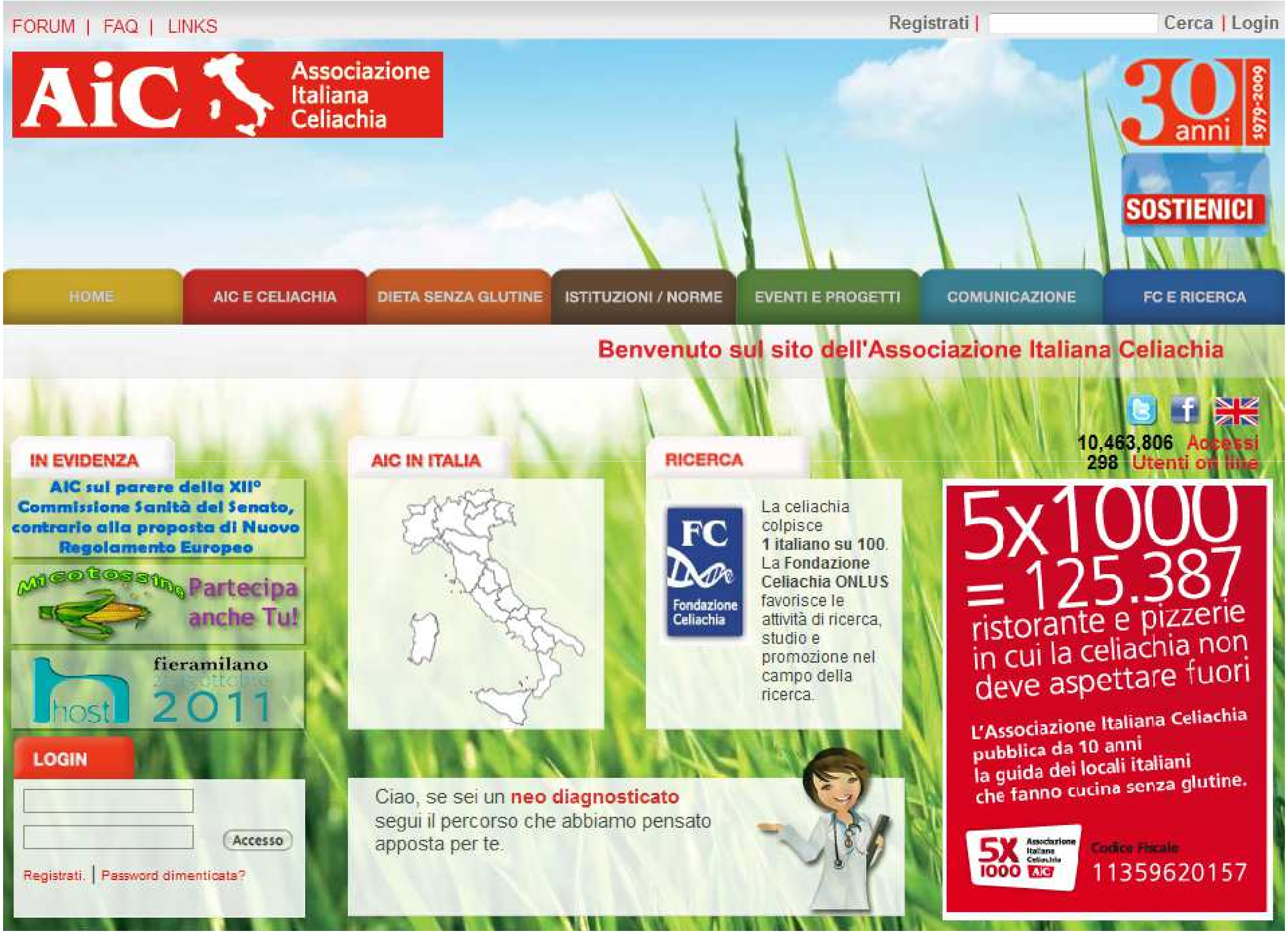
morbo celiaco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La celiachia colpisce 1 italiano su 100. La Fondazione Celiachia ONLUS favorisce le attività di ricerca, studio e promozione nel campo della ricerca.
5x1000 = 125.387
ristorante e pizzerie in cui la celiachia non deve aspettare fuori
L'Associazione Italiana Celiachia pubblica da 10 anni la guida dei locali italiani che fanno cucina senza glutine.
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Ciao, se sei un neo diagnosticato segui il percorso che abbiamo pensato apposta per te.

Morbo celiaco

celiac disease, celiac sprue, gluten-sensitive enteropathy
nontropical sprue

Lesione mucosale caratteristica dell'intestino tenue con malassorbimento che migliora eliminando le gliadine (glutine) del frumento dalla dieta.

Il morbo celiaco colpisce prevalentemente i soggetti di razza caucasica ed è rara negli africani, giapponesi e cinesi.
In Europa la prevalenza è di 1:100-1:200, negli Usa 1:130-300

CELIAC DISEASE IS A UNIQUE AUTOIMMUNE DISORDER, UNIQUE BECAUSE the environmental precipitant is known. The disorder was previously called celiac sprue, based on the Dutch word *sprue*, which was used to describe a disease similar to tropical sprue that is characterized by diarrhea, emaciation, aphthous stomatitis, and malabsorption.[1,2] Celiac disease is precipitated, in genetically predisposed persons, by the ingestion of gluten, the major storage protein of wheat and similar grains.[3] Originally considered a rare malabsorption syndrome of childhood, celiac disease is now recognized as a common condition that may be diagnosed at any age and that affects many organ systems. The therapy for the disease is a gluten-free diet; however, the response to therapy is poor in up to 30% of patients, and dietary nonadherence is the chief cause of persistent or recurrent symptoms. Small intestinal adenocarcinoma, refractory sprue, and enteropathy-associated T-cell lymphoma are complications of celiac disease that must be ruled out when alarming symptoms such as abdominal pain, diarrhea, and weight loss develop despite a strict gluten-free diet.

THE ROLE OF GLUTEN

Celiac disease is induced by the ingestion of gluten, which is derived from wheat, barley, and rye. The gluten protein is enriched in glutamine and proline and is poorly digested in the human upper gastrointestinal tract. The term "gluten" refers to the entire protein component of wheat; gliadin is the alcohol-soluble fraction of gluten that contains the bulk of the toxic components. Undigested molecules of gliadin, such as a peptide from an α-gliadin fraction made up of 33 amino acids, are resistant to degradation by gastric, pancreatic, and intestinal brush-border membrane proteases in the human intestine and thus remain in the intestinal lumen after gluten ingestion.[4] These peptides pass through the epithelial barrier of the intestine, possibly during intestinal infections or when there is an increase in intestinal permeability, and interact with antigen-presenting cells in the lamina propria.

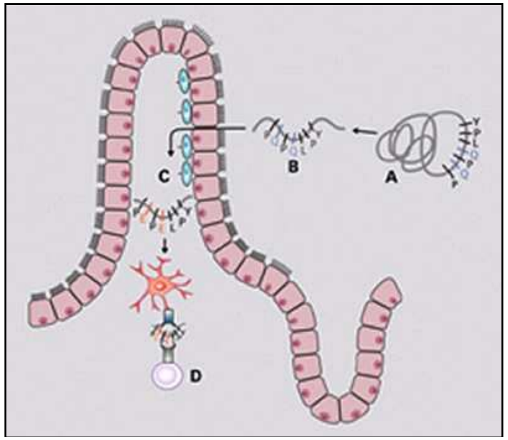
Patogenesi

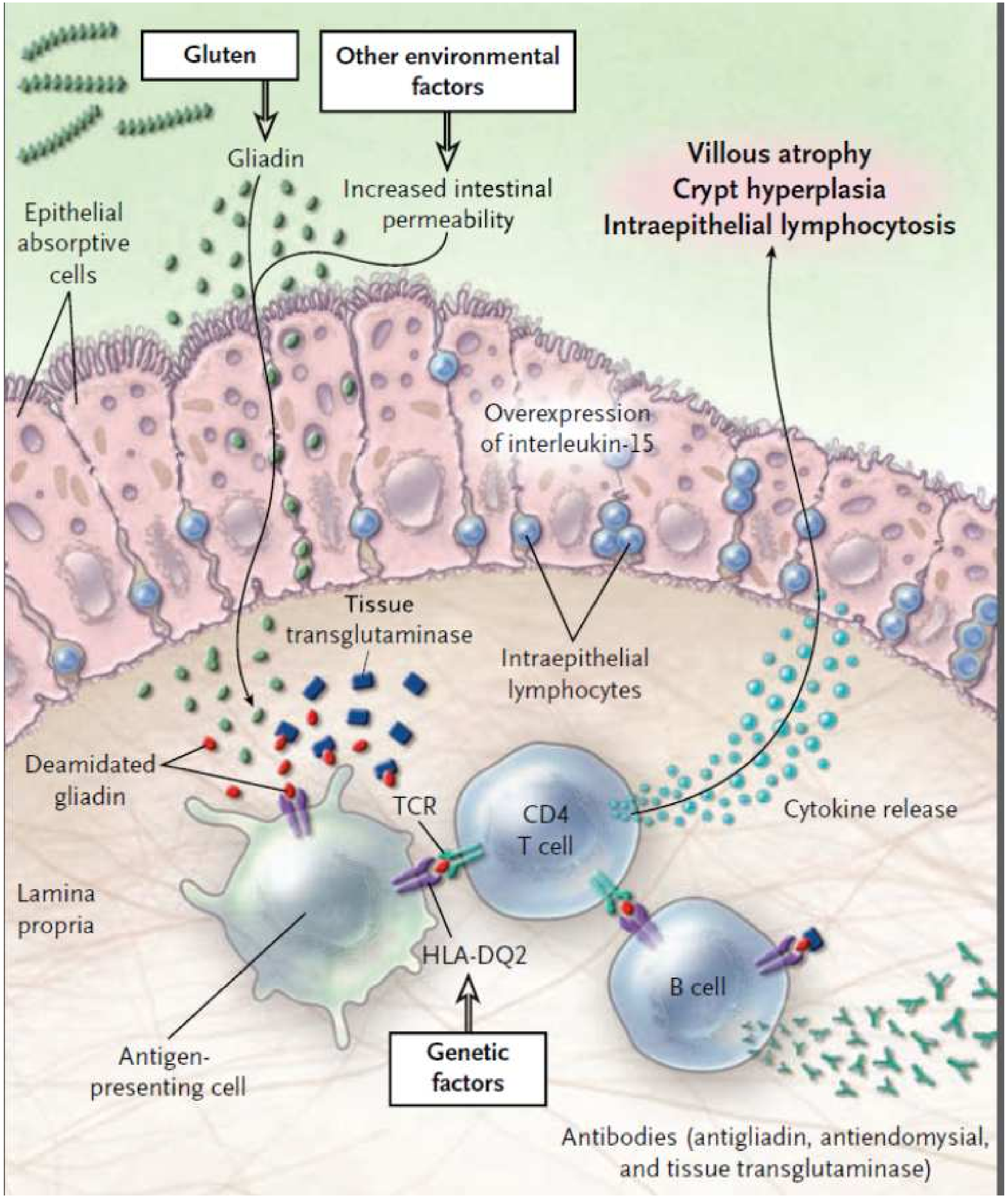
Ipersensibilità al glutine, che è la proteina (gliadina) alcool-solubile, insolubile in acqua componente il frumento e del grano di avena, orzo e segale.

Reazione infiammatoria cronica, da parte dei linfociti T, con una componente autoimmune, che si sviluppa probabilmente come conseguenza della perdita di tolleranza nei confronti del glutine.
La mucosa dell'intestino tenue, quando esposta al glutine, accumula linfociti CD8+ a livello intraepiteliale e numerosi CD4+ nella lamina propria, sensibilizzati nei confronti della gliadina.

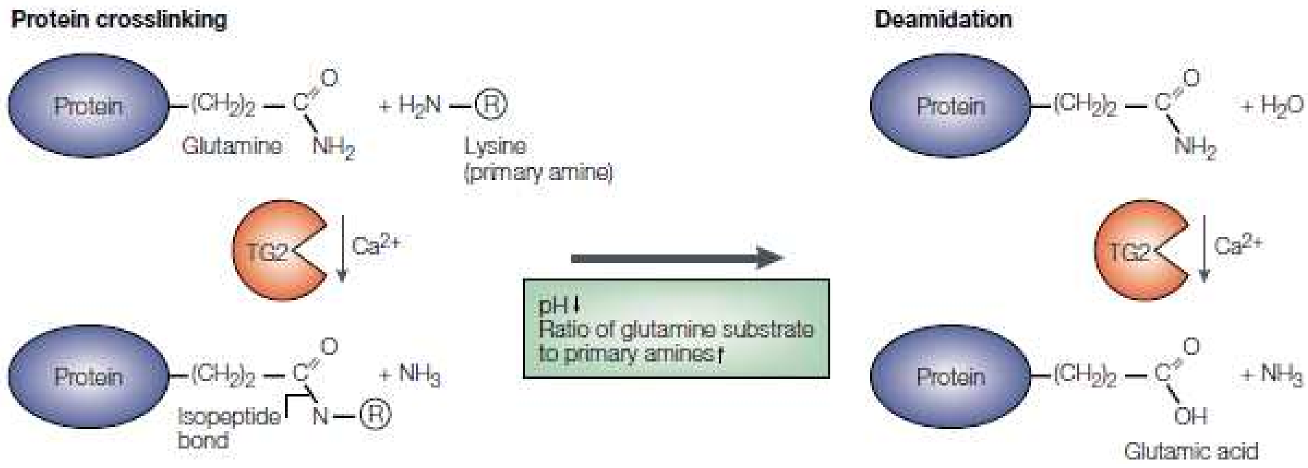
Nella <u>patogenesi</u> della malattia sono compresi fattori genetici predisponenti, il tipo di risposta del sistema immunitario e fattori ambientali.
Quasi tutti gli individui con morbo celiaco, condividono gli aplotipi per il complesso maggiore di istocompatibilità II HLA-DQ2 o HLA-DQ8: sembra che la gliadina venga deaminata dalla transglutaminasi e che i peptidi deaminati si leghino a DQ2 e DQ8. Il riconoscimento di questi peptidi da parte dei linfociti CD4+ porta alla secrezione di interferone γ che danneggia la mucosa intestinale.
E' un'ipotesi che deve essere ancora dimostrata così come il perché i CD8+ si accumulano nell'epitelio. Infatti i linfociti CD8+ non riconoscono la gliadina, ma sembrano rispondere alle molecole indotte dallo stress (IL-15) sulle cellule epiteliali.
Le cellule epiteliali secernono grandi quantità di IL-15 che attivano le cellule T CD8+ e aumentano il rischio di sviluppo di linfoma intestinale.

