Πρωτοπαθείς Ανοσοανεπάρκειες

Primary immunodeficiencies -an overview-

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???
Primary Immunodeficiency (PID)

- **Group of rare diseases caused by genetically defective or abnormal one or more essential parameter(s) of the immune system**
  (Today, more than 200 syndromes have been recognized)
- **Infections are the most common illnesses among the PID patients**
- **although,**
  allergic, autoimmune or lymphoproliferative disease are not rare

Definitions for Primary Immunodeficiencies

- **….diverse group of illnesses that, as a result of one or more abnormalities of the immune system, increase susceptibility to infection (*Stiehm*, *2004*)**
- **…mostly monogenic, predisposing individuals to different sets of infections, allergy, autoimmunity and cancer (*Fischer*, *2004*)**
- **..failure to achieve immune function to provide efficient, self limited host defense against biotic and abiotic environment while preserving tolerance to self (*Casanova, 2005*)**

Today, for most of the PID

- **We know the genetic background**
- **We do better clinical diagnosis**
- **We understand the immunopathogenetic mechanisms**
- **New therapies are available**

PID

Diseases of the immune system,

as a consequence of a

deficiency, disorder or even dysregulation,

↓

inefficient or fault immune response

↓

leads to disease

↓

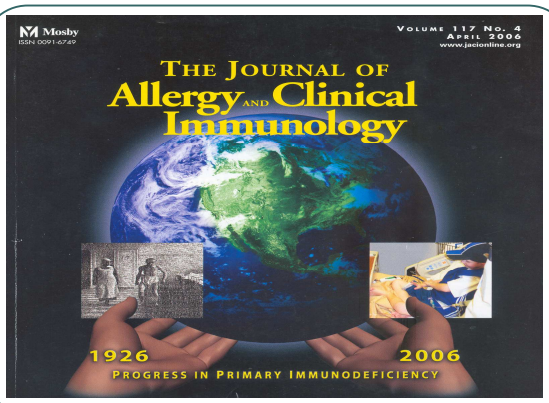
if

one or more of essential components of the immune system does not work correctly

- **there is no differentiation and maturation of the immune cells**
- **there is no proper immune response**

↓

Disease *(Primary Immunodeficiency)*



PID

The understanding of immune diseases
and the immunopathogenetic mechanisms
has based on
the phenotype of the PID disorders
in combination
with genetic experiments in rodents

Classification of PID
(WHO/IUIS, up to 2000)

- Combined immunodeficiencies
- Predominantly antibody deficiencies
- Other well defined immunodeficiency syndromes
- Defects of phagocyte function
- Complement deficiencies
- Other primary immunodeficiency diseases

Classification of PID
(IUIS, Geha et al, JACI2007)

- Combined T cell and B cell immunodeficiencies
- Predominantly antibody deficiencies
- Other well defined immunodeficiency syndromes
- Diseases of immune dysregulation
- Congenital defects of phagocyte number, function, or both
- Defects in innate immunity
- Autoinflammatory disorders
- Complement deficiencies

Genetic & Environmental factors are modifiers of the phenotype

- a clinical phenotype can be the consequence of distinct genotype
- mutations in the same gene can lead to different phenotype

gene identification is not always the answer for the disease

Human Primary Immunodeficiency

"in vivo experiments of Nature"

Study of the immune diseases
(give insights into the pathophysiology of the immunological conditions)

Novel approaches to therapy
for Immune Diseases

Treatment

- **Replacement therapy**
  γ-globulin/antibody replacement
  - *iv (IVIG)*
  - *sc (SCIG)*

