From basic immune understanding to clinical breakthrough

Prediction and prevention of autoimmunity

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Baltimore
The mosaic of autoimmunity
Yehuda Shoenfeld MD, FRCP

Immune deficiency state
(IgA def., Tlr, Trg, C’ def., NK)

Genetic
HLA, Genes

Environmental
(Infection, Vacc, Drugs, UV, Smoking)

Hormonal
(Estrogen↑, Testosterone↓, Prolactin↑, Vit. D↓)

1989

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The mosaic of autoimmunity
(The factors associated with autoimmune disease)
Natural history of autoimmune diseases (AIDs)

SCREENING / PREVENTION?

PRECLINICAL PHASE

CLINICAL DISEASE

130 SLE subjects US Army
520 controls

US Army Serum Repository (sera stored up to 30 yrs)

→ 115 (88%) Ab positive before diagnosis
→ 0

Table 1. Detection of Autoantibodies before Diagnosis and before the Onset of Symptoms in 130 Patients with Systemic Lupus Erythematosus.*

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Positive Test before Diagnosis</th>
<th>Time from First Detection to Diagnosis</th>
<th>Positive Test in First Serum Sample</th>
<th>Total Patients with Positive Test</th>
<th>Interval between Positive Test and Diagnosis</th>
<th>Positive Test before Onset of Symptoms</th>
<th>Interval between Positive Test and Onset of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies</td>
<td>101 (78)</td>
<td>9.2</td>
<td>50</td>
<td>109 (84)</td>
<td>3.01±0.25</td>
<td>89 (77)</td>
<td>2.25±0.27</td>
</tr>
<tr>
<td>Anti-Ro antibodies</td>
<td>61 (47)</td>
<td>9.4</td>
<td>64</td>
<td>64 (49)</td>
<td>3.68±0.34</td>
<td>55 (48)</td>
<td>2.97±0.39</td>
</tr>
<tr>
<td>Anti-La antibodies</td>
<td>44 (34)</td>
<td>8.1</td>
<td>62</td>
<td>45 (35)</td>
<td>3.61±0.38</td>
<td>39 (34)</td>
<td>2.83±0.43</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>24 (18)</td>
<td>7.6</td>
<td>67</td>
<td>27 (21)</td>
<td>2.94±0.50</td>
<td>19 (17)</td>
<td>2.29±0.56</td>
</tr>
<tr>
<td>Anti–double-stranded DNA antibodies</td>
<td>72 (55)</td>
<td>9.3</td>
<td>48</td>
<td>80 (62)</td>
<td>2.24±0.31</td>
<td>54 (47)</td>
<td>1.24±0.31</td>
</tr>
<tr>
<td>Anti-Sm antibodies</td>
<td>41 (32)</td>
<td>8.1</td>
<td>31</td>
<td>49 (38)</td>
<td>1.47±0.34</td>
<td>28 (24)</td>
<td>0.47±0.44</td>
</tr>
<tr>
<td>Anti–nuclear ribonucleoprotein antibodies</td>
<td>34 (26)</td>
<td>7.2</td>
<td>23</td>
<td>43 (33)</td>
<td>0.88±0.32</td>
<td>23 (20)</td>
<td>0.20±0.47</td>
</tr>
</tbody>
</table>

PPV ranged from 95% (dsDNA) to 100% (Sm) (mean for all antibodies, 96%)
Specific autoantibodies precede the symptoms of Rheumatoid Arthritis


Table 2. Diagnostic value of IgM-RF and anti-CCP for RA

<table>
<thead>
<tr>
<th></th>
<th>Blood donor population 0–5 years before symptom onset</th>
<th>Risk of developing RA within 5 years (PPV, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity, %</td>
<td>Specificity, %</td>
</tr>
<tr>
<td>IgM-RF</td>
<td>20.5</td>
<td>98.6</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>28.9</td>
<td>99.5</td>
</tr>
<tr>
<td>IgM-RF or anti-CCP</td>
<td>36.5</td>
<td>98.1</td>
</tr>
<tr>
<td>IgM-RF and anti-CCP</td>
<td>13.0</td>
<td>100</td>
</tr>
</tbody>
</table>

* IgM-RF = IgM rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; PPV = positive predictive value; NPV = negative predictive value.
† Defined as individuals who have ≥2 first-degree relatives with rheumatoid arthritis (RA) (5-year incidence of RA among such individuals has been reported to be 3.9% [10]).
Multiple autoantibodies as predictors
Autoantibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients

Sherer Y, Gorstein A, Fritzler MJ, Shoenfeld Y.

Sherer-Shoenfeld; Volcano of autoantibodies-187

Yehuda Shoenfeld, MD, FRCP.
Kulmala P, et al.  

755 siblings of IDDM patients 
32 developed IDDM within 8 yrs

<table>
<thead>
<tr>
<th>Antibody</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>43%</td>
</tr>
<tr>
<td>IA-2</td>
<td>55%</td>
</tr>
<tr>
<td>GAD</td>
<td>42%</td>
</tr>
<tr>
<td>insulin</td>
<td>29%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1%</td>
</tr>
<tr>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>3-4</td>
<td>70%</td>
</tr>
</tbody>
</table>
Genetics and autoantinodies
In Caucasian patients the HLA A1, B8, DR3 haplotype carries a relative risk of 8.3 for the development of lupus.

A combination of autoantibodies to cyclic citrullinated peptide (CCP) and HLA-DRB1 locus antigens is strongly associated with future onset of rheumatoid arthritis

*Berglin E, et al.*
*Arth Res Ther 2004; 6; R303-8*

- SE (shared epitopes) (odds ratio [OR] = 2.35), anti-CCP antibodies (OR = 15.9), and IgA-RF (OR = 6.8) significantly predicted RA.