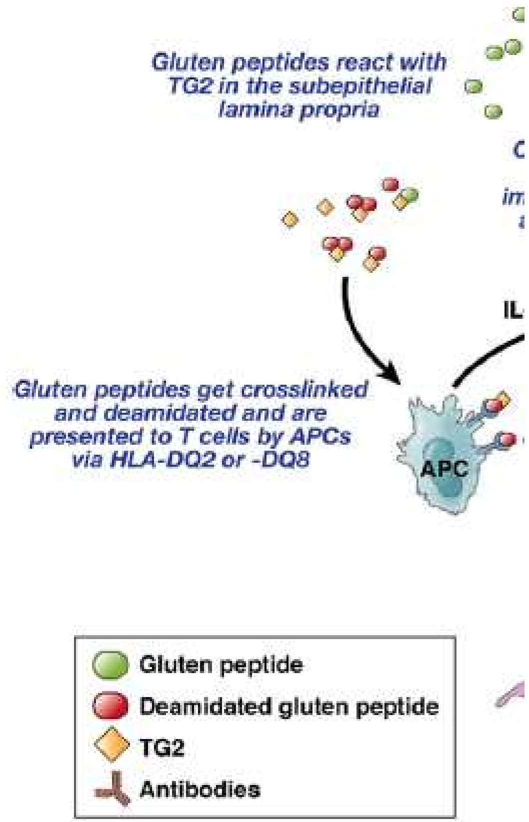
Esiste una forte evidenza che genitori e fratelli di celiaci hanno un aumentato rischio di sviluppare la malattia, con una prevalenza che va dal 6 al 12%.

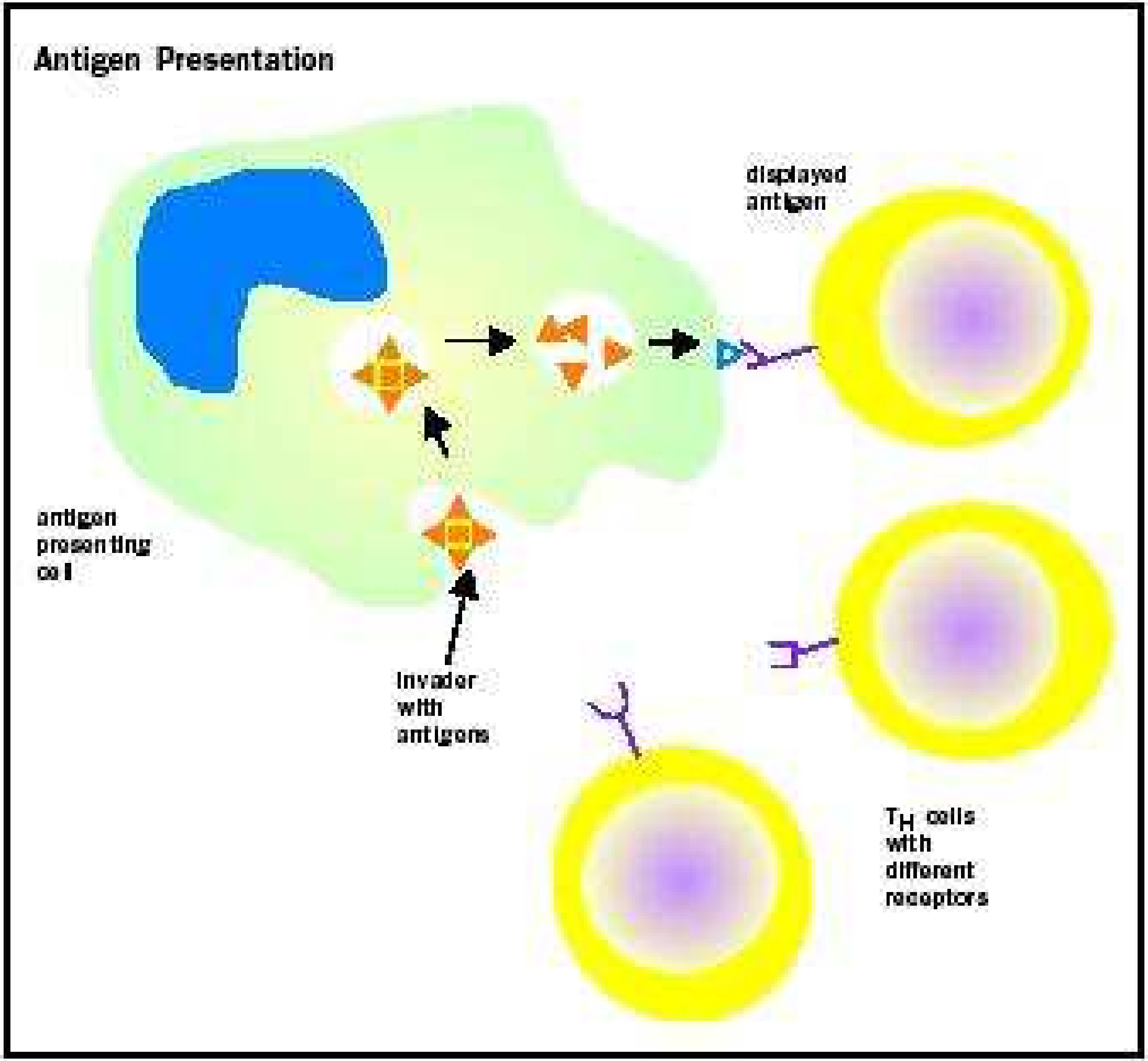


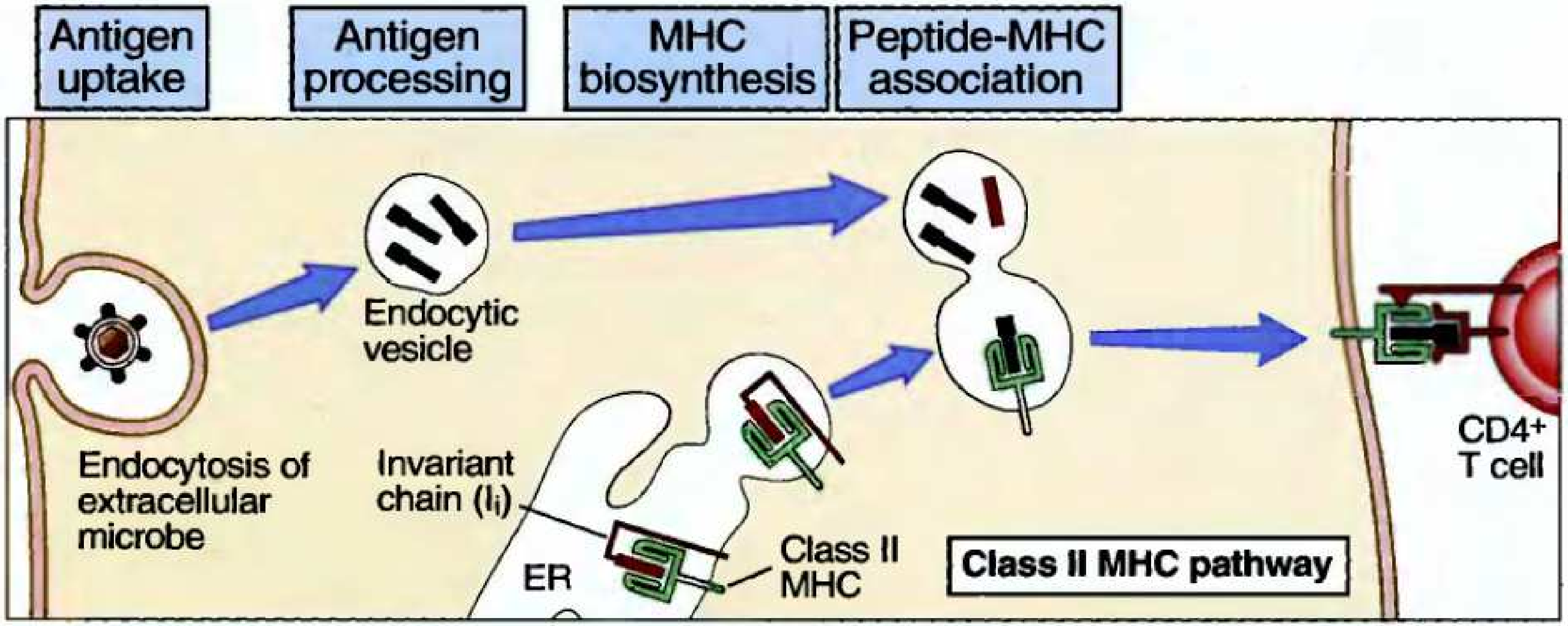


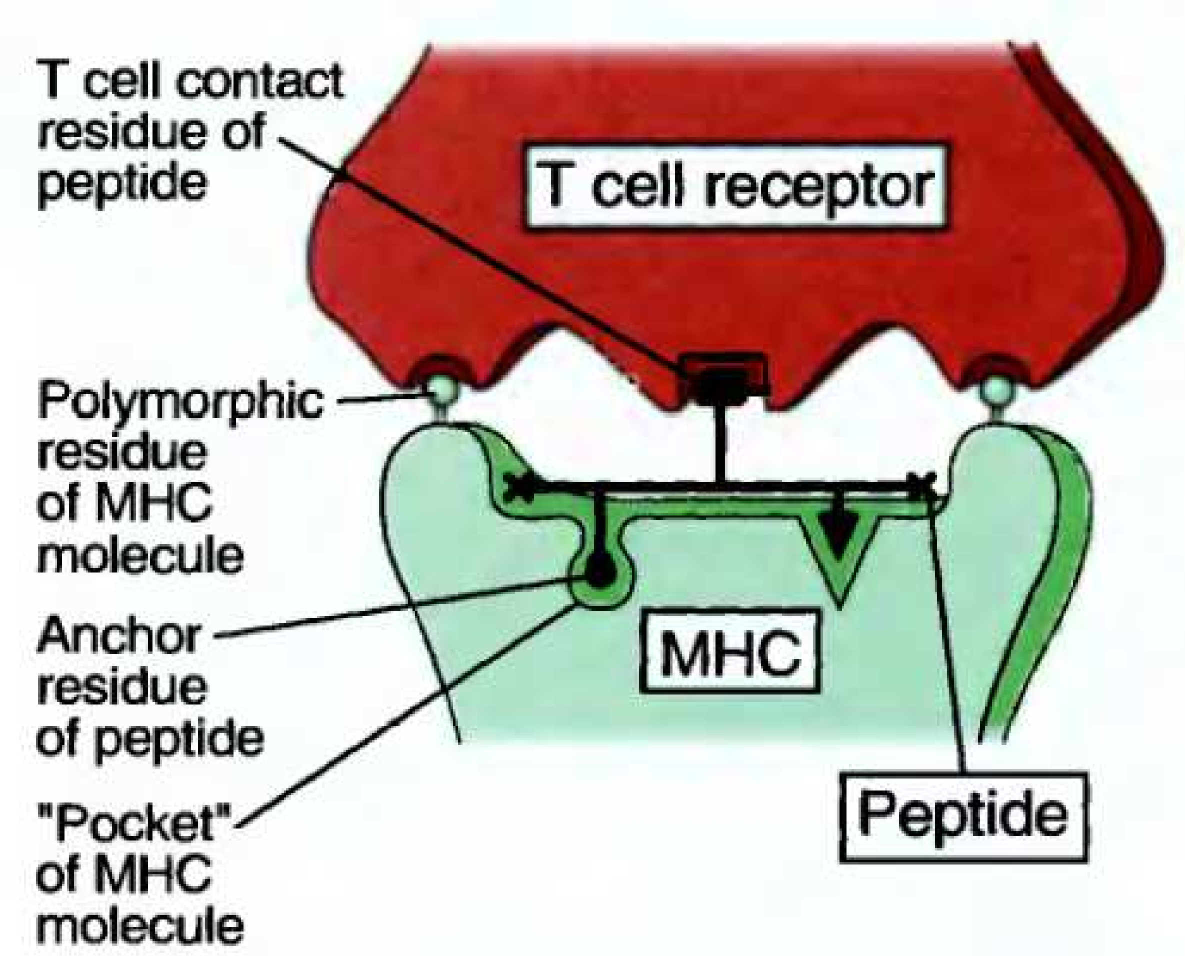
Gluten
Other environmental factors
Gliadin
Increased intestinal permeability
Villous atrophy
Crypt hyperplasia
Intraepithelial lymphocytosis
Epithelial absorptive cells
Overexpression of interleukin-15
Tissue transglutaminase
Intraepithelial lymphocytes
Deamidated gliadin
TCR
CD4 T cell
Cytokine release
Lamina propria
HLA-DQ2
B cell
Antigen-presenting cell
Genetic factors
Antibodies (antigliadin, antiendomysial, and tissue transglutaminase)

