

Non Coeliac Gluten Sensitivity



Simon Murch

Are you suffering from any of these symptoms?

✓ Depression

✓ Fatigue

✓ Irritable bowel syndrome

✓ Bloating

✓ Abdominal pain

✓ Diarrhea

✓ Lethargy

✓ Headaches and migraines

✓ **ADD** (attention-deficit disorder)
and hyperactivity

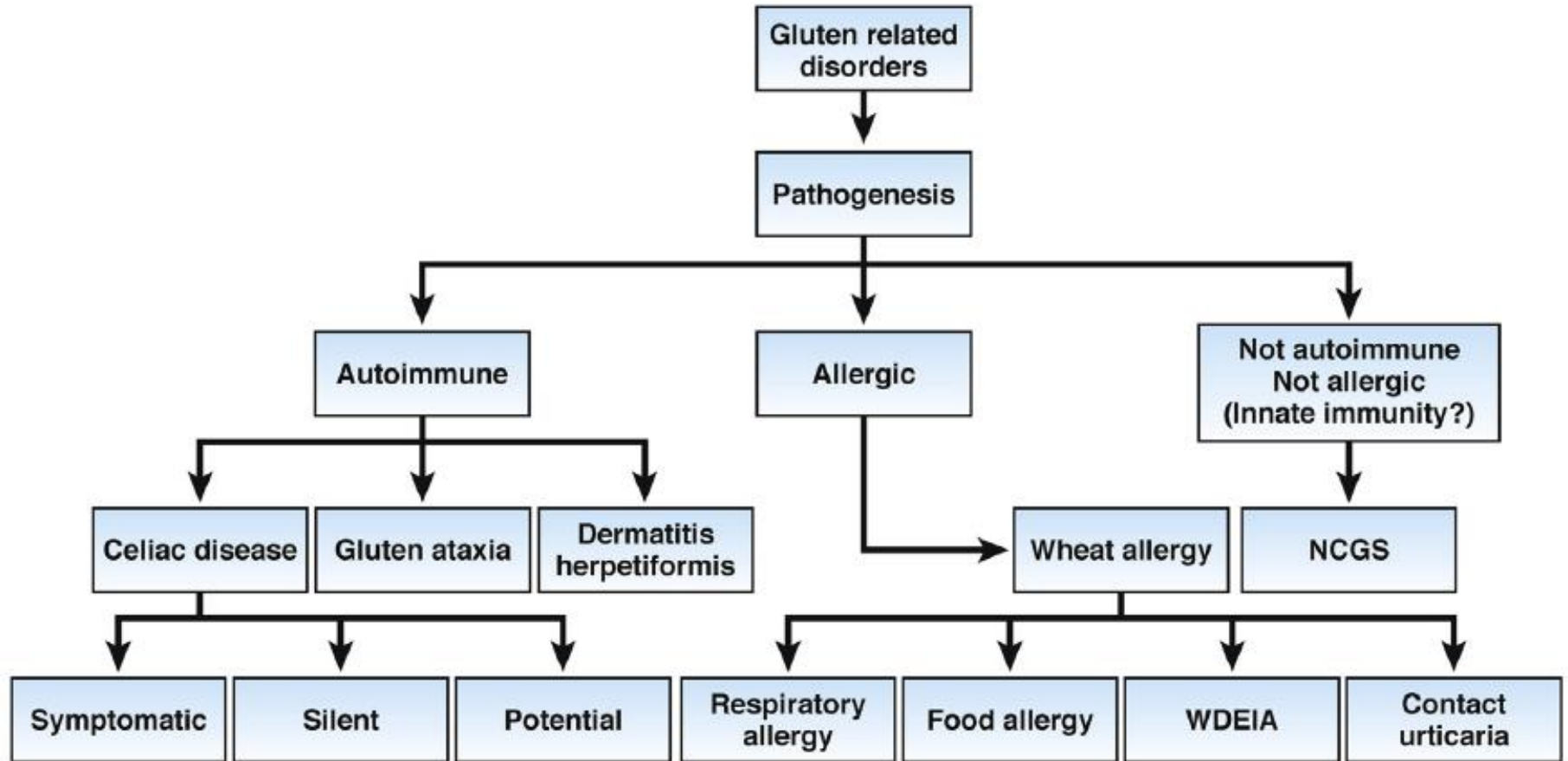
✓ Bone and joint pain

... and other symptoms nobody is able to explain?

Chances are you, just like at least **31,354,400 Americans**, have gluten sensitivity, or even worse – the **coeliac disease**.

Nonceliac Gluten Sensitivity

Fasano et al Gastroenterology 2015;148:1195–1204



Non coeliac gluten sensitivity

● Oslo definition

- One or more of a variety of immunological, morphological, or symptomatic manifestations that are precipitated by the ingestion of gluten in individuals in whom CD has been excluded
- Absence of enteropathy, normal permeability
- Negative TTG, EMA, DGP antibodies
- May show innate immune activation

Non coeliac gluten sensitivity – A new disease with gluten intolerance

Grażyna Czaja-Bulsa

Clinical Nutrition xxx (2014) 1–6

Symptoms of non-coeliac gluten sensitivity disorders (NCGS).

Disturbances

Intestinal

- Abdominal pains (68%)^a
- Diarrhoea (33%)^a
- Nausea
- Body mass loss
- Bloating, flatulence

Cutaneous 40%^a

- Erythema
- Eczema

General

- Headache (35%), bone and joint pain (11%)^a
- Muscle contractions (34%)^a
- Numbness of hands and feet (20%)^a
- Chronic tiredness (33%)^a

Haematological

- Anaemia (20%)^a

Behavioural

- Disturbance in attention^a
- Depression (22%)^a
- Hyperactivity
- Ataxia

Dental

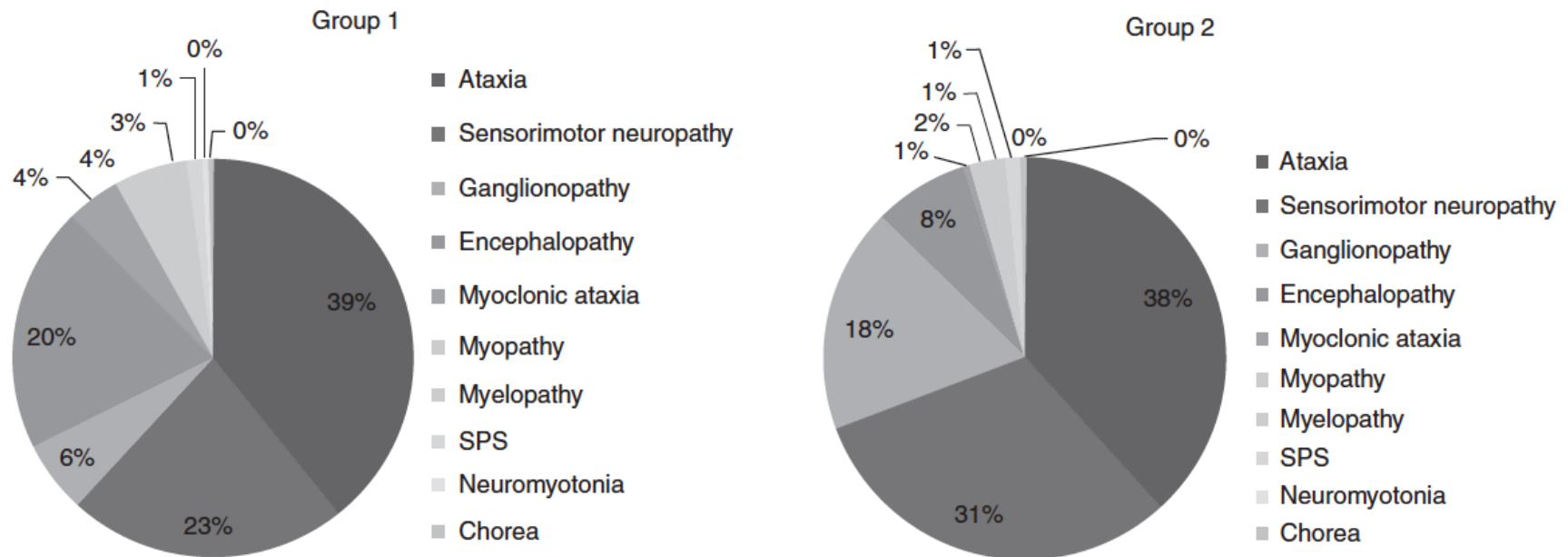
- Chronic ulcerative stomatitis
-

^a 347 patients treated at the Center for Celiac Research University of Maryland in 2004–2010 [1].

