Cross-reactivity of CD4+ gluten-reactive T cell receptors in celiac disease

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Celiac disease (CeD) is a chronic inflammatory autoimmune-like condition characterised by disease-relevant HLA-DQ.2.5/8 molecules that present gluten epitopes derived from wheat, rye and barley to reactive T cells [1, 2]. We investigated CD4+ T cell responses towards immunodominant gluten epitopes; DQ2.5-glia-α1a (PFPQPELPY) and DQ2.5-glia-α1 (PFPQPEQP) by examining patient T cell repertoire [3, 4]. It was found to be composed of highly specific and cross-reactive T cell clones (TCCs) [4].

Next, we determined the ternary complex structures of cross-reactive T cell receptor (TCR) bound to HLA-DQ2.5-glia-α1a and HLA-DQ2.5-glia-α1 and epitope-specific TCR bound to HLA-DQ2.5-glia-α1 specific TCR [3, 5]. The interactions at the interface of TCR: peptide-HLA-DQ2.5 required for specificity provide an insight into how the TCRs distinguish between these highly similar peptides [5]. Comparison of the TCR footprint contacts of the ternary complexes for both peptides revealed similar canonical TCR docking with slight shift in docking angle [3, 5, 6]. The hypervariable CDR3 loops were shown to be responsible for differential TCR recognition capacities of the cross-reactive versus discriminatory TCRs [5, 7]. We measured SPR binding affinities of the TCR-pHLA interaction and found that the cross-reactive TCR is selectively promiscuous in binding as this TCR only bound these epitopes with similar affinity [5, 7].

This study highlights that cross-reactive T cells may also contribute to CeD pathogenesis [5, 7]. Furthermore, these cross-reactive and discriminatory T cells may prove to be important therapeutic targets in treatment of CeD [5, 7, 8].