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Structural bases of T cell antigen receptor recognition in celiac disease

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Abstract

Celiac disease (CeD) is a human leukocyte antigen (HLA)-linked autoimmune-like disorder that is triggered by the ingestion of gluten or related storage proteins. The majority of CeD patients are HLA-DQ2.5$^+$, with the remainder being either HLA-DQ8$^+$ or HLA-DQ2.2$^+$. Structural studies have shown how deamidation of gluten epitopes engenders binding to HLA-DQ2.5/8, which then triggers an aberrant CD4$^+$ T cell response. HLA tetramer studies, combined with structural investigations, have demonstrated that repeated patterns of TCR usage underpins the immune response to some HLADQ2.5/8 restricted gluten epitopes, with distinct TCR motifs representing common landing pads atop the HLA–gluten complexes. Structural studies have provided insight into TCR specificity and cross-reactivity towards gluten epitopes, as well as cross-reactivity to bacterial homologues of gluten epitopes, suggesting that environmental factors may directly play a role in CeD pathogenesis. Collectively, structural immunology-based studies in the CeD axis may lead to new therapeutics/diagnostics to treat CeD, and also serve as an exemplar for other T cell mediated autoimmune diseases.

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Introduction

T cells detect pathogens and consequently protect against microbial infection. Central to this activity is the ability of T cells to distinguish between self and non-self peptide antigens. The heterodimeric αβT cell receptor (TCR) expressed on the surface of T cells recognises peptide (p) antigens presented by the human leukocyte antigen (HLA) molecule on antigen presenting cells [1,2]. Each TCR chain possesses three complementarity determining regions (CDRs) that, to varying degrees, interact with the pHLA complex, whereby the TCR co-recognises the peptide and the HLA [3,4]. A consensus docking polarity underpins this TCR–pHLA interaction, which has been linked to T cell signaling constraints [4].

Detection of non-self peptide antigens triggers T cells to mount an inflammatory response to rid the body of infection [5,6]. Likewise, a breakdown in tolerance, can also lead to an aberrant immune response against self-peptides leading to autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and diabetes [7–9]. Indeed, many autoimmune diseases are characterised by a strong genetic association with the *HLA* locus [7,8]. However, unraveling the mechanistic bases of T cell mediated autoimmunity has proven challenging due to the highly polymorphic nature of the HLA, enormous diversity in the T cell repertoire, the need to identify the auto-antigens triggering the immune response, plus additional confounding variables including environmental factors [7,8,10–13]. However, major progress has been made in understanding the bases underpinning celiac disease (CeD).

Celiac disease

CeD is a T cell mediated autoimmune-like disease that causes tissue damage in the small intestine [14]. CeD is triggered by the consumption of dietary gluten, the main storage protein of wheat, barley, and rye, as well as related proteins [15–17]. CeD poses a very significant health concern, particularly for westernised countries where about 1% of the population is impacted [17,18]. Unrecognised CeD that is on the rise [19], is associated with three-fold increase in all-cause mortality, mostly attributed to cancers of the upper digestive tract and lymphoma, as well as sepsis [20–22]. The only treatment presently available is exclusion of foods containing gluten, namely any food derived from wheat, barley, or rye [23,24]. However, in longitudinal studies, fewer than half of adults achieve full histological remission on a

gluten free diet [25] and this carries an increased risk of cancer and osteoporosis compared to those with normal small bowel histology [26]. CeD is essentially restricted to genetically predisposed individuals, specifically those who possess HLA-DQ2.5 (~95% of patients) or HLA-DQ8 (~5% of patients), as CeD patients that are neither HLA-DQ2$^+$ nor HLA-DQ8$^+$ are extremely rare (< 5%) [27,28]. It is well established that CD4$^+$ T cell responses specific for gluten peptides presented by HLA-DQ2.5 or HLA-DQ8 molecules play a major role in CeD, as such T cells are consistently found in the small intestine of CeD patients [17].

Presentation of gluten epitopes by HLA-DQ2.5 and HLA-DQ8

The proline-rich nature of gluten prevents its complete digestion by gastric proteases of the GI tract [29,30]. CeD patients have gluten-reactive T cells that recognise highly immunogenic epitopes within proteolytically-stable regions of gluten [5,31]. In HLA-DQ2.5-mediated CeD, peptides derived from the heterogeneous mixture of proteins making up wheat gluten (α, β, γ, and ω gliadin and glutenins) and homologous sequences in rye secalins and barley hordeins can activate T cells [5,32–35]. These peptides themselves are poor binders for HLA-DQ2.5, instead glutamine residues are deamidated to glutamate by tissue transglutaminase 2 (TG2) (Figure 1a), which in turn have chemically favourable residues for increased binding strength to HLA-DQ2.5 [36]. Typically, the gluten epitopes are deamidated at specific glutamine residues that correspond to positions P4 or P6 of the HLA peptide binding pocket register (Figure 1b) [37] and structural studies revealed the importance of a hydrogen bond network, whereby the presence of glutamate leads to higher affinity binding to HLA-DQ2.5 (Figure 1c) [38,39]. In HLA-DQ2.5-associated CeD, most T cell activity is directed towards five gluten epitopes observed in three peptides [5]. Regarding wheat, the four main gluten peptides encompass two overlapping T cell epitopes within α-gliadin (LQPFPQPELPYPQPQ and epitopes within: DQ2.5-glia-α1a,PFPQPELPY and DQ2.5-glia-α2, PQPELPYPQ) and ω-gliadin (QPFPQPEQPFPWQP and epitopes within: DQ2.5-glia-ω1, PFPQPEQPF, and DQ2.5-glia-ω2, PQPEQPFPW) [2,5,11,29,32,40]. The third peptide derived from barley hordein (PEQPIPEQPQPYPQQ) incorporates the fifth epitope, DQ2.5-hor-3a (PIPEQPQPY) [2,5,40]. A number of these immunodominant epitopes are found within other gluten peptides [40].