  enzymes replacement
- **Bone marrow Transplantation**
- **Gene therapy**

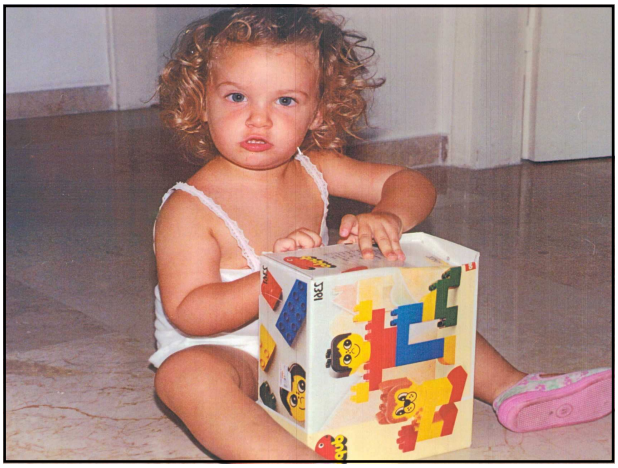
The prognosis of children with PID

is steadily progressing

in relation to the advancement

that is marked in

genetics and immunology



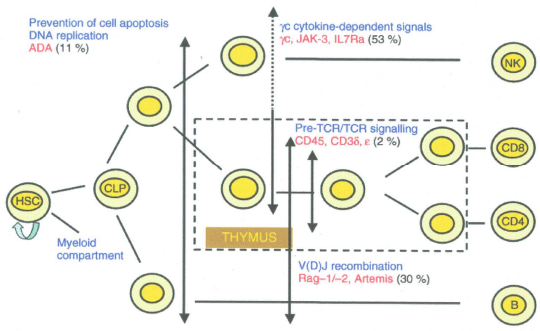
Combined Immunodeficiencies

the most & well known one

Severe Combined Immunodeficiency
(SCID)

Severe Combined Immunodeficiency (SCID)

(Fischer et al., 2005)



SCID immunophenotype

Phenotype	Inheritance
T (-) B (+)	X-linked recessive autosomal
T (-) B (-)	recessive autosomal

SCID

Two main mechanisms

Defective signaling
- γ_c chain
- JAK3

Defective rearrangements of Ag specific TCR & BCR
- RAG1 / RAG2
- Omen Syndrome (additional factors)

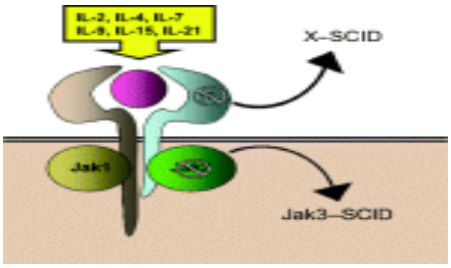
Other mechanisms
Artemis

SCID

γ_c chain deficiency ≠ IL-2R deficiency

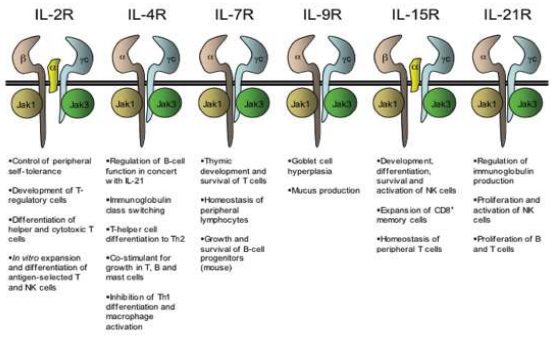
- γ_c chain: shared by the IL-2, IL-4, IL-, IL-7, IL-9, IL-15, IL-21 Rec
- IL-7Ra deficiency required for T-cell development
- IL-15: required for NK development

SCID
(T-B+λεμφοκυτταρικός φαινότυπος)



From: Pesu M. et al.Immunol Rev 2005

Cytokine receptors which share the γ_c chain
(Pesu M. *et al.*,Immunol Rev, 2005)

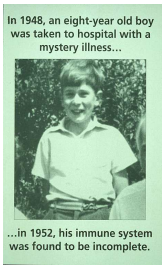


SCID

Insight into the physiology of T-cell.

Differentiation & Maturation

PID



1952
The first case of proven PID (antibody deficiency)

BRUTON OC
Agammaglobulinemia
Pediatrics. 1952 Jun;9(6):722-8.

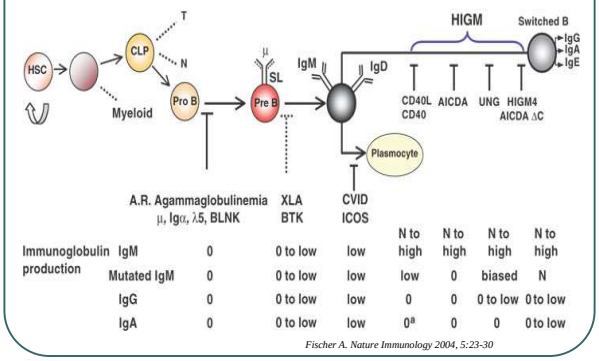
BRUTON OC, APT L, GILTIN D, JANEWAY CA
Absence of serum gamma globulins
AMA Am J Dis Child. 1952 Nov;84(5):632-6

A-γ-globulinaemia

X-linked a-γ-globulinaemia (XLA)
(Bruton Disease, Btk)

Autosomal reccessive a-γ-globulinaemias
(additional molecules)

Blocks which cause antibody defect



		A.R. Agammaglobulinemia μ, Igα, λ5, BLNK	XLA BTK	CVID ICOS				
Immunoglobulin production	IgM	0	0 to low	low	N to high	N to high	N to high	N to high
	Mutated IgM	0	0 to low	low	low	0	biased	N
	IgG	0	0 to low	low	0	0	0 to low	0 to low
	IgA	0	0 to low	low	0[a]	0	0	0 to low

