

Primary Immune Deficiencies: Experiments of Nature That Serve as Great Teachers

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“Analysis of each of the immune system diseases in its own way represents the molecular interpretation of an informative experiment of nature. In aggregate, these analyses help us understand more deeply how man can exist free of infection while living in a veritable sea of Microorganisms the greatest teachers of modern immunology: patients with immunodeficiency diseases.”

Robert A. Good, M.D., Ph.D., D.Sc. 1998

Discussion

- Clinical findings and immunologic lessons associated with antibody and combined immunodeficiencies
- Four cases demonstrating the clinical findings that define recently described immunodeficiencies

X-Linked Agammaglobulinemia (XLA)

- Originally described by Col Bruton in 1953
- 85% of patients with agammaglobulinemia
- Typically develop recurrent sinopulmonary pyogenic infections in infancy after maternal IgG is exhausted



X-Linked Agammaglobulinemia (XLA)

- Significant incidence of mycoplasma or ureaplasma arthritis
- Susceptibility to enteroviral meningoencephalitis (vaccine strain poliomyelitis)
- Approximately 50% have positive family history
- IgG usually <100 mg/dL
- B cells < 2% of lymphocytes (usually 0.05-0.3%)
- Normal T cell number and function
- Caused by mutations in the gene encoding the Bruton Tyrosine Kinase (BTK) protein blocks B cell development
- Therapy: replacement with IVIg or subcut Ig

Other Forms of Antibody Deficiency

- Autosomal recessive agammaglobulinemia: far less frequent than XLA
- Common variable immune deficiency (CVI): the most common symptomatic antibody deficiency that is probably multiple different diseases, adult presentation most common
- Subclass and specific antibody deficiency: relatively uncommon and controversial
- IgA deficiency: most common of all antibody deficiencies but majority of these patients do not have recurrent infections

Severe Combined Immune Deficiency (SCID)

- Failure to thrive, diarrhea
- Recurrent opportunistic infections early in life
- Absent T cell function is a uniform finding
- Typically lymphocytopenia is present (<3000 cells/mm³)
- The presence of B and/or NK cells is defined by the specific gene defect



Defects Resulting in SCID

- More than 12 different gene defects have now been identified to result in SCID
- Clues as to the genetic basis are derived by presence or absence: B cells & NK cells
- If the diagnosis of SCID is considered: the patient must not receive non-irradiated blood products or live viral vaccines
- Stem cell transplantation is curative and earlier treatment results in better outcome

Genetics is More Complicated

Patient 1



- Diarrhea and FTT
- Erythroderma and lymphadenopathy
- Increased IgE and eosinophilia
- Oligoclonal T cells with absent (or very low) B cells
- Profound immune defect

Patient 2



- Complications associated with viral infections
- Granulomas of the skin, mucus membranes and internal organs
- Hypogammaglobulinemia
- Low numbers of B and T cells

Mutation in the Same Gene with Varied Clinical Phenotype

- The two previous patients (#1 & #2) both have mutations in a gene originally defined as a cause of T-/B-/NK+ SCID (gene is required for antigen receptor production)
- These two patients have what is referred to as “hypomorphic” mutations resulting in in Omenn’s Syndrome (Patient #1) and a newly described immune disorder (Patient #2 – NEJM 358:2030, 2008)

Case Studies

Patient 3

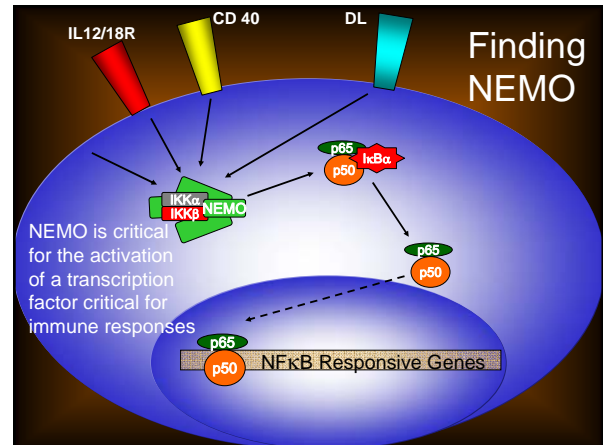
- 6 yo: recurrent *H. influenzae* bacteremia
- 14 yo: disseminated *M. avium* complex infection involving the abdominal lymph nodes and the blood stream
- Family history: 5 yo brother developed disseminated *M. avium* complex infection



