UPDATE ON PRIMARY IMMUNODEFICIENCIES

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Disclosure of conflicts of interest

I have nothing to disclose
The human immune system

Parts of the Immune System

- Adenoid
- Tonsil
- Lymph nodes
- Right lymphatic duct, entering vein
- Thoracic duct, entering vein
- Thymus
- Spleen
- Peyer’s patch (small intestine)
- Appendix
- Bone marrow
- Lymphatic vessels
- Lymphatic vessel
- Blood capillary
- Tissue cells
- Interstitial fluid
- Lymphatic capillary
- Masses of lymphocytes and macrophages
The human immune system

Immune system

Acquired

T-cell immunity
(cell-mediated immunity)

Whole T-cells released into:

Suppressor T-cells
Helper T-cells
Cytotoxic T-cells

Death of the body’s cells that are infected with a virus or otherwise damaged

B-cell immunity
(humoral immunity)

Antigen exposure

Lymphoblasts

Plasma cells
Antibodies
Complement cascade
Classical pathway

Clonal B-cells

Memory B-cells

Bloodbourne

Complement cascade
Alternative pathway

Phagocytes

1. Neutrophils
2. Macrophages
3. Basophils
4. Eosinophils
5. Natural killer cells

Direct killing of bacteria

Death of dangerous organisms

Physical barriers

1. Skin
2. Mucous membranes
3. Saliva
4. Flushing action of urine and tears
5. Stomach acid

Stops infection before it enters the body

Virtual Medical Centre
Agammaglobulinemia: the prototype of primary humoral immunodeficiency

- Pediatrics Vol. 9 No. 6 June 1, 1952; pp. 722 -728
- AGAMMAGLOBULINEMIA
- ODGEN C. BRUTON
Agammaglobulinemia

Low to absent serum immunoglobulin serum levels

Absence of peripheral B lymphocytes (CD19+:<1%)
Presentation of agammaglobulinemia

✓ No symptoms for the first 6-9 months of life
✓ Recurrent infections by encapsulated bacteria (Pneumococcus, H.influenzae) and G. lamblia.
✓ Almost complete lack of tonsils; not palpable lymph nodes
✓ IgG, IgA, IgM, IgE <2SD
✓ Mutations in Btk > absence of peripheral B cells
✓ Treatment: immunoglobulin replacement
Bruton's tyrosine kinase (BTK)

A Antigen-independent

- Surrogate light chains
  - $\lambda_5$
  - VpreB
  - IgH HC
- Pre-BCR
  - Ig$\alpha$
  - Ig$\beta$
- $V_{D\gamma H}$
  - $J_L$
  - BLNK
  - BTK
  - Pro-B-cell
  - Pre-B-cell
  - Defects in BTK, BLNK, $\lambda_5$, IgH HC, Ig$\alpha$, Ig$\beta$, LRRG8
  - Agammaglobulinemias

B Antigen-dependent

- Secreted Ig, any isotype
  - Plasma cell
  - Membrane Ig, any isotype
  - Memory B-cell
  - CSR defects, CVID, specific antibody deficiencies

VDJH

Absence of Serum Gamma Globulins in an Adult

Jay P. Sanford, M.D.†, Cutting B. Favour, M.D.‡, and Melvin S. Tribeman, M.D.§

Common Variable Immunodeficiency

✓ Pediatric and adult onset (2\textsuperscript{nd}-3\textsuperscript{rd} decade)

✓ Recurrent infections by encapsulated bacteria (Pneumococcus, H.influenzae)

✓ Autoimmune cytopenias; splenomegaly; autoimmune enteropathy; granulomas

✓ Low IgG, with low IgA, and/or IgM

✓ Absent recall response to vaccinations

✓ Treatment: immunoglobulin replacement
Primary Immunodeficiencies (PIDs)

- Prenatal diagnosis
- Newborn screening
  - Focused screening (Positive family history)
- Symptomatic diagnosis
- Diagnosis and therapeutic interventions
  - Natural course of disease
    - Asymptomatic period
    - Symptomatic period
    - Late consequences of PIDs
    - Death

