Inborn errors of immunity:
single-gene mutations causing primary immunodeficiencies & primary immune regulatory disorders

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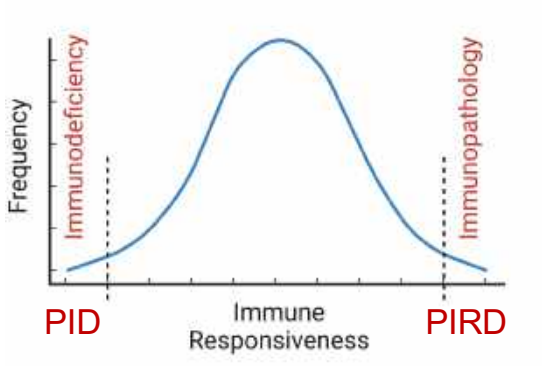
Yale University School of Medicine
Department of Immunobiology

February 2024

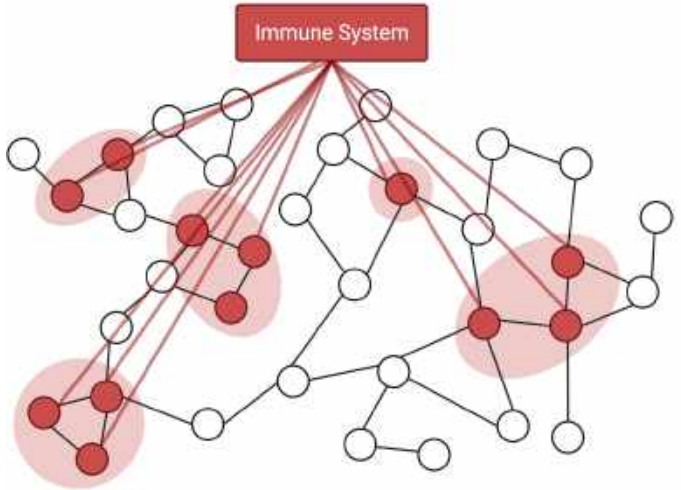
Rare diseases, common insights

Forward human genetics can teach us translationally relevant basic biology.



PID: Primary immunodeficiency
PIRD: Primary immune regulatory disorder

Graphic by Bruce Rolff, Shutterstock.

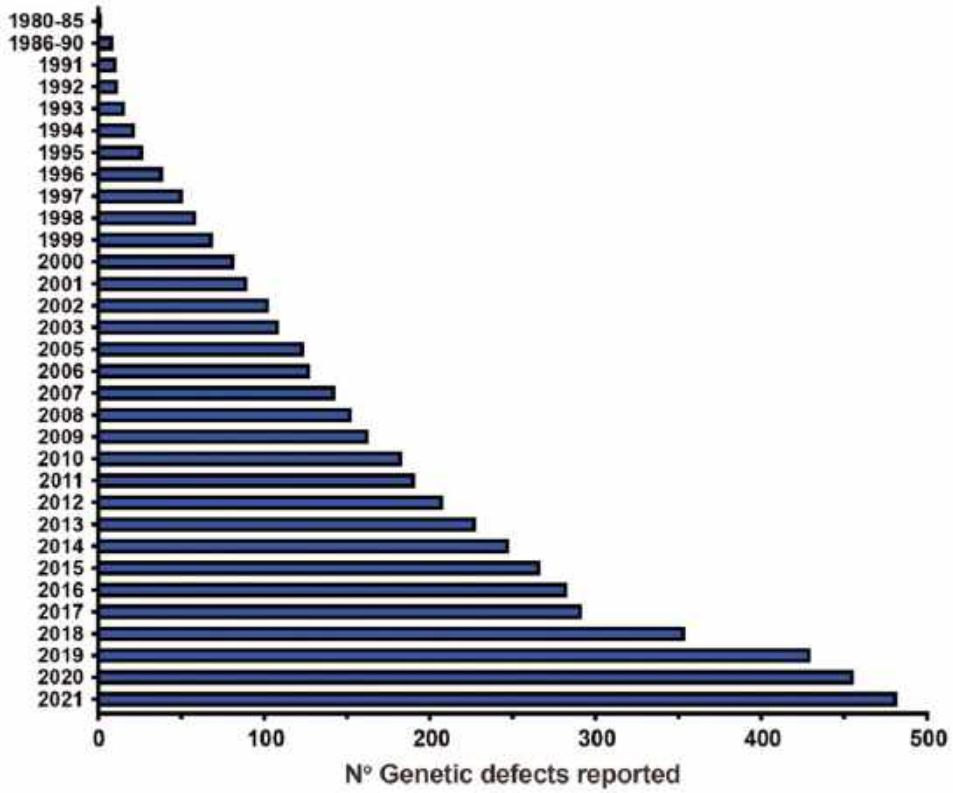


New principles/mechanisms enable

- New conceptual frameworks
- Genetic diagnoses that improve patient care
- Novel therapies for rare and common diseases with related underlying pathophysiology

Genetic diseases fuel discovery: 500+ disorders

- Germ theory, antibiotics, and mass vaccination made it possible to recognize 'outlier' patients with severe infection susceptibility.
  - First PID and PIRD recognized in 1950s
- Nature does the screening for us:
  - Disease from both loss- and gain-of-function germline mutations.
  - Many de novo. Emerging somatic mutations.
  - Sometimes relatively mild phenotypes.
- Collectively not that rare.



Journal of Clinical Immunology
https://doi.org/10.1007/s10875-022-01289-3

Primary immunodeficiencies

- Caused by gene mutations (as opposed to secondary)
- Commonly include recurrent and overwhelming infections but can also manifest with associated inflammation.
- The type of recurring infection gives an indication of the immune defect
  - Pyogenic (pus-forming) bacteria → antibody, complement, or phagocytes may be defective
  - Fungal skin infections or recurrent viral infections → T cells or neutrophils may be defective
- Diagnosis challenges: rare/sporadic, maternal IgG may mask, infections in infants are common, genetics/environment interplay

Outline

- PID: Primary immunodeficiency: An IEI that leads to infection susceptibility as the primary feature
  1. Intrinsic immunity defects
  2. Phagocyte defects
  3. Antibody defects
  4. CD4 T cell defects
  5. CD8 T cell defects

- PIRD: Primary immune regulatory disorder: An IEI that leads to aberrant immune responses that cause excessive tissue damage
  1. Failed lymphocyte homeostasis
  2. Cytokinopathies: inflammasome-opathies, type I interferonopathies, frustrated cytotoxicity
  3. Barrier defects

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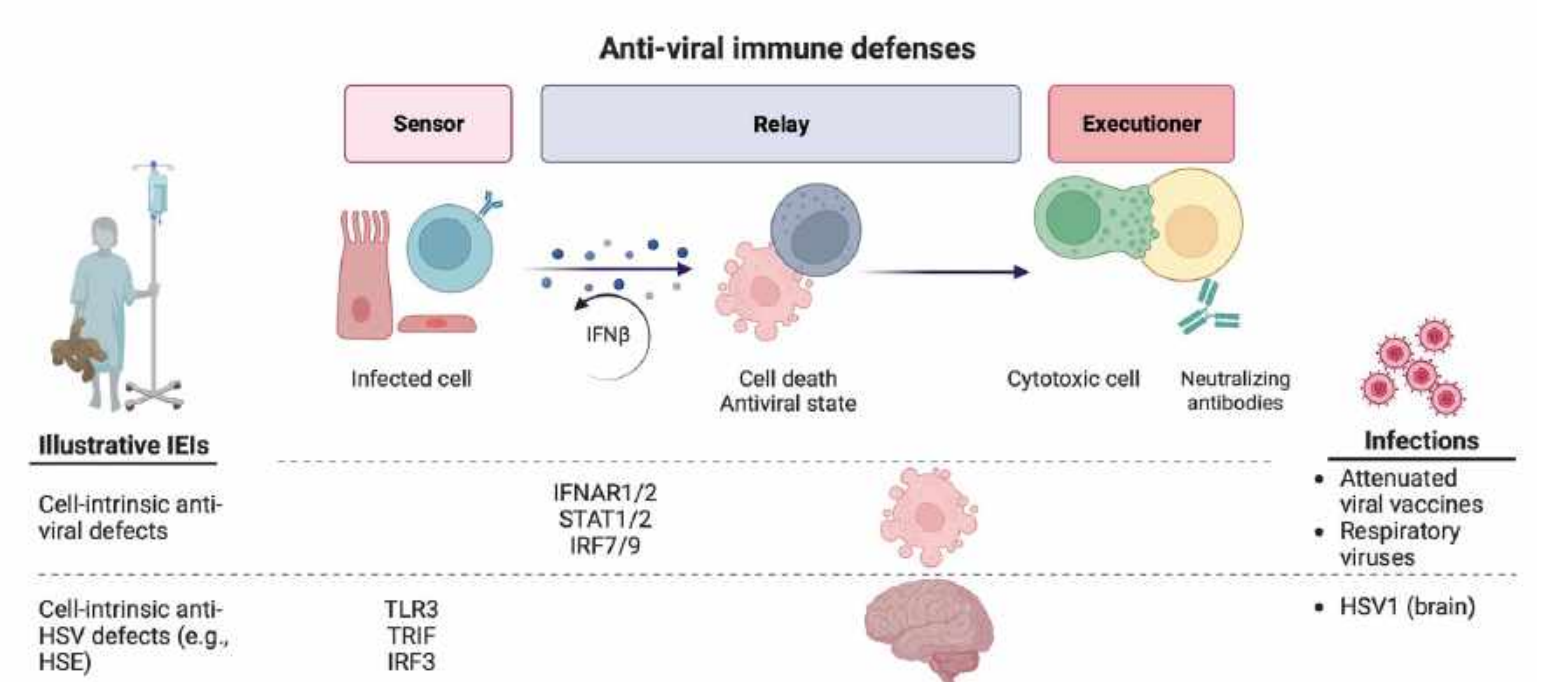
PID1: Intrinsic immune defects

- Intrinsic immunity: immune responses by any cell type in the body (not just immune cells) that help protect from infection (viral)



Lucas CL. **Trends in Immunology**. 2024.

PID1 : IFNAR deficiency

Human IFNAR2 deficiency: Lessons for antiviral immunity

+12 authors Authors Info & Affiliations

SCIENCE TRANSLATIONAL MEDICINE

Article | July 03 2019

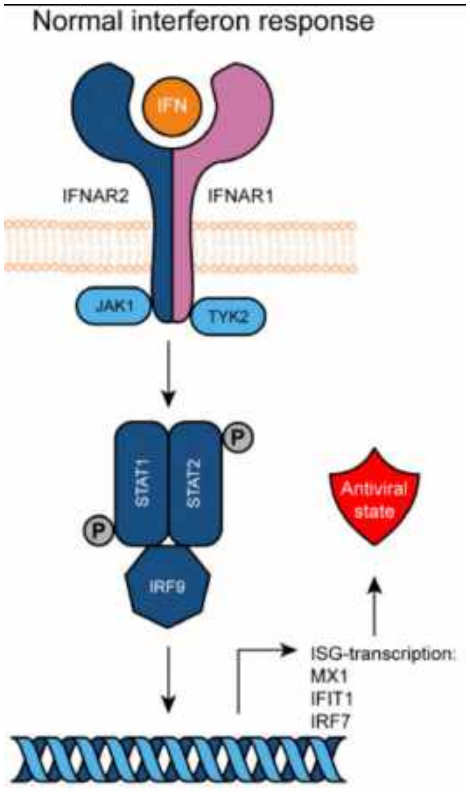
Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines

In Special Collection: 2020 Nobel Prize Collection

Nicholas Hernandez, Giorgia Bucciol, Leen Moens, Jérémie Le Pen, Mohammad Shahrooei, Ekaterini Goudouris, Afshin Shirkani, Majid Changi-Ashtiani, Hassan Rokni-Zadeh, Esra Hazar Sayar, Ismail Reisli, Alain Lefevre-Utile, Dick Zijlmans, Andrea Jurado, Ruben Pholien, Scott Drutman, Serkan Belkaya, Aurelie Cobat, Robbert Boudewijns, Dirk Jochmans, Johan Neyts, Yoann Seeleuthner, Lazaro Lorenzo-Diaz, Chibuzo Enemchukwu, Ian Tietjen, Hans-Heinrich Hoffmann, Mana Momenilandi, Laura Pöyhönen, Marilda M. Siqueira, Sheila M. Barbosa de Lima, Denise C. de Souza Matos, Akira Homma, Maria de Lourdes S. Maia, Tamiris Azamor da Costa Barros, Patricia Mouta Nunes de Oliveira, Emersom Ciclini Mesquita, Rik Gijsbers, Shen-Ying Zhang, Stephen J. Seligman, Laurent Abel, Paul Hertzog, Nico Marr, Reinaldo de Menezes Martins, Isabelle Meyts, Qian Zhang, Margaret R. MacDonald, Charles M. Rice, Jean-Laurent Casanova, Emmanuelle Jouanguy, Xavier Bossuyt

+ Author and Article Information

J Exp Med (2019) 216 (9): 2057–2070. https://doi.org/10.1084/jem.20182295 Article history



Brief Definitive Report | April 20 2022

Life-threatening viral disease in a novel form of autosomal recessive *IFNAR2* deficiency in the Arctic

In Special Collection: JEM Clinical Immunology Collection 2022

Christopher J.A. Duncan, Morten K. Skouboe, Sophie Howarth, Anne K. Hollensen, Rui Chen, Malene L. Børresen, Benjamin J. Thompson, Jarmila Stremenova Spegarova, Catherine F. Hatton, Frederik F. Staiger, Mette K. Andersen, John Whittaker, Søren R. Paludan, Sofie E. Jørgensen, Martin K. Thomsen, Jacob G. Mikkelsen, Carsten Heilmann, Daniela Buhas, Nina F. Øbro, Jakob T. Bay, Hanne V. Marquart, M. Teresa de la Morena, Joseph A. Kiejka, Matthew Hirschfeld, Line Borgwardt, Isabel Forsa, Tania Masmas, Anja Poulsen, Francisco Noya, Guy Rouleau, Torben Hansen, Sirui Zhou, Anders Albrechtsen, Reza Alizadehfar, Eric J. Allenspach, Sophie Hambleton, Trine H. Mogensen