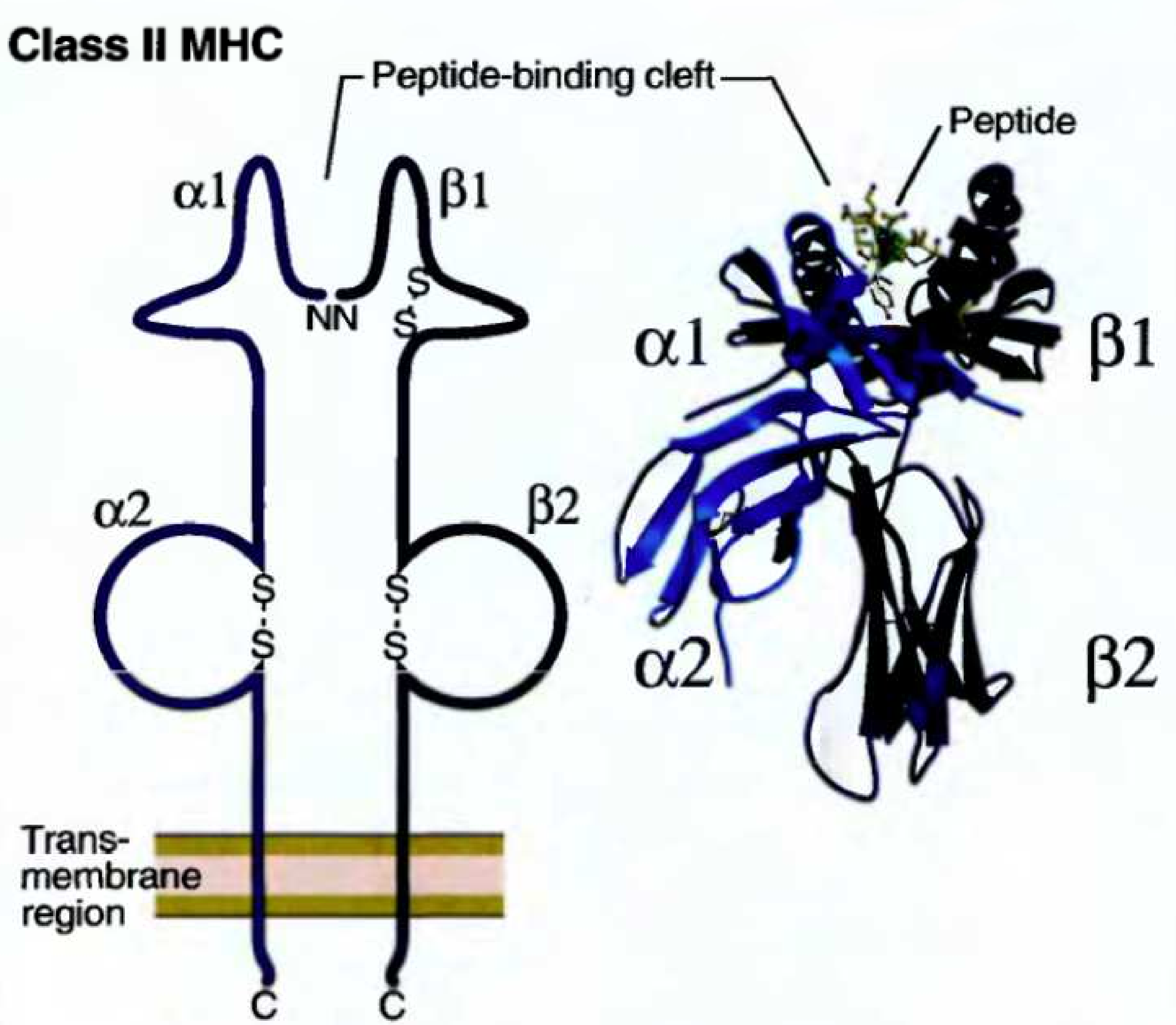

Protein crosslinking
Protein
$-(CH_2)_2-C(=O)NH_2$
Glutamine
$+ H_2N-$(R)
Lysine
(primary amine)
TG2
Ca^{2+}
Protein
$-(CH_2)_2-C(=O)-N-$(R)
$+ NH_3$
Isopeptide bond
pH ↓
Ratio of glutamine substrate to primary amines ↑
Deamidation
Protein
$-(CH_2)_2-C(=O)NH_2$
$+ H_2O$
TG2
Ca^{2+}
Protein
$-(CH_2)_2-C(=O)OH$
$+ NH_3$
Glutamic acid


Gluten peptides react with TG2 in the subepithelial lamina propria
Gluten peptides get crosslinked and deamidated and are presented to T cells by APCs via HLA-DQ2 or -DQ8
APC
Gluten peptide
Deamidated gluten peptide
TG2
Antibodies

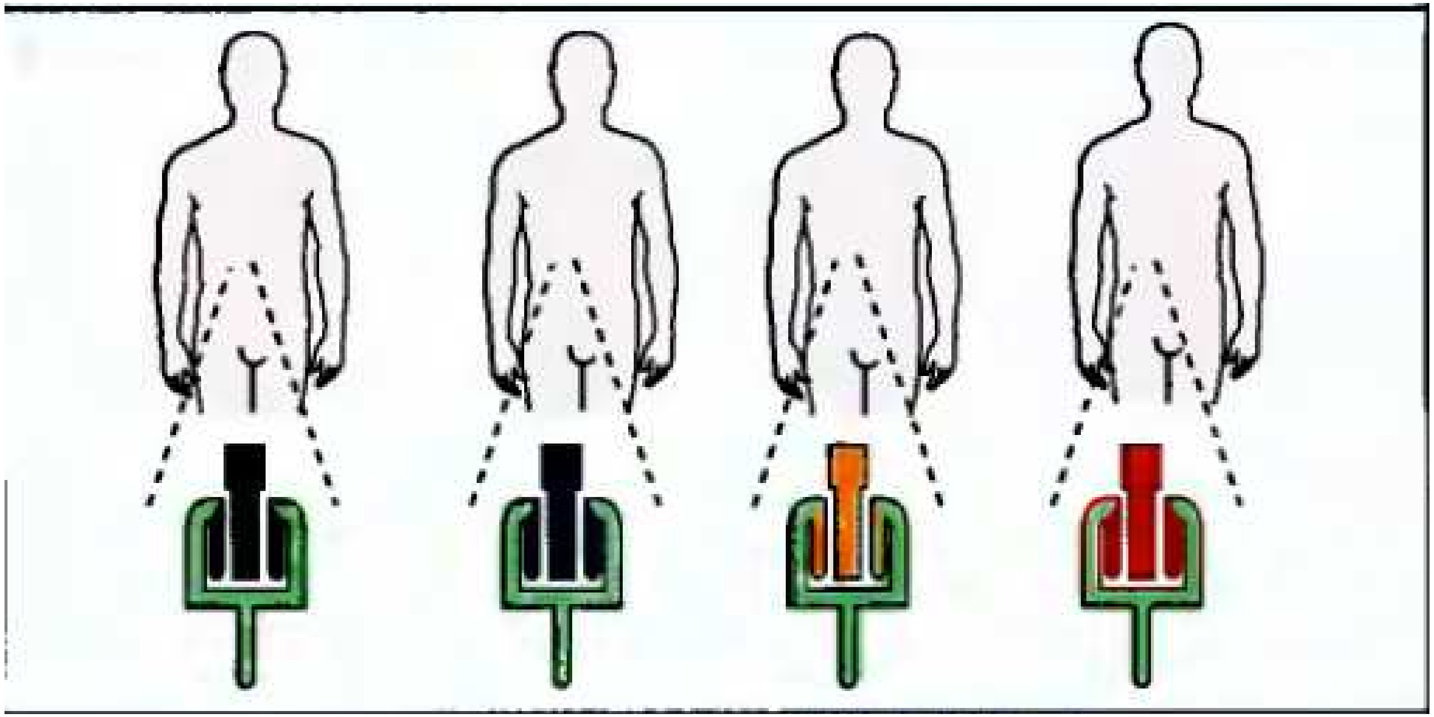

Antigen Presentation
displayed antigen
antigen presenting cell
invader with antigens
T_H cells with different receptors

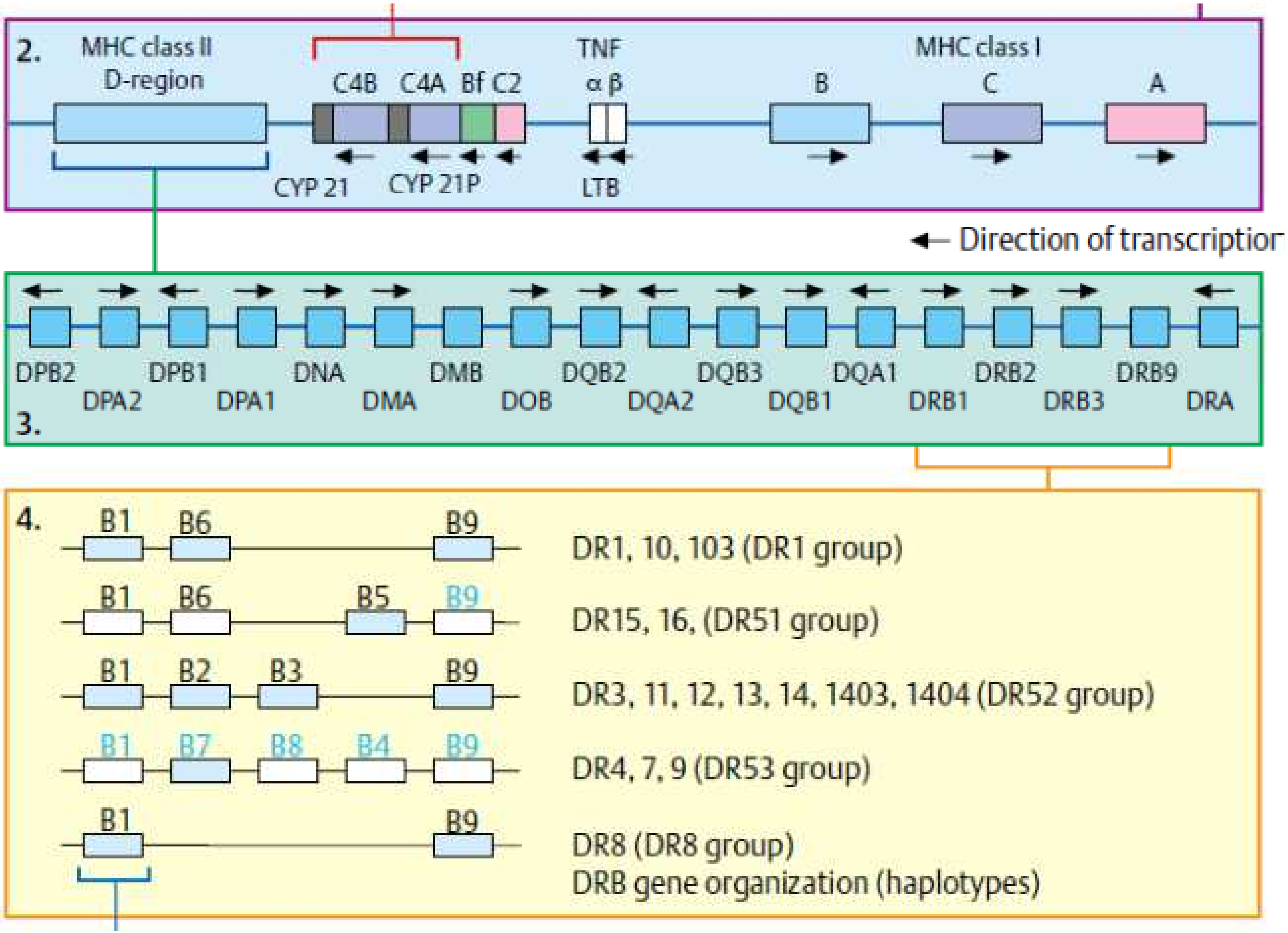

Antigen uptake
Antigen processing
MHC biosynthesis
Peptide-MHC association
Endocytic vesicle
Endocytosis of extracellular microbe
Invariant chain (I_i)
ER
Class II MHC
Class II MHC pathway
CD4+ T cell

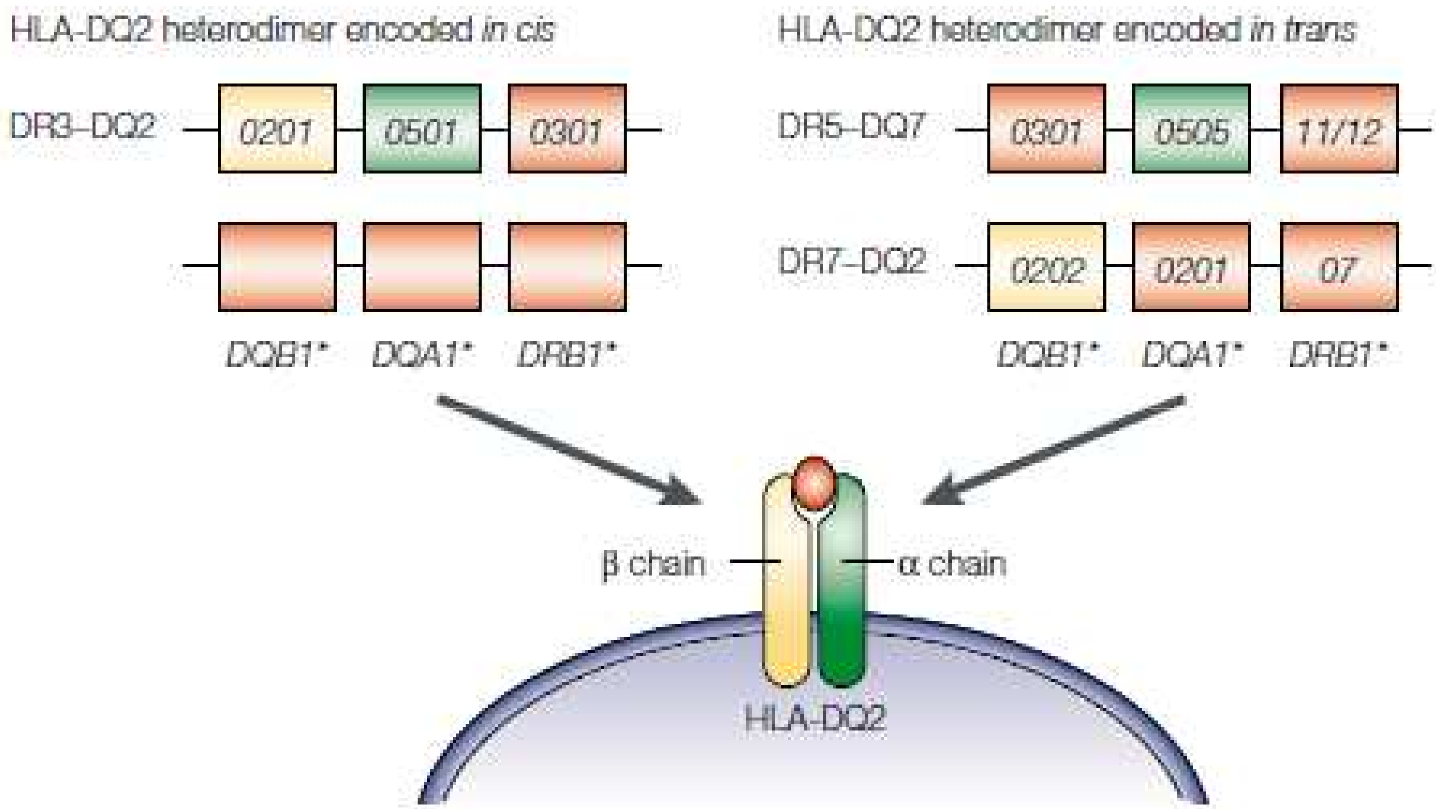

T cell contact residue of peptide
T cell receptor
Polymorphic residue of MHC molecule
MHC
Anchor residue of peptide
"Pocket" of MHC molecule
Peptide