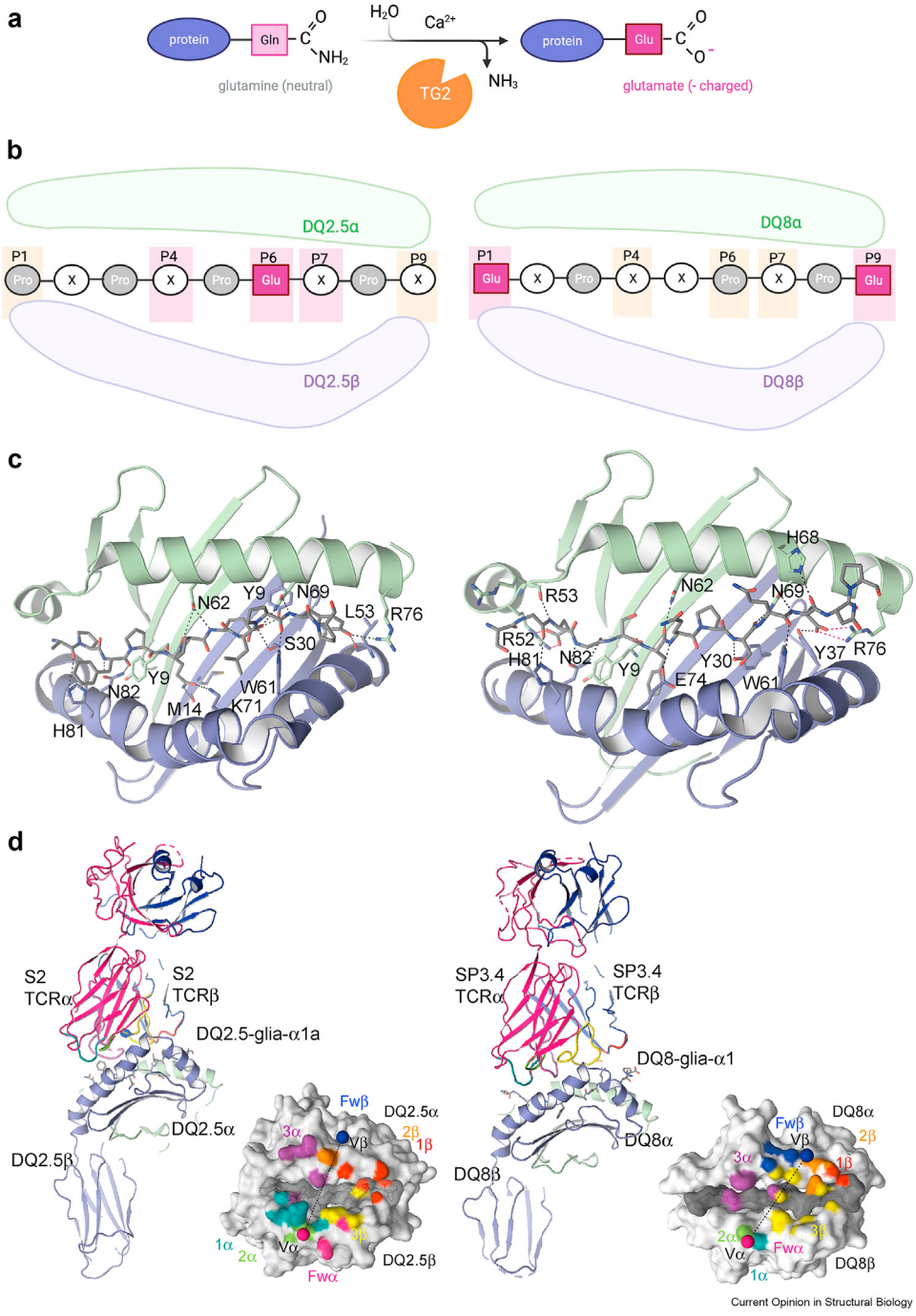
The DQ8-glia-α1 (EGSFQPSQE) epitope is the immunodominant peptide associated with T cell reactivity in HLA-DQ8$^+$ CeD patients [41,42]. HLA-DQ8 has a strong preference for acid residues occupying the P1 and P9 pockets of the antigen binding cleft (Figure 1b) [7]. Hence, glutamic acid residues of the P1 and P9 residues to produce the DQ8-glia-α1 epitope (EGSFQPSQE) engenders this peptide with a high affinity for HLA-DQ8, where salt bridges between the peptide and HLA-DQ8 in the positively charged P1 and P9 anchor pockets were observed [30].

The identification of the peptide antigens linked to CeD pathogenesis has enabled the isolation of gluten reactive T cells by the use of either HLA-DQ2.5$^+$ or HLA-DQ8$^+$ gliadin epitope tetramer reagents [1,3,9,39,43–49]. pHLA tetramers, generated by mixing biotinylated recombinant pHLA molecules with fluorescently labeled streptavidin, have increased avidity for the pHLA–TCR interaction. Hence, these reagents have proven highly useful in the detection of gliadin reactive T cells that would otherwise not be possible if pHLA monomers were used [9,45]. Tetramers incorporating one of five epitopes (DQ2.5-glia-α1a, DQ2.5-glia-α2, DQ2.5-glia-ω1, DQ2.5-glia-ω2 or DQ2.5-hor-3a) [5] have been predominantly used as they comprise the majority of the T cell antigen response to wheat gliadin and barley hordein in CeD [1,9,11,43–50]. This has provided the ability to quantify and characterise, in gluten-challenged individuals, T cells present in CeD patients from peripheral blood and diseased tissue, including the determination of the TCR repertoires (i.e., T cell *TRAV/TRBV* gene usage and CDR3α/β sequences), thereby leading the way towards structural studies underpinning TCR interactions central to CeD [44,45]. These structural studies give us an insight into molecular features of pathogenic T cells in the responding CeD repertoire [1,3,10,39,43]. Studies have shown that tetramers may be used to define immunological signatures of the gluten-specific CD4$^+$ T cell response for CeD diagnosis and monitor the efficacy of epitope-specific immunotherapies directed against these T cells in CeD [2,11,44,47–49].

Structural basis of HLA-DQ8-mediated CeD

The T cell response to HLA-DQ8-glia-α1 is characterised by biased TCR usage, whereby the largest population of HLA-DQ8-glia-α1 restricted T cells used the *TRBV9*01* gene most frequently paired with TRAV26-2 [1]. Most of the TRBV9$^-$ TCRs used TRBV6-1 with no apparent *TRAV* gene preference. The crystal structure of a TRBV9$^+$ TCR bound to HLA-DQ8-glia-α1 (Table 1, Figure 2) [1] provided a structural framework for understanding the basis of TRBV91 bias and how these TCRs specifically recognised the DQ8-glia-α1 peptide [1]. The responding TCR repertoire was also characterised by a non-germline encoded Arg residue in the TRAV26-1 CDR3α loop which played a key role in contacting both the DQ8-glia-α1 epitope and HLA-DQ8 [43]. The non-germline encoded CDR3β Arg observed in the TRBV9$^-$ TCRs, remarkably, had a similar role in ternary complex structures. And finally, the structure of a TRAV20/TRBV9$^+$ TCR that was devoid of

Figure 1



Deamidation of gluten peptides enhance binding to HLA molecules. (**a**) The Ca^{2+}-dependent tissue transglutaminase (TG2) upon recognition of "Gln-X-Pro" motif mediates deamidation of specific glutamine to glutamate. (**b**) Left panel, HLA-DQ2.5 peptide-binding cleft pocket 4 (P4) and P6 are positively charged (+) and show preference for negative (–) acidic glutamate residues. Right panel, HLA-DQ8 peptide binding cleft P1 and P9 have preference for acidic glutamate residues. "X" indicates any amino acid residue. (**c**) HLA-DQ2.5-glia-α1a structure (PDB: 6MFG) [53] on the left and HLA-DQ8-glia-α1 structure (PDB: 2NNA) [30] on the right. The structural overview and TCR docking footprint atop peptide-HLA of (**d**) S2-HLA-DQ2.5-glia-α1a (4OZI) [39] on the left and SP3.4-HLA-DQ8-glia-α1 (4GG8) [1] on the right. The cartoon HLA α- and β-chains are pale green and purple, respectively, the cartoon TCR α- and β-chains are dark pink and blue, respectively, with the peptide as grey stick representation. The CDR loops of the TCR are coloured as follows; 1α, turquoise; 2α, green; 3α, purple; 1β, red; 2β, orange and 3β, yellow. Surface representation of TCR footprint with peptide in grey and TCR contact atoms coloured based on closest CDR loop. The non-CDR TCR framework-α (dark pink) and -β contacts (dark blue). The centre of mass of TCR variable α- and β-domains are represented as dark pink and dark blue spheres with approximate TCR docking angle. Oxygen and nitrogen atoms are coloured red and blue, respectively. Hydrogen bonds and salt−bridge interactions are shown by dashed black and dark pink lines, respectively. Single amino acid residue code was used to label HLA residues that interact with the deamidated peptides.

Table 1

TCR/TCR-like antibody Fab-pHLA-DQ2/8 complexes published to date.

