Vaccination and Autoimmune Diseases

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Vaccination and Autoimmunity

In relatively rare instances, vaccination has been associated with autoimmune diseases

Vaccine	Associated Auto-ID	Attributable cases / 10^5
Rabies (phenolized sheep brain vaccine)	**Encephalitis** anti-Myelin T-cells & Ab	30 - 300
Swine Influenza (1976-1977)	**Guillain-Barre** anti-ganglioside ab?? anti-myelin T-cells? ?	0.8-1.0
Pandemic Flu AS03-pH1N1	**Narcolepsy** anti-hypocretin T-cells???	2-6

Vaccination and Autoimmunity

- **Overwhelming number of individual case reports of autoimmune events following vaccination ; usually only reflecting temporal association with vaccination**
- **Google: vaccination+ autoimmunity = >2 million hits!**

"A study has documented that, given enough vaccine injections, everyone will develop an autoimmune disorder"

www.thelibertybeacon.com; allnurses.com;
ref to Tsumiyama et al., PLoS 2009 % 2014
Every 5 days,500 microgr OVA IP X 12/mouse

What is the real risk of autoimmunity following vaccination?

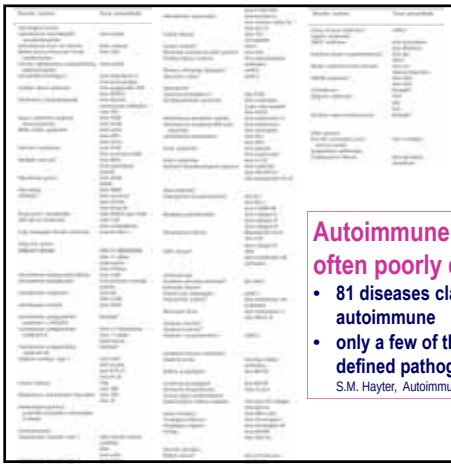
Autoimmune response ≠ Autoimmune disease

Autoimmunity

- **Antibodies or T-cells directed against self-antigens**
- Autoantibodies are quite frequent (e.g. in older adults); most often, not associated with pathologic consequences (low avidity, anti-intracellular ag)

Autoimmune disease

- **Pathology** directly or indirectly **caused by auto-reacting** antibodies or effector T-cells
- e.g.
  -Autoimmune Haemolytic Anemia: red cell destruction due to auto-antibodies.
  -Multiple Sclerosis: anti-myelin T-cell mediated pathology



Autoimmune diseases are often poorly defined

- **81 diseases classified as autoimmune**
- **only a few of these have a defined pathogenic process**

S.M. Hayter, Autoimmunity Reviews 2012

Level of evidence for auto-immune pathology

evidence of auto-immune process

Direct evidence of pathogenic autoantibody
e.g. AHA, SLE, Goodpasture, Myasthenia, Grave's (materno-foetal transfer!)

Indirect evidence of autoimmune pathogenesis
e.g. thyroiditis, multiple sclerosis, type1- diabetes (autoreactive T-cells within lesion)

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"Everything is autoimmune until proven otherwise"
Yehuda Shoenfeld, Clin Rev Allergy Immunol. 2013.

Suggestive evidence
-disease associated with presence of tissue specific auto-reactive antibodies or T cells
-strong association with a particular HLA haplotype (class II)

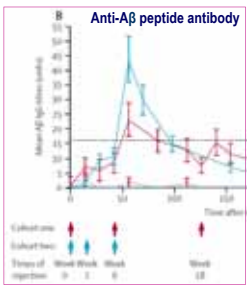
Questionable evidence
Idiopathic inflammation in presence of some auto-antibodies
e.g. ASIA syndrome

Many diseases are called "autoimmune" without much evidence for an autoimmune pathogenesis

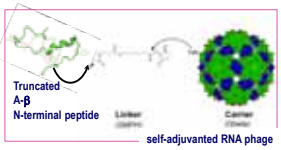
What is the risk of vaccination-induced autoimmune disease?