Article | April 20 2022

A loss-of-function *IFNAR1* allele in Polynesia underlies severe viral diseases in homozygotes

In Special Collection: JEM Clinical Immunology Collection 2022

Paul Bastard, Kuang-Chih Hsiao, Qian Zhang, Jeremy Chon, Emma Best, Jie Chen, Adrian Gervais, Lucy Bizien, Marie Materna, Christine Harmant, Maguelonne Roux, Nicola L. Hawley, Daniel E. Weeks, Stephen T. McGarvey, Karla Sandoval, Carmina Barberena-Jonas, Consuelo D. Quinto-Cortés, Erika Hagelberg, Alexander J. Mentzer, Kathryn Robson, Boubacar Coulibaly, Yoann Seeleuthner, Benedetta Bigio, Zhi Li, Gilles Uzé, Sandra Pellegrini, Lazaro Lorenzo, Zineb Sbihi, Sylvain Latour, Marianne Besnard, Tiphaine Adam de Beaumais, Evelyne Jacqz-Aigrain, Vivien Béziat, Ranjan Deka, Litara Esera Tulifau, Satupa'itea Viali, Muagututi'a Sefuiva Reupena, Take Naseri, Peter McNaughton, Vanessa Sarkozy, Jane Peake, Annaliesse Blincoe, Sarah Primhak, Simon Stables, Kate Gibson, See-Tarn Woon, Kylie Marie Drake, Adrian V.S. Hill, Cheng-Yee Chan, Richard King, Rohan Ameratunga, Iotefa Teiti, Maite Aubry, Van-Mai Cao-Lormeau, Stuart G. Tangye, Shen-Ying Zhang, Emmanuelle Jouanguy, Paul Gray, Laurent Abel, Andrés Moreno-Estrada, Ryan L. Minster, Lluis Quintana-Murci, Andrew C. Wood, Jean-Laurent Casanova

+ Author and Article Information

J Exp Med (2022) 219 (6): e20220028. https://doi.org/10.1084/jem.20220028 Article history

Live, attenuated viral vaccines (MMR/yellow fever)
Flu/COVID

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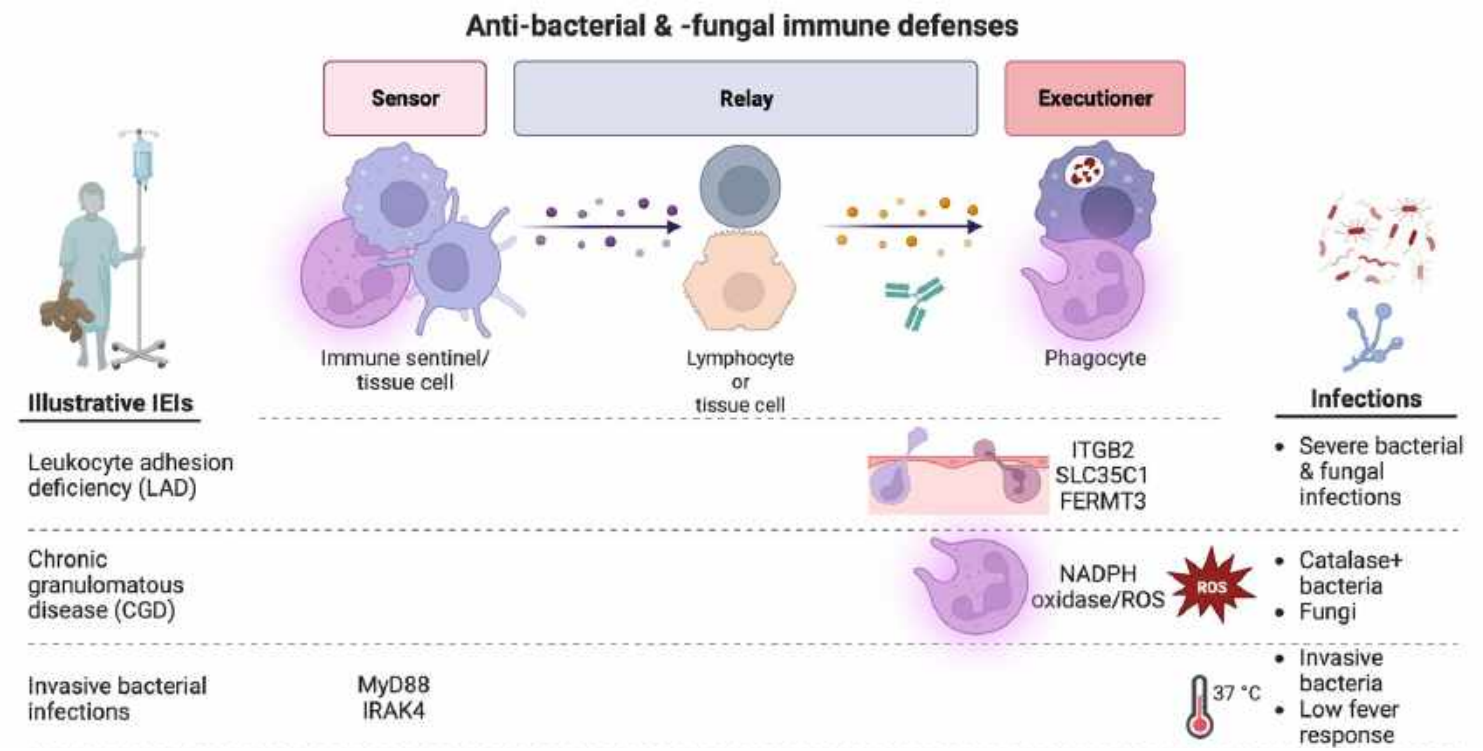
PID2: Phagocyte defects

- Phagocytes are critical for clearance of pathogens (bacterial/fungal)



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CGD: Chronic granulomatous disease

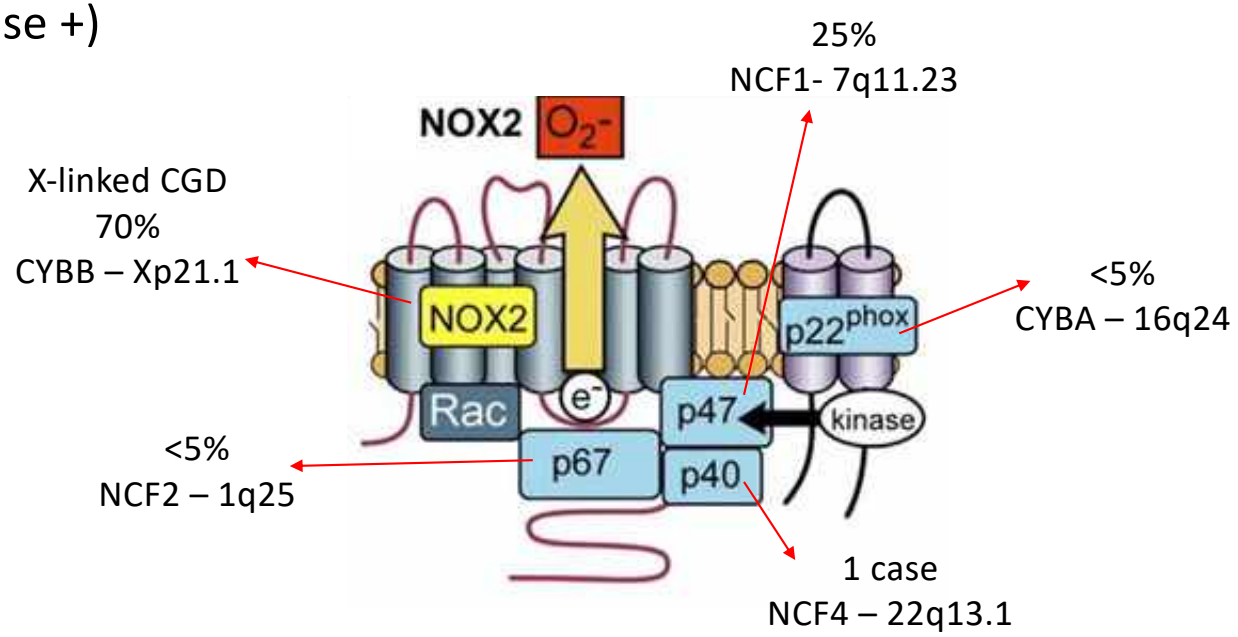
ROS production impaired because of defective NADPH oxidase (phagocyte oxidase = phox)

Severe, recurrent infections (catalase +)
- Barrier tissues (lung, skin, LN)
- Later liver, bone, spleen, etc.

High risk for IBD (Crohn's-like)

↓

PID and inflammation often go hand in hand.



O'Neill SO, et al. Redox Biology. 2015. 6:135.
Morry J, et al. Redox Biology. 2016; 11:240.

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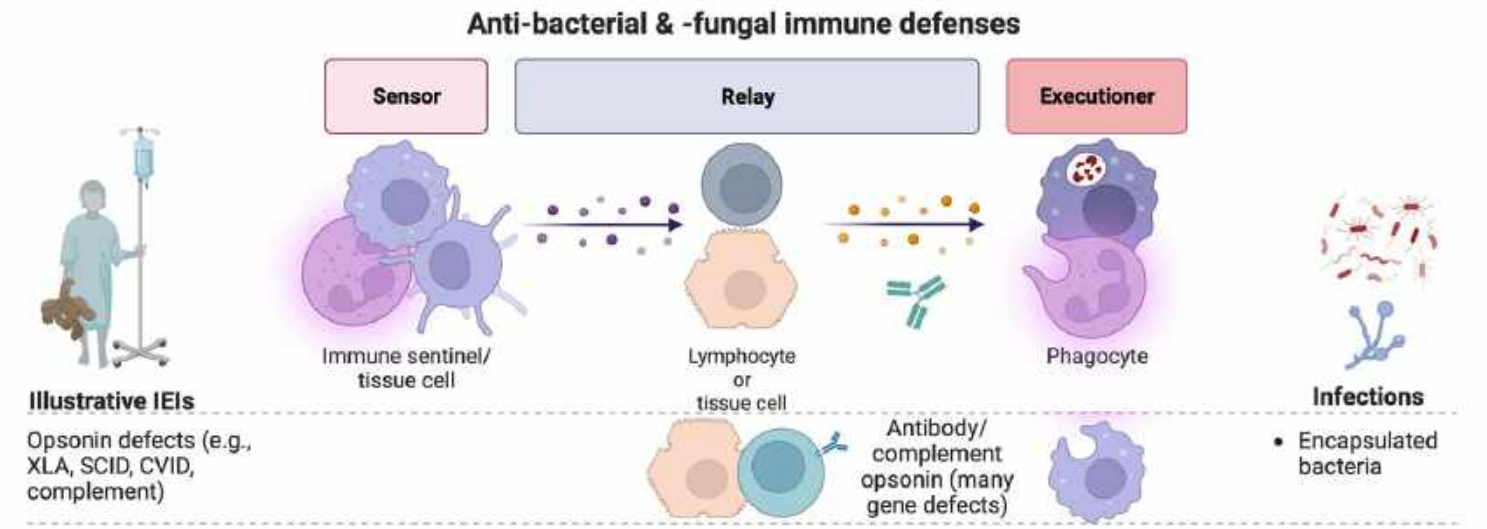
PID3: Isolated B cell/antibody defects

- Antibodies are critical for opsonization (bacterial/fungal)



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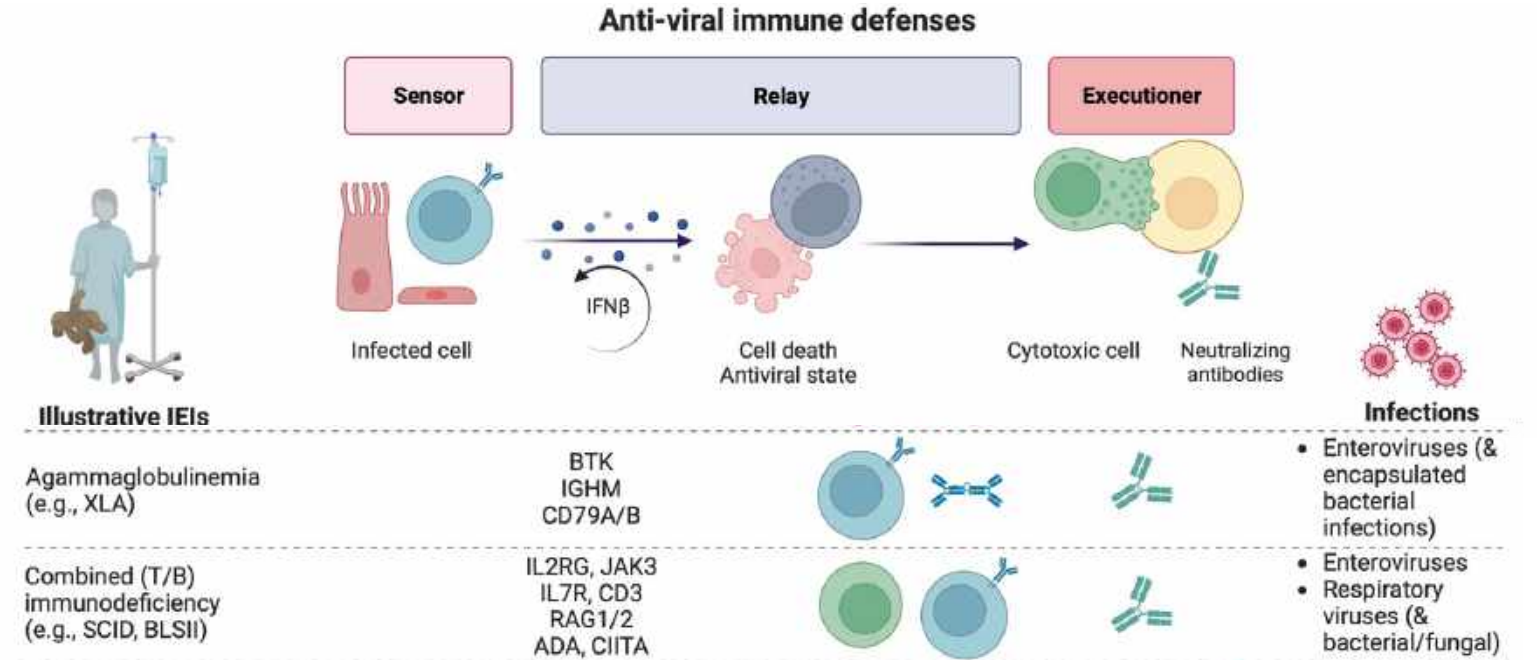
PID3: Isolated B cell/antibody defects

