Mass General Brigham
Mass General for Children

Immune Cell Function in Mitochondrial Disorders:
A patient centered approach

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Disclosures:

- U.S. Provisional Patent Application, 63/034,740, filed June 4, 2020 *(not yet awarded)*
- NIH/NINDS K08NS117889 - research funding
- NIH/NHGRI U01HG007690 Center for Integrated Approached to Undiagnosed Diseases (Undiagnosed Disease Network consortium co-investigator)– research funding
- American Academy of Neurology – prior honorarium for education subcommittee service
- Child Neurology Foundation, United Mitochondrial Disease Foundation – completed research funding

Immune Cell Function in Mitochondrial Disorders:
A patient centered approach

- What are Mitochondria and Primary Mitochondrial Disorders?
- What are Immune Cells and what roles do Mitochondria play in them?
- Do Primary Mitochondrial Disorders lead to ...
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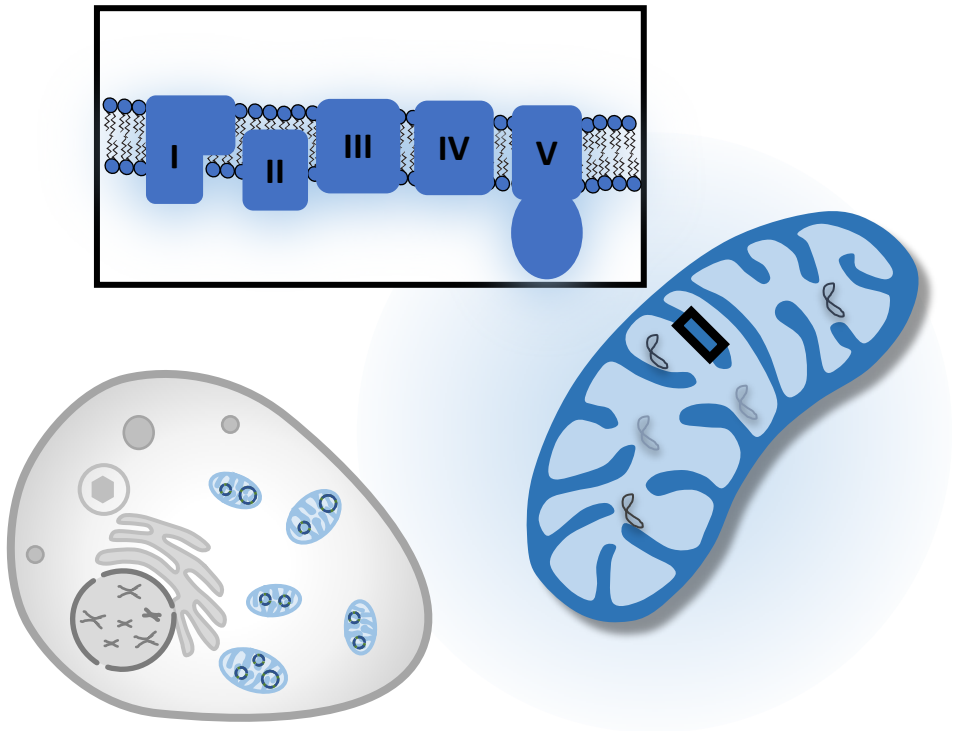
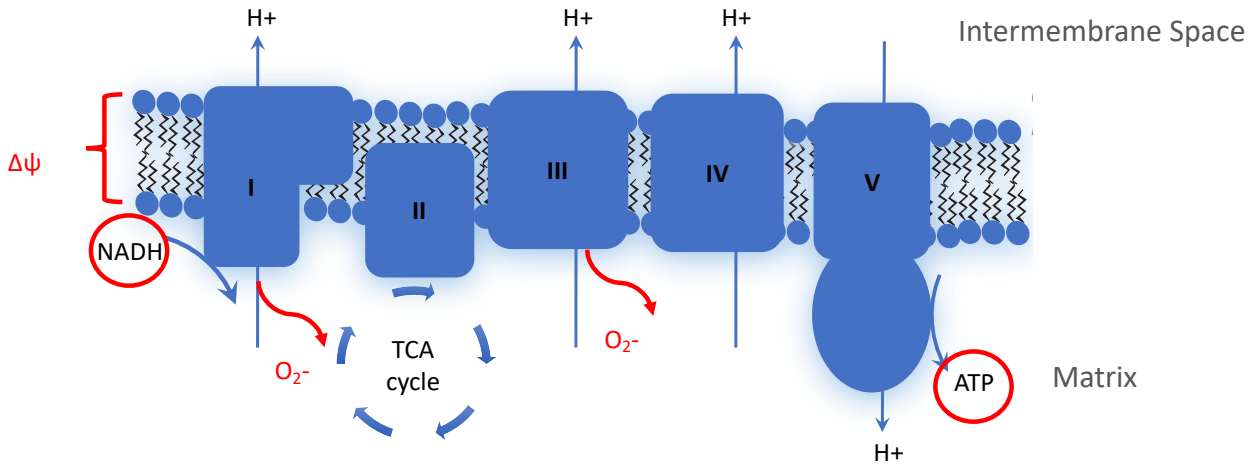
What are mitochondria, and what do they do?

