Qualitative Neutrophil Disorders

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Chief Hematology-Oncology Fellow
March 1st, 2017
Objectives

- Review normal neutrophil function and movement
- Review the enzymatic reactions in neutrophil
- Develop an approach to organizing various qualitative neutrophil disorders
- Review the qualitative neutrophil disorders
How this talk is going to go…

- Bolded in red are genes/enzymes that are associated with each disease
- Bolded in purple are things that are important or unique to that particular disease
- I recognize this is not the most exhilarating talk and it is 7AM so...
is the average number of "sheep counted" before someone falls asleep?

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When to suspect a qualitative WBC disorder?

- Clinical presentation is consistent with defective phagocytic function (i.e. chronic bacterial and/or fungal infections) and patient has normal ANC
REVIEW OF NEUTROPHIL FUNCTION/MOVEMENT
Adhesion defects
- Leukocyte adhesion defect I (LAD I; β integrin deficiency)
- LAD II (fucosylated [Sialyl Lewis] carbohydrate deficiency)

Chemotactic defects
- LAD I
- Chediak-Higashi syndrome
- Hyper IgE/Job syndrome
- Actin polymerization defect
- Localized aggressive periodontitis
- Acquired motility defects

Phagocytic defects
- LAD I
- Actin polymerization defect

Bacterial killing defects
- Chronic granulomatous disease
- Chediak-Higashi syndrome
- Neutrophil specific granule deficiency
- Neutrophil G6PD deficiency
Glucose-6-phosphate dehydrogenase is required for the production of NADPH, an essential component of the NADPH oxidase system (1). The phagocyte NADPH oxidase system generates $O_2^{-}$ by transferring e$^{-}$ from NADPH to O$_2$ (2). Superoxide is metabolized to H$_2$O$_2$ by superoxide dismutase (3). Hydrogen peroxide can follow different metabolic pathways inside the cell. Myeloperoxidase can convert it into HOCI (4), which is involved in the oxygen-dependent killing of microorganisms in combination with other reactive oxygen species (5). Alternatively, hydrogen peroxide can be degraded to H$_2$O and O$_2$, thereby avoiding deleterious effect on the cell (6). Hydrogen peroxide can also diffuse outside the cell and can augment other defective cells (7).

NADPH: reduced form of nicotinamide adenine dinucleotide phosphate; NADP$^+$: nicotinamide adenine dinucleotide phosphate; p47 phox: 47 kilodalton (KD) phagocyte oxidase; p67 phox: 67 kilodalton (KD) phagocyte oxidase; p40 phox: 40 kilodalton (KD) phagocyte oxidase; p22 phox: 22 kilodalton (KD) phagocyte oxidase; gp91 phox: 91 kilodalton (KD) glycoprotein oxidase; GTP: guanosine triphosphate; rap1: a small GTP hydrolase (GTPase); rac: GTPase-activating protein; H$_2$O$_2$: hydrogen peroxide; O$_2$: molecular oxygen; e$^{-}$: electron; $O_2^{-}$: superoxide anion; HOCI: hypochlorous acid.
Qualitative WBC Disorders

Enzymopathies
1. Chronic Granulomatous Disease
2. Myeloperoxidase Deficiency
3. Severe G6PD Deficiency
4. Glutathione Synthase Deficiency

Adherence and Movement Disorder
1. Leukocyte Ahesion Deficiency Type 1
2. Leukocyte Ahesion Deficiency Type 2
3. Hyperimmunoglobulin IgE syndrome

Granular Disorder
1. Chediak-Higashi Syndrome
2. Neutrophil Specific Granule Deficiency
ENZYMOPATHIES
A 30-year-old female suffers from recurrent infections due to fungus species, Pseudomonas species, and Staphylococcus aureus. The patient's neutrophils are examined in the laboratory and they fail to react during the nitroblue tetrazolium test. Which of the following is most likely dysfunctional in this patient?

- Lymphocytes
- Immunoglobulin class switching
- Superoxide dismutase
- Myeloperoxidase
A 5-year-old female suffers from recurrent infections by Aspergillus species, Pseudomonas species, and Staphylococcus aureus. The patient's neutrophils are examined in the laboratory and they fail to react during the nitroblue tetrazolium test. Which of the following is most likely dysfunctional in this patient?