Patient Has Findings of Ectodermal Dysplasia and More

- Anhidrotic Ectodermal Dysplasia (ED): absent or reduced sweat glands, abnormal hair patterns, conical or peg teeth
- Primary disorder due to defects in the genes that encode ectodysplasin (EDA, X-linked recessive) or its receptor dysplasin (DL/EDAR, autosomal dominant)
- Patient #3 has clinical ED but also has a history of recurrent infections and this is not seen with defects in EDA or DL

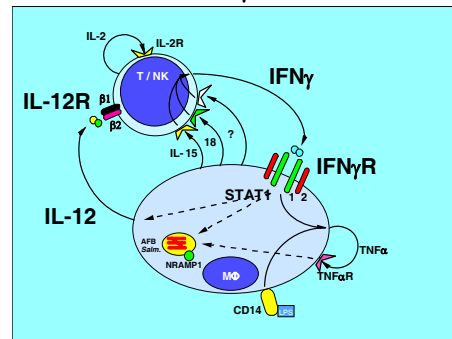
Patient 3 is Part of a Group of Patients that Helped Find “NEMO”



NEMO Deficiency

- Disorder related to hypomorphic NEMO mutation
- Some patients have gram positive and gram negative bacterial infections
- Some patients have recurrent mycobacterial infections: particularly NTB
- Other patients have opportunistic infections: CMV, pneumocystis
- Not all NEMO patients have ectodermal dysplasia
- In a male with a history of recurrent serious infection (with T cells): think NEMO even in the absence of ectodermal dysplasia

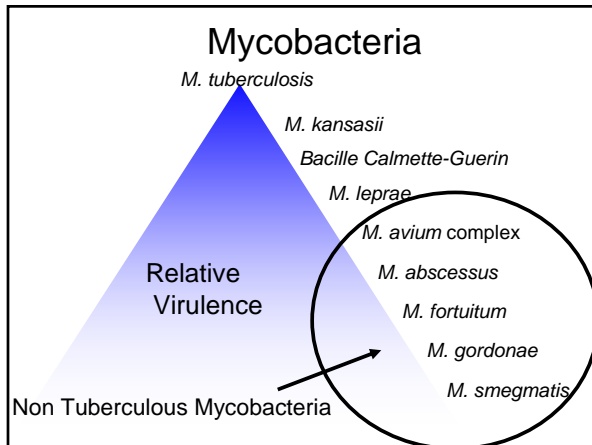
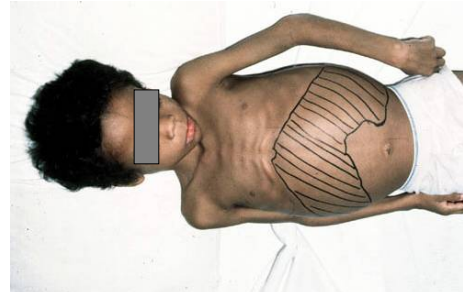
Response to Mycobacteria Involves the IFN γ /IL-12 Pathway



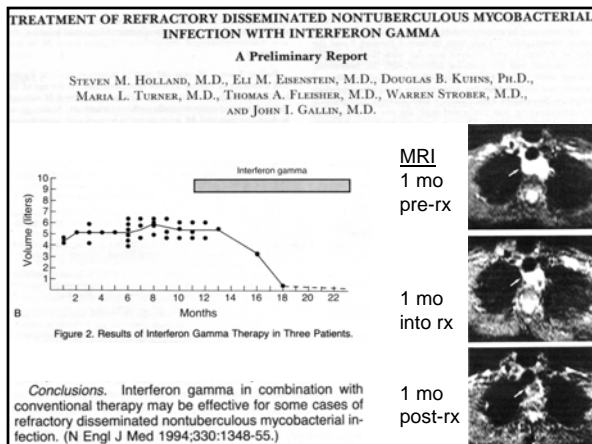
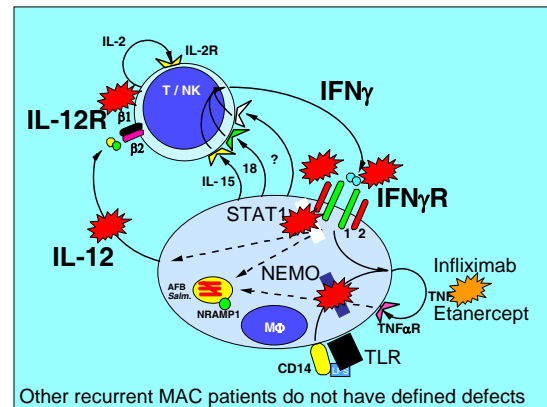
Patient 4

