Metabolism, Infection and Immunity in Mitochondrial Disease

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No conflicts of interest to declare
Outline

• What is the immune system and why is it important?

• Infection and mitochondrial disease

• Immune function in mitochondrial disease
Why is the immune system important?

• Protects us against

- Bacteria
- Viruses
- Fungi
- Parasites
- Cancer
- Pollution
The immune system has multiple lines of defense.
The immune system is composed of organs and cells.
The immune system has many different types of cells. These cells include:

- Bone graft
- Hematopoietic stem cell
- Multipotential stem cell
- Erythrocytes
- Macrophage
- Myeloid progenitor cell
- Monocyte
- Neutrophil
- Megakaryocyte
- Mast cell
- Basophil
- Eosinophil
- Platelets
- Lymphoid progenitor cell
- T lymphocyte
- B lymphocyte
- Natural killer cell
- Dendritic cell
How does the immune system protect us?

• Body learns to defend itself by:
  – Natural infection
  – Vaccination
How does the immune system protect us?
How does the immune system protect us?
Why study the immune system immune and mitochondrial disease (MD)?

• Because:
  – Infection is bad for patients with mitochondrial disease

• Our questions:
  – What happens to patients with MD during infection?
  – Does having MD affect immune function?
Infection is bad for patients with MD

• **Point #1**: Infection increases energy requirements

  – For every 1°C of fever, metabolic rate can increase 10% or more

  – **Problem**: need more calories, but you don’t feel like eating; ⬇️ability to generate energy
Infection is bad for patients with MD

- **Point #2:** Infection can lead to an increase in tissue lactate production

![Image showing lactate and alanine production in control and Poly I:C conditions]
Infection is bad for patients with MD

• **Point #3:** Immune reactions can damage mitochondria

Tarasenko et al (submitted)
Infection is bad for patients with MD

• **Point #3:** Immune reactions can damage mitochondria

Tarasenko et al (submitted)
Infection is bad for patients with MD

• **Point #4:** The immune response may be part of the problem - cytokines

Cytokines produced as part of the immune response inhibit mitochondrial metabolism in human liver cells.
Infection is bad for patients with MD

• **Point #5:** What do we see clinically with infection?

![Graph showing neurologic events (%)](image)

- Encephalopathy
- Ataxia
- Acidosis
- SLE

43%

Edmonds et al. (2002)
The need for translational research in MD

Metabolic decompensation

- *In extremis* (life-threatening)
  - Bioenergetic failure
  - Lactic acidosis
  - Organ failure (e.g. liver failure)
  - Encephalopathy
  - Stroke
  - Sequelae
- Extensive ICU care

Clinical question: How did we arrive at this point?
1) Are patients with MD immunodeficient?
2) What is the role of inflammation in MD pathophysiology?
Immune function in MD

• Since infection can be very serious...
  – How well does the immune system function in patients with MD?
Fatal Neonatal-Onset Mitochondrial Respiratory Chain Disease with T Cell Immunodeficiency

JANINE REICHENBACH, RALF SCHUBERT, RITA HORVÁTH, JENS PETERSEN, NANCY FÜTTERER, ELISABETH MALLE, ANDREAS STUMPF, BORIS R. GEBHARDT, ULRIKE KOEHL, BURKHART SCHRAVEN, AND STEFAN ZIELEN

- mtDNA depletion syndrome
- Complex II+III and IV in muscle
- Recurrent infections, RIP 18 months with septicemia
- Hypogammaglobulinemia by 15 months
- Memory T-cells, CD8+ T-cells, NK cells
- T-cell response to IL-2
Predisposition to infection and SIRS in mitochondrial disorders: 8 years’ experience in an academic center

Melissa A. Walker, MD, PhD, Nancy Slate, MS, Alexandra Alejos, BS, Stefano Volpi, MD, Rajashri S. Iyengar, MD, MPH, David Sweetser, MD, PhD, Katherine B. Sims, MD, PhD, and Jolan E. Walter, MD, PhD

Clinical Implications

- Mitochondrial disorders are multisystem diseases that, although not previously described, may include predisposition to infection and immunodysfunction.
- Immune phenotyping of these patients may be useful to identify individuals who require immunoglobulin replacement and/or antibiotic prophylaxis to decrease hospitalization and improve outcomes.
Immune function and MD

• What do we know? Not much, but…
  – Immune cells don’t like high levels of toxins
  – Mitochondrial RC deficiencies can also be present in immune organs and cells
Immune function and MD: toxins (lactate)
Mitochondrial dysfunction in immune cells

It all started with a clinical case…

• 15 year old male
• Complex III deficiency
• Multisystem disease
  – Neurologic
  – Musculoskeletal
  – Endocrine
  – Immunologic
    • Multiple infections
    • Hypogammaglobulinemia
    • Loss of pneumococcal titers
• Research exome pending

McGuire et al. (unpublished data)
Clinical features of MD

- Multisystem
- Energy organs
- mtDNA and nDNA inheritance
- Most common IEM
- Lactic acidosis
- Complications during/after decompensation (Edmonds et al, 2002)
- Pathophysiology: energy deficiency, ROS
Recurrent infection is common in patients with MD

Recurrent or severe infections:
- Upper RTI
- Lower RTI
- Otitis media
- Sinusitis
- Thrush
- Dermatitis
- UTH
- GI infection
- Bacteremia/sepsis
- Ig therapy