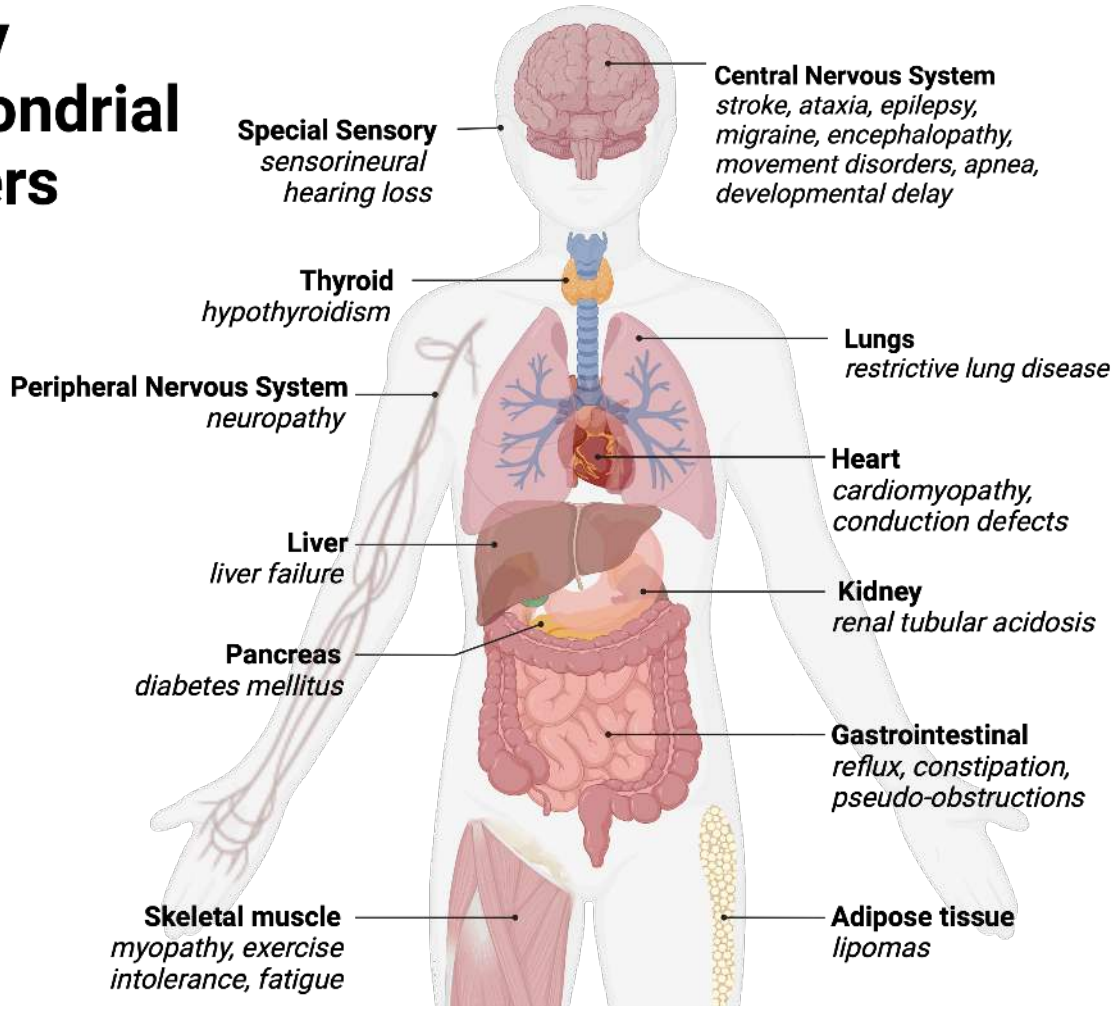




- Oxidative Phosphorylation (ATP synthesis)
- Fatty acid oxidation
- One carbon metabolism
- Nucleotide pool homeostasis
- Iron sulfur complex biogenesis
- Cell cycle progression
- Immune signaling

Images by M. Walker; reviewed by Vafai Nature 2012

What are Primary Mitochondrial Disorders?



M. A. Walker, created with Biorender.com

- Linked to ~300 distinct genes (Frazier J Biol Chem 2019)
- Marked phenotypic heterogeneity (Vafai Nature 2012)
- Mechanistic link between metabolism, physiology, and disease symptoms is unknown (Frazier J Biol Chem 2019)
- No proven biomarkers (Parikh Genet Med 2015)
- No FDA approved therapies *(excepting Friedreich Ataxia)* (Parikh Genet Med 2015)

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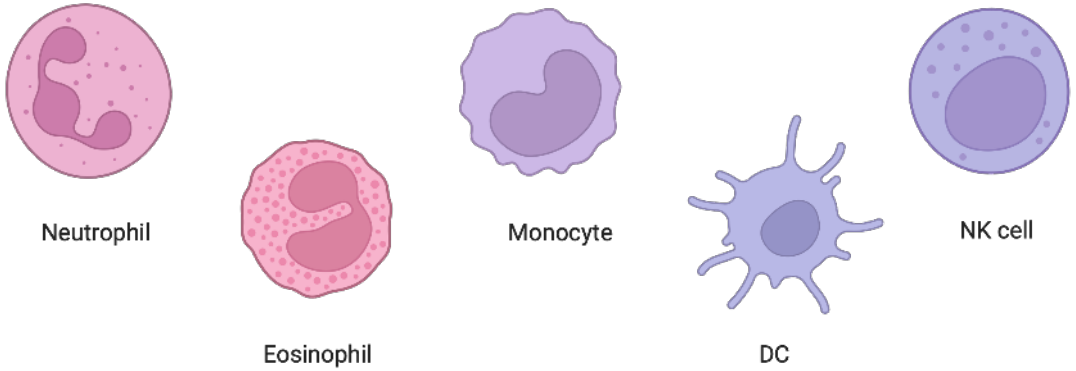
Immune system:

1. Innate immune system

   Not specific to the infectious agent/pathogen (bacteria, virus, etc)

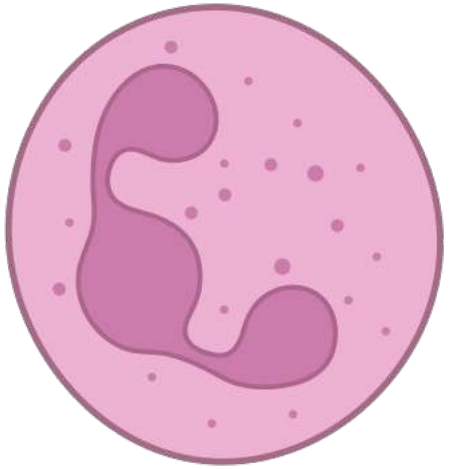


2. Adaptive immune system

   Tailored to the specific pathogen

Images created with Biorender.com

Immune Cells: *Innate Immune System*



Neutrophil

Created with Biorender.com

Engulf & kill:

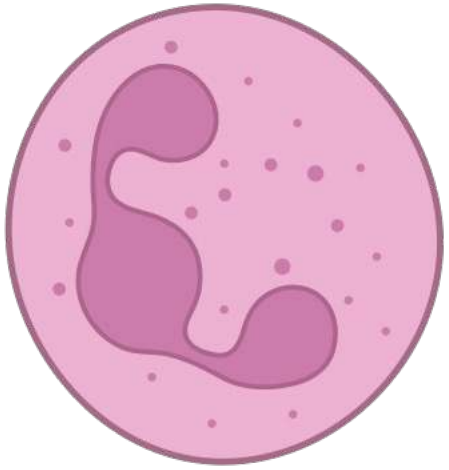
- Bacteria
- Fungi

Deficiency can lead to:

- Cellulitis
- Pneumonia
- Septicemia
- Infectious Bronchitis
- Infectious Diarrhea

e.g. Rigaud Orphanet J Rare Dis 2013

Immune Cells: *Innate Immune System*



Neutrophil

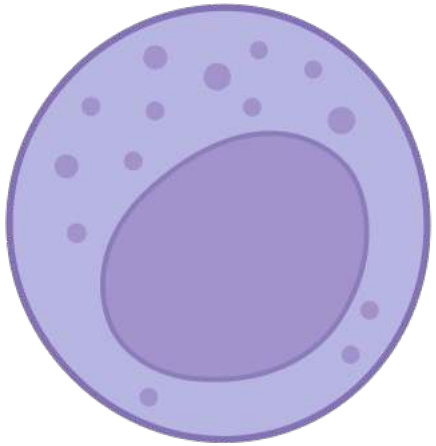
Created with Biorender.com

Mitochondrial are involved in:

- Neutrophil development
- Neutrophil movement within the body
- Neutrophil bacterial killing

Reviewed by Peng Immunolog Rev 2022

Immune Cells: *Innate Immune System*



NK cell

Created with Biorender.com

Attack & kill:

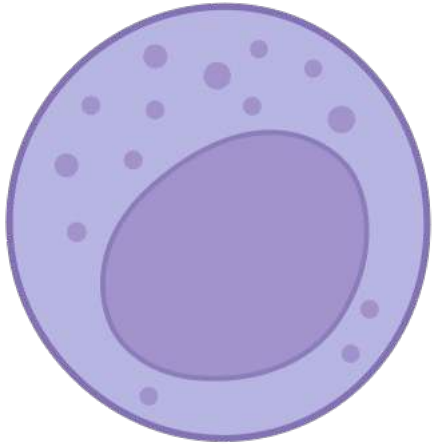
- Virally infected cells
- Tumor cells

Deficiency can lead to

- Increased susceptibility to herpetic infections (CMV, HSV1/2, VZV, EBV)

e.g. Bernard Pediatrics 2004

Immune Cells: *Innate Immune System*



NK cell

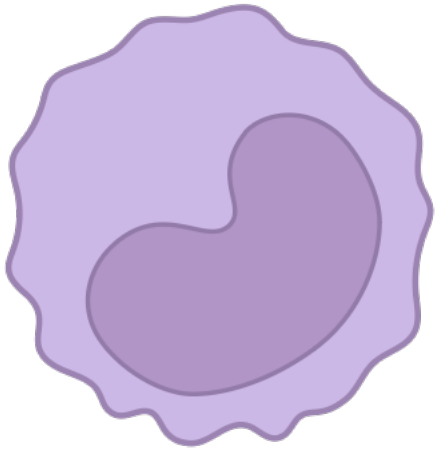
Created with Biorender.com

Mitochondria are involved in:

- Switching between NK cell types/functions
- Survival of long-lived NK cells

Surace Blood Adv 2021

Immune Cells: *Innate Immune System*



Monocyte

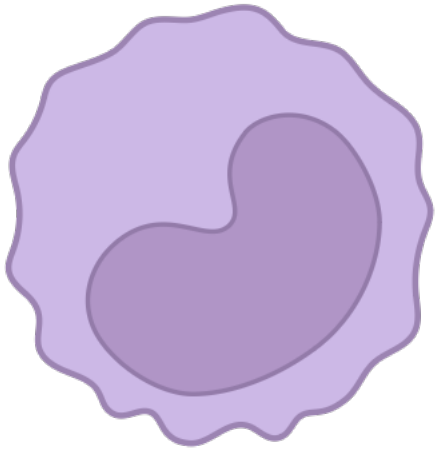
Created with Biorender.com

Transition to
Macrophages & kill:

- Fungi
- Mycobacteria
- *Salmonella*

e.g. Rigaud Orphanet J Rare Dis 2013

Immune Cells: *Innate Immune System*



Monocyte

Created with Biorender.com

Mitochondria are involved in:

- Macrophage inflammatory (inflammasome activation) responses
- Switching between macrophage types/functions

Reviewed by Mehta 2017

Immune Cells: *Innate Immune System*

Eosinophil

Created with Biorender.com

- Fight parasite infections
- Mount allergic responses

Reviewed by Wechsler Mayo Clinic Proceed 2021

Immune Cells: *Innate Immune System*

Eosinophil

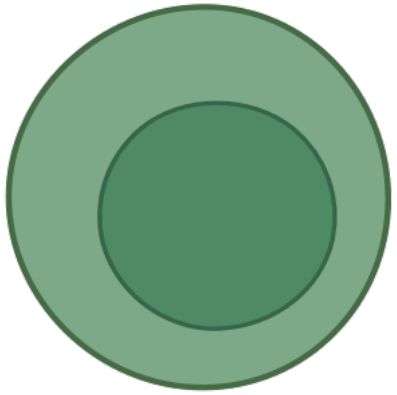
Created with Biorender.com

Mitochondria are involved in:

- Apoptosis (programmed cell death)
- Not ATP generation

Peachman roc Natl Acad Sci USA 2001

Immune Cells: *Adaptive Immune System*



T cell

Created with Biorender.com

Multiple functions:

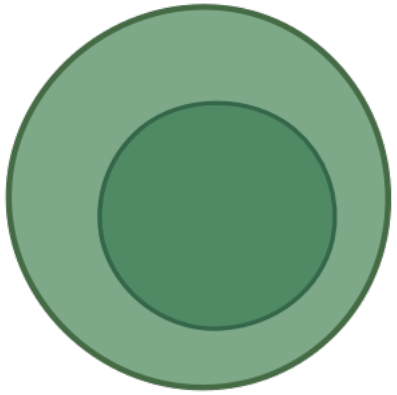
- Coordinate adaptive immune response
- Kill virus-infected cells
- Kill tumor cells
- ”Remember” prior infections

Deficiency can lead to

- Severe Combined Immune Deficiency
- Viral infection
- Fungal infection
- Opportunistic infection

e.g. Rigaud Orphanet J Rare Dis 2013

Immune Cells: *Adaptive Immune System*



T cell

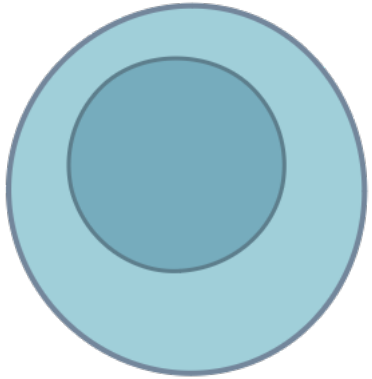
Created with Biorender.com

Mitochondria are involved in T cell:

- Development & maturation
- Transition to different T cell types
- Activation, immune responses

Reviewed by Mehta 2017

Immune Cells: *Adaptive Immune System*



B cell

Created with Biorender.com

Multiple functions:

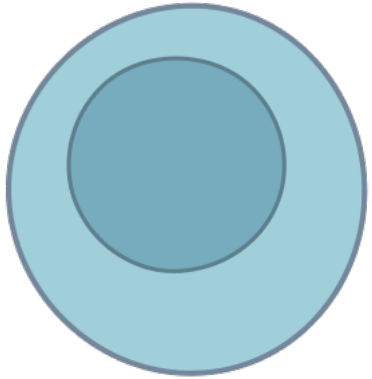
- Make antibodies against viruses
- Make antibodies against bacteria

Deficiency can lead to

- Agammaglobulinemia
- Bacterial infection
- Viral infection

e.g. Ochs Medicine 1996

Immune Cells: *Adaptive Immune System*



B cell

Created with Biorender.com

Mitochondria are involved in:

- Survival of plasma B cells
- Switching between different B cell functions

Reviewed by Mehta 2017

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Some Genetic Immunodeficiencies are caused by Defects in Mitochondrial Genes

Syndrome	**Gene**	**Immunologic Phenotype**
Cartilage Hair Hypoplasia	*Mitochondrial RNA processing endoribonuclease (RMRP)*	T cell dysfunction
Pearson Syndrome	Single large mitochondrial DNA deletion	Pancytopenia
Barth Syndrome	*Tafazzin (TAZ*)	Neutropenia
Omenn Syndrome	*Adenylate Kinase 2 (AK2*)	Leaky severe combined immunodeficiency
Fumarase Hydratase deficiency	*Fumarate Hydratase (FH)*	Neutropenia

Adapted from Walker J Immunol Res 2014

Retrospective Studies suggest increased rates of infection in Mitochondrial Disease

Massachusetts General Hospital Cohort

- 106 biochemically or genetically diagnosed patients
- 8 years' follow up
- 13% had ≥ 1 episode of System Immune Response Syndrome (SIRS)

No. Patients	% Patients	Serious/Recurrent Infection Types(s)
40	42	Any
20	21	Bacterial
7	7	Bacterial + Fungal
7	7	Bacterial + Viral
6	6	Bacterial + Fungal + Viral

