Tissue-mediated control of the immunopathology in Coeliac Disease

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MASTERING THE COELIAC CONDITION
Florence 29th of March 2012
NORMAL MUCOSA

+ gluten

- gluten

CELERIAC DISEASE MUCOSA

antibodies to gluten (gliadin) transglutaminase 2 (TG2)
COLLECTING INTESTINAL BIOPSIES FROM CELIAC DISEASE PATIENTS

Stig Tollefsen

Ice cold RPMI

Endoscope

Intestinal biopsy

Knut Lundin

Celiac patient
Genetic and environmental factors involved in development of Celiac Disease

**Genes**

- **HLA**
  - 35-50%

- **HLA** + 39 non-HLA loci
  - (other immune genes with small effects)

**Environment**

- Gluten

GWAS studies (van Heel & Wijmenga labs)
HLA ASSOCIATION CELIAC DISEASE

Those few CD pts who are HLA-DQ2 neg, are HLA-DQ8 pos.

**HLA in celiac disease is necessary, but not sufficient**
Binding of peptides to HLA-DQ2

van de Wal et al Immunogenetics 1996 & 1997
Godkin et al J Immunol 1998
Gliadin-specific, HLA-DQ(α1*0501, β1*0201) Restricted T Cells Isolated from the Small Intestinal Mucosa of Celiac Disease Patients

By Knut E. A. Lundin,* Helge Scott,‡ Torbjørn Hansen,* Gunnar Paulsen,* Trond S. Halstensen,‡ Olav Fausa,§ Erik Thorsby,* and Ludvig M. Sollid*

In DR4DQ8 pts, DQ8 restricted gluten reactive T cells are found
Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease

Øyvind Molberg¹, Stephen N. McAdam¹, Roman Körner², Hanne Quarsten¹, Christel Kristiansen¹, Lars Madsen³, Lars Fugger³, Helge Scott⁵, Ove Norén⁶, Peter Roepstorff², Knut E.A. Lundin³, Hans Sjöström⁸ & Ludvig M. Sollid¹

NATURE MEDICINE • VOLUME 4 • NUMBER 6 • JUNE 1998
Transglutaminase 2 (TG2) can deamidate gluten peptides.
T-cell recognition and DQ2 binding of DQ2-α-I gliadin epitope variants

QLQPFPQPQLPY

QXP

TG2

QLQPFPQPQLPY

---E---

---E---

---E---

---E---

*not tested

IC50 (µM)

103

118

*not tested

Arentz-Hansen et al, JEM 2000
Generation of T cell epitopes in the gut

α2-gliadin (AJ133612)

\[
\begin{align*}
\text{1} & \quad \text{MVRVPVPLQLPQNPSPQQQPQ EQVPLVQQQQ FPQGQQQFPFP QQPYPQPQPF PSQQPYLQLQ} \\
\text{61} & \quad \text{PPQPLYPQ PLPQPPQPFQ PRQYPQPSQ PQSQPQPQPIS HQQQQQQQQQQ} \\
\text{121} & \quad \text{QQKQQQQQQQ QILQQILQQQ LIPCRDVVLQ QHISAYGSSQ VLPQSTYQLV QQLCCQQLWQ} \\
\text{181} & \quad \text{IPEQISRCQAI HNVHAILHL QQQQQQQQQQ QPLPSQVSFQ QPQQQYPQSG QSFQPSQQNP} \\
\text{241} & \quad \text{QAOGSVQPQQ LPQFEEIRNL ALETLPAMCN VYIPPPYCTIA PGVIFGTNYR} \\
\end{align*}
\]

Transglutaminase (QXP)

\[
\begin{align*}
\text{61} & \quad \text{PPQPELPY QPELPYPQPE LPYPQPQPF} \\
\end{align*}
\]

after transglutaminase treatment

\[\text{LQLQ}\]

peptide (33 amino acids)

6 copies of T cell epitopes

Shan et al, Science 2002; Arentz-Hansen et al, Gastroenterology 2002
DQ2.5 restricted T cell epitopes

DQ2-α-I

DQ2-α-II

DQ2-α-III

DQ2-γ-I

DQ2-γ-II

DQ2-γ-III

DQ2-γ-IV

DQ2-γ-VI

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Why HLA-DQ2?

X-ray crystal structure (2.2 Å resolution)

Kim, Quarsten et al. PNAS, 2004
The celiac lesion

Hüe et al
Meresse et al
Immunity 2004
Key questions

1. How are the gluten reactive Th cells that produce IFN-γ generated?

2. How are the intraepithelial T cells licensed to kill enterocytes?
Tissue-mediated control of immunopathology in coeliac disease

Bana Jabri* and Ludvig M. Sollid†

Abstract | Coeliac disease is an inflammatory disorder with autoimmune features that is characterized by destruction of the intestinal epithelium and remodelling of the intestinal mucosa following the ingestion of dietary gluten. A common feature of coeliac disease and many organ-specific autoimmune diseases is a central role for T cells in causing tissue destruction. In this Review, we discuss the emerging hypothesis that, in coeliac disease, intestinal tissue inflammation — induced either by infectious agents or by gluten — is crucial for activating T cells and eliciting their tissue-destructive effector functions.

Nature Reviews Immunology 2009
Main points

1. Gluten reactive CD4+ Th cells producing IFN-γ are key players in the pathogenesis.

2. Epithelial cell destruction is mediated by CD8+ intraepithelial T cells.

3. Activation of CD4+ Th cells and killing by CD8+ intraepithelial T cells seem to be dependent on tissue inflammation - induced by infectious agents or gluten.
a Steady-state conditions

Gut lumen

IgA

Gluten

IEC

Intraepithelial CTL

Lamina propria

CD71

Tolerogenic DC

Gluten-specific Th1 cell

T_{Reg} cell

TGFβ

B cell

IgA CSR

Plasma cell

Tissue maintenance
b Inflammation or infection

Intraepithelial 
CTL

Gluten

Epithelial cell changes

IEC

Gluten-specific 
T_{reg} cell

Inflammatory mediators

APC

FcR

IGG

Inflammatory B cell

Plasma cell

Blood vessel

Tissue damage

Systemic manifestations?