Neurological Dysfunction in Coeliac Disease and Non-Coeliac Gluten Sensitivity

Marios Hadjivassiliou, MD¹, Dasappaiah G. Rao, MD¹, Richard A. Grünewald, DPhil¹, Daniel P. Aeschlimann, PhD², Ptolemaios G. Sarrigiannis, MD¹, Nigel Hoggard, MD³, Pascale Aeschlimann, BSc³, Peter D. Mooney, MD⁴ and David S. Sanders, MD⁴

Out of 700 patients, 562 were included.



Am J Gastroenterol advance online publication, 2 February 2016;

Non coeliac wheat/gluten responses

● Allergic responses

- IgE-mediated
- Non IgE-mediated

● Toxic responses

- Gluten exorphins (Gliadomorphines)

● Innate immune responses

- Different gliadin peptide to immunodominant CD peptide

A CONSISTENT PATTERN OF MINOR IMMUNODEFICIENCY AND SUBTLE ENTEROPATHY IN CHILDREN WITH MULTIPLE FOOD ALLERGY

FRANCES LATCHAM, MRCP, MRCPCH, FRANCISCA MERINO, MD, ALISON LANG, BSc, SRD, JOSEPHINE GARVEY, BSc, SRD,
MICHAEL A. THOMSON, MD, FRCP, FRCPC, JOHN A. WALKER-SMITH, MD, FRCP, FRACP, SUSAN E. DAVIES, FRCPATH,
ALAN D. PHILLIPS, BA, PhD, AND SIMON H. MURCH, PhD, FRCP, FRCPC

Table III. Responses to individual antigens in groups 1 (n = 41) and 2 (n = 77)

	Group 1	Group 2
Cow's milk	Rash/urticaria: 27 cases, Vomiting: 15 cases, Angioedema 6 cases, Wheezing: 11 cases, Eczema flare: 11 cases, Loose stools: 10 cases Constipation: 5 cases Hypotension: 1 case	Eczema flare: 22 cases, Non-eczema rash: 6 cases, Vomiting: 15 cases, Abdominal pain: 20 cases, Loose stools: 24 cases Blood in stools: 3 cases, Constipation: 14 cases Wheezing: 3 cases, Rhinitis: 6 cases
Soya	Rash/Urticaria: 7 cases Vomiting: 9 cases Wheezing: 7 cases, Eczema flare: 9 cases Loose stools: 11 cases, Constipation: 4 cases	Eczema flare: 10 cases, Non-eczema rash: 6 cases Vomiting: 7 cases, Abdominal pain: 4 cases Loose stools: 11 cases, Constipation: 4 cases Wheezing: 2 cases, Rhinitis: 2 cases
Egg	Rash/Urticaria: 11 cases, Vomiting: 4 cases Angioedema: 2 cases, Wheezing: 5 cases Eczema flare: 8 cases	Eczema flare: 7 cases, Non-eczema rash: 4 cases Vomiting: 6 cases, Constipation: 1 case
Wheat	Rash/Urticaria: 1 case, Vomiting: 5 cases Wheezing: 2 cases, Eczema flare: 7 cases Loose stools: 6 cases, Constipation: 6 cases	Eczema flare: 12 cases, Non-eczema rash: 4 cases Vomiting: 7 cases, Abdominal pain: 7 cases Blood in stools: 2 cases, Loose stools: 11 cases Constipation: 9 cases, Rhinitis: 3 cases
Peanut	Rash/Urticaria: 5 cases, Vomiting: 1 case Angioedema: 3 cases, Hypotension: 1 case	
Tree nuts	Rash/Urticaria: 2 cases Angioedema: 1 case	

Extraintestinal Manifestations in Children With Gastrointestinal Food Allergy

G. Domínguez-Ortega, O. Borrelli, R. Meyer, R. Dziubak, C. De Koker, H. Godwin, C. Fleming, N. Thapar, M. Elawad, F. Kiparissi, A.T. Fox, and N. Shah

JPGN 2014;59: 210–214

TABLE 3. Comparison of extraintestinal manifestation prevalence between patients with IBD and gastrointestinal food-allergic patients with and without atopy

EIM	IBD versus atopic GIFA, %		IBD versus nonatopic GIFA, %	
	IBD group, n = 74	GIFA atopic, n = 306	IBD group, n = 74	GIFA nonatopic, n = 130
Allergic shiners	13.50	53.90 ^{***}	13.50	37.70 ^{***}
Fatigue	20.30	57.20 ^{***}	20.30	43.10 ^{**}
Night sweats	4.10	37.60 ^{***}	4.10	27.70 ^{***}
Poor sleep	6.80	37.30 ^{***}	6.80	27.70 ^{***}
Mouth ulcers	14.90	43.80 ^{***}	14.90	27.70
Joint pain/hypermobility	18.90	39.50 ^{***}	18.90	26.90
Bed-wetting	5.40	19.30 ^{**}	5.40	13.80
Headache	12.20	26.80 [*]	12.20	13.10

Gluten exorphins

- Bioactive morphine analogues derived from degradation of gluten in the intestine
 - Degraded by dipeptidyl peptidase-4 (DPP4)
 - Compete with substance P, Glucagon-like peptide 1
 - Inhibits DPP4 at higher concentrations
- Local effects
 - Slow transit, ↑ substance P, ? analgesic effect
- Systemic effects
 - Modify learning and anxiety responses in mice
 - Substance P induced anxiety, memory loss

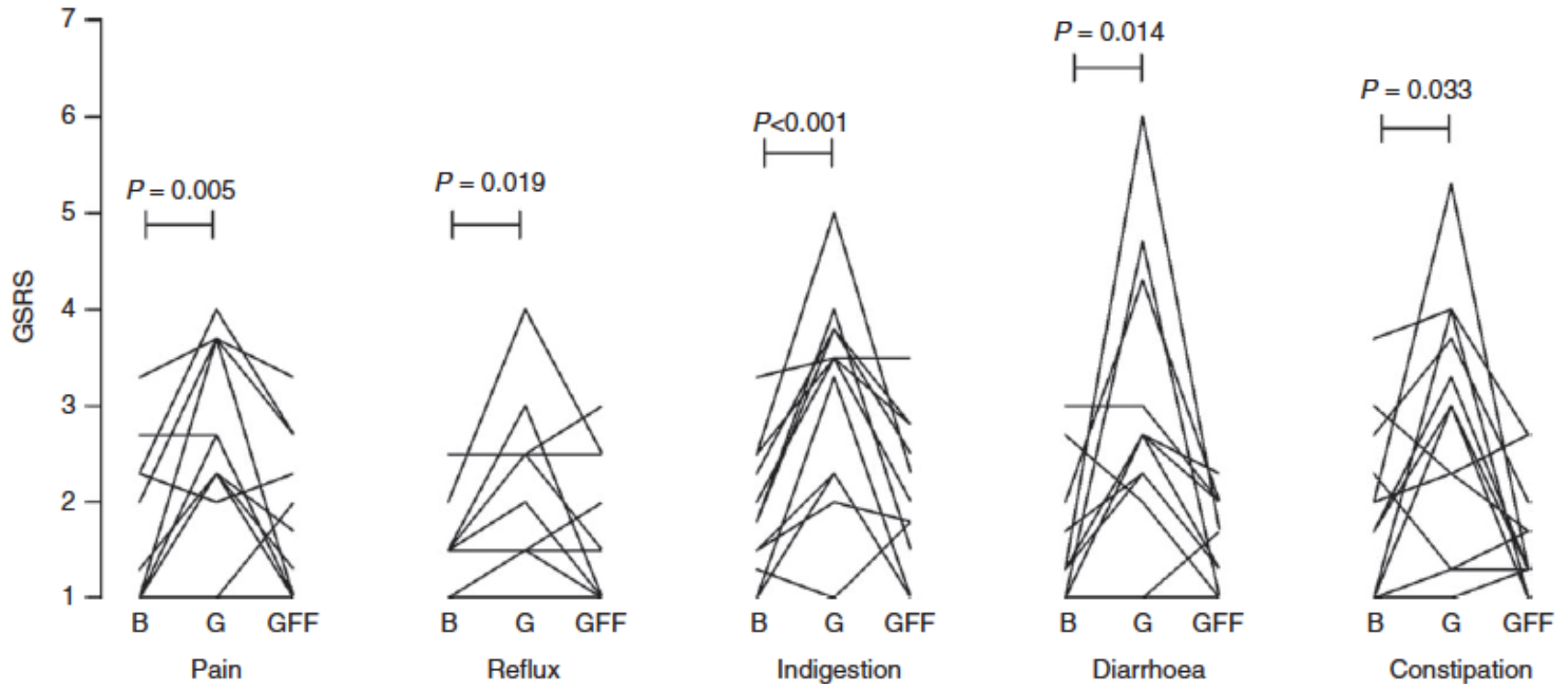
NCGS studies

- Placebo-controlled cross-over trial
 - Small but significant effect
(Di Sabatino A, Clin Gastroenterol Hepatol 2015)
- DBPC study – no crossover
 - Significant effect. (Biesiekierski J, Am J Gastro 2011)
- Crossover study
 - Clinical response related to FODMAPs rather than gluten (Biesiekierski J, Gastroenterology 2013)