Respiratory symptoms of PIDs
- Infectious
  - Upper respiratory airways
    - Sinusitis
    - Tonsillitis
  - Lower respiratory airways
    - Bronchitis
    - Pneumonia
    - Empyema
- Non-infectious
  - Structural
  - Inflammatory
  - Tumors
    - Lymphoreticular malignancies
    - Solid tumors

Primary Immunodeficiencies (PIDs)
PI3K and primary humoral immunodeficiencies

Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency

Phosphoinositide 3-Kinase δ Gene Mutation Predisposes to Respiratory Infection and Airway Damage

A human immunodeficiency caused by mutations in the PIK3R1 gene

Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K
Mutations in p110δ and novel immune findings
Mutations in p85α and novel immune findings
**Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: A large patient cohort study**

**TABLE I. Clinical manifestations of APDS**

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Frequency, n/total studied (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious complication</strong></td>
<td></td>
</tr>
<tr>
<td>Recurrent respiratory tract infections</td>
<td>51/53 (98)</td>
</tr>
<tr>
<td>Pneumonia†</td>
<td>39/46 (85)*</td>
</tr>
<tr>
<td>Bronchiectasis‡</td>
<td>32/53 (60)</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>24/53 (45)</td>
</tr>
<tr>
<td>Recurrent otitis media</td>
<td>26/53 (49)</td>
</tr>
<tr>
<td>(with permanent hearing loss)</td>
<td>4/53 (8)</td>
</tr>
<tr>
<td>Severe or persistent herpesvirus infection</td>
<td>26/53 (49)</td>
</tr>
<tr>
<td>EBV</td>
<td>14/53 (26)</td>
</tr>
<tr>
<td>CMV</td>
<td>8/53 (15)</td>
</tr>
<tr>
<td>HSV and VZV</td>
<td>11/53 (21)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>15/53 (28)</td>
</tr>
<tr>
<td>(with tonsillectomy)</td>
<td>7/53 (13)</td>
</tr>
<tr>
<td>Ocular infections</td>
<td>10/53 (19)</td>
</tr>
<tr>
<td><strong>Noninfectious complication</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy§</td>
<td>34/53 (64)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>31/53 (58)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>24/53 (45)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>22/53 (42)</td>
</tr>
<tr>
<td>Nodular mucosal lymphoid hyperplasia</td>
<td>17/53 (32)</td>
</tr>
<tr>
<td>Enteropathy</td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td>10/53 (19)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7/53 (13)</td>
</tr>
</tbody>
</table>

* B cell counts in patients with APDS decrease with age.
Clinical and immunologic phenotype associated with activated phosphoinositol 3-kinase δ syndrome 2: A cohort study

- upper respiratory tract infection
- pneumonia
- lymphoproliferation
- adenopathy
- splenomegaly
- ENT lymphoid hyperplasia
- autoimmunity
- malignancy
- neurodev. delay
- growth retardation

% of APDS2 cohort

A

B

survival

lymphoma-free living

Time (years)

Time (years)
Clinical case - part 1

Female, 18 months  
Reurrent respiratory infections  
Poor growth

Hypogammaglobulinemia
  IgG: 20 mg/dl  
  IgA: 10 mg/dl  
  IgM: 158 mg/dl

ALC: normal  
ANC: normal

CD3: 70,5%  
CD4: 38,5%  
CD8: 34,0%  
CD19: 13,0%

Switched memory B cells: <0,3%  
CD16: 13,4%

DIFFUSE  
LYMPHOADENOMEGALY  
TONSILLAR HYPERTROPHY

AR- HIGM syndrome:  
Negative for mutations in known genes (AID, CD40, UNG)
Clinical case - part 3

