Mechanisms of Immune Tolerance: The Liver as Immunoprivileged Organ

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Immunological tolerance

• Definition:
  – unresponsiveness to an antigen induced by exposure of lymphocytes to that antigen; antigen-specific (unlike “immunosuppression”)

• Significance:
  – All individuals are tolerant of their own antigens to a greater or lesser extent (self-tolerance); breakdown of self-tolerance results in autoimmunity
  – Therapeutic potential: Inducing tolerance may be exploited to prevent graft rejection, treat autoimmune and allergic diseases, and prevent immune responses in gene therapy and stem cell transplantation
How Self is Self?

Self proteins can be immunogenic and tolerance to them broken (eg by administration of a therapeutic homolog). Tolerogenicity/Immunogenicity of self proteins depends largely on:

- **Abundance**: determines the degree to which developing, potentially autoreactive T and B cells are tolerized

- **Alteration** in chemical/physical structure: aggregation, post-translational modifications (PTMs), chemical degradation

- **Adjuvants:**
  - **Extrinsic**: innate immune response modifiers
  - **Intrinsic**: immunomodulatory properties of the protein
Foreign proteins

Expect Immunogenicity
No tolerance
Neutralize Product
Hypersensitivity

Self Proteins

Rare Immunogenicity
Autoimmunity
FOREIGN

- Low abundance self-protein
- Aggregates of self proteins
- Chemical degradation/modification of self proteins
- Adjuvants

SELF

Expect Immunogenicity
No tolerance
Neutralize Product
Hypersensitivity

Potential Immunogenicity
Incomplete tolerance
Altered structure/
Antigen Present
Epitope spreading

Rare Immunogenicity
Robust tolerance
Novel Route of Administration
Adjuvants
HLA Haplotype Specific
Antibody Response to Proteins: The Mediators

Antigen

DC

Peptide

MHCII TCR

Helper T cell Tfh

BCR

Cytokines

CD4 TCR

CD40L

CD86

Antibodies

CD28

CTLA4

Memory B cell

Short lived Plasma cell

Long lived Plasma cell

Antibodies

MHCII TCR
Cellular Interactions in Generation of T cell Mediated Responses
(Sanchez-Fueyo A and TB Strom Gastroenterology 2011)

A

CD8\(^+\) T cell

\(\text{T cell help}\)

CD4\(^+\) T cell

TCR

MHC class-I

MHC class-II

APC

B

Cell

Necrotic and apoptotic cell material

Uptake by APC

CD4\(^+\) T cell

TCR

MHC class-II

APC
T Cells More Robustly Tolerant than B Cells to Self Proteins
(Weigle, 1980)
T Cells More Robustly Tolerant to Self-Proteins: Thymic Mechanisms

- **Negative selection**
  - T cells with high affinity for thymic/peripheral tissue antigens that access thymus in sufficient quantities
  - T cells with high affinity for peripheral tissue antigens whose expression in thymus is mediated by transcription factor AIRE

- **Natural (thymically generated) regulatory T cells (Tregs)**
  - Lineage deviation of T cells with high affinity to proteins expressed in thymus to immune suppressive regulatory T cells (Tregs) distinguished by FOXP3 transcription factor, neuropilin and helios
Consequences of Self Antigen Recognition in Thymus

Negative selection: deletion

Development of regulatory T cells

Thymus

Immature T cells specific for self antigen

Regulatory T cell

Periphery

Abbas, Lichtman and Pillai. Cellular and Molecular Immunology, 7th edition, 2011 © Elsevier
Mutations in Tregulatory cell Transcription Factor FoxP3 Confer Autoimmunity by Deficiency of Tregs

(Sakaguchi et al 2008)

Mother of IPEX patient

IPEX patient

Normal

Autoimmune disease
Inflammatory bowel disease
Allergy
Tregs Arise in the Periphery (i/p Tregs) as well as in the Thymus (t/nTregs)

Natural tTreg, nTreg, originate in the thymus; positively selected

Induced/peripheral (i/p)Tregs generated in the periphery; originate from CD4+ T cells in response to environmental antigens.

What Self Antigens are Seen in the Thymus?