TCR/TCR-like Fab	pHLA restriction	TRAV/TRBV usage	Affinity (Kd)[b]	General comments
S2	HLA-DQ2.5-glia-α1a[a]	*TRAV4-TRBV20-1*	70 μM	Immunodominant TCR complex: central canonical docking polarity; CDR1α, CDR3α, CDR1β and CDR3β contact peptide and HLA; CDR2α, CDR2β, FWα and FWβ contact HLA [39]
LS2.8/3.15	HLA-DQ2.5-glia-α1a[a,c]/*P. fluor-α1a*	*TRAV8-3-TRBV5-5*	91.5 μM/39.6 μM	Bacterial mimic TCR complex: central canonical docking polarity; CDR3α and CDR3β contact peptide and HLA-II; CDR1β and CDR2β contacts peptide; CDR1α, CDR2α, FWα and FWβ contacts HLA [10]
S16	HLA-DQ2.5-glia-α2[a]	*TRAV26-1-TRBV7-2*	24.8 μM	Immunodominant TCR complex central canonical docking polarity; CDR1α, CDR3α, CDR1β and CDR3β contact peptide and HLA; CDR2α, CDR2β, FWα and FWβ contact HLA [39]
D2	HLA-DQ2.5-glia-α2[a]	*TRAV26-1-TRBV7-2*	15.8 μM	Immunodominant TCR complex: central canonical docking polarity; CDR1α, CDR1β and CDR3β contact peptide and HLA; CDR2α, CDR2β, FWα and FWβ contact HLA [39]
JR5.1	HLA-DQ2.5-glia-α2[a]/*P. aeru-α2a*	*TRAV26-1-TRBV7-2*	79.4 μM/132 μM	TCR complexed to immunodominant and mimic epitopes: central canonical docking polarity; CDR1β and CDR3β contact peptide and HLA; CDR1α, CDR1β, CDR2β, FWα and FWβ contact HLA. [10,39]. CDR1α also contacts mimic peptide.
Fab 3.C11	HLA-DQ2.5-glia-α2[a]	N/A	0.24 μM	TCR-like antibody Fab complexed with immunodominant epitope: CDR L1, CDR H1 and CDR H3 contact peptide and HLA; CDR L2-L3 and CDR H2 contact HLA. [63].
1005.2.56	HLA-DQ2.2-glut-L1[a]	*TRAV21*02-TRBV7-3*	22.2 μM	Immunodominant TCR complex; central canonical docking polarity; CDR1α, CDR3α, CDR1β, CDR2β and CDR3β contact peptide and HLA; CDR2α and FWβ contact HLA [12].
594	HLA-DQ2.2-glut-L1[a]	*TRAV9-2-TRBV11-2*	21 μM	Immunodominant TCR complex; central canonical docking polarity; CDR3α and CDR3β contact peptide and HLA; CDR1α, CDR2α, CDR2β, FWα and FWβ contact HLA [12].
SP3.4	HLA-DQ8-glia-α1[a]	*TRAV26-2-TRBV9*	11.4 μM	Immunodominant TCR complex: central canonical docking polarity; CDR3α, CDR1β, CDR2β and CDR3β contact peptide and HLA; CDR1α, CDR2α and FWβ contact HLA [1].
L3-12	HLA-DQ8-glia-α1[a]	*TRAV26-2-TRBV9*	7.0 μM	Immunodominant TCR complex: central canonical docking polarity; CDR1α, CDR3α, CDR1β, CDR2β and CDR3β contact peptide and HLA; CDR2α and FWβ contact HLA [1,43]
S13	HLA-DQ8-glia-α1[a]	*TRAV26-2-TRBV9*	1.1 μM	Immunodominant TCR complex: central canonical docking polarity; CDR1α, CDR3α, CDR1β, CDR2β and CDR3β contact peptide and HLA; CDR2α, FWα and FWβ contact HLA [1,43].
T316	HLA-DQ8-glia-α1[a]	*TRAV8-3-TRBV6-1*	N/D	Immunodominant TCR complex: central canonical docking polarity; with $V\beta9^-$ TCR shift toward N-terminus of peptide compared to $V\beta9^+$ DQ8-glia-α1 TCRs [43]; CDR1α, CDR3α, CDR1β, CDR3β and FWβ contact peptide and HLA; CDR2α, CDR2β and FWα contact HLA [43].
Bel502	HLADQ8[a]/8.5[c]-glia-α1	*TRAV20-TRBV9*	2.8 μM/19.5 μM	Immunodominant TCR complex: central canonical docking polarity with TCR shift 2–3 Å toward peptide N-terminus when compared $V\alpha26\text{-}2^+$:$V\beta9^+$ TCRs [3,43]; CDR1α, CDR3α, CDR1β, CDR2β and CDR3β contact peptide and HLA; CDR2α, FWα and FWβ contact HLA [3].
Bel602	HLA-DQ8[a,c]/8.5-glia-γ1	*TRAV20-TRBV9*	13.9 μM/4.7 μM	Immunodominant TCR complex; central canonical docking polarity; TCR shifted 3–4 Å toward peptide-C-terminus compared to Bel502 TCR; CDR1α, CDR3α, CDR1β, CDR2β and CDR3β contact peptide and HLA; CDR2α, FWα and FWβ contact HLA [3]
T15	HLA-DQ8[a,c]/8.5-glia-γ1	*TRAV20-TRBV9*	3.6 μM/2.0 μM	Immunodominant TCR complex; central canonical docking polarity; Position of TCR similar to Bel602 TCR only differing in docking angle by 8 °; CDR1α, CDR3α, CDR1β, CDR2β and CDR3β contact peptide and HLA; CDR2α, FWα and FWβ contact HLA [3].

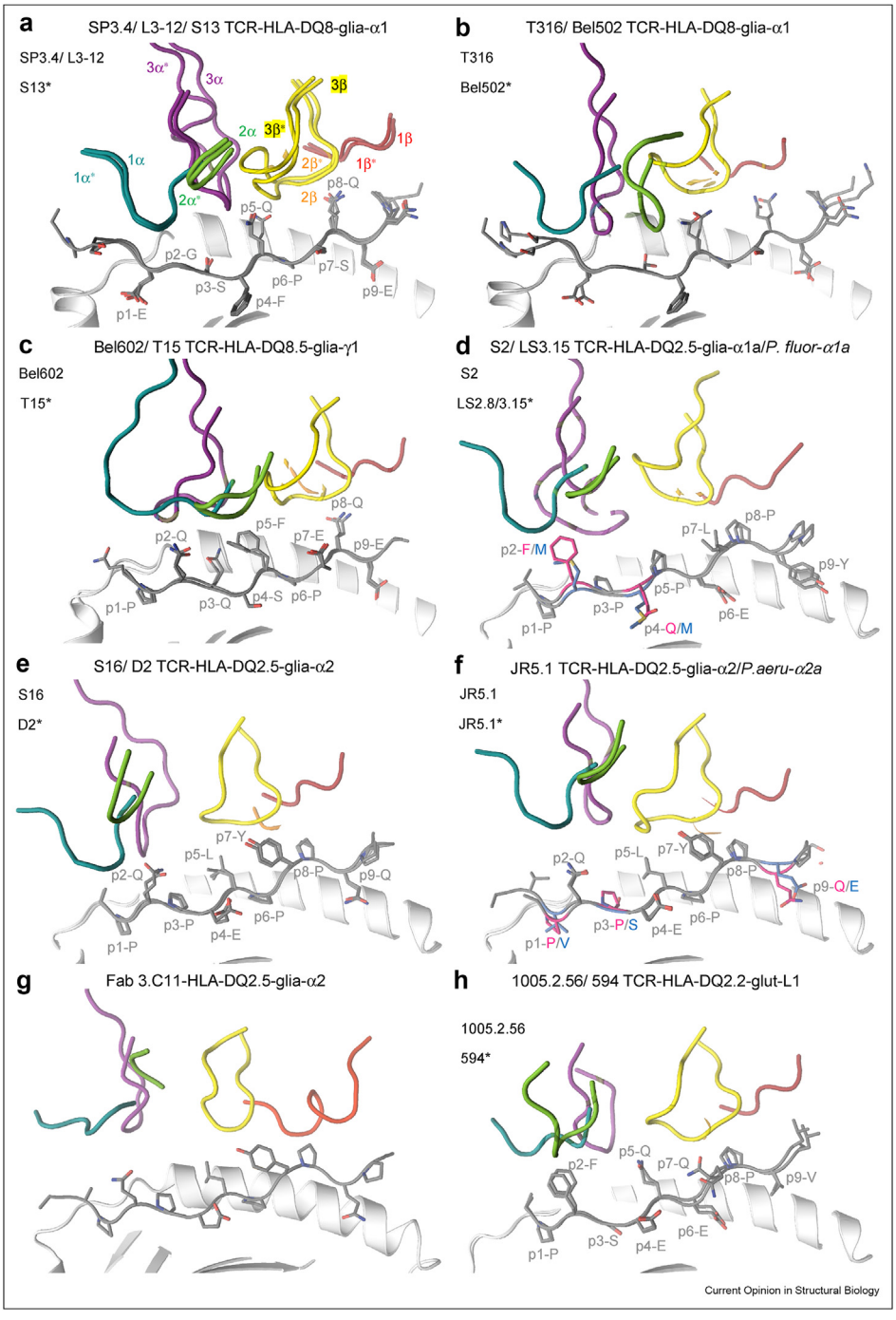
TCCs, T-cell clones. N/D, not determined. N/A, not applicable. CDR, complementarity determining region. FW, framework. CDR, complementarity determining region. Fab, fragment antigen-binding. L, light. H, heavy