Adapted from Walker J Allergy Clin Immunol Pract 2014

While Serious/Recurrent Infection is common, there is no clear pattern of a single specific Immune Deficiency Mitochondrial Disease

TABLE I. Pathogen, number of patients affected, and infection site*

Pathogen	No. affected	Sites
Acinetobacter calcoaceticus	1	Bacteremia with sepsis
Acinetobacter lwoffii	2	Bacteremia with sepsis (1), bacteremia (1)
β-Hemolytic *Streptococcus*	2	Recurrent pharyngitis and ear infection (1, surgical culture), recurrent pharyngitis
Borrelia burgdorferi	1	Systemic
Citrobacter braaki	1	Bacteremia with sepsis
Clostridium difficile	6	Colitis with sepsis (2), colitis (4)
Enterobacter	4	Bacteremia with sepsis (1), bacteremia (2), pneumonia (1)
Enterococcus	5	Bacteremia with sepsis (2), urosepsis (1), pneumonia with sepsis (1), pneumonia (1)
Escherichia coli	5	Bacteremia with sepsis (2), bacteremia (1), urosepsis (1), acute otitis media (1)
Flavimonas oryzihabitans	1	Pneumonia
Flavobacterium	1	Pneumonia
Fusarium species	1	Colitis
Klebsiella	3	Bacteremia with sepsis (1), urosepsis (1), pneumonia (1)
Moraxella	2	Bacteremia (1), pneumonia (1)
Pseudomonas aeruginosa	5	Bacteremia with sepsis (1), bacteremia (1), pneumonia (1), acute otitis media (2)
Serratia marcescens	3	Bacteremia with sepsis (2), pneumonia (1)
Shigella species	2	Colitis
Staphylococcus aureus	15	MSSA bacteremia with sepsis (4), MSSA bacteremia (2), MRSA bacteremia (1), meningitis (1, also with bacteremia), peritonitis and tracheitis (1), MSSA cellulitis (1), recurrent MRSA skin abscesses (1), pneumonia (2, 1 also with bacteremia), foot ulcer (1), abdominal wound (1)
Staphylococcus epidermis	2	Bacteremia with sepsis (1), foot ulcer (1)
Stenotrophomonas	3	Pneumonia (3)
Streptococcus salivarius	1	Bacteremia with sepsis
Streptococcus pyogenes	2	Recurrent pharyngitis
Cytomegalovirus	2	Systemic illness (2)
Herpes simplex virus	1	Encephalitis
Influenza A	1	Systemic illness with sepsis
Influenza B	1	Systemic illness with sepsis
Respiratory syncytial virus	5	Pneumonia with sepsis (1), bronchiolitis with sepsis (2), pneumonia (1), bronchiolitis (1)
Rotavirus	3	Colitis (all born prior to institution of routine immunization)
Varicella	1	Chickenpox and recurrent shingles
Candida albicans	8	Fungemia (3, 2 with sepsis), esophagitis (1), nonhealing foot ulcer (1), abdominal wound (1), chronic vaginitis (1)
Candida guilliermondii	1	Fungemia with sepsis
Candida parapsilosis	3	Fungemia with sepsis (1), fungemia (1), acute otitis media (1)

Walker J Allergy Clin Immunol Pract 2014

Retrospective Studies suggest increased rates of infection in Mitochondrial Disease