- Antibodies are critical for neutralization (viral)



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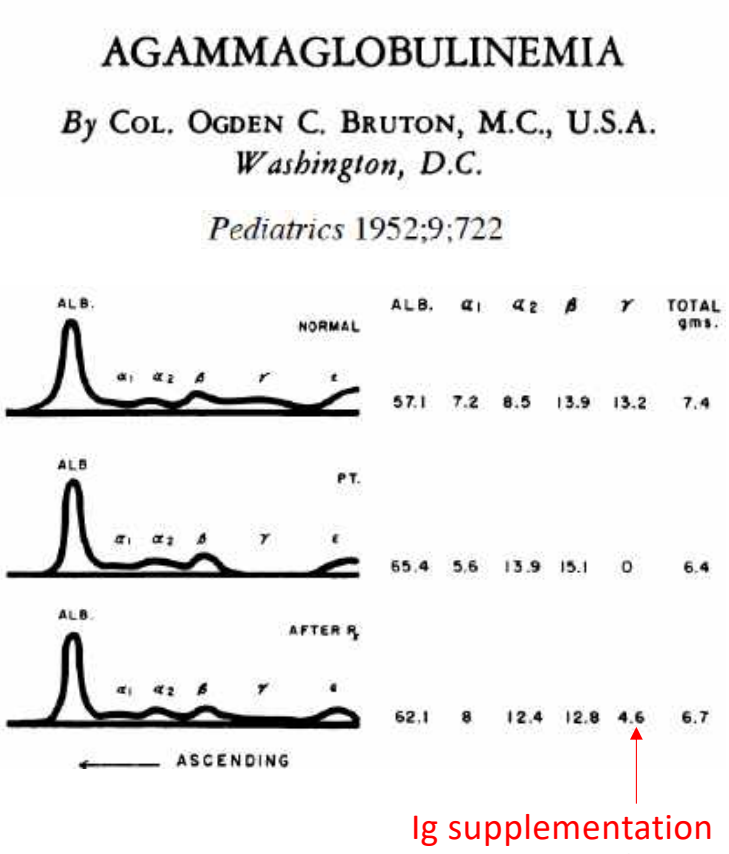
PID3: Bruton's tyrosine kinase deficiency: XLA

- X-linked agammaglobulinemia
- Profound lack of circulating B cells and Igs
  - Block at pre-B cell stage
- After maternal Ig wanes, recurrent infections with encapsulated organisms that need to be opsonized by Ab
  - Bacterial pharyngitis, sinusitis, otitis media, bronchitis, pneumonia
  - *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*
  - Enteroviral infections (e.g., coxsackievirus)
  - *Giardia lamblia* (parasite) infections
- Atrophic tonsils/adenoids


AGAMMAGLOBULINEMIA

By Col. Ogden C. Bruton, M.C., U.S.A.
Washington, D.C.

Pediatrics 1952;9;722

	ALB.	α_1	α_2	β	γ	TOTAL gms.
NORMAL	57.1	7.2	8.5	13.9	13.2	7.4
PT.	65.4	5.6	13.9	15.1	0	6.4
AFTER Rx	62.1	8	12.4	12.8	4.6	6.7

ASCENDING

Ig supplementation

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  4. **CD4 T cell defects: (i) B cell help, (ii) phagocyte help**
  5. CD8 T cell defects

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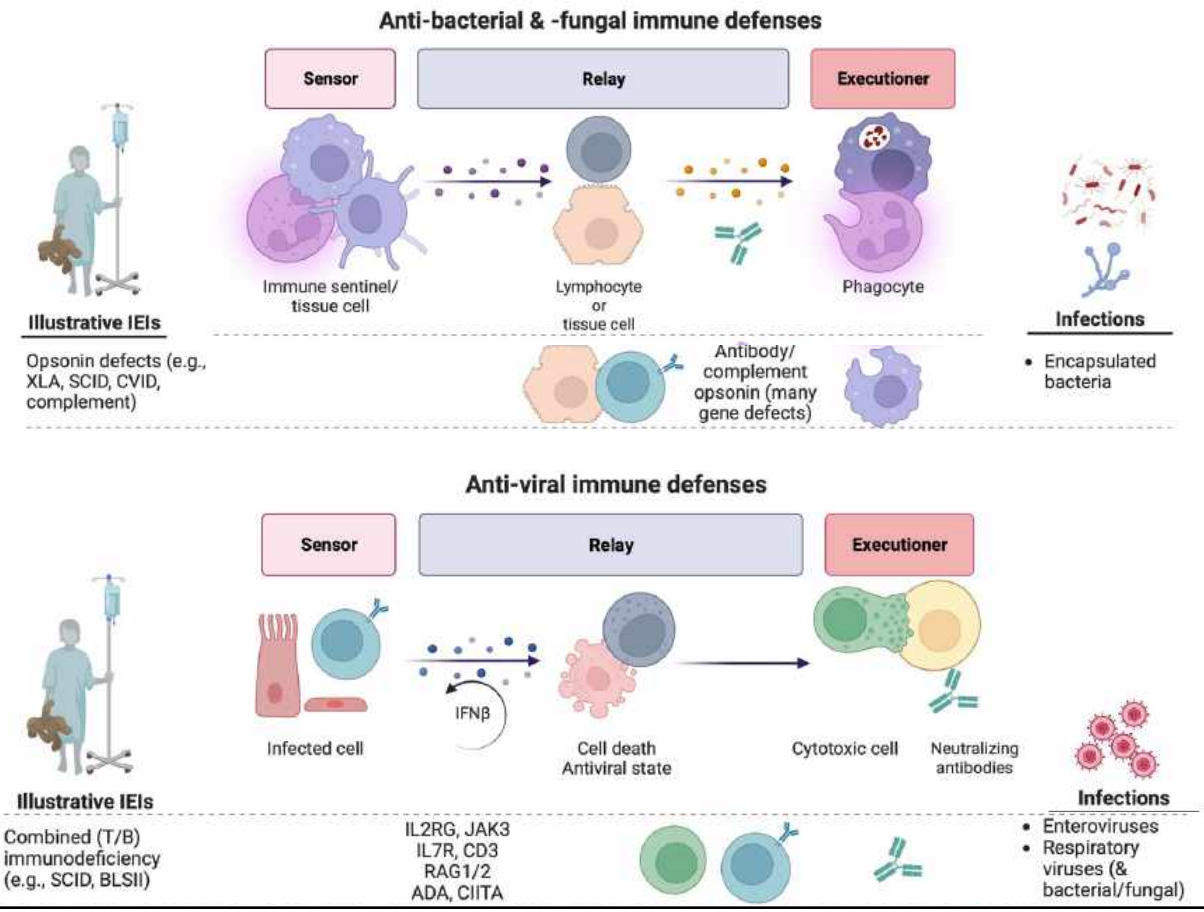
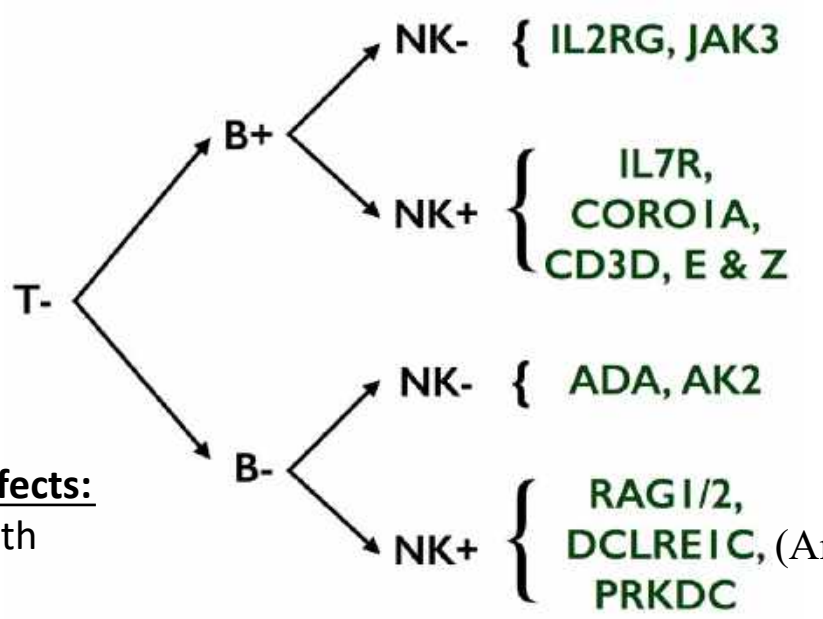
PID4(i): CD4 T cell defects can disrupt B cell help: 'combined immunodeficiencies'



PID4(i): Severe combined immunodeficiency (SCID)



Cell-mediated immunity defects:

Opportunistic infections with
- viruses
- fungi (candida, PJP)
- mycobacteria

Humoral defects:

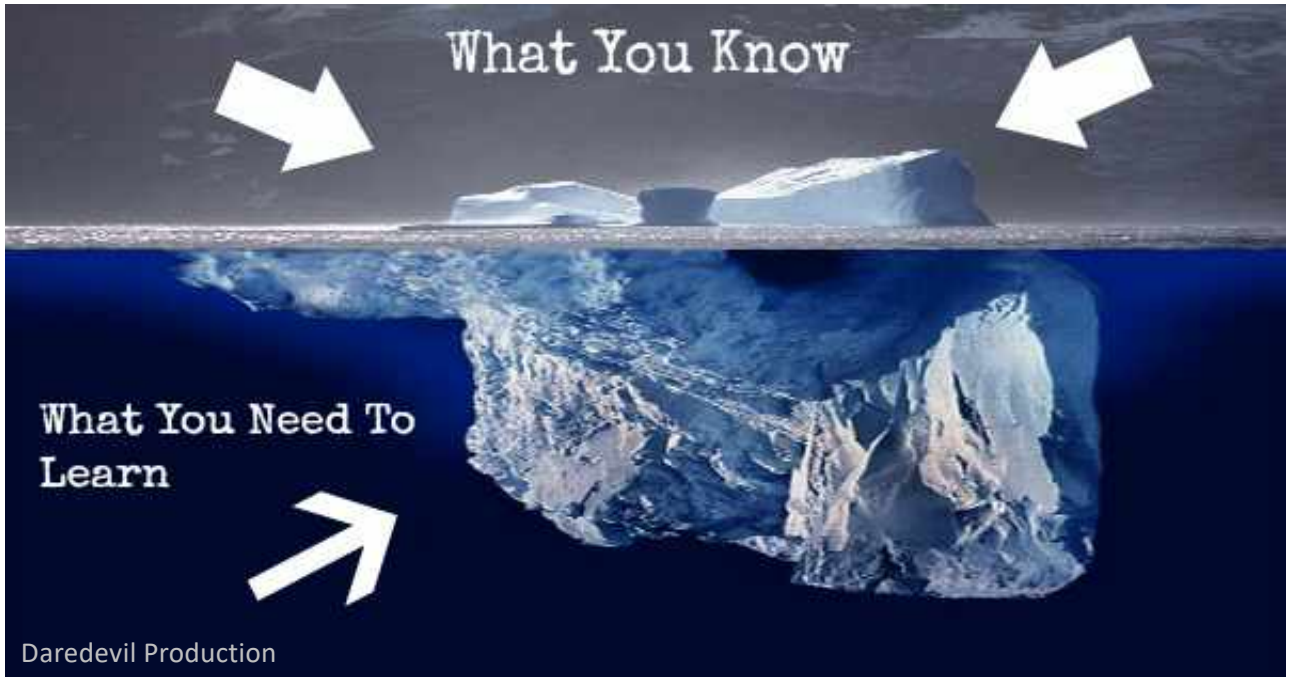
Sinopulmonary infections
- encapsulated bacteria (e.g., *Haemophilus influenzae*, pneumococci)

Daniel Wells.
Al-Herz, et al. Frontiers in Immunology. 2014. 5(62).