[a] Fine specificity of TCR's parental T cell clone determined using alanine scan of epitopes in T cell stimulation assays.

[b] As measured by surface plasmon resonance.

[c] No structure determined.

Figure 2



Side views of TCR/TCR-like Ab-pHLA-DQ2/8 complexes solved to date. Peptides are represented as grey sticks from amino terminus to carboxyl terminus, left to right. Amino acids denoted by one-letter abbreviation. Oxygen atoms are shown in red, nitrogen atoms in dark blue. The cartoon of HLA-α chain is shown in white. The CDR loops of the TCR and TCR-like antibody (bracketed) are coloured as follows; 1α (L1), turquoise; 2α (L2), green; 3α (L3), purple; 1β (H1), red; 2β (H2), orange and 3β (H3), yellow. Overlay of ternary structures of (**a**–**b**) DQ8-glia-α1-specific TCRs; SP3.4, L3-12, S13, T316, Bel502 (PDB: 4GG6, 4Z7V, 4Z7U, 4Z7W, 5KS9) [1,3,43], (**c**) DQ8-glia-γ1-specific TCRs; Bel602 and T15 (PDB: 5KSA,5KSB) [3], (**d**) DQ2.5-glia-α1a-specific TCRs; S2 and LS2.8/3.15 (PDB: 4OZI, 6U3N) [10,39], (**e**–**f**) DQ2.5-glia-α2-specific TCRs; S16, D2 and JR5.1 (PDB: 4OZH, 4OZG, 4OZF, 6U3O) [10,39], (**g**) DQ2.5-glia-α2-specific TCR-like antibody; 3.C11 (PDB: 6XP6) [63], (**h**) DQ2.2-glut-L1-specific TCRs; 1005.2.56 and 594 (PDB: 6PX6, 6PY2) [12]. The superimposed TCR (denoted as TCR*) CDR loops are transparent. Fab, fragment antigen-binding of antibody. L, light chain. H, heavy chain. The 9mer sequence of the epitopes are as follows; DQ8-glia-α1 (EGSFQPSQE), DQ8.5-glia-γ1 (PQQSFPEQE), DQ2.5-glia-α1a (PFPQPELPY), DQ2.5-*P. fluor-α1a* (PMPMPELPY), DQ2.5-glia-α2 (PQPELPYPQ), DQ2.5-*P. aeru-α2a* (VQSELPYPE) and DQ2.2-glut-L1 (PFSEQEQPV). The DQ2.5-glia-α1a/α2 residues that differ from respective bacterial mimic peptides shown by dark pink sticks. The bacterial mimic DQ2.5-*P. fluor-α1a/P. aeru-α2a* residues that differ from that of the homologous gliadin peptide are indicated by blue sticks.

a non-germline encoded CDR3α or CDRβ Arg, in complex with HLA-DQ8-glia-α1, was shown to compensate for the lack of this residue by using a CDR1α germline encoded Arg in a structurally analogous manner (Table 1, Figure 2) [3]. For the HLA-DQ8-glia-α1 restricted TCRs tested, mutation of the non-germline encoded CDR3 Arg (or germline encoded CDR1α Arg) resulted in a complete loss of antigen recognition [1,3,43]. The sum of these observations represented a remarkable conserved selection, both non-germline and germline, of this residue in recognition of HLA-DQ8-glia-α1.

Structural basis of HLA-DQ2.5-mediated CeD

Biased TCR usage to some gluten epitopes is also a feature of HLA-DQ2^{+} CeD. Namely, the DQ2.5-glia-α2 specific T cell repertoire displays preferential pairing and usage of *TRAV26-1/TRBV7-2* genes, conservation of a CDR3β motif containing a non-germline encoded Arg residue, as well as *TRAV4* bias across multiple unrelated individuals with CeD [11,39,46,51,52]. Despite close sequence homology between DQ2.5-glia-α2 and DQ2.5-glia-ω2 epitopes, the DQ2.5-glia-ω2-specific repertoire is separate and non-overlapping, yet share the same *TRAV4* bias [46]. Biased *TRAV4* and *TRBV20-1* or *TRBV29-1* gene usage were observed toward both DQ2.5-glia-α1a and DQ2.5-glia-ω1 epitopes [52,53]. Additionally, approximately 5% of the responding T cells were cross-reactive thus able to recognise both DQ2.5-glia-α1a and DQ2.5-glia-ω1 epitopes [53].

The structures of TRBV7-2^{+} TCR-HLA-DQ2.5-glia-α2 and TRAV4*01^{+} TCR-DQ2.5-glia-α1a complexes have been subsequently solved providing a structural basis underpinning these TCR biases [39,50,51,54], and also showed differing docking geometries between these ternary complexes (Table 1, Figure 2). The conserved presence of the non-germline-encoded Arg in the HLA-DQ2.5-glia-α2 restricted response mirrored that observed in the HLA-DQ8-glia-α1. That is the, non-germline CDR3β Arg made crucial interactions with both the gliadin epitope as well as HLA-DQ2.5, effectively acting as a lynchpin. Indeed, mutation of the CDR3β Arg in TRAV26-2/TRBV7-2^{+} TCRs abolished recognition of HLA-DQ2.5-glia-α2 [39,50]. Whether such conservation in patterns of TCR usage underpins the response to distinct gluten determinants remains unclear.

