Thyroid and the Thymus

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The moving place of the thymus in the history of medicine

Claude Galen – 2nd ‘father’ of Western medicine  
(129 – 210 or 216 AD)

«The thymus is the seat of soul, eagerness and fortitude.»

“Troubles thymiques” in French medical language = mood disorders, i.e. bipolar and unipolar depression.

The new views as to the morphology of the thymus gland and their bearing on the problem of the function of the thymus. JA Hammar (1921) Endocrinology 5: 43-73.

«The cases in which hyperplasia of the thymus is found are relatively rare. Such findings have been made chiefly after castration, in Graves’ disease, myasthenia and acromegaly.»


Integrated evolution of the immune and neuroendocrine systems

Invertebrates
Protochordates
Jawless vertebrates (lamprey)

VCBP  VLR

Jawed vertebrates (shark, ray)

RAG-mediated anticipatory and adaptive immunity

RAG1 and RAG2

TCRα – TCRβ – TCRγ - TCRδ

IgV germline diversity

Somatic hypermutation

Polymorphic MHC

Thymoids (Foxn4) (lamprey)

« Horror autoxicus »
First thymus (Foxn1)

Innate immunity (TLR)

Neuroendocrine system

≈ -450 Millions years

T-cell differentiation in the thymus

**Cortex**
- Subcapsular T blasts
- Small cortical T cells
- T progenitors (from liver & bone marrow)

**Medulla**
- Medullary T cells
- Dendritic cell

**Generation of self-tolerant and competent naïve T cells (2-5%)**

+ Selection of nTreg (CD4+ CD25+ Foxp3+)

**TEC**
- TEC
  - MHC
  - TCR
  - Self-Ag?
Thymic repertoire of neuroendocrine self precursors

<table>
<thead>
<tr>
<th>FAMILY</th>
<th>THYMIC SELF ANTIGENS</th>
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<tbody>
<tr>
<td>Neurohypophysial peptides</td>
<td>Oxytocin / OT (&gt;&gt; Vasopressin / VP)</td>
</tr>
<tr>
<td>Neurotensin/Neuromedins</td>
<td>Neurotensin / NT</td>
</tr>
<tr>
<td>Tachykinins</td>
<td>Neurokinin A</td>
</tr>
<tr>
<td>Natriuretic peptides</td>
<td>ANP</td>
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<tr>
<td>Somatostatins</td>
<td>Cortistatin</td>
</tr>
<tr>
<td>Insulin family</td>
<td>IGF-2 (&gt; IGF-1 &gt; Insulin)</td>
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</table>

Thymic expression of tissue-restricted antigens (TRA)

TSHR expression in the thymus

Thymic expression of thyroid antigens

Dutton et al. (1997) Thyroid 6: 879-884
Spitzweg et al. (1999) Thyroid 9: 133-141
Graves' Disease and Massive Thymic Hyperplasia

Maria Raquel Correia, Teresa Dias, Fernando Baptista, and Isabel do Carmo

Dear Editor:

Graves' disease is an autoimmune thyroid condition in which autoantibodies against the thyroid-stimulating hormone (TSH) receptor stimulate the autonomous production of thyroid-stimulating hormone (TSH). It is characterized by diffuse goiter and thyrotoxicosis, and it may be accompanied by an infiltrative ophthalmopathy and dermatopathy. A seldom-recognized feature of this disease is thymic hyperplasia. We would like to highlight this association and consider the pitfalls that can occur when this is encountered by describing a patient with Graves' disease and massive thymic hyperplasia.

A 22-year-old woman presented with Graves' disease. Serum biochemistry revealed TSH receptor autoantibodies (TRAbs) 178 U/L (normal range: <1.0 U/L), TSH receptor antibody (TRAb) was 30.2 U/L (normal range: <6 U/L), free thyroxine (T4) 4.37 mg/dL (3.5-5.5 mg/dL), free triiodothyronine (T3) 10.10 pg/mL (2.5-4.5 pg/mL), and suppression of TSH by levothyroxine 0.6 ng/mL (0.5-2.0 ng/mL).