Exclusion of intestinal lymphoma

IVIG

IBD-like

SCIG

rapamycin

Recurrent respiratory infections

Class IA PI3K

Pan-PI3K inhibitors
• LY294002
• wortmannin
• BKM120

isoform-specific PI3K inhibitors
• p110α inhibitors
• INK1117
• BYL719

Dual PI3K/mTOR inhibitors
• VS-5584
• NVP-BEZ235
• PI103

Akt inhibitors
• AZD5363
• MK2206

mTORC1 inhibitors
• Rapamycin
• Everolimus

PTEN

mTORC2

mTORC1
p85α and human NK cells

Inositol Phospholipid Signaling and the Biology of Natural Killer Cells

William G. Kerr and Francesco Colucci

Departments of *Microbiology and Immunology, and #Pediatrics, SUNY Upstate Medical University, Syracuse, N.Y., USA; *Clinical School, Department of Obstetrics and Gynaecology, and #NIHR Centre for Biomedical Research, University of Cambridge, Cambridge, UK.

References and Notes

11. For RIH analysis, [3H]MIP-1α was added to NIH 3T3 cells that had been stimulated with 1 μg/ml of DNA. After 16 hours, the cells were harvested and the supernatant was assayed for [3H]MIP-1α. The supernatant was plated and processed, and the data were analyzed by a Student’s t-test. A p-value of 0.01 or less was used to determine statistical significance. A p-value of 0.05 or less was used to determine statistical significance. Notation of statistical significance is indicated with an * for p < 0.05 and an ** for p < 0.01. A p-value of 0.01 or less was used to determine statistical significance. Notation of statistical significance is indicated with an * for p < 0.05 and an ** for p < 0.01.
p85α and human NK cells

A.

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>Pt.1</th>
<th>Pt.2</th>
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<tr>
<td>CD56 positive cells</td>
<td><img src="image" alt="HD CD56 positive cells" /></td>
<td><img src="image" alt="Pt.1 CD56 positive cells" /></td>
<td><img src="image" alt="Pt.2 CD56 positive cells" /></td>
</tr>
<tr>
<td>% CD107a</td>
<td>15%</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>% CD56 positive cells</td>
<td><img src="image" alt="HD CD56 positive cells" /></td>
<td><img src="image" alt="Pt.1 CD56 positive cells" /></td>
<td><img src="image" alt="Pt.2 CD56 positive cells" /></td>
</tr>
<tr>
<td>% CD107a</td>
<td>68%</td>
<td>23%</td>
<td>34%</td>
</tr>
</tbody>
</table>

B.

C.

p85α and human NK cells

A. 

CD56 positive cells

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>Pt. 1</th>
<th>Pt. 2</th>
<th>NS</th>
<th>IL-12 + IL-18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td></td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>76%</td>
<td>8%</td>
<td>21%</td>
<td></td>
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</tr>
</tbody>
</table>

B.

Stimulus: IL12+IL18

C.

% IFN-γ

p85α and human NK cells

A.

B.

Effective “activated PI3Kδ syndrome”–targeted therapy with the PI3Kδ inhibitor lenalisib

V. Koneti Rao, Sharon Webster, Virgil A. S. H. Dalm, Anna Šedivá, P. Martin van Hagen, Steven Holland, Sergio D. Rosenzweig, Andreas D. Christ, Birgitte Sloth, Maciej Cabanski, Aniket D. Joshi, Stefan de Buck, Julie Doucet, Danilo Guerini, Christoph Kalis, Ilona Pylvaeneainen, Nicolas Soldermann, Anuj Kashyap, Gulbu Uzel, Michael J. Lenardo, Dhavalkumar D. Patel, Carrie L. Lucas, and Christoph Burkhardt

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Immune dysregulation in human subjects with heterozygous germline mutations in **CTLA4**