• Ubiquitous cell-associated and circulating proteins

• Peripheral tissue antigens: expression mediated by Autoimmune Regulator (AIRE) transcription factor in thymic medullary epithelial cells and extrathymic bone marrow derived APC (eTACs)
  • signal self-reactive thymocytes for death or lineage deviation to Tregs
AIRE Promotes Expression of Peripheral Tissue Antigens in the Thymus, Deleting/Deviating High Affinity Autoreactive T cells
(Mathis and Benoist 2007)
AIRE Mutations are Associated with Autoimmune Polyendocrine Syndrome Type 1 (Kampe et al 2008)

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>APS-1</th>
<th>APS-1 and NALP5 Autoantibodies</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>With Manifestation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>number/total number (percent)</td>
<td></td>
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<td>Hypoparathyroidism</td>
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<td>Hypogonadism</td>
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<td>29/69 (42)</td>
<td>7/18 (39)</td>
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<td>Type 1 diabetes mellitus</td>
<td>11/87 (13)</td>
<td>2/11 (18)</td>
<td>34/76 (45)</td>
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<tr>
<td>Vitiligo</td>
<td>17/87 (20)</td>
<td>7/17 (41)</td>
<td>29/70 (41)</td>
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<td>Alopecia</td>
<td>30/87 (34)</td>
<td>11/30 (37)</td>
<td>25/57 (44)</td>
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<td>Hepatitis</td>
<td>15/87 (17)</td>
<td>8/15 (53)</td>
<td>28/72 (39)</td>
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<td>Malabsorption</td>
<td>22/87 (25)</td>
<td>10/22 (45)</td>
<td>26/65 (40)</td>
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<td>Pernicious anemia</td>
<td>14/87 (16)</td>
<td>5/14 (36)</td>
<td>31/73 (42)</td>
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<tr>
<td>Candidiasis</td>
<td>83/87 (95)</td>
<td>34/83 (41)</td>
<td>2/4 (50)</td>
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</table>
# AIRE Mediated Expression of Liver Proteins in the Thymus

<table>
<thead>
<tr>
<th>Gene ID</th>
<th>Gene Annotation</th>
<th>WT</th>
<th>Aire KO</th>
<th>Fold Change</th>
<th>Liver Expression Protein atlas*</th>
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<tbody>
<tr>
<td>Cyp1a2</td>
<td>Cytochrome P450, family 1, subfamily A, polypeptide 2</td>
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<td>20.6</td>
<td>11</td>
<td>223</td>
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<tr>
<td>Prg4</td>
<td>Proteoglycan 4</td>
<td>263.1</td>
<td>31.7</td>
<td>8</td>
<td>94</td>
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<tr>
<td>Apoa1</td>
<td>Apolipoprotein A-I</td>
<td>626.8</td>
<td>95.9</td>
<td>6</td>
<td>8043</td>
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<tr>
<td>Fgg</td>
<td>Fibrinogen gamma chain</td>
<td>174.9</td>
<td>27</td>
<td>6</td>
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<td>Tdo2</td>
<td>Tryptophan 2,3-dioxygenase</td>
<td>138.4</td>
<td>22.5</td>
<td>6</td>
<td>279</td>
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<tr>
<td>Ambp</td>
<td>Alpha-1-microglobulin/bikunin precursor</td>
<td>139.2</td>
<td>26.6</td>
<td>5</td>
<td>3641</td>
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<td>Gys2</td>
<td>Glycogen synthase 2 (liver)</td>
<td>92.2</td>
<td>19.5</td>
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<td>Fgb</td>
<td>Fibrinogen beta chain</td>
<td>153.5</td>
<td>36.7</td>
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<tr>
<td>Alb</td>
<td>Albumin</td>
<td>146.5</td>
<td>43.9</td>
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<tr>
<td>Itih4</td>
<td>Inter-alpha-trypsin inhibitor heavy chain family, member 4</td>
<td>191</td>
<td>58</td>
<td>3</td>
<td>681</td>
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<tr>
<td>Apoa2</td>
<td>Apolipoprotein A-II</td>
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<td>Apoc2</td>
<td>Apolipoprotein C-II</td>
<td>345.6</td>
<td>121.6</td>
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<td>249</td>
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<td>Mat1a</td>
<td>Methionine adenosyltransferase I, alpha</td>
<td>99.5</td>
<td>37.8</td>
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<tr>
<td>Orm1</td>
<td>Orosomucoid 1</td>
<td>298.3</td>
<td>116</td>
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<tr>
<td>Itih3</td>
<td>Inter-alpha-trypsin inhibitor heavy chain 3</td>
<td>144.8</td>
<td>58</td>
<td>2</td>
<td>300</td>
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<tr>
<td>Hp</td>
<td>Haptoglobin</td>
<td>108.3</td>
<td>49.6</td>
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<tr>
<td>Igfbp1</td>
<td>insulin-like growth factor binding protein 1</td>
<td>15.2</td>
<td>8.3</td>
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<td>Reln</td>
<td>reelin</td>
<td>12.0</td>
<td>22.3</td>
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<td>Hal</td>
<td>Histidine ammonia-lyase</td>
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<td>2278.6</td>
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<td>Cyp26a1</td>
<td>cytochrome P450, family 26, subfamily a, polypeptide 1</td>
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<td>71.4</td>
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<td>Hamp</td>
<td>Hepcidin antimicrobial peptide</td>
<td>337</td>
<td>946.1</td>
<td>0.4</td>
<td>163</td>
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</tbody>
</table>

