TSH Receptor Autoantibodies: Differentiation and Clinical Relevance

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<table>
<thead>
<tr>
<th>Thyroid Autoantibodies</th>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSH-Receptor (TSH-R)</strong></td>
<td>Graves' disease</td>
<td>90-99%</td>
</tr>
<tr>
<td></td>
<td>Hashimoto's thyroiditis</td>
<td>0-10%</td>
</tr>
<tr>
<td><strong>Peroxidase (TPO)</strong></td>
<td>Graves' disease</td>
<td>70-80%</td>
</tr>
<tr>
<td></td>
<td>Hashimoto's thyroiditis</td>
<td>90-95%</td>
</tr>
<tr>
<td><strong>Thyroglobulin (Tg)</strong></td>
<td>Graves' disease</td>
<td>20-40%</td>
</tr>
<tr>
<td></td>
<td>Hashimoto's thyroiditis</td>
<td>30-50%</td>
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</tbody>
</table>
3 Types of TSHR Autoantibodies

- **Stimulators**
  - cAMP/PKA
  - PI3/PKC
  - $G_s$ and $G_q$

- **Blockers**
  - None or weak signal
  - $G_s$

- **Neutrals**
  - MAPK/PI3/PKC/ROS
  - $G_q$
  - Apoptosis
TSHR Autoantibody Assays

• **Binding Assays:**
  - Competitive-binding immunoassays (TRAb or TBII)
  - Measure total anti-TSHR binding activity
  - Do not discriminate functional type

• **Cell-based Bioassays:**
  - Transfected cell lines: TSHR/reporter gene
  - Stimulating antibody-specific (TSI)
  - Blocking antibody-specific (TBI)
Anti-TSHR Nomenclature

- **TRAb**: TSH Receptor antibody
  - General term for anti-TSHR, but usually means antibodies measured in binding assays

- **TBII**: TSHR-Binding Inhibitory Immunoglobulin
  - Anti-TSHR measured using a competitive binding assay. Used in most commercial assays.
Anti-TSHR Nomenclature

• **TSI**: Thyroid-stimulating immunoglobulin
• **TSAb**: Thyroid-stimulating antibody
  Stimulating activity of anti-TSHR measured in a cell-based bioassay

• **TBI**: Thyroid-blocking immunoglobulin
• **TBAb**: Thyroid-blocking antibody
  Blocking activity of anti-TSHR measured in a cell-based bioassay
TSH-R Antibody Binding Assays

„First generations-assay“

Labeled TSH

TBII

porcine TSH-R

„Second generations-assay“

Labeled TSH

TBII

human TSH-R

„Third generations-assay“

Labeled TSH

TBII

porcine TSH-R

Labeled Monoclon. Ab. (M22)

Automated in IU/L

"First generations-assay"

"Second generations-assay"

"Third generations-assay"
TSAb Bioassay
(Genetically engineered cells)

cAMP → CREB → CRE-FF luc → mRNA → Luciferase

TSAb

TSH receptor
TSAb measured with genetically engineered cells versus porcine thyrocytes

Good correlation between new and old bioassays

Kamijo et al. *Thyroid* 20:851, 2010
Graves’ disease + orbitopathy

Graves’ disease only

410.8

92.1

mean ± 95% CI

p < 0.001

p = 0.114

Ponto et al. Ophthalmology 2011

GD + GO (n=155)

GD only (n=45)
Clinical Relevance of TBAb

• Transient Neonatal Hypothyroidism
  (Sutherland, NEJM 1960; Goldstein, JCEM 1973; Matsuura, NEJM 1980; Iseki JCEM 1983)

• TBI in Graves’ disease and Hashimoto’s thyroiditis
  (Endo, JCEM 1978)

• TBI in nongoitrous hypothyroidism
  (Arikawa JCEM 1985)

• Incidence of TBI in Autoimmune thyroiditis and Hashimoto’s thyroiditis
  (Chiovato, JCEM 1990)

• TSI and TBI in the same patient from whom pure blocking and pure stimulatory MAbs were isolated
  (Evans, Clin Endocrinol 2010)
Binding versus Bioassays

IU/L

TRAb  TSAb  TBA  TNAb
Bioassays measure the sum of the functional activity

Hyperthyroid

Hypothyroid

TSAb

TBAb
Key points

1. Anti-TSHR autoantibodies have direct role in the pathogenesis of Graves’ disease

2. Anti-TSHR autoantibodies can have either stimulating or blocking activity causing hyperthyroidism or hypothyroidism

3. TSHR-binding inhibitory immunoglobulin (TBII) levels reflect total anti-TSHR autoantibodies and do not differentiate functional type.

4. New anti-TSHR tests have high sensitivity and specificity for GD and can be useful diagnostically especially in atypical cases.
Key points

5. TSAb/TBAb bioassays measure the sum total of the stimulatory or blocking activity of the anti-TSHR activity.

6. TSAb measured in a bioassay are a useful biomarker for activity, severity, and/or systemic involvement of Graves´ disease (GD).

7. TSAb levels may be an early predictor of disease progression, remission, or response to therapy.

8. TSAb and TBAb bioassays are useful for predicting fetal risk for hyper or hypothyroidism in pregnant women with active or treated GD.