Hye Sun Kuehn,1* Weiming Ouyang,2* Bernice Lo,3,4* Elissa K. Deenick,5,6 Julie E. Niemela,1 Danielle T. Avery,5 Jean-Nicolas Schickel,7 Dat Q. Tran,8 Jennifer Stoddard,4 Yu Zhang,4,9 David M. Frucht,2 Bogdan Dumitriu,10 Phillip Scheinberg,10 Les R. Folio,11 Cathleen A. Frein,12 Susan Price,3,4 Christopher Koh,13 Theo Heller,13 Christine M. Seroogy,14 Anna Huttenlocher,14,15 V. Koneti Rao,1,4 Helen C. Su,4,9 David Kleiner,16 Luigi D. Notarangelo,17 Yajesh Rampertaap,18 Kenneth N. Olivier,19 Joshua McElwee,19 Jason Hughes,19 Stefania Pittaluga,16 João B. Oliveira,20 Eric Meffre,10 Thomas A. Fleisher,1† Steven M. Holland,1,10 Michael J. Lenardo,1,4† Stuart G. Tangye,5,6 Gulbu Uzel18†

Autosomal dominant immune dysregulation syndrome in humans with **CTLA4** mutations.

Desirée Schubert1,2,15, Claudia Bode1,15, Rupert Kenefeeck3,15, Tie Zheng Hou3,15, James B Wing4, Alan Kennedy3, Alla Bulashevska1, Britta-Sabina Petersen5, Alejandro A Schäffer6, Björn A Grünig7, Susanne Unger1, Natalie Frede1, Ulrich Baumann8, Torsten Witte8, Reinhold E Schmidt8, Gregor Dueckers9, Tim Niehues9, Suranjith Seneviratne3, Maria Kanariou10, Carsten Speckmann1, Stephan Eh11, Anne Rensing-Ehl1, Klaus Warnatz1, Mirzokhidi Rakhmanov1, Robert Thimme11, Peter Hasselblatt11, Florian Emmerich12, Toni Cathomen1,12, Rolf Backofen7, Paul Fisch13, Maximilian Seidl13, Annette May13, Annette Schmitt-Graeff13, Shinji Ikemizu14, Ulrich Salzer1, Andre Franke5, Shimon Sakaguchi4, Lucy S K Walker3,15, David M Sansom3,15 & Bodo Grimbacher1,3,15
Monoallelic CTLA-4 mutations and PIDs
# Monoallelic CTLA-4 mutations and PIDS

## Table 1 Clinical phenotype of patients with CTLA4 mutations

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Patients</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea/enteropathy</td>
<td>A.II.5, A.II.8, A.II.9, A.III.1, A.III.3, B.II.1, B.II.2, B.II.4, C.II.4, E.II.3, F.II.2</td>
<td>11/14 (78%)</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>A.II.5, A.II.8, A.II.9, A.III.1, A.III.3, C.II.3, B.III.2, D.III.1, E.II.3, F.II.2</td>
<td>10/13 (76%)</td>
</tr>
<tr>
<td>Granulomatous lymphocytic interstitial lung disease</td>
<td>A.II.8, A.II.9, A.III.3, B.II.4, B.III.2, C.II.3, D.III.1, E.II.3</td>
<td>8/12 (66%)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>A.II.5, A.II.8, A.II.9, B.II.4, B.III.2, C.II.3, E.II.3, F.II.2</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td>Organ infiltration (bone marrow, kidney, brain, liver)</td>
<td>A.II.9, A.III.1, A.III.3, B.II.2, B.II.4, C.II.3, D.III.1</td>
<td>7/14 (50%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>A.II.5, A.II.9, A.III.3, C.II.3, D.II.1, E.II.3</td>
<td>6/12 (50%)</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia</td>
<td>A.III.1, A.III.3, C.II.3, E.II.3, F.II.2</td>
<td>5/14 (35%)</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>C.II.3, D.II.1, E.II.3, F.II.2</td>
<td>4/14 (28%)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>A.III.3, C.II.3, D.II.1, E.II.3</td>
<td>4/14 (28%)</td>
</tr>
<tr>
<td>Psoriasis and other skin diseases</td>
<td>A.III.1, B.II.1, B.II.2</td>
<td>3/14 (21%)</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>A.II.5, D.II.1</td>
<td>2/13 (15%)</td>
</tr>
<tr>
<td>Autoimmune arthritis</td>
<td>A.II.5, A.III.1</td>
<td>2/14 (14%)</td>
</tr>
<tr>
<td>Solid cancer</td>
<td>B.II.4</td>
<td>1/14 (7%)</td>
</tr>
</tbody>
</table>
Monoallelic CTLA-4 mutations and PIDs
Clinical case - part 1