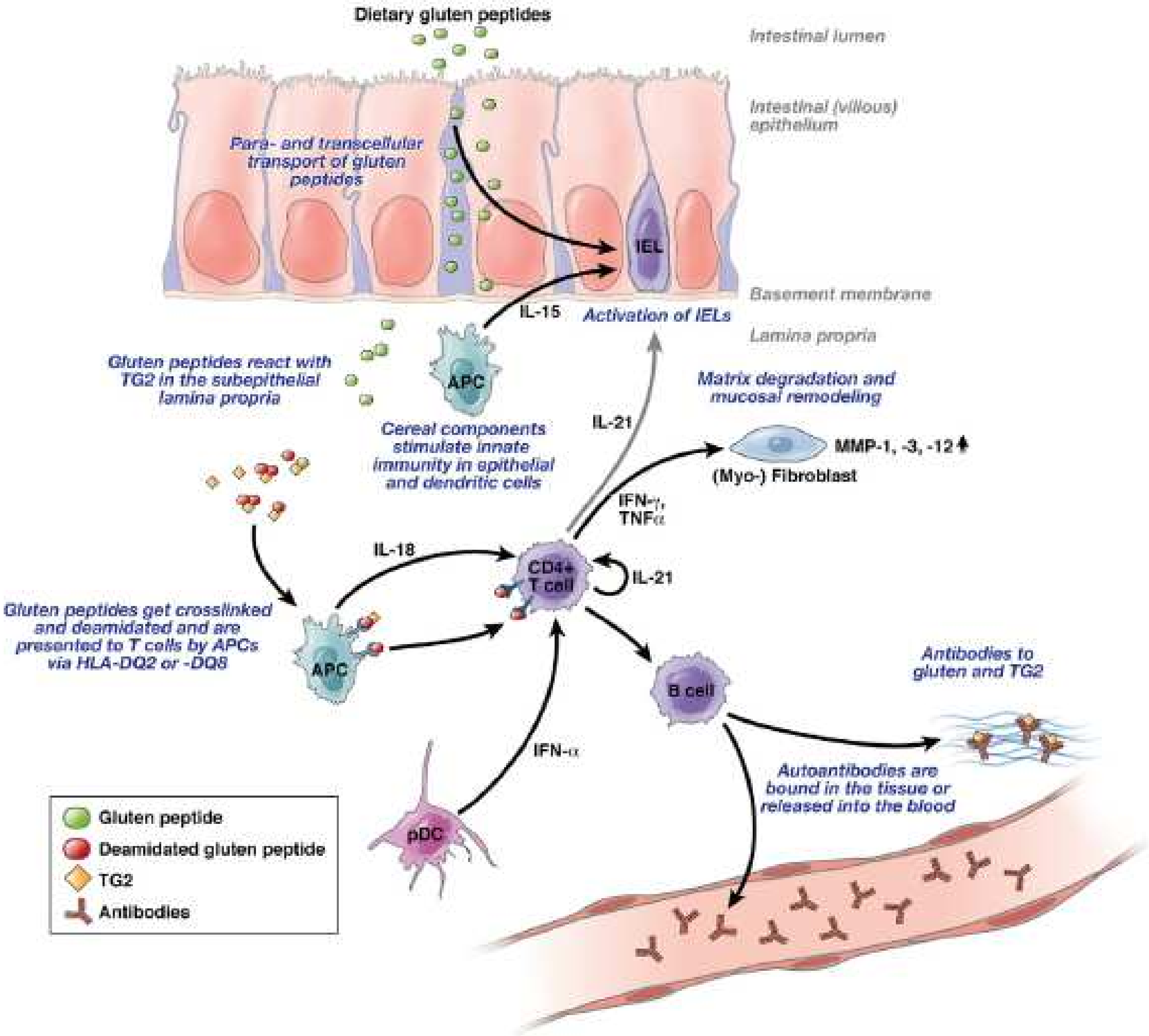

Class II MHC
Peptide-binding cleft
Peptide
α1
β1
NN
S
S
α2
β2
S
S
S
S
Trans-
membrane
region
C
C
α1
β1
α2
β2

Polymorphic genes: Many different alleles are present in the population	Ensures that different individuals are able to present and respond to different microbial peptides

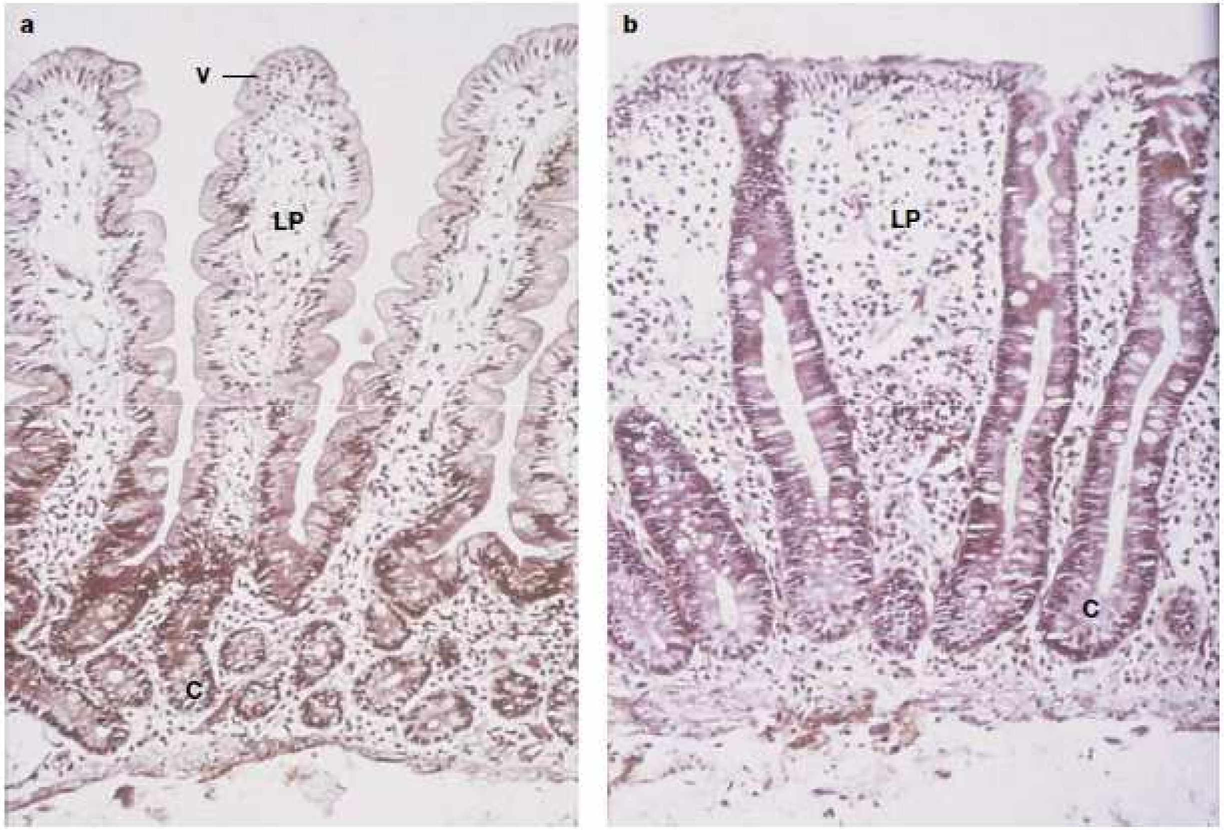



2.
MHC class II
D-region
C4B
C4A
Bf
C2
TNF
α β
MHC class I
B
C
A
CYP 21
CYP 21P
LTB
Direction of transcriptior
DPB2
DPA2
DPB1
DPA1
DNA
DMA
DMB
DOB
DQB2
DQA2
DQB3
DQB1
DQA1
DRB1
DRB2
DRB3
DRB9
DRA
3.
4.
B1
B6
B9
DR1, 10, 103 (DR1 group)
B1
B6
B5
B9
DR15, 16, (DR51 group)
B1
B2
B3
B9
DR3, 11, 12, 13, 14, 1403, 1404 (DR52 group)
B1
B7
B8
B4
B9
DR4, 7, 9 (DR53 group)
B1
B9
DR8 (DR8 group)
DRB gene organization (haplotypes)


HLA-DQ2 heterodimer encoded *in cis*
DR3–DQ2
0201
0501
0301
HLA-DQ2 heterodimer encoded *in trans*
DR5–DQ7
0301
0505
11/12
DR7–DQ2
0202
0201
07
*DQB1**
*DQA1**
*DRB1**
*DQB1**
*DQA1**
*DRB1**
β chain
α chain
HLA-DQ2



Dietary gluten peptides
Intestinal lumen
Intestinal (villous) epithelium
Para- and transcellular transport of gluten peptides
IEL
Basement membrane
IL-15
Activation of IELs
Lamina propria
Gluten peptides react with TG2 in the subepithelial lamina propria
APC
Cereal components stimulate innate immunity in epithelial and dendritic cells
IL-21
Matrix degradation and mucosal remodeling
MMP-1, -3, -12
(Myo-) Fibroblast
IFN-γ, TNFα
IL-18
CD4+ T cell
IL-21
Gluten peptides get crosslinked and deamidated and are presented to T cells by APCs via HLA-DQ2 or -DQ8
APC
B cell
Antibodies to gluten and TG2
IFN-α
Autoantibodies are bound in the tissue or released into the blood
pDC
Gluten peptide
Deamidated gluten peptide
TG2
Antibodies


a
V
LP
C
b
LP
C

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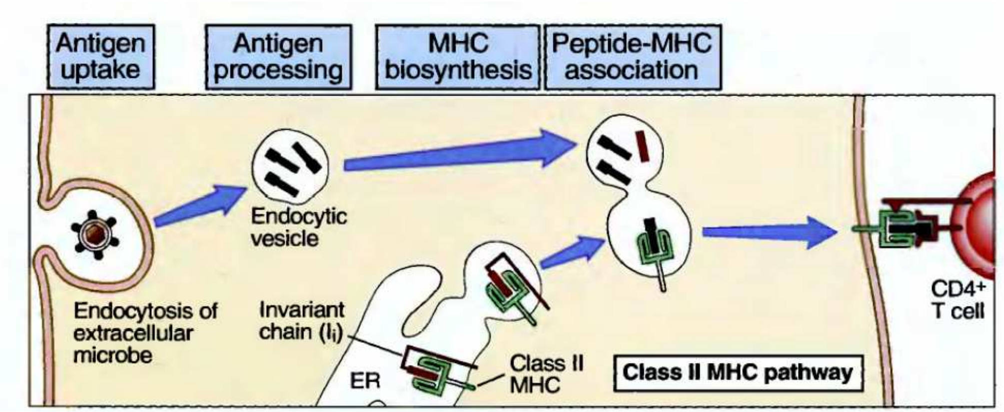
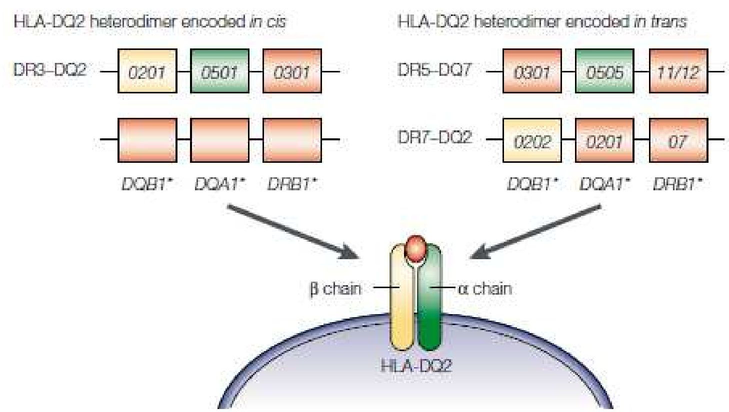
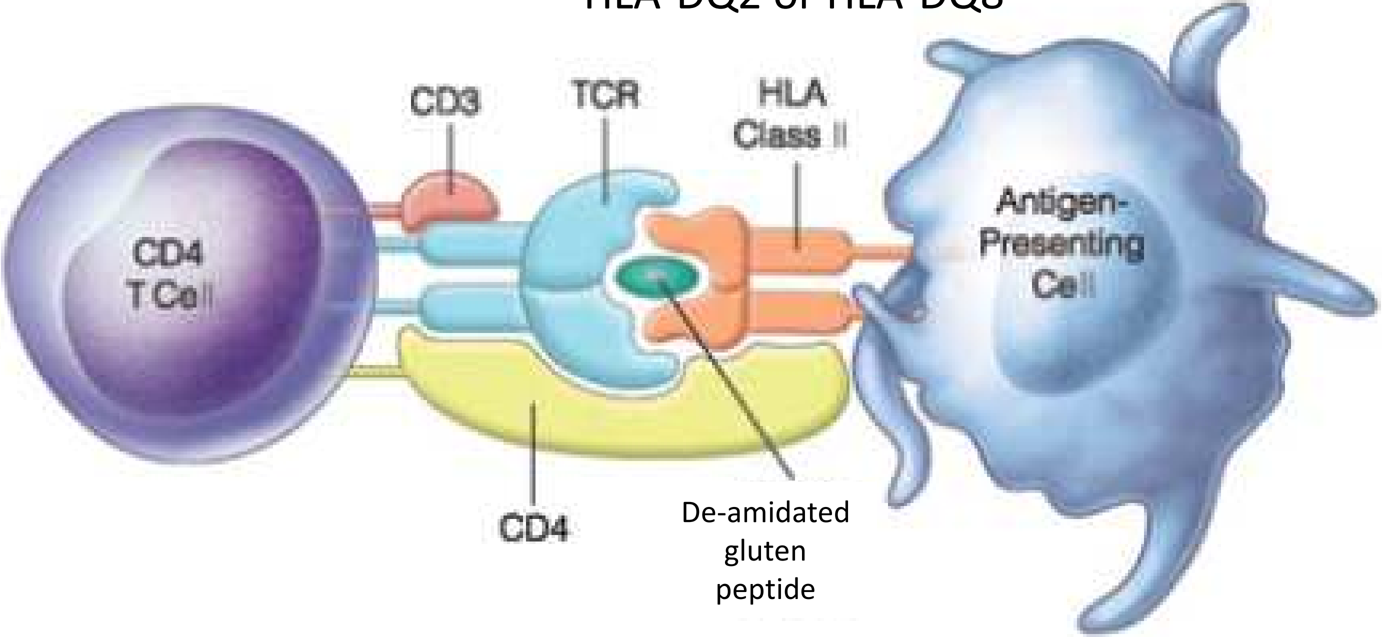
The Irish setter can develop mucosal atrophy in response to wheat ingestion,[139] but the pathogenesis is unlike celiac disease; because disease does not develop when the first gluten exposure occurs after an age of 8–9 months,[140] villous atrophy is not linked to major histocompatibility complex class genes and no serum antibodies to gluten can be detected.[141]

Because all patients with celiac disease bear HLA-DQ2 or HLA-DQ8, HLA-DQ2 or HLA-DQ8 transgenic mice should render suitable models that replicate the pathogenesis of celiac disease. Several transgenic mice have been developed that express human CD4 and DQ8 in the absence of their murine counterparts that would interfere with human immunology.