1- Lessons from intentional induction of autoimmune responses in human subjects

Human anti-self Amyloid β peptide vaccines (Alzheimer's disease)



Winblad B et al., Lancet Neurol. 2012,

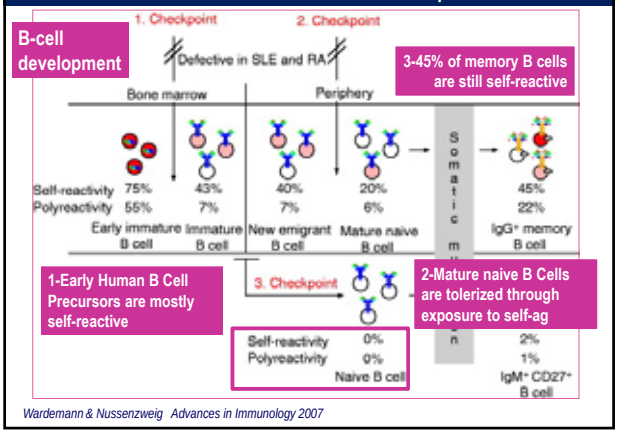


Inducing auto-antibody responses
Requirements:
1- self B-cell epitope (preferably from antigen with a low level of expression; no B-cell tolerance)

2- linked with dominant foreign CD4 T cell epitope(s) e.g. of microbial origin

3- in presence of appropriate co-stimulation

Human B-cell self-tolerance is incomplete



Wardemann & Nussenzweig Advances in Immunology 2007

What is the risk of vaccination-induced autoimmune disease?

2- Risk of vaccine-induced auto-antibody response ?

Risk of vaccine-induced auto-antibody response ?

Increased risk if:

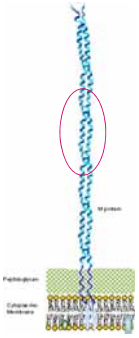
1- cross-reacting B cell epitope on vaccine antigen, particularly if :
- area of extensive sequence homology with a host antigen (e.g. >35% identity on >50-80 aa sequences)
- low level of expression of the homologous host antigen (e.g. myelin, gangliosides)

2- the cross-reacting epitope is linked with a dominant CD4 helper T cell epitope(s) of microbial origin

3- formulated with strong activator of Antigen Presenting Cells

Such risks are usually identified at pre- or early clinical stages; May be of little clinical relevance

Cross-reacting antibodies



VACINATION & B-CELL EPITOPE MIMICRY

Post-streptococcal immune-mediated syndrome (Rheumatic fever): anti-myosin antibodies

Extensive homology of Group A Streptococcal M5 protein peptide B2 and human cardiac myosin

Similar cross-reactive antibodies have been seen in clinical trials of some bacterial vaccines (Pn)- No Go!

VACINATION & B-CELL EPITOPE MIMICRY

Particular relevance for some polysaccharide vaccines

Structural homologies involving oligosaccharide (repetitive epitopes) have been sufficient to select out some vaccine antigens : No Go!

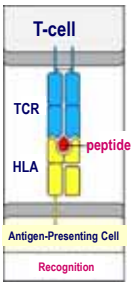
e.g.

- Campylobacter crossreaction of LPS with human gangliosides (risk of Guillain-Bare Syndrome!)
- Group B mening.: crossreaction of capsular PS with human Neural Cell Adhesion Molecule (NCAM)

What is the risk of vaccination-induced autoimmune disease?

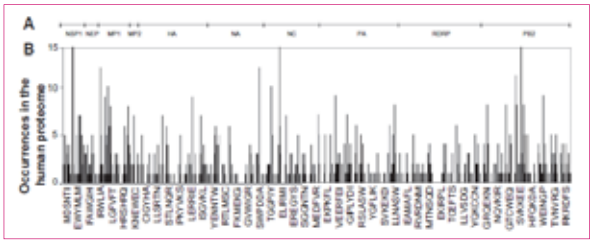
3- Risk of vaccine-induced autoimmune T-cell response ?

Importance of small peptide mimicry?



Sequence homologies between microbial proteins and human proteins are extremely frequent (6-9 mer peptides)

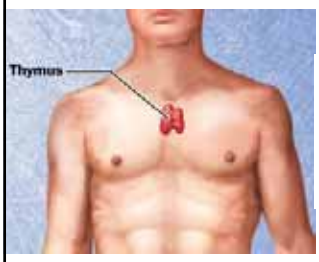
Similarity profile of influenza A H5N1 polyprotein vs the human proteome



The columns indicate the number of viral hexapeptide occurrences in the human proteome. .

