Rudiments of vaccine design

Last Time: continued discussion of stealth particles
           basic immunobiology underlying vaccination

Today: basics of vaccine design and vaccine immune responses


Supplementary Reading:

ANNOUNCEMENTS:

Note on take-home exam: 6-page limit includes any schematics or figures from the literature (1/3 of space max)
KEY EFFECTORS OF ADAPTIVE IMMUNITY

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1) Attraction to sites of infection

2) Antigen loading and activation

3) Trafficking to lymph nodes

4) Activation of naïve T cells in the lymph nodes

**Chemotaxis:**
Migration ‘up’ concentration gradients of chemoattractant
PAMP recognition of microbes by dendritic cells

Immune cells integrate many signals to ‘fingerprint’ pathogens:

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Biology of dendritic cells in T cell activation

Classical pathways of antigen processing and presentation:

- classical Class I antigen loading pathway
- exogenous ANTIGEN
- Classical II antigen loading pathway
Antigen is one of (at least) two signals that must be delivered by a vaccine.

- MAXIMAL T CELL PROLIFERATION
- GENERATION OF FULL EFFECTOR FUNCTIONS
- GENERATION OF MEMORY T CELLS
- NO T CELL ACTIVATION
- T CELLS TOLERIZED

Signal 1 - antigen
Signal 2 - costimulation
B cell activation

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Induction of immunological memory (the basis of vaccination)

OBJECTIVES OF VACCINATION

T + B MEMORY:

MEM. T CELLS ➔ RESPOND QUICKLY DIRECTLY AT INFECTION SITE

POPULATE PERIPHERAL TISSUES

(NAIVE T STAY IN CIRCUIT LNS ↔ BLOOD)

MEM. B CELLS ➔ BONE MARROW / PERIPHERAL TISSUES

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Prophylactic vs. therapeutic immunization

Two situations where vaccination is of interest:

(1) Therapeutic vaccine:  
- Treat an ongoing condition
  - Cancer
  - HIV
  - Generate effector cells against pathogen/tumor
  - Made challenging by ongoing "subversive functions of microbes/tumors"

(2) Prophylactic vaccine:  
- Prepare memory cells against future exposure
  - Made challenging by need for safety
ROUTES OF IMMUNIZATION

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Rudimentary components of vaccines

• Antigen: FRAGMENT FROM ORIGINAL PATHOGEN / TUMOR, OFTEN PROTEIN (PEPTIDE FOR T CELLS)
  ALUM DRIVES "TH2" RESPONSE → GENERATES ABS, \( \uparrow \) BUT T CELL RESPONSE \( (ALLERGIC REACTION) \) IS POOR

• Adjuvant: "2ND SIGNAL" THAT ACTIVATES DCs, PROMOTES EFFECTOR AND MEMORY LYMPHOCYTE DEVELOPMENT
  DEPOT / ANTIGEN
  \( \rightarrow \) ONLY 2 FDA-APPROVED ADJUVANTS:
  1. ALUM (ALUMINUM HYDROXIDE)
  2. MF59 (SQUALANE / OIL) + SURFACTANTS
Compositions of vaccines - clinical and experimental

- **Live attenuated pathogen**
- **Killed pathogen**

  - **Traditional**: e.g., adenoviral vectors
  - **Live**: e.g., Polio vaccine
    - Fixation or disruption
    - Manufacture and characterization is challenging
    - Safety is an issue (e.g., HIV)
    - Strongest immune response
      - Built-in adjuvant
      - Self-replicating antigen
Compositions of vaccines - clinical and experimental

‘engineered’ vaccines:

• Subunit vaccines
  – Whole protein
  – Peptide vaccines
  – Virus-like particles

- EASIER MANUFACTURE/CLEAN
- BETTER SAFETY
- IMMUNE RESPONSE NOT AS STRONG AS LIVE VECTORS

PURIFIED PROTEIN + ADJUVANTS

WEAK CD8+ T CELL RESPONSES

GREAT Ab RESPONSES

CROSS PRESENTATION
Compositions of vaccines - clinical and experimental

‘engineered’ vaccines:

• DNA vaccines

- DNA is cheap, robust
- Not yet effective in humans

Dendritic cell

CD4+ T cells

CD8+ T cells

Inject (naked) DNA

Self-replicating antigen

Encoding antigen
Compositions of vaccines - clinical and experimental

‘engineered’ vaccines:

• DNA vaccines
Existing vaccines

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Existing vaccines

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Biomaterials to adjuvant subunit vaccines:

intracellular drug delivery and the design of protein and peptide vaccines that stimulate cytotoxic T cell responses
Cross presentation and Particulate antigen delivery

- Classical Class I antigen loading pathway
- Exogenous ANTIGEN
- Class II antigen loading pathway
- CD4+ T cells
- CD8+ T cells
Pathways of intracellular import

**Endocytosis:**
(nearly all cells)

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Pathways of intracellular import

macropinocytosis:

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Please see: http://www.cellsalive.com
How do exogenous antigens get presented on class I MHC?

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Particle-stimulated cross presentation

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Particle-stimulated cross presentation

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ENDOSOMAL ESCAPE:

Enhancing cross presentation
cytosolic delivery of large macromolecules
Mechanisms for endosomal escape by polymeric carriers

(1) ‘proton sponge’ effect

(2) Direct membrane interaction/destabilization

(3) pH-activated CPPs
Proton sponge effect

polyethyleneimine

Endosome interior

Ion transporters

Proton pumps

\[
\left( \text{NH CH}_2 \text{CH}_2 \right)_x \left( \text{N} \right. \left. \begin{array}{c} \text{CH}_2 \text{CH}_2 \text{NH}_2 \\ \text{CH}_2 \text{CH}_2 \text{NH}_2 \end{array} \right)_y
\]

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Further Reading

Further Reading