David Vetter: 1971-1984

Genetic basis solved (*IL2RG*) in 1993

Baylor College of Medicine

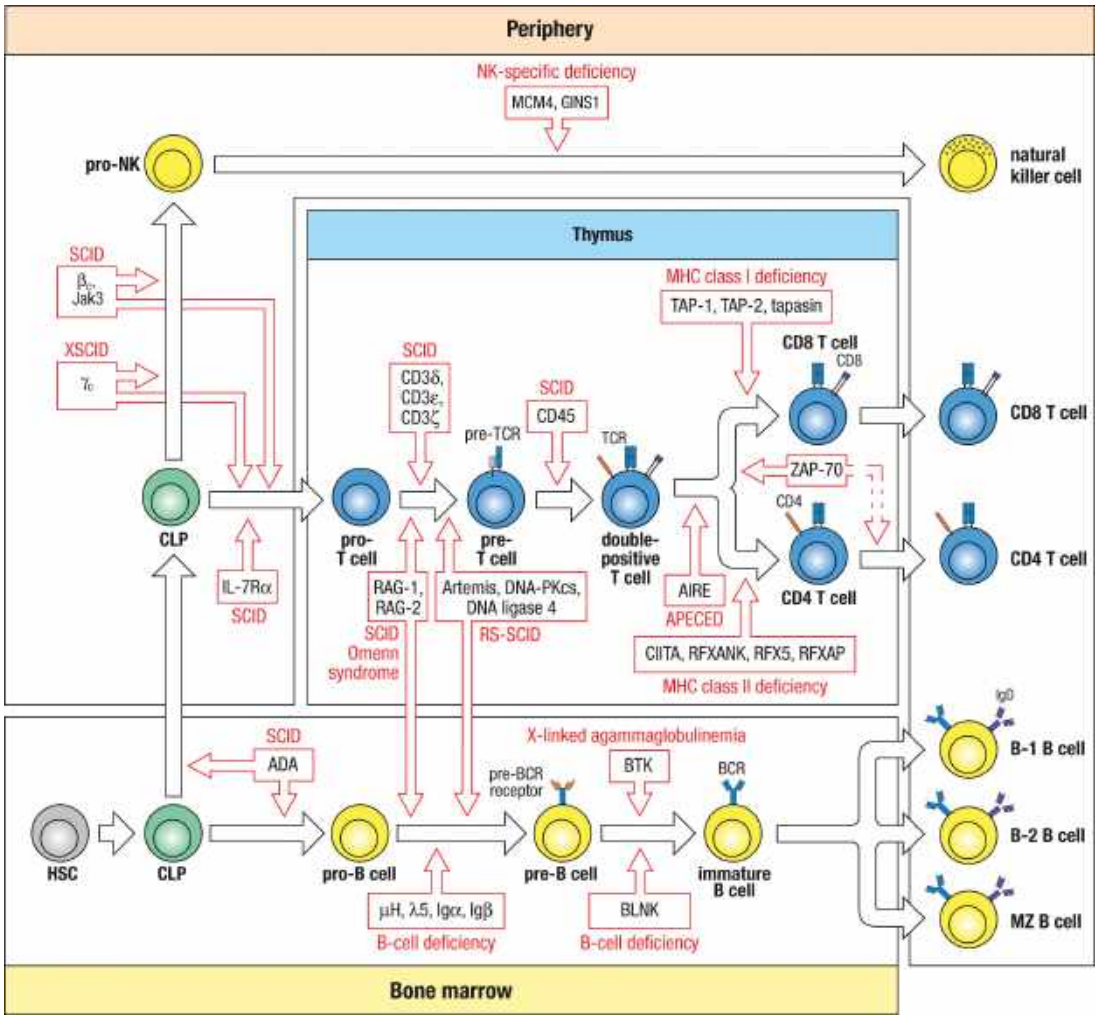


Question at the time: Why is IL-2Rγ required for T cell development and B cell activation?

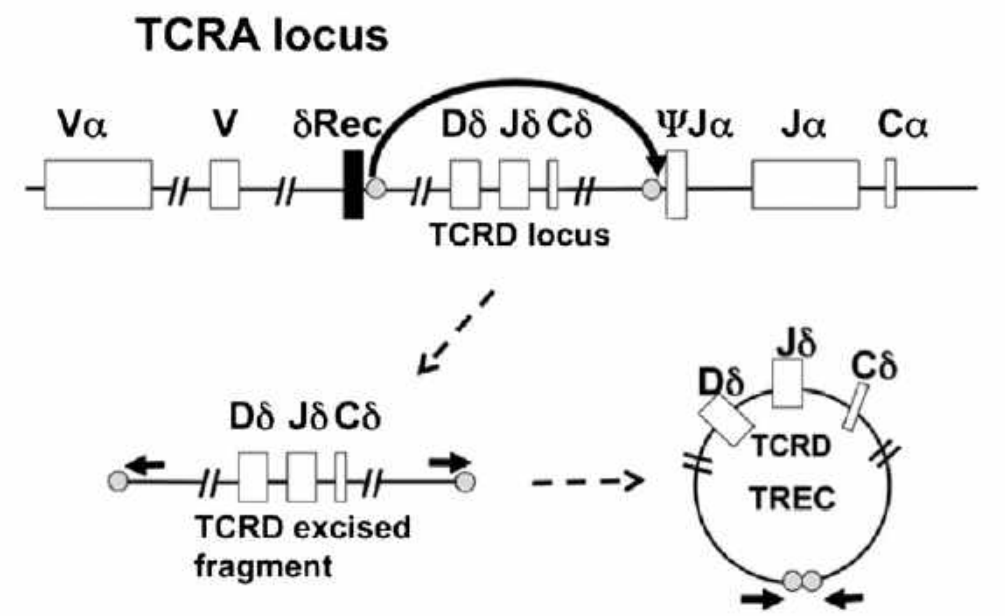
Loss of IL-2 (mouse in 1991) = T cells still present

…A common gamma chain shared by receptors for: IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21

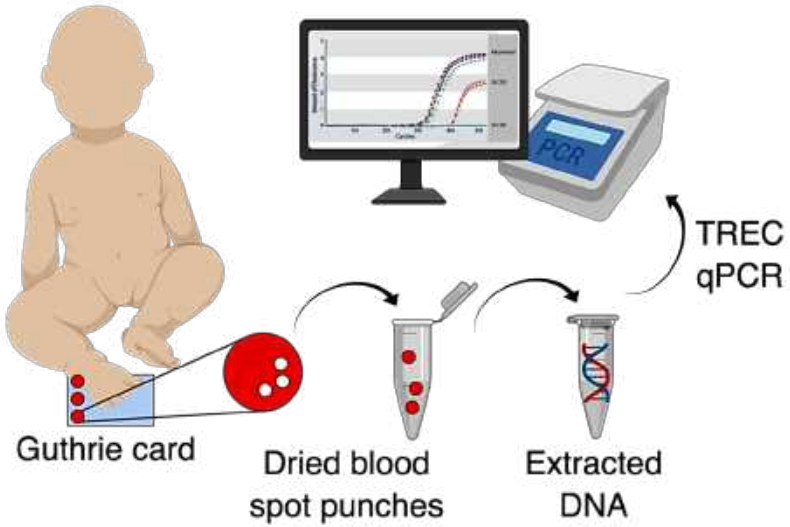
Defects in T-cell and B-cell **development** that cause immunodeficiency



T cell receptor excision circles to test for SCID



Newborn screening for TRECs

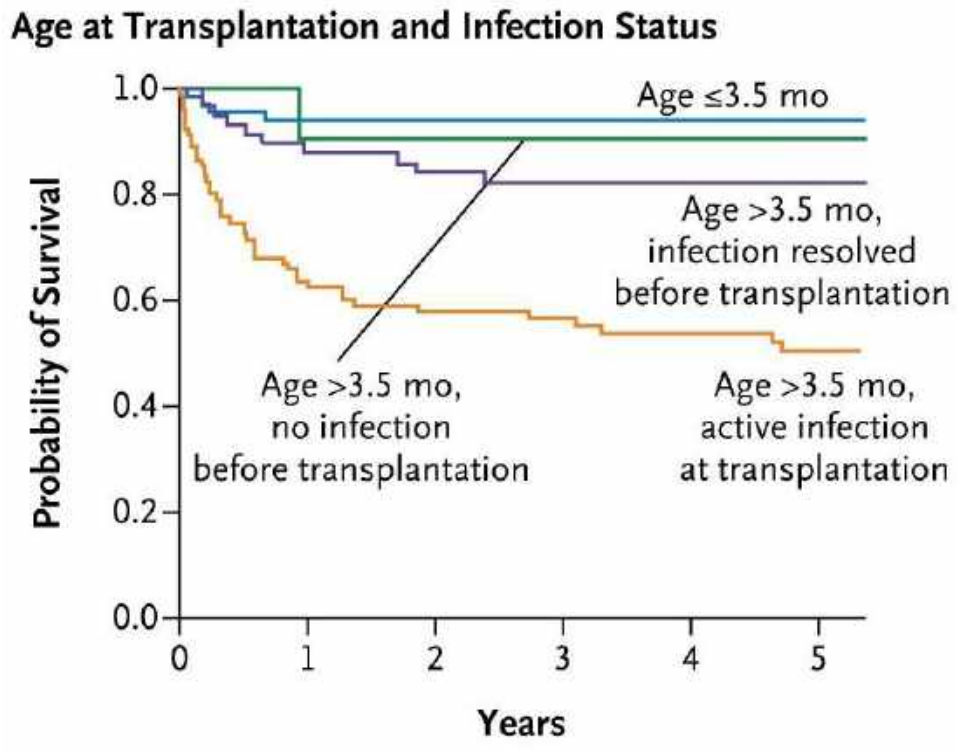


Dr. Puck

Dr. Buckley

Seminars in Perinatology. 39 (2015) 194-205.

Hematopoietic stem cell transplantation in SCID…age matters



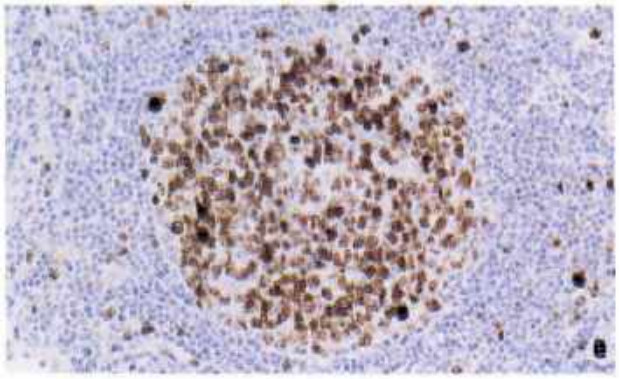
Pai SY. NEJM. 2014. 371(5):434-46.

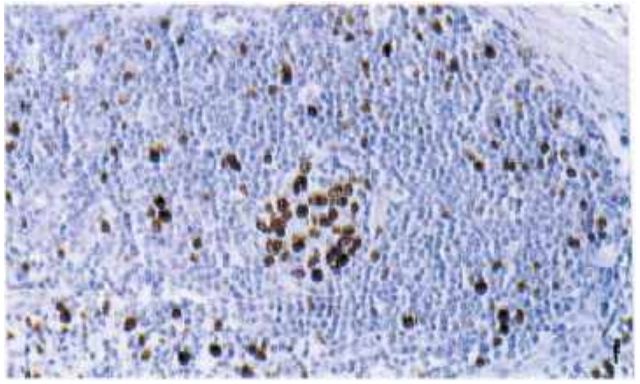
Hyper-IgM syndromes from germinal center defects

