Genetics Susceptibility to Infectious Diseases

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Learning Objectives

• Define and classify primary immunodeficiency diseases

• Review the role of clinical laboratory in the diagnosis of primary immunodeficiency diseases

• Demonstrate the utility of molecular diagnosis in primary immunodeficiency diseases

• Review the genetics of
  (1) Mendelian susceptibility to chronic mucocutaneous candidiasis
  (2) Mendelian susceptibility to mycobacterial infections
  (3) Herpes simples encephalitis
Primary immunodeficiency (PID): genetic

(Secondary immunodeficiency: infection, malignancy, iatrogenic)

PID - changing definition:
from very severe Mendelian traits to varying degree of susceptibility to infections
Identification of patients with PID

- Diagnosis of PIDs requires integration of data from clinical findings with laboratory immunological analyses and genetic testing

  → Infections
    - recurrent
    - life-threatening
    - unusual

  → Autoimmune diseases

  → Malignancies
Primary immunodeficiencies

PIDs are like other genetic diseases, but

- **Diagnosis:**
  - secondary causes of ID are more common than primary (esp. in adults)
  - manifestations (infections) can be the same in both primary and secondary ID as well in “healthy” individuals

- **Therapy(!):**
  - Hematopoietic Stem Cell Transplantation (HSCT) (gene therapy)
  - Replacement, anti-microbials
Clinical and family history-based diagnostic approach

Diagnostic immunology lab supports, refine phenotype
Diagnosis of PIDs

Clinical and family history-based diagnostic approach

Diagnostic immunology lab supports, refine phenotype

Molecular lab
## Mutation analysis in PIDS

- Definitive diagnosis (atypical presentations)
- Presymptomatic identification
- Carrier identification, genetic counseling, prenatal diagnosis
- Prognosis (strong genotype-phenotype correlation)
- Technical considerations (DNA stability vs. live cells)
Mutations in PIDs

- ~200 recognized PIDs, >250 genes (growing fast ~1/month)
  - candidate genes
  - mapping studies
  - novel technologies (genome/exome)

- Pathways not genes - Mendelian susceptibility to:
  - chronic mucocutaneous candidiasis
  - mycobacterial infections
  - herpes simplex encephalitis

- Normal vs. immune deficient (not all-or-nothing)
  - quantitative traits/pathways
Candida albicans is present in GI flora and reproductive mucosa of healthy subjects.

Immunocompromised patients C albicans can cause systemic or mucosal disease.

Systemic candidiasis is an acute, disseminated, and invasive disease. Candidemia is one of the most prevalent bloodstream infections in hospital settings and is associated with significant morbidity and mortality.

CMC is localized to the skin, nails, and mucous membranes (no predisposition to invasive disease, such as sepsis or pneumonia).
Immunity to candida

• Impaired T cell immunity: HIV/AIDS, SCID, DiGeorge syndrome, DOCK8 deficiency, etc.

• Congenital neutropenias or secondary neutropenia (e.g. after chemotherapy)

• Recognition:
  - mannans (outer portion of the cell wall)  
    → TLR4, Mannose Receptor, DC-SIGN, and Dectin2
  - β-glucans (inner portion of the fungal cell wall)  
    → Dectin1, and MINCLE
Genetics of CMC

- Dectin-1 deficiency (AR)
- CARD-9 deficiency (AR)
- AD Hyper IgE syndrome or Job syndrome: STAT3 deficiency
- AR Hyper IgE syndrome: DOCK8 deficiency
- STAT1 mutations (AD)
- IL-17F deficiency (AR)
- IL-17RA deficiency (AR)
- APECED (or APS type I): AIRE deficiency (AR)

Molecular testing → diagnosis, prognosis, inheritance

Immune response: receptors → signaling → effector functions
Fungal Pathogen Associated Molecular Patterns (PAMPs)

O-linked mannans, Zymosan

Toll-Like Receptors

TLR2

TLR4

DC-SIGN

MINCLE

Mannose R

β-glucan

Dectin1*

Dectin2

N-linked mannans

C-type lectin receptors

Toll-Like Receptors

MyD88

Signaling complex

NF-κB activation

CARD9*

Signaling complex

AIRE*

IL1β

Pro-IL1β

Th17 priming cytokines

Co-stimulatory molecules

Fungal Pathogen Associated Molecular Patterns (PAMPs)

