Innate host defense against infections: lessons learned from the clinic

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Immune function

**Innate**
- Phylogenetically more primitive
- Phagocytes (neutrophils, macrophages, eosinophils)
- Dendritic cells
- NK cells
- Complement
- Chemoattractants (C5, LTB4, PAF, N-formyl peptide, chemokines)

**Adaptive**
- Phylogenetically more advanced
- Specific response to foreign antigens
- Cell-mediated immunity
- Humoral immunity
Basic requirements of phagocytes

- Adequate numbers
- Migrate to where they are needed
- Sense and respond to microbes
- Sense and respond to inflammatory mediators (e.g., cytokines, chemokines)
- Kill pathogens
- Mechanisms to “turn off” inflammation once pathogen threat has been eliminated
Neutrophil development

G-CSF
C/EBPε

Myeloblast
Promyelocyte
Myelocyte
Metamyelocyte
Band
Segmented

1° granules (azurophilic)
MPO
Collagenase
β-glucocuronidase
Defensins

2° granules (specific)

3° granules (gelatinase)
Neutrophil granules

NUCLEUS

PRIMARY (AZUROPHILIC) GRANULES

GIANT (FUSED) lysosome of Chediak-Higashi syndrome

SECONDARY (SPECIFIC) GRANULES
(ABSENT IN NEUTROPHIL SPECIFIC GRANULE DEFICIENCY)
Neutrophil trafficking

http://www.youtube.com/watch?v=WEGGMaRX8f0&feature=player_detailpage
Sensing microbes and mediators of inflammation
Innate Immunity against Aspergillus

Segal, BH, N Engl J Med. 2009 Apr 30;360(18):1870-84
Intracellular killing

Phagolysosome:

Mechanisms of killing
-- Acidification
-- Antimicrobial proteins
-- Reactive oxidant and nitrogen intermediates
When to think of a primary phagocytic disorder?

• Usually (not always) first manifest during childhood
• Unusually severe or recurrent infection by common pathogens
  – *S. aureus* liver abscess
  – Multiple soft tissue infections requiring I&D
  – Severe dental infections --> premature tooth loss
• Opportunistic pathogens
  – Molds, candidiasis, nocardiosis, atypical mycobacterial infection (disseminated)
When to think of a primary phagocytic disorder?

• Systemic features
  – CGD --> inflammatory complications
  – Chediak-Higashi --> oculocutaneous albinism
  – HIESRI (Job’s) --> atopic dermatitis, skeletal/craniofacial abnormalities

• Family history
Management: basic principles

- Patients may be sicker than they look
- Aggressively pursue a microbiologic dx -- “Tissue is the issue”
- Prolonged systemic antimicrobial therapy
- Surgical debridement of localized disease
- Prophylactic ABX
- Cytokine therapy, granulocyte transfusions, BMT, gene therapy
Neutrophil disorders

- Quantitative
- Qualitative phagocytic disorders
  - Adhesion (Leukocyte adhesion deficiency)
  - NADPH oxidase (CGD)
  - Granular deficiencies (MPO deficiency, Chediak-Higashi, specific granular deficiency)
  - Job’s
Neutropenia: secondary causes

• Cytotoxic agents
  – Used principally as antineoplastic chemotherapy
• Other drugs with potential for marrow suppression
  – Bactrim, chloramphenicol, linezolid, ganciclovir, zidovudine, clozoril
• Immune-mediated
• Infections
  – Overwhelming sepsis, neonatal sepsis, viral
Risk of infection related to degree of neutropenia
Severe chronic neutropenias

- Heterogenous group of rare disorders
  - Congenital (Kostmann syndrome)
  - Cyclic neutropenia
    - Linked to mutations in Neutrophil Elastase gene
  - Adult-onset cyclic neutropenia
  - Primary autoimmune
Neutrophil disorders

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Skin Infection in LAD I

- Minimal to no erythema
- Failure to form pus at the site of infection
- Healing with dysplastic scars
- Often requiring prolonged antibiotic course and surgical debridement
How do neutrophils kill pathogens?
How do neutrophils kill pathogens?

• Neutrophils kill microorganisms through oxygen-independent and oxygen-dependent mechanisms

• Oxygen-independent mechanisms include the release of peptides and proteins from the granules, such as bactericidal permeability-increasing proteins (BPI), defensins and cathelicidins
NADPH oxidase

Cytoplasm

\[ \text{HEME} \]

\[ \text{HOCI} \rightarrow \text{MPO} \]

\[ \text{H}_2\text{O}_2 \]

\[ \text{SOD} \]

\[ \text{O}_2 \]

\[ \text{O}_2^- \]

\[ e^- \]

\[ \text{p22}^{\text{phox}} \]

\[ \text{gp91}^{\text{phox}} \]

\[ \text{FAD} \]

\[ \text{rac} \]

\[ \text{GTP} \]

\[ \text{GDP} \]

\[ \text{p47}^{\text{phox}} \]

\[ \text{p40}^{\text{phox}} \]

\[ \text{p67}^{\text{phox}} \]

\[ \text{NADPH} \rightarrow \text{NADP}^+ + \text{H}^+ \]

Activation
NUCLEUS

PRIMARY (AZUROPHILIC) GRANULES

GIANT (FUSED) LYSOSONE OF CHEDIAK-HIGASHI SYNDROME

SECONDARY (SPECIFIC) GRANULES

(Absent in neutrophil specific granule deficiency)
Neutrophil extracellular traps (NETs)

Shigella

Candida
Neutrophil disorders

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Chronic granulomatous disease (CGD)