The patient had marked Graves' ophthalmopathy and an incidentally discovered anterior mediastinal mass (8 x 5 cm) with no invasive characteristics on magnetic resonance imaging (Fig. 1a, b). She was started on treatment with methimazole. There was marked improvement of her thyrotoxic state and concomitant reduction in the size of her thymus (Fig. 2a, b). The patient was treated with total thyroidectomy. Ten months after surgery, the thyrotoxic state improved, and the mass regressed to its normal size (Fig. 2a, b).

Thymic hyperplasia is a common and reversible feature in Graves' disease. There are no consistent data between thymic hyperplasia and other hyperthyroid states. However, thyrotoxicosis and thyrotoxicosis, and there is some evidence that TSH receptor antibodies (TRAbs) may be increased in patients with Graves' disease. It has been suggested that one-third of patients with Graves' disease have microscopic abnormalities in the thymus, and in most cases, however, thyrotoxicosis and thyrotoxicosis, and the thymus may enlarge. Indeed, massive enlargement of the thymus has been reported only infrequently in Graves' disease. The pathophysiology of thyrotoxicosis in this setting has not been fully determined. However, the fact that treatment of the hyperthyroid state in Graves' disease with concomitant decrease in TRAbs leads to regression of the dimensions of the thymus suggests that thyrotoxicosis is more likely to be the result of Graves' disease. Actually, Montiel et al. postulated that both an indirect action of the lowering of thyroid hormone levels and the lowering of TRAbs could induce reduction in the thymus size. It seems that antithyroid drugs, besides causing a blockade of thyroid hormone synthesis, can also have an immunosuppressive effect, eventually, reducing TRAbs levels. The same authors have demonstrated the presence of TRAb receptors in normal thyroid tissue, suggesting that this receptor may serve as an autoreceptor (4). Their findings support the concept that TRAbs in Graves' disease stimulate that thyrotoxicosis and thyrotoxicosis, and they reduce goiter in Graves' disease.

FIG. 1. (a, b) Thoracic MRI (pretreatment). MRI, magnetic resonance image.
Thymus and Graves disease

CT-scan
A. Control
B. Before treatment
C. After treatment

TSHR
1. Thyroid
2-3. Thymus

Northern
1. Thyroid
2-3. Thymus

ICC for TSHR
A. Thyroid
B-D. Thymus

Graves disease and thymus hyperplasia

APS-I or APECED syndrome

- Very rare autosomal recessive disease
- AIRE identified on 21q22.3 (positional cloning)
- 14 exons, transcription factor of 545 aa, > 45 mutations
- Maximal transcription in *thymic epithelium*
The thymus is essential for development of AIRE-associated autoimmunity

A.

Level of Aire expression in tissues

B-D.