Fischer A. Nature Immunology 2004, 5:23-30

???
Based on the clinical manifestations of XLA patients

- Why Antibodies are so important for enteroviruses
- Why T-cytolytic cells are not sufficient to kill the infected by enterovirus cells

Modifier genes

Microbacterial infections at the age of ≥6 months

↓

Possible diagnosis a-γ-globulinaemia

↓

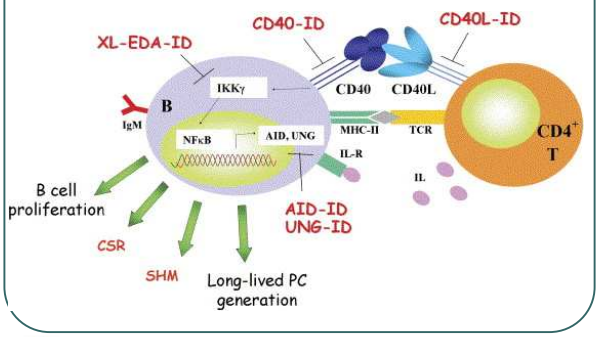
replacement therapy
(IVIG)

Hyper-IgM Syndromes

Clinical presentation
- Boys (ussually)
- Infancy
- Bacterial infections
- Opportunistic infections
  (Pneumonocystis Carinii, cryptosporidium)
- lymphadenopathy
- Autoimmune phenomena (autoimmune cytopenias)
- tumors

Immunological findings
- IgG: ↓ IgA: ↓ IgM: Φ ή ↑
- Κυκλοφορούντα Β λεμφοκ. ↓
- Κυκλοφορούντα Τ λεμφοκ. Φ

Hyper-IgM Syndromes
(Notarangelo L et al, JACI 2006)



Successful antibody repertoire means production of functional antibodies of different isotypes

two steps

a. Ag independent process:
   V(D)J recombination process
b. Ag dependent process:
   - class switch recombination – CSR
   - somatic hypermutation – SHM

selection of B cells, which express high affinity to antigen BCR

Hyper-IgM Syndrome

could be considered as a one of the best models which illustrates the power of molecular medicine and applies

"from bedside to bench and back to the bedside"

CVID

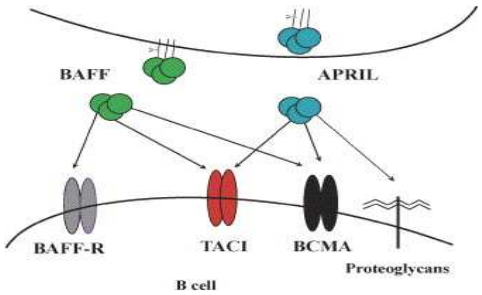
- Variable decreased concentrations of all immunoglobulin isotypes
- Recurrent bacterial infections
- Autoimmune phenomena / diseases
- Increased risk of lymphomas & digestive carcinomas

CVID

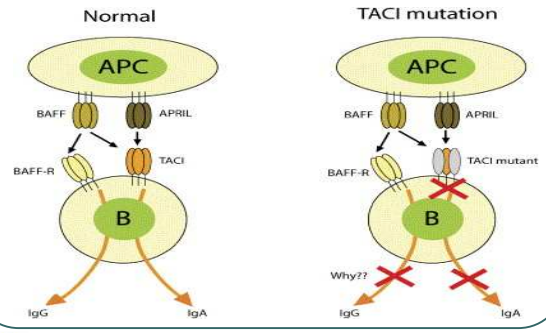
- Some patients partial IgG deficiency with or without IgA deficiency
- Intrinsic B cell abnormalities
- Some T cell defects
- Complex genetic controls
- Environmental factors

BAFF, APRIL, and their receptors on B cells

(Castigli & Geha, JACI, 2006)



Speculative mechanism for the pathogenesis of CVID in the setting of the TACI mutation (Berglund et al, JACI, 2006)



Treatment

- Replacement therapy
  γ-globulin/antibody replacement (1952)
  - *iv (IVIG)*
  - *sc (SCIG)*

  enzymes replacement
- Bone marrow Transplantation (1968)
- Gene therapy (2000)

Primary Immunodeficiency

Constant "feedback" between

Clinical & Basic Immunology

can bring fruitful results for

complex multifactorial diseases

Useful internet sites

http://www.paed-anosia.gr
http://www.esid.org
http://www.info4pi.org
http://www.primaryimmune.org
http://www.ingid.org
http://www.ipopi.org