The list is the combination of SI from PNAS 2012 by Matthieu Giraud and 02670 Table2 (Microarray data from Affymetrix MgU74Av2 gene chip by using 2004.04.29 Affymetrix annotation *FPKM values or 'number of Fragments Per Kilobase gene model and Million reads', were calculated as the sum of all its protein-coding transcripts, and the average FPKM value for replicate samples were used as abundance scores) from RNA-seq analysis.
CD4+ T cells Specific for Tissue Restricted Antigens do not Undergo Extensive Thymic Deletion: Expanded Tregs Mediate Tolerance

**Thymus**
- Ubiquitous self-antigen
  - Tconv
  - Deletion
- Tissue-restricted self-antigen (no thymic expression)
  - Tconv
  - Treg
- No self-antigen
  - Tconv
  - Treg

**Periphery**
- Ignorance
- Suppression
- Treg expansion
- Low affinity self-antigen
  - Lung or intestinal self-antigen

Legoux et al. 2015 Immunity 43, 896–908
CD4+ T cell Fate Depends on Cytokine Milieu in Site of Activation

- Naïve CD4+ T cell
- IL-12: Stat4 T-bet → TH1 (IFNγ)
- IL-4: Stat6 Gata3 → Th2 (IL-4, IL-5, IL-13)
- IL-23, IL-6, IL-21: Stat3 RORγ → TH17 (IL-17)
- TGFβ: Stat5 Foxp3 → Treg (IL-10, TGFβ)

Liver graft rejection
Immunosuppression Engraftment

(Sanchez-Fueyo A and TB Strom, Gastroenterology 2011)
Autoimmunity is Suppressed by both Thymic and Peripheral Tregs

Immune homeostasis
Autoimmune responses

Thymus

tTreg

Nrp-1

Teff

Tnaive

pTreg

Site of Inflammation

Local immune suppression
Oral tolerance
Fetal tolerance
Mucosal tolerance

Yadav M et al Frontiers in Immunology 2013
Mechanisms by which Tregs Suppress Immune Responses

(a) Inhibitory cytokines
- Membrane-tethered TGFβ
- IL-35
- IL-10

(b) Cytolysis
- Granzyme A or granzyme B
- Perforin pore
- Apoptotic effector T cell

(c) Metabolic disruption
- cAMP
- CD25
- IL-2
- Death due to cytokine deprivation

(d) Targeting dendritic cells
- cAMP
- CD39
- CD73
- Adenosine
- Death due to cytokine deprivation
- CD80/CD86
- MHC class II
- IDO
- Inhibition of DC maturation and function
Tolerance Mechanisms in the Liver

• 80% of the blood that passes through the liver sinusoids comes from the GI tract, carrying harmless dietary and commensal organism antigens: the default immune response must be tolerance…..maintained by the myriad of tolerogenic APC in the liver.” …continuous exposure of liver cells to these entities leads to “endotoxin tolerance”. “

• Antigen presentation within the liver, mediated by a variety of cell types including plasmacytoid and myeloid dendritic cells (p/mDC), Kupffer Cells, sinusoidal endothelial cells, hepatic stellate cells, and hepatocytes generally leads to T cell tolerance and not immunity
  – pDC-IL-27 secretion mediates expression of PDL-1 on pDC promoting activation and expansion of Tregs
  – mDC express PDL-1; induce IDO
  – KC- expression of Fas-L: kills CD8T cells; IDO; IL-10, expression of PDL-1
  – Hepatocytes: induce apoptosis of CD4+ and CD8+ Tcells
  – LSEC: functional inactivation of CD8+ T cells and bias CD4+ T cells to Treg-dependent on a cell surface expressed lectin (LSEC lectin)

• CD8+T cells transiently activated then undergo apoptosis or exhaustion

• Generating robust immune responses appears to hinge on full activation of CD4+ T cells which provide help to CD8+ T cells.
Immunosuppressive Circuits in Liver Mediated Mainly Through Liver Resident Myeloid Cells