Trost B. et al., Self/Nonself 1:4, 2010

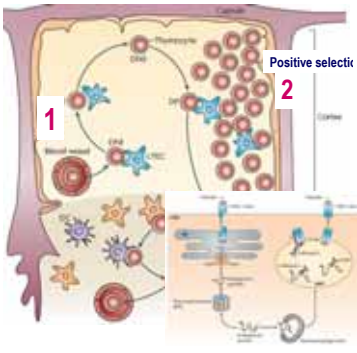
Mimicry is everywhere …



Thymus
main site of T-cell maturation, education and selection.

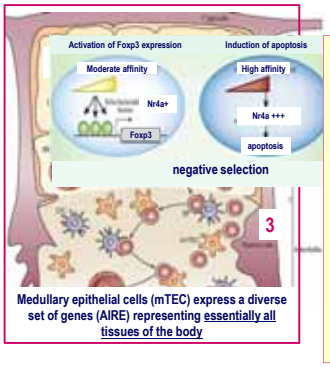
The development of the T-cell repertoire depends on self-recognition!

Development of T-cell repertoire depends on self-recognition



1. T-cell precursors migrating from BM to the thymus recognize a nearly infinite number of antigens.
2. Positive selection: only T-cells with sufficient affinity for endogenous self peptides* survive

(*presented on self HLA by cortical Thymus Epithelial Cells)



Medullary epithelial cells (mTEC) express a diverse set of genes (AIRE) representing essentially all tissues of the body

3. **Negative selection :**

T-cell that recognize self-peptides on self MHC (presented by medullar epithelial cells or cDC)

3.1 with high affinity: are eliminated by apoptosis

3.2 with moderate affinity: become CD4-Treg

3.3 with low affinity = survive & recognize foreign epitopes

Emigrant naïve T cells are all self-peptide reactive

The immune system has developed several strategies to prevent the activation of autoreactive T-cells in the periphery.

These include :

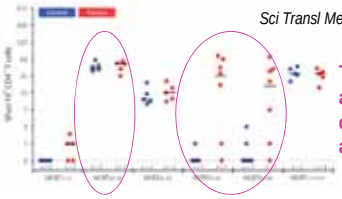
- **Inhibition by regulatory T-cells (Treg).**
- **Restriction of the expression of co-stimulatory molecules**
- **Expression of inhibitory receptors (e.g. Ctla-4, PD-1),**
- **Limiting the availability of growth factors (such as IL-2)**
- **Production of inhibitory cytokines (e.g. TGF-β)**

Autoimmune T-cell responses largely reflect missing tolerogenic signals or Treg dysregulation : relatively rare events

CD4+ T Cell Autoimmunity to Hypocretin/Orexin and Cross-Reactivity to a 2009 H1N1 Influenza A Epitope in Narcolepsy

Narcolepsy & T-cell epitope mimicry

Sci Transl Med **5**, 216ra176 (2013);



The presence of autoreactive T-cells does not imply an autoimmune process

- **anti-HCRT peptides T-cells do exist in healthy controls; additional specificities in NP**
- **modest increase of anti-HCRT56-68 & HCRT87-99 T-cell reactivity after H1N1 seasonal immunization**

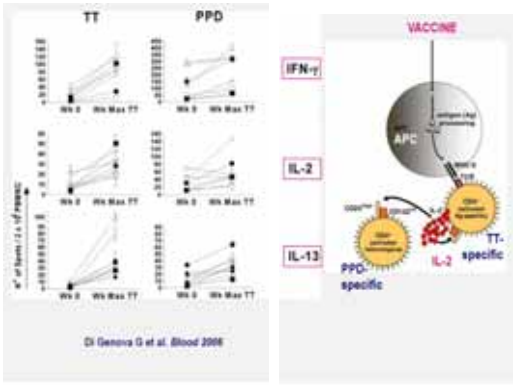
- **HLA-DQB1*06.02 is not expressed on neurons**
- *«Our results do not explain the particular association of narcolepsy with the Pandemrix vaccine." "Other factors are likely to be involved"*

What is the risk of vaccination-induced autoimmune disease?