Randomised clinical study: gluten challenge induces symptom recurrence in only a minority of patients who meet clinical criteria for non-coeliac gluten sensitivity

Aliment Pharmacol Ther 2015; 42: 968-976

B. Zanini*, R. Baschè*, A. Ferraresi*, C. Ricci*, F. Lanzarotto*, M. Marullo*, V. Villanacci[†], A. Hidalgo[‡] & A. Lanzini*



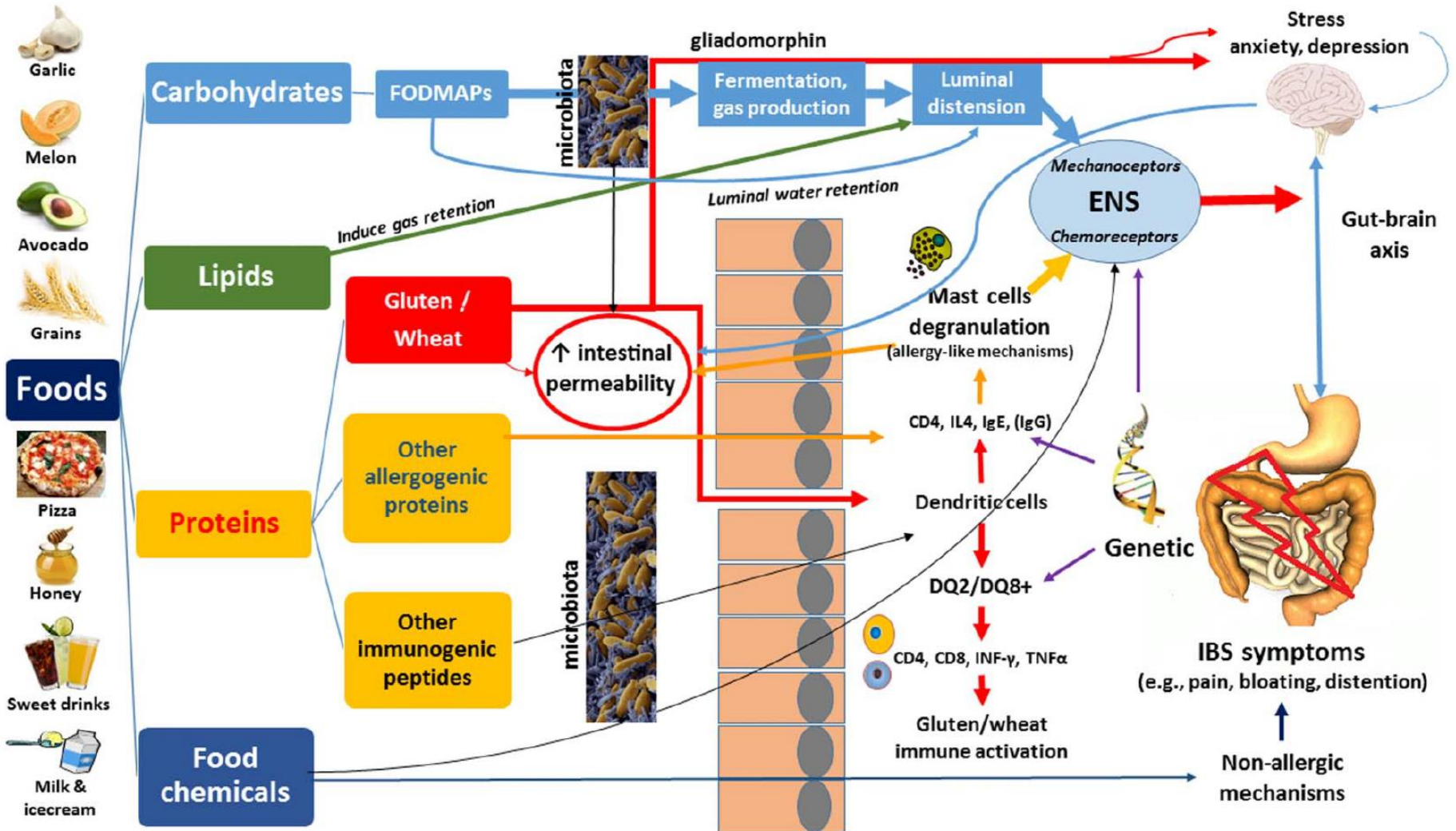
Conclusion

Double-blind gluten challenge induces symptom recurrence in just one-third of patients fulfilling the clinical diagnostic criteria for non-coeliac gluten sensitivity.

Sensitivity to wheat, gluten and FODMAPs in IBS: facts or fiction?

Roberto De Giorgio,¹ Umberto Volta,¹ Peter R Gibson²

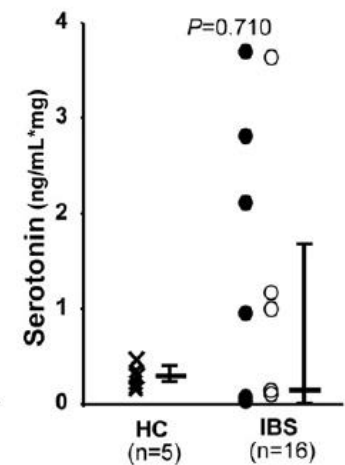
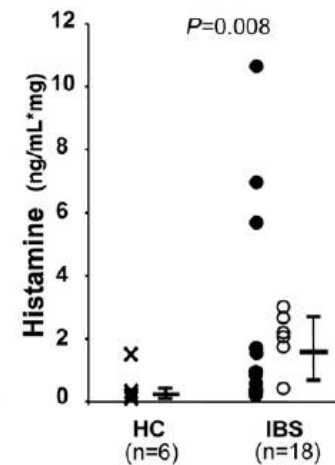
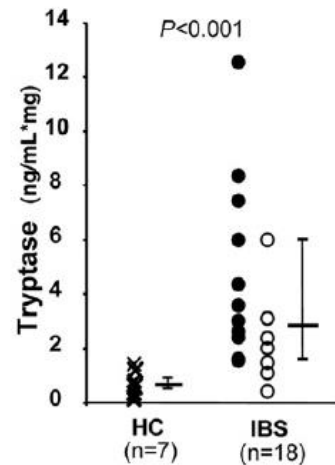
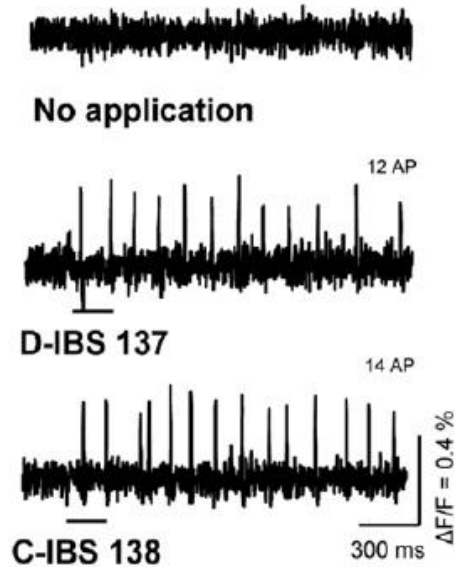
Gut 2016;**65**:169–178.