A: Lymphocytes
B: Immunoglobulin Class Switching
C: Superoxide Dismutaase
D: Myeloperoxidase
E: Respiratory Burst
Chronic Granulomatous Disease

- **Inheritance**: X-linked (70%) and rest are autosomal recessive
- **Incidence**: 1:200,000
- **Genes**: CYBB (X-Linked) and CYBA, NCF-1, NCF-2, NCF-4 (autosomal)
- **Defects**: NADPH oxidase
Glucose-6-phosphate dehydrogenase is required for the production of NADPH, an essential component of the NADPH oxidase system (1). The phagocyte NADPH oxidase system generates O²⁻ by transferring e⁻ from NADPH to O₂ (2). Superoxide is metabolized to H₂O₂ by superoxide dismutase (3). Hydrogen peroxide can follow different metabolic pathways inside the cell. Myeloperoxidase can convert it into HOCI (4), which is involved in the oxygen-dependent killing of microorganisms in combination with other reactive oxygen species (5). Alternatively, hydrogen peroxide can be degraded to H₂O and O₂, thereby avoiding deleterious effect on the cell (6). Hydrogen peroxide can also diffuse outside the cell and can augment other defective cells (7).

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Chronic Granulomatous Disease

- **Inheritance**: X-lined (70%) and rest are autosomal recessive
- **Incidence**: 1:200,000
- **Genes**: CYBB (X-Linked) and CYBA, NCF-1, NCF-2, NCF-4 (autosomal)
- **Defects**: NADPH oxidase
- **Issue**: inability of neutrophils to make superoxide which is the major mechanism of intracellular killing of bacteria (lack of respiratory burst)
- **Treatment**: prophylactic antibiotics/antifungal, chronic IFN reduces infections by ~70%, HSCT is curative
- **Diagnosis**:
  - *Flow Cytometry*: inability to reduce dihydrodamine (DHR) to its fluorescent form
  - *NBT Slide Test*: inability to reduce nitroblue tetrazolium
Testing of the ability of neutrophils to generate superoxide is used in the diagnosis of chronic granulomatous disease (CGD). This testing can be done using flow cytometry to detect the ability to reduce dihydrorhodamine (DHR) to its fluorescent form, or the ability to reduce nitroblue tetrazolium (NBT), which is assayed on a slide. Normally functioning neutrophils will generate high fluorescence intensity from DHR (blue bar in flow cytometry panels) and high levels of reduced NBT (blue cytoplasm in cells on the slide). Refer to UpToDate topics on CGD and laboratory testing for disorders of neutrophil function for further details.

PMA: phorbol myristate acetate (used to stimulate neutrophils); DHR: dihydrorhodamine; NBT: nitroblue tetrazolium.
Myeloperoxidase Deficiency (MPO)

- **Inheritance**: autosomal recessive
- **Incidence**: most common disorder of phagocytes; 1:2,000-4,000
- **Issue**: mutations in **MPO gene** (chromosome 17)
Glucose-6-phosphate dehydrogenase is required for the production of NADPH, an essential component of the NADPH oxidase system (1). The phagocyte NADPH oxidase system generates $O_2^{-}$ by transferring $e^{-}$ from NADPH to $O_2$ (2). Superoxide is metabolized to $H_2O_2$ by superoxide dismutase (3). Hydrogen peroxide can follow different metabolic pathways inside the cell. Myeloperoxidase can convert it into HOCl (4), which is involved in the oxygen-dependent killing of microorganisms in combination with other reactive oxygen species (5). Alternatively, hydrogen peroxide can be degraded to $H_2O$ and $O_2$, thereby avoiding deleterious effect on the cell (6). Hydrogen peroxide can also diffuse outside the cell and can augment other defective cells (7).

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Myeloperoxidase Deficiency (MPO)

- **Inheritance**: autosomal recessive
- **Incidence**: most common disorder of phagocytes; 1:2,000-4,000
- **Issue**: mutations in **MPO gene** (chromosome 17)
  - MPO is the primary granule enzymes that catalyzes that conversion of H2O2 to hypochlorous acid that greatly enhances PMH microbicidal activity
- **Clinical**: (a) most patients (95%) are asymptomatic (b) increase in candidal infections especially in diabetics
- **Diagnosis**: histochemical assays for MPO on PMN
Severe Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

- **Issue**: G6PD is important for ensuring the adequate availability of NADPH which is needed for respiratory burst
Glucose-6-phosphate dehydrogenase is required for the production of NADPH, an essential component of the NADPH oxidase system (1). The phagocyte NADPH oxidase system generates $O_2^-$ by transferring $e^-$ from NADPH to $O_2$ (2). Superoxide is metabolized to $H_2O_2$ by superoxide dismutase (3). Hydrogen peroxide can follow different metabolic pathways inside the cell. Myeloperoxidase can convert it into HOCl (4), which is involved in the oxygen-dependent killing of microorganisms in combination with other reactive oxygen species (5). Alternatively, hydrogen peroxide can be degraded to $H_2O$ and $O_2$, thereby avoiding deleterious effect on the cell (6). Hydrogen peroxide can also diffuse outside the cell and can augment other defective cells (7).

