(Almost) All Immunity is Local—Implications for Vaccines from Tissue Immunodynamics

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February 7, 2017
Antibody and T Cell Levels—A Broad Picture of Immunity but Does not Provide Tissue Level Resolution

Antibodies: Percent of adult levels

Janeway’s Immunobiology 7th Edition

Farber et al Nature Reviews Immunology 2014
Importance of Characterizing Immune Cells in Tissues

- Peripheral blood provides an incomplete picture
  - Blood contains less than 3% of total T cells
  - Lacks significant information about local immunity, such as T-, B-, and antigen presenting cells of mucosal tissues

- Dynamic changes occur in different tissues from infancy through adulthood

- Immune memory is established and maintained in tissues

- Most previous studies were from mice or human tissues removed during surgery; systematic studies of healthy humans now feasible
Characterization of T cells in Tissue Compartments of Healthy Human Transplant Donors

- TCM—T central memory
- TEM—T effector memory
- TEMRA—Terminal effector

Adopted from Thome et al... Farber, DL; Cell159:814-828 (2014)
Major Human Memory T Cell Subsets by Tissue

a

Spleen

Lymph node

Lungs

Bone marrow

Integrin α2

Blood

CCR4
CLA
CCR10

Skin

Lymph node

Intestine

CCR6

CCR7

CCR0
Integrin α4β7

b

Circulating memory T cells

Resident memory T cells

Farber et al Nature Reviews Immunology 2014
Findings from Recent Human Tissue Compartmentalization Studies

- T cells are the major immune cell population in tissues.
- T cell subsets are similarly distributed across healthy individuals of a given age group.
- Memory T cells predominate in all tissues and accumulate with age; however, aging memory cells exhibit reduced effector function.
# Emerging Model of Human T Cell Memory Dynamics According to Age and Organ/Tissue

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<thead>
<tr>
<th>Localization</th>
<th>Frequency</th>
<th>Specificity (Extrapolated from published studies)</th>
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Implications for Vaccines

- T cell memory establishes early in life—importance of first vaccines
- Antigen specificities differ by organ and account for differences in protection at distinct sites
- Responses to commensal microbiota are important for establishing and maintaining immune defenses and regulatory responses in mucosal tissues and skin
- Regulatory T cells are strongly expressed in most infant tissues except lungs and small intestines—sites to induce immune protection in early life
- Dendritic cells and other antigen presenting cells provide a sentinel function in skin and intestines
Adjuvants for More Effective Vaccination at Different Ages

- Antigen presenting cells that initiate responses in different tissues and age groups require activation via their innate immune receptors by adjuvants
  - Infants—may need adjuvants to promote long-lived Th1 responses not achieved with alum (e.g. pertussis)
  - Elderly—The GSK trial shingles vaccine contained an adjuvant (AS01) especially effective in older adults

- Adjuvants specifically designed for boosting secondary responses are needed
Pertussis Vaccine Adjuvants Related to Long-Term Protection

- Whole cell pertussis vaccine (discontinued in the US) provided long term immunity
  - Adjuvant activity provided by bacterial cell wall components
  - Reactogenicity varied with vaccine strain

- Acellular pertussis vaccine exhibits waning immunity
  - Adjuvant activity provided by alum (Th2 promoting)
  - Animal model data suggest that an adjuvant eliciting Th1 and Th17 immunity may lead to longer memory
  - Will the acellular vaccine become reactogenic with such an adjuvant?
New Developments in Vaccine Adjuvants: Separating Efficacy from Toxicity

Focusing Responses to the Less Inflammatory Trif Pathway
This TRIF-selective signaling response resulted in the production of substantially less of the proinflammatory mediators that are associated with MyD88 signaling, thereby potentially reducing toxicity and improving the therapeutic index of this syntheticTLR4 agonist and vaccine adjuvant.
A Non-Inflammatory Adjuvant in Development

Vaccine

Volume 30, Issue 36, 3 August 2012, Pages 5373–5381

Advax™, a polysaccharide adjuvant derived from delta inulin, provides improved influenza vaccine protection through broad-based enhancement of adaptive immune responses

Yoshikazu Honda-Okubo*, Fadi Saade*, Nikolai Petrovsky*
Multiplexed Ion Beam Imaging: New Technology for Monitoring Immunity in Tissues

From: Multiplexed ion beam imaging of human breast tumors
Current NIH Research Programs that Address Human Immune Complexity

- Human Immunology Project Consortium
- Sample-Sparing Assays
- Mucosal Immunology Studies Team
- Infant and Elderly Immunity
- ImmPort Database
- Immune Epitope Database
- NIH Tetramer Facility
- Multiple grants/contracts on
  - Metabolomics
  - Antigen processing and presentation
  - Adjuvants/combination adjuvants