Activation of Human Enteric Neurons by Supernatants of Colonic Biopsy Specimens From Patients With Irritable Bowel Syndrome

SABINE BUHNER,* QIN LI,*[†] SHEILA VIGNALI,* GIOVANNI BARBARA,[§] ROBERTO DE GIORGIO,[§] VINCENZO STANGHELLINI,[§] CESARE CREMON,[§] FLORIAN ZELLER,^{||} RUPERT LANGER,^{||} HANNELORE DANIEL,[#] KLAUS MICHEL,* and MICHAEL SCHEMANN*

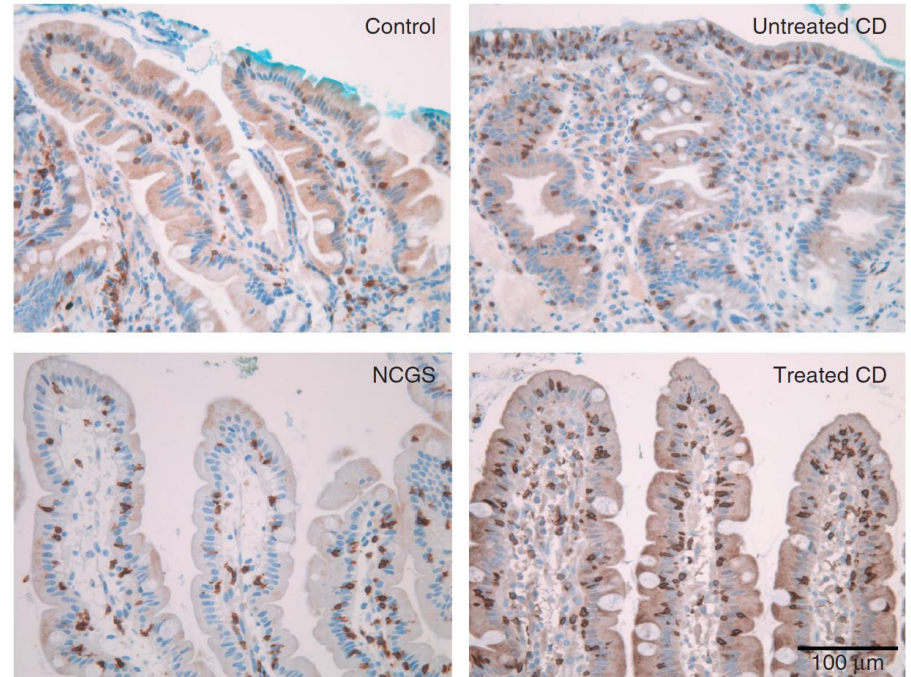
GASTROENTEROLOGY 2009;137:1425-1434



CONCLUSIONS: Mediators released from mucosal biopsies of IBS patients can activate human submucosal neurons. The activation required histamine, serotonin and proteases but was not associated with IBS subtype. Altered signaling between mucosa and the enteric nervous system might be involved in IBS pathogenesis.

Gut mucosal changes in NCGS

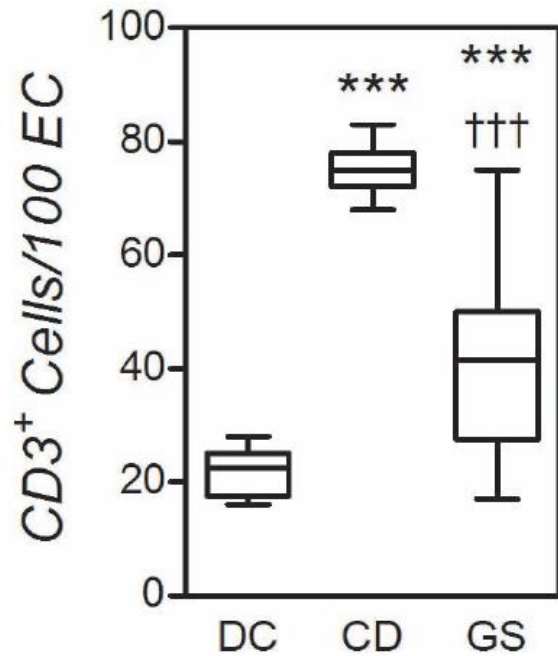
- Increased intraepithelial lymphocytes
- Activated innate immune responses
- Induced interferon- γ response



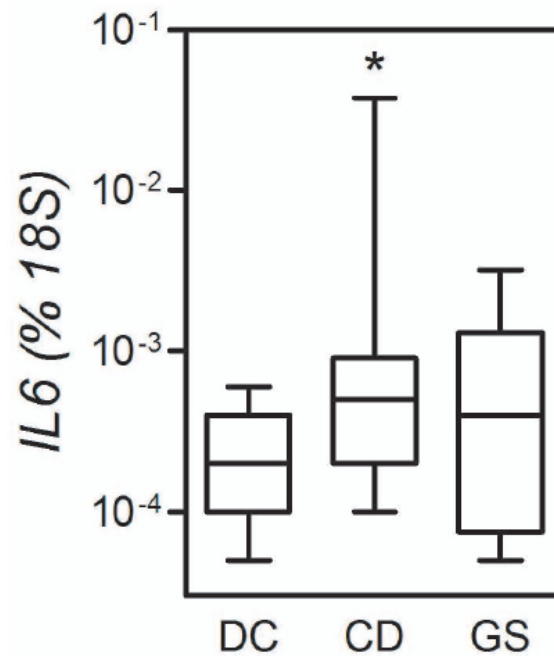
Brottveit et al, Am J Gastro 2013

Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity

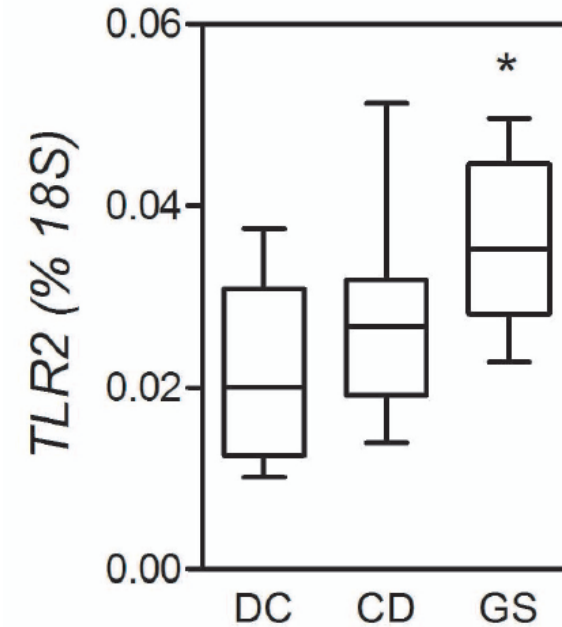
Anna Sapone^{1,2}, Karen M Lammers², Vincenzo Casolaro^{2,3}, Marcella Cammarota⁴, Maria Teresa Giuliano⁴, Mario De Rosa⁴, Rosita Stefanile⁵, Giuseppe Mazzarella⁵, Carlo Tolone⁶, Maria Itria Russo⁷, Pasquale Esposito⁷, Franca Ferraraccio⁸, Maria Carteni⁴, Gabriele Riegler¹, Laura de Magistris¹, Alessio Fasano^{2*}