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Severe Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

- **Issue**: G6PD is important for ensuring the adequate availability of NADPH which is needed for respiratory burst

- **Clinical**: **Caucasians** (not Asian or African-American) with severe G6PD with recurrent infections (present similarly to CGD), hemolysis

- **Diagnosis**: G6PD levels, **NBT dye reduction also negative**
Glycogen Storage Disease Type 1b (von Gierka Disease)

- **Issue**: inborn disorder of metabolism caused by inherited defects of the **glucose 6-phosphatase complex (chromosome 11)**

- **Presentation**:  
  - Hypoglycemia, hyperlactacidemia, hyperuricemia, **hepatomegaly**, growth retardation, osteopenia, enlarged kidneys, and neutropenia with neutrophil dysfunction (often ANC < 500)

- **Bone Marrow**: both myeloid hyper and hypo-cellularity have been reported

- **Etiology of Neutropenia**: PMNs have a striking tendency to undergo apoptosis in circulation

- **Treatment**: G-CSF reduces incidence of infection
Glutathione Synthetase Deficiency

- **Incidence**: very rare
- **Issue**: decreased production of glutathione (potent anti-oxidant) and those with deficiency have decreased respiratory burst
- **Presentation**: child with recurrent ear infection and hemolysis
- **Diagnosis**: low glutathione synthetase levels
ADHERENCE AND MOVEMENT
Which of the following patient presentations would be found in an infant with defective LFA-1 integrin protein on phagocytes, in addition to recurrent bacterial infections?

- Eczema and thrombocytopenia
- Skin infections with absent pus formation, delayed umbilicus separation
- Cardiac defects, hypoparathyroidism, palatal defects, and learning disabilities
- Chronic diarrhea, oral candidiasis, severe infections since birth, absent thymus

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Which of the following patient presentations would be expected in an infant with defective LFA-1 integrin (CD18) protein on phagocytes, in addition to recurrent bacterial infections?

A: Eczema and thrombocytopenia
B: Skin infections with absent pus formation, delayed umbilicus separation
C: Cardiac defects, hypoparathyroidism, palatal defects, and learning disabilities
D: Chronic diarrhea, oral candidiasis, severe infections since birth, absent thymus
E: Progressive neurological impairment and cutaneous telangiectasia
Leukocyte Adhesion Deficiency I (LAD-I)

- **Inheritance**: autosomal recessive
- **Issue**: reduction/absence of **beta-2 intergrin (CD18)** that results in inability of neutrophils to leave the circulation in response to infection (PMNs can roll but unable to adhere firmly or emigrate to tissue)
Adhesion defects
- Leukocyte adhesion defect I (LAD I; β integrin deficiency)
- LAD II (fucosylated [Sialyl Lewis] carbohydrate deficiency)

Chemotactic defects
- LAD I
- Chediak-Higashi syndrome
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- Actin polymerization defect
- Localized aggressive periodontitis
- Acquired motility defects

Phagocytic defects
- LAD I
- Actin polymerization defect

Bacterial killing defects
- Chronic granulomatous disease
- Chediak-Higashi syndrome
- Neutrophil specific granule deficiency
- Neutrophil G6PD deficiency
Leukocyte Adhesion Deficiency I (LAD-I)

- **Inheritance**: autosomal recessive
- **Issue**: reduction/absence of **beta-2 intergrin (CD18)** that results in inability of neutrophils to leave the circulation in response to infection (PMNs can roll but unable to adhere firmly or emigrate to tissue)
  - Beta-2 Intergrin is a heterodimer of alpha subunits (**CD11a/b/c**) and beta subunit (**CD18**)
- **Clinical**: delayed separation of umbilical cord, delayed wound healing, recurrent bacterial infections (not viral)
- **Lab**: *peripheral and marrow neutrophilia*
- **Diagnosis**: flow cytometry against CD11b or CD18
- **Treatment**: allogenic HSCT (5 year survival rate of 75%)
Flow cytometry for CD11b in leukocyte adhesion deficiency I (LAD-I).