O-linked mannans, Zymosan
**Fungal Pathogen Associated Molecular Patterns (PAMPs)**

O-linked mannans, Zymosan

Toll-Like Receptors

TLR2, TLR4, Dectin1*, Dectin2, MyD88, CARD9*, Mannose R, DC-SIGN, MINCLE

**Signaling complex**

NF-κB activation

β-glucan

Pro-IL1β, IL1β

Th17 priming cytokines, Co-stimulatory molecules

IL1β, IL6, IL23, TGFβ

Naïve T cells

STAT1*, STAT3*
**Fungal Pathogen Associated Molecular Patterns (PAMPs)**

O-linked mannans, Zymosan

Toll-Like Receptors

TLR2, TLR4

MyD88

NF-κB activation

CARD9*

Dectin1*

β-glucan

Dectin2

N-linked mannans

C-type lectin receptors

DC-SIGN, MINCLE, Mannose R

Pro-IL1β

IL1β

Th17 priming cytokines

Co-stimulatory molecules

IL1β, IL6, IL23, TGFβ

Naïve T cells

STAT1

STAT3*

Th17 cells

IL17A/F

Fungal Pathogen Associated Molecular Patterns (PAMPs) include O-linked mannans, Zymosan, and β-glucan. These PAMPs are recognized by Toll-Like Receptors (TLR2, TLR4) and C-type lectin receptors (Dectin1*, Dectin2) which activate MyD88 and CARD9 signaling complexes. This leads to the activation of NF-κB, resulting in the production of IL1β, Pro-IL1β, Th17 priming cytokines, and co-stimulatory molecules. Naïve T cells are primed to differentiate into Th17 cells, which produce IL17A/F.
Fungal Pathogen Associated Molecular Patterns (PAMPs)

O-linked mannans, Zymosan

Toll-Like Receptors

MyD88

NF-κB activation

CARD9*

β-glucan

Dectin1*

Dectin2

N-linked mannans

C-type lectin receptors

O-linked linked mannans, Zymosan

IL1β, IL6, IL23, TGFβ

Th17 priming cytokines

Co-stimulatory molecules

Naïve T cells

Th17 cells

IL17A/F

CCR4 / CCR6 → Chemotaxis

IL22 and Inflammatory cytokines

STAT1

STAT3*

Naïve T cells

Th17 cells
Fungal Pathogen Associated Molecular Patterns (PAMPs)

- O-linked mannans, Zymosan
- TLR2, TLR4
- DC-SIGN, MINCLE, Mannose R
- Dectin1, Dectin2
- Pro-IL1β, IL1β
- Th17 priming cytokines, Co-stimulatory molecules

**Signal Transduction Pathways**

- MyD88
- CARD9
- NF-κB activation
- STAT1, STAT3
- Th17 cells
- IL17A/F
- CCR4 / CCR6 → Chemotaxis
- AR Dectin1 deficiency
- AR CARD9 deficiency
- AR IL17RA deficiency
- Gain-of-Function STAT1
- Dominant neg. (Job syndrome)
- IL1β, IL6, IL23, TGFβ
- AIRE

**Autoimmune Diseases**

- Anti-IL17 Autoantibody (APECED)
- IL22 and Inflammatory cytokines

**Immune Cells**

- Naïve T cells
- Th17 cells

**Pathways**

- Toll-Like Receptors
- C-type lectin receptors
- Fungal Pathogen Associated Molecular Patterns (PAMPs)
- AR Dectin1 deficiency
- AR CARD9 deficiency
- AR IL17RA deficiency
Immunity to candida

• Gain-of-function STAT1 mutations:
  → dimorphic fungi:  - coccidioidomycosis
  - histoplasmosis

• CARD9 deficiency:
  → increased risk of invasive candidiasis
    (Candida dubliniensis meningoencephalitis)

Mendelian susceptibility to mycobacterial disease

- Predisposition of otherwise apparently healthy individuals to infections caused by weakly virulent mycobacteria Bacille Calmette Guerin (BCG) and atypical (or nontuberculous) mycobacteria, *M. tuberculosis* and Salmonella