IEL %



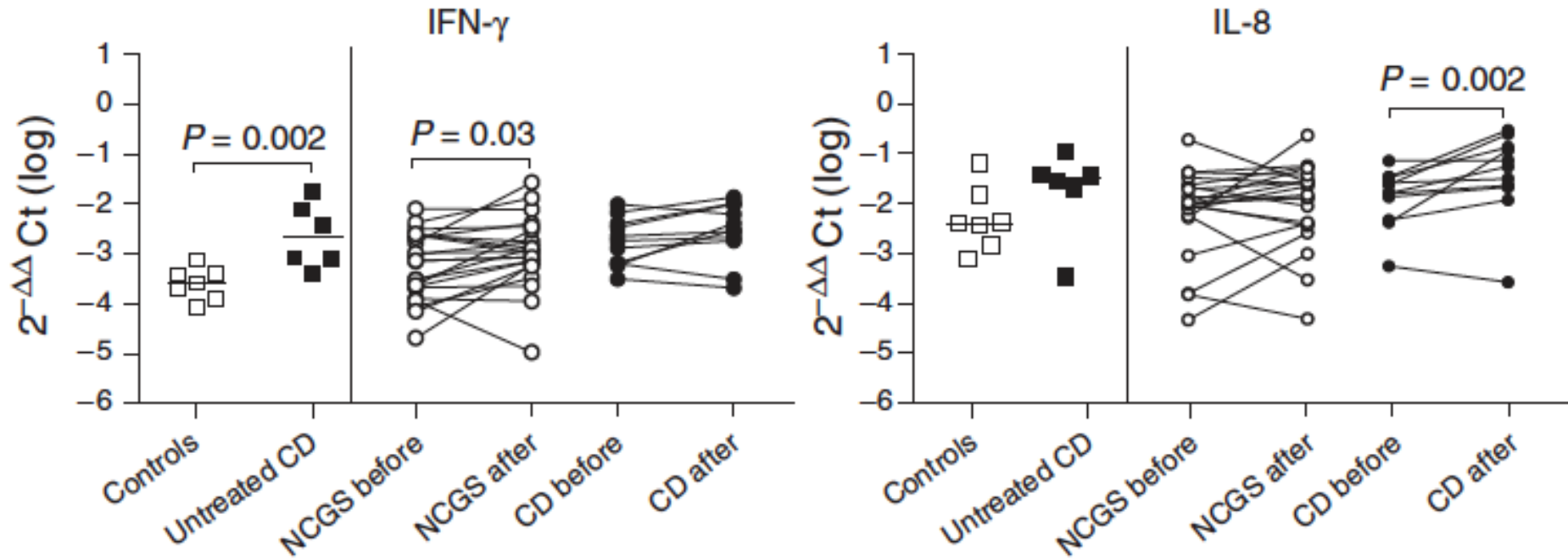
IL-6 mRNA



TLR2 mRNA

Mucosal Cytokine Response After Short-Term Gluten Challenge in Celiac Disease and Non-Celiac Gluten Sensitivity

Margit Brottveit, MD, PhD^{1,7}, Ann-Christin R. Beitnes, MD, PhD^{2,7,8}, Stig Tollefsen, MSc, PhD^{2,9}, Jorunn E. Bratlie, BLS³, Frode L. Jahnsen, MD, PhD⁴, Finn-Eirik Johansen, MSc, PhD⁴, Ludvig M. Sollid, MD, PhD⁵ and Knut E.A. Lundin, MD, PhD^{2,6}



**3 day challenge with gluten
30 with NCGS and 15 with CD**

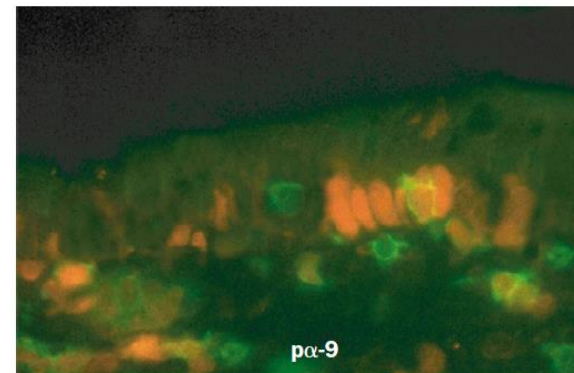
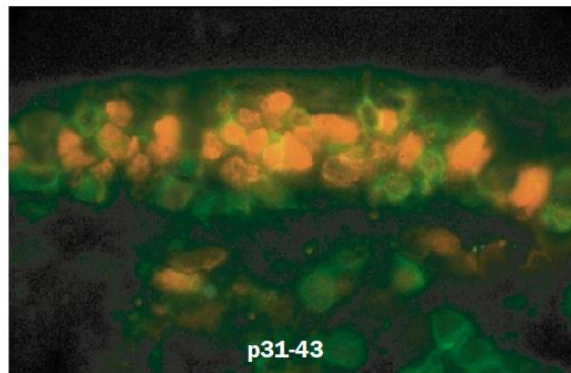
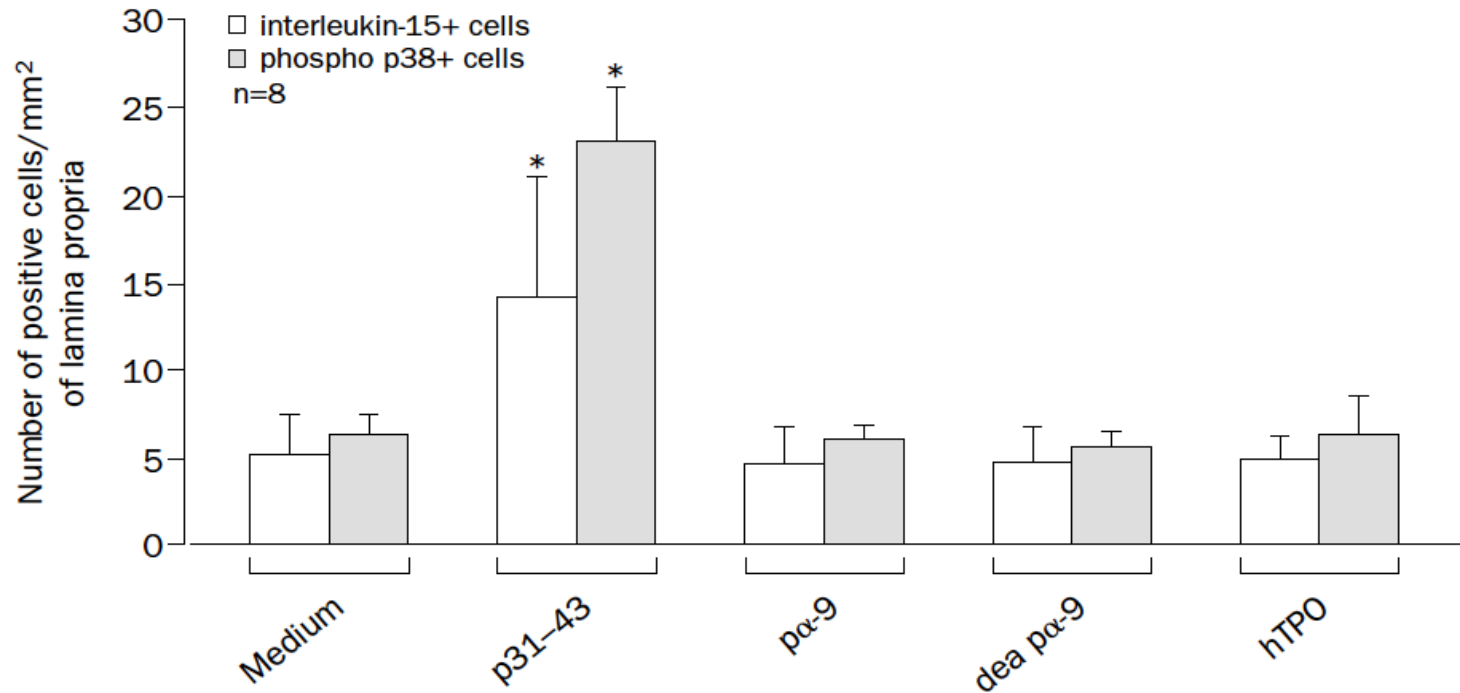
Innate immune responses induced by gliadin in vitro

- Human Caco-2 gut epithelial cells.
 - Nanakkayara et al, AmJ Clin Nutr 2013
- Mouse peritoneal macrophages
 - Tuckova et al, J Leukocyte Biol 2003
- Human monocyte cell line Thp-1
 - Jelinkova et al, FEBS Lett 2004
- Monocytes from coeliacs and healthy donors
 - Palova-Jelinkova, PLoS One 2013

Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease

Lancet 2003; **362**: 30–37

Luigi Maiuri, Carolina Ciacci, Ida Ricciardelli, Loredana Vacca, Valeria Raia, Salvatore Auricchio, Jean Picard, Mohai