HLA-DQ2 or HLA-DQ8



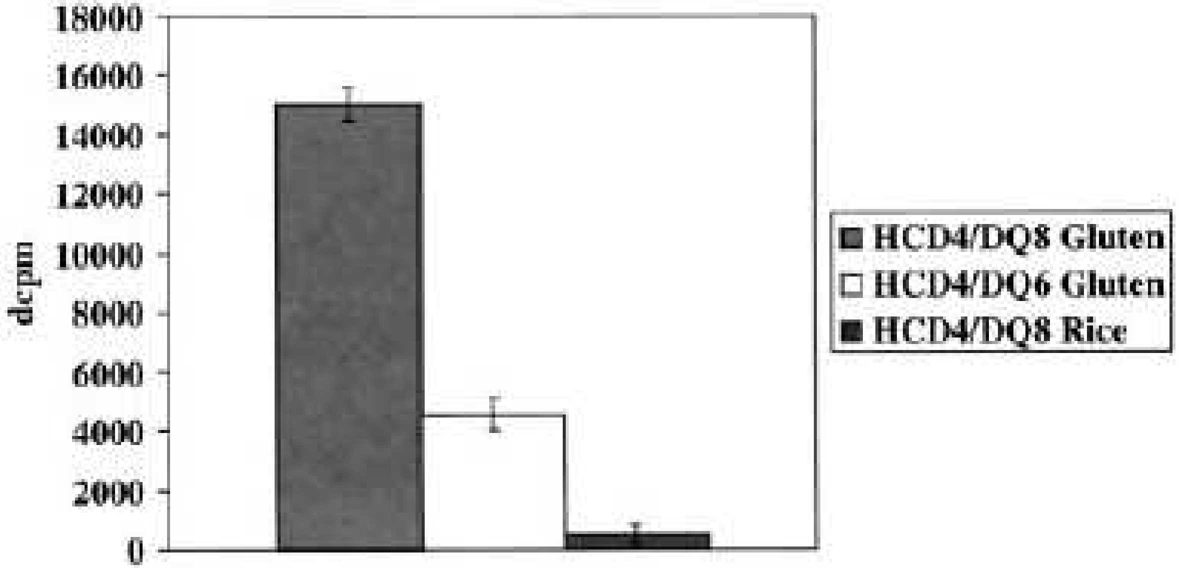


FIGURE 1. HCD4/DQ8and HCD4/DQ6 lymph node cell response to in vitro challenge of gluten and rice protein. Data represent the Δcpm from the mean [^{3}H]thymidine incorporation for triplicate cultures ($p < 0.001$).

After being immunized with gliadin, the T cells of these mice showed in vitro responses to gluten in a HLA-DQ8– and CD4-restricted manner, whereas T cells from HLA-DQ6 CD4 control mice did not develop a gliadin-specific immune response.

Black et al. 2002

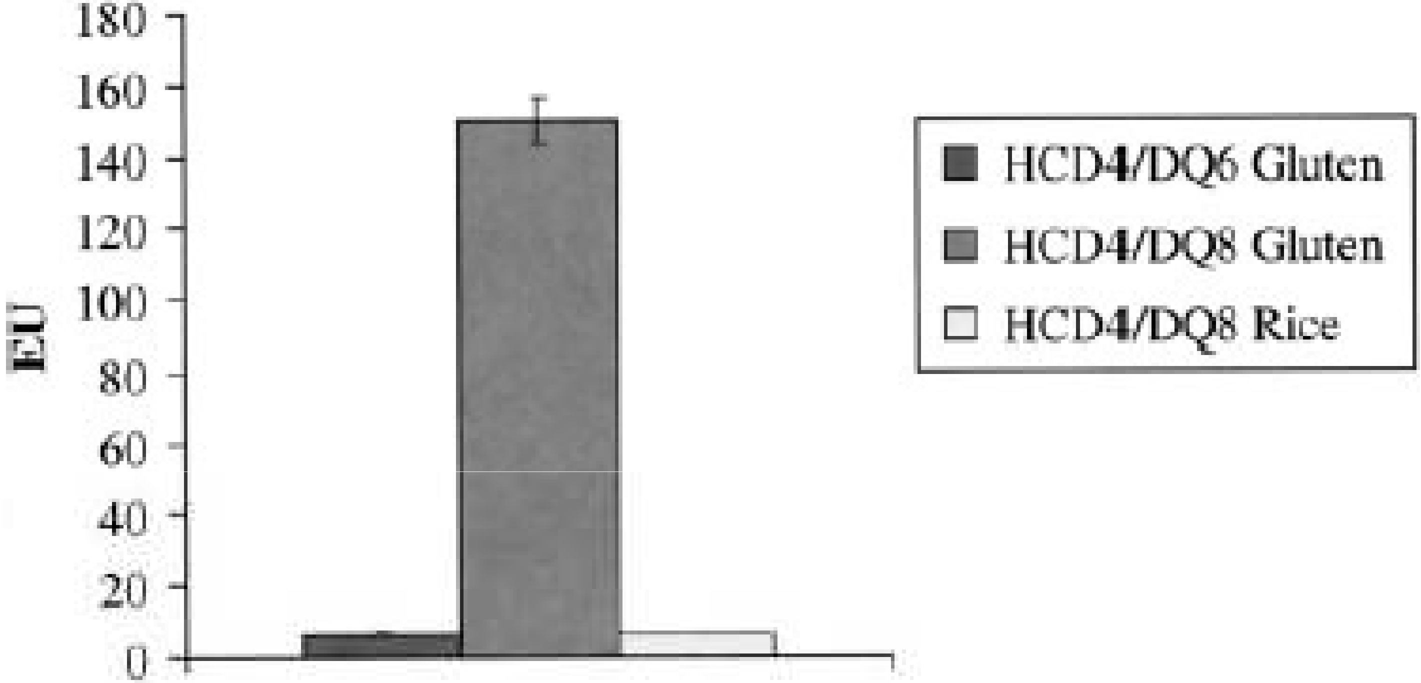
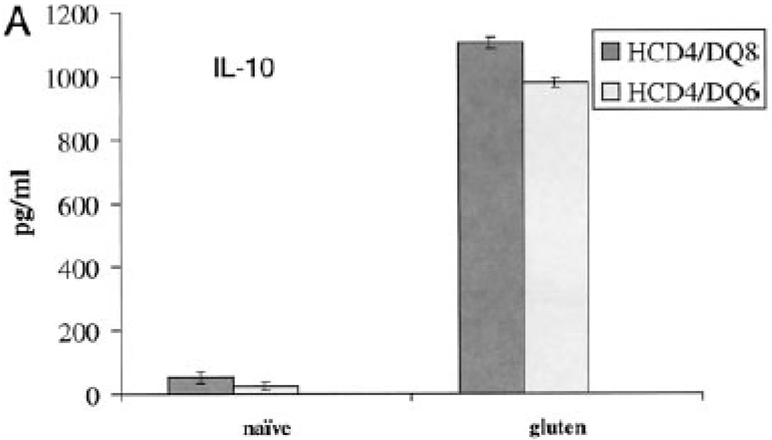
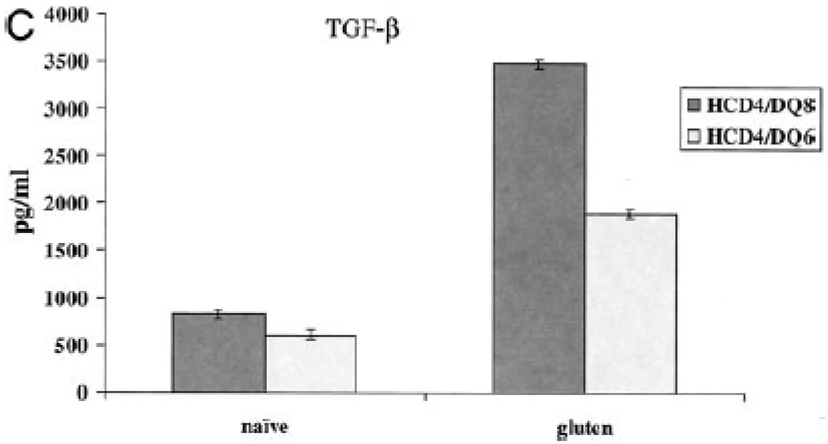
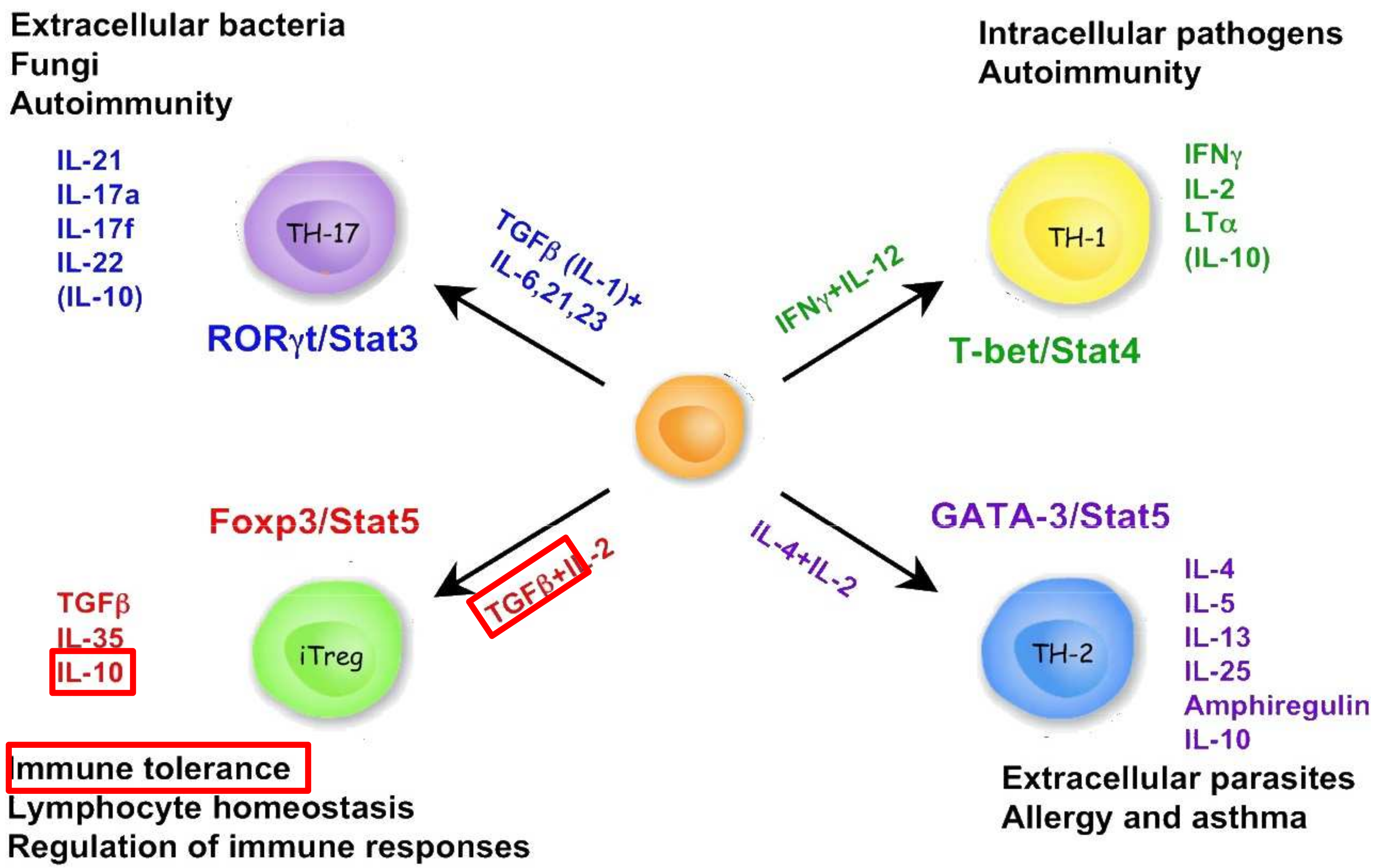


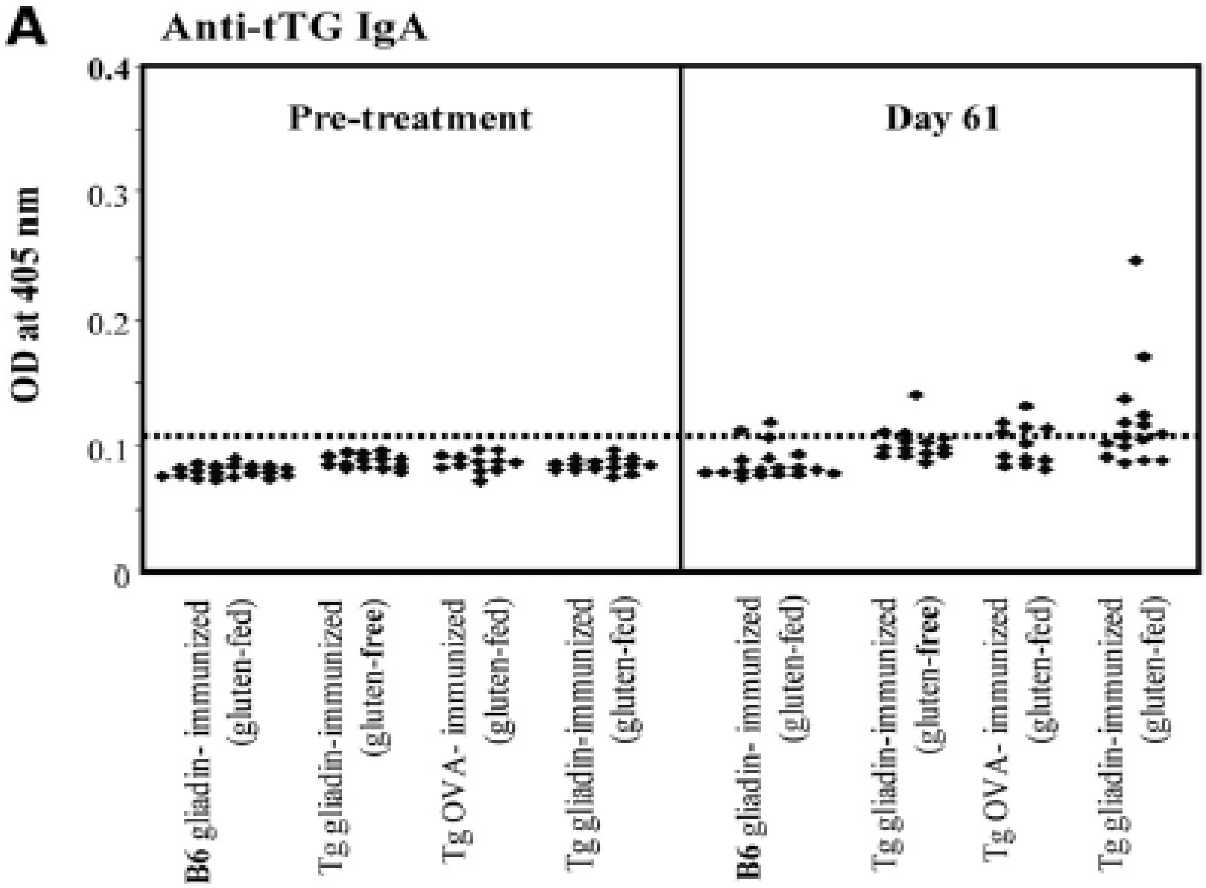
FIGURE 6. HCD4/DQ8 mice immunized with gluten produce anti-gliadin IgG Abs. Results are expressed as EU using the following equation: EU = Absorbance mouse sera − Absorbance blank (405)nm) × 100. n = 6 mice per group; $p < 0.002$.



