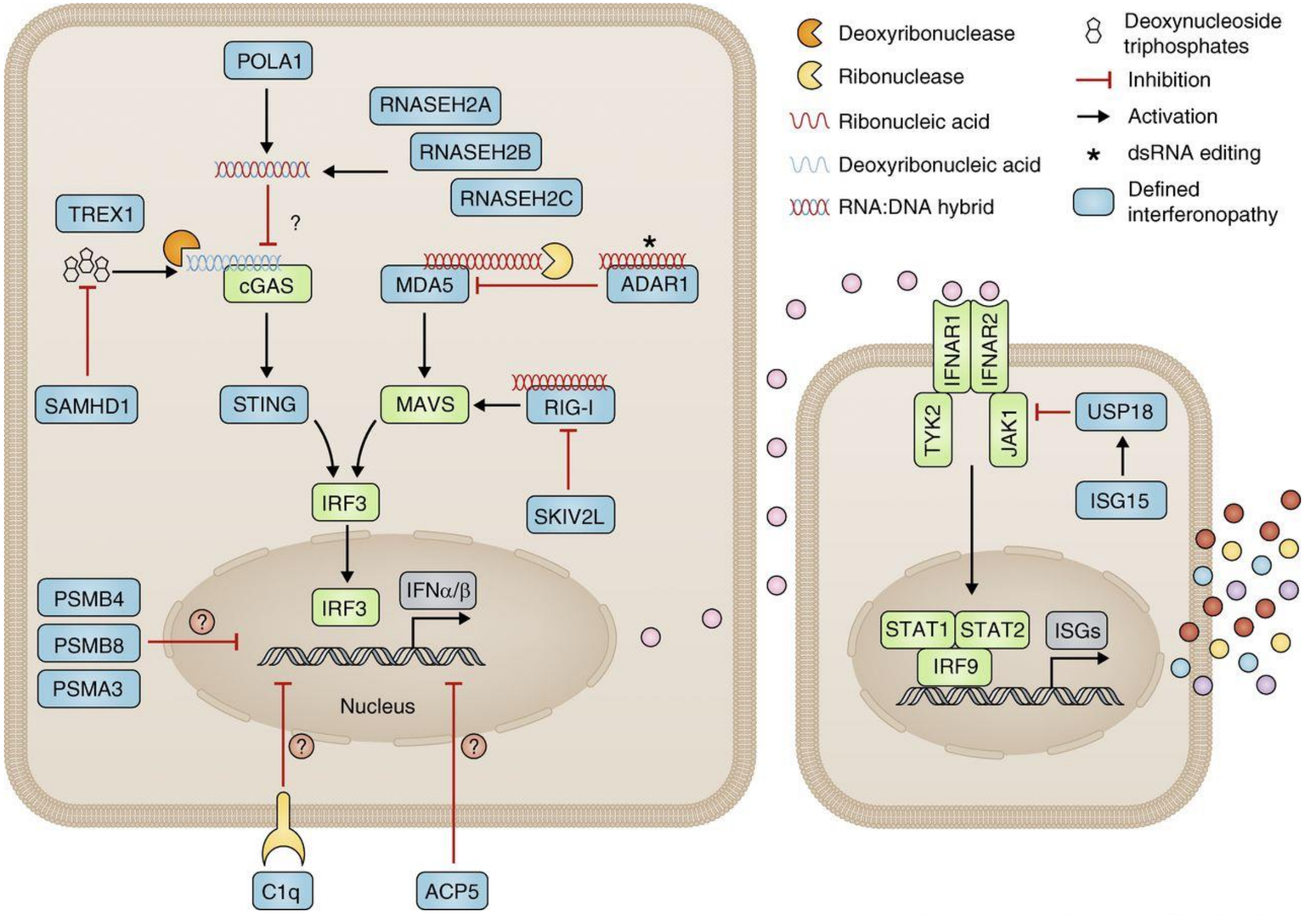
- Type 1 interferonopathies
- Inflammasomopathies
  - Familial Mediterranean Fever
- NFKB-opathies
- Proteosome-opathies

Type 1 interferonopathies

- Interferon alpha (12 genes)
- Interferon beta (1 gene)

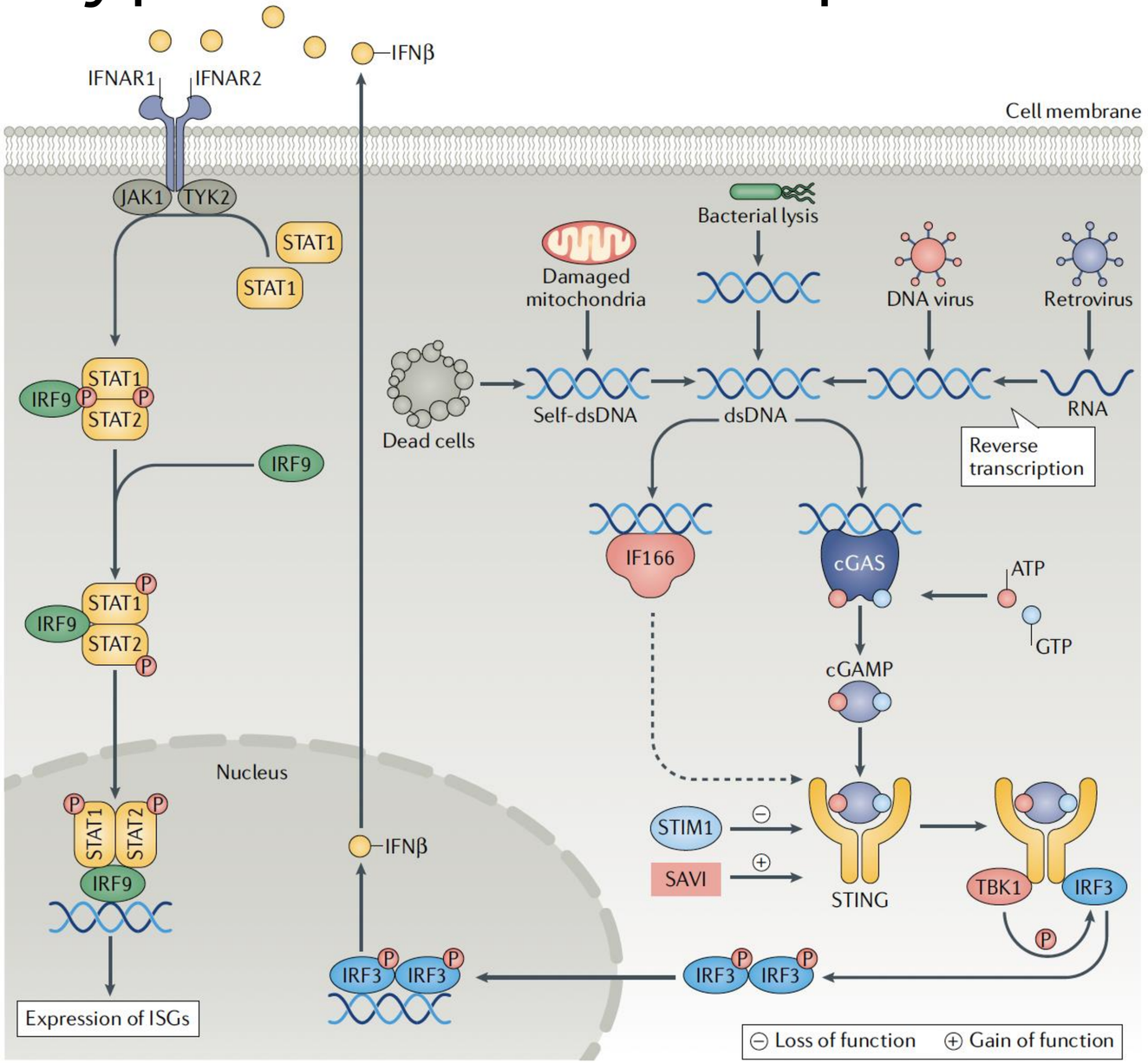
- The diseases are
  - Sensing intracellular viral infections when they aren’t there
  - Over-reactions to type-I interferon

Type 1 interferonopathies



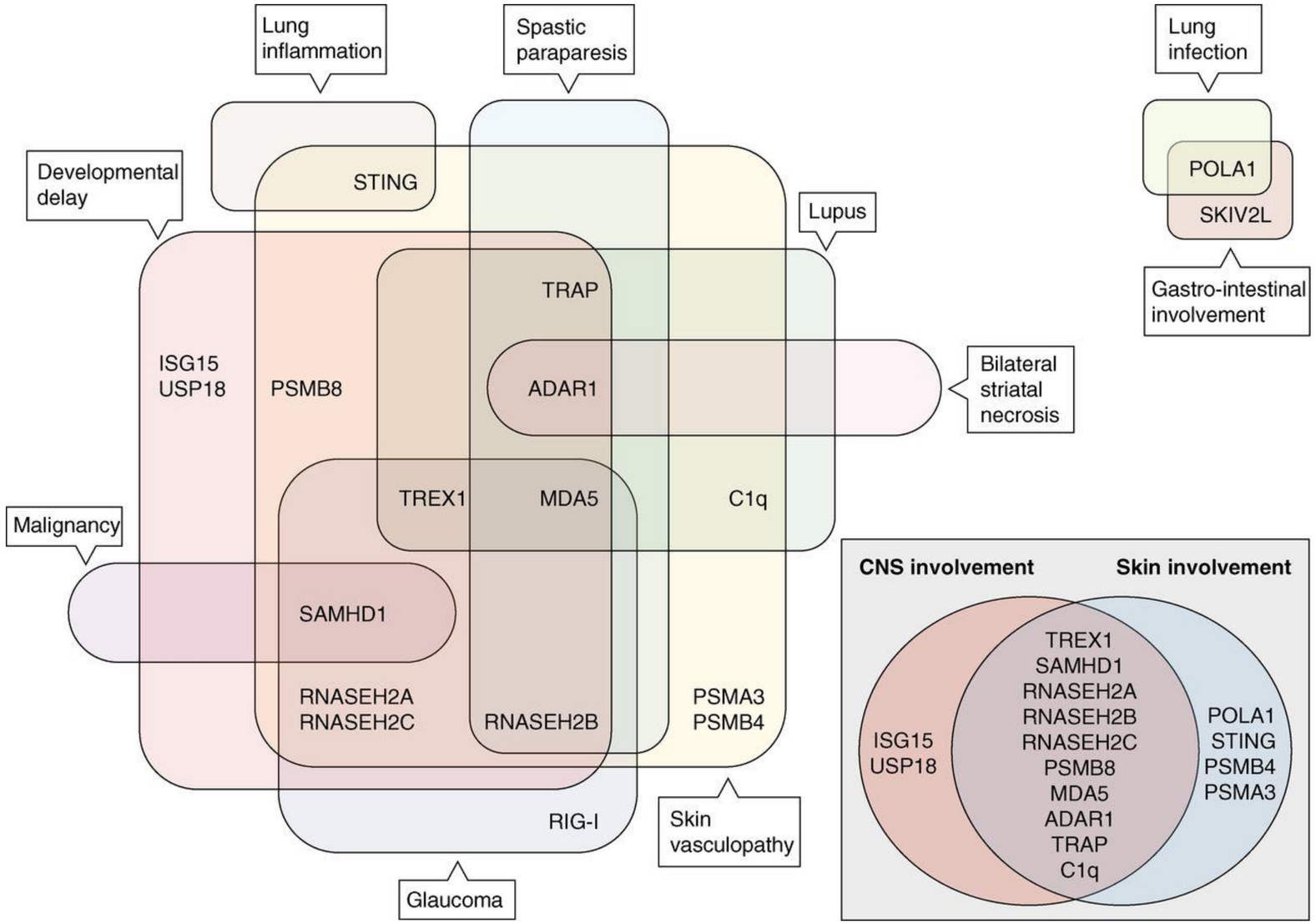
Rodero and Crow Y, JEM 2016

Type 1 interferonopathies



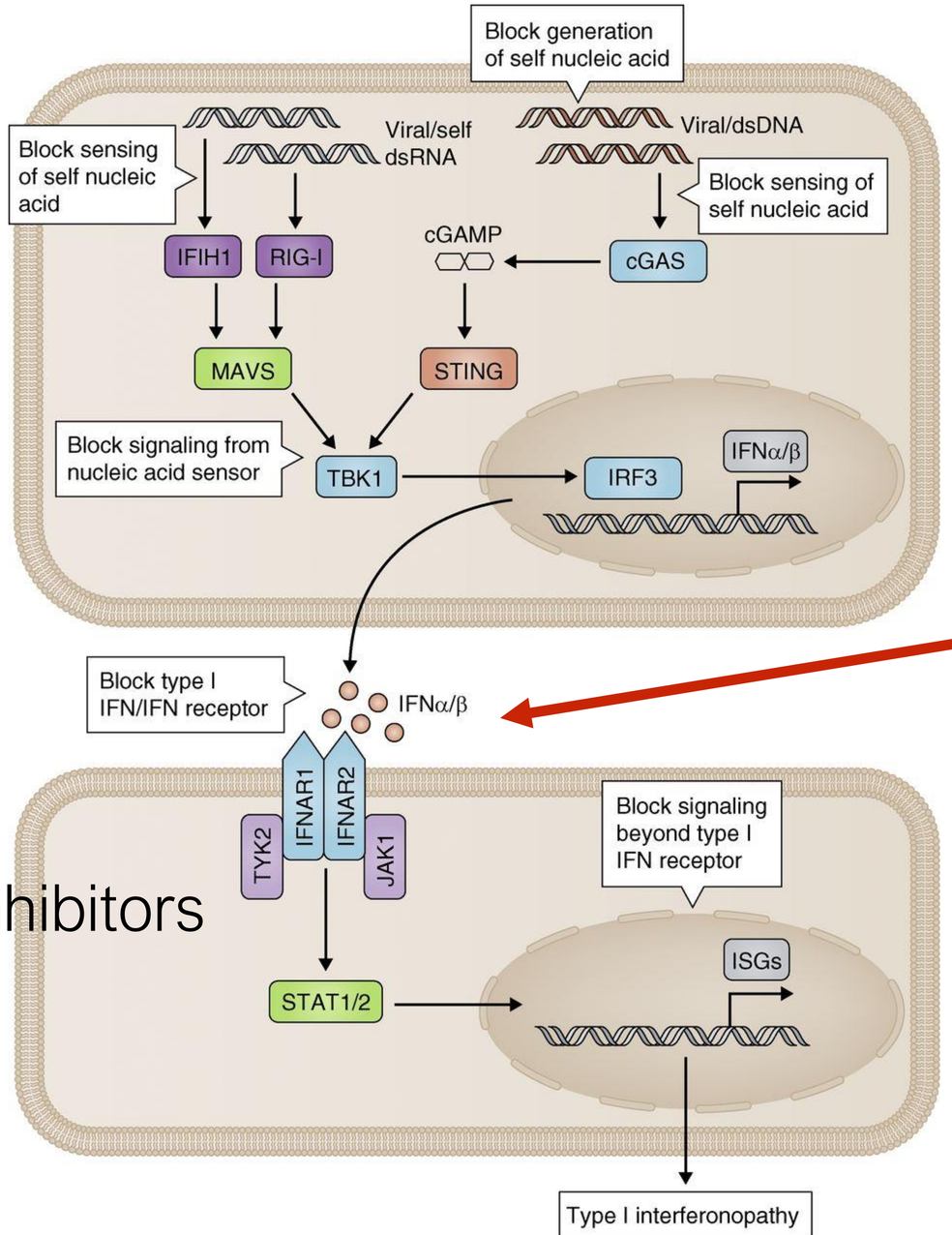
Savic et al, Nat Rev Rheum 2020

Clinical phenotypes overlap



Rodero and Crow Y, JEM 2016

Treatment strategies



Rev transcriptase inhibitors

hydroxychloroquine

Jak inhibitors

Clinical Communication

Anifrolumab to treat a monogenic interferonopathy

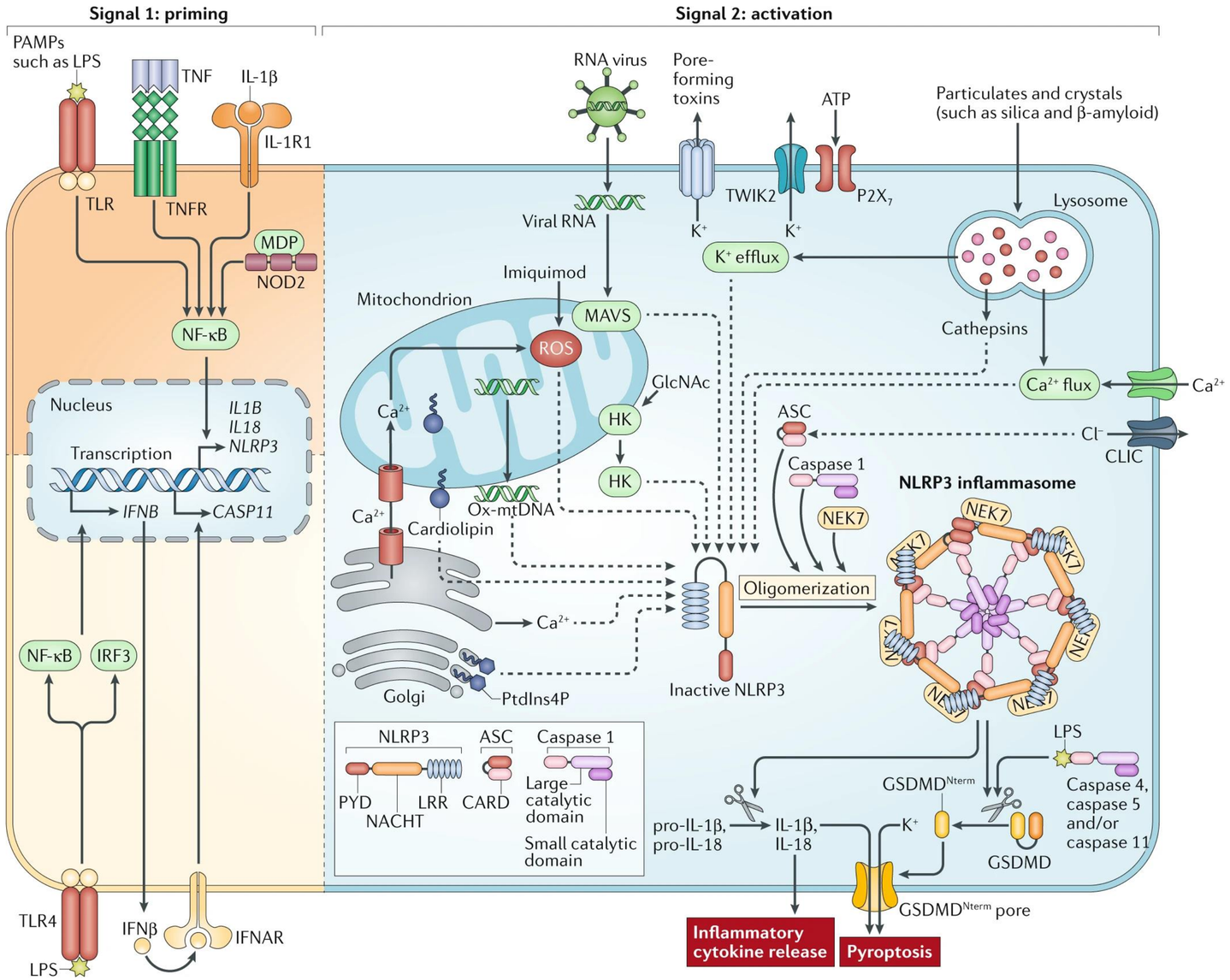
Mohammad-Ali Doroudchi, MD[a], Timothy J. Thauland, PhD[a], Bhavita A. Patel, MD[b,c], and Manish J. Butte, MD, PhD[a,d,e]

Clinical Implications

Anifrolumab blocks the IFN-α/β receptor and can be used to treat monogenic autoinflammatory diseases driven by excessive type-1 interferon production as an alternative to Janus kinase inhibitors.

