Immunological Competition and the Infant Immune Response to Vaccines

Richard Insel
University of Rochester
Goals

• Neonatal and Infant Immune System
• Broad Effects of Vaccines on Immunity or Immune Responses
• Vaccine Antigen Competition or Interference
Immunologic Responses to Vaccines

Innate Immunity

Adaptive Immunity
Activation of Antibody Responses by Vaccines

Vaccine Antigens and Adjuvant → Peptide-specific T Cell → Activated T Cell → Activated B Cell

Antigen Presentation by Dendritic Cell

Memory B Cell → Antibody Secretion → Plasma Cell
Neonatal and Infant Immune System

- Intact but naïve immune system
- “Immaturity” of innate and adaptive immunity
- Human neonatal immune system is more “mature” than murine immune system
- Stringent activation requirements
- Environmental influences
- Vaccine and age-specific effects
Neonatal Innate Immunity

- Decreased dendritic cell migration, differentiation, maturation, T-cell activation, IL-12 production - upregulated by cytokines
- Decreased NK cell and ADCC activity - upregulated by cytokines
- Decreased soluble proteins - complement, etc.

- Insufficient exposure to microbial products
Neonatal/Infant T-Cell Immunity

- No T-cell memory, naïve repertoire
- Decreased proliferation, cytokine responses (IFN$\gamma$, IL-2), higher activation threshold, costimulation imperative, diminished CTL responses
- Can generate adult-like Th1-type responses to BCG, not to measles vaccine

- Vaccine-specific, age-specific responses, not intrinsic T-cell deficiency but optimal APC-T cell interactions are critical
Neonatal/Infant B-Cell Immunity

- Low and transient and lower affinity antibody titers
- Inhibited by maternal antibody
- Decreased germinal centers but activation of memory B cells > induction of primary antibody responses
- Restricted repertoires/responses
- Age-related hierarchy of responses (polysaccharides, paramyxoviruses)
Neutralizing Antibody Responses After Measles (A) or Mumps (B) Immunization

Broad Effects of Vaccines on Immunity or Immune Responses

- ? Antigen-specific immune tolerance (anergy, deletion)
- ? Global immune deviation (Th1↔Th2)
- ? Global immune unresponsiveness
Immunization-Induced Antigen-Specific Immune Tolerance

• No evidence of immune tolerance to FDA licensed vaccines
• Hib-OMP vaccine in neonates, high dose PS vaccines in infants generated transient decreased immune responses to reimmunization
• Neonatal immunization with Hepatitis B and BCG are immunogenic and with Hib-TT conjugates primes
Immunization-Induced Immune Deviation

- Neonatal or infant BCG immunization, which induces adult-like Th1 immune responses (IFN-γ, IL-12), fails to polarize simultaneous or subsequent immune responses to Hepatitis B and other vaccines

Arnaud Marchant, Martin Ota, Claire-Anne Siegrist
The Gambia: MRC Laboratories, EPI Program
Switzerland: Centre for Neonatal Vaccinology
Influence of BCG on Antibody and Cytokine Responses to Vaccination in Early Life

<table>
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Newborns Develop a Th1 Type Immune Response to BCG Vaccination

IFN-γ Production by CD4 Lymphocytes Following Neonatal BCG Vaccination

Vekemmans A et al, Eur J Imm 2001; 31:1531.
BCG Increases both Th1 and Th2 Cytokine Responses to HBV

IFN-γ (pg/ml)

IL-5 (pg/ml)

IL-13 (pg/ml)

Age at sampling

BCG at 4.5 months
BCG at 2 months
BCG at birth

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No Influence of BCG on Global Cytokine Responses

IFN-γ (pg/ml)

IL-5 (pg/ml)

IL-13 (pg/ml)

Controls : BCG at 4.5 months
BCG at 2 months
BCG at birth

Birth               2months            4.5 months
Birth               2months            4.5 months
Birth              2months           4.5 months

P = 0.92
P = 0.47
P = 0.92
P = 0.14
P = 0.48
P = 0.20
P = 0.86
P = 0.79
P = 0.37
P = 1.0

A. Marchant, M. Ota, C.A. Siegrist
BCG Does Not Induce Th1 Cytokine Responses to TT

- IFN-γ (pg/ml)
  - Controls: BCG at 4.5 months
  - BCG at 2 months
  - BCG at birth

- IL-5 (pg/ml)

- IL-13 (pg/ml)