Crispe, IN 2014. Hepatology
Generating Immune Responses in the Liver

• NK, NKT, $\gamma\delta$, and mucosal associated innate IT cell (MAIT) activation and responses may be critical in response to infectious organisms
  – Promote DC maturation into APCs: activate CD4+, CD8+ T cells, Bcells, PMNs and macrophages via contact and cytokine dependent interactions
• However, none of these populations uses HLA, the single greatest risk factor for autoimmune disease as restriction element for immune response suggesting criticality for mediating response to infection but potentially only indirect mechanism of action in triggering AIH spectrum
**Innate T Cells Present at High Levels in the Human Liver Recognize Microbial or Stress Induced Antigens Indicative of Infection but not in the Context of HLA**

*(Doherty D 2016 J. Autoimmunity)*

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>T Cell Receptor</th>
<th>Antigen-presenting Molecule</th>
<th>Stimulatory Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 NKT cell</td>
<td>Vα24Jα18</td>
<td>CD1d</td>
<td>Glycolipids</td>
</tr>
<tr>
<td>Type 2 NKT cell</td>
<td>Diverse</td>
<td>CD1d</td>
<td>Glycolipids</td>
</tr>
<tr>
<td>MAIT cell</td>
<td>Vα7.2Jα33</td>
<td>MR1</td>
<td>Riboflavin metabolites</td>
</tr>
<tr>
<td>γδ T cell</td>
<td>Vδ1</td>
<td>MICA, MICB, Rae1</td>
<td>Stress-inducible proteins</td>
</tr>
<tr>
<td>γδ T cell</td>
<td>Vδ1</td>
<td>CD1c, CD1d</td>
<td>Glycolipids</td>
</tr>
<tr>
<td>γδ T cell</td>
<td>Vγ9Vδ2</td>
<td>Butyrophilin 3A1</td>
<td>Pyrophosphates</td>
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<tr>
<td>γδ T cell</td>
<td>Vδ3</td>
<td>CD1d</td>
<td>Glycolipids</td>
</tr>
</tbody>
</table>
Genetic Basis of Tolerance/Autoimmunity

• Genetic predisposition of autoimmune diseases
  • HLA genes
    – Major genetic association with autoimmune diseases
    – Disease-associated alleles are present in normal individuals
  • Non-HLA genes
    – Many loci identified by genomic methods (e.g. genome wide association studies [GWAS])
    – Examples include FoxP3, AIRE, CD25 (IL2R-\(\alpha\)), NOD (sensor of microbes), PTPN22 (tyrosine phosphatase)
• Multiple genes are associated with autoimmunity
  – No single mutation causes common autoimmune diseases
# HLA is the Strongest Genetic Factor for Susceptibility to Autoimmune Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA allotype</th>
<th>Frequency (%)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
<td>&gt; 95</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>DQ6</td>
<td>&gt; 95</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>DQ2 and DQ8</td>
<td>95</td>
<td>30</td>
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<tr>
<td>IDDM</td>
<td>DQ8 and DQ2</td>
<td>81</td>
<td>14</td>
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<tr>
<td>Subacute thyroiditis</td>
<td>B35</td>
<td>70</td>
<td>14</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>DQ6</td>
<td>86</td>
<td>12</td>
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<td>Rheumatoid arthritis</td>
<td>DR4</td>
<td>81</td>
<td>9</td>
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<td>Juvenile rheumatoid arthritis</td>
<td>DR8</td>
<td>38</td>
<td>8</td>
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<td>Psoriasis vulgaris</td>
<td>Cw6</td>
<td>87</td>
<td>7</td>
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<td>Addison's disease</td>
<td>DR3</td>
<td>69</td>
<td>5</td>
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<td>Graves' disease</td>
<td>DR3</td>
<td>65</td>
<td>4</td>
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<td>Myasthenia gravis</td>
<td>DR3</td>
<td>50</td>
<td>2</td>
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<tr>
<td>IDDM</td>
<td>DQ6</td>
<td>&lt; 0.1</td>
<td>0.02</td>
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</table>

*Figure 11-23 The Immune System, 2/e (© Garland Science 2005)*
# Non-HLA Genes in Autoimmunity