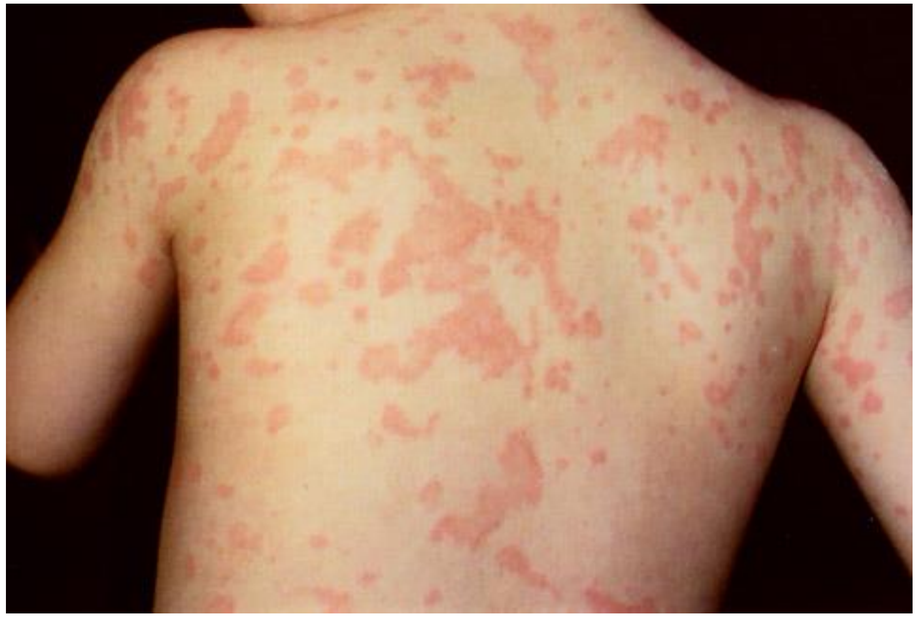
Rodero and Crow Y, JEM 2016

NLRP3 controls much inflammation

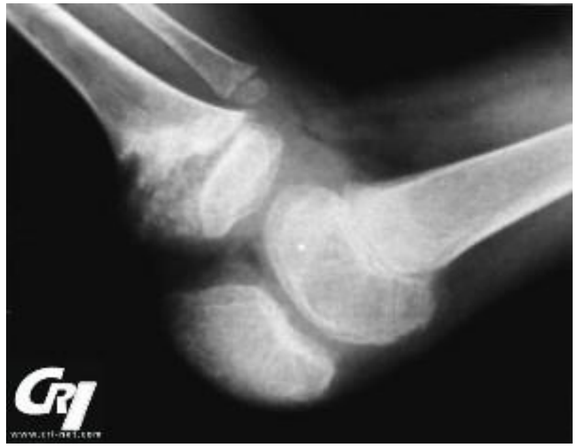


Swanson…Ting, NatRevImm 2019

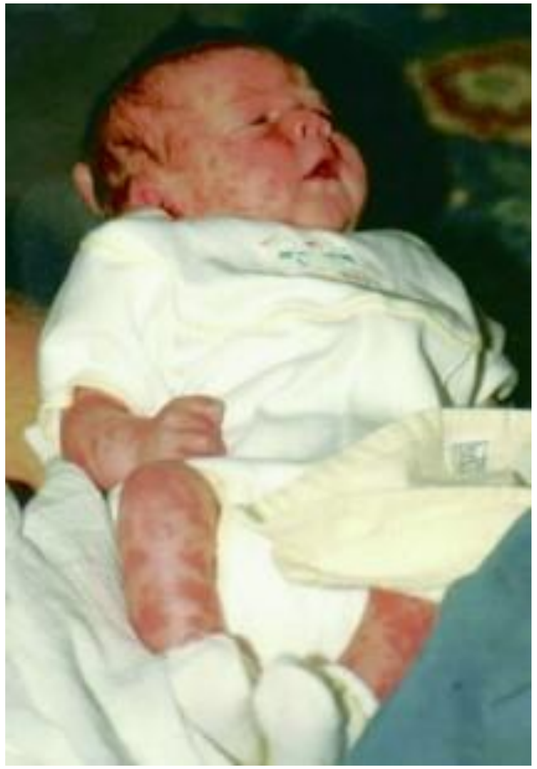
NLRP3 gof



Cold urticaria



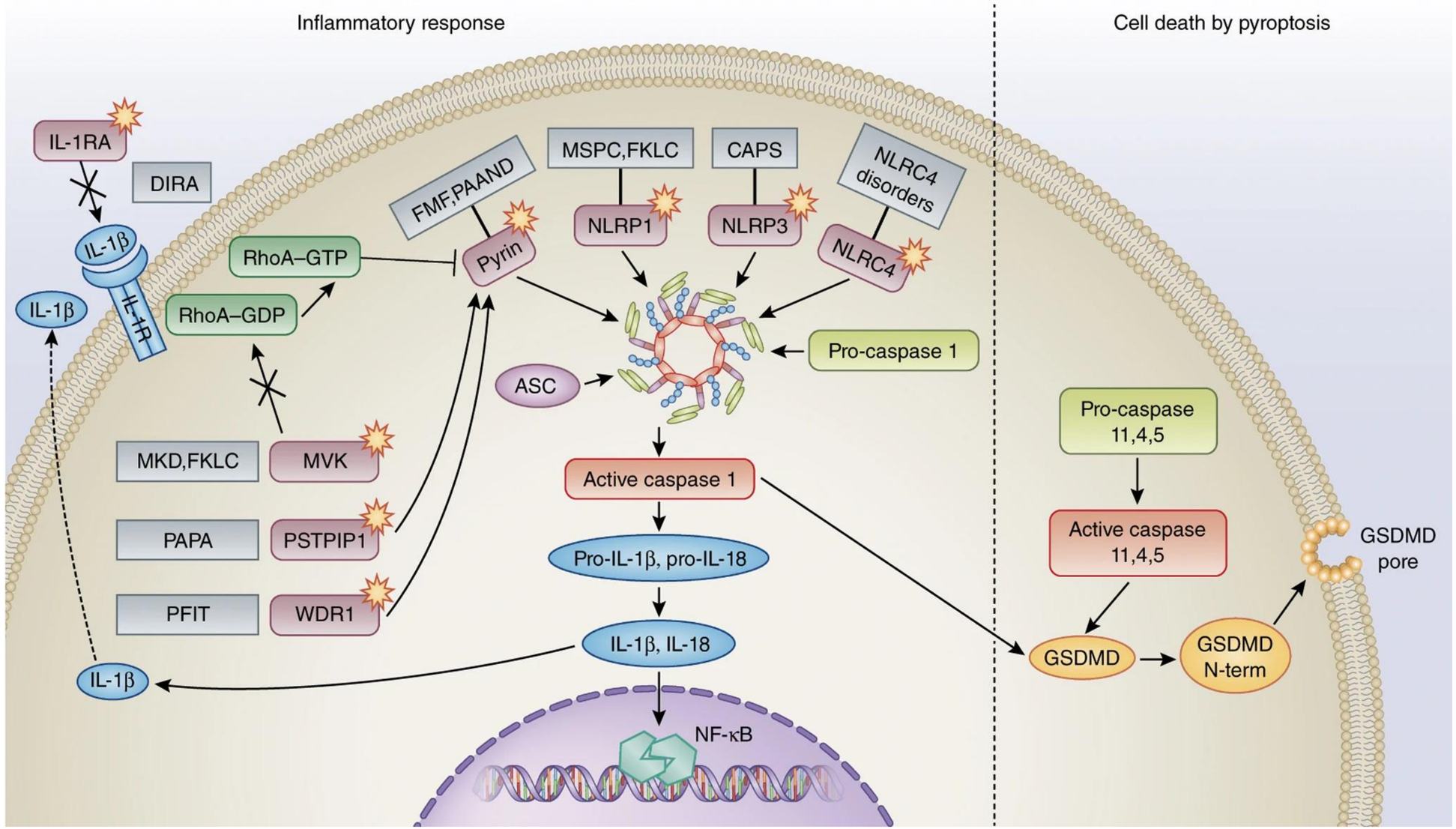
Bone overgrowth



Neonatal onset

CNS and eye inflammation

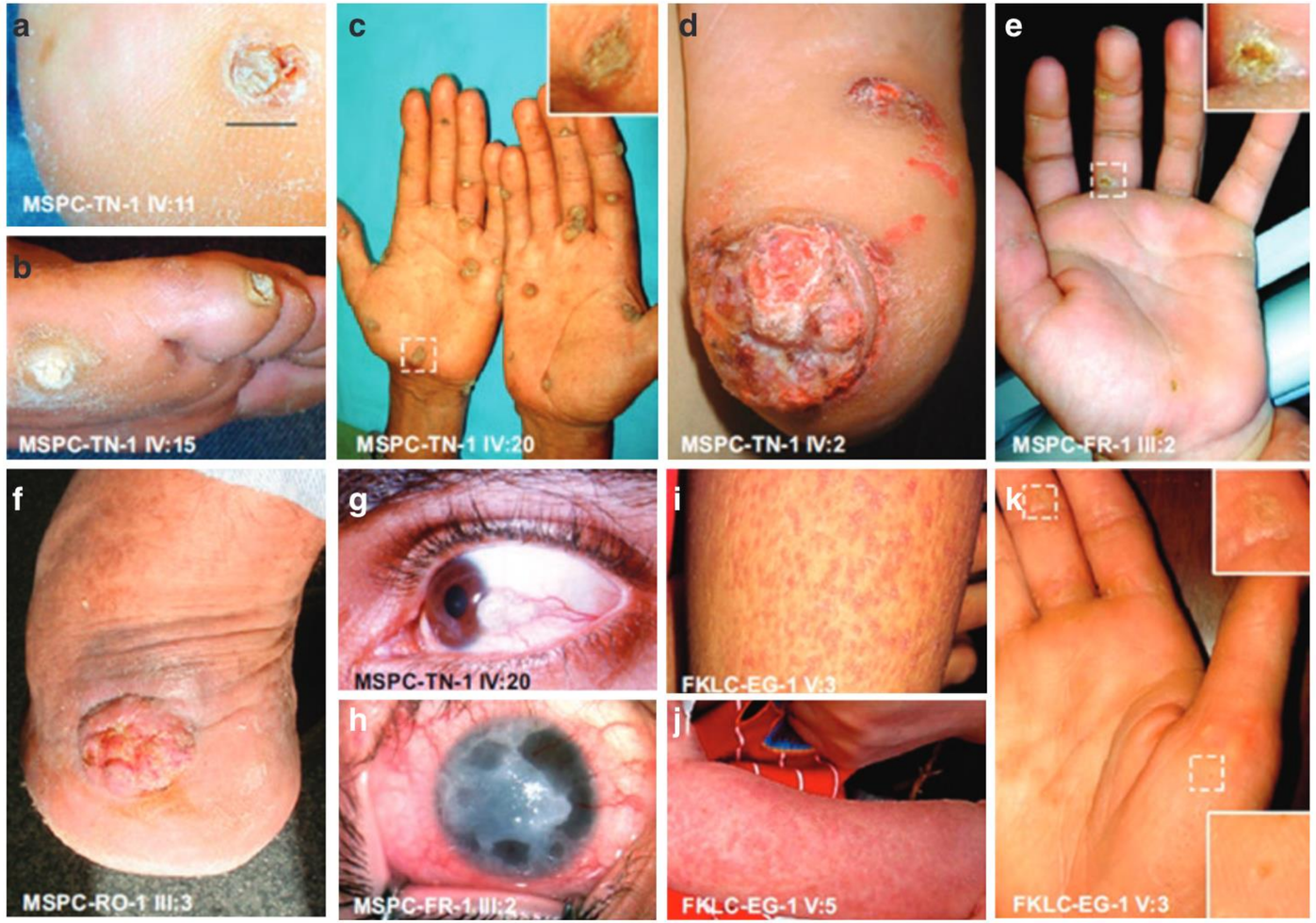
Inflammasome



Manthiram…Kastner, Nat Imm 2017

Inflammasome diseases are multi-system

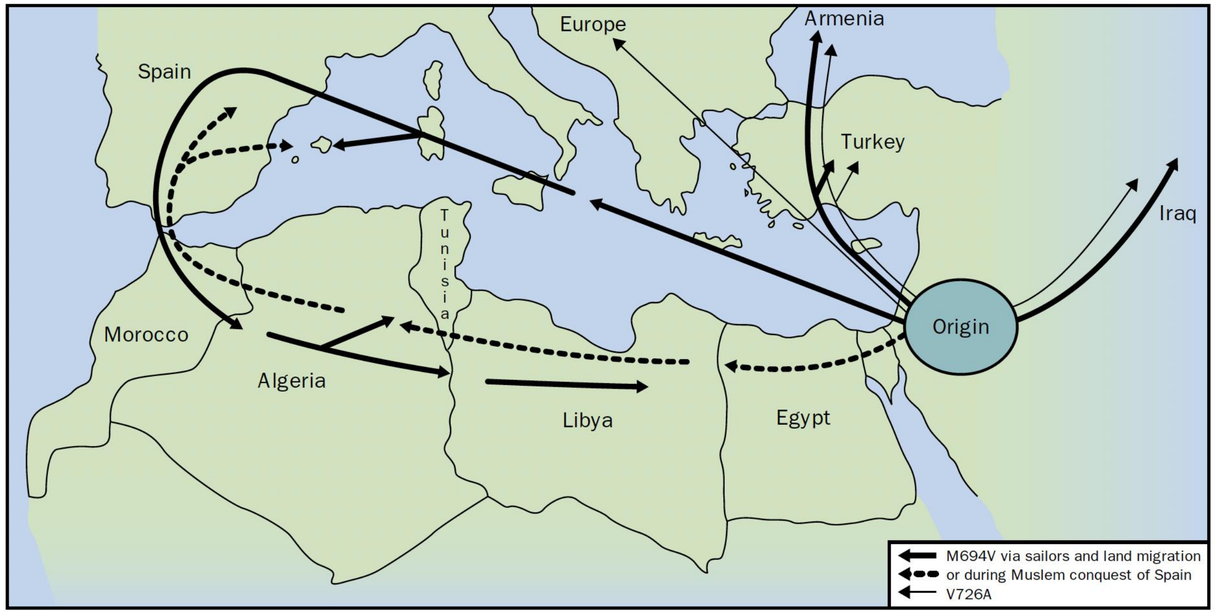
Cutaneous symptoms are common



NLRP1 gain of function

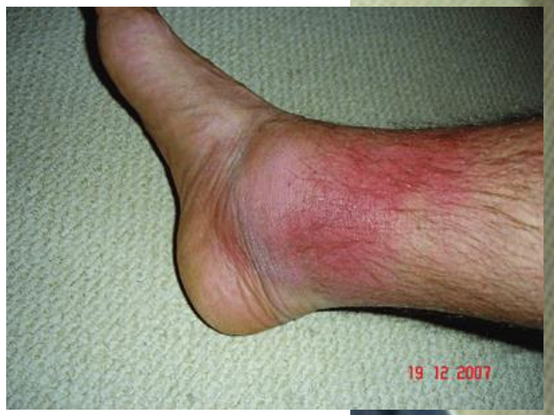
Familial Mediterranean Fever

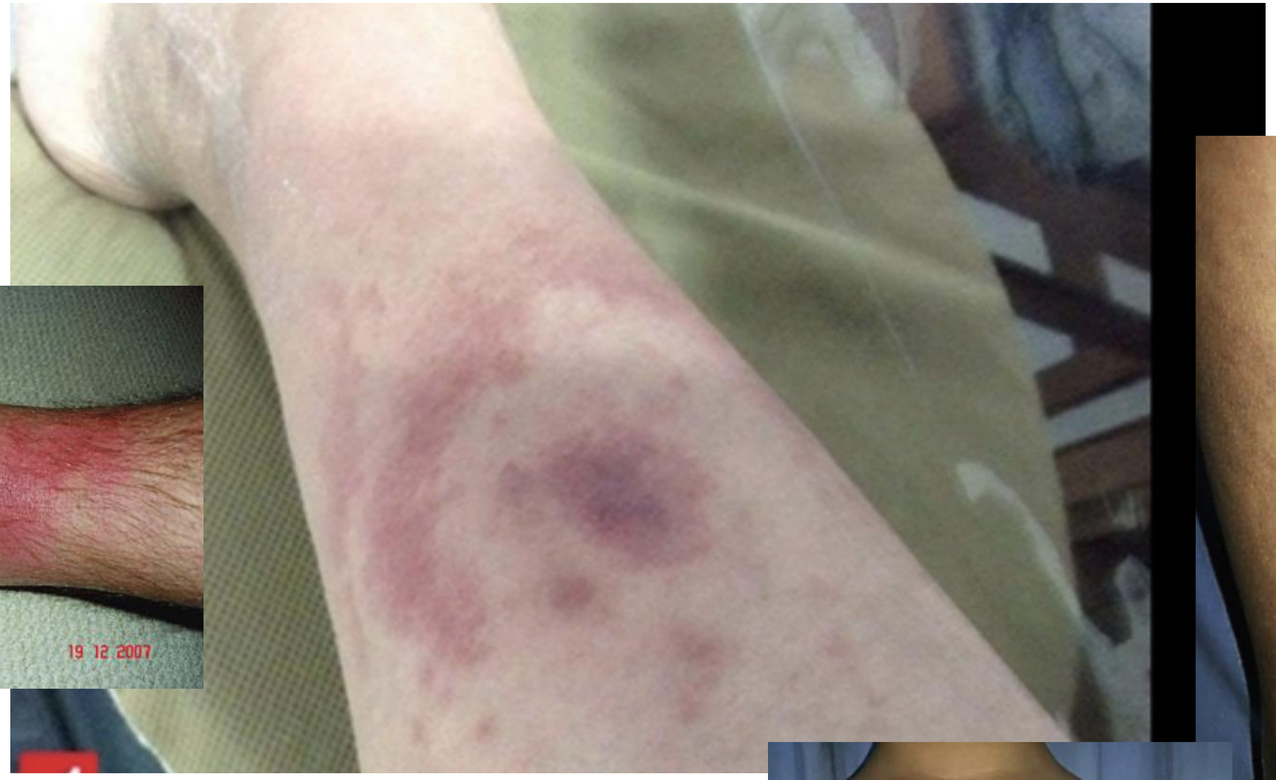
- Periodic fevers, peritonitis, pleuritis, arthritis, erysipelas-like rashes
- 65% have their first attack before age 10
- Attacks 1-2 times monthly
- Diagnostic delay is huge (decades!)
- First described in 1945

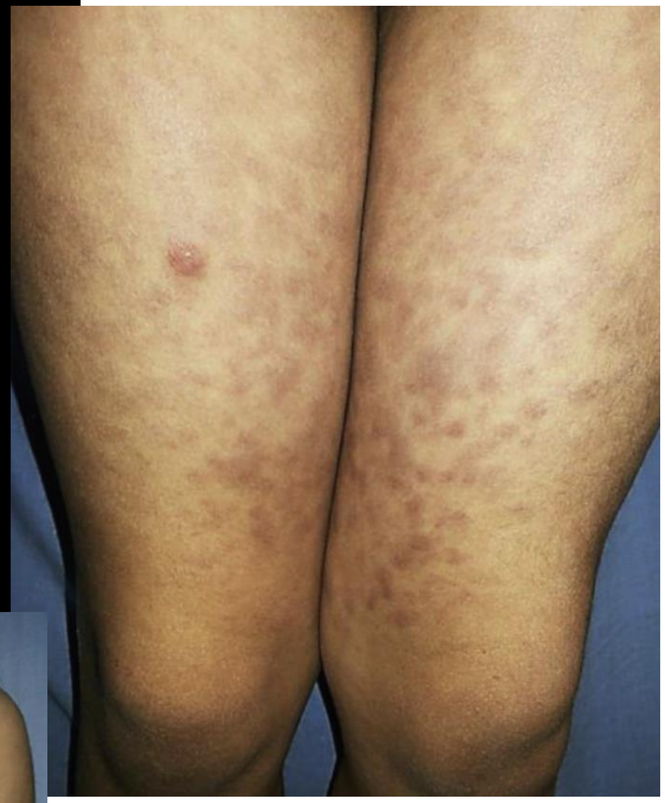


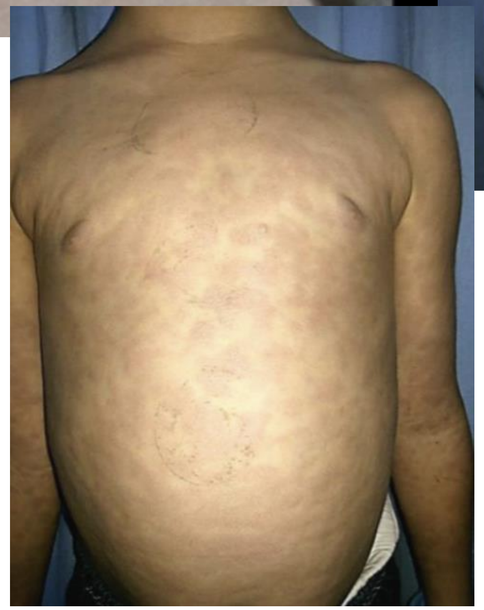
M694V
V726A

Figure 1: **Map suggesting likely distribution of two main mutations responsible for FMF**