Structural basis of HLA-DQ2.2-mediated CeD

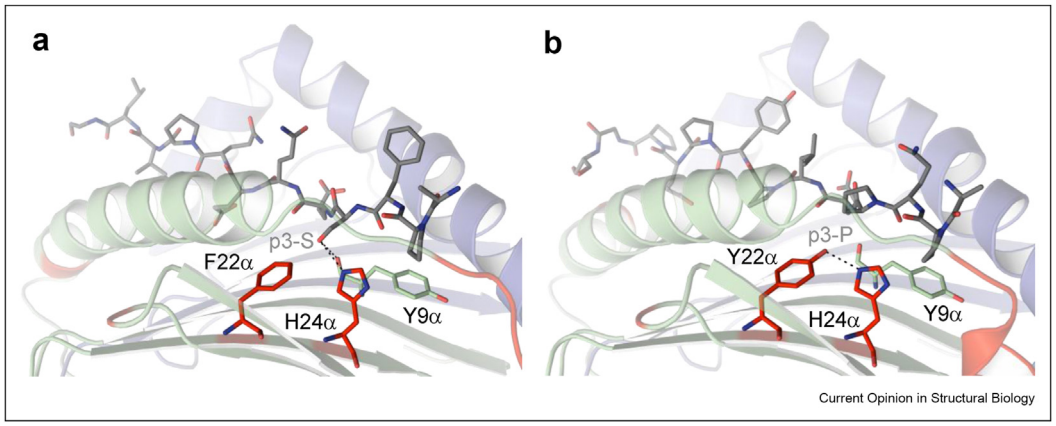
HLA-DQ2.5 is strongly associated with CeD, yet HLA-DQ2.2, which differs from HLA-DQ2.5 by a single polymorphic residue (HLA-DQ2.2-Phe22α, HLA-DQ2.5-Tyr22α) is weakly associated with being a risk factor for CeD [6]. The binary HLA-DQ2.2-glut-L1 and HLA-DQ2.5-glia-α2 structures revealed that the difference in epitope binding preference of HLA-DQ2.5 and HLA-DQ2.2 molecules was attributed to this single polymorphic residue at position 22 of HLA-DQ2 α-chain (Figure 3) [12]. This DQα22 polymorphism perturbs a crucial hydrogen (H)-bonding network with the gluten epitope main chain required for stability [6,31]. Since HLA-DQ2.2-Phe22α cannot contribute to the H-bond network, unlike HLA-DQ2.5-Tyr22α, the HLA-DQ2.2 has an additional selectivity constraint toward epitopes containing p3-Ser needed for compensatory H-bonds with nearby HLA residues (Figure 3) [6,12,31]. These differences in epitope specificity then resulted in markedly different T cell responses towards HLA-DQ2.2 [6,12]. Nevertheless, the ternary structures of DQ2.2-glut-L1-specific TCRs showed that the CDR3β loops dominated the TCR−pHLA interface with both TCRs contacting key p5-Gln of peptide (Figure 2h) [12]. Interestingly the DQ2.2-glut-L1-specific *TRAV9-2*$^{+}$*-TRBV11-2*$^{+}$ TCR contained a CDR3β Trp (Trp111β) that formed analogous interactions with to those mediated by CDR3β Arg of the DQ2.5-glia-α2-specific TCRs despite differing natures of the peptides [12,39]. Thus, a single polymorphism within the antigen-binding cleft of HLA-DQ2.2 determines disease penetrance by altering frequency of peptides that can bind, which subsequently impacts on the nature of the T cell response.

Evidence for TCR cross-reactivity to gliadin and microbial peptides in CeD

The presence of *HLA-DQ2.5*, *HLA-DQ8* or *HLA-DQ2.2* alleles is insufficient to cause disease, and accordingly environmental risk factors likely contribute to disease burden, although the mechanisms of such associations are ill-defined. Of relevance, there have been reports of a link between both gastrointestinal infection and altered gut microbiota (dysbiosis) with CeD [13,18,55−62]. Recently, proteolytic activity attributed to *Pseudomonas aeruginosa*, an opportunistic pathogen isolated from CeD patients, has been shown to process gluten into T cell reactive epitopes whereas bacterial species from healthy controls inactivates these reactive epitopes by further proteolytic breakdown [55].

These observations spurred a structurally-driven investigation into TCR cross-reactivity between gluten and bacterial epitopes. Through previous structural and functional studies of TCR-HLA-DQ2.5 complexes [39], the regions of the DQ2.5-glia-α1a and DQ2.5-glia-α2 peptides that were important for either HLA-DQ2.5 or TCR binding were determined. With these constraints in hand, bacterial protein databases were mined to find matches against DQ2.5-glia-α1a and DQ2.5-glia-α2 peptides [10]. A series of candidate "hits" from a number of bacteria, including *Bordetella* sp. and *Pseudomonas* sp., pathogens of clinical relevance were obtained.

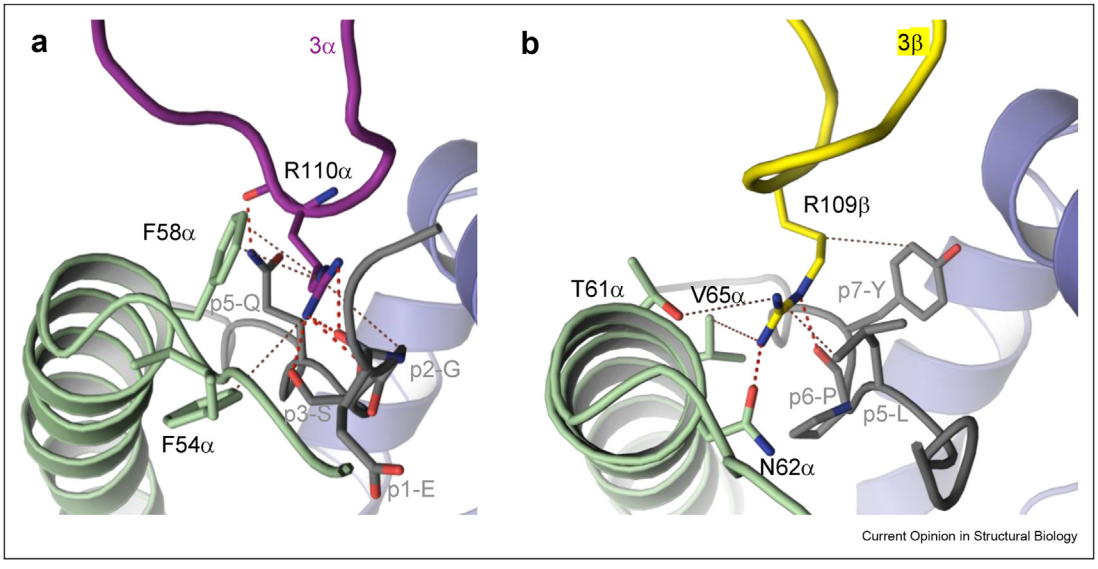
Figure 3



Single HLA-DQα22 polymorphism affects epitope specificity of HLA-DQ2 molecules. (**a**) Interactions between HLA-DQ2.2 and DQ2.2-glut-L1 peptide enabled by HLA-DQ2.2-F22α in the 594-HLA-DQ2.2-glut-L1 complex (PDB: 6PY2) [12] and (**b**) interactions between HLA-DQ2.5 and DQ2.5-glia-α2 enabled by HLA-DQ2.5-Y22α in the JR5.1-HLA-DQ2.5-glia-α2 complex (PDB: 4OZF) [39]. Peptide residues are shown as grey sticks and cartoon without main chain atoms. Oxygen atoms are shown in red, nitrogen atoms in dark blue. Red areas of the HLA-α chain are polymorphic between HLA-DQ2.2 and HLA-DQ2.5. Cartoon HLA-DQ2-α chain (light green) and -β chain (violet). TCR omitted from figure for clarity. Amino acid residues are denoted by single-letter codes.