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype of mutant or knockout mouse</th>
<th>Mechanism of failure of tolerance</th>
<th>Human disease?</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIRE</td>
<td>Destruction of endocrine organs by antibodies, lymphocytes</td>
<td>Failure of central tolerance</td>
<td>Autoimmune polyendocrine syndrome (APS)</td>
</tr>
<tr>
<td>C4</td>
<td>SLE</td>
<td>Defective clearance of immune complexes; Failure of B cell tolerance?</td>
<td>SLE</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Lymphoproliferation; T cell infiltrates in multiple organs, especially heart; lethal by 3-4 weeks</td>
<td>Failure of anergy in CD4+ T cells</td>
<td>CTLA-4 polymorphisms associated with several autoimmune diseases</td>
</tr>
<tr>
<td>Fas/Fasl</td>
<td>Anti-DNA and other autoantibodies; immune complex nephritis; arthritis; lymphoproliferation</td>
<td>Defective deletion of anergic self-reactive B cells; reduced deletion of mature CD4+ T cells</td>
<td>Autoimmune lympho-proliferative syndrome (ALPS)</td>
</tr>
<tr>
<td>FoxP3</td>
<td>Multi-organ lymphocytic infiltrates, wasting</td>
<td>Deficiency of regulatory T cells</td>
<td>IPEX</td>
</tr>
<tr>
<td>IL-2; IL-2Rα/β</td>
<td>Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies</td>
<td>Defective development, survival or function of regulatory T cells</td>
<td>None known Lymphadenopathy, enteropathy, eczema, infection</td>
</tr>
<tr>
<td>SHP-1</td>
<td>Multiple autoantibodies</td>
<td>Failure of negative regulation of B cells</td>
<td>None known</td>
</tr>
</tbody>
</table>

*Abbreviations: AIRE, autoimmune regulator gene; IL-2, interleukin-2; IPEX, Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome; SHP-1, SH2-containing phosphatase-1.*
# HLA Association with AIH

<table>
<thead>
<tr>
<th>Locus</th>
<th>Allele</th>
<th>OR</th>
<th>p Value</th>
<th>n</th>
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<td>DQB</td>
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<td>2.18</td>
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<td>66</td>
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<tr>
<td>DQA</td>
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<td>4.55</td>
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<td>DRB1</td>
<td>1301</td>
<td>6.80</td>
<td>0.00247</td>
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<tr>
<td>DRB1</td>
<td>1302</td>
<td>0.16</td>
<td>0.00845</td>
<td>39</td>
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<tr>
<td>DRB3</td>
<td>101</td>
<td>1.49</td>
<td>ns</td>
<td>84</td>
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<tr>
<td>DRB3</td>
<td>202</td>
<td>0.55</td>
<td>ns</td>
<td>95</td>
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</tbody>
</table>

**Previous data***

| DRB1 | 13    | 6.9  | 1.00E-06 | 111 |
| DRB1 | 13 + 3| 10.6 | 1.00E-07 | 111 |
| DRB1 | 3     | 5.3  | 1.00E-04 | 33  |

DRB1*1301 appears the major susceptibility factor; its only amino acid different from DRB1*1302 is in position 86, corresponding to pocket 1 in the peptide-presenting groove-glycine for valine

* Previous data refer to odds ratio (OR) observed when a larger cohort of patients was analyzed by low resolution PCR-SSP for the HLA-DRB1 locus

Goldberg AC et al 2001 Human Immunology
Polymorphisms in TNF-α Gene Associated with AIH

Of note is high degree of linkage disequilibrium between the TNFA locus and both HLA B8 and HLA DRB1*0301 within the extended haplotype B8-TNFA*2- DRB1*0301.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Patients</th>
<th>Controls</th>
<th>Comparison</th>
<th>OR</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>TNFA*2</td>
<td>HLA-A1</td>
<td>(n = 83)</td>
<td>(n = 98)</td>
<td>+ + vs. --</td>
<td>3.6</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>+ -- vs. --</td>
<td>NS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-- + vs. --</td>
<td>NS</td>
</tr>
<tr>
<td>TNFA*2</td>
<td>HLA-B8</td>
<td>(n = 83)</td>
<td>(n = 98)</td>
<td>+ + vs. --</td>
<td>3.6</td>
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<td>NS</td>
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<tr>
<td>TNFA*2</td>
<td>HLA-DRB1*0301</td>
<td>(n = 85)</td>
<td>(n = 102)</td>
<td>+ + vs. --</td>
<td>3.6</td>
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</table>
Failure of control mechanisms is the underlying cause of most autoimmune diseases.
Deliberately Breaking Self Tolerance

- Monoclonal antibodies to checkpoint inhibitors (PD-1, PDL-1)
- Monoclonal antibodies to suppressive molecules (eg CTLA-4, IL-2Ra)
- Chimeric Antigen Receptor T cells (CAR-T)
- Inhibitors of Indoleamine Dioxygenase (IDO)
The Immune System on a Knife’s Edge: Tipping the Balance for Therapy of Serious Diseases

- Cancer
- Chronic Infection
- Autoimmunity
- Graft Rejection

Checkpoint Inhibitor Antagonists
Checkpoint Inhibitor Agonists

Treg
Teff

Autoimmunity
Cancer/Chronic Infection
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