These ancient mutations appear to have originated in the Middle East in biblical times. Mutation M694V migrated to Spain and north-Africa, either via early sailors from the Middle East or eastward via land migration later during the Moslem conquest of Spain. V726A also migrated from the Middle East to Armenia, Turkey, and Europe (Ashkenazi Jews). FMF in Mallorcan Chuetas could have originated as in Sephardic Jews, although additional mutations may also have occurred. (Adapted from ref 19).



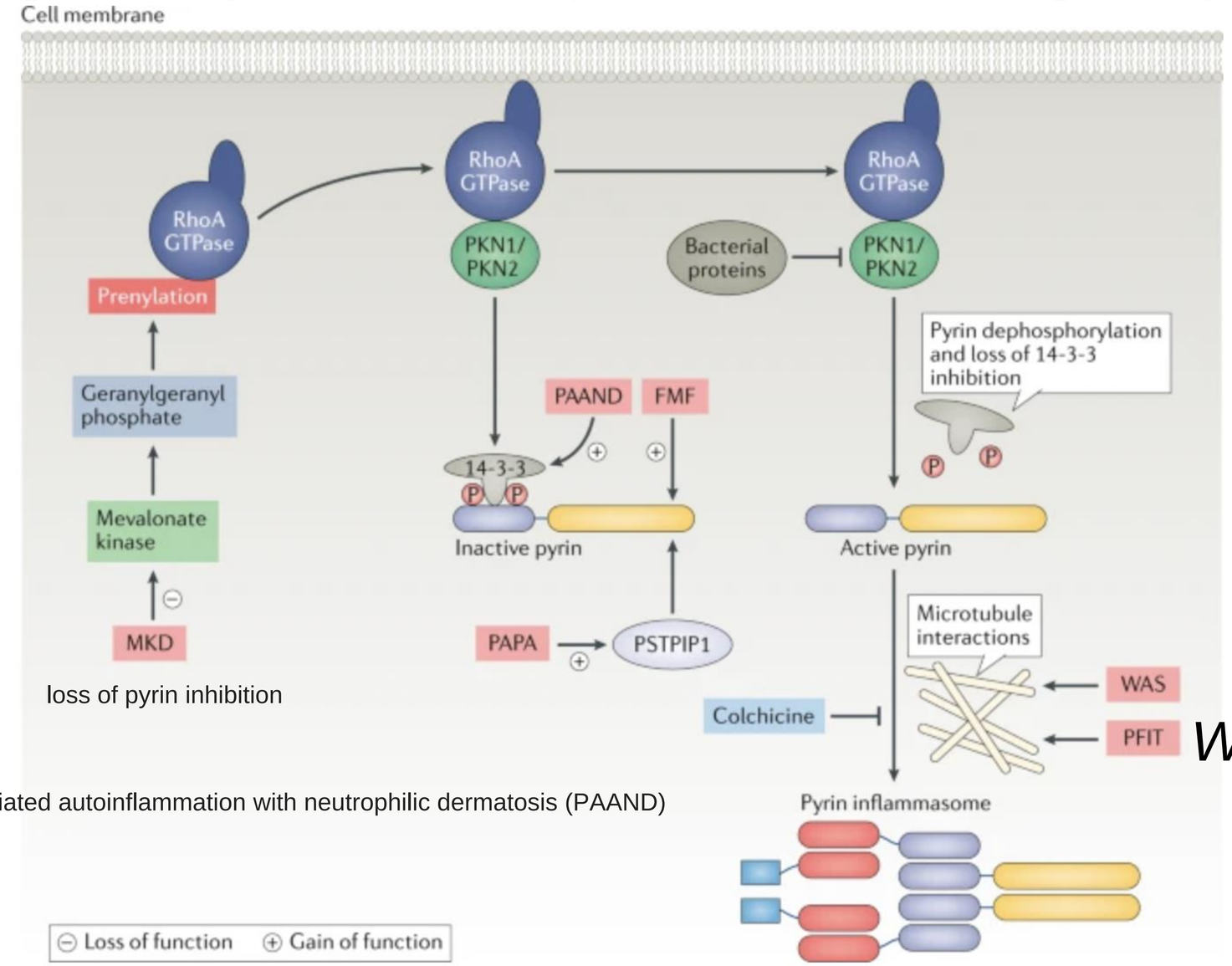






Erysipelas like rashes
Ankle and hands

Pyrinopathies (*MEFV* or Pyrin)



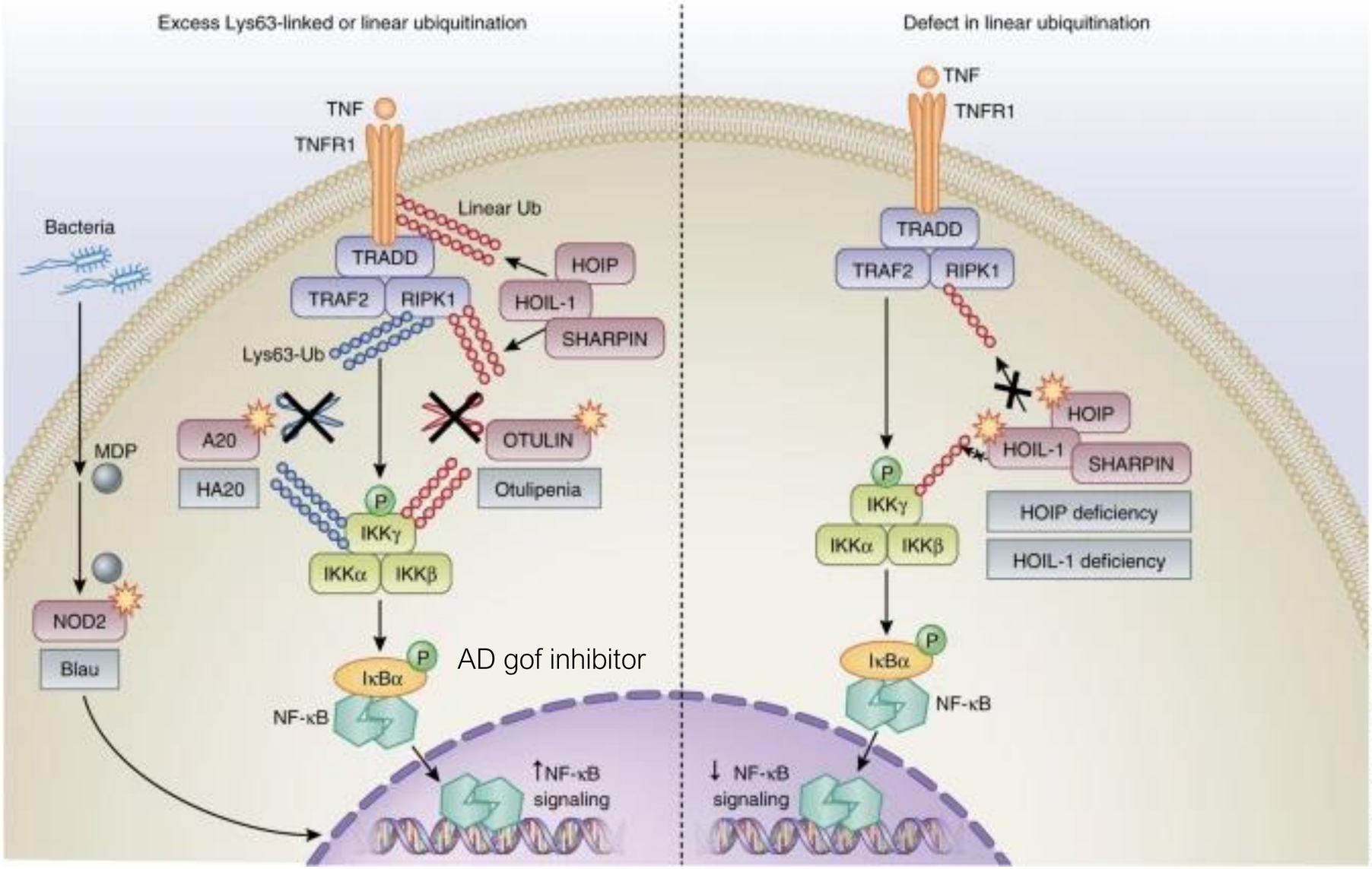
loss of pyrin inhibition

pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)

WDR1

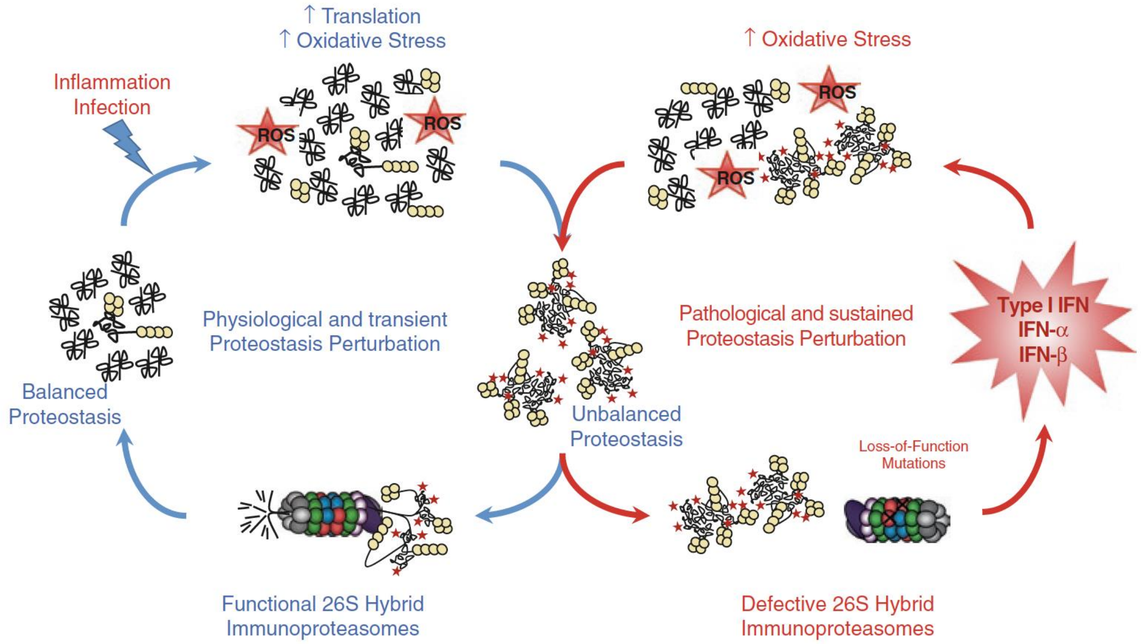
Savic et al, Nat Rev Rheum 2020

NF-κB-opathies



Proteosomes

- The ubiquitin proteasome system (UPS) is responsible for selective, energy-dependent protein degradation of ubiquitin-modified protein substrates to ensure protein homeostasis, regulatory protein function and antigen presentation
- Decides cell fate between repair and death



