Immune response markers in serum prior to the occurrence of thyroid antibodies

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DISCLOSURE
Nothing to Disclose
Learning objectives

- Understand that:
  - role myelomonocytic cells in regulation and tissue homeostasis and development of autoimmunity
  - reduction of T regulatory cells leads to loss of tolerance
  - target organ abnormalities precede autoimmunity
  - serum analytes in individuals at risk for development of AI reflect these abnormalities
What is the immune morphology of pre-AITD?

Animal models: essential to tell us the principles.

Spontaneous models: BB rat, NOD mouse
- Poly-endocrine AI: thyroiditis, diabetes
- Long prodromal pre-phase: abnormal architecture and mild leukocyte infiltrations from earliest observation onwards.
- Followed by an early accumulation of dendritic cells and macrophages in the thyroid prior to lymphocyte accumulation

A paradigm change.
The myelo-monocytic cell system in steady state:
A multipurpose homeostasis regulator system.

Primarily
"A peace-keeping force"
in
steady state conditions
Steady state

1. Homeostasis and regulation

Local precursor

Coculture of thyroid dendritic cells with thyroid follicles (24 hrs, Wistar rats)

DC suppress thyrocyte proliferation via IL-1 and IL-6

Coculture of thyroid dendritic cells with thyroid follicles (24 hrs, Wistar rats)

Thyroid DC interacting with thyroid follicles regulate the growth of the follicles (IL-1/IL-6), Simons et al. 1998
Myelo-monocytic cell system as a multipurpose regulator system

Morphogenesis and hormone secretion regulation: Thyroid Islets Ovaries Pituitary

Steady state

2. Tolerogenesis iDC and MØ take up self-antigens like thyroglobulin or insulin

steady state semi-mature DC and MØ support expansion of T suppressor/regulator cells:
CD4CD25FOXP3+
GM-CSF treatment of mice prevents thyroiditis by generation of
a. semi-mature (steady state) DC
b. CD4+CD25+ T reg cells as shown by adoptive transfers in Tg immunized mice

Steady state (semi-mature) DC

Mononuclear phagocytes switch to a “fighting” force in situations of danger

Morphogenesis and hormone secretion regulation:
- Thyroid
- Islets
- Ovaries
- Pituitary

Destruction:
- Cytotoxic activity

Immunization:
- T effector cells,
- B cells,
- Antibodies

Treg cells:
- Tolerance
ECM abnormal
Dysmorphogenesis

Animal models
I. Pro-dromal stages
Homeostasis and regulation

Tissue DC and MØ are abnormal
NOD mouse (islet)
1. Poor infiltration
2. Reduced proliferation HSC precursors
3. Tissue DC provide less growth factors

BB rat (thyroid)
1. Fewer differentiated DC, more precursors cells
2. Abnormal endocrine regulation

Target organ: NOD islets abnormal prior to insulitis and autoantibody development
1. high frequency of irregularly shaped islets with more α cells
2. high fibronectin content and a higher, but modest early influx of MØ
3. later development of mega-islets, which are primarily the target of infiltration.
Thyrocytes of BB-DP rats show low proliferation potential

Already at very early age prior to thyroiditis and Aabs (3-8 weeks of age)

Animal models
II. Pro-dromal stages
Tolerance induction

**Tissue and mo-DC**
- NOD mouse
  - Lack of tolerogenic tissue
  - DC populations
  - Hyper reactive to inflammatory stimuli (LPS)

**BB rat**
- Poor generation of DC

**Lymph node DC**
- BB rat:
  - Poor T cell stimulation particularly for T regs

**Defective T suppressor cells in BB rat**
Pro-dromal phases in animal models

**Endocrine tissue**
1. Reduced/abnormal proliferation endocrine cells
2. ECM abnormalities
3. Altered architecture

**Myelo-monocytic cells**
1. Poor infiltration in the tissues
2. Poor proliferation and differentiation
3. Poor providers of growth factors
4. Poor generation of tolerogenic DC
5. Hyper reactive to inflammatory stimuli

**T cells**: Intrinsic defect in T regulator populations

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Human thyroid autoimmune disease

Are similar proliferation and differentiation abnormalities in endocrine cells, ECM and immune cells detectable in pre-stages of human thyroid autoimmune disease?
Amsterdam AITD cohort

Female 18-65 years old

At least one 1st or 2nd degree relative with AITD

No personal history of thyroid disease

5 years follow up

Annual visits & blood testing:
TSH, FT4, T3, TPO-Ab, Tg-Ab, TSH-R Ab

smoking habits
use of oral contraceptives or other estrogen

Current pregnancy: exclusion criterion

Matching seroconverters with de novo TPO-Ab to controls and NSC

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<th>healthy controls</th>
<th>non seroconverters</th>
<th>seroconverters</th>
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<tr>
<td>n</td>
<td>32</td>
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<tr>
<td>Age, y, mean (range)</td>
<td>35 (22–61)</td>
<td>33 (19–62)</td>
<td>33 (18–61)</td>
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<td>BMI, kg/m², mean (range)</td>
<td>23.8 (18.1–33.7)</td>
<td>24.0 (18.7–42.1)</td>
<td>24.2 (19.1–40.8)</td>
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<td>TSH median (IQR)</td>
<td>1.50 (1.20–2.00)</td>
<td>1.20 (1.09–1.65)</td>
<td>1.40 (1.20–2.00)</td>
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<tr>
<td>FT₄ median (IQR)</td>
<td>13.0 (12.2–14.7)</td>
<td>13.5 (12.3–14.6)</td>
<td>12.0 (11.9–14.5)</td>
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<td>Current smoking, %</td>
<td>15 (47%)</td>
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<td>Current estrogen use, %</td>
<td>6 (19%)</td>
<td>12 (38%)</td>
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Results serum analytes

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growth and connective tissue abnormalities in individuals with an inborn risk for AITD
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#### Growth and connective tissue abnormalities in individuals with an inborn risk for AITD

A reduced infiltration and migration of immune cells into the tissues of individuals with an inborn risk to develop AITD.

Beumer et al., 2013

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Marjan Versnel)
Overall conclusion animal models

The proneness to develop endocrine autoimmune disease (before sero-positivity) is characterized by
1. Growth and ECM abnormalities of the endocrine tissue,
2. Growth and differentiation abnormalities of the myelo-monocytic lineage leading to
   - a poor development of DC and MØ particularly of those with a tolerogenic function and
   - an inflammatory hyper reactivity to LPS of such DC and MØ
3. Defects in T regulator cell populations.

Overall conclusions human study

There are indications that the pro-dromal stage of thyroid autoimmunity in humans at risk (family members) can be detected – similar to the abnormal processes in animal models –
by studying serum analytes reflecting
1. growth and ECM abnormalities of endocrine tissues (e.g. PDGF-BB, FN)
2. poor development of myelo-monocytic cells (e.g. DC and MØ cytokines)
3. poor infiltration capacity of myelomonocytic cells (e.g. chemokines)
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