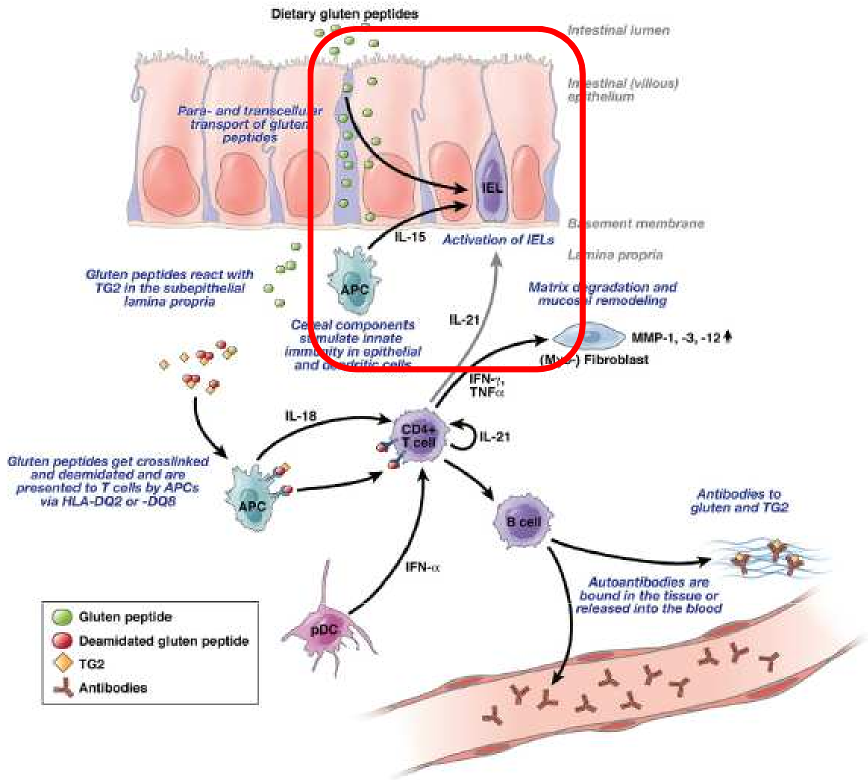


However, apart from high levels of anti-gliadin IgG antibodies, the mice did **not show any celiac pathology**. The cytokine profile in these mice resembled that of a **regulatory phenotype**, characterized by CD4CD25 T cells and production of IL-10 and TGF-1, likely leading to tolerance to gliadin, whereas celiac disease is driven by a Th1 response dominated by IFN-γ. Furthermore, mice did not have circulating anti-TG2 or IgA anti-gliadin antibodies.


Extracellular bacteria
Fungi
Autoimmunity
IL-21
IL-17a
IL-17f
IL-22
(IL-10)
TH-17
RORγt/Stat3
TGFβ (IL-1)+
IL-6,21,23
Intracellular pathogens
Autoimmunity
IFNγ
IL-2
LTα
(IL-10)
TH-1
IFNγ+IL-12
T-bet/Stat4
Foxp3/Stat5
TGFβ+IL-2
TGFβ
IL-35
IL-10
iTreg
Immune tolerance
Lymphocyte homeostasis
Regulation of immune responses
GATA-3/Stat5
IL-4+IL-2
IL-4
IL-5
IL-13
IL-25
Amphiregulin
IL-10
TH-2
Extracellular parasites
Allergy and asthma



2 out of 14 gluten-fed HLA-DR3-DQ2 transgenic mice developed IgA autoantibodies to TG2 and only 2 animals developed an increase in IELs. These humanized mouse models indicate that gluten ingestion can be tolerated without intestinal pathology even when HLA-DQ2-restricted CD4 T cell immunity to gluten is established, thereby implicating additional factors in controlling the penetrance of celiac disease. deKauwe et al. 2009



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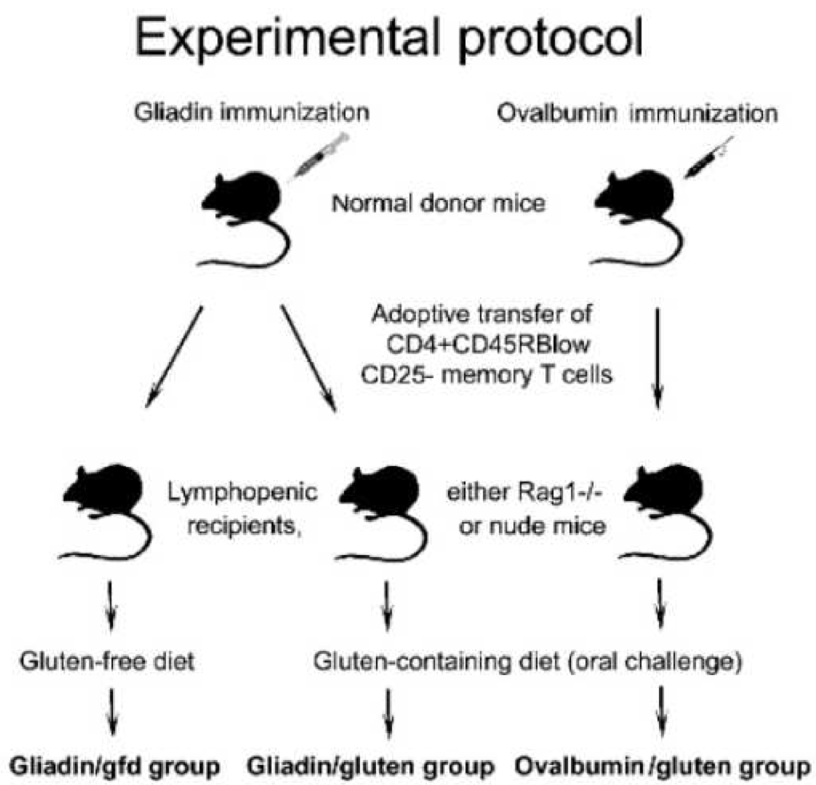
deKauwe et al. 2009

Gut 2009;**58**:1597–1605. doi:10.1136/gut.2009.186361

Gliadin-primed CD4+CD45RBlowCD25− T cells drive gluten-dependent small intestinal damage after adoptive transfer into lymphopenic mice

T L Freitag,[1,2] S Rietdijk,[3] Y Junker,[1] Y Popov,[1] A K Bhan,[4] C P Kelly,[1] C Terhorst,[3] D Schuppan[1]



Gliadin-primed CD4+CD45RBlowCD:
gluten-dependent small intestinal da
adoptive transfer into lymphopenic

T L Freitag,[1,2] S Rietdijk,[3] Y Junker,[1] Y Popov,[1] A K Bhan
D Schuppan[1]

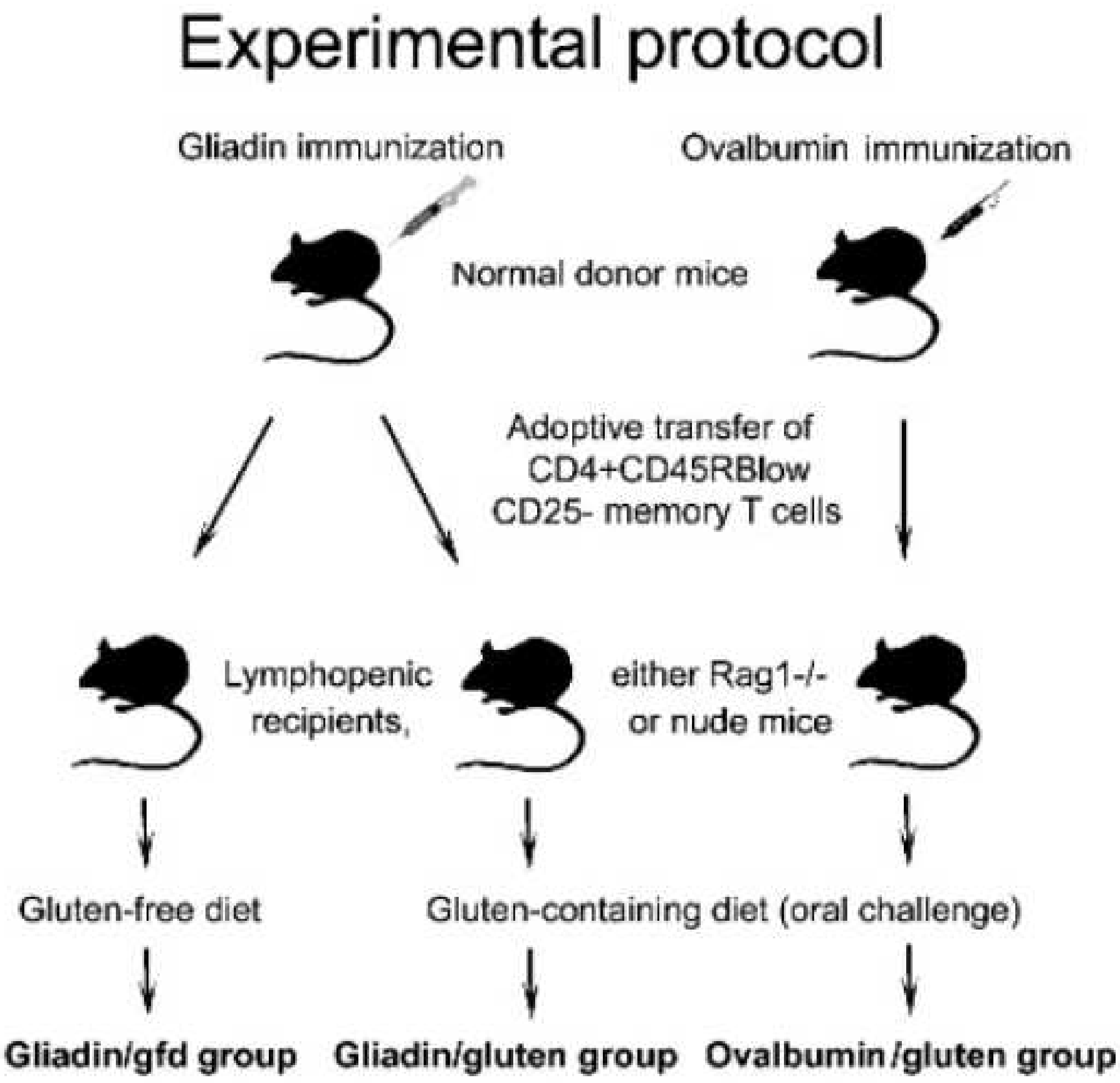


Figure 1 Generation of a mouse model of gluten-sensitive enteropathy. (a) Splenic CD3+ T cell fractions from immunised donor mice were stained with fluorescent antibodies. Rag1−/− or nude mice were injected i.p. with 4.5×10^5 CD4+CD45RBlow CD25− T cells (FACS) from gliadin-immunised donors, or from ovalbumin (control)-immunised donors. After T cell transfer, recipients were either maintained on GFD (gliadin/GFD), or challenged with gluten (gliadin/gluten, ovalbumin/