N = 62
Immunodeficiency screen for MD patients

- 4+ OM/yr
- 2+ sinus inf/yr
- 2+ PNA/yr
- FTT/GF
- IV Abx
- Need ICU Admit
- Recovery
- Deep Abscess
- Fungal Inf
- 2+ Inf/Sepsis
- FHx
- 1° ID
- Pt Hx
- ID Immuno Eval
- IVIG
- Abx PPx

% positive
Patients with MD may have poor immune memory

CD45RA$^+$

CD45RO$^-$

Naïve

CD45RA$^-$

CD45RO$^+$

Memory
(protective)
Immunization Recommendations for Children With Metabolic Disorders: More Data Would Help

Michael T. Brady, MD

Department of Pediatrics, Columbus Children’s Hospital, Columbus, Ohio

Biochemical changes that are present in children with inborn errors of metabolism may affect their immune response system and not only increase risk for infection but also diminish their ability to develop protective immunity after immunization. Understanding the immunogenicity and ability of vaccines to provide protective immunity in each of the specific metabolic disorders will be critical to understanding the child’s risk/benefit equation. Immunogenicity of vaccines and protection have not been well characterized in children with most metabolic disorders. A recent review of immune deficien-
Figure 1. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2018.

(For those who fall behind or start late, see the catch-up schedule [Figure 2]).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded in gray.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Range of recommended ages for all children</th>
<th>Range of recommended ages for catch-up immunization</th>
<th>Range of recommended ages for certain high-risk groups</th>
<th>Range of recommended ages for non-high-risk groups that may receive vaccine, subject to individual clinical decision making</th>
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<td>Influenza (IV)</td>
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<td>Measles, mumps, rubella (MMR)</td>
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<td>Varicella (VAR)</td>
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<td>Meningococcal B [12]</td>
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<td>Pneumococcal polysaccharide (PPSV23)</td>
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NOTE: The above recommendations must be read along with the footnotes of this schedule.
Vaccination Rate

Vaccination rates MMR
- 92%
- 8%

Vaccination rates VAR
- 84%
- 16%

YES
INCOMPLETE

Kruk et al (unpublished data)
MMR seropositivity

Measles cases per year

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<td>2018</td>
<td>63</td>
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</tbody>
</table>

Kruk et al (unpublished data)
Varicella seropositivity

Kruk et al (unpublished data)
How does the immune system protect us?

The immune system protects us through the production of antibodies. The diagram shows the concentration of antibodies (IgM and IgG) in the serum over time.

**Primary Response**
- **IgM** peaks at 10 days and **IgG** peaks at 20 days.

**Secondary Response**
- **IgM** peaks at 10 days again.
- **IgG** concentration increases significantly after the secondary antigen exposure.

The diagram illustrates the antibody response after primary and secondary antigen exposures.
Hypothesis: Bioenergetic deficiency in MD may extend to immune cells leading to immunodeficiency.

Tarasenko et al, Cell Metab, 2017
How many patients have problems with infection?

How many patients are on IVIg?
The mystery of IVIg

IVIg
- intravenous immune globulin
- aka “antibodies”
- produced from human plasma
- Immune mediated conditions
- Immunodeficiency
- Other effects? Benefits?
- Does the pathology of MD have an immune component?
### Hypothesis

Bioenergetic deficiency in MD may extend to immune cells leading to immunodeficiency.

- 8 y/o male with MD
- Received PICC line 2 weeks prior for access
- Presented with fever and hospitalized
Hypothesis: Bioenergetic deficiency in MD may extend to immune cells leading to immunodeficiency.

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- Received PICC line 2 weeks prior for access
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**Translational model: TCox10**

**COX10**
- Maturation of cytochrome C oxidase (CIV)
- Present in lymphocytes
- Deficiency: MD or Leigh phenotype
- KO in T-cells only
- Mice are generally healthy

Tarasenko et al, Cell Metab, 2017
Compromised respiratory chain in TCox10\(^{-/-}\) T-cells

Tarasenko et al, Cell Metab, 2017
TCox10-/- peripheral lymphocyte counts

Baseline

- WBC (K/µL)
- Lymphocytes (K/µL)
- Lymphocytes %

Infection

- WBC (K/µL)
- Lymphocytes (K/µL)
- Lymphocytes %

Tarasenko et al, Cell Metab, 2017
How does the immune system protect us?

![Diagram showing antibody concentration in serum over time, with primary and secondary responses highlighted.](image)
Vaccination response is impaired in TCox⁻/⁻

Clinical correlate: loss of vaccine titers

Tarasenko et al, Cell Metab, 2017
How does the immune system protect us?
Influenza viral clearance is impaired in TCox10⁻/⁻

Tarasenko et al, Cell Metab, 2017
Summary

• The immune system is important for vaccination and protection against infection

• Infection may be detrimental to patients with MD

• Subsets of patients with MD may have immune dysfunction
  – Toxicity
  – Metabolic dysfunction
Longitudinal natural history study of immunity in MD

The NIH MINI Study: Metabolism, Infection, and Immunity in Inborn Errors of Metabolism (NCT01780168)

Goal:

- Mitigate risk in patients with MD
  - Identify immune susceptibilities and risks in patients with MD
  - Characterize organ systems which may be susceptible to dysfunction/damage during infection in MD
Travel, lodging and meals provided
Children’s Inn at NIH
The immune phenotype in patients with MD (NIH MINI Study)

Primary immunodeficiency
Allergic/Inflammatory diseases

Immune dysfunction

Stress-induced immune dysfunction

Absent immune phenotype

Risk of decompensation
MINI Study contact information

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