Healthy lymph node 2º follicle

Patient lymph node 2º follicle

Ki67 stain

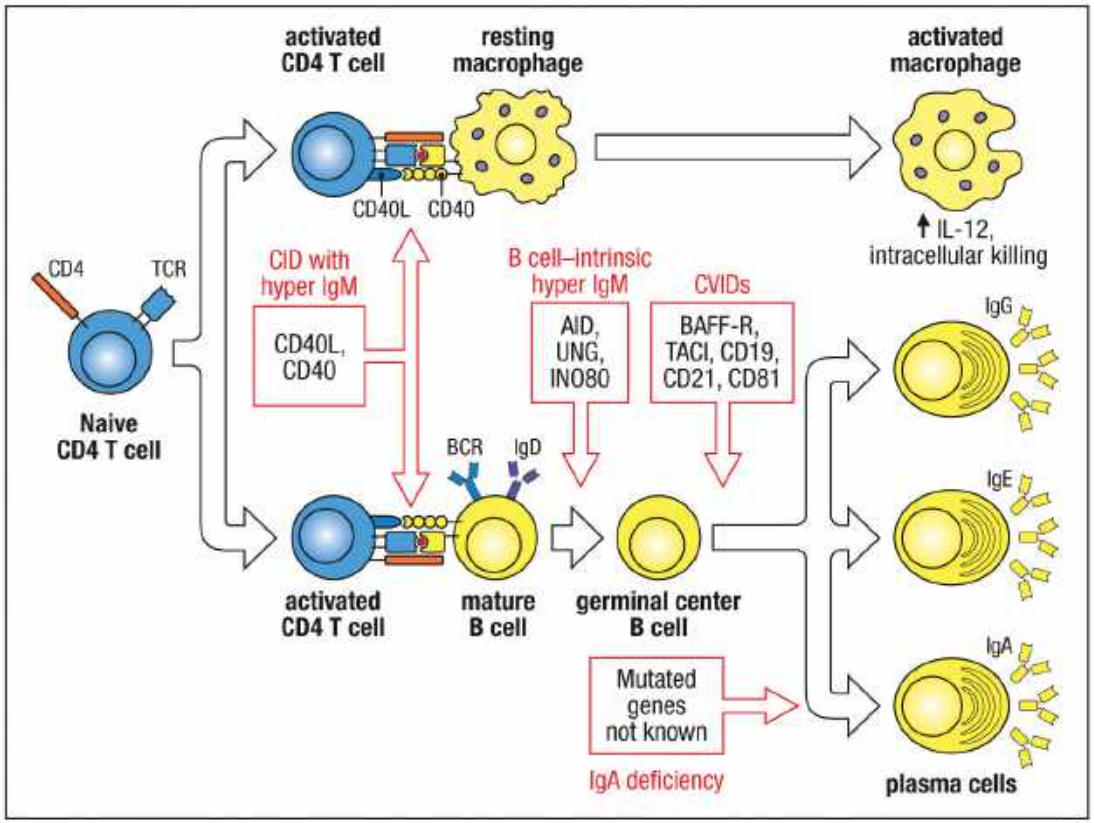




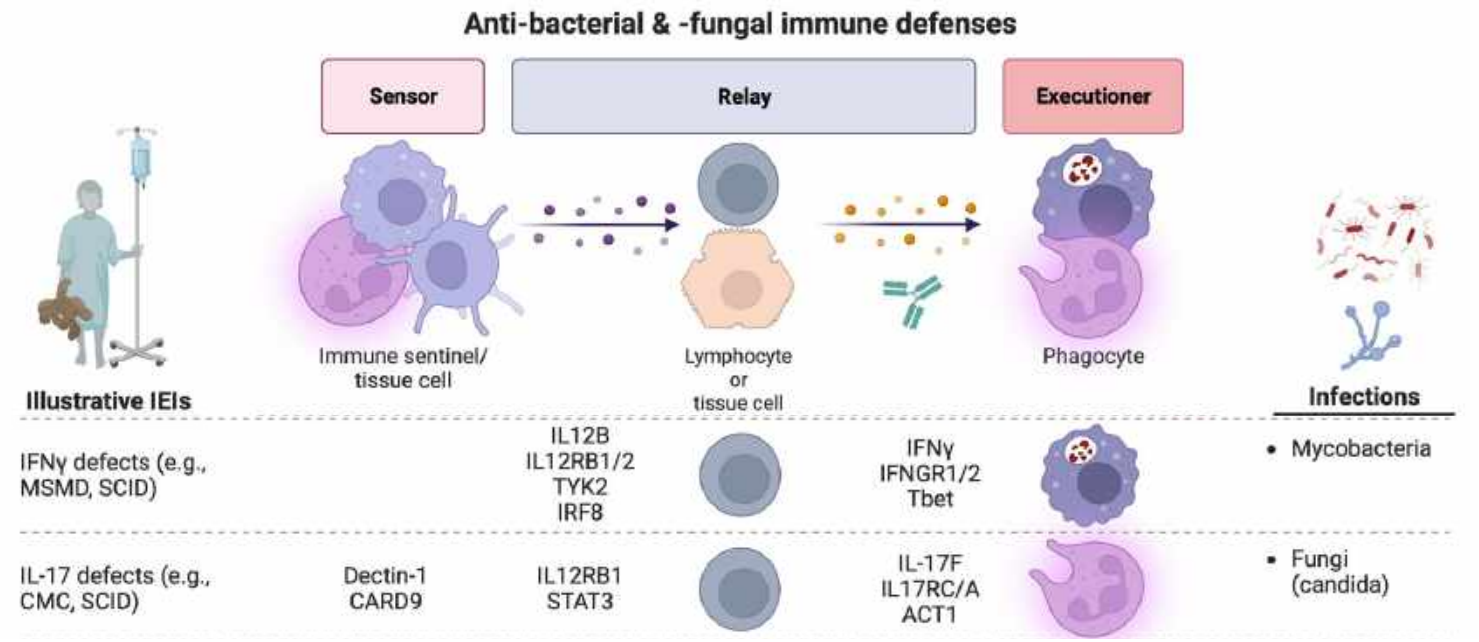
-B cells are present
-Low specific antibody against antigens that require T cell help
-Severely impaired class switching
= susceptible to infection with extracellular pathogens
-Gene defects:
CD40L, CD40, AID, UNG

The Journal of Immunology, 1995, 154: 6624–6633.

Defects in T-cell and B-cell **activation and differentiation** cause immunodeficiencies



PID4 (ii): Other CD4 T cell defects disrupt phagocyte help



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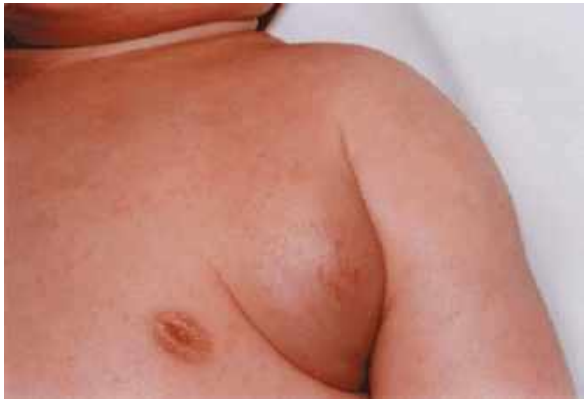
MSMD: Mendelian susceptibility to mycobacterial disease

-Includes pathogens causing tuberculosis (*Mycobacterium tuberculosis*) and leprosy (*Mycobacterium leprae*) and Buruli ulcer (*Mycobacterium ulcerans*)

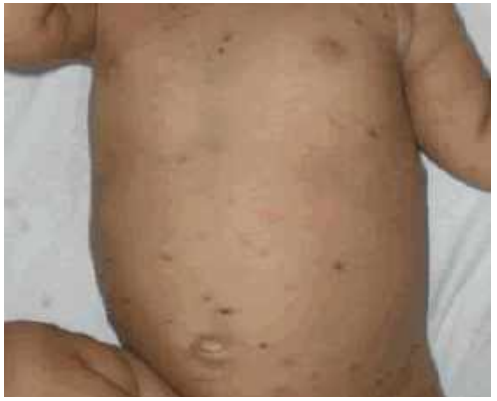
-BCG (bacilli Calmette-Guerin) vaccine made from *Mycobacterium bovis* (live, attenuated)

BCG lymphadenitis
(sometimes suppurative)



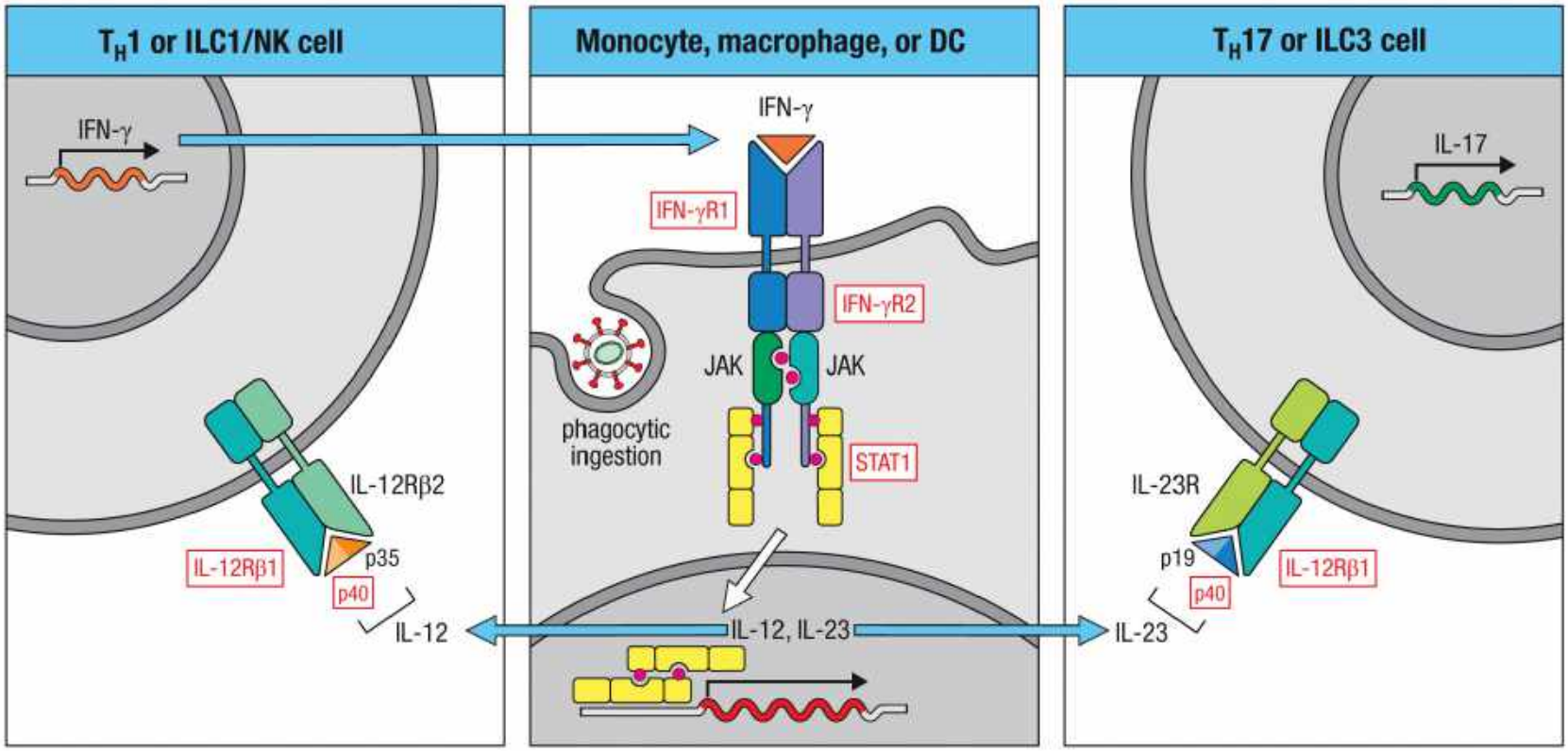
Ali S and Almoudaris M. Archives of Disease in Childhood. 2004; 89:812.

Disseminated BCG in PID patient
Papulo-nodular, erythematous rash

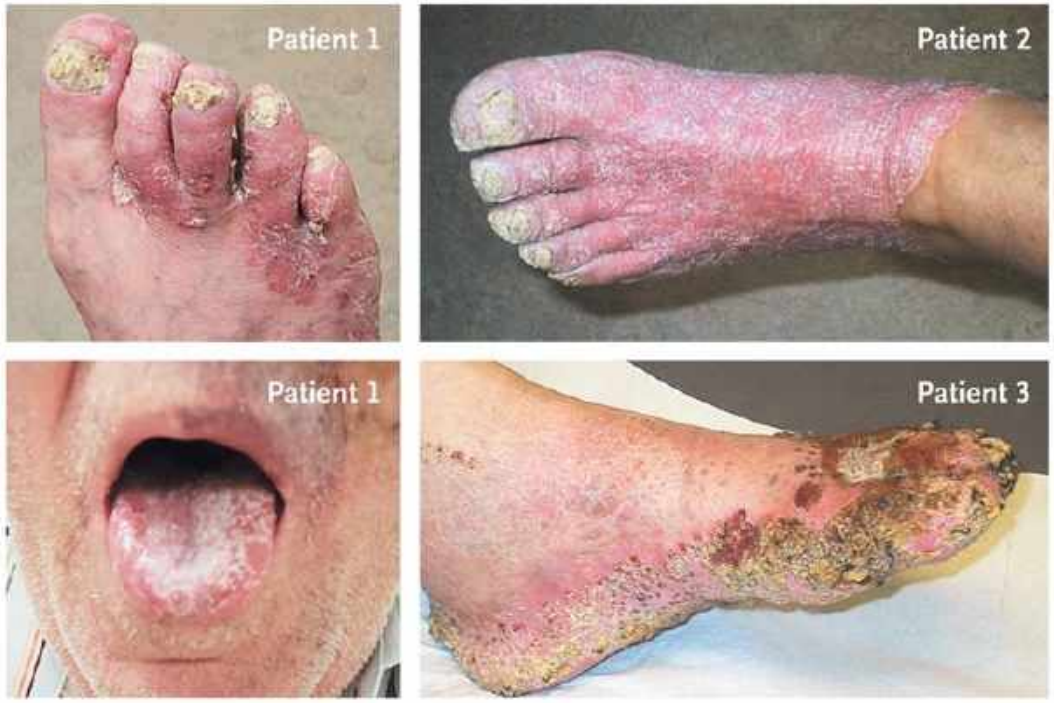


Mandal, et al. J Clin Infect Dis Pract. 2016; 1(2): 112.

MSMD (mycobacteria) and CMC (candida)



CMC: Chronic mucocutaneous candidiasis (defective anti-fungal immunity)

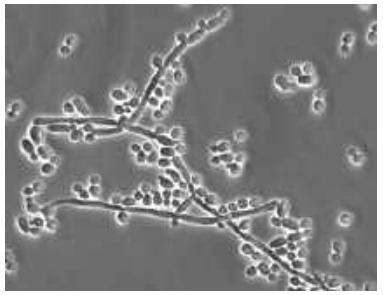


Van de Veerdonk FL, et a. NEJM. 2011. 365:54.

Genes:
Dectin-1, CARD9
Th17 biology (IL-17F, IL-17RA, IL-17RC, ACT1, STAT3, RORγt)

STAT1 hyperactivation

Cytokine autoantibodies



Candida albicans

Dominant-negative STAT3 mutations

JOB'S SYNDROME

Recurrent, "Cold", Staphylococcal Abscesses

STARKEY D. DAVIS
M.D. Baylor
ASSISTANT PROFESSOR

JANE SCHALLER
M.D. Harvard
INSTRUCTOR

RALPH J. WEDGWOOD
M.D. Harvard
PROFESSOR AND CHAIRMAN
DEPARTMENT OF PEDIATRICS,
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

THE LANCET MAY 7, 1966

-Boils
-Epithelial bacterial and fungal infections
-Recurrent shingles

-Also non-hematopoietic features: face, bone, heart, vessels, brain, lungs

EXTREME HYPERIMMUNOGLOBULINEMIA E AND UNDUE SUSCEPTIBILITY TO INFECTION

Rebecca H. Buckley, M.D., Betty B. Wray, M.D., *and* Elaine Z. Belmaker, M.D.