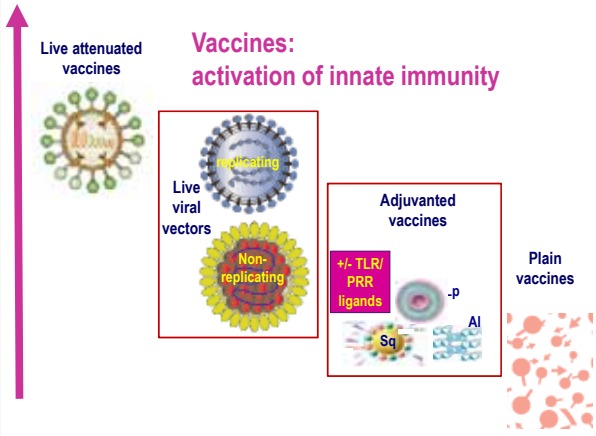
4- Can vaccines exacerbate a pre-existing autoimmune disease?

Importance of by-stander activation?

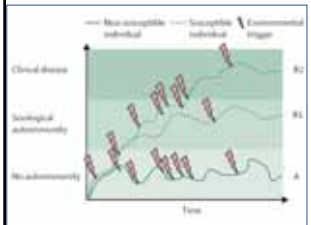
Human TT boosting can expand unrelated memory T-cells



Vaccines: activation of innate immunity



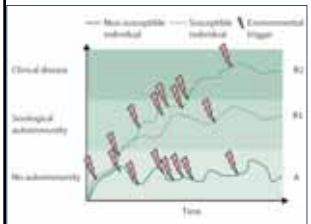
Role of environmental trigger & of genetic susceptibility in autoimmune diseases



Genetically susceptible and identical individuals (B1 and B2) might progress (or might not progress) into autoimmune disease depending on the environmental factors they are exposed to.

Wahren-Herlenius, M. Lancet 2013

Environmental trigger & genetic susceptibility in autoimmune diseases



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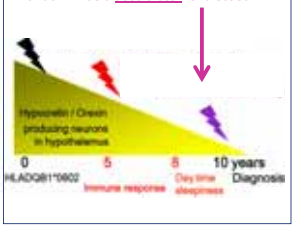
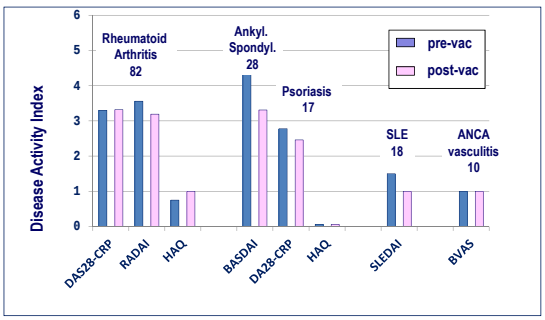
Narcolepsy-Cataplexy

-likely to be slowly progressive, over several years
- unknown immunological mechanism

-Pandemrix as a accelerator of disease?



Unchanged disease activity scores in patients with autoimmune rheumatic diseases after pH1N1-AS03 adjuvanted vaccine (2 doses)



Gabay C et al., Arthritis and Rheum. 2011

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VACCINATION AND AUTOIMMUNE DISEASES

1. Diagnosis of autoimmune events should be evidence-based and essential criteria should be respected
2. Temporal association of autoimmunity with vaccination is not sufficient to support a causal relationship. Most case reports are irrelevant if not confirmed by good epidemiological studies.
3. The risk of inducing pathogenic autoantibodies through epitopic mimicry is relatively low and can often be identified at early stage of vaccine development.

VACCINATION AND AUTOIMMUNE DISEASES

4. The risk of inducing cell-mediated autoimmune pathology through epitope mimicry appears extremely limited in the context of highly regulated T-cell responses.
   A causal relationship is rarely demonstrated.
5. Such rare events may reflect the acceleration of an on-going process in a context of individual genetic susceptibility.
6. The absence of disease exacerbation following adjuvanted H1N1 vaccines in patients with known autoimmune diseases is reassuring. It does not suggest a high risk of triggering an underlying autoimmune disease after vaccination.