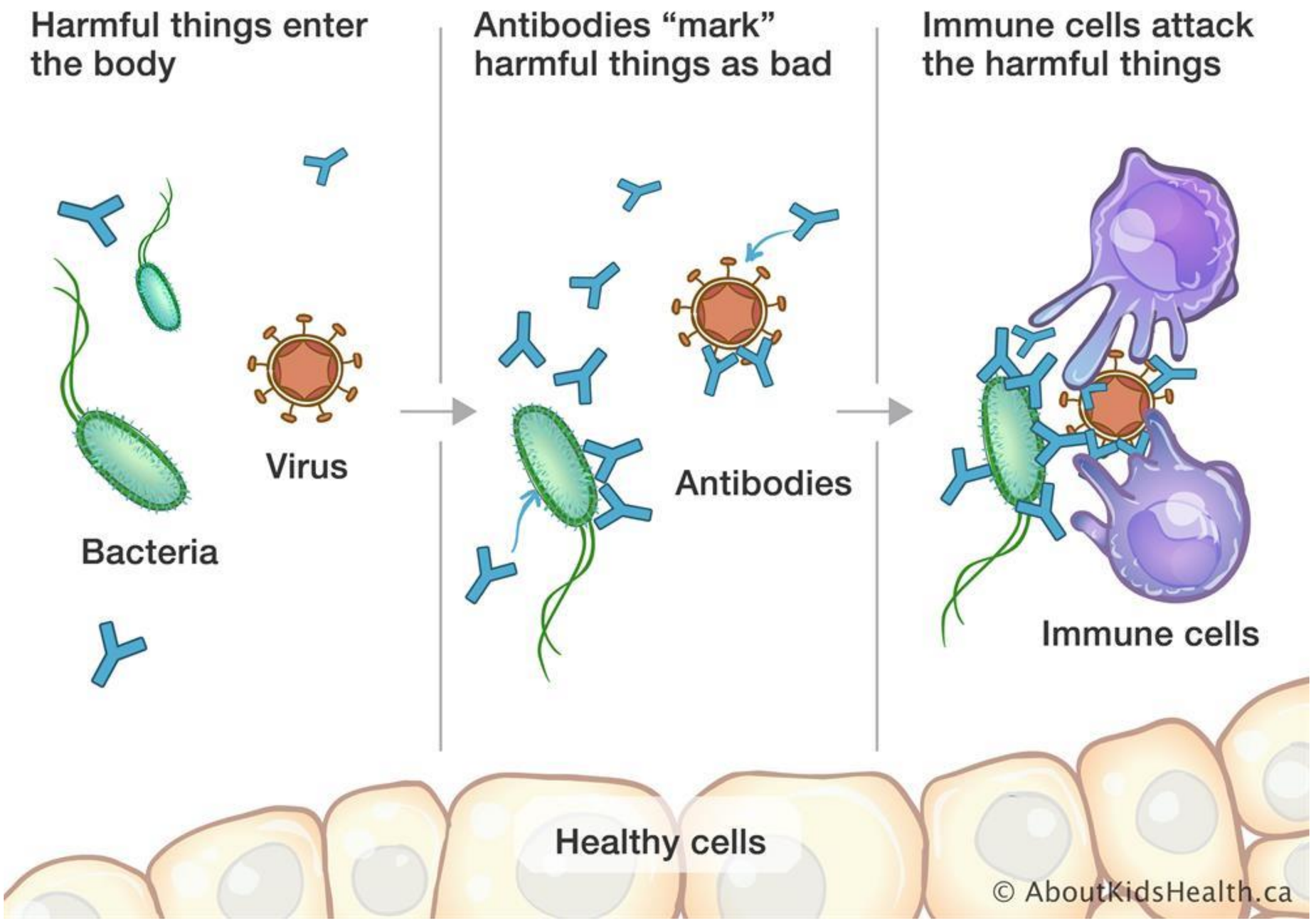
Brehm et al, Ch 7 in Textbook of Autoimmunity, 2019

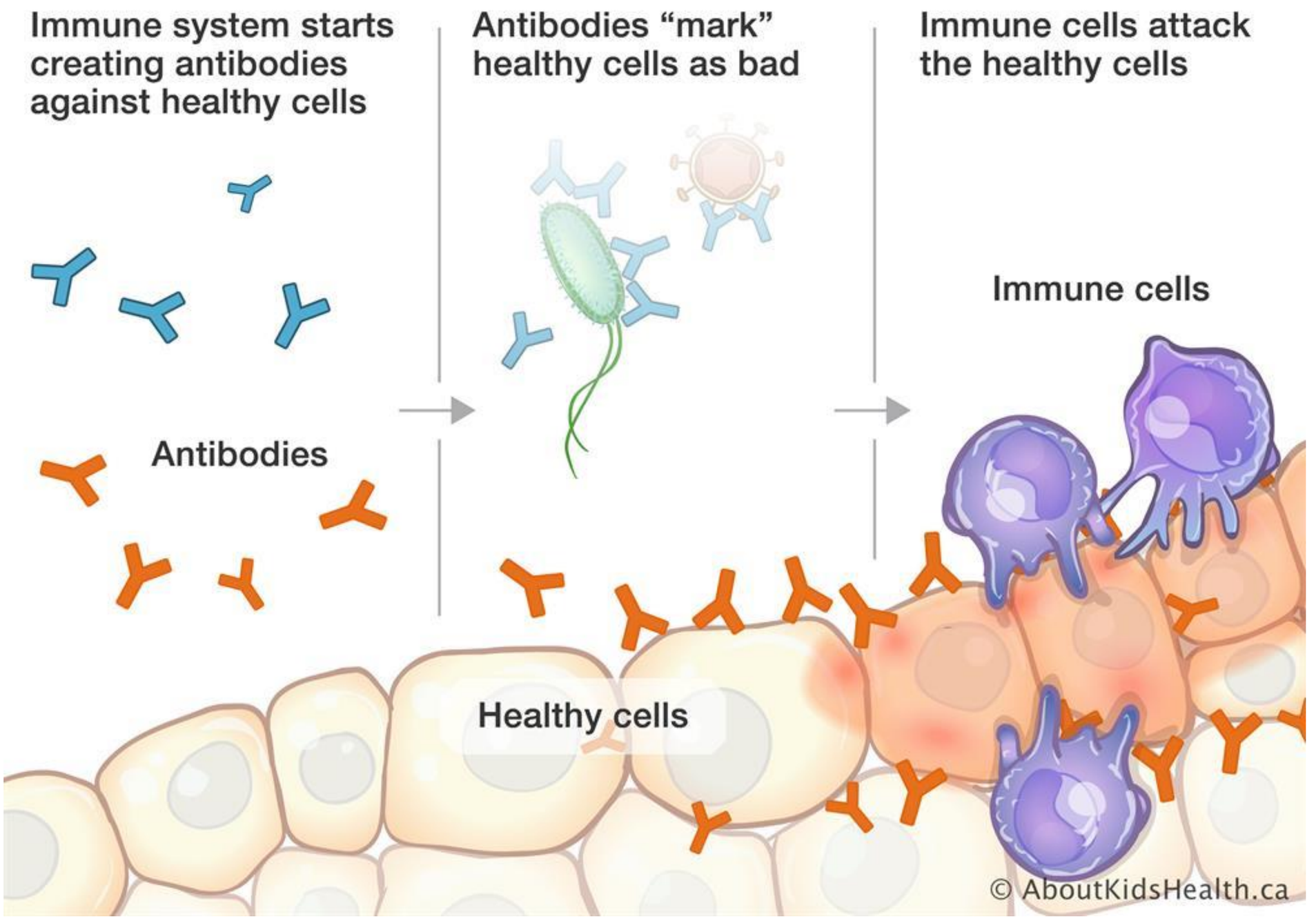
Monogenic autoimmunity

Two kinds of autoimmunity

Antibody autoimmunity
("humoral", B cells)

Cellular autoimmunity
(T cells)


Harmful things enter the body
Antibodies "mark" harmful things as bad
Immune cells attack the harmful things
Virus
Bacteria
Antibodies
Immune cells
Healthy cells
© AboutKidsHealth.ca

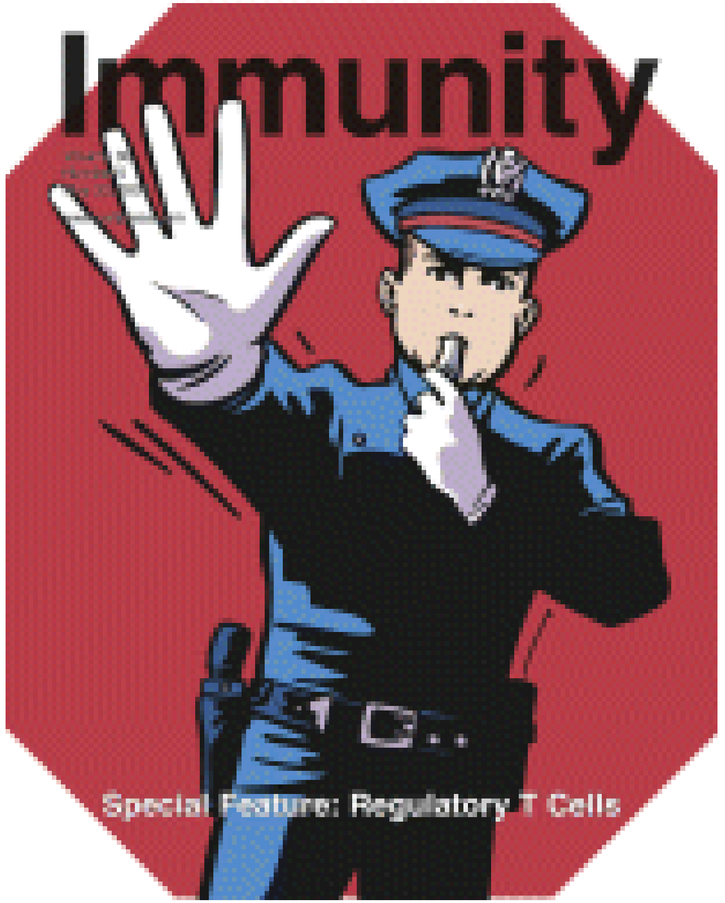

Immune system starts creating antibodies against healthy cells
Antibodies “mark” healthy cells as bad
Immune cells attack the healthy cells
Antibodies
Immune cells
Healthy cells
© AboutKidsHealth.ca

Humoral Autoimmunity examples

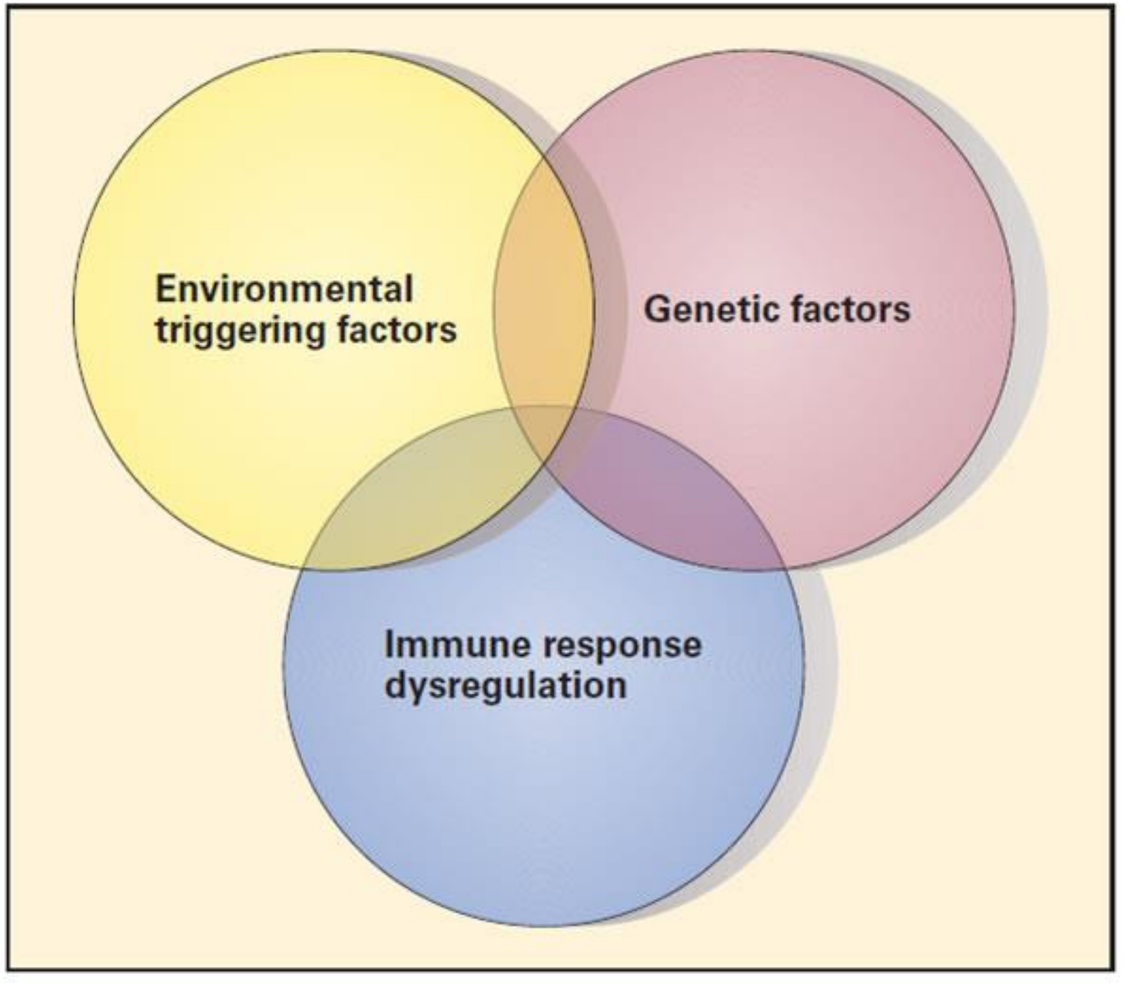
- **Systemic disorders**
  - anti-dsDNA
  - anti-histone
  - ANCA
  - ANA
- **Clotting**
  - Lupus anticoagulants
  - Antiphospholipid antibodies
- **Thyroid**
- **GI**
- **Liver**
  - Smooth muscle, microsome, mitochondria
- **Muscle**
  - Acetylcholine receptor
- **CNS**
  - GAD65
- **Blood cells**
  - Hemolytic anemia
  - Thrombocytopenia

Cellular Autoimmunity Examples

- Type 1 diabetes
- Multiple sclerosis
- Narcolepsy
- Inflammatory Bowel Diseases

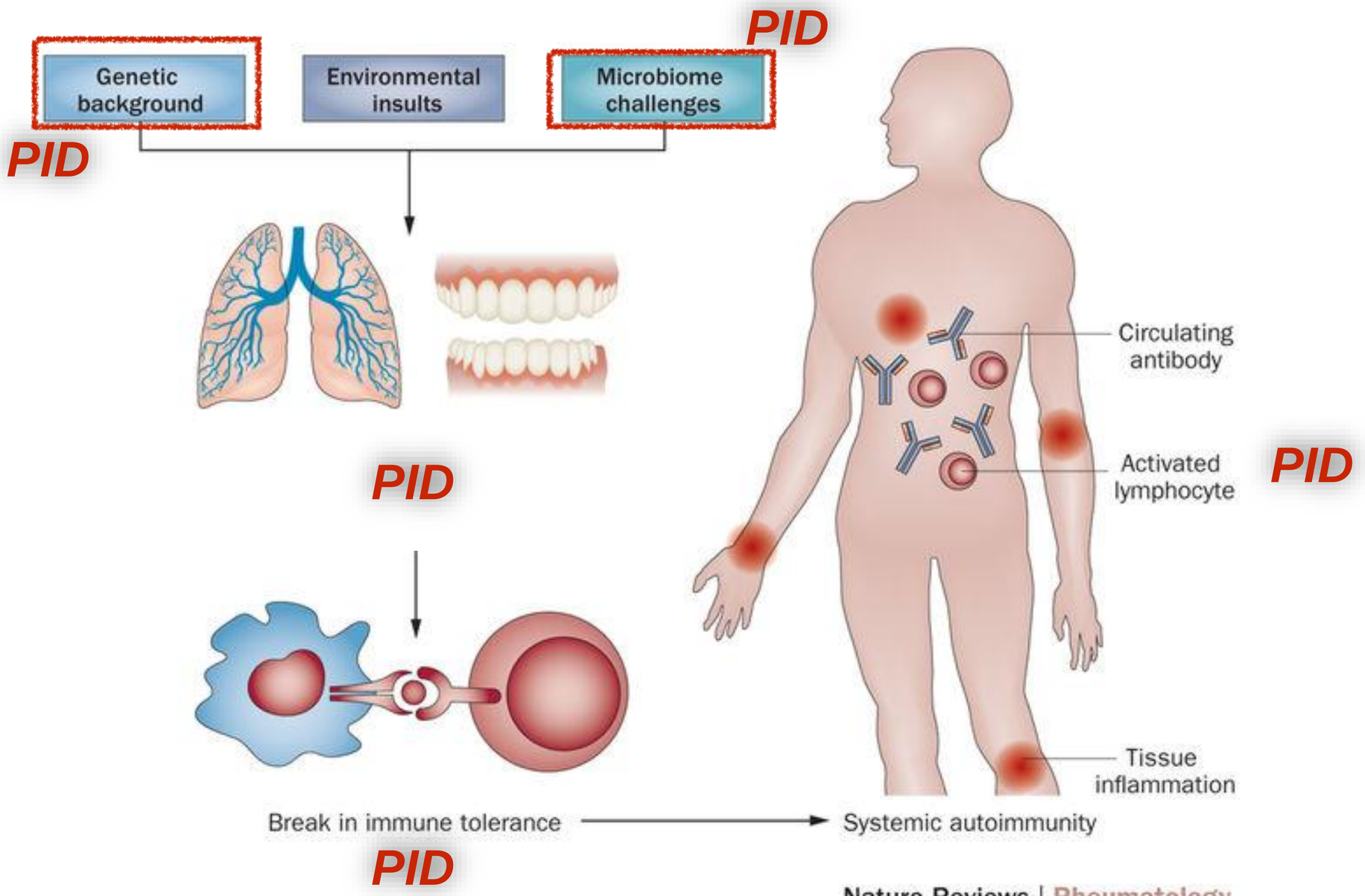


Important role of Tregs



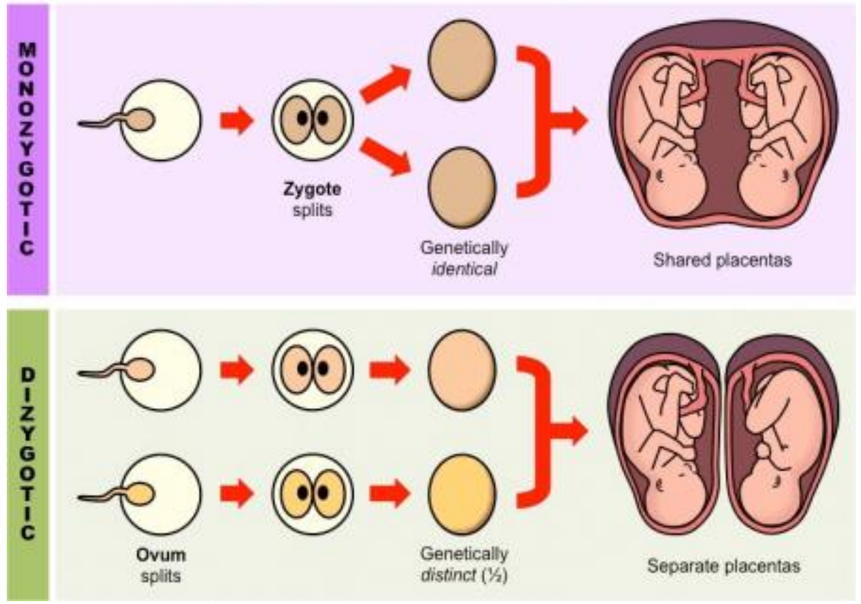
Bellanti JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012]