From the Departments of Pediatrics and Microbiology and Immunology, the Duke University School of Medicine, Durham, North Carolina, and the Department of Pediatrics, the Medical College of Georgia, Augusta, Georgia

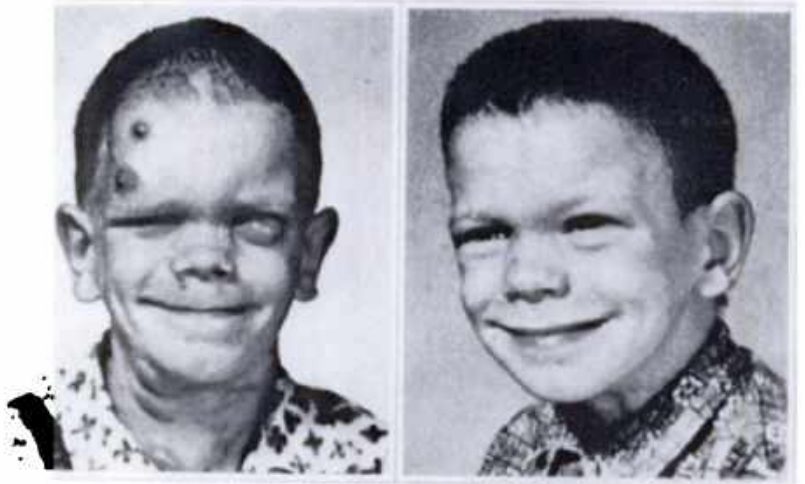


FIG. 1. Patient B.S. at 8 years of age, before and after initiation of oxacillin therapy. (Reproduced by permission of Bristol Laboratories).

PEDIATRICS, Vol. 49, No. 1, January 1972

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CD8 T cell defects

- CD8A
- MHCI: TAP1, TAP2, TAPBP
- (Perforin, etc. in PIRDs section)

- Recurrent respiratory bacterial infections starting in late childhood
- Chronic necrotizing granulomatous lesions, small-vessel vasculitis (NK/γδT cells)
- Notable lack of major viral infection burden

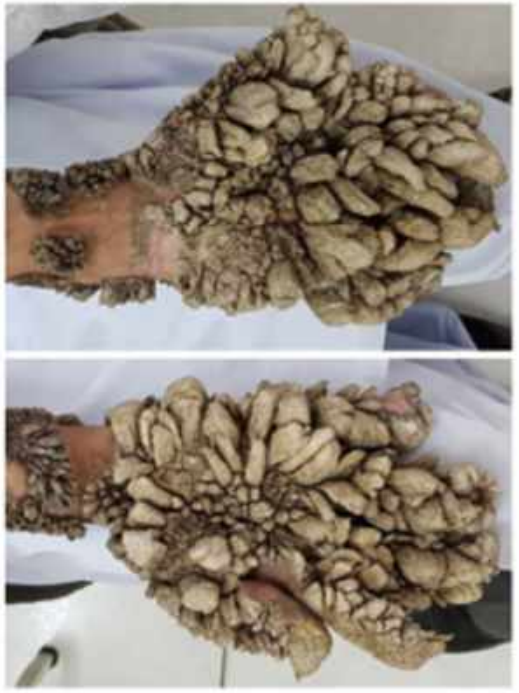
Another unexpected finding: CD28 deficiency

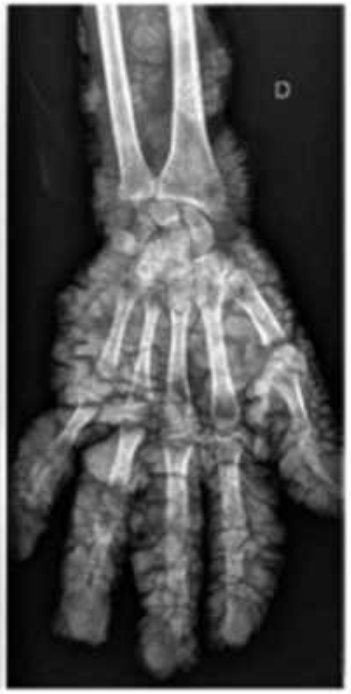
Cell

Article

Humans with inherited T cell CD28 deficiency are susceptible to skin papillomaviruses but are otherwise healthy

Béziat et al., 2021, Cell *184*, 3812–3828





Questions?

Review of PIDs

- What is widely considered the first solved PID that also pointed to a new B cell drug target?
- What new immunology insight was facilitated by the discovery of the gene causing X-SCID?
- List two genes that when mutated can cause hyper-IgM.
- How might a newborn be diagnosed early with SCID?
- Which cytokine axis is defective in patients with MSMD?
- Which cytokine axis is defective in patients with CMC?

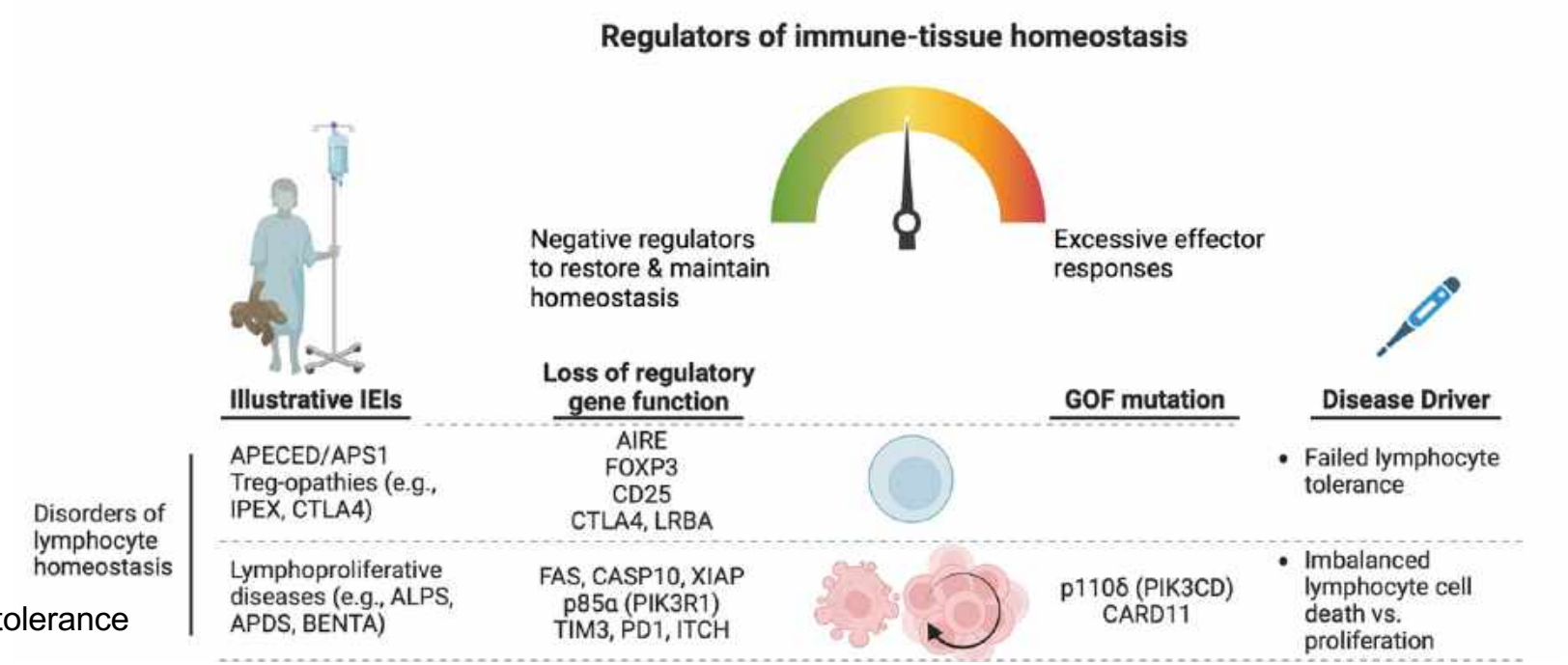
Outline

- PID: Primary immunodeficiency: An IEI that leads to infection susceptibility as the primary feature
  1. Intrinsic immunity defects
  2. Phagocyte defects
  3. Antibody defects
  4. CD4 T cell defects
  5. CD8 T cell defects

- PIRD: Primary immune regulatory disorder: An IEI that leads to aberrant immune responses that cause excessive tissue damage
  1. **Failed lymphocyte homeostasis**
  2. Cytokinopathies: inflammasome-opathies, type I interferonopathies, frustrated cytotoxicity
  3. Barrier defects

Disorders of lymphocyte homeostasis

Failed regulation
Failed apoptosis
Hyperproliferation
Failed peripheral tolerance



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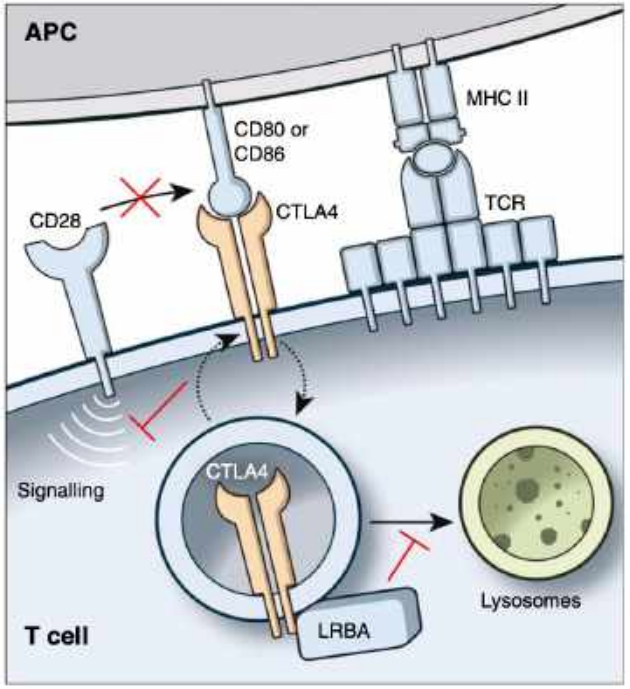
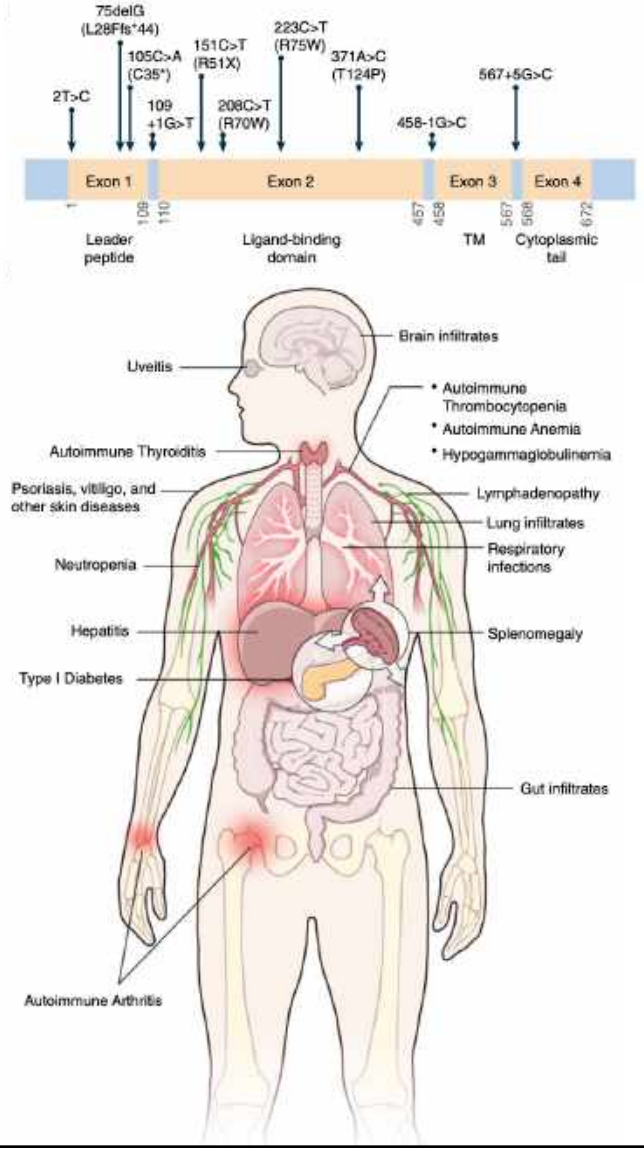
Treg-opathies: CTLA4

CHAI: "CTLA-4 haploinsufficiency with autoimmune infiltration"

Targeted therapy with CTLA4-Ig





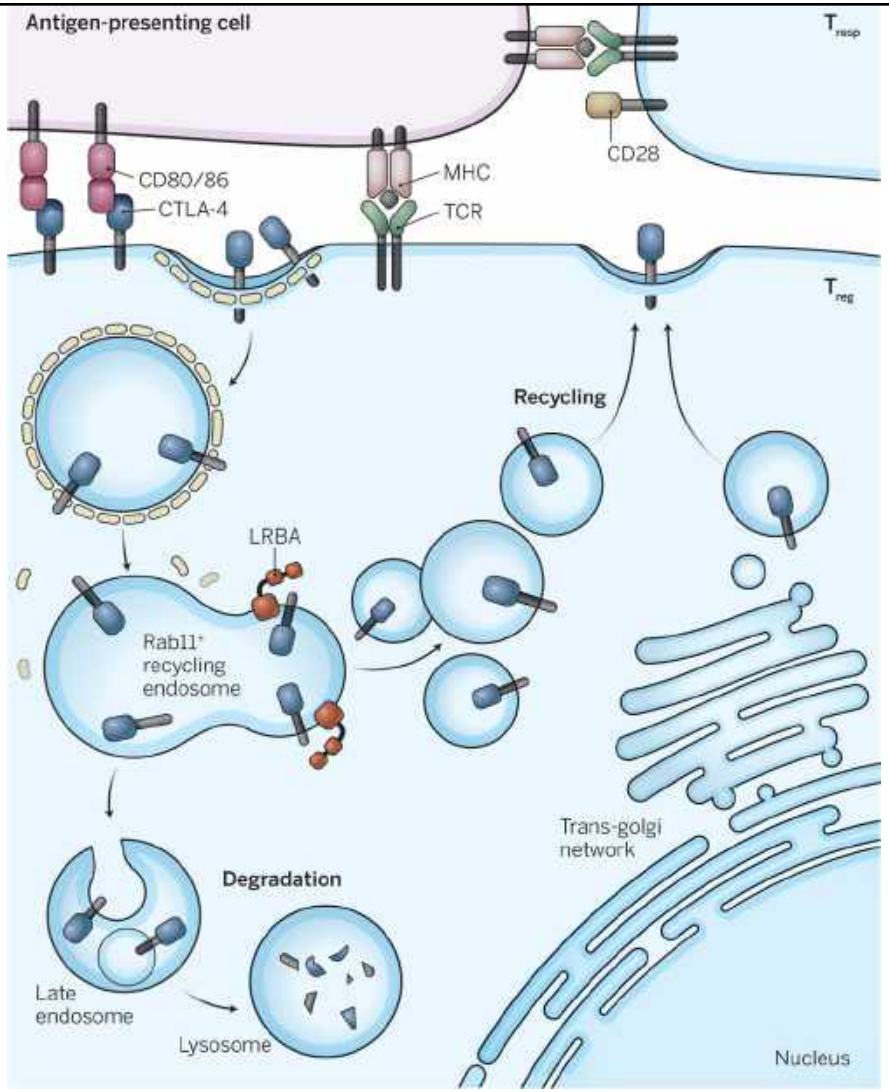
https://doi.org/10.1182/blood-2016-04-712612