- Genes:
  - IFNGR1 (AR/AD)
  - IFNGR2 (AR)
  - STAT1 (AD)
  - IL12B (AR)
  - IL12RB1 (AR)*
  - NEMO (IKBKG) (XL)
  - CYBB (XL)
  - IRF8 (AR/AD)
  - ISG15 (AR)
  - TYK2 (AR)

→ Impaired IFN-γ-mediated immunity (~50% have unknown genetics)
Herpes Simplex Encephalitis

- HSE is the most common cause of sporadic fatal encephalitis worldwide (70% mortality if untreated)
- Acyclovir
- Lifelong neurological sequelae of varying severity in survivors is common (>30%)
- Genes:
  - TLR3 (AR/AD)
  - UNC-93B (AR)
  - TRIF (AR/AD)
  - TRAF3 (AD)
  - TBK1 (AD)
  - NEMO (XR)
  - STAT1 (AR)
  - TYK2 (AR)
Herpes Simplex Encephalitis

- TLR3* (AR/AD TLR3 deficiency)
- UNC93B* (AR UNC93B def.)
- TRIF* (AR/AD TRIF def.)
- TRAF3*
- TBK1*
- NEMO* (XD NEMO def.)
- NF-κB activation
- Type I/III IFN

- dsRNA
- Endosome

- AR STAT1 def.
- RNaseL, PKR

- IFNα/β
- IFNLR1
- IFNAR1
- IFNAR2
- IL10RB
- ISRE

- Interferon Response Genes

- AD TRAF def.
- AD TBK1 def.
Different genes – same/similar clinical phenotype

- **CMC:**
  - IL-17RA, IL-17F, STAT1, DECTIN1, CARD9, STAT3, DOCK8, AIRE

- **MSMD:**
  - IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1, NEMO, CYBB, IRF8, ISG15, TYK2

- **HSE:**
  - TLR3, UNC-93B, TRIF, TRAF3, TBK1, NEMO, STAT1

→ Molecular networks/pathways, not genes
→ Single gene testing vs. gene panels
One gene – multiple phenotypes

• **AD STAT1** deficiency: *dominant negative* mutations
  ➔ susceptibility to mycobacterial and salmonella infections

• **AD STAT1** deficiency: *gain-of-function* mutations
  ➔ chronic mucocutaneous candidiasis

• **AR STAT1** deficiency: *loss-of-function* mutations
  ➔ susceptibility to severe viral and mycobacterial disease
Genetic susceptibility

• Monogenic primary immunodeficiency diseases
  – Classic PIDs: opportunistic infections
  – Novel PIDs: restricted susceptibility/single organisms (e.g. HSE is genetic)
    → rare

• Immune response is a complex trait
  – complex traits (such as height and weight), arise from the combination of large number of (hundreds/thousands) of individual small genetic effects across the genome
  – Genome Wide Association Studies (GWAS) Increasing knowledge
    → Common (everybody!)
Genetic susceptibility

- Candida infections (Smeekens et al. 2013):
  - Dectin1 → Candida colonization
  - TLR1/2/3/4 → Susceptibility candidemia
  - IL4/MBL2/NLPR3 → Recurrent vulvo-vaginal candidiasis

- Tuberculosis susceptibility (Barreiro et al. 2012; Qu et al. 2011):
  - MSMD and TB: monozygotic/dizygotic twin studies
  - DUSP14 → pulmonary TB
  - HLA/NRAMP1/IFNG/IL12B/NOS2A

- Susceptibility to HSV encephalitis:
  - HSE (de Diego et al. 2013)
  - TLR3 variants → Resistance to HSV2 (Svensson et al. 2012)

→ Pathways
Genetic susceptibility

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→ Pathways
Genetic susceptibility - Environment

- Genetic variants: ‘pathogenic’, ‘neutral’, ‘beneficial’
- HbS, HbC, and α-thalassemia → protection from malaria

- CCR5Δ32
  → Protection against HIV infection (Liu et al. 1996)
  → Increases risk of symptomatic West Nile virus infection (Glass et al. 2006)

→ Europe 3-16% allele frequencies (south to north)
References

- Primary Immunodeficiencies

- Chronic Mucocutaneous Candidiasis
  - Smeekens SP et al. EMBO Mol Medicine 5:805-13, 2013

- Mendelian susceptibility to mycobacterial disease
  - de Beaucoudrey L et al. Medicine 89:381-402, 2010

- Genetic susceptibility to herpes simplex encephalitis