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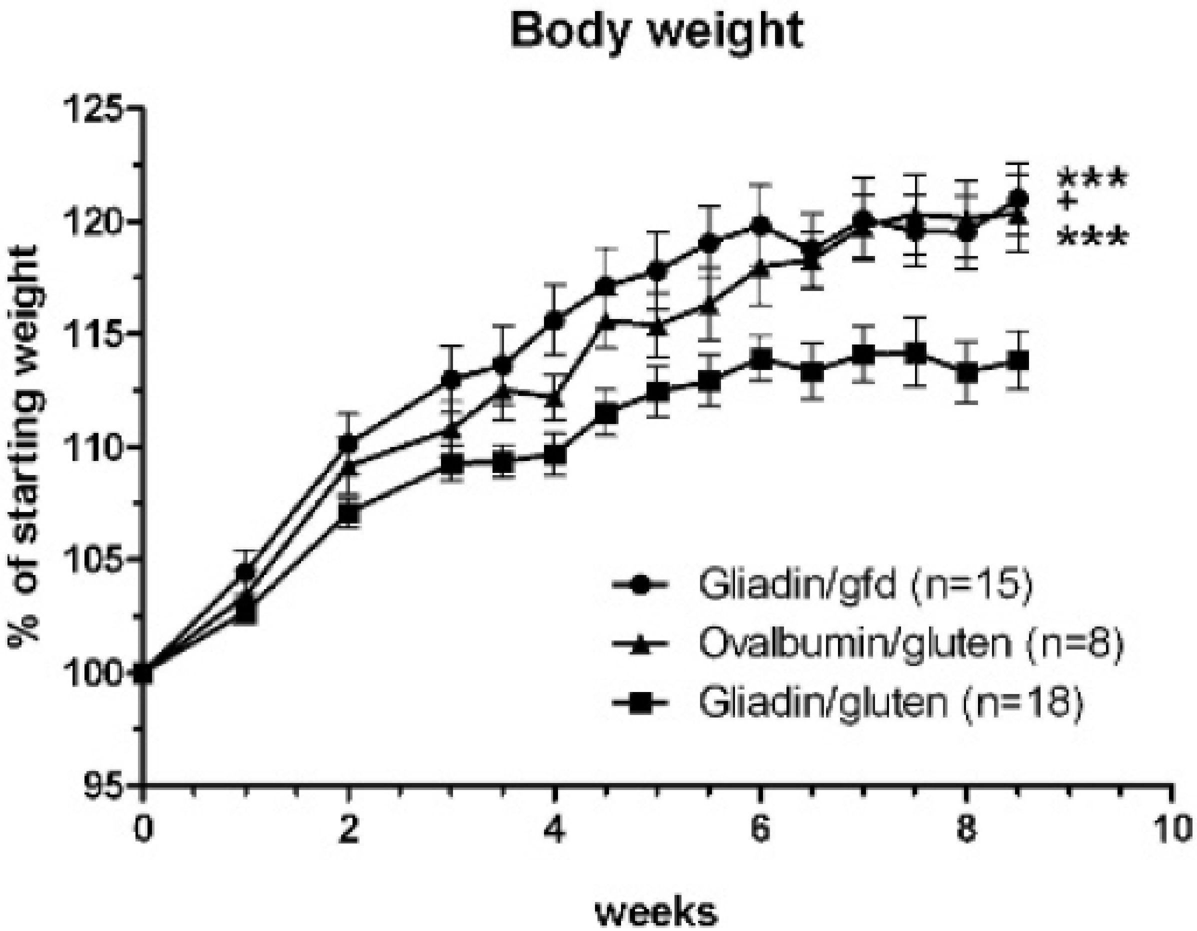

gluten). (b) Changes in body weight in relation to individual starting weights of Rag1−/− mice (n = 8–18 per group) during 8.5 weeks after transfer. Significantly lower weights in the gliadin/gluten vs gliadin/GFD group (***p = 0.001) or vs ovalbumin/GFD (***p = 0.001); while differences between gliadin/GFD vs ovalbumin/gluten, although significant ($^{+}p<0.05$), were small and transient.

Gliadin-primed CD4+CD45RBlowCD25− T cells drive gluten-dependent small intestinal damage after adoptive transfer into lymphopenic mice

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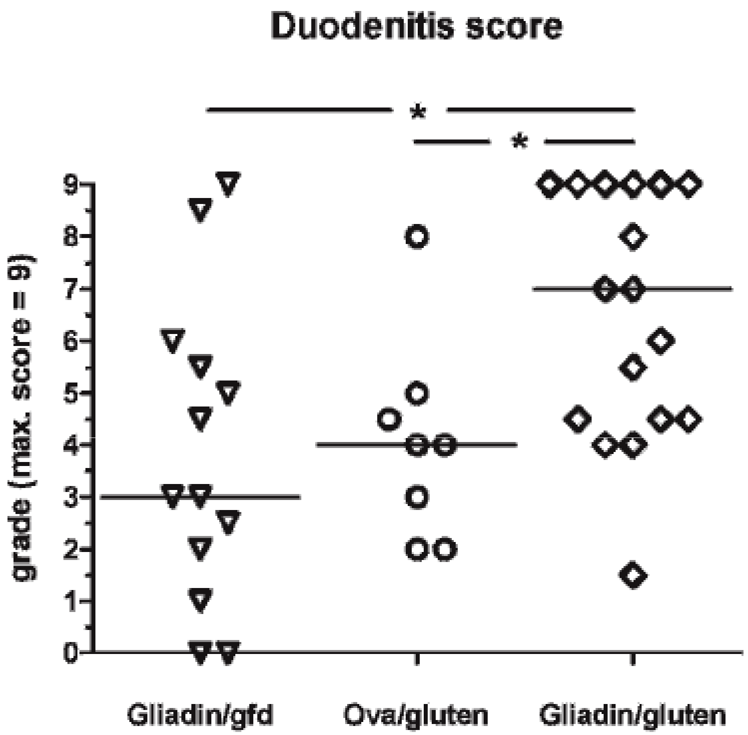

Figure 4 Exacerbation of histological duodenitis in gluten challenged Rag1−/− recipients of gliadin-presensitised CD4+CD45RBlowCD25− T cells. Composite duodenitis scores integrating crypt/villus (C/V) ratio, mononuclear cell and neutrophil infiltration scores (maximum score 3+3+3 = 9). Significant differences between the gliadin/gluten vs the gliadin/GFD group (*p = 0.02), and the ovalbumin/gluten group (*p = 0.02; n = 8–17). GFD, gluten-free diet.

Gliadin-primed CD4+CD45RBlowCD25− T cells drive gluten-dependent small intestinal damage after adoptive transfer into lymphopenic mice

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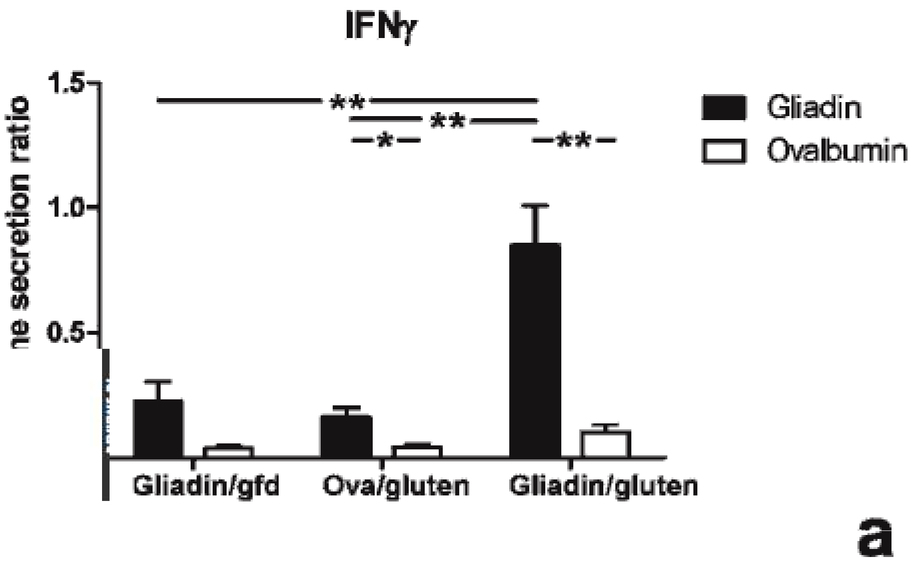

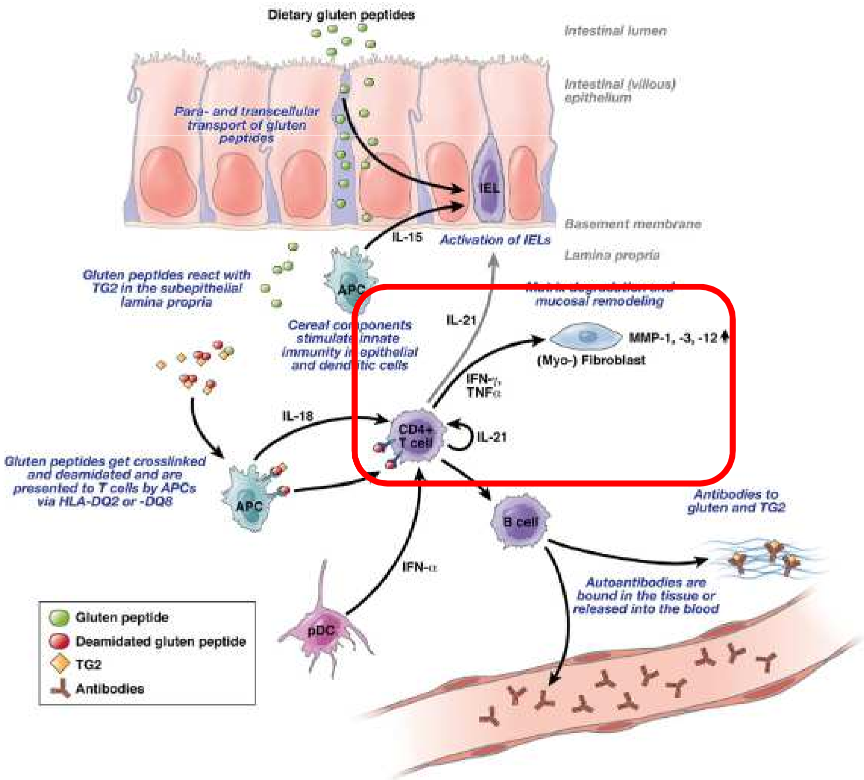

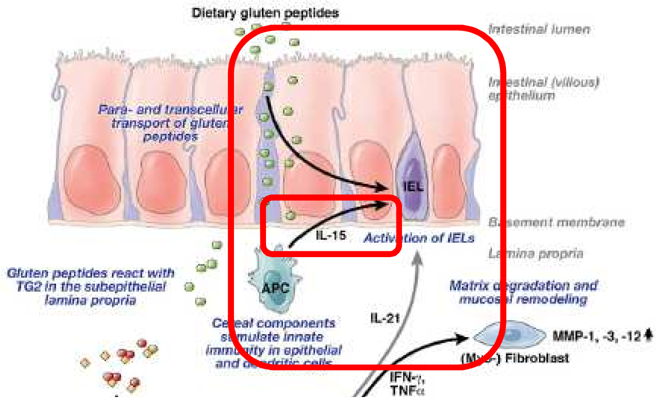

J Clin Immunol (2011) 31:1038–1044
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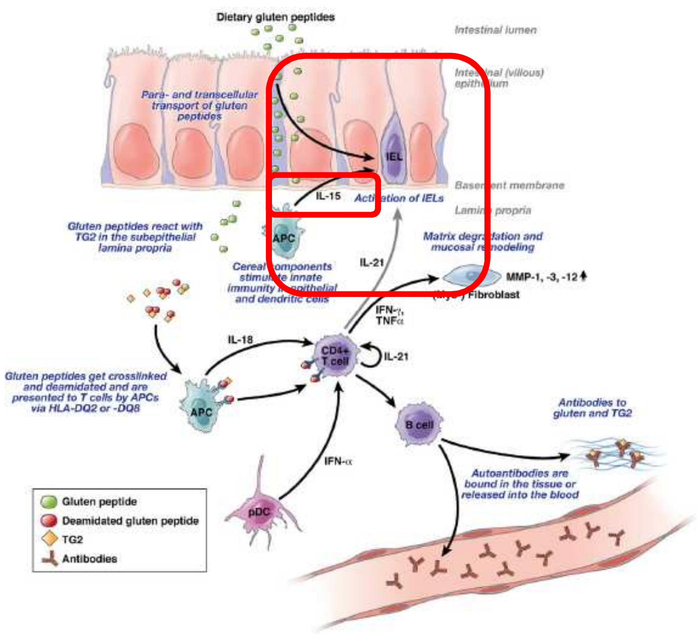

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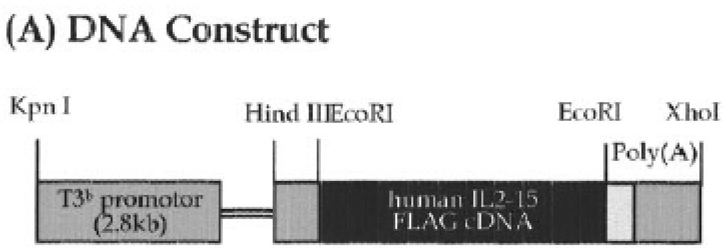

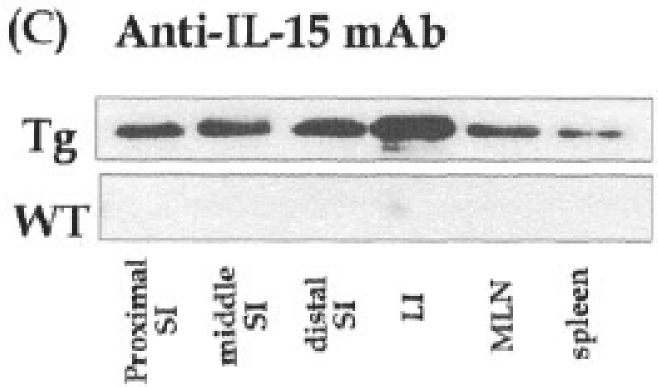

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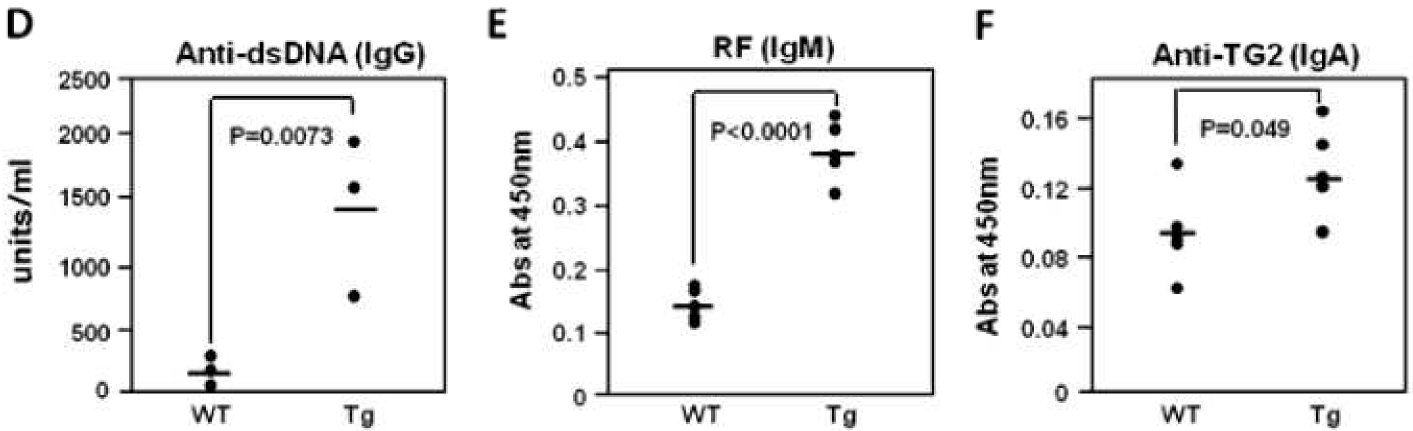

