Immunization Safety Review Committee 11/12/01

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Autoimmunity

• Frequent in the population
• Subclinical autoimmune phenotypes are common
• Can occur in clusters (seasonal, geographic)
• Incidence is increasing
Progression to Autoimmunity

- Susceptibility
- Amplification
- Triggering
- Failure of Regulation

- An individual with potential for autoimmunity
- An individual prone to autoimmunity
- Subclinical autoimmunity with immune markers
- Autoimmune disease
Progression to Autoimmunity

- Susceptibility
  - Amplification
    - Triggering
      - Failure of Regulation
  - Genetic, guiding immune development
  - Environmental, expanding immune potential
    - Environmental, infectious or random tissue damage
  - Genetic & environmental
Are vaccines plausible environmental factors in progression to autoimmunity?

- Agent or Adjuvant?
- Accelerant or de novo Activator?
- At-risk subsets or general population?
Are vaccines plausible environmental factors in progression to autoimmunity?

- Specific antigenic stimuli (mimicry of self antigens); Triggering factors

- Stimuli of innate immunity exacerbating subclinical disease; Amplification factors

- Deviation of immune responses; Cofactors in impaired regulation
Mimicry

T cell specific for antigen

MHC molecule

T cell Receptor

Antigen Presenting Cell

Antibody specific for antigen
Plausibility? Example 1: mimicry

- Viral-immune T cells at high frequency in mice react with self antigens to give ocular keratitis.

Plausibility? Example 1: mimicry

- T cells from HSV-1 immunized mice transfer keratitis to recipients exposed to HSV-1; the self-antigen target is only recognized when the viral immunogen contains a mimetic sequence.

- HSV-1 extract injection
- HSV-1 mutant extract injection
- Mock extract injection

Plausibility? Example 1: mimicry

- Human T cell clones to MBP from MS patients;
- One immunodominant peptide used as motif for database search;
- 7 viral peptides, 6 bacterial peptides found;
- Little or no sequence homology with MBP;

Wucherpfennig, et al; Cell 80:695-705, 1995

Assessment: mimicry

- Rare
- Strong tolerance mechanisms to overcome
- Similar issues with natural infections
- No current methods to identify cryptic mimetics
- May be different for individuals with different genes; e.g., HLA
Plausibility? Example 2: innate mechanisms

Toll Receptors:

- Innate immune system;
- Danger signals;
- Pattern recognition;

Stimulate activation via multiple mechanisms, e.g. interferons, costimulation upregulation;

- Viral RNA pattern mimetic: poly I-C; recognized by TLR3;
- Bacterial DNA pattern mimetic: unmethylated CpG; recognized by TLR9;
Plausibility? Example 2: innate mechanisms

- Bacterial DNA pattern mimetic: unmethylated CpG; recognized by TLR9;
- Boost of pre-activated T cell response


Transfer of EAE by T cells Activated by CpG oligo
Plausibility? Example 2: innate mechanisms

Not all bacterial DNA is the same; outcomes variable

<table>
<thead>
<tr>
<th>Identification of CpG ODN with distinct immune profiles</th>
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<tbody>
<tr>
<td>Sequence</td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td>TCCATGACGTTCTGCCGTT</td>
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<tr>
<td>GGGGTCAACGTTGAGGAGGG</td>
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Murine spleen cell cultures, 4-24 hrs;
Assessment: Amplification via the innate immune system

- Likely
- May require pre-activation of potentially autoimmune cells
- Similar issues with natural infections
- No current methods to predict specific outcomes
- Both viral RNA and bacterial DNA implicated in experimental systems
Dysregulation: a balancing act

Influenced by:
- Cytokines
- Strength of response
- Costimulators
- Adjuvants
- Site of exposure
- Age
- Sex

Introduction of Antigen
Plausibility? Example 3: dysregulation

Relapsing EAE

- Cytokine modulation is a potent inducer and remitter of relapsing autoimmune encephalomyelitis

Plausibility? Example 3: dysregulation

- Bacterial DNA pattern mimetic: unmethylated CpG; recognized by TLR9;
- IL-12 dependent