24 years AIHA (Hb: 5.6 gr/dl)
- Steroids
- High IVIG

25 years
- Diagnosis of hypogammaglobulinemia
- IVIG (monthly)

Starting at 28 years
- Recurrent ITP, lymphopenia, splenomegaly
- Steroids
- High IVIG
- cotrimoxazole

36 years GLILD
- Pulmonary granulomas
- Specific treatment
- steroids

40 years
- Systemic CMV infection
- ganciclovir

36 years GLILD
- Pulmonary granulomas
- Recurrent g-i infections (Salmonella, rotavirus, Giardia lamblia)
Clinical case - part 2

- **42 years**
  - Splenomegaly, lymphopenia, lung function worsening
  - Steroids rituximab

- **44 years**
  - IBD-like disease
  - Steroids anti-TNF-a

- **46 years**
  - IBD-like disease
  - Abatacept

- **48 years**
  - IBD-like disease
  - vedolizumab

Diagnosis of CTLA-4 haploinsufficiency
Clinical case- lung CT scans

Pulmonary nodular lesion (36 years old, white arrow)
Resolution/disappearance of pulmonary nodular lesion present at 36 years (38 years old, white arrow)
Resolution/disappearance of pulmonary nodular lesion present at 36 years (38 years old, white arrow) bronchiectasis (black arrows)
Diffuse ground glass abnormalities (similar to pulmonary fibrosis) (38 years old)
Clinical case- lung CT scans

Diffuse ground glass abnormalities (similar to pulmonary fibrosis) (38 years old)
# CTLA-4 related disorders and treatments

| Healthy Control | | Healthy Control |
|-----------------|----------------|
| **T\textsubscript{reg}** | **T\textsubscript{FH}** | **T\textsubscript{reg}** | **T\textsubscript{FH}** |
| High CTLA4 expression in T\textsubscript{reg} cells | Low T\textsubscript{FH} frequency | Control of Autoimmunity |

<table>
<thead>
<tr>
<th>LRBA or CTLA4 deficiency</th>
<th>LRBA or CTLA4 deficiency + CTLA4-Ig therapy</th>
<th>LRBA or CTLA4 deficiency + CTLA4-Ig therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T\textsubscript{reg}</strong></td>
<td><strong>T\textsubscript{FH}</strong></td>
<td><strong>T\textsubscript{FH}</strong></td>
</tr>
<tr>
<td>↓ CTLA4</td>
<td>↑ CTLA4 expression</td>
<td>CTLA4-Ig supplementation</td>
</tr>
<tr>
<td>XL</td>
<td>↑ T\textsubscript{FH} frequency</td>
<td>↓ T\textsubscript{FH} frequency</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Control of Autoimmunity</td>
<td></td>
</tr>
</tbody>
</table>

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**Note:** The diagram illustrates the effects of CTLA-4 deficiency and the potential benefits of CTLA4-Ig therapy in controlling autoimmunity. The symbols and notations indicate changes in T-cell populations and CTLA-4 expression levels.
CTLA-4 related disorders and treatments

- Ig replacement
- Antibiotics
- Steroids
- Anti-TNF-a
- Abatacept
- Vedolizumab
- HSCT
The genetic advances in the field of PIDs have allowed to better understand the pathogenesis of PIDs.

Recent genetic findings and related immunological studies allow for the application of personalized medicine in PIDs.

Metabolic (PI3K) and immunologic (CTLA-4) checkpoints are becoming intriguing players in the field of PIDs.
Thank you for your attention