Inflammation is the fertile soil for autoimmunity



Klareskog and Catrina, Nat Rev Rh 2015

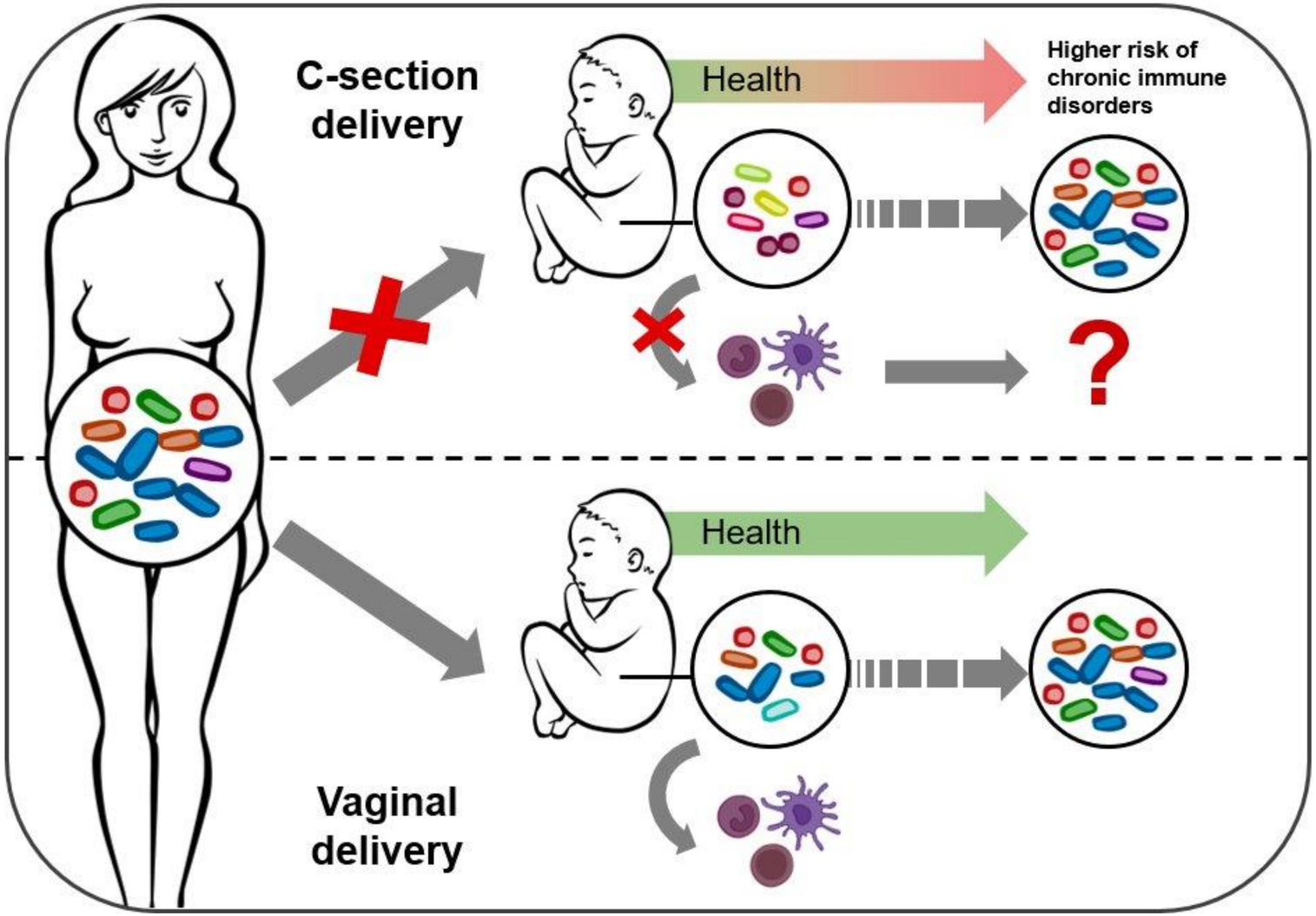
Autoimmunity: Is it genetic?



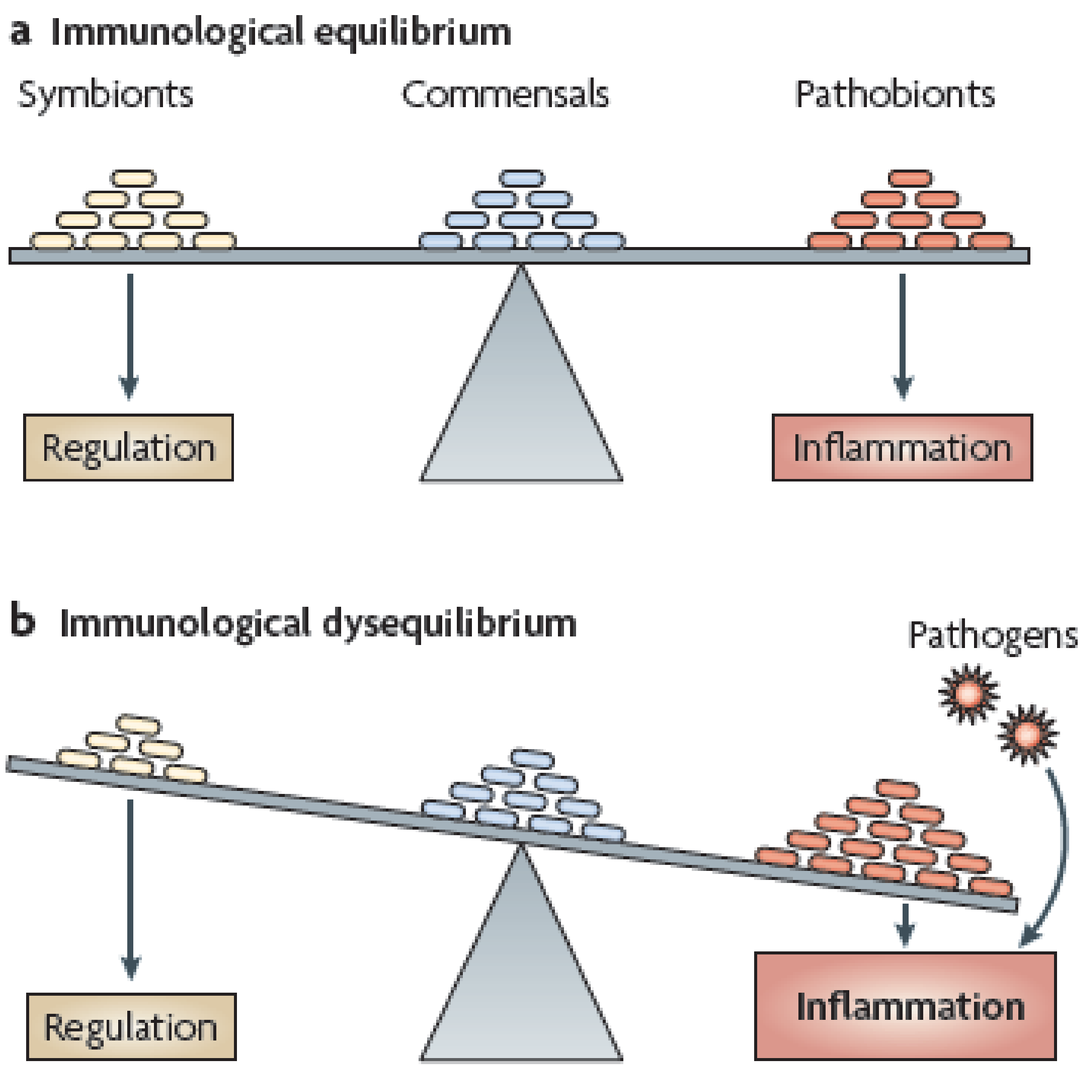
Disease	Monozygotic	Dizygotic
Celiac disease	75–83%	11%
Psoriasis	67%	15%
Primary biliary cirrhosis	60%	Not available
Ankylosing spondylitis	50%	20%
Systemic lupus erythematosus	33%	2%
Crohn's disease	25%	7%
Multiple sclerosis	25–31%	3–5%
Type 1 Diabetes	21–70%	0–13%
Ulcerative colitis	18.7%	3%
Graves' disease	17–31%	1.9–4.7%
Rheumatoid arthritis	12–15%	3.5%

Gale twins, both with CVID

The gut microbiome: something you ate?



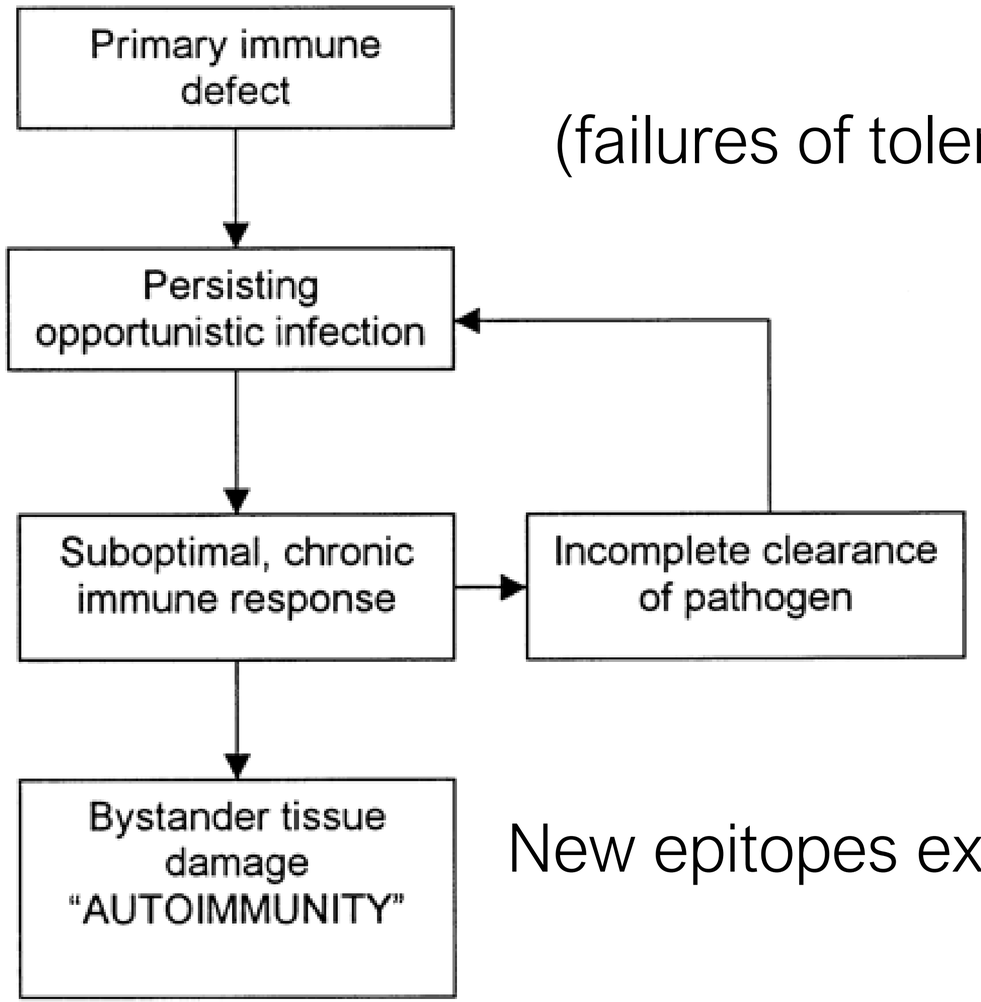
Wampach et al Nat Comm 2018



Round et al, Nat Rev Immunol 2009

Inflammatory bowel disease, asthma, skin infections, sinus infections

Why IEI leads to autoimmunity



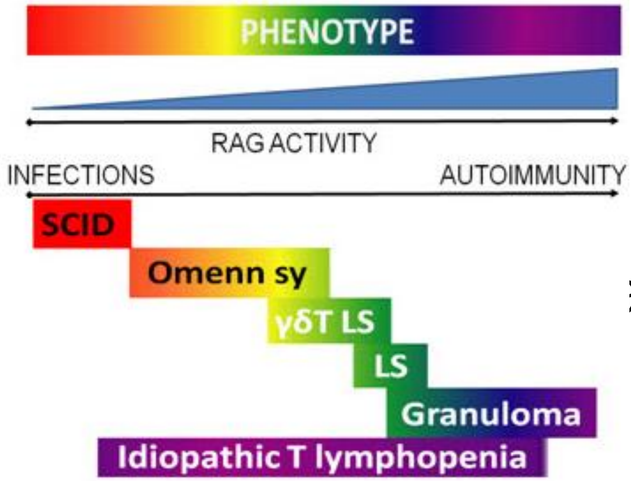
(failures of tolerance)

New epitopes exposed

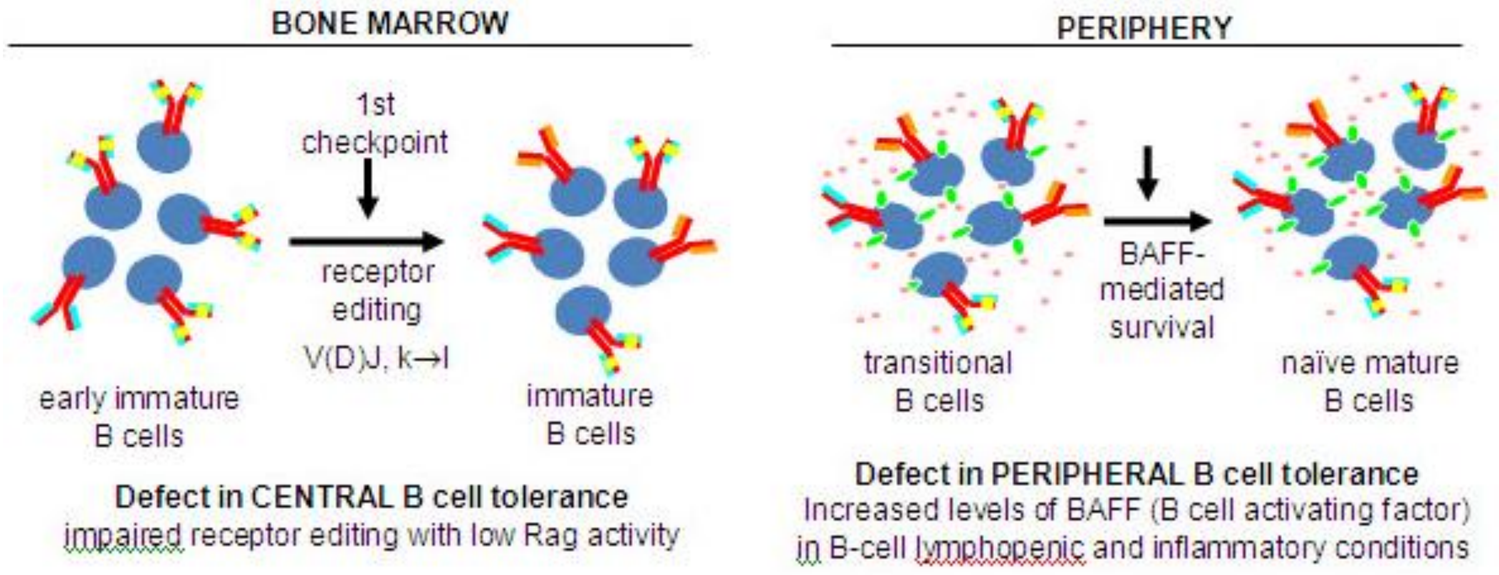
1. Low T and B cell counts leads to autoimmunity

Lymphopenia

- Hypomorphic Rag, Artemis deficiency
  - Range of severities
  - Can present in adulthood
  - **1:5476** Europeans has pathogenic (homoz or co ants!