University of Texas, Houston Cohort

- 26 clinically defined patients

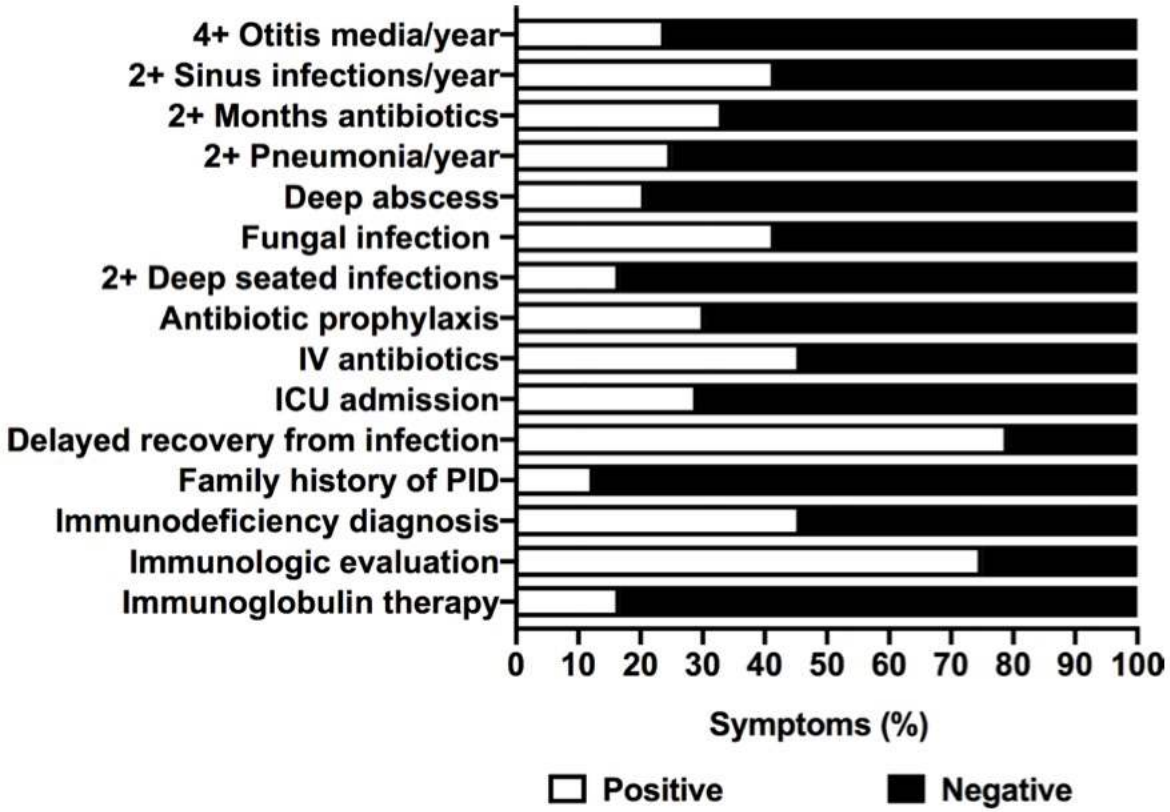

Figure 1: Immune symptoms in patients with MD.

Kruk J Allergy Clin Immunol Pract 2019

Retrospective Studies suggest increased rates of infection in Mitochondrial Disease

Gangnam Severance Hospital Cohort

- 31 clinically defined patients

Overview of Cause of Death in Pediatric Patients With Mitochondrial Disease (n = 31)

Cause of Death	Prevalence
Sepsis	17 (55)
Pneumonia	13 (42)
Disseminated intravascular coagulation	9 (29)
Acute respiratory distress syndrome	7 (23)
Pulmonary hemorrhage	2 (7)
Status epilepticus	3 (10)
Gastrointestinal bleeding	3 (10)
Sudden unexpected death	9 (29)
Number of causes of death	2.03 ± 0.91 (1-3)

Data are given as the mean ± standard deviation (range), or as total number (percentage).

Eom Pediatr Neurol 2017

COVID19 and Primary Mitochondrial Disease

European Cohort: PMD + COVID

- 79 patients, 10 countries
- 32% (25) hospitalized
- 61% (48) full recovery
- 35% (28) improved w/ sequelae
- 4% (3) died

- Respiratory dysfunction was independently associated with hospitalization for COVID19 in PMD patients (odds ratio 7.66)

Pizzamiglio Neurol 2022

Mitochondrial Medicine Society Recommendations: Immune Function

- *Immune function should be evaluated early in any mitochondrial disease patient experiencing **recurrent** or **severe infections***

"**Recurrent or severe infections**"
= those that are complicated, in multiple locations, resistant to treatment, caused by unusual organisms, or consisting of > 10 upper respiratory infections a year

Parikh Genet Med 2017

Mitochondrial Medicine Society Recommendations: Immune Function

- *Immune testing may be useful to identify patients that may benefit from prophylactic treatment strategies including antibiotic prophylaxis, immunoglobulin replacement therapy, and granulocyte colony-stimulating factor.*

Parikh Genet Med 2017

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Some Primary Mitochondrial Disease patients may have incomplete titer responses to immunization

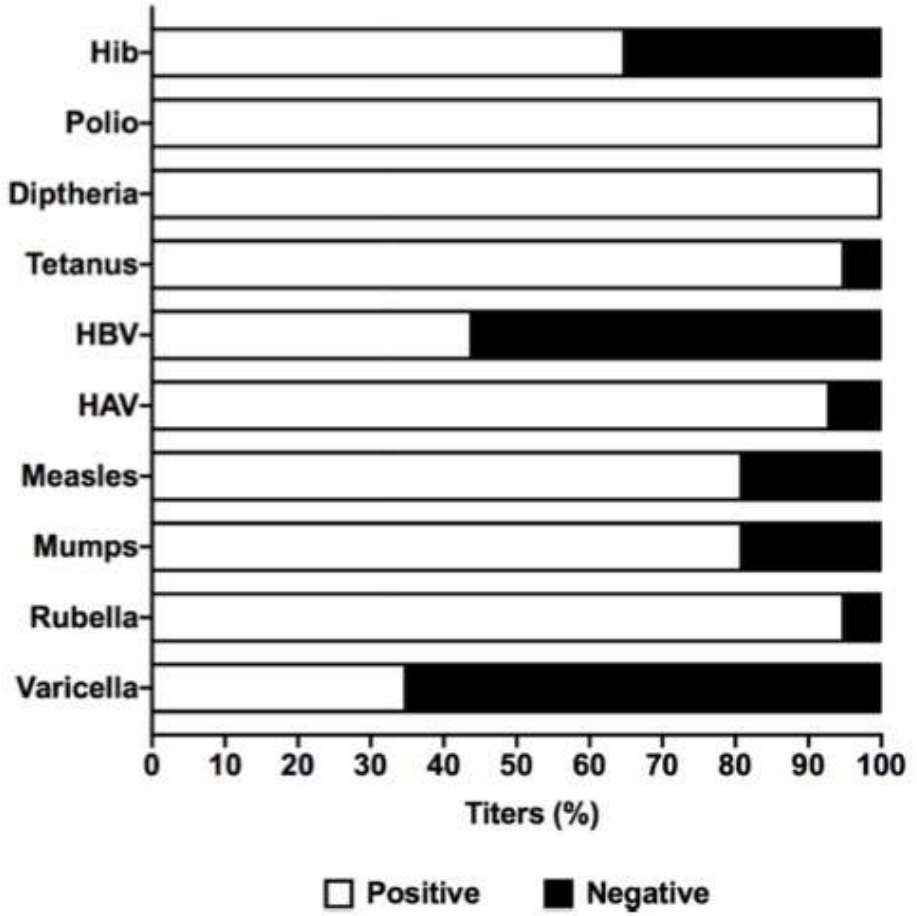
TABLE II. Immune phenotyping, clinical history, and treatment of a subset of patients with a mitochondrial disorder with laboratory evidence of immune dysfunction