Intriguingly, two of the *Pseudomonas* peptides were derived from the same parent protein, succinylglutamate desuccinylase (SGDS), and had an overlap in their sequence, which mirrored that of DQ2.5-glia-α1a and DQ2.5-glia-α2 in gliadin. CeD TCC showed cross-reactivity to some of the peptides within the panel, including the two *Pseudomonas* SGDS peptides and the parental protein, indicating correct antigen processing and presentation of the peptides [10]. The crystal structures of TCRs in complex with two different bacterial peptides presented by HLA-DQ2.5 displayed highly similar interactions observed for the same TCRs bound to HLA-DQ2.5 presenting the original gluten epitopes (Table 1, Figure 4) [36]. Overall, the data

Figure 4



Convergent non-germline CDR3–arginine interactions at TCR–pHLA interface. (**a**) SP3.4 TCR-HLA-DQ8-glia-α1 complex (PDB: 4GG6) [1] and (**b**) S16 TCR-HLA-DQ2.5-glia-α2 complex (PDB: 4OZH) [39]. Peptide residues that contact TCR CDR3-arginine (Arg) residue are shown as grey stick representation. Oxygen atoms are shown in red, nitrogen atoms in dark blue. The cartoon HLA α- (light green) and β-chain (violet). The cartoon CDR3 α- (3α) and β- (3β) loop are coloured magenta and yellow, respectively. Amino acid residues are denoted by single-letter codes.

demonstrated that molecular mimicry was the basis for the cross-reactivity of these gliadin restricted T cells with the bacterial peptides. Taken together, this study indicates that prior exposure to microbial antigens may be a contributing factor in the development and/or persistence of CeD pathology.

Future directions and challenges

Collectively, all of the ternary structures of CeD-related TCR-HLA-DQ2-gluten and TCR-HLA-DQ8-gluten complexes determined to date display standard canonical TCR docking mode over pHLA despite differences and *TRAV/TRBV* usage and CDR3 loop sequences (Table 1) [1,3,10,12,39,43]. These structures have shown that although the diverse TCR gene usage for TCRs specific for DQ2.5-glia-α1a, DQ2.5-glia-α2, DQ2.2-glut-L1, DQ8-glia-α1 or DQ8.5-glia-γ1 do form unique interactions, there is also a convergence into consensus binding solution observed amongst many TCRs particularly those using Arg residues in pHLA recognition (Table 1, Figure 4) [39]. These studies have provided a basis for the biased *TRAV/TRBV* usage, CDR3 motif selection and some insight into epitope-specificity of the responding T cells in HLA-DQ2/8-mediated CeD. The extent of TCR cross-reactivity between gluten epitopes remains to be established, although it was interesting to observe TCR cross-reactivity across bacterial mimics of gluten epitopes.

A key consideration is how such structural information can lead to future diagnostics/therapeutics to monitor or treat CeD. The commonalities at the TCR–pHLA interface suggest that small molecule blockers may represent one possible modality. Developing biologics to bind to the HLA-DQ2.5-gluten complex is also a distinct possibility. Indeed, it was shown recently that an antibody that specifically recognises HLA-DQ2.5-glia-α2 on plasma cells of the gut has an extremely high affinity, binds in a TCR-like fashion and blocks T cell activation at low concentrations [63]. The crystal structure of the Fab fragment of TCR-like antibody bound to HLA-DQ2.5-glia-α2 docked and interacted reminiscent of the prototypical DQ2.5-glia-α2-specific TCRs (Figure 2g). Further structural work is required to provide a more comprehensive and general understanding of the fundamental TCR–pHLA interactions driving CeD. This may have implications in understanding pathogenesis of other autoimmune diseases with strong HLA genetic associations.

Conflict of interest statement

JR receives funds Janssen Research & Development, LLC to undertake work on CeD.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Broughton SE, Petersen J, Theodossis A, Scally SW, Loh KL, Thompson A, van Bergen J, Kooy-Winkelaar Y, Henderson KN, Beddoe T: **Biased T cell receptor usage directed against human leukocyte antigen DQ8-restricted gliadin peptides is associated with celiac disease**. *Immunity* 2012, **37**:611–621.

2. Goel G, King T, Daveson AJ, Andrews JM, Krishnarajah J, Krause R, Brown GJ, Fogel R, Barish CF, Epstein R: **Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: two randomised, double-blind, placebo-controlled phase 1 studies**. *The lancet Gastroenterology & hepatology* 2017, **2**:479–493.

3. Petersen J, Kooy-Winkelaar Y, Loh KL, Tran M, Van Bergen J, Koning F, Rossjohn J, Reid HH: **Diverse T cell receptor gene usage in HLA-DQ8-associated celiac disease converges into a consensus binding solution**. *Structure* 2016, **24**: 1643–1657.

4. Zareie P, Szeto C, Farenc C, Gunasinghe SD, Kolawole EM, Nguyen A, Blyth C, Sng XY, Li J, Jones CM: **Canonical T cell receptor docking on peptide–MHC is essential for T cell signaling**. *Science* 2021, **372**:1–13.

5. Tye-Din JA, Stewart JA, Dromey JA, Beissbarth T, van Heel DA, Tatham A, Henderson K, Mannering SI, Gianfrani C, Jewell DP: **Comprehensive, quantitative mapping of T cell epitopes in gluten in celiac disease**. *Sci Transl Med* 2010, **2**:1–14.

6. Bodd M, Kim CY, Lundin KE, Sollid LM: **T-cell response to gluten in patients with HLA-DQ2.2 reveals requirement of peptide-MHC stability in celiac disease**. *Gastroenterology* 2012, **142**:552–561.

7. Tran MT, Faridi P, Lim JJ, Ting YT, Onwukwe G, Bhattacharjee P, Jones CM, Tresoldi E, Cameron FJ, La Gruta NL: **T cell receptor recognition of hybrid insulin peptides bound to HLA-DQ8**. *Nat Commun* 2021, **12**:1–13.

8. Lim JJ, Jones CM, Loh TJ, Ting YT, Zareie P, Loh KL, Felix NJ, Suri A, McKinnon M, Stevenaert F: **The shared susceptibility epitope of HLA-DR4 binds citrullinated self-antigens and the TCR**. *Science Immunology* 2021, **6**:1–16.

9. Quarsten H, McAdam SN, Jensen T, Arentz-Hansen H, Molberg Ø, Lundin KE, Sollid LM: **Staining of celiac disease-relevant T cells by peptide-DQ2 multimers**. *J Immunol* 2001, **167**:4861–4868.

10. ** Petersen J, Ciacchi L, Tran MT, Loh KL, Kooy-Winkelaar Y, Croft NP, Hardy MY, Chen Z, McCluskey J, Anderson RP: **T cell receptor cross-reactivity between gliadin and bacterial peptides in celiac disease**. *Nat Struct Mol Biol* 2020, **27**:49–61.
The authors provide evidence to support exposure to micobes as an envronmental risk factor the development of CeD. They showed that TCR cross-reactivity between gluten and bacterial-mimic epitopes was enabled by the TCR detecting and maintaining interactions with conserved residues of the gluten and bacterial-mimic pHLA.

11. ** Dahal-Koirala S, Risnes LF, Neumann RS, Christophersen A, Lundin KE, Sandve GK, Qiao S-W, Sollid LM: **Comprehensive analysis of CDR3 sequences in gluten-specific T-cell receptors reveals a dominant R-motif and several new minor motifs**. *Front Immunol* 2021, **12**:1–13.
This study described analysis of the HLA-DQ2.5 restricted T cell response to four immunodominant gluten epitopes in a very large cohort of CeD patients. Single cell tetramer sorting and αβTCR sequencing of the corresponding large number of clonotypes determined, across the patient cohort, shared TRAV, TRBV, TRAV/TRBV gene usage CDR3 motifs.

12. ** Ting YT, Dahal-Koirala S, Kim HSK, Qiao S-W, Neumann RS, Lundin KE, Petersen J, Reid HH, Sollid LM, Rossjohn J: **A molecular basis for the T cell response in HLA-DQ2.2 mediated celiac disease**. *Proc Natl Acad Sci Unit States Am* 2020, **117**:3063–3073.