J Walter (USF)



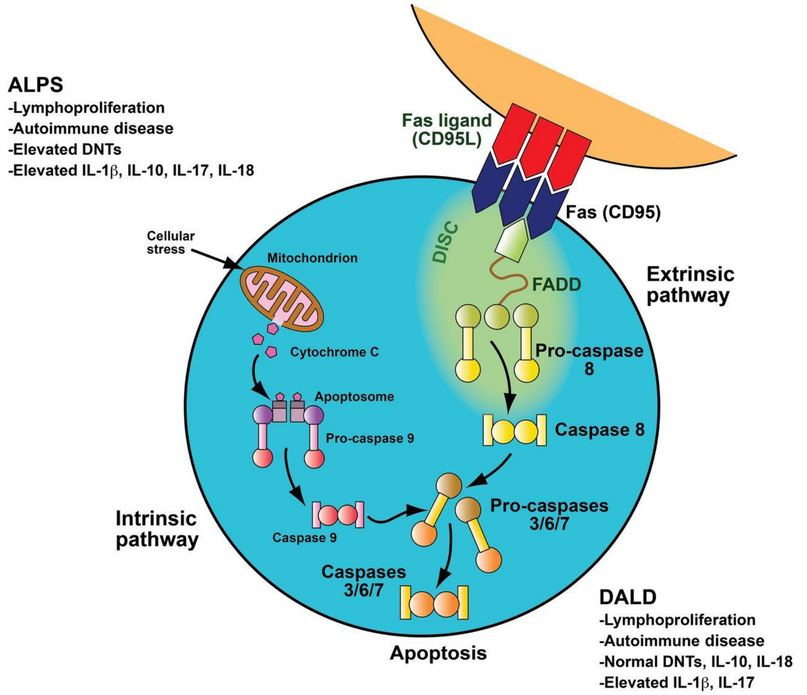
J Walter (USF)

2. When T and B cells cannot kill themselves, leads to autoimmunity

ALPS (autoimmune lymphoproliferative disorder)

ALPS: defects of apoptosis

- Lymphadenopathy, HSmegaly, multi-autoimmune cytopenias, autoimmune organ dz, risk of lymphoma
- Treatments: Suppress T cells (sirolimus), Targeting IL-17, HSCT



Teachy D, Blood 2014

Required
1. Chronic (>6 mo), nonmalignant, noninfectious lymphadenopathy; splenomegaly; or both
2. Increased $CD3^+TCR\alpha\beta^+CD4^-CD8^-$ DNT cell counts (≥1.5% of total lymphocytes or 2.5% of $CD3^+$ lymphocytes) in the setting of normal or increased lymphocyte counts

Accessory

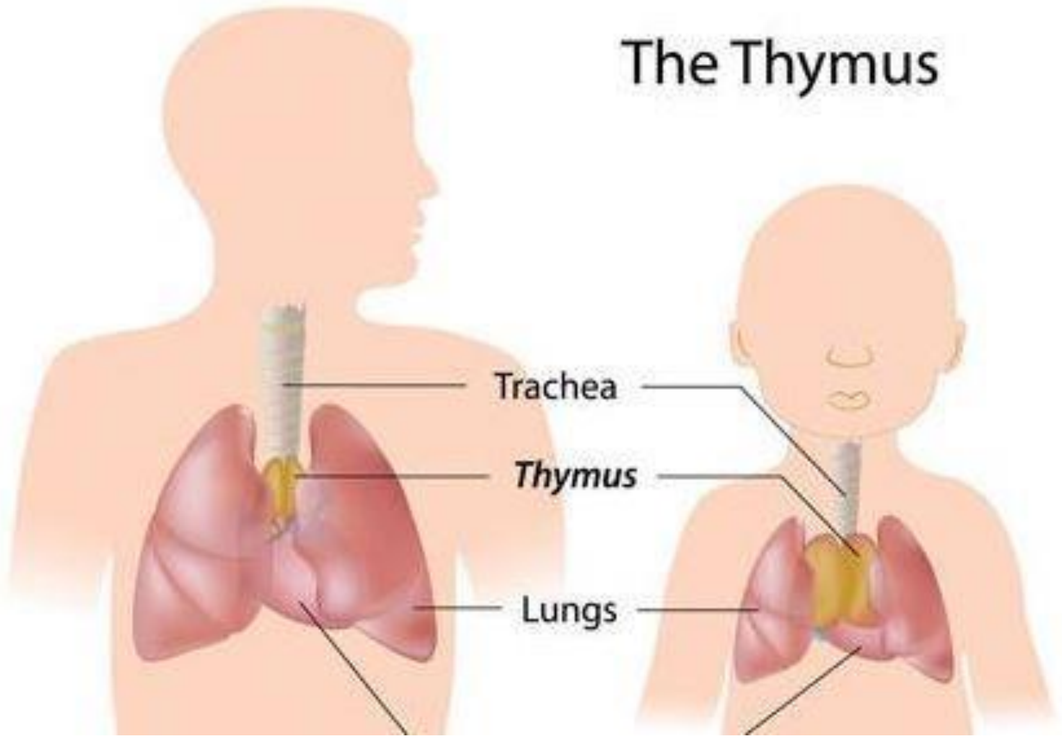
Primary
1. Defective lymphocyte apoptosis (in 2 separate assays)
2. Somatic or germline pathogenic mutation in *FAS*, *FASLG*, or caspase 10 *(CASP10)*

Secondary
1. Increased plasma sFASL levels (>200 pg/mL) OR increased plasma IL-10 levels (>20 pg/mL) OR increased serum or plasma vitamin B12 levels (>1500 ng/L) OR increased plasma IL-18 levels (>500 pg/mL)
2. Typical immunohistologic findings, as reviewed by an experienced hematopathologist
3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND increased IgG levels (polyclonal hypergammaglobulinemia)
4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

DNT, Double-negative T.
*A definitive diagnosis is based on the presence of both required criteria plus 1 primary accessory criterion. A probable diagnosis is based on the presence of both required criteria plus 1 secondary accessory criterion.

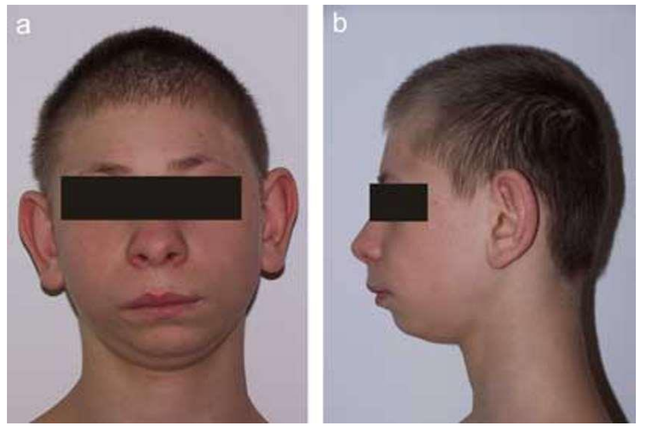
Grimbacher B, et al, JACI 2016

3. Central tolerance is needed to prevent autoimmunity



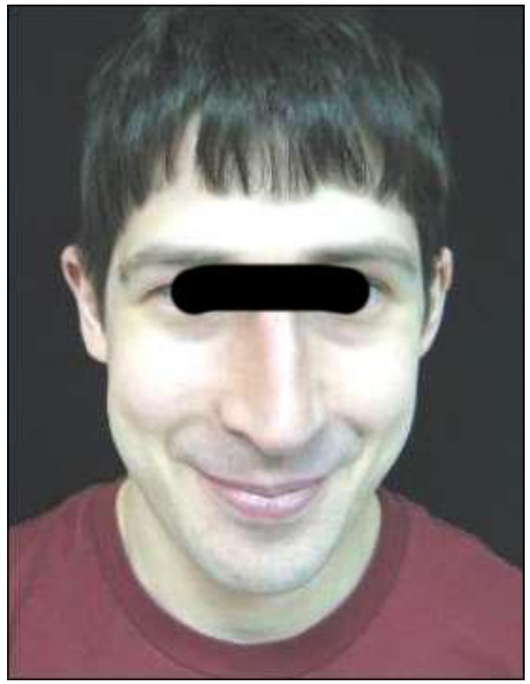
22q11.2DS (DiGeorge) Syndrome

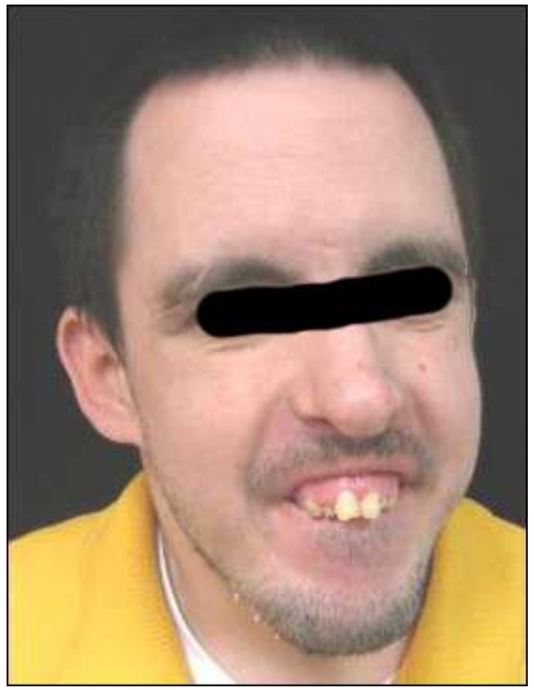
- Speech and swallowing trouble
- Low ears, Small face
- Heart defects (75%)
- Low calcium levels
- **Immunodeficiency (75%): thymus deficiency**
- 1:3000 live births
- Autoimmunity ~10%
  - Arthritis, thyroid, autoimmune cytopenias

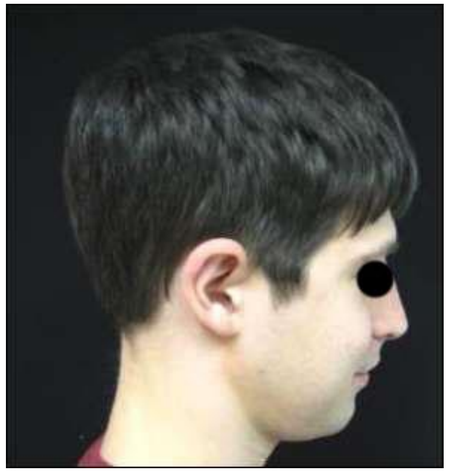


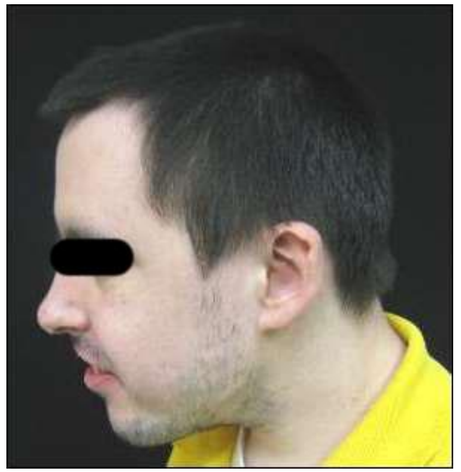
K Sullivan (CHOP)

Adults with DiGeorge Syndrome





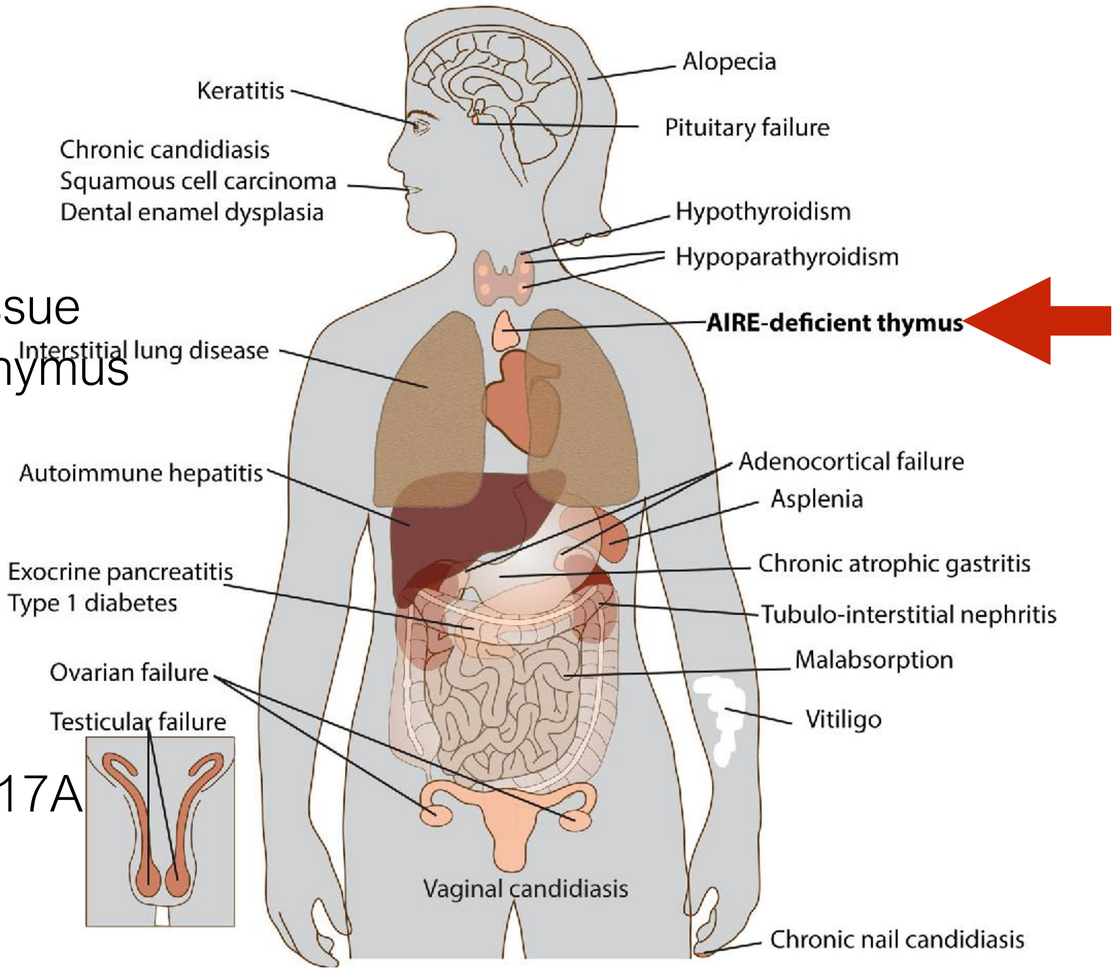




K Sullivan (CHOP)

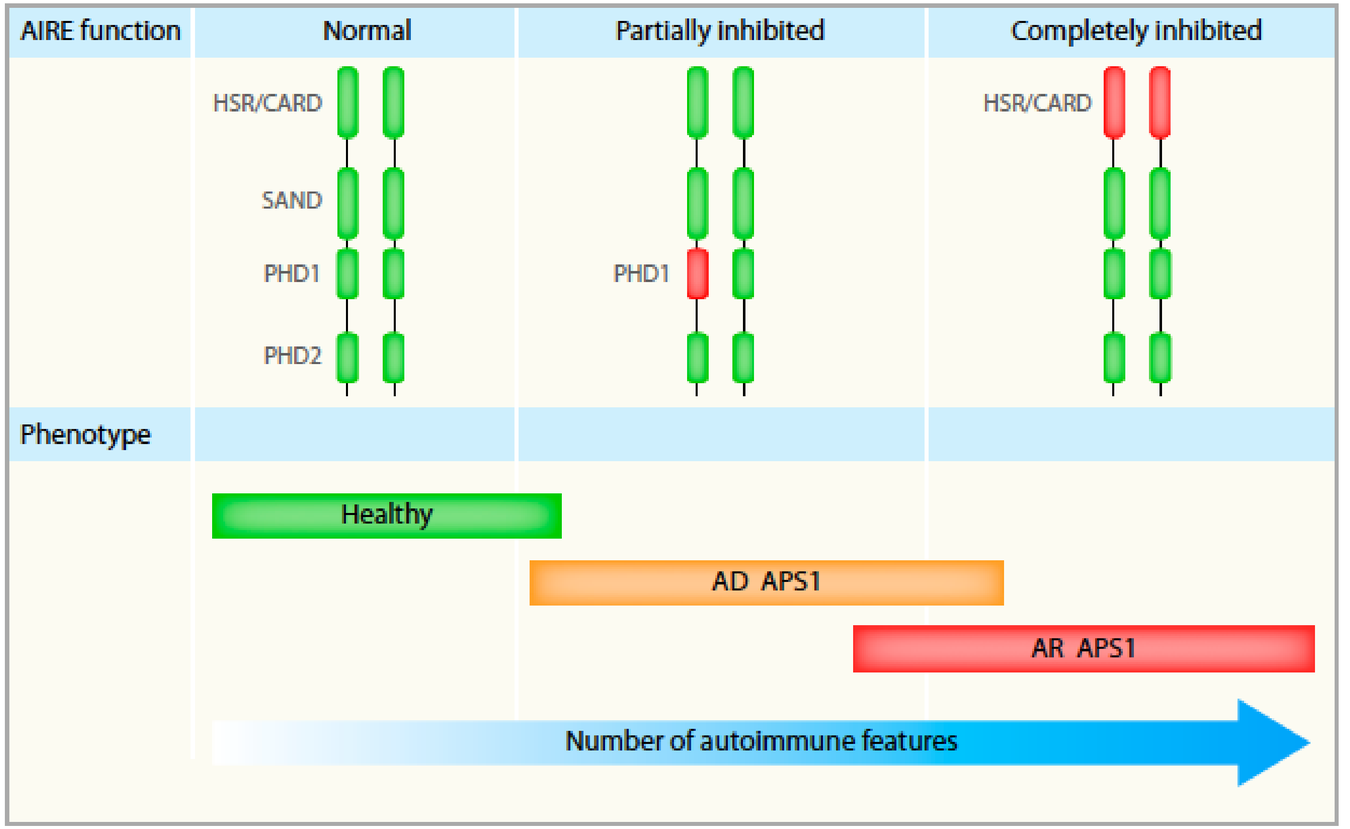
APECED/APS-1 (*Aire* deficiency)

- Transcriptional coactivator
- Expression of peripheral tissue antigens in the medullary thymus
- AI adrenal insufficiency, hypopara, mucocutaneous candidiasis, anti-interferon antibodies
- auto-antibodies against IL-17A explains the chronic mucocutaneous disease



- Kaj Kisand, Pärt PetersonPublished in Journal of Clinical Immunology 2015

Dominant APS-1



Pathogenic mutations in PHD1 domain occur in 1:1250!