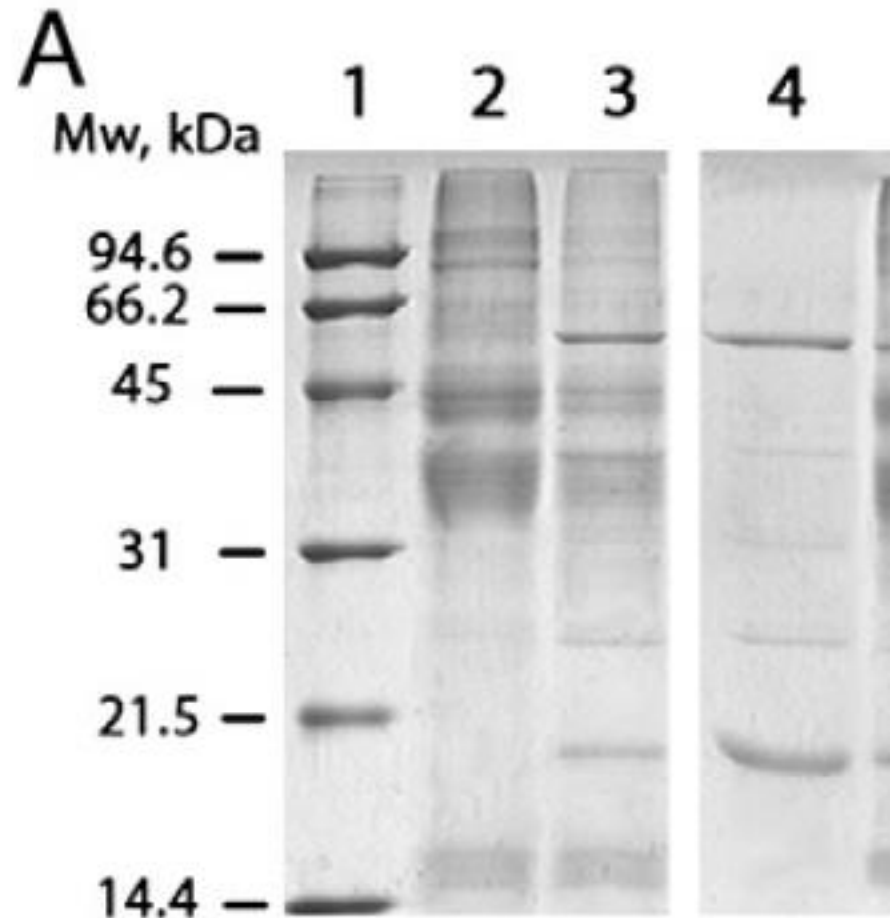


Enterocyte apoptosis

Innate immune responses protect wheat against insect predation?

● Only a few insects can eat wheat

- All digest gliadin with salivary enzymes that hydrolyse around glutamine repeats
- Separate evolution in northern and southern hemispheres
 - *Eurogaster integriceps*
 - *Nysius huttoni*





Eurygaster integriceps



Nysius huttoni

Cysteine digestive peptidases function as post-glutamine cleaving enzymes in tenebrionid stored-product pests

Comparative Biochemistry and Physiology, Part B 161 (2012) 148–154

I.A. Goptar ^a, T.A. Semashko ^b, S.A. Danilenko ^b, E.N. Lysogorskaya ^a, E.S. Oksenoit ^a, D.P. Zhuzhikov ^c, M.A. Belozersky ^d, Y.E. Dunaevsky ^d, B. Oppert ^{e,*}, I.Yu. Filippova ^a, E.N. Elpidina ^d

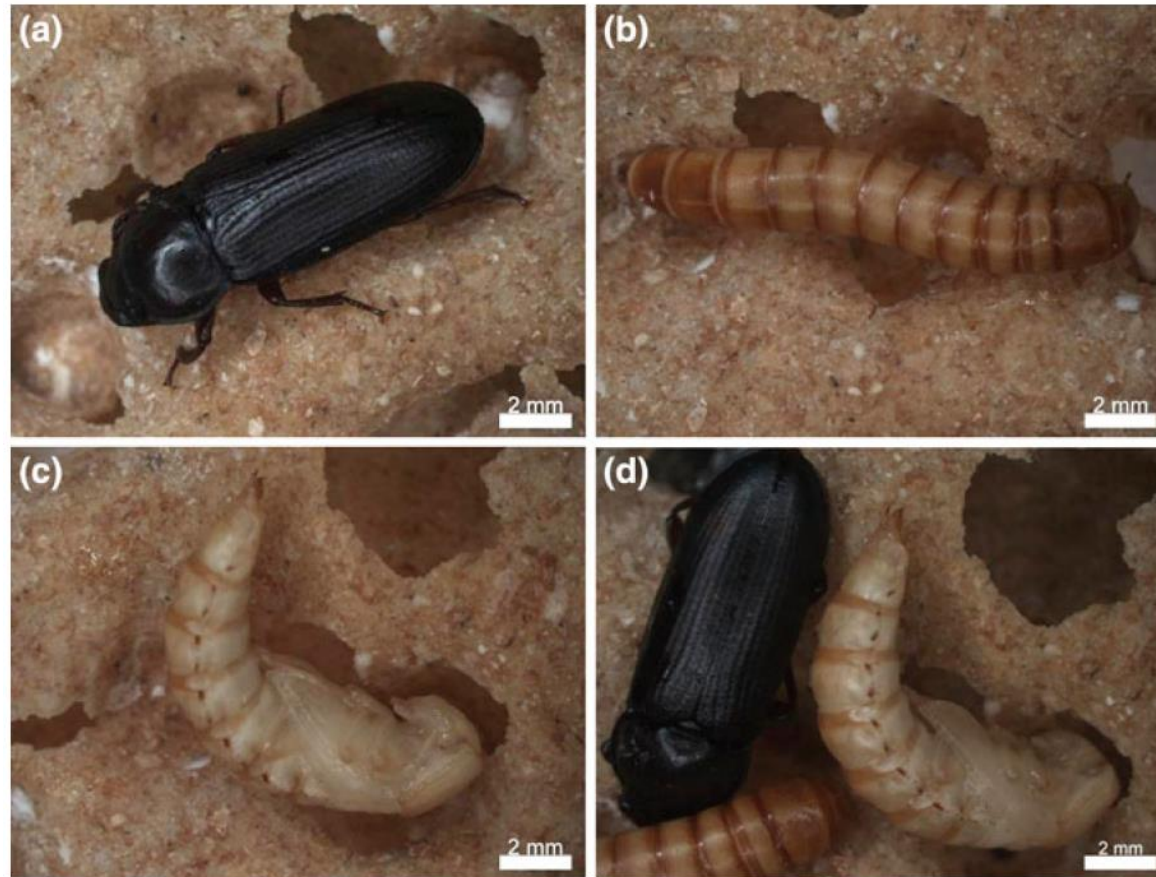


Fig. 2 Adult beetle (a, d), larva (b, d) and nymph (c, d) of *T. molitor*

3 digestive enzyme functions as post-glutamine cleaving peptidases

Wheat Cultivar Susceptibility to Grain Damage by
the New Zealand Wheat Bug, *Nysius huttoni*, and
Cultivar Susceptibility to the Effects of Bug Proteinase
on Baking Quality

