Tissue-mediated control of the immunopathology in Coeliac Disease

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

CELIAC DISEASE MUCOSA

+ gluten

- gluten

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

Stig Tollefsen
Endoscope
Ice cold RPMI

Knut Lundin

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

*Genes*

**HLA**

35-50%

+ 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
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

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NATURE MEDICINE • VOLUME 4 • NUMBER 6 • JUNE 1998
Transglutaminase 2 (TG2) can deamidate gluten peptides.

TG2

Gluten peptide

H₂N-CO
(CH₂)₂

Ca²⁺

NH₃

TG2-substrate complex

H₂O

NH₂-R

Transamidation

Primary amine

H₂O

H₂O

Isopeptidase activity

Deamidation

O-CO
(CH₂)₂
T-cell recognition and DQ2 binding of DQ2-α-I gliadin epitope variants

IC50 (μM)

QXP

TG2

QLQPFPQPQLPY

--- E- - - - - - - -

118

----- E-----

* not tested

----- E-----

4

*not tested

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

α2-gliadin (AJ133612)

1 MV RV PVPQLP QNPSPQQQPQ EQVP LVQQQQ FPGQQQPFPP QQYPQPOPQF PSQQPYLQLQ
61 PFPQPLPYP QPQLPYPQPF LPYPQPF PFPQPPLLPY PQPQPQPQPP LPYQPLPJLQ PQYPQPLPYP LQLQ
121 QQKQQQQQLQ QLLLLQCQQ LI PCR DVLQ QHSI AYGSS QVLQSTYQLV QQLCCQQLWQ
181 IPEOSRCQAI HNVVHAI ILH QQQQQQQQQQ QQPLSQQSFQQPQQYPSQ GSFQPSQQNP
241 QAQGQPVQQO LQPFEI RNQ ALETLPAMCN VYI PYYCTI A PVI FGNYR

Transglutaminase (QXP)

after transglutaminase treatment

61 PFPQPELPYP QPELPYPQPE LPYQPLPYP

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

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<tr>
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<th>DQ2-α-I</th>
<th>DQ2-α-II</th>
<th>DQ2-α-III</th>
<th>DQ2-γ-I</th>
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<th>DQ2-γ-III</th>
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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

Wheat

Deamidation by TG2

CD8 T cell
NKG2D
MIC

TCR

Enterocyte

CD4 T cell

APC

Th1

IFN-γ

TH1

APC

CD4 HLA-DQ2 (or −DQ8)

Wheat

Deamidation by TG2
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 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.