
Recent insight in the pathophysiology of coeliac disease: relevance to rheumatoid arthritis

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ABSTRACT

Coeliac disease (CD) is a T cell mediated inflammatory disorder of the small intestine that affects approximately 1% of the population (1, 2). CD is triggered by gluten ingestion, proteins found in wheat, barley and rye. CD4⁺ T cells specific for post-translationally modified gluten peptides bound to the disease-predisposing HLA-DQ2 or HLA-DQ8 molecules are typically found in patients with CD, explaining the strong association between these HLA-alleles and the occurrence of CD (1, 2). In addition, antibodies specific for modified gluten are also present in patients with CD, implying a role for B to T cell presentation (1). Recent studies have determined the T cell repertoire (TCR) that is utilised by gluten-specific T cells in HLA-DQ2⁺ and HLA-DQ8⁺ patients and structures between such TCR and HLA-DQ-gluten peptide complexes have been solved (3-7). In HLA-DQ2 patients the TCR repertoire specific for an immunodominant gluten peptide is dominated by the expression of TRAV26 and TRBV7-2 (3-5) while in HLA-DQ8⁺ patients such T cells frequently express TRAV26 and TRBV9 (6, 7). Moreover, in the TCR-HLA-DQ-gluten complexes a non-germline encoded arginine is positioned in the interface between the TCR and HLA-DQ-gluten which makes critical interactions with both HLA-DQ and the bound peptide (5-7). Collectively, these observations point to stringent selection of a high affinity TCR repertoire in patients with CD. Similar mechanisms are likely to play a role in rheumatoid arthritis (RA).

The role of HLA in autoimmunity

The strong link between autoimmune diseases and particular HLA-alleles is well established: ankylosing spondylitis (HLA-B27; ref 8), CD (HLA-DQ2/8; ref 9), narcolepsy (HLA-DQ6;

ref 10), type 1 diabetes (HLA-DQ8/2; ref 11) and RA (HLA-DR4; ref 12) are amongst these diseases, implying a role for the associated HLA-alleles in disease pathogenesis. In view of the critical role of HLA in antigen presentation it is assumed that the disease predisposing HLA-dimers bind and present disease related (auto)antigen-derived peptides to T cells, leading to tissue damage. However, the large majority of individuals that express a predisposing HLA-allele will never develop the associated autoimmune disease. Moreover, concordance rate in monozygotic twins is never 100% and GWAS studies have now implied many genetic variants, often located near immune related genes, influencing the development of autoimmunity (13). Finally, the incidence of autoimmune diseases is steadily rising (14). Together this implies that next to HLA other genetic factors and (changing) environmental factors play a critical role in disease development.

The example of coeliac disease

While in most HLA-associated diseases the nature of the disease related self-antigens has remained elusive, we have detailed insight into the nature of the disease-inducing antigens and the corresponding T cell receptor repertoire in patients with CD. CD almost exclusively develops in HLA-DQ2 and/or HLA-DQ8 positive individuals. CD patients are intolerant to gluten, a complex mixture of proteins present in the commonly consumed cereals wheat, barley and rye. CD4 T cells specific for gluten-derived peptides bound to the disease-predisposing HLA-DQ2 or HLA-DQ8 dimers have been identified in biopsies and peripheral blood of patients but not in healthy controls (1, 2). These T cells secrete pro-inflammatory cytokines including IFN γ and IL21 and are thus major drivers of disease

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pathogenesis. Strikingly, native gluten-derived peptides bind poorly to HLA-DQ2 and HLA-DQ8 and elicit only weak T cell responses. For high affinity binding such peptides must first be modified which is mediated by tissue transglutaminase (TG2), an enzyme released in the intestine upon tissue damage (15-17). TG2 selectively modifies glutamine residues in target sequences in gluten into glutamic acid, introducing the negative charge(s) in gluten peptides that are required for high affinity binding to either HLA-DQ2 or HLA-DQ8. Thus a scenario presents itself where weak gluten-specific T cell responses lead to limited tissue damage and release of intracellular TG2 release followed by gluten modification, unleashing an amplification of the gluten specific T cell response by enhancing the binding of gluten peptides to HLA-DQ. Alternatively, tissue damage due to other causes may lead to the generation of high affinity binding gluten peptides, lowering the threshold for T cell reactivity towards gluten peptides. The disease-inducing capacity of gluten is linked to its unusual properties: two amino acids, proline and glutamine, make up half of the proteins. Due to this high proline-content gluten is highly resistant to degradation in the gastrointestinal tract, leaving large fragments intact that can be modified by TG2 (18). Moreover, gluten contains many repetitive sequences, often in the degradation resistant fragments and these contain highly immunogenic and immunodominant sequences to which responses are found in virtually all patients. T cells specific for such immunodominant gluten peptides have been isolated from a large number of patients and their T cell receptor usage has been determined. Strikingly, a highly biased TCR usage was observed, dominated by the use of TRAV26 and TRBV7-2 in HLA-DQ2 positive patients and TRAV26 and TRBV9 in HLA-DQ8 positive patients (3-7). Moreover, in such TCR a non-germline encoded arginine residue was present in either the CDR3 α or CDR3 β region. Structural studies demonstrate that this arginine in the TCR plays a crucial role by acting as a lynchpin as it interacts

with both HLA-DQ and the bound gluten peptide (5-7). Moreover, such TCR display a high affinity for their cognate ligand. Together these results indicate that in CD patients a highly biased and high-affinity gluten-specific TCR repertoire has been selected that mediates the disease-causative T cell response. Next to T cells specific for modified gluten, antibodies to both modified gluten and the gluten-modifying enzyme TG2 are typically found in patients with CD (1). Measuring the presence of such antibodies in serum is a highly sensitive and specific diagnostic tool and the antibodies disappear upon the introduction of a gluten-free diet, indicating that the production of both is driven by gluten-specific T cells (1). In turn, both types of antibodies are likely to boost the gluten-specific T cell response. B cells expressing antibodies to modified gluten would be highly efficient in the uptake, processing and presentation of modified gluten to gluten-specific T cells. Also, TG2 can crosslink itself to gluten and uptake of such TG2-gluten complexes by TG2 specific B cells would likewise result in highly efficient gluten presentation. T cell help for B cells and B to T cell presentation thus create a powerful amplification loop driving disease development.

Relevance to rheumatoid arthritis

Similar to CD, IgG and IgA antibodies to modified proteins are present in a distinct subset of patients with RA (1). In RA the modification involves the conversion of positively charged arginine residues into uncharged citrulline by the enzyme protein arginine deiminase (1). The appearance of such anti-citrulline protein antibodies (ACPA) predicts disease development and may just like in CD mediate B to T cell presentation. Conversely, the presence of such antibodies and isotype switching implies the involvement of T to B cell help. Thus, also in RA the antigen-specific interaction between B and T cells is likely to drive an amplification loop. The nature of the T cell antigens, however, is still poorly understood although recent evidence points to cross-reactivity towards microbial and self-

antigens (19). Future studies aimed to elucidate the TCR repertoire driving the autoreactive immune response may provide clues for the development of novel intervention strategies.

Concluding remarks

Protein modification is an important step towards loss of tolerance and the development of HLA-associated immune mediated diseases. In both CD and RA immune responses to modified protein antigens are present. B to T cell presentation likely plays an important role in disease pathogenesis as it functions as an amplification loop for both T and B cell responses towards the target proteins involved. Interference in this amplification loop may thus be a promising therapeutic avenue.

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