The immunological jigsaw of coeliac disease:

Is there a role for microbes?

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Les Pensières
June 10,12, 2013
COELIAC DISEASE: autoimmune-like enteropathy induced by dietary proteins

Genetic factors
- 80% concordance monozygotic twins
- HLA-DQ2 or DQ8

Environment: dietary gluten prolamines wheat, barley, rye

Abnormal immune activation
- Activated CD4+LPL
- IgA anti-gliadins
- IgA anti-transglutaminase

Villous atrophy

IELs

Incidence 0.3-1%
- Children/adults
- Increased incidence? Up to 3% during the «Swedish Epidemics»

K, T lymphomas
- autoimmunity

1/1000-8000
digestive Spt
1/100-300
extradigestive Spt

0
The keystone of CD pathogenesis:

Intestinal gluten-specific adaptive CD4+ response orchestrated by the main genetic risk factor MHC class II HLA-DQ2.5/8

Gliadins + Glutenins = PROLAMINES
34% glutamine (Q) 20% proline (P)

Tissue transglutaminase 2 (TG2)

L. Sollid, F. Koning
THE INTESTINAL GLIADIN-SPECIFIC RESPONSE
IN HLA-DQ2.5/DQ8 INDIVIDUALS: THE KEYSTONE OF COELIAC DISEASE

- Gluten
- Incomplete digestion
- Gut lumen
- Lamina propria
- Epithelium
- Ttgase
- CD4+ TL
- TG2
- IFNγ, IL-21
- SIgA anti-TG2
- SIgA anti-gliadins
- Mucosal effector site
- Homing of antigen-specific B and T cells
- Initiation: Peyer’ patches?
  Mesenteric lymph nodes
THE INTESTINAL HLA-DQ RESTRICTED GLIADIN-SPECIFIC RESPONSE IS NECESSARY BUT NOT SUFFICIENT TO DEVELOP CD

1- < 5% HLA-DQ2.5/DQ8 individuals develop CD

2- No gluten induced enteropathy in humanized HLADQ2/8 mice even if crossed with transgenic mice bearing gliadin-specific TCR

De Kauwe AL et al J Immunol 2009; Du Pré F et al Gastroenterology 2011

No IFNγ, nor IL-21
But production of TGF-β or IL-10 in response to gluten → TOLERANCE

QUESTION?

TOLERANCE TO GLUTEN → TISSUE DAMAGE
ACTIVATION/ OF INTRAEPITHELIAL LYMPHOCYTES
A HALLMARK OF COELIAC DISEASE

Uncomplicated CD

Accumulation/ activation of polyclonal IEL
CD103+ CD8+ TcRαβ+/TcRγδ expressing NKR

Duodenal biopsy ACD
CD3 staining

LP CD4+ T cells

IFNγ, IL-21

HLA-DQ2/8

APC

TG2

gluten

Uncomplicated CD

Malignant transformation

RCD II

CD3 staining

Uncomplicated CD

?
IL15 is a key player in the activation of IEL in CD

**Diagram:**
- Gluten
- HLA-DQ2/8
- APC
- LP CD4+ T cells
- TG2
- IFNγ, IL-21
- IL-15
- NKR Ligands
- NKR
- TCR?
- IL-15 chronically overexpressed in active CD drives the expansion and cytotoxicity of IEL

**References:**
- Mention et al, Gastroenterology 2003
- Hue et al, Immunity 2004
IL-15 IMPAIRS LOCAL IMMUNOREGULATORY MECHANISMS

- **Gluten**
- **IL-15**
- **Accumulation/activation of polyclonal IEL**

**Renders effector cells (notably CD8+)**
insensitive to TGFβ and CD4+FOXP3+ Treg

**IFNγ, IL-21**

**BenAhmed et al Gastroenterology 2007**
**J. Immunol 2009**
**Am J Gastroenterol 2012**
IL-15 PROMOTES THE EMERGENCE OF IEL-DERIVED LYMPHOMAS

Spencer et al Am J Pathol 1988
Cellier et al 1998, Lancet 2000,
Mention et al 2003, Verkarre et al 2004
Malamut et al Gastroenterology 2009 & 2012

Uncomplicated CD ➔ Clonal refractory CD (RCDII) ➔ EATL

invasive T lymphoma CD30+

50% at 5y

CLINICAL CHALLENGE

TARGETED THERAPIES?