Treg-opathies: LRBA

LATAIE: "LRBA deficiency with autoantibodies, regulatory T (Treg) cell defects, autoimmune infiltration, and enteropathy"

New cell biology of CTLA4 cycling

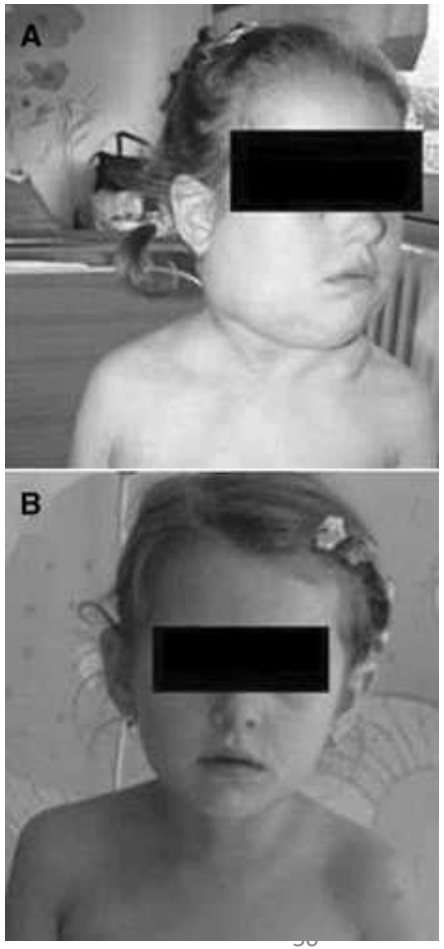
Targeted therapy with CTLA4-Ig



https://doi.org/10.1126/science.aac7888

Failed lymphocyte homeostasis from a variety of gene defects such as:

- Monogenic autoimmunity:
  - AIRE, PD-1, etc.
  - Treg-opathies: FOXP3, CD25, CTLA4, LRBA
- Autoimmune lymphoproliferative syndrome (ALPS) or ALPS-like diseases:
  - Failure of immune cell death after expansion
    - FAS, FASL, CASP10, etc.
  - Hyperproliferation:
    - PI3Kδ, CARD11, etc.
- Exciting developments in precision medicine:
  - CTLA4 haploinsufficiency and CTLA4-Ig
  - Activated PI3K-delta Syndrome (APDS) and PI3K-delta inhibitor



https://doi.org/10.1002/pbc.22151

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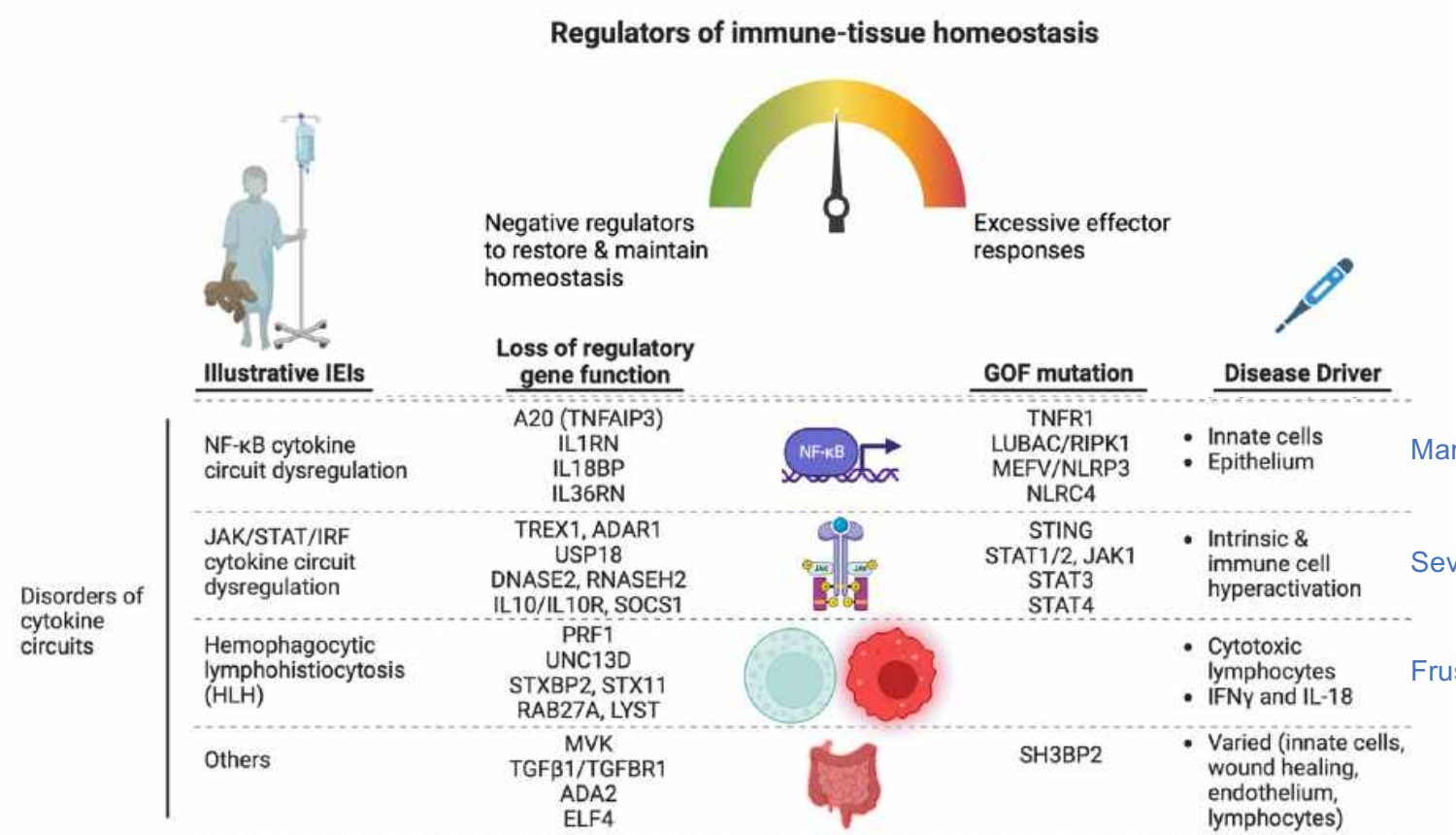
Dysregulation of cytokine circuits = cytokinopathy



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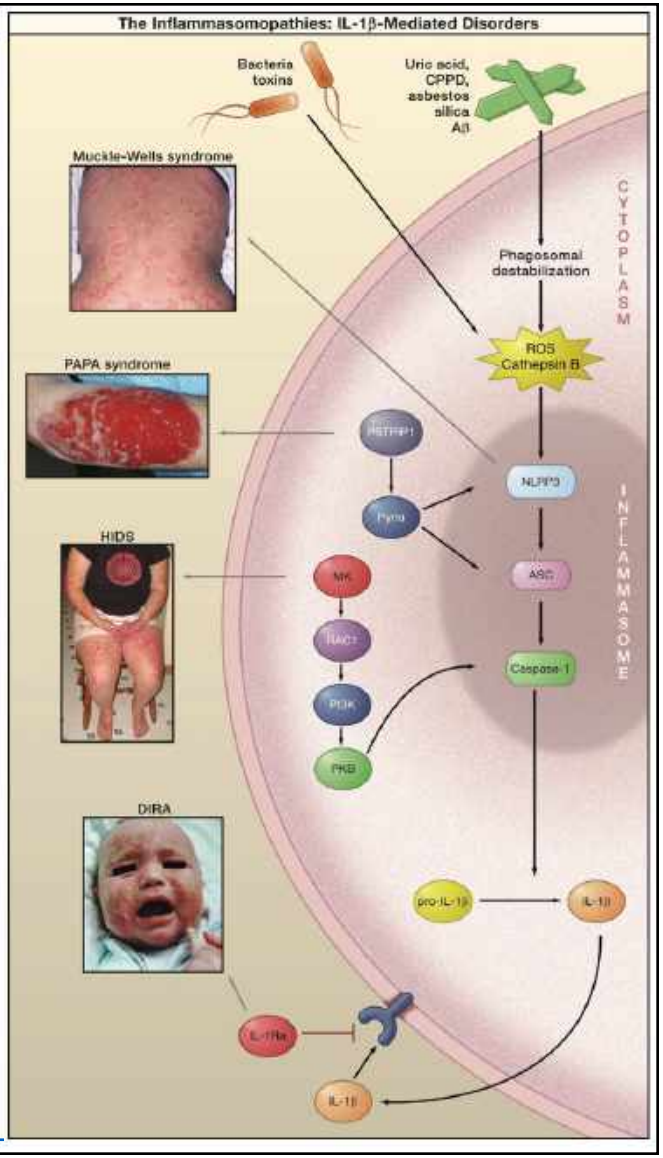
Inflammasome-opathy

Disease (common abbreviation)	Clinical features	Inheritance	Mutated gene	Protein (alternative name)
Familial Mediterranean fever (FMF)	Periodic fever, serositis (inflammation of the pleural and/or peritoneal cavity), arthritis, acute-phase response	Autosomal recessive	*MEFV*	Pyrin
TNF receptor–associated periodic syndrome (TRAPS) (also known as familial Hibernian fever)	Periodic fever, myalgia, rash, acute-phase response	Autosomal dominant	*TNFRSF1A*	TNF-α 55 kDa receptor (TNFR-I)
Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA)		Autosomal dominant	*PSTPIP1*	CD2-binding protein 1
Muckle–Wells syndrome	Periodic fever, urticarial rash, joint pains, conjunctivitis, progressive deafness	Autosomal dominant	*NLRP3*	Cryopyrin
Familial cold autoinflammatory syndrome 1 (FCAS1) (familial cold urticaria)	Cold-induced periodic fever, urticarial rash, joint pains, conjunctivitis			
Chronic infantile neurologic cutaneous and articular syndrome (CINCA)	Neonatal-onset recurrent fever, urticarial rash, chronic arthropathy, facial dysmorphia, neurologic involvement			
Hyper IgD syndrome (HIDS)	Periodic fever, elevated IgD levels, lymphadenopathy	Autosomal recessive	*MVK*	Mevalonate synthase



https://doi.org/10.1016/j.cell.2010.03.002

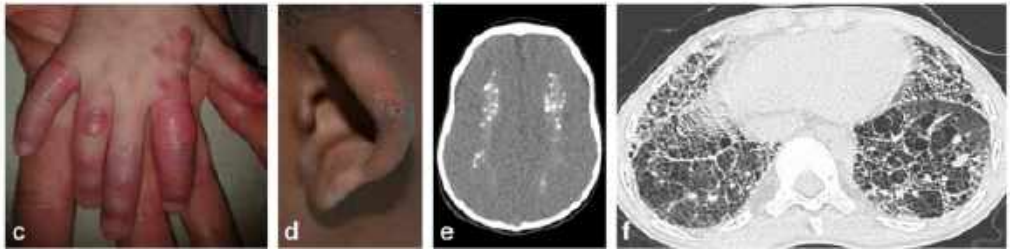
Type I interferon-opathy

Autoinflammatory disease from overproduction or hyper-responsiveness to type I interferons.