This study elucidates the basis for differential risks of HLA-DQ2.2 and HLA-DQ2.5 allomorphs. A single polymorphic residue at position 22 of the HLA-DQ2 α-chain accounts for the much lower disease risk of HLA-DQ2.2 compared to the highly homologous HLA-DQ2.5.

13. Ashorn S, Raukola H, Välineva T, Ashorn M, Wei B, Braun J, Rantala I, Kaukinen K, Luukkaala T, Collin P: **Elevated serum anti-Saccharomyces cerevisiae, anti-I2 and anti-OmpW antibody levels in patients with suspicion of celiac disease**. *J Clin Immunol* 2008, **28**:486–494.

14. Dubé C, Rostom A, Sy R, Cranney A, Saloojee N, Garritty C, Sampson M, Zhang L, Yazdi F, Mamaladze V: **The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review**. *Gastroenterology* 2005, **128**: S57–S67.

15. Jabri B, Sollid LM: **Tissue-mediated control of immunopathology in coeliac disease**. *Nat Rev Immunol* 2009, **9**:858–870.

16. Koning F: **Celiac disease: caught between a rock and a hard place**. *Gastroenterology* 2005, **129**:1294–1301.

17. Abadie V, Sollid LM, Barreiro LB, Jabri B: **Integration of genetic and immunological insights into a model of celiac disease pathogenesis**. *Annu Rev Immunol* 2011, **29**:493–525.

18. Riddle MS, Murray JA, Porter CK: **The incidence and risk of celiac disease in a healthy US adult population**. *Am J Gastroenterol* 2012, **107**:1248–1255.

19. Anderson RP: **Coeliac disease is on the rise**. *Med J Aust* 2011, **194**:278–279.

20. Rubio–Tapia A, Kelly DG, Lahr BD, Dogan A, Wu TT, Murray JA: **Clinical staging and survival in refractory celiac disease: a single center experience**. *Gastroenterology* 2009, **136**:99–107.

21. Metzger M-H, Heier M, Mäki M, Bravi E, Schneider A, Löwel H, Illig T, Schuppan D, Wichmann H-E: **Mortality excess in individuals with elevated IgA anti-transglutaminase antibodies: the KORA/MONICA Augsburg cohort study 1989–1998**. *Eur J Epidemiol* 2006, **21**:359–365.

22. Logan R, Rifkind E, Turner I, Ferguson A: **Mortality in celiac disease**. *Gastroenterology* 1989, **97**:265–271.

23. Dicke W-K, Weijers H, Kamer JvD: **Coeliac disease the presence in wheat of a factor having a deleterious effect in cases of coeliac disease**. *Acta Paediatr* 1953, **42**:34–42.

24. Kamer J, Weijers H, Dicke W: **Coeliac disease: an investigation into the injurious constituents of wheat in connection with their action on patients with coeliac disease**. *Acta Paediatr* 1953, **42**:223–231.

25. Bardella M, Velio P, Cesana B, Prampolini L, Casella G, Di Bella C, Lanzini A, Gambarotti M, Bassotti G, Villanacci V: **Coeliac disease: a histological follow-up study**. *Histopathology* 2007, **50**:465–471.

26. Kaukinen K, Peräaho M, Lindfors K, Partanen J, Woolley N, Pikkarainen P, Karvonen AL, Laasanen T, Sievänen H, Mäki M: **Persistent small bowel mucosal villous atrophy without symptoms in coeliac disease**. *Aliment Pharmacol Ther* 2007, **25**:1237–1245.

27. Sollid LM: **Coeliac disease: dissecting a complex inflammatory disorder**. *Nat Rev Immunol* 2002, **2**:647–655.

28. Karell K, Louka AS, Moodie SJ, Ascher H, Clot F, Greco L, Ciclitira PJ, Sollid LM, Partanen J: **Disease EGCoC: HLA types in celiac disease patients not carrying the DQA1* 05-DQB1* 02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease**. *Hum Immunol* 2003, **64**:469–477.

29. Arentz–Hansen H, Mcadam SN, Molberg Ø, Fleckenstein B, Lundin KE, Jørgensen TJ, Jung G, Roepstorff P, Sollid LM: **Celiac lesion T cells recognize epitopes that cluster in regions of gliadins rich in proline residues**. *Gastroenterology* 2002, **123**:803–809.

30. Henderson KN, Tye-Din JA, Reid HH, Chen Z, Borg NA, Beissbarth T, Tatham A, Mannering SI, Purcell AW, Dudek NL: **A structural and immunological basis for the role of human leukocyte antigen DQ8 in celiac disease**. *Immunity* 2007, **27**: 23–34.

31. Dørum S, Bodd M, Fallang L-E, Bergseng E, Christophersen A, Johannesen MK, Qiao S-W, Stamnaes J, De Souza GA, Sollid LM: **HLA-DQ molecules as affinity matrix for identification of gluten T cell epitopes**. *J Immunol* 2014, **193**: 4497–4506.

32. Anderson RP, Degano P, Godkin AJ, Jewell DP, Hill AV: **In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope**. *Nat Med* 2000, **6**:337–342.

33. van de Wal Y, Kooy YM, van Veelen P, Vader W, August SA, Drijfhout JW, Peña SA, Koning F: **Glutenin is involved in the gluten-driven mucosal T cell response**. *Eur J Immunol* 1999, **29**:3133–3139.

34. Vader W, Kooy Y, Van Veelen P, De Ru A, Harris D, Benckhuijsen W, Peña S, Mearin L, Drijfhout JW, Koning F: **The gluten response in children with celiac disease is directed toward multiple gliadin and glutenin peptides**. *Gastroenterology* 2002, **122**:1729–1737.

35. Arentz-Hansen H, Körner R, Molberg Ø, Quarsten H, Vader W, Kooy Y, Lundin KE, Koning F, Roepstorff P, Sollid LM: **The intestinal T cell response to α-gliadin in adult celiac disease is focused on a single deamidated glutamine targeted by tissue transglutaminase**. *J Exp Med* 2000, **191**:603–612.

36. Høydahl LS, Richter L, Frick R, Snir O, Gunnarsen KS, Landsverk OJ, Iversen R, Jeliazkov JR, Gray JJ, Bergseng E: **Plasma cells are the most abundant gluten peptide MHC-expressing cells in inflamed intestinal tissues from patients with celiac disease**. *Gastroenterology* 2019, **156**:1428–1439.

37. Qiao S-W, Piper J, Haraldsen G, Øynebråten I, Fleckenstein B, Molberg Ø, Khosla C, Sollid LM: **Tissue transglutaminase-mediated formation and cleavage of histamine-gliadin complexes: biological effects and implications for celiac disease**. *J Immunol* 2005, **174**:1657–1663.

38. Kim C-Y, Quarsten H, Bergseng E, Khosla C, Sollid LM: **Structural basis for HLA-DQ2-mediated presentation of gluten epitopes in celiac disease**. *Proc Natl Acad Sci Unit States Am* 2004, **101**:4175–4179.

39. Petersen J, Montserrat V, Mujico JR, Loh KL, Beringer DX, Van Lummel M, Thompson A, Mearin ML, Schweizer J, Kooy-Winkelaar Y: **T-cell receptor recognition of HLA-DQ2–gliadin complexes associated with celiac disease**. *Nat Struct Mol Biol* 2014, **21**:480–488.

40. Sollid LM, Tye-Din JA, Qiao SW, Anderson RP, Gianfrani C, Koning F: **Update 2020: nomenclature and listing of celiac disease-relevant gluten epitopes recognized by CD4(+) T cells**. *Immunogenetics* 2020, **72**:85–88.

