Triggering Thyroid Autoimmunity: Genes, Viruses, and Epigenetics

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Genes
Viruses
Interactions
TSHR
CD40
CD25

GD

HLA-DRb1-Arg74
CTLA-4
PTPN22
Tg
ARID5B

12q (BTG1)

HT

Reviewed in:
Tomer. Thyroid 2010; 20: 715-725

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Yaron Tomer)
Genes
Viruses
Interactions
### Hepatitis C and Thyroiditis

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Patients</th>
<th>Controls</th>
<th>P-value</th>
<th>Study</th>
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<td>No.</td>
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<td>%TAb’s</td>
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</table>

Reviewed in: Mandac, Chaudhry, Sherman, and Tomer. Hepatology; 2006; 43: 661-672
How can HCV infection trigger thyroiditis?

Non-specific effects of the virus

Can HCV infect human thyroid cells
Detection of HCV-RNA in the thyroid by in-situ hybridization

HCV Infection in the Presence or Absence of anti-CD81

Huh 7.5

ML-1

Blackard et al. Thyroid 2013; 23: 863-870
Mechanisms of induction of Thyroiditis by HCV: Bystander Activation

- Inflammatory response
- Exposure of cryptic Ag’s
- Secretion of cytokines (IL-8)
- Alteration of self Ag’s

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Genes
Viruses
Interactions
Non-coding effects on gene expression/function that are mitotically stable (i.e. long lasting)

- DNA methylation
- Histone modifications
- microRNA activation
Non-coding effects on gene expression/function that are mitotically stable (i.e. long lasting)

- DNA methylation
- Histone modifications
- microRNA activation

Which environmental factor triggers epigenetic changes in thyroid cells?
Interferon $\alpha$ and AITD

- IFN$\alpha$ is a key cytokine secreted during infections
- IFN$\alpha$ therapy has been associated with autoimmunity – AITD, type 1 DM, SLE
- Transgenic mice expressing IFN$\alpha$ in thyroid develop thyroiditis

IFN$\alpha$ is a Key Cytokine Triggering AITD

Tomer. J Autoimmun 2010; 34: J322-J326
Epigenetic Effects of IFNa

IFNa

Human Thyroid Cells

Global histone modifications

H3K4me1

H3K4me3

Genetic Variants Associated with AITD
A Tg Promoter SNP That is Associated with AITD Shows Enrichment in H3K4me1

Stefan et al. JBC 2011; 286; 31168-31179

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Yaron Tomer)
Tg Promoter -1623 G Allele Binds IRF-1

Stefan et al. JBC 2011; 286; 31168-31179

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Yaron Tomer)
Binding of IRF-1 to the -1623 G-Allele Induces Epigenetic Changes Driving TG Transcription

**TG -1623 G**

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<th>+Ab</th>
<th>IgG</th>
<th>T1</th>
<th>H2O</th>
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**Enhancer Element**

- H3Ac
- H3K4me3
- H3K4me1

**TG proximal promoter**

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**Active Transcriptional Element**

- H3Ac
- H3K4me3
- H3K4me1

Stefan et al. JBC 2011; 286: 31168-31179
**Construct**

- pGL4.10-TG (A)
- pGL4.10-TG (G)
- pGL4.10-TG (del)

**Luciferase Activity**

- p = 0.007
- p = 0.008

*Stefan et al. JBC 2011; 286: 31168-31179*
Interferon α Induces Tg Expression in Thyroid Cells

How can upregulation of Tg trigger AITD?
Collaborators

**Molecular Modeling**
Roman Osman
Taiji Oashi

**Proteomics**
Rong Wang

**Bioinformatics**
Weijia Zhang
Lucy Skrabanek

**Statistical Genetics**
David Greenberg
Susan Hodge
Cristina Monti

**Next gen Sequencing, Genotyping**
Mehdi Keddache

**Small molecule screening**
Dan Felsenfeld