Flow cytometry on stimulated neutrophils from an individual with normal neutrophil function, an LAD-I carrier (heterozygote), and moderate and severe LAD-I, showing CD11b fluorescence (solid line) versus a nonspecific control (dashed line). Percentages refer to the amount of fluorescence intensity relative to the normal control.
Leukocyte Adhesion Deficiency II (LAD-II)

- **Issue:** decreased sialyl-Lewis-X (sLeX) on the PMN surface due to defect in fucose transferase enzyme
  - sLeX mediates selectin-mediated rolling adhesion of PMNs to the vascular endothelium, chemotaxis, and phagocytosis
Adhesion defects
- Leukocyte adhesion defect I (LAD I; β integrin deficiency)
- LAD II (fucosylated [Sialyl Lewis] carbohydrate deficiency)

Chemotactic defects
- LAD I
- Chediak-Higashi syndrome
- Hyper IgE/Job syndrome
- Actin polymerization defect
- Localized aggressive periodontitis
- Acquired motility defects

Phagocytic defects
- LAD I
- Actin polymerization defect

Bacterial killing defects
- Chronic granulomatous disease
- Chediak-Higashi syndrome
- Neutrophil specific granule deficiency
- Neutrophil G6PD deficiency
Leukocyte Adhesion Deficiency II (LAD-II)

- **Issue**: decreased sialyl-Lewis-X (sLeX) on the PMN surface due to defect in fucose transferase enzyme
  - sLeX mediates selectin-mediated rolling adhesion of PMNs to the vascular endothelium, chemotaxis, and phagocytosis
- **Clinical**: mental retardation, short stature, abnormal facies, mild neutrophilia, recurrent infections (not as bad as type 1)
- **Diagnosis**: flow cytometry with absence of CD15a (sLeX)
Flow cytometric analysis of adhesion molecules on neutrophils
A 5-year-old boy with a history of multiple infections presents with an intensely itchy rash. His skin is covered with a purpuric, hematous, crusty, scaly rash. Excoriations are seen where he scratched his skin. His face has thickened skin (coarse facies) and a wide-set nose. He has several abscesses without any pus formation over his arms. Labs come back with IgE levels of 3000 IU/mL. Which gene of the following is most likely involved?

- LYST
- STAT3
- MLL
- DPHase

Start the presentation to activate live content.
A 3-year-old boy with a history of multiple infections presents with an intensely itchy rash. His skin is covered with an erythematous, crusty, scaly rash. Excoriations are seen where he scratched his skin. His face has thickened skin (coarse facies) and a wide-set nose. He has several abscesses without any pus formation over his arms. Labs come back with IgE levels of 3000 IU/mL. Which gene of the following is most likely involved?

A: LYST  
B: STAT3  
C: MLL  
D: NADPH Oxidase  
E: MPO
Hyperimmunoglobulin E Syndrome (Job Syndrome)

- **Inheritance**: autosomal dominant/recessive and sporadic
- **Mutation**: STAT3 (60-70%) and DOCK8 (many of autosomal recessive forms)
- **Characteristics**: disorder of cytokine function associated with (a) abnormal T cell function (b) increased IgE production (c) intermittent defects in PMN chemotaxis
- **Clinical**: recurrent infection (bacterial and fungal), dermatitis, skeletal and dental abnormalities
  - Recurrent *staphylococcal infection of skin and lungs*
- **Diagnosis**: marked elevation of IgE, Th17 (helper) cell, and genetic testing
DISORDERS OF GRANULES
3 year female with fair skin and silvery hair is evaluated for recurrent bacterial infections and easy bruising. Medicine team calls you to review case and smear (below)

What gene mutation do you suspect is affected?
A: LYST
B: DOCK8
C: SBDS
D: G6PD
E: MPO
What gene mutation do you suspect is affected?
3 year female with fair skin and silvery hair is evaluated for recurrent bacterial infections and easy bruising. Medicine team calls you to review case and smear (below)

What gene mutation do you suspect is affected?
A: LYST
B: DOCK8
C: SBDS
D: G6PD
E: MPO
Chediak-Higashi Syndrome