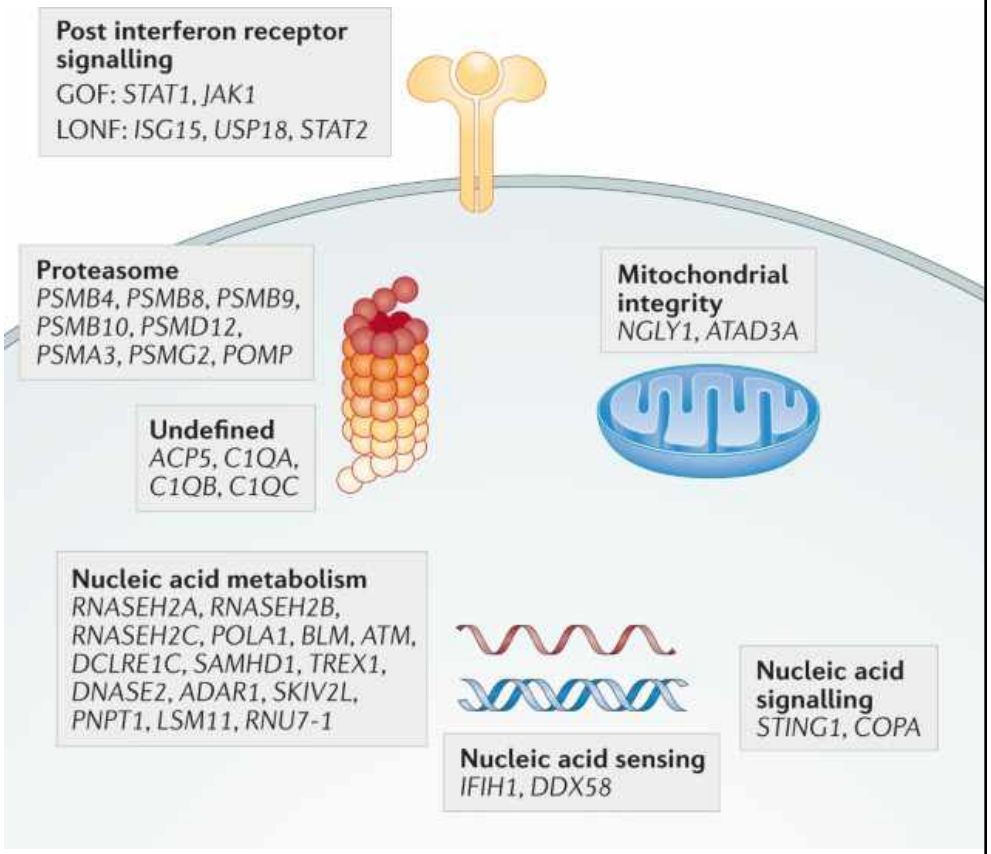
Chilblain lesions (toes, fingers, ears, nose)

Brain CT: intracranial calcifications

Chest CT: interstitial lung disease



https://doi.org/10.1007/s11926-020-00909-4



The type I interferonopathies: 10 years on

Yanick J. Crow & Daniel B. Stetson

Nature Reviews Immunology **22**, 471–483 (2022) | Cite this article

HLH: Hemophagocytic lymphohistiocytosis

***Table 3:* Diagnostic criteria for HLH.**

Familial disease or known genetic defect consistent with HLH OR Clinical, laboratory and histopathologic criteria (5 of the following 8)	
Clinical criteria:	• Fever • splenomegaly
Laboratory criteria:	• Cytopenia: affecting 2 of 3 lineages in the peripheral blood • Hb <90g/L • Platelets $<100 \times 10^9$/L • Absolute neutrophil counts $<1 \times 10^9$/L • Hypertriglyceridemia and/or (fasting triglyceride level ≥3 SD) or hypofibrinogenemia (≤3 SD of normal for age) • Hyperferritinemia (>500 μg/L)* • Increased CD 25 level (≥2400 U/L) • Low or absent NK function
Histopathological criteria	Hemophagocytosis in marrow, spleen, or lymph nodes with no evidence of malignancy

*A higer ferritin levels >3000 μg/L is considered highly indicative of HLH.

https://doi.org/10.14785/lymphosign-2017-0010

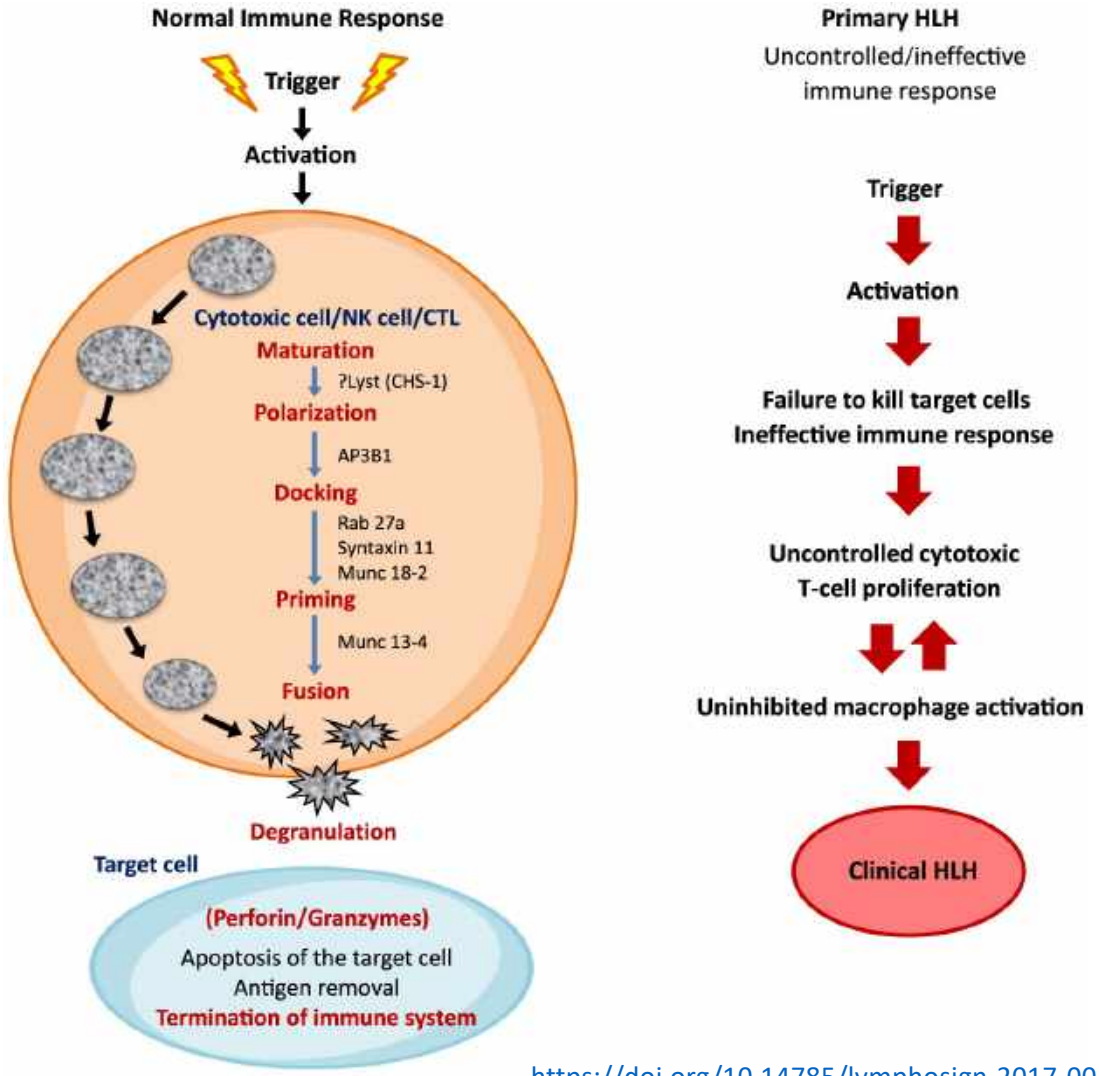
HLH

HLH genes:

- PRF-1
- Munc13-4/UNC13D
- STX11
- Munc18/STXBP2

HLH-like genes:

- RAB27A (Griscelli syndrome type 2)
- LYST (Chediak-Higashi syndrome)
- SAP/SHD2D1A (XLP1)
- XIAP/BIRC4 (XLP2)
- ITK



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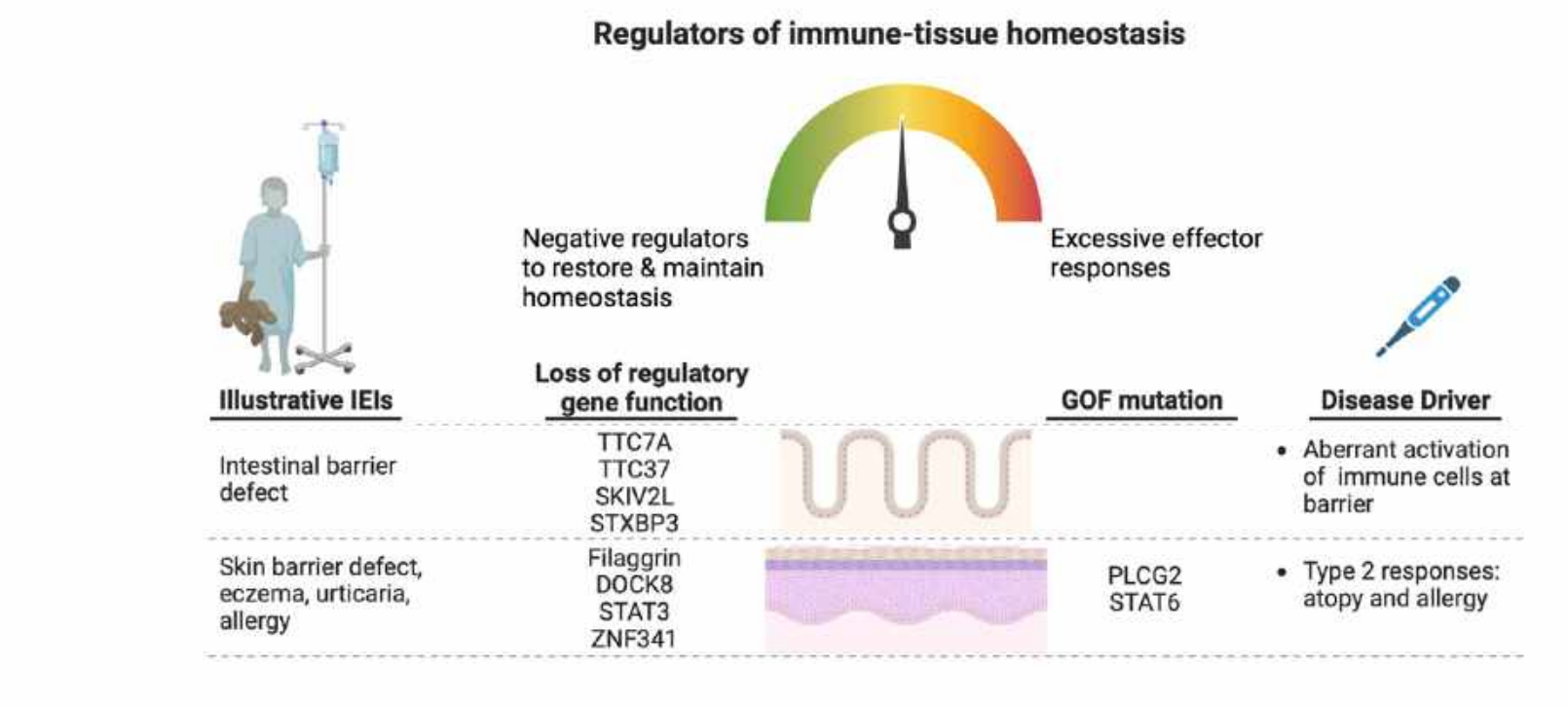
Barrier defects disrupt epithelial-microbiota-immune cell homeostasis



VEO-IBD: Very early onset inflammatory bowel disease

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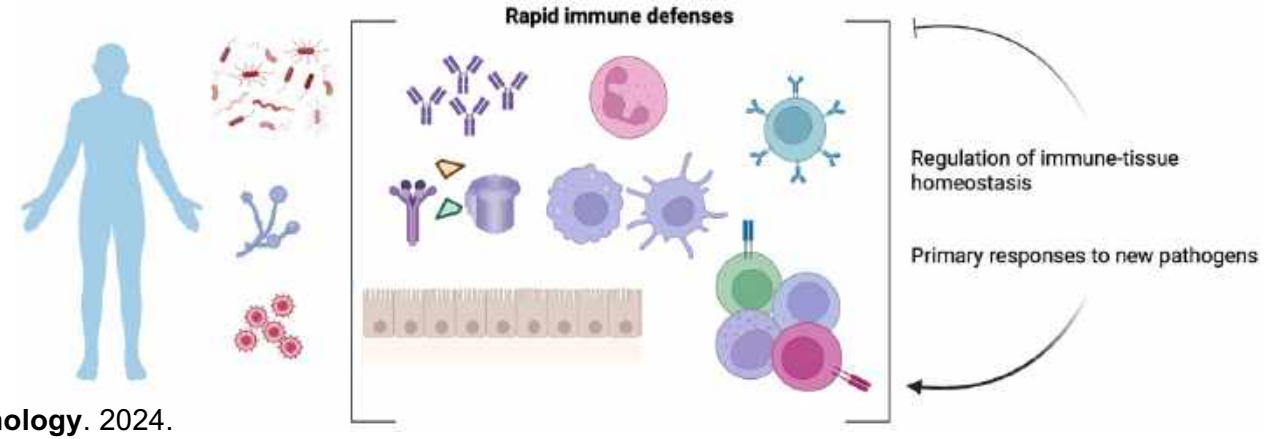
Recap: PIRDs

- Define ‘primary immune regulatory disorder’ (PIRD).
- Disorders of lymphocyte homeostasis:
  - Name a gene defect that disrupts Treg function.
  - Name a gene defect that disrupts lymphocyte apoptosis.
  - Name a gene defect that disrupts peripheral T cell tolerance.
- Dysregulation of cytokine circuits:
  - Describe two categories of cytokines that, when aberrantly elevated, cause autoinflammation.
  - What biological process is disrupted in HLH?

Closing: Human immunology *in natura*: essential immune defenses and regulation

Defense	Key function	
IgG	Opsonize/neutralize	****Prior exposures affect future immune outcomes****
Complement	Opsonize/lyse	
Epithelium	Barrier/intrinsic immunity	
Neutrophil	Phagocytose/degranulate	
Macrophage/DC	Phagocytose/present antigen	
Memory B cell → plasmablast	Rapid boost in Ig stored as memory	
Memory T cell, γδT, MAIT, NKT, (ILC)	Rapid cytokine production to instruct phagocytes	



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Conclusions

- Resources for more on monogenic disorders of the immune system:
  - IUIS papers:
    https://pubmed.ncbi.nlm.nih.gov/35748970/
    https://pubmed.ncbi.nlm.nih.gov/36198931/
  - https://www.omim.org – searchable human genetics database
- Human genomics databases are critical to assess frequency of variants in the general population: https://gnomad.broadinstitute.org
- Basic science through human studies – inherently translational
  - Ideal treatments may often be hard to predict
- Requires changing our thinking
  - Rare doesn't mean unimportant

Questions?