Anderson M and Casanova JL, Immunity 2015

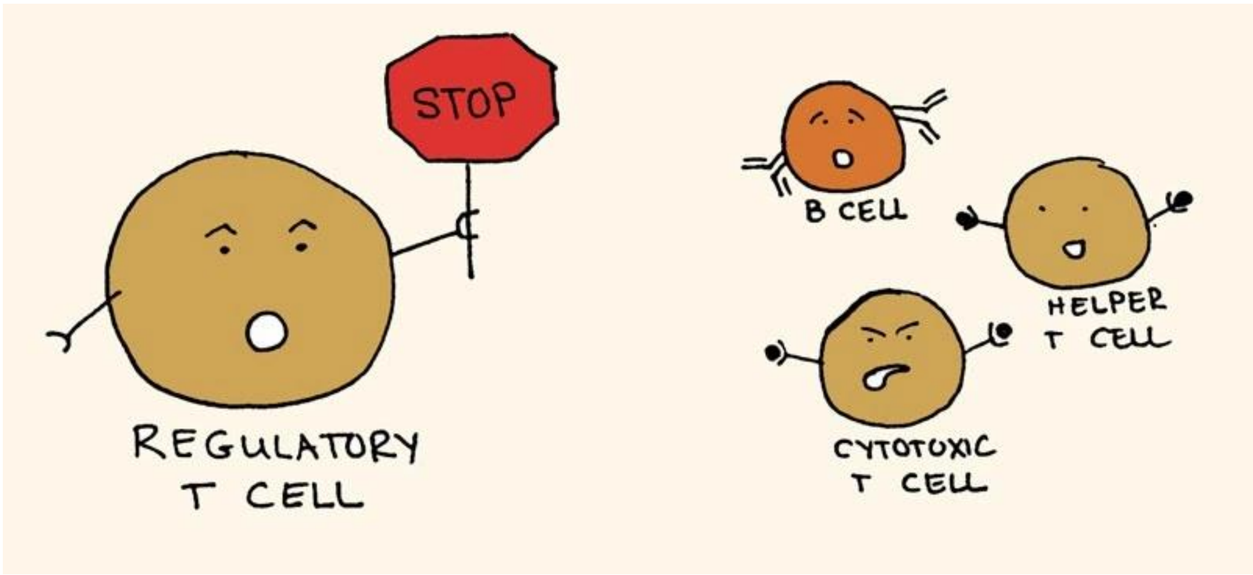
4. Impaired Treg function leads to autoimmunity

IPEX (*Foxp3* deficiency)

- autoimmune GI disease
- Type 1 diabetes
- severe allergies
- severe autoimmunity
- severe infections
- Eosinophilia and high IgE

LRBA
CTLA4
CD25
many others

Orencia treatment



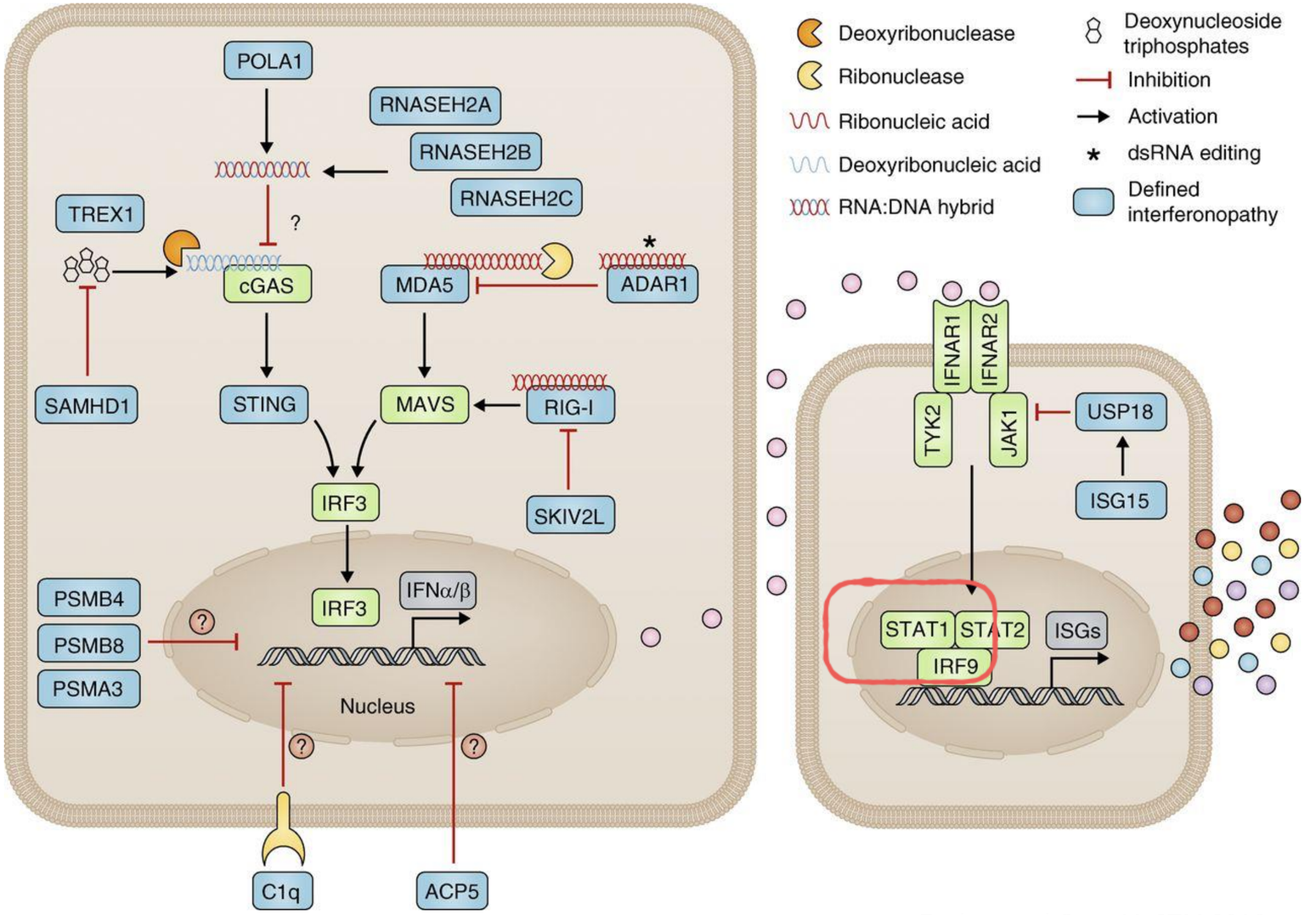
5. Increased Type-1 interferons leads to autoimmunity

Type 1 interferonopathies

- Aicardi Goutieres syndromes
- Broad spectrum of auto-antibodies
- Cells think they’re infected with DNA or RNA viruses

- Lung inflammation
- Lupus
- Severe brain inflammation
- Skin vasculitis
- Glaucoma
- Developmental delays (if present early)

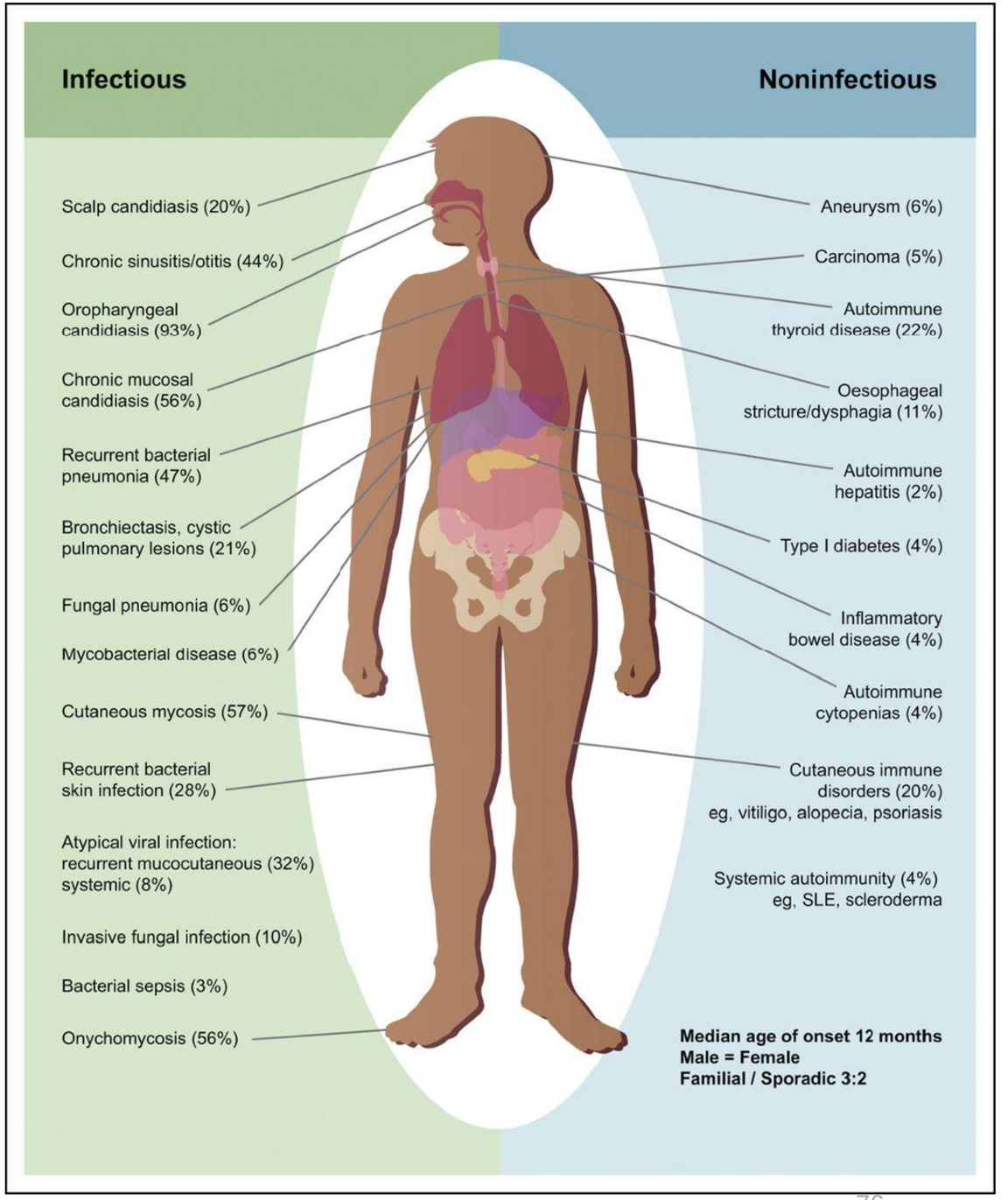
Type 1 interferonopathies



Rodero and Crow Y, JEM 2016

STAT1 gain of function

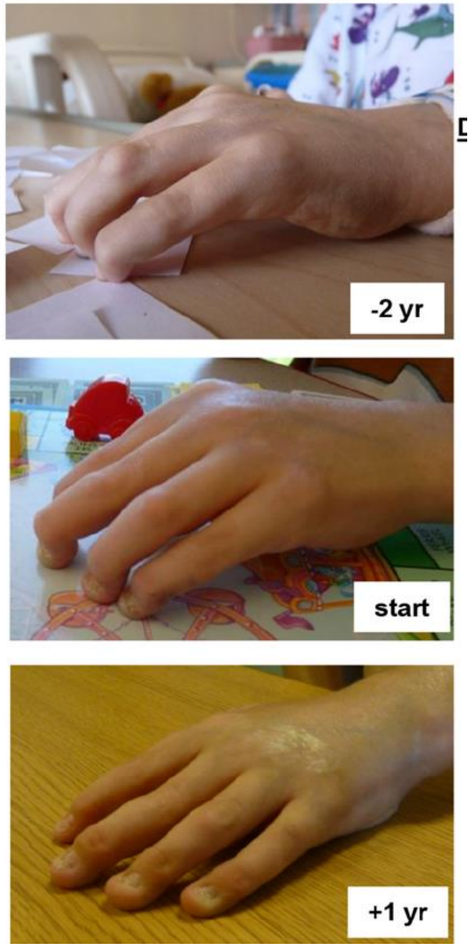
- Autosomal dominant
- Highly variable
- Chronic thrush
- Viral and bacterial infections
- AIHA, ITP, Autoimmune hepatitis



Hambleton Blood 2016

STAT3 gain of function

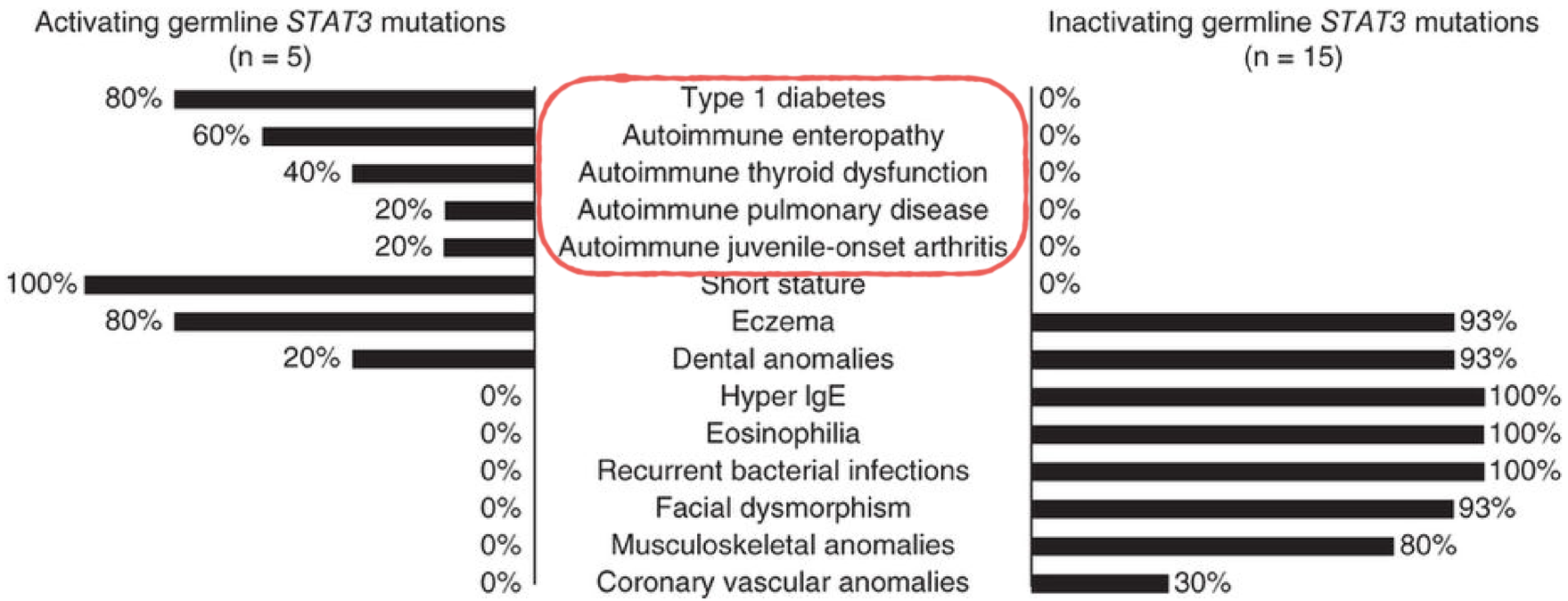
- “ALPS + IPEX + STAT5b”
- Lymphoproliferation, prominent cytopenias
- dermatitis (>90%)
- T1D, enteropathy, hypothyroidism, arthritis
- recurrent infections, hypogam
- High IL6 - responds well to tocilizumab



STAT3 GOF is not STAT3 LOF

gof

lof



Flanagan, et al, Nat Gen 2014

8. Hyperactivation of lymphocytes leads to autoimmunity

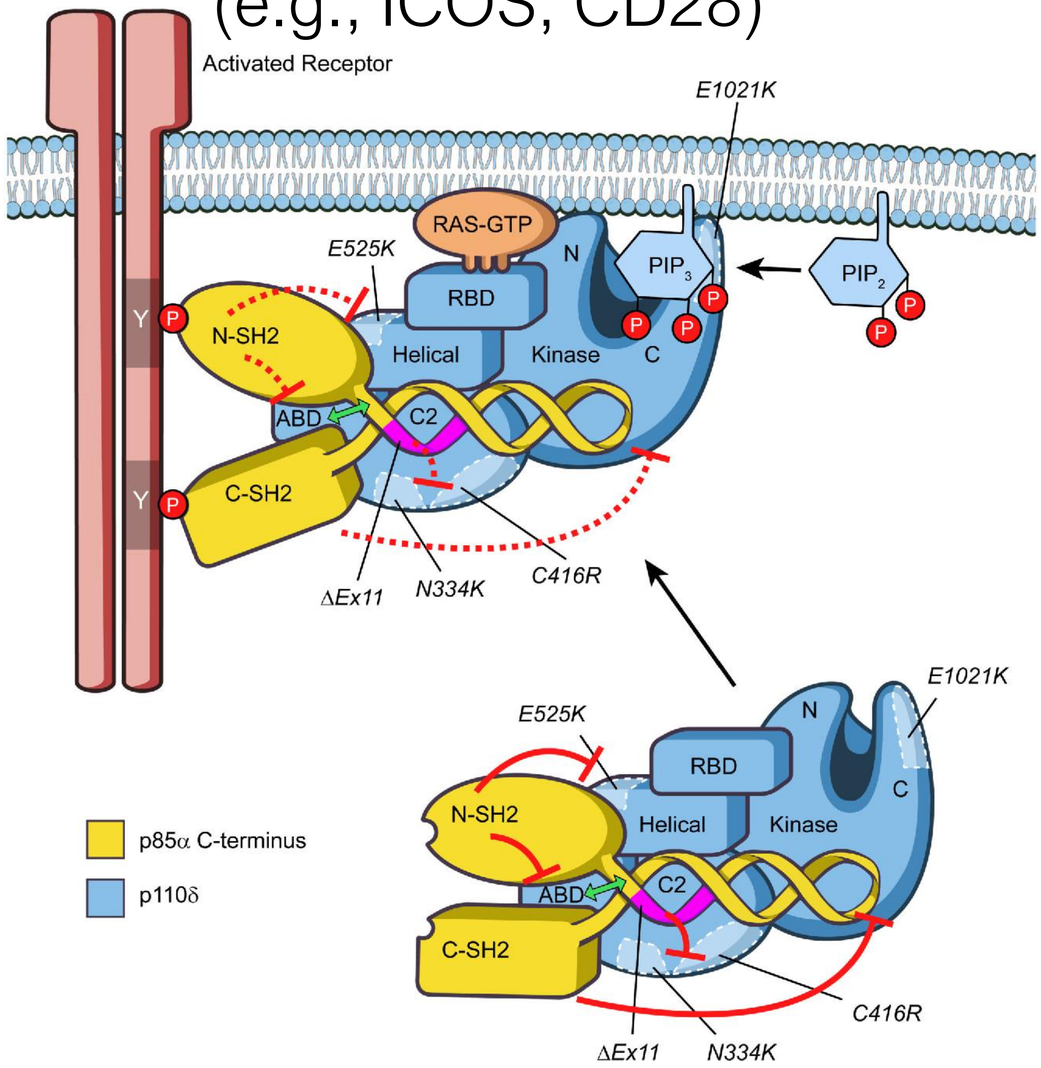
PIK3CD and PIK3R1

- Activated PI3 Kinase Delta Syndrome (APDS)
- Incidence: 1.5 per million
- Lung and sinus infections
- Severe, recurrent, persistent herpes virus infections
  - EBV and CMV
- Opportunistic infections (warts, molluscum)
- Abscesses
- Enlarged Lymph nodes
- Autoimmune anemia
- Poor growth
- Lymphoma is common