- **Inheritance**: autosomal recessive
- **Issue**: primarily a granule fusion defect that affects WBCs, nerve endings, and melanocytes.
  - Granule defect in WBC results in defects in chemotaxis and bactericidal killing
- **Presentation**: partial albinism, mild bleeding diathesis, peripheral neuropathy, predisposition to hemophagocytic syndromes after viral infection (i.e. EBV), mild neutropenia as well ineffective erythropoiesis
- **Mutation**: LYST (lysosomal trafficking gene) that encodes a protein necessary for vesicle transport (chromosome 1)
- **Treatment**: only curative therapy is HSCT
CHEDIAK-HIGASHI NEUTROPHIL

Large, cytoplasmic lysosomal inclusions

Neutral staining specific granules

Mature, segmented nucleus

10 μm

Rashidi H MD, Nguyen J MD et al. HematologyOutlines.com
Figure 15-2  Photomicrographs of blood smears showing typical neutrophil morphology from (a) a healthy individual; (b) a patient with sepsis showing Döhle bodies (arrow) and toxic granulations; (c) a patient with Chédiak-Higashi syndrome showing large cytoplasmic inclusions.
Neutrophil-Specific Granule Deficiency

- **Inheritance:** autosomal recessive
- **Incidence:** extremely rare
- **Mutation:** C/EBP-episolon
- **Clinical:** increased susceptibility of pyogenic infections
- **Diagnosis:** peripheral blood smear for paucity/absence of granules and bilobed nuceli (pseudo Pelger-Huet anomaly)
brings his 3-year-old son to the pediatrician concerned about his health. He states that throughout his son's life he has had recurrent infections despite proper treatment and hygiene. Upon reviewing the patient's chart, the pediatrician notices that the child has been infected multiple times with S. aureus, Aspergillus, and E. coli. Which of the following would confirm the most likely cause of this patient's symptoms?

- Negative nitroblue-tetrazolium test
- Normal dihydrorhodamine (DHR) flow cytometry test
- Positive nitroblue-tetrazolium test
A father brings his 3-year-old son to the pediatrician because he is concerned about his health. He states that throughout his son's life he has had recurrent infections despite proper treatment and hygiene. Upon reviewing the patient's chart, the pediatrician notices that the child has been infected multiple times with S. aureus, Aspergillus, and E. coli. Which of the following would confirm the most likely cause of this patient's symptoms

A. Negative nitroblue-tetrazolium test  
B. Normal dihydorhodamine (DHR) flow cytometry test  
C. Positive nitroblue-tetrazolium test  
D. Increased IgM, Decreased IgG, IgA, and IgE  
E. Increased IgE and IgA, Decreased IgM
Conclusions/Review
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cellular abnormality</th>
<th>Immune defect</th>
<th>Associated infections and other diseases</th>
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<tr>
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<td>Defective CD18 (cell adhesion molecule)</td>
<td>Defective migration of phagocytes into infected tissues</td>
<td>Widespread infections with capsulated bacteria</td>
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<td>Defective NADPH oxidase. Phagocytes cannot produce $O_2^-$</td>
<td>Impaired killing of phagocytosed bacteria</td>
<td>Chronic bacterial and fungal infections. Granulomas</td>
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<td>Deficiency of glucose-6-phosphate dehydrogenase. Defective respiratory burst</td>
<td>Impaired killing of phagocytosed bacteria</td>
<td>Chronic bacterial and fungal infections. Anemia is induced by certain agents</td>
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<td>Deficiency of myeloperoxidase in neutrophil granules and macrophage lysosomes and impaired production of toxic oxygen species</td>
<td>Impaired killing of phagocytosed bacteria</td>
<td>Chronic bacterial and fungal infections</td>
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<td>Defect in vesicle fusion</td>
<td>Impaired phagocytosis due to inability of endosomes to fuse with lysosomes</td>
<td>Recurrent and persistent bacterial infections. Granulomas. Effects on many organs</td>
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<td>Chediak-Higashi syndrome (CHS)</td>
<td>CBC, BM evaluation</td>
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<td>Characteristic very large granules in leukocytes</td>
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<td>Leukocyte adhesion deficiency-I (LAD-I)</td>
<td>CBC, flow cytometry for deficiency of CD11b/CD18</td>
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<td>Neutrophilic leukocytosis, omphalitis in newborn period</td>
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<td>Chronic granulomatous disease (CGD)</td>
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<td>Hyperimmunoglobulin E (IgE) syndrome (Job syndrome)</td>
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<td>Oculocutaneous albinism, peripheral neuropathy, and large granules in WBC</td>
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<td>Shwachman-Diamond Syndrome</td>
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