Patient no.	Deficiency	Age, y	WBC/ALC (10^3/cells cm^3)	Lymphocyte subsets	Antibody deficiency	Vaccine response	T-cell proliferation	IgE and eosinophil	Serious and/or recurrent infections	Antibiotic prophylaxis	Immunoglobulin therapy	Response to IvIg	Clinical history of other immune dysfunction
1	SCHADD	5	6.3/2.3	Intermittent T- cell lymphopenia	Low IgG	Low Hib and pneumococcal, normal tetanus	NA	Normal	Bacterial, fungal	Yes	Yes, since 2 y old	Yes	Atopy (AR, asthma, food intolerance and medication allergy)
2	ETC I with POLG1 mutation	10	8.0/3.4	NA	Low IgG, IgA	NA	NA	Normal	Bacterial	NA	Yes, since 2.5 y old	Yes	Atopy (asthma, food intolerance)
3	ETC I, II, III mtDNA depletion	13	4.8/1.48 (low)	Low switched memory B cells (2.9%)	Low IgG	NA	Mildly decreased with mitogen (PHA) and absent with antigen (tetanus), normal with interleukins	Transient high and low IgE	Bacterial, fungal, viral	No	Yes, since 2 y old	Yes	Atopy (AD, AR, asthma, food and medication allergy)
4	ETC I, III	21	6.4/1.7	NA	Low IgG	Normal	NA	Normal	Bacterial	No	Yes, since 18 y old	Yes	Transient atopy (AR, asthma)
5	ETC I	29	4.5/2.4	NA	Elevated IgG	Normal titers but low pneumococcal avidity, normal tetanus and Hib	Low T-cell proliferation to mitogen and antigen	Transient high IgE	Bacterial, fungal, viral	Yes	Yes, since 28 y old	Yes	Atopy (asthma, food, medication allergies), autonomic dysfunction
6	ETC I, III	10	9.5/5.6	Low switched memory B cells (1.9%)	Transient low IgG and IgA	Low pneumococcal, normal tetanus	NA	Transient high IgE	Bacterial, viral (warts)	Yes	No		Atopy (AD, FA, EoE), AI (Hashimoto thyroiditis)
7	ETC III	30	4.6/1.3	NA	Low IgG	NA	NA	Normal	Bacterial, fungal	No	No		Atopy (AR, asthma)
8	ETC I, II	10	5.7/3.5	NA	Low IgA	NA	NA	Normal	Bacterial, viral	No	No		Autonomic dysfunction with small fiber neuropathy
9	ETC I	12	4.2/2.8	NA	None	Low antipneumococcal titers	NA	Normal	Bacterial, fungal	No	No		Allergic rhinitis

AD, Atopic dermatitis; *AI*, autoimmunity; *ALC*, absolute lymphocyte count; *AR*, allergic rhinitis; *EoE*, eosinophilic esophagitis; *ETC*, electron transport chain; *FA*, food allergy; Hib, Haemophilus influenzae type B; *IVIg*, intravenous immunoglobulin; mtDNA, mitochondrial DNA; *NA*, not available; *POLG*, polymerase gamma; *SCHADD*, short-chain hydroxyl acyl-co A dehydrogenase efficiency; *WBC*, white blood cell.
Vaccine response was assessed before IvIg treatment.

Walker J Allergy Clin Immunol Pract 2014

Some Primary Mitochondrial Disease patients remain seronegative despite immunization



Kruk J Allergy Clin Immunol Pract 2019

Some Primary Mitochondrial Disease patients (LSFC) may have incomplete immunization responses

Table 3. Antibody titers and seroconversion interpretation for LSFC patients.

Patient ID	Vaccine doses	Measles IgG (AU/ml)		Mumps IgG (AU/ml)		Rubella IgG (IU/ml)		Global response to MMR
*101**	N/A	91.4	+	<5.00	-	3.15	-	unconfirmed
102	N/A	28.2	+	40.1	+	24.4	+	responder
103	1	59.4	+	<5.00	-	2.6	-	non-responder
104	2	31.8	+	115	+	11.6	+	responder
105	2	152	+	138	+	30	+	responder
106	0	<5.0	-	<5.0	-	0.1	-	-
108	N/A	216	+	20	+	54	+	responder
110	1	<5.0	-	<5.0	-	4.2	-	non-responder

* Compound heterozygous patient.

N/A information not available.