Transplantation of Aire^{-/-} thymus

Aire controls thymic transcription of tissue-specific Ags


### Table A

<table>
<thead>
<tr>
<th>Probe name</th>
<th>Gene name</th>
<th>Tissue(s)</th>
<th>WT signal</th>
<th>KO signal</th>
<th>KO/WT</th>
<th>t-test p-val</th>
<th>FPR Quad</th>
<th>FPR SAM</th>
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<td>961030_at</td>
<td>casein alpha</td>
<td>mammary</td>
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<td>fetal erythrocytes</td>
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<td>0.0803</td>
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<td>100206_at</td>
<td>intestinal trefoil factor</td>
<td>intestinal goblet cells</td>
<td>74.59</td>
<td>1.99</td>
<td>0.027</td>
<td>0.0504 &lt; 0.02</td>
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<td>101820_at</td>
<td>neurotoxin homologue</td>
<td>granulocytes, monocytes</td>
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<td>1.034</td>
<td>0.1105</td>
<td>&lt; 0.02</td>
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<td>cryptdin,related sequence 2</td>
<td>Paneth cells</td>
<td>100.47</td>
<td>3.85</td>
<td>0.038</td>
<td>0.2661</td>
<td>0.164</td>
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<td>101862_f_at</td>
<td>major urinary protein IV</td>
<td>lacrimal gland, parotid gland</td>
<td>26.49</td>
<td>1.2</td>
<td>0.045</td>
<td>0.0392</td>
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<td>cytochrome P450 1a2</td>
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<td>lactotransferrin</td>
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<td>hair follicles, brain</td>
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<td>mammary gland</td>
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<td>brain, epididymis</td>
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<td>neutrophilic granule</td>
<td>granulocytes</td>
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<td>Purkinje cell protein 4</td>
<td>brain, eye (lens)</td>
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<td>2.05</td>
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<td>major urinary protein I</td>
<td>liver</td>
<td>31.23</td>
<td>2.04</td>
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<td>98858_at</td>
<td>glucose dependent insulinoctropic polypeptide</td>
<td>K cells of small intestine</td>
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<td>liver</td>
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<td>98623_g_at</td>
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<td>embryo, choroid plexus and leptomeninges in adult</td>
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<td>6.96</td>
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<td>preproenkephalin</td>
<td>brain</td>
<td>19.54</td>
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<td>0.0143</td>
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<td>103887_at</td>
<td>5100 calcium binding protein A9</td>
<td>immature BM myeloid cells, monocytes, neutrophils</td>
<td>68.93</td>
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<td>aldose reductase</td>
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<td>1.48</td>
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<td>0.0121</td>
<td>0.279</td>
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<td>97889_at</td>
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<td>intestine</td>
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<td>94045_at</td>
<td>o-1-microglobulin/bikunin precursor</td>
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</table>

### Diagram B

- **Aire controls thymic transcription of tissue-specific Ags**
- **“top 30” random set**
- **one specific tissue**
- **several specific tissues**
- **hematopoietic cells**
- **housekeeping**

Thymus physiology

- Intrathymic AIRE-mediated transcription of neuroendocrine and ‘peripheral’ genes (TSA).
- Deletion of T cells with high affinity for TSA.
- Selection of CD4+ CD25+ Foxp3+ nTreg, specific of TSA.

A defect in thymus T-cell education to self?
TSHR mRNA expression in 17 human tissues

TSHR expression in the human thymus related to rs179247


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TSHR expression in thymic cell populations

TTF1 expression in TSHR-expressing thymic cell populations

Transcription of *Insulin*-related genes in the thymus of BB rats

Diabetes-prone BB rats

![Gel electrophoresis image showing transcription levels of Igf2, Igf1, and Ins genes in diabetic BB rats.](image)

Kecha O et al., Diabetes Metabolism Research, 2001
Impaired thymic tolerance to α-myosin directs autoimmune myocarditis

Lv H et al. (2011) J Clin Invest 121:1561-73
The role of the thymus in the development of autoimmunity

**Thymus physiology**
- Intrathymic AIRE-mediated transcription of neuroendocrine and 'peripheral' genes (TSA).
- Deletion of T cells with high affinity for TSA.
- Selection of CD4+ CD25+ Foxp3+ nTreg, specific of TSA.

**Thymus physiopathology**
- Absence or decrease in thymic expression/presentation of TSA (APECED, Down syndrome, BB rat, NOD…)
- Enrichment of T-cell repertoire with ‘forbidden’ self-reactive T cells (Teff).
- Decrease in selection of nTreg with specificity TSA.

**Bridge between self-reactive Teff and peripheral autoantigens**
- Role of intra- and extra-MHC loci.
- Role of environmental factors (viruses, diet, vitamin D deficiency, stress…).

Geenen V & Chentoufi AA (2011) *Clin Dev Immunol*
✓ A thymus dysfunction in T-cell education to self-antigens is the primary event in the development of organ-specific autoimmunity (such as autoimmune thyroiditis).

✓ Since T-cell self-education occurs during fetal development, most of autoimmune diseases are programmed during fetal life.

✓ Resulting from this thymic defect in T-cell self-education, the enrichment of T-cell repertoire with self-reactive T cells and its deficiency in self-specific nTreg is a condition necessary but not sufficient for priming the autoimmune response.
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**First Spin-off - ThymUP**

**FRIA**