Survival (%)

Time from RCD diagnosis (months)

RCDII 5y-survival : 44%

5y survival rate 20%

Clonal TCRγ/1q trisomy CD103+ sCD3-iCD3+
IL-15 delivers an anti-apoptotic signal (dependent on JAK3, Stat5, Bcl-xL) driving the progressive accumulation of transformed IEL and likely allowing further acquisition of oncogenic mutations

Malamut et al JCI 2010
CD pathogenesis

HLA-DQ2/8+ gluten → TG2
GLUTEN-SPECIFIC CD4+ T CELLS

+ IL-15

CYTOTOXIC IEL

VILLOUS ATROPHY

Other factors predisposing to abnormal intestinal activation ?

1- Genetics?

HLA-DQ2/8 < 40 % genetic predisposition

Genome wide associations studies

~57 associations in 39 non HLA loci
common allelic variants
accounting overall for 13.7% predisposition

pointing to genes controlling adaptive immunity
overlapping with autoimmune diseases
CD pathogenesis

- HLA-DQ2/8+ gluten
  - TG2
  - GLUTEN-SPECIFIC T CELLS
    - +
    - IL-15
    - CYTOTOXIC IEL
      - VILLOUS ATROPHY

Other factors predisposing to abnormal intestinal activation:
- 2- additional environmental factors
  - Microbes?
  - Viruses?
  - Microbiota??
Rotavirus Infection Frequency and Risk of Celiac Disease Autoimmunity in Early Childhood: A Longitudinal Study
Stene et al Am J Gastroenterol 2006;101:2333–2340
1,931 children

Rotavirus ➔ TLR3 ➔ type I IFN ➔ IL-15

Type 1 Diabetes Is Associated With Enterovirus Infection in Gut Mucosa
Oikarinen et al Diabetes 2012

Infectious associations of Celiac disease
Leeor Plot, Howard Amital* Autoimmunity Reviews 8 (2009) 316–319

1- Treatment by IFN: can trigger CD
2- Viral hepatitis ???
**CD pathogenesis**

- HLA-DQ2/8+ gluten
- TG2
- GLUTEN-SPECIFIC T CELLS
  +
  - IL-15
  - CYTOTOXIC IEL
  - VILLOUS ATROPHY

Other factors predisposing to abnormal intestinal activation?

2- additional environmental factors

Microbes?

Viruses? Microbiota??
Cesarean Delivery Is Associated With Celiac Disease but Not Inflammatory Bowel Disease in Children

**OBJECTIVES:**

- The study aimed to investigate the association between perinatal and postnatal factors and the development of Crohn's disease and celiac disease in children.

**METHODS:**

- The study was a retrospective, population-based study involving 16,500 children.
- The data included information on perinatal and postnatal factors, such as mode of delivery, breastfeeding duration, and various medical conditions.

**RESULTS:**

- Cesarean delivery was associated with an increased risk of celiac disease (OR: 1.54, 95% CI: 1.15-2.06, p = 0.004).
- There was no association between cesarean delivery and the incidence of inflammatory bowel disease (odds ratio for Crohn's disease: 0.91, 95% CI: 0.68-1.22).

**CONCLUSIONS:**

- Cesarean delivery is associated with an increased risk of celiac disease in children, but not with inflammatory bowel disease.

**ALTERNATIONS AND DISCUSSION:**

- The study highlights the importance of perinatal and postnatal factors in the development of gastrointestinal disorders.
- Further research is needed to understand the mechanisms behind these associations.
Composition and diversity of the duodenal mucosa-associated microbiome in children with untreated coeliac disease

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C.M. FRANK KNEEPKENS¹, PAUL H.M. SAVELKOUL² & M. LUISA MEARIN³


16S–23S rDNA interspace (IS)-region-based profiling method

No difference between 21 untreated CD and 21 age-matched controls

No duodenal dysbiosis?
Induction of Colonic Regulatory T Cells by Indigenous *Clostridium* Species

Koji Atarashi, Takeshi Tanoue, Tatsuichiro Shima, Akemi Imaoka, Tomomi Kuwahara, Yoshika Momose, Genhong Cheng, Sho Yamasaki, Takashi Saito, Yusuke Ohba, Tadatsugu Taniguchi, Kiyoshi Takeda, Shohei Hori, Ivaylo I. Ivanov, Yoshinori Umesaki, Kikuji Itoh, Kenya Honda

Result: Clostridium species colonizing the colon can dampen peripheral TH2 response to OVA (given IP+Alum).

Question: can colonic bacteria influence response to dietary proteins in the upper part of intestine? Positively or negatively...
CD pathogenesis and microbes?

- HLA-DQ2/8+ gluten
- GLUTEN-SPECIFIC T CELLS
- +
  - IL-15
  - CYTOTOXIC IEL
  - VILLOUS ATROPHY

TOLERANCE TO GLUTEN

GLUTEN FREE DIET

microbiota

TISSUE DAMAGE

VILLOUS ATROPHY