Anti-IL-12 inhibits transfer of EAE by T cells activated by CpG oligo or bacterial DNA

Assessment: Dysregulation via cytokine deviation

- Possible
- May require pre-activation of potentially autoimmune cells
- Similar issues with natural infections
- Adjuvant matters
- Naïve cells may be sensitive to deviation as well
Progression to Autoimmunity
(Example from human autoimmune diabetes)

- Susceptibility
  - Genetic, ~10-15% of Caucasian population carry susceptibility alleles
- Amplification
  - Antigen exposure and cytokine milieu leading to determinant spreading, 1.6% of population have anti-islet antibodies
- Triggering
  - 0.4% of the population have clinically defined autoimmune diabetes
- Failure of Regulation
Questions

- Genetic, ~10-15% of Caucasian population carry susceptibility alleles

- Antigen exposure and cytokine milieu leading to determinant spreading, 1.6% of population have anti-islet antibodies

- 0.4% of the population have clinically defined autoimmune diabetes

Is the penetrance influenced by vaccines? (innate and specific activation & amplification)
Questions

- Genetic, ~10-15% of Caucasian population carry diabetogenic susceptibility alleles

- Antigen exposure and cytokine milieu leading to determinant spreading, 1.6% of population have anti-islet antibodies

- 0.4% of the population have clinically defined autoimmune diabetes

Is the outcome accelerated by vaccines? (innate and regulatory cytokine responses)
Conundrums

• Given the high frequency of susceptibility alleles, it is problematic to exclude individuals potentially genetically at-risk;
• We do not know if the increasing incidence is occurring in those with pre-existing autoimmunity or de novo;
• We do not currently use assays for the types of immune perturbations outlined when evaluating vaccines;
The Hygiene Hypothesis

Is the rising incidence of autoimmunity/allergy in childhood the result of reducing infectious stressors?

Is this a necessary and acceptable price to pay for the marked suppression in infant mortality from improved sanitation & vaccination?
The Hygiene Hypothesis

- Lack of conditioning of the immune response, leading to lack of counter-regulatory mechanisms (e.g., IL-10, TGFβ);
- Lack of maternal exposures, leading to deficient protective passive immunity in the neonate, with unbalanced responses in later childhood;
- Lower level of TH2 stimuli from gastrointestinal parasites in childhood;
The Hygiene Hypothesis

IL-10
TGFβ
Maternal Antibodies
Site

Antigen
Beyond the Hygiene Hypothesis

If childhood infections can be beneficial in conditioning the immune response, can vaccines be surrogates?

In murine models of IDDM, BCG and Q fever vaccines prevent diabetes.

IL-10
TGFβ
Maternal Antibodies
Site
Problems with the Hygiene Hypothesis as applied to vaccination strategies

- Vaccines do not prevent childhood or maternal exposure to many pathogens & immunogens
- Other potent environmental influences are more likely to be complicit (e.g., intestinal worms)
- Vaccination for diabetes prevention in murine models more likely due to TH2 skewing as an active immunoregulatory process; i.e., indirect immunotherapy, in the context of preclinical immunity.
The Bottom Line

• Improved maternal-child health has changed the immunologic milieu for early exposure to pathogens;
• There are overwhelming advantages on a population level (greatly decreased morbidity and mortality);
• One consequence is that childhood exposure to pathogens happens in a milieu lacking conditioning elements which may help establish host-pathogen balance.
• Innate immune pathways involving IL-12 production subsequent to LPS, viral RNA or bacterial DNA exposure may bias responses towards autoimmune potential.
The Bottom Line (cont.)

- Vaccines are one such potential exposure, along with viral and bacterial infections that provide similar stimuli; properties which likely contribute include the specific vaccine antigen, adjuvant, viral RNA or bacterial DNA content, and route of administration.
- Strong counter-regulatory mechanisms and tolerance fail-safe systems operate in vivo which attenuate risk in most individuals;
- In individuals with pre-existing autoimmunity (subclinical), such exposures may accelerate—earlier onset—or precipitate clinical autoimmune disease;
- The risk/benefit ratio for a given individual is not known;
- Methods to predict, monitor, recognize and intervene if necessary are lacking;