- 34 mo: cough and pulmonary infiltrates rxd with clarithromycin and bactrim without resolution
- 4 yo: lymphadenopathy, hsmegaly and fevers. Lymph node biopsy histiocytic infiltrates, no granulomas; culture - MAC
- Five drug antimicrobial therapy but fevers persisted and cultures remained positive

Disseminated MAC Infection



Defects Associated with Recurrent MAC Infection



Patient 5

- 1 mo: *S. aureus* buccal cellulitis
- 10 mo: *S. aureus* severe impetigo
- 11 mo: *S. pneumoniae* pneumonitis and sepsis
- 13 mo: *S. pneumoniae* arthritis
- 15 mo: *S. pneumoniae* cellulitis
- 25 mo: *S. pneumoniae* lymphadenitis
- 4 yo *E. coli* pyelonephritis
- 4-7 yo *P. aeruginosa*, *S. maltophilia*, *S. marcescens* sinusitis

Range of Infections in This New Immunodeficiency

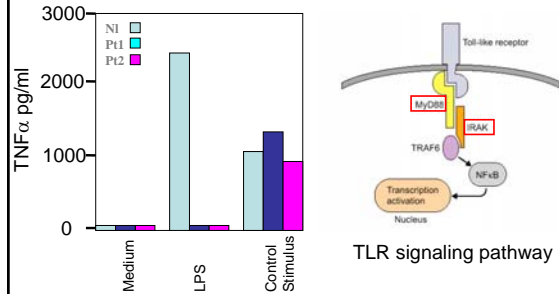
Infections with:

Encapsulated bacteria
(*S. pneumoniae*)
S. aureus
Anaerobes (some)

Lack of infections with:

Viruses
Mycobacteria
Fungi

Critical Laboratory Finding



Science 299:2076-2079, 2003

Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency

Science 2003, 299:2076-79

“We describe three unrelated children with IRAK-4 deficiency....The otherwise healthy children developed infections caused by pyogenic bacteria. These findings suggest that the TIR-IRAK signaling pathway is crucial for protective immunity against specific bacteria but is redundant against most other microorganisms.”

Interesting Question Regarding IRAK-4 (MyD88) Deficiency?

- Diminished TLR signaling
- Diminished IL-1 signaling
- Diminished IL-18 signaling
- Significant mortality during childhood but it appears that there is little or no problem after adolescence

This raises the question as to how critical are IRAK/MyD88 pathways for normal host defense after childhood?

Scienceexpress

Report

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency

Armanda Casrouge,^{1*} Shen-Ying Zhang,^{1,2*} Céline Eidenschien,^{1*} Emmanuelle Jouanguy,^{1,2*} Anne Puel,¹ Kun Yang,^{1,2} Alexandre Alcais,¹ Capucine Picard,^{1,2} Nora Mahfoufi,¹ Nathalie Nicolas,¹ Lazaro Lorenzo,¹ Sabine Plancoulaine,¹ Brigitte Sénéchal,¹ Frédéric Geissmann,¹ Koichi Tabeta,^{2*} Kasper Hoebe,² Xin Du,² Richard L. Miller,² Bénédicte Héron,¹ Cyril Mignot,¹ Thierry Billette de Villemeur,¹ Pierre Lebon,¹ Olivier Dulac,¹ Flore Rozenberg,¹ Bruce Beutler,³ Marc Tardieu,^{1*} Laurent Abel,^{1*} Jean-Laurent Casanova^{1,2,1*}

Herpes simplex virus-1 (HSV-1) encephalitis (HSE) is the most common form of sporadic viral encephalitis it affects otherwise healthy patients and only a small minority of HSV-1-infected individuals. Here, we elucidate a genetic etiology for HSE in two children with autosomal recessive deficiency in the intracellular protein UNC-93B, resulting in impaired cellular interferon-alpha/beta and -lambda antiviral responses.....

September 14, 2006

Newly Identified Genetic Defects Associated with Recurrent Infections

- CD40/CD40L: encapsulated bacteria, pneumocystis, cryptosporidia
- IFN-γR1&2, STAT-1, IL12p40, IL12-Rβ1, NEMO: mycobacteria (salmonella)
- IRAK-4, MyD88: bacterial pathogens
- UNC93B, TLR3: HSV encephalitis

Primary Immune Deficiencies

- Continue to yield insights into host defense
- Demonstrate range of possible outcomes resulting from specific genetic defects
- New disorders provide additional information regarding specifics of the immune response
- Define potential targets for immunologic manipulation
- New immunodeficiencies will continue to be identified providing new insight into the immune system, posing new questions and opening new avenues of therapy

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