- Anti-CCP antibodies combined with SE had the highest OR (66.8, 95% confidence interval 8.3-539.4) in predicting RA.
Prediction of autoimmune rheumatic diseases; myth or reality?

N Bizzaro, Y Shoenfeld

Arthritis @Rheumatism 2007
Predicting and Preventing Autoimmunity

**Environmental Factors**
- Infections (EBV, CMV, HCV, *Helicobacter pylori, Streptococcus pyogenes*)
- UV light
- Vaccines (Diphtheria, Tetanus toxoid, Polio and measles vaccines → GBS, MMR vaccines → ITP-like thrombocytopenia, Rubella vaccine → Arthritis)
- Drugs (Hydralazine, Quinidine, Procainamide)
- Toxins (Silica dust, aromatic hydrocarbons, aliphatic chlorinated hydrocarbons, phthalate)
- Silicone implants (?)
- Hormones (pregnancy, ERT, OC, prolactin)
- Smoking
- Stress

**Candidate genes**
- C1q def.
- C4 def.
- C2 def.
- Selective IgA deficiency
- Complement abnormality
- HLA
- FcGR2A, FcGR3A, IL-10, CTLA-4, PDCD-1, TNFα, TNFβ, C4, MBL, FASL, FAS, Bcl-2

**The patient with already one AI disease**
- A1-B8-DR3
- DQ3-DR4
- DQ5-DR9
- DQ5-DR1
- DQ5-DR10
- Autoimmune-prone individual

**Approximated time until clinical appearance of disease**
- anti-PL, anti-Ro, anti-La – 3.4 yrs prior to SLE
- anti-dsDNA – 2.2 yrs prior to SLE
- anti-Sm, anti-nuclear ribonucleoprotein – 1.2 yrs prior to SLE

**Appearance of Autoantibodies**
- Disease Type
  - anti-Islet cell Abs → DM
  - RF, anti-CCP → RA
  - anti-PL, anti-Ro, anti-La, anti-dsDNA, anti-nuclear ribonucleoprotein, anti-HS, anti-nucleosome, anti-Histone, anti-rP protein → SLE
  - anti-Ro, anti-La → Sjorgren’s
  - anti-gp120, anti-PDC → PBC
  - ASCA → crohn’s disease

**Treatment/Prevention**
- Ursodeoxycholic acid tx for PBC
- Dietary enrichment with PUFA for SLE
- Avoiding UV light and OC for SLE
- Aspirin tx for APS
- Vitamin D receptor agonist
- Synthetic peptides

Harel M, Shoenfeld Y
Predicting and preventing autoimmunity, myth or reality?
*Ann. N.Y. Acad. Sci.*
THE PRESENT
Multiplex bead array (MBA)
THE FUTURE
(tomorrow...)

7 mm
Micro chips
Martin Luther King, Jr. (January 15, 1929-April 4, 1968) directed the peaceful march on Washington, D.C. of 250,000 people to whom he delivered his address, "I Have a Dream", he conferred with President John F. Kennedy and campaigned for President Lyndon B. Johnson; he was awarded five honorary degrees; was named Man of the Year by Time magazine in 1963; and became not only the symbolic leader of American blacks but also a world figure.

August 28, the anniversary of Dr. King’s 1963 I Have a Dream speech, is called “Dream Day".
I have a dream

1) Multi autoantigenic chips
2) Multi genetic chips
3) Environmental; infectious, silicone
4) Easy informatics
Preventive therapy
Hepatitis-C and Autoimmune Diseases

1) Mixed cryoglobulinemia.
2) Ch. Active hepatitis.
3) Polyarteritis nodosa.
4) Leukocytoclastic vasculitis.
5) Autoimmune thyroid disease.
6) Glomerulonephritis.
7) Polymyositis + anti-Jo-1 Ab.
8) Formation of autoantibodies and CIC (A@R. 3: 437, 1995).

The prevalence of anti-HCV antibodies was 9.5% (116/1228) in our cohort.
Soluble BAFF levels in HCV
Toubi et al. *J Autoimmunity* 2006;27;134-9

![Graph showing BAFF levels in different groups: Control, HBV, HCV, SLE. The p-value is 0.001.]

BAFF (ng/ml)

- Control: 1
- HBV: 1
- HCV: 3
- SLE: 4

P = 0.001
How to avoid autoimmune diseases

Triggers of autoimmune diseases

ASIA syndrome (Breast implants, Vaccines)
Infections; EBV vaccines, HCV eradication
Drugs; avoid response to biologics
Stress
Sun exposure
Diet; unsaturated fatty acid
Address (Geoepidemiology)
Hygiene theory; TPC from Helminthes
Vitamin D: a pleiotropic molecule

- Bone disease
- Cognitive function
- Pain
- Cardiovascular disease
- Autoimmune diseases
- Cancer

Vitamin-D supplementation = 7% reduction in mortality from any cause

Average Vitamin D concentration

25 OH Vitamin D ng/mL

Insufficiency

Deficiency

Controls, MS, PM, SSc, RA, Thy, APS, SLE
Vitamin D prevention of autoimmune models

Kamen DL et al. Autoimmunity Reviews 2006

1,25-Dihydroxyvitamin D₃ reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis

(Margherita T. Cantorna, Colleen E. Hayes, and Hector F. DeLuca*)

Collagen-induced arthritis

1,25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis.

Cantorna MT, J Nutr. 1998
Go for the sun
Thank You!