Fois PLOS One 2020

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Retrospective Study Supports Safety of Immunization in Inborn Errors of Metabolism (IEM)

Kaiser Northern California IEM cohort

- Infants
  - 77 with IEM
  - 1540 controls
- Children
  - 271 with IEM
  - 1540 controls

- No increased risk of Emergency Room visit or hospitalization at 30 days post-immunization
- There maybe increased risk of hospitalization 2 weeks post-immunization for the sickest IEM patients

Klein Pediatrics 2011

Retrospective Study Supports Safety of Immunization in Inborn Errors of Metabolism (IEM)

- Children aged 0-18 years w/ IEM
- N = 43 children w/ IEM
- Compared 30 days prior to 30 after immunization
- No difference in Emergency Room visits or hospitalizations in the 30 days after compared to the 30 days before immunization

Schmidt Pediatrics 2019

Important Caveats

- All of these studies were **retrospective**
  - High risk of multiple biases (ascertainment bias, chronology bias, etc)
- Only the immunization studies used control comparisons
- All of these studies looked at multiple different disorders
- **More work will be required to know with certainty what the risk of infection and the response to immunization is in any given person with a Primary Mitochondrial Disease**

Mitochondrial Medicine Society Recommendations: Routine Immunizations

- *Patients with mitochondrial diseases should be offered* ***age-appropriate vaccination*** *including the influenza vaccine as well as other relevant vaccines when there is an underlying pulmonary pathology (i.e., pneumococcal vaccine).*

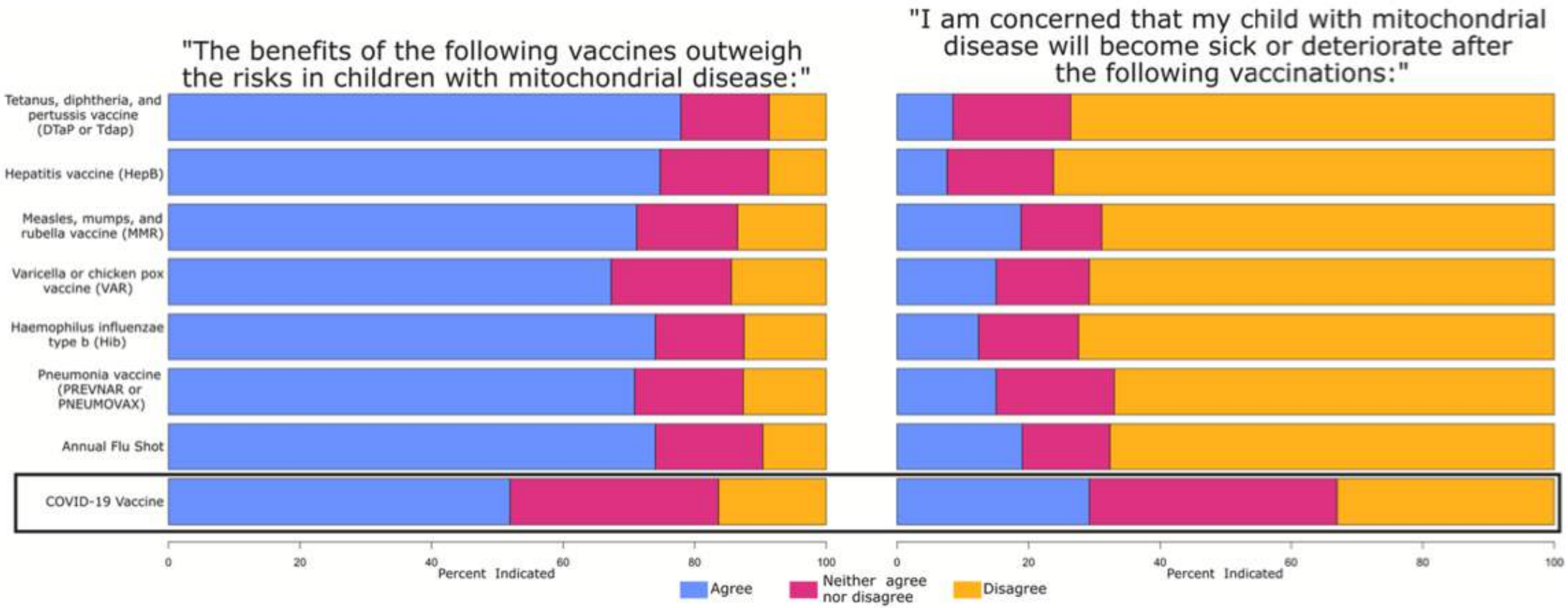
Parikh Genet Med 2017

Mitochondrial Medicine Society Recommendations: COVID19 Immunization

Are the COVID-19 vaccines recommended for mitochondrial disease patients?
Clinical trials have not been conducted in patients with rare diseases or children. Although knowledge concerning all the potential vaccine effects in mitochondrial disease is currently unknown, the safety profile of the vaccine so far suggests that the benefit of preventing COVID-19 infection outweigh the risk of vaccine reaction. We do expect patients with mitochondrial disease to have a similar response to the vaccine as the general population.

Mitochondrial Medicine Society:
https://www.umdf.org/mitochondrial-medicine-society-response-to-covid19-vaccine/

Parents of Children with Primary Mitochondrial Diseases think Vaccine Benefits Outweigh Risks



Gordon-Lipkin Research Dev Disabil 2022

Immune Cell Function in Mitochondrial Disorders:
A patient centered approach

- Mitochondria are intracellular organelles with multiple functions, disruption of which causes multisystem Primary Mitochondrial Disorders
- Immune Cells are specialized cells that move throughout the body to fight different types of infection in a cell-type specific manner
- Patients with Primary Mitochondrial Disorders ...
  - *May* have a higher risk of immune deficiency and/or infection
  - Are likely at higher risk of COVID19 complications if they have respiratory disease
  - Should be evaluated by an immunologist if they have recurrent or severe infections
  - *May* have differences in their ability to make antibodies after getting vaccines
  - Likely do not have have side effects requiring emergency room or hospital care 30 days after immunization
  - Have a likely greater potential benefit than risk with routine and COVID immunization

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