A. Marchant, M. Ota, C.A. Siegrist
Non Specific Effects of Vaccination in Early Life

- BCG does not Th1 polarize HBV or TT T-cell responses in neonates or infants
- BCG increased antibody responses to HBV but not to TT or DT
Immunization-Induced Global Immune Unresponsiveness

- No conclusive evidence
- Measles vaccine may alter delayed hypersensitivity skin tests to TB but does not activate or promote TB infection
- Measles and BCG immunization are associated with decreased infant mortality in the developing world (Shann F, BMJ 2000; 321:1424)
Immunization-Induced Global Immune Unresponsiveness

Broad Effects of Vaccines on Immunity or Immune Responses

- Low antigen dose of vaccines (killed or replicating) vs infection
- Continuous mucosal antigenic exposure - circulating bacterial DNA
- Immunization commences after 1-2 months of age
- Neonatal human immune system more mature than neonatal mouse immune system
- “Immune Space” is vast, memory pool size
- “Set Points” for immune responses
Antigenic Competition or Interference

- Old observation
- Multifactorial
- Multiple vaccines
Antigenic Competition or Interference: Variations

- High dose antigenic tolerance
- Immune response to one determinant inhibited by prior or simultaneous exposure to antigens on same or different molecules
- Carrier-induced epitopic suppression
- T cell responses to dominant, subdominant, cryptic epitopes
- Interclonal competition
- Original antigenic sin
Antigenic Competition or Interference

• Recent human vaccine issues
  – *Haemophilus influenzae* b combination vaccines
  – Pneumococcal conjugates
  – Other- Hepatitis, Poliovirus
## Interference in Generation of Antibodies to Hib After Primary Immunization with Hib Conjugates and DTPa-Based Combinations

<table>
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<th>Hib Conjugate</th>
<th>Associated DTPa (n)</th>
<th>Schedule (Age in Months)</th>
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Antibody (Ab) to HibPS Induced by DTPa/Hib Combination Vaccines

- ↓↓ total and IgG Ab and % >1μg/ml with primary immunization series
- ↓ total and IgG Ab to booster immunization with either HibPS or DTPa/HibPS
- ↓ Ab to carrier protein (TT, DT)
Decreased Hib and TT Ab with Increased TT Protein in Combination Vaccines

Micrograms of TT protein: 39, 48, 63, 111

Antigen Uptake and Presentation of Combination Vaccines
Vaccine Competition or Interference

• Antigen capture
  – B cell vs B cell
  – B cell vs dendritic cell
• Antigen processing, presentation, recognition
  – Immunodominant vs cryptic epitopes
• $T_H$ cell activation
  – $T_H1/T_H2$, anergy
B Cells as Antigen Presenting Cells (APCs)

- More efficient at low antigen doses than professional APC
- Virgin, not memory, T cells tolerized by antigen presented by B cells
Decreased Immunogenicity of Vaccines

• High dose protein
  – Carrier-induced epitopic suppression
  – T cell anergy, immune deviation, suppression or immunoregulation
Carrier-Induced Epitopic Suppression (CIES): Pathogenesis

- Increased carrier-specific B cells
- Memory B cells generated but fail to differentiate to AbSC - reversible
- Antigen presentation
Carrier-Induced Epitopic Suppression (CIES): Pathogenesis
B Lymphocyte Competition for Ag Capture/Presentation and T Cell Help
Antigen Processing and Presentation in Antigenic Competition and CIES

- CIES prevented with DC, adjuvants
- Competition for:
  - uptake and processing
  - MHC loading and antigen presentation
  - APC cytokines
- Competition of T cells for access to APC (peptide, factors, co-stimulation)
Antigenic Competition
Antigenic Competition

- Epitope dominance
- Interclonal competition
- Interference
- Immune deviation
- Anergy
- Immunoregulation
Antigenic Competition or Interference

- More apparent with immature immune system
- More apparent for “immature” immune responses
- Greater for “subdominant” epitopes
- Serum antibody (plasma cell production) preferentially affected compared to generation of memory B cells
Goals

• Neonatal and Infant Immune System
• Broad Effects of Vaccines on Immunity or Immune Responses
• Vaccine Antigen Competition or Interference
Gaps in Knowledge

- Human vaccine immunology studies
- Evidence-based approaches
- Ontogeny of human immunity
- Vaccine-innate immunity interactions
- Genetic differences in immune responses