D. Every, J. A. Farrell, M. W. Stufkens and A. R. Wallace

Journal of Cereal Science 27 (1998) 37–46

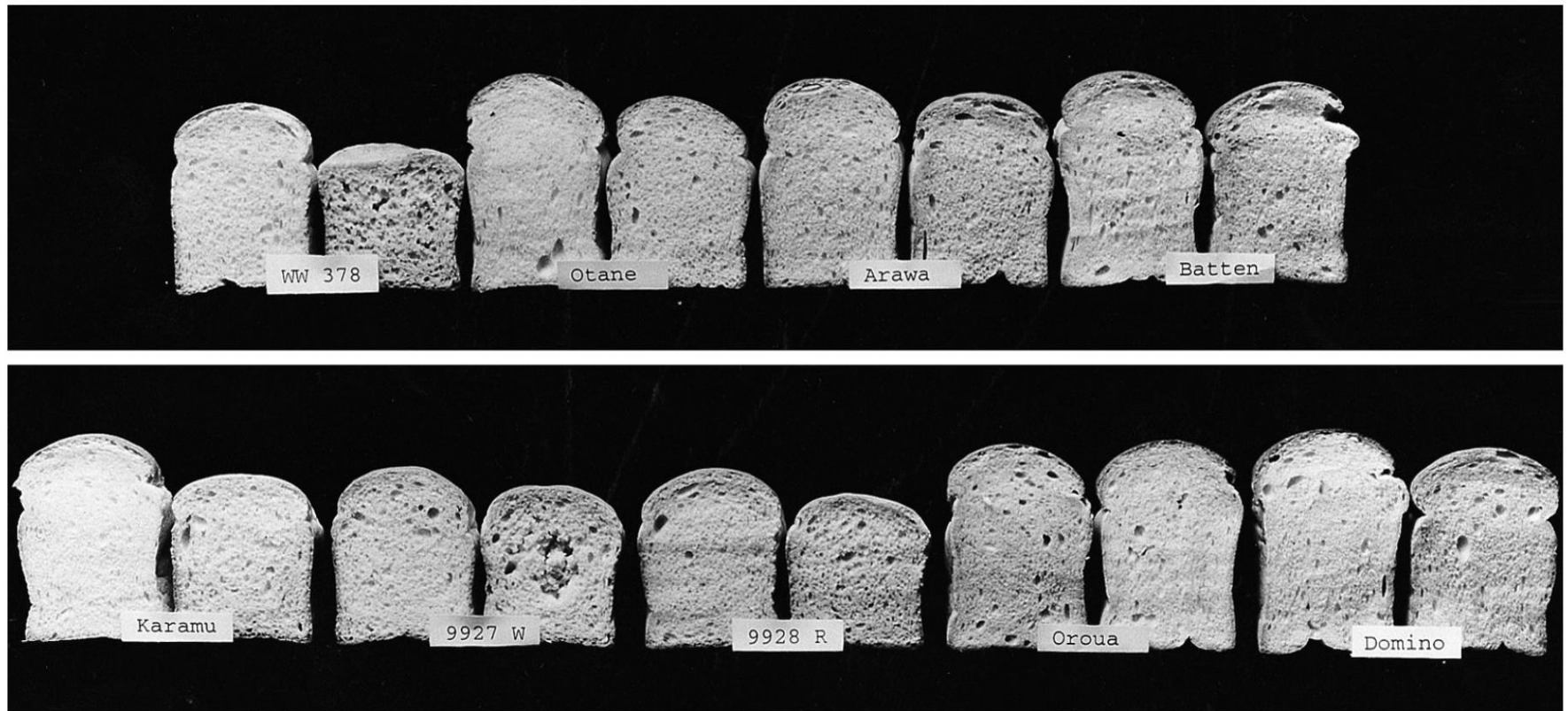
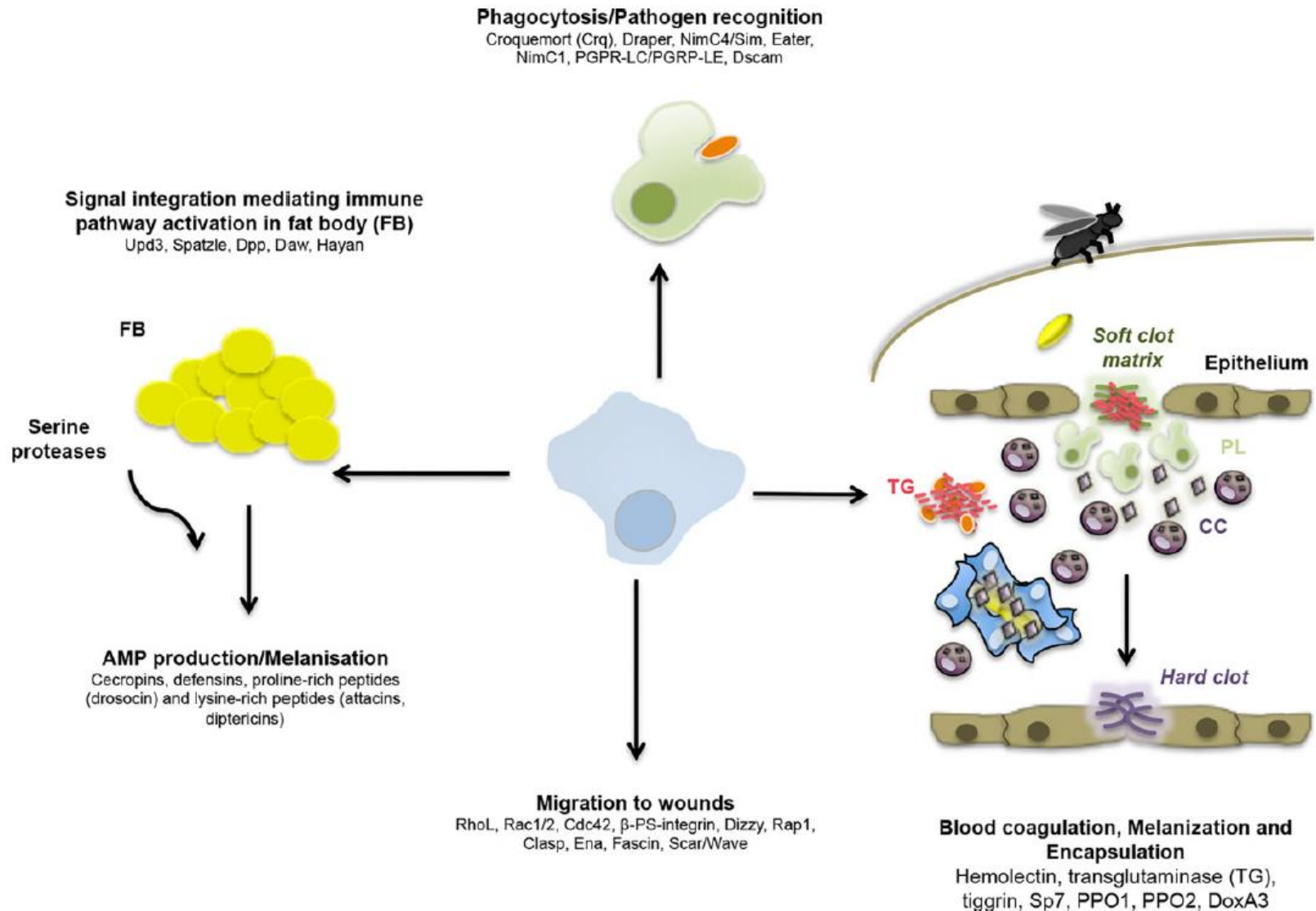


Figure 2 Comparison of loaves baked from sound wheat cultivars (left loaf of labelled pair) and loaves baked from *N. huttoni*-damaged wheat (right loaf of labelled pair) from the 1992/1993 trial.

Drosophila blood cells and their role in immune responses

Isabella Vlisidou and Will Wood

FEBS Journal 282 (2015) 1368–1382

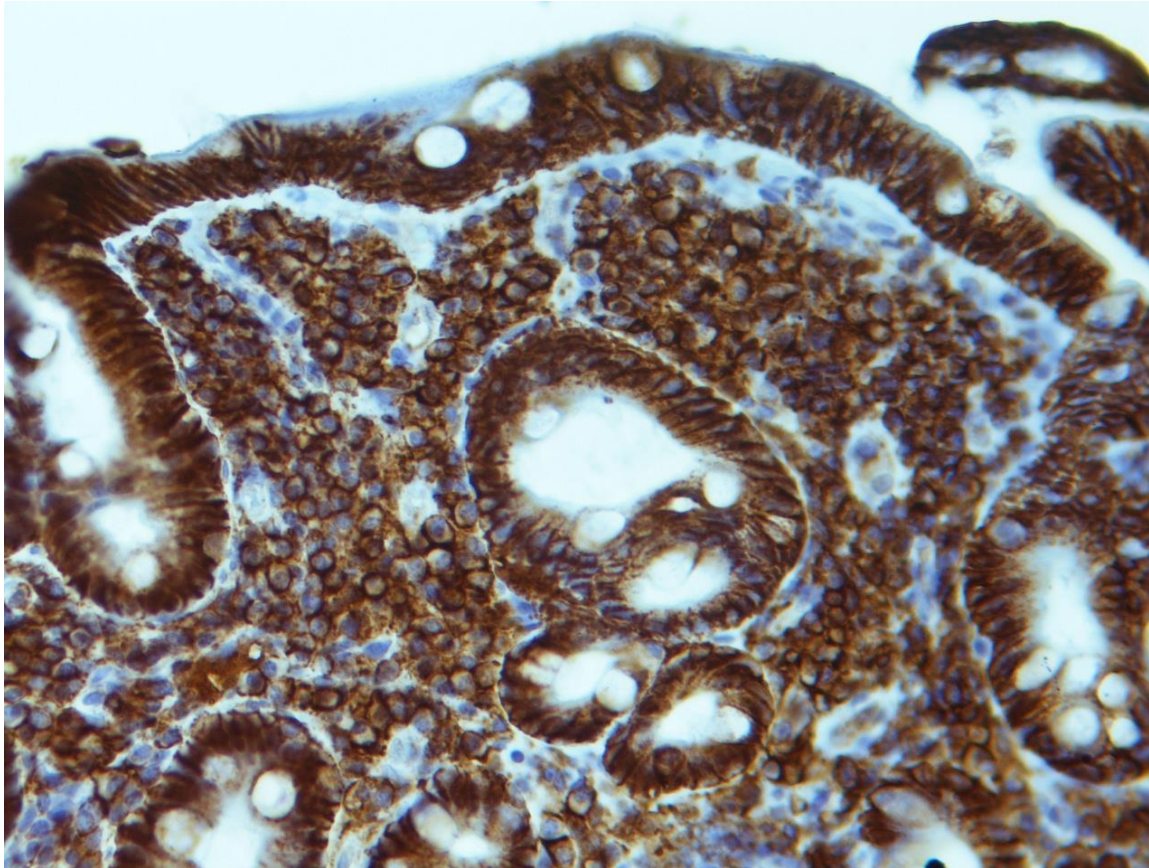


Matrix Expansion and Syncytial Aggregation of Syndecan-1⁺ Cells Underpin Villous Atrophy in Coeliac Disease