- Inherited deficiency of NADPH oxidase
- X-linked and AR forms
- Incidence ~ 1 in 250,000
- Major pathogens
  - Staph aureus (deep soft tissue, pneumonia, liver)
  - Nocardia (lung, brain, bone/soft tissue)
  - Burkholderia cepacia (pneumonia)
  - Serratia (bone)
  - Aspergillus and other moulds (lung, disseminated)
NADPH oxidase

Cytoplasm

Activation

p22\textsubscript{phox}  gp91\textsubscript{phox}  p22\textsubscript{phox}  gp91\textsubscript{phox}  p47\textsubscript{phox}  p40\textsubscript{phox}  p67\textsubscript{phox}  rac

HEME  FAD  HEME  HEME  HEME  HEME

RhoGDI

NADPH  NADP\textsuperscript{+} + H\textsuperscript{+}

HOCI  H\textsubscript{2}O\textsubscript{2}

SOD  O\textsubscript{2}  O\textsubscript{2}\textsuperscript{-}

e\textsuperscript{-}  e\textsuperscript{-}

GTP  GDP
Infectious complications in CGD patients
Inflammatory complications of CGD
Prophylaxis in CGD

• Several non-randomized studies have shown benefit of antibacterial prophylaxis
• Bactrim is most commonly used
• randomized placebo-controlled study showed protective benefit of itraconazole prophylaxis (Gallin et al. NEJM, 2003)
rIFN-g prophylaxis in CGD

- rIFN-g increased phagocyte superoxide production in vitro
- increased reactive oxidant intermediates (ROI) production in human monocytes ex vivo after administration of rIFN-g to patients with advanced malignancy and lepromatous leprosy
- Early studies in patients with CGD showed that rIFN-g led to partial restoration of NADPH oxidase function, increased NADPH oxidase constituents, and enhanced bactericidal and fungicidal killing
rIFN-g and prophylaxis in CGD

- These preliminary studies led to an international, double-blinded, placebo controlled trial of IFN-g therapy as prophylaxis in CGD.
- IFN-g reduced the number and severity of infections in CGD by about 70%, regardless of antibiotic prophylaxis or genetic subtype of CGD.
- However, no augmentation of NADPH oxidase activity occurred.
- Benefit of prophylactic rIFN-g likely occurs mainly through non-oxidative dependent mechanisms.
Current and future approaches

- Allogeneic stem cell transplantation
- Gene therapy
  - Major hurdle is maintenance of a stable long-term population of gene-corrected cells
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Myeloperoxidase deficiency

• Most common primary phagocytic disorder, affecting ~ 1 in 2000
• Usually asymptomatic
• Occasionally invasive candidiasis observed in diabetics with MPO
• Diagnosis made by direct assay of MPO
Chediak-Higashi syndrome

- severe autosomal recessive condition of *LYST* gene (lysosomal trafficking regulator)
- partial oculocutaneous albinism with photophobia
- increased susceptibility to infections (mostly *Staphylococcus* and streptococci)
- Neurologic manifestations
- widespread visceral infiltration of lymphohistiocytic cells gives rise to fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, bleeding
- most children dying before age of 10 from an accelerated lymphomatous phase
CHS

-- Abnormally large leukocyte granules result from fusion of lysozymes.
-- may affect granulocytes and monocytes
-- Chemotaxis and phagocytosis are defective
-- Platelets lack dense granules and platelet function is abnormal.
Albinism associated with CHS
Neutrophil disorders

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Job’s syndrome

- Hyper-IgE syndrome with recurrent infections (HIESRI)
- Severe eczema starting at infancy
- Deep soft tissue infections (cold abscesses), usually caused by Staphylococcus aureus
- Pneumonias (pneumatoceles)
- ↑IgE
- Differentiate from atopic dermatitis by frequency and severity of infections
- Non-immunologic manifestations
  - Delayed shedding of the primary teeth owing to lack of root resorption, recurrent fractures, hyperextensible joints and scoliosis, characteristic facial appearance
Pneumonia with pneumatocele in a patient with Job’s
Failure of Dental Exfoliation in Patients with the Hyper-IgE Syndrome

Characteristic Facial Appearance of Men and Women of Different Races with the Hyper-IgE Syndrome

Serum IgE Levels in Patients with the Hyper-IgE Syndrome Whose Levels Declined

Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome

PBLs from Job’s patients

-- Normal STAT3 levels at baseline and after IFN-α stimulation
-- Decreased DNA binding of STAT3
-- Defective responses to IL-6 and IL-10
-- Reduced Th-17 development and IL-22-induced signaling

Holland et al. NEJM, 2007
Chronic intracellular infections

- Herpes viruses
- Mycobacteria
- Certain fungi (e.g., Histoplasma)
- Require ongoing surveillance
- Don’t believe anyone that says the immune system evolved for cancer surveillance…
M. tuberculosis

- Worldwide
  - > 1 Billion people infected
  - 8 million new cases per year
  - 3 million deaths per year
- Person-to-person contact through inhalation
- Prolonged multi-drug regimen
Disseminated Mycobacterium avium infection in a patient with IFN-g receptor deficiency
Dendritic cells (DCs) prime naïve T cells

http://dermatology.cdlib.org/111/reviews/acne/jones.html
Conclusions

• Primary phagocytic defects are for the most part rare
• Many have extra-immunologic manifestations
• “Experiments of nature” teach us about neutrophil development and host defense pathways
• Management relies on targeted prophylaxis, vigilance for early signs of infection, and judicious diagnostic work-up
• Opportunities for novel therapeutics (e.g., cytokines, BMT, gene therapy)