Activated PI3 Kinase Disease

- Autoimmunity
- Lymphoproliferation
  - looks like ALPS
- Antibody deficiency
  - can look like CVID
- CMV and EBV infections

(e.g., ICOS, CD28)

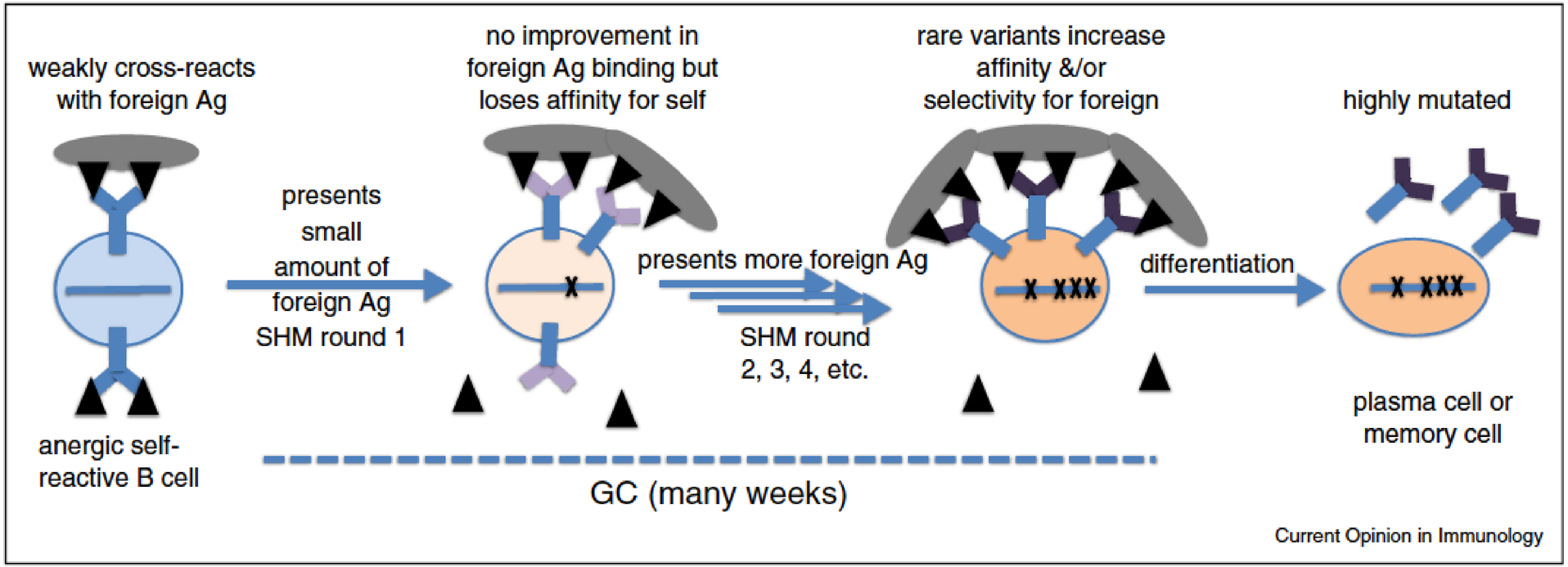


9. Impaired B cell repertoire leads to autoimmunity

Clonal redemption

We are all born with auto-reactive B cells!

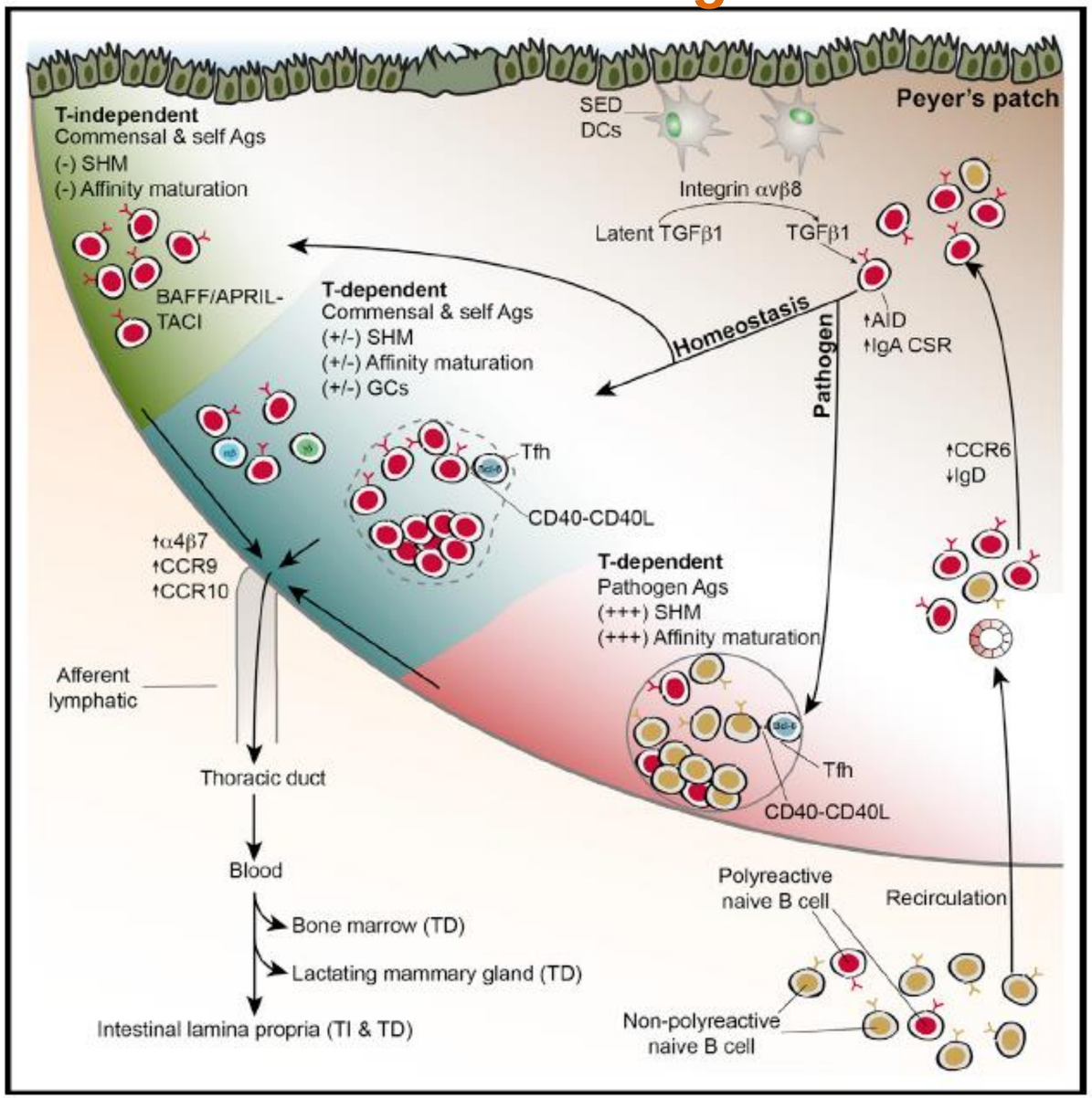
AIHA: Vh4-34 recognizes the I/i carbohydrate ag on RBCs



IgA bound to commensals
helps us get rid of autoimmunity

Microbiome regulates B-cell repertoire

gut bacteria



B cells primed by commensal antigens

start here

polyreactive B cells

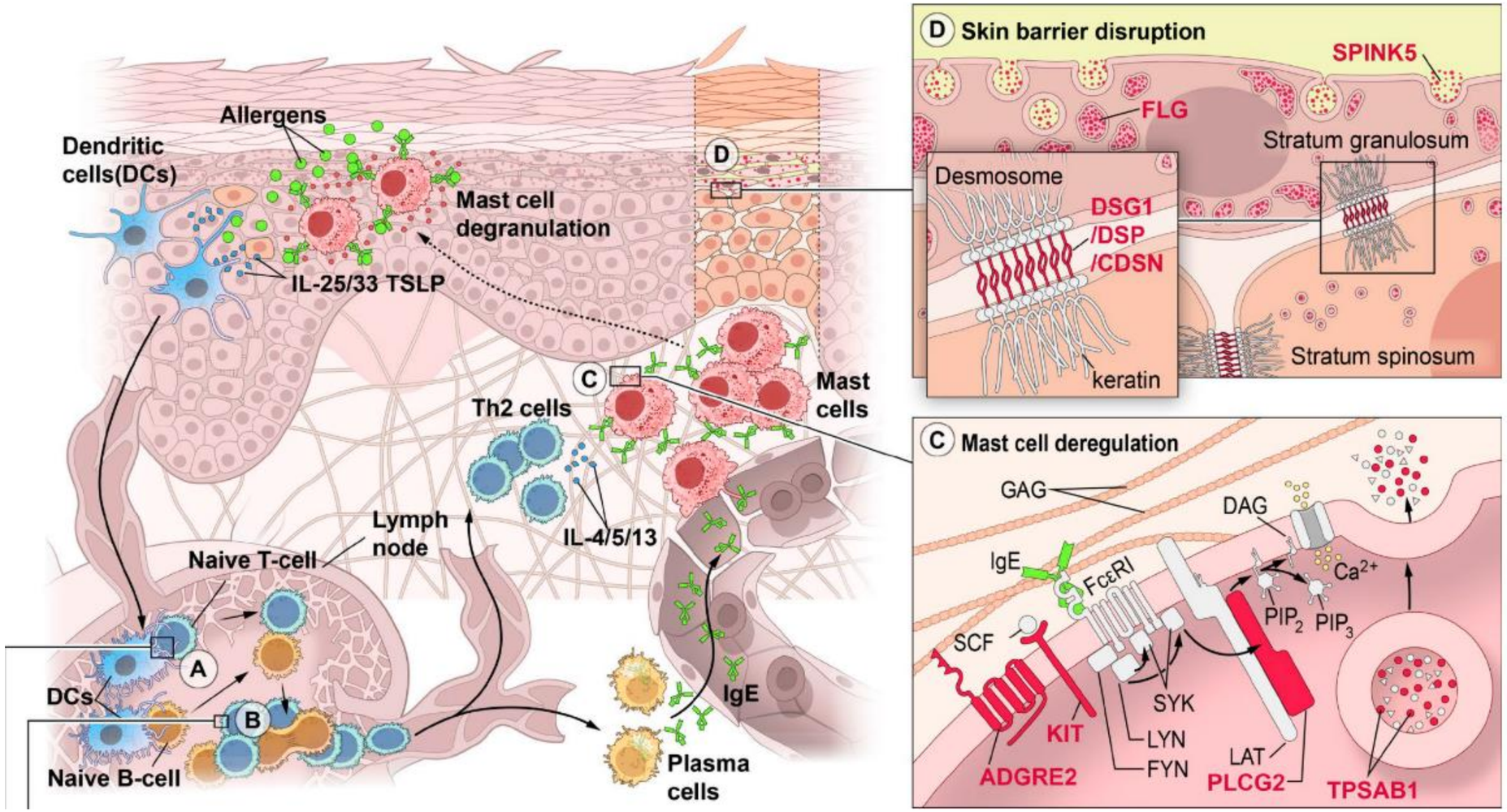
Bunker Bendelac Immunity 2016

Autoimmunity Treatments

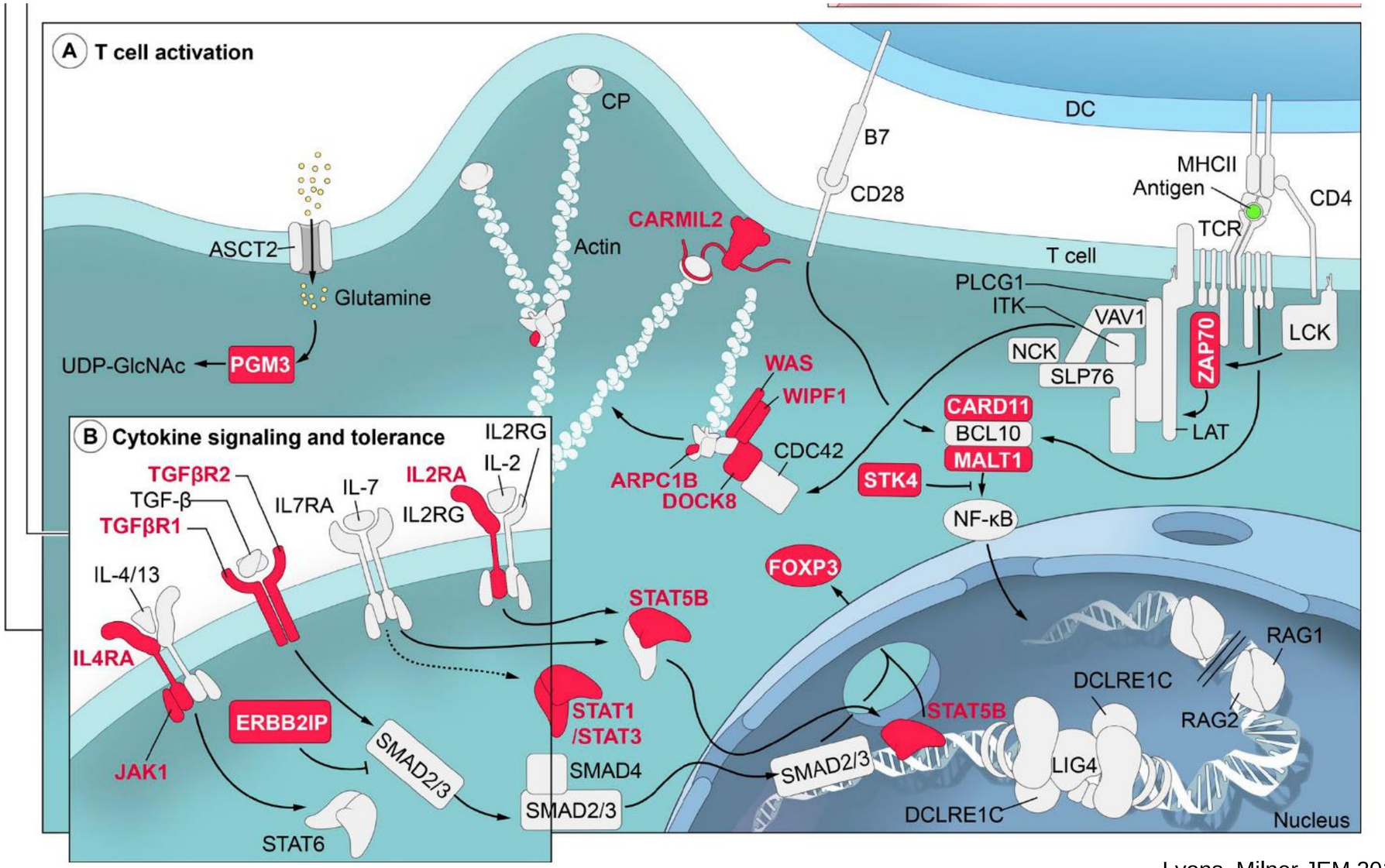
- **Anti-inflammation**
  - Low dose steroids
  - Colchicine
  - Plaquenil
  - Thalidomide
- **Immune suppression**
  - Steroids
  - Azathioprine
- **B cell depletion**
  - Rituximab and other CD20
  - Inebilizumab
- **Strong immune suppression/ablation**
  - Cyclophosphamide
  - Campath (alemtuzumab)
- **Hematopoietic stem cell transplantation**

Monogenic atopy

Monogenic atopic disorders



Lyons, Milner JEM 2018



Lyons, Milner JEM 2018

Table 1. **Genetic mutations associated with primary atopic disorders.**

Altered process	Genes
Impaired TCR signaling and cytoskeletal remodeling	*ZAP70, CARD11, MALT1, WAS, WIPF1, ARPC1B, DOCK8, CARMIL2*
Altered cytokine signaling	*STAT3^{DN}, STAT1^{GOF}, STAT5B^{LOF}, STAT5B^{GOF}, JAK1^{GOF}, IL4RA^{GOF}, TGFBR1, TGFBR2, ERBB2IP*
T cell repertoire restriction	*RAG1, RAG2, DCLRE1C, ADA, IL2RG, IL7RA, CHD7, LIG4, ZAP70,* 22q11del
Tolerance failure	*FOXP3, IL2RA, STAT5B^{LOF}, TGFBR1, TGF BR2, WAS, CARD11, STAT1^{GOF}*
Metabolic disturbance	*PGM3, CARD11, MALT1*
Skin barrier disruption	*FLG, CDSN, DSG1, DSP, SPINK5*
Mast cell deregulation	*KIT, PLCG2, ADGRE2, TPSAB1*

Lyons, Milner JEM 2018