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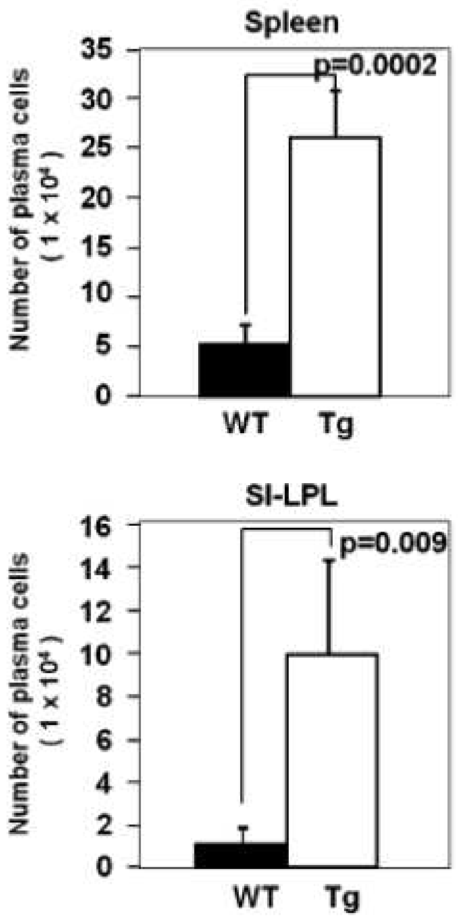

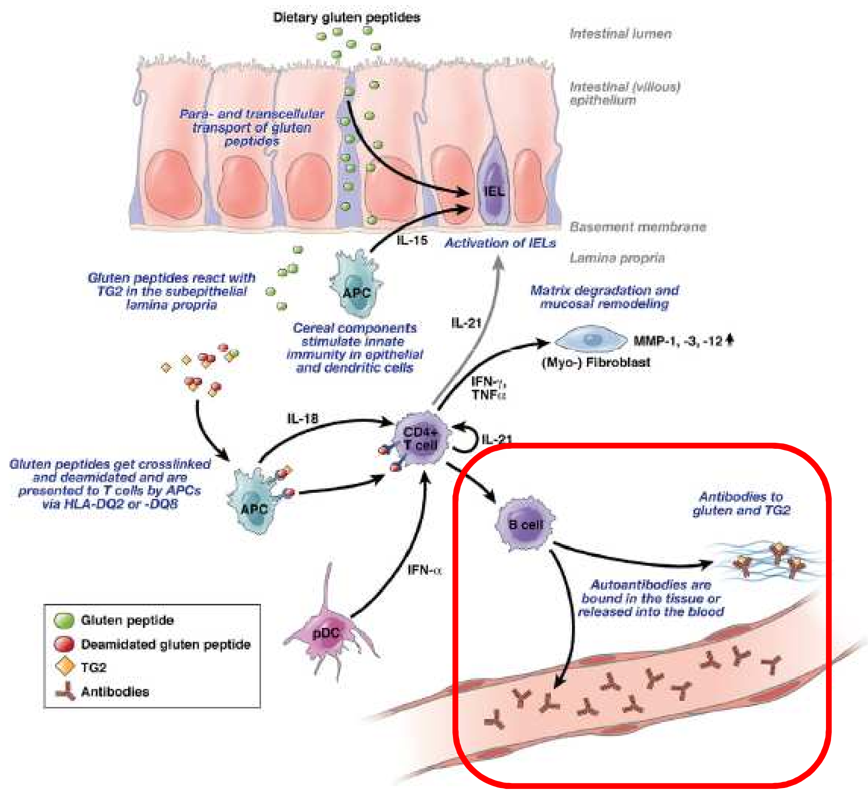

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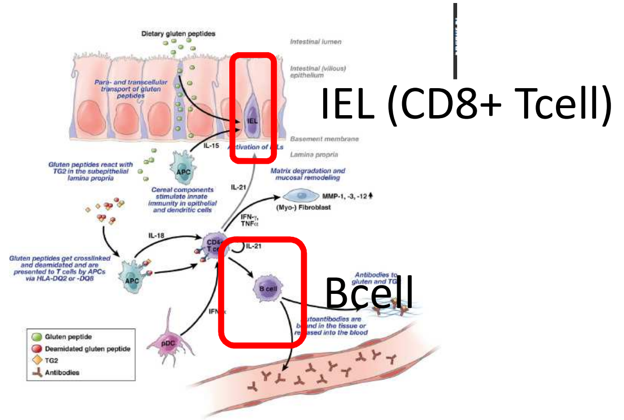

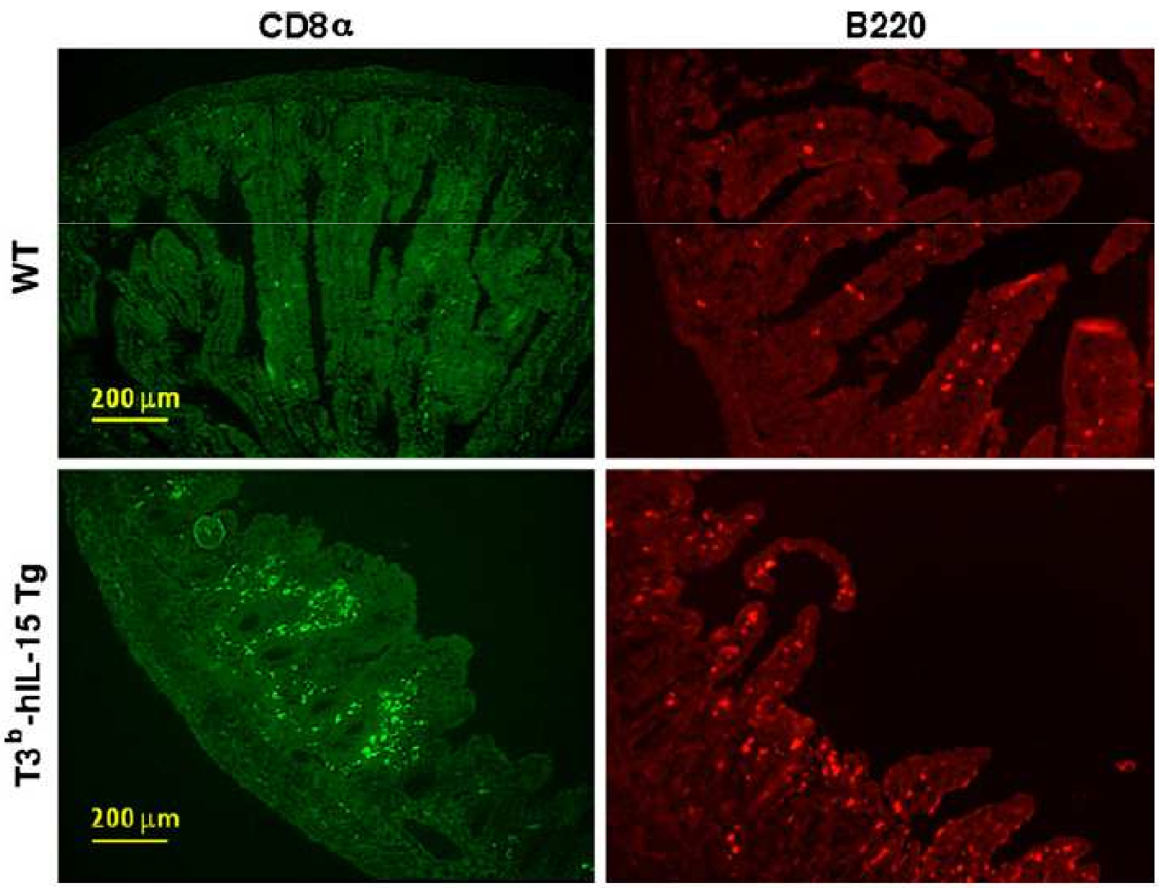

Fig. 3 Enhanced accumulation of $CD8^+$ T cells and B cells in the proximal small intestines of $T3^b$-hIL-15 Tg mice as detected by immunohistochemistry. Immunostaining was performed on sections from the duodenojejunal region of the small intestines with FITC-conjugated CD8α antibody and biotinylated B220 antibody. PE-conjugated streptavidin was used to detect bound biotin. The data shown are representative of three independent experiments

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A Non-Human Primate Model for Gluten Sensitivity

Michael T. Bethune[1], Juan T. Borda[2], Erin Ribka[2], Michael-Xun Liu[2], Kathrine Phillippi-Falkenstein[2], Ronald J. Jandacek[3], Gaby G. M. Doxiadis[4], Gary M. Gray[5], Chaitan Khosla[1,6,7], Karol Sestak[2,8]*

Methods: Using ELISA-based antibody assays, we screened a population of captive rhesus macaques with chronic diarrhea of non-infectious origin to estimate the incidence of gluten sensitivity. A selected animal with elevated anti-gliadin antibodies and a matched control were extensively studied through alternating periods of gluten-free diet and gluten challenge. Blinded clinical and histological evaluations were conducted to seek evidence for gluten sensitivity.

Results: When fed with a gluten-containing diet, gluten-sensitive macaques showed signs and symptoms of celiac disease including chronic diarrhea, malabsorptive steatorrhea, intestinal lesions and anti-gliadin antibodies. A gluten-free diet reversed these clinical, histological and serological features, while reintroduction of dietary gluten caused rapid relapse.

Conclusions: Gluten-sensitive rhesus macaques may be an attractive resource for investigating both the pathogenesis and
the treatment of celiac disease.

Table 2. Anti-gliadin antibodies (AGA) in TNPRC rhesus macaques with histories of clinical diarrhea

		History of diarrhea	IgG AGA		IgA AGA	
Age Category	**Total**		+	−	+	−
Healthy juveniles (≤4 years)	11	No	3	8	1	10
Symptomatic juveniles (≤4 years)	66	Yes	46	20	63	3
Symptomatic adults (>4 years)	17	Yes	6	11	17	0
Total (Symptomatic)	83		52	31	80	3

A subset of 15 AGA+ animals (including those with the highest AGA levels) and all healthy controls were further tested for the presence of anti-TG2 antibodies, which are known to be more specific and sensitive indicators of celiac disease than AGA. Although three of these AGA+ individuals exhibited elevated anti-TG2 antibodies relative to the controls, the increase was small (2-fold), and did not correlate with AGA levels.

Spontaneously occurring gluten sensitivity was detected in 3% of a rhesus macaque strain. Upon oral gluten ingestion, the affected monkeys developed small intestinal pathology reminiscent of celiac disease, combined with malabsorption and weight loss. Affected monkeys recovered after reinstitution of a gluten-free diet. Gluten-sensitive animals had circulating IgA and IgG antibodies to gliadin, and 3 of 15 displayed mildly elevated IgG anti–TG2 levels. A problem is the rare spontaneous occurrence of the complete celiac disease phenotype (0.6%) and the animal species (primates), which currently precludes large-scale exploration of novel nondietary therapies in this model.

Table 2. Novel Therapies for Celiac Disease

Target	Drug/modification
Intraluminal therapies	
Wheat varieties	(Ancient) wheat variants with low immunogenicity Genetically modified wheat variants or deletion lines of common wheat with lower immunogenecity
Flour/dough	Pretreatment with lactobacilli Transamidation of gliadin
Ingested gliadin peptides	Prolyl endopeptidases from Aspergillus niger *Sphingomonas capsulate* in combination with (EP)-B2 from germinating barley Intraluminal gliadin binding by polymers Gluten neutralizing cow's milk antibodies

Transepithelial uptake	
Epithelial tight junctions	ZOT receptor antagonist AT1001
Dampening of the adaptive immune response	
TG2	Transglutaminase inhibitors
	"Inhibitory" innate gluten peptides
HLA-DQ2	Blocking DQ2 analogues
Immune modulators	
	Hookworm infection
	Gluten "vaccination" (Nexvax2)
Biologicals (systemic T-cell or cytokine blockers)	
Small intestine homing T cells	CCR9 antagonists (Ccx282-B, CCX025)
Gut homing T cells	Anti-integrin $\alpha 4 \beta 7$ (LDP-02)
Clonal IELs	Anti–IL-15 (AMG 714), Anti-Jak3 (CP-690-550)
Clonal intestinal T cells	Autologous bone marrow transplantation
	Mesenchymal stem cell transplantation (prochymal)
Mucosal destruction in refractory celiac disease	Anti–tumor necrosis factor α, anti–IFN-γ (HuZAF)
	Anti-CD52 (Alemtuzumab)

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ORIGINAL RESEARCH

Tofacitinib, a Janus Kinase Inhibitor Demonstrates Efficacy in an IL-15 Transgenic Mouse Model that Recapitulates Pathologic Manifestations of Celiac Disease

Seiji Yokoyama · Pin-Yu Perera · Thomas A. Waldmann · Takachika Hiroi · Liyanage P. Perera

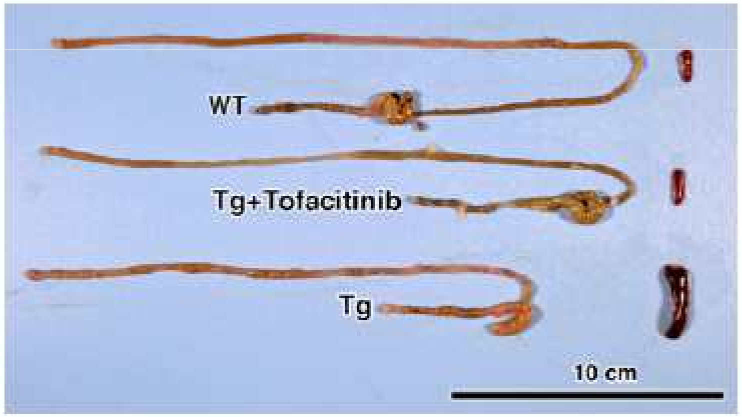

Fig. 3 A 42-day course of tofacitinib therapy reverses the macroscopic inflammatory pathologic manifestations in T3[b]-hIL-15 Tg mice. Following tofacitinib therapy, the intestines and spleens were harvested from T3[b]-hIL-15 Tg mice and a gross examination of organs for length and size, swelling/distention with serosal surface hyperemia with distended blood vessels was performed. For comparison, wild type litter-mates (WT) and sham-treated T3[b]-hIL-15 Tg mice were also included in the assessment. Affected organs from one representative mouse from each group of 6 mice are shown and the other mice displayed similar profiles