Camilla Salvestrini¹, Mark Lucas², Paolo Lionetti³, Franco Torrente¹, Sean James⁴, Alan D. Phillips², Simon H. Murch^{5*}

PLOS ONE | www.plosone.org

September 2014 | Volume 9 | Issue 9 | e106005



Lamina propria expanded by aggregates of syndecan-1 cells

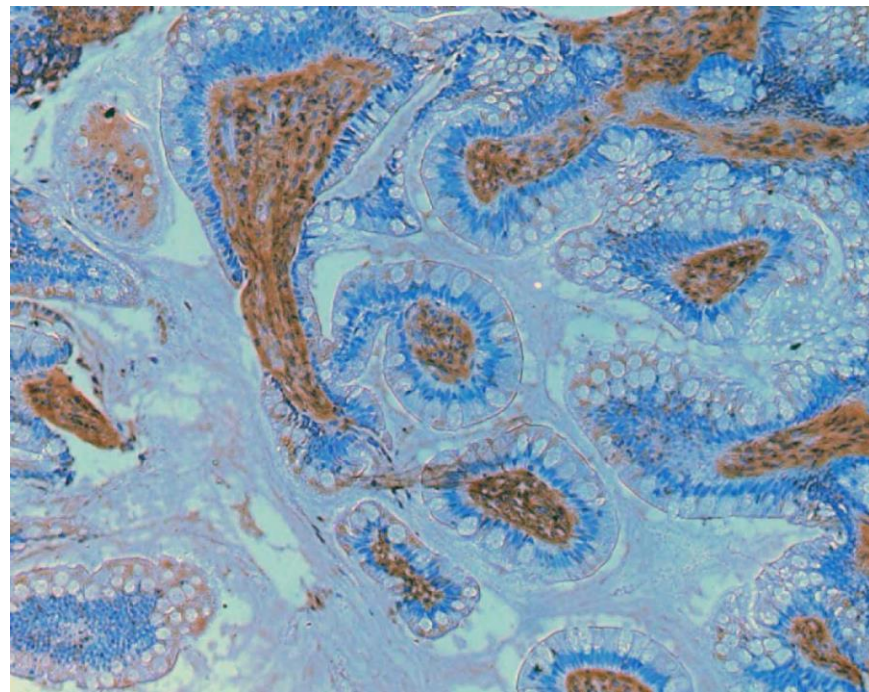
Other bioactive wheat components

- Wheat germ agglutinin

- ↓ epithelial repair
- ↑ cytokines
- Binds nerve fibrils

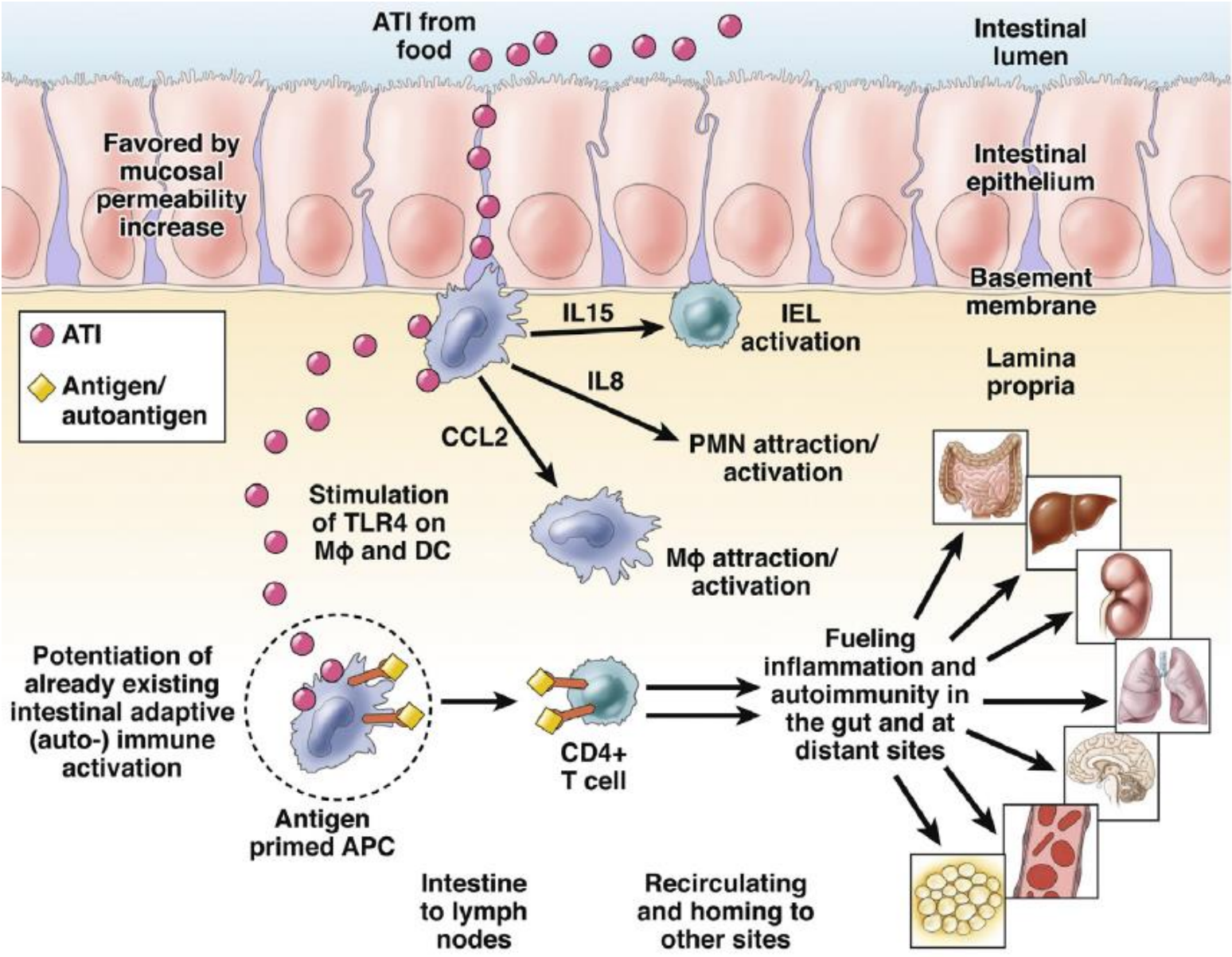
- Amylase trypsin inhibitors

- Activates TLR4
- ↑ Innate immune responses



**Wheat germ agglutinin binding
in small bowel**

Nonceliac Gluten Sensitivity Fasano et al Gastroenterology 2015;148:1195-1204



Wheat/gluten tolerance may depend on...

- Ability to degrade bioactive components
 - Gliadin – immunodominant region
 - Gliadin p31-43 - innate immune trigger
 - Wheat germ agglutinin
 - Amylase trypsin inhibitor
 - Wheat exorphins – DPP4

Summary

- Non-coeliac gluten sensitivity exists
 - Not a single entity (Wheat sensitivity?)
 - HLA-DQ2 more frequent
 - Still poorly categorised
- Gluten induces innate immune responses
 - Non-HLA-linked susceptibility
 - Digestion of gluten required to prevent this
 - Evolved in insects but not man