41. Van De Wal Y, Kooy YM, Van Veelen PA, Peña SA, Mearin LM, Molberg Ø, Lundin KE, Sollid LM, Mutis T, Benckhuijsen WE: **Small intestinal T cells of celiac disease patients recognize a natural pepsin fragment of gliadin**. *Proc Natl Acad Sci Unit States Am* 1998, **95**:10050–10054.

42. Tollefsen S, Arentz-Hansen H, Fleckenstein B, Molberg Ø, Ráki M, Kwok WW, Jung G, Lundin KE, Sollid LM: **HLA-DQ2 and-DQ8 signatures of gluten T cell epitopes in celiac disease**. *J Clin Invest* 2006, **116**:2226–2236.

43. Petersen J, van Bergen J, Loh KL, Kooy-Winkelaar Y, Beringer DX, Thompson A, Bakker SF, Mulder CJ, Ladell K, McLaren JE: **Determinants of gliadin-specific T cell selection in celiac disease**. *J Immunol* 2015, **194**:6112–6122.

44. Christophersen A, Ráki M, Bergseng E, Lundin KE, Jahnsen J, Sollid LM, Qiao S-W: **Tetramer-visualized gluten-specific CD4+ T cells in blood as a potential diagnostic marker for coeliac disease without oral gluten challenge**. *United European gastroenterology journal* 2014, **2**:268–278.

45. Bodd M, Ráki M, Bergseng E, Jahnsen J, Lundin KE, Sollid LM: **Direct cloning and tetramer staining to measure the frequency of intestinal gluten-reactive T cells in celiac disease**. *Eur J Immunol* 2013, **43**:2605–2612.

46. Dahal-Koirala S, Risnes LF, Christophersen A, Sarna VK, Lundin KE, Sollid LM, Qiao S-W: **TCR sequencing of single cells reactive to DQ2. 5-glia-α2 and DQ2. 5-glia-ω2 reveals**

clonal expansion and epitope-specific V-gene usage. *Mucosal Immunol* 2016, **9**:587–596.

47. Sarna VK, Lundin KE, Mørkrid L, Qiao S-W, Sollid LM, Christophersen A: **HLA-DQ–gluten tetramer blood test accurately identifies patients with and without celiac disease in absence of gluten consumption**. *Gastroenterology* 2018, **154**: 886–896.

48. Sarna VK, Skodje GI, Reims HM, Risnes LF, Dahal-Koirala S, Sollid LM, Lundin KE: **HLA-DQ: gluten tetramer test in blood gives better detection of coeliac patients than biopsy after 14-day gluten challenge**. *Gut* 2018, **67**:1606–1613.

49. Leonard MM, Silvester JA, Leffler D, Fasano A, Kelly CP, Lewis SK, Goldsmith JD, Greenblatt E, Kwok WW, McAuliffe WJ: **Evaluating responses to gluten challenge: a randomized, double-blind, 2-dose gluten challenge trial**. *Gastroenterology* 2021, **160**:720–733.

50. Qiao S-W, Ráki M, Gunnarsen KS, Løset G-Å, Lundin KE, Sandlie I, Sollid LM: **Posttranslational modification of gluten shapes TCR usage in celiac disease**. *J Immunol* 2011, **187**: 3064–3071.

51. Qiao S-W, Christophersen A, Lundin KE, Sollid LM: **Biased usage and preferred pairing of α-and β-chains of TCRs specific for an immunodominant gluten epitope in coeliac disease**. *Int Immunol* 2014, **26**:13–19.

52. Gunnarsen KS, Høydahl LS, Risnes LF, Dahal-Koirala S, Neumann RS, Bergseng E, Frigstad T, Frick R, du Pré MF, Dalhus B: **A TCRα framework–centered codon shapes a biased T cell repertoire through direct MHC and CDR3β interactions**. *JCI insight* 2017, **2**:1–13.

53. Dahal-Koirala S, Ciacchi L, Petersen J, Risnes LF, Neumann RS, Christophersen A, Lundin KE, Reid HH, Qiao S-W, Rossjohn J: **Discriminative T-cell receptor recognition of highly homologous HLA-DQ2–bound gluten epitopes**. *J Biol Chem* 2019, **294**:941–952.

54. Han A, Newell EW, Glanville J, Fernandez-Becker N, Khosla C, Chien Y-h, Davis MM: **Dietary gluten triggers concomitant activation of CD4+ and CD8+ αβ T cells and γδ T cells in celiac disease**. *Proc Natl Acad Sci Unit States Am* 2013, **110**: 13073–13078.

55. Caminero A, Galipeau HJ, McCarville JL, Johnston CW, Bernier SP, Russell AK, Jury J, Herran AR, Casqueiro J, Tye-Din JA: **Duodenal bacteria from patients with celiac disease and healthy subjects distinctly affect gluten breakdown and immunogenicity**. *Gastroenterology* 2016, **151**:670–683.

56. D'argenio V, Casaburi G, Precone V, Pagliuca C, Colicchio R, Sarnataro D, Discepolo V, Kim SM, Russo I, Blanco GDV: **Metagenomics reveals dysbiosis and a potentially pathogenic N. flavescens strain in duodenum of adult celiac patients**. *Am J Gastroenterol* 2016, **111**:879–890.

57. Riddle MS, Murray JA, Cash BD, Pimentel M, Porter CK: **Pathogen-specific risk of celiac disease following bacterial causes of foodborne illness: a retrospective cohort study**. *Dig Dis Sci* 2013, **58**:3242–3245.

58. Sánchez E, Donat E, Ribes-Koninckx C, Fernández-Murga ML, Sanz Y: **Duodenal-mucosal bacteria associated with celiac disease in children**. *Appl Environ Microbiol* 2013, **79**: 5472–5479.

59. Viitasalo L, Iltanen S, Huhtala H, Saavalainen P, Kaukinen K, Lindfors K, Kurppa K: **First-degree relatives of celiac disease patients have increased seroreactivity to serum microbial markers**. *Nutrients* 2020, **12**:1–10.

60. Viitasalo L, Kurppa K, Ashorn M, Saavalainen P, Huhtala H, Ashorn S, Mäki M, Ilus T, Kaukinen K, Iltanen S: **Microbial biomarkers in patients with nonresponsive celiac disease**. *Dig Dis Sci* 2018, **63**:3434–3441.

61. Viitasalo L, Niemi L, Ashorn M, Ashorn S, Braun J, Huhtala H, Collin P, Mäki M, Kaukinen K, Kurppa K: **Early microbial markers of celiac disease**. *J Clin Gastroenterol* 2014, **48**: 620–624.

62. Wacklin P, Laurikka P, Lindfors K, Collin P, Salmi T, Lähdeaho M-L, Saavalainen P, Mäki M, Mättö J, Kurppa K: **Altered duodenal microbiota composition in celiac disease patients suffering from persistent symptoms on a long-term gluten-free diet**. *Official journal of the American College of Gastroenterology| ACG* 2014, **109**:1933–1941.

63. * Frick R, Høydahl LS, Petersen J, du Pré MF, Kumari S, Berntsen G, Dewan AE, Jeliazkov JR, Gunnarsen KS, Frigstad T: **A high-affinity human TCR-like antibody detects celiac disease gluten peptide–MHC complexes and inhibits T cell activation**. *Science Immunology* 2021, **6**:1–16.
This study provides the structural basis for antibody recognition of the HLA-DQ2.5-glia-α2 complex. The antibody adopted a similar docking mode as seen previously in prototypic TCRs with the same specificity and that it is a potential therapeutic as it was shown to prevent activation of gluten-specific $CD4^+$ T cells.