

COELIAC DISEASE: MECHANISM OF THE DISEASE AND NEW THERAPEUTIC OPTIONS

Coeliac disease is an incurable, acquired immune disease with strong genetic determinants that, in most cases, begins in infancy, and is caused by storage proteins of wheat, rye, barley and, possibly, oats (gluten = antigen).

Coeliac disease is caused by a cellular (T-cell) immune response to gluten peptides. Coeliac disease is also associated with production of antibodies to human proteins such as tissue transglutaminase (autoantigen) that disappear with gluten exclusion. Antibodies to transglutaminase and gluten are generally present, but have not been implicated in the disease process causing tissue damage. Untreated disease is characterised by varying degrees of flattening (villous atrophy with crypt hyperplasia) of the mucosa of the duodenum and jejunum and, in consequence, by the generalised malabsorption of nutrients.

Over 99% of patients with 'biopsy-proven' coeliac disease possess either of the immune recognition genes encoding HLA DQ2 (HLA DQA1*05 and HLA DQB1*02) and/or HLA DQ8 (HLA DQA1*03 and HLA DQB1*0302) compared with approximately a third of the general Caucasian and West Asian population (Sollid et al 1989). Approximately 90% of coeliac disease is associated with possession of both HLA DQA1*05 and HLA DQB1*02, 4% with HLA DQB1*02 without HLA DQA1*05, 2% with HLA DQA1*05 without HLA DQB1*02, and 6% with the two genes HLA DQ8 without HLA DQ2 (Karell et al 2003).

Since the function of HLA molecules in the human immune system is presentation of short peptides (nine amino acids flanked by at least one or more additional amino-acids) to T-cells (Townsend 1986), the association and later proof of the causative role of HLA DQ2 and HLA DQ8 in coeliac disease by Sollid in 1989, implied the existence of gluten-specific T-cells, and that coeliac disease is an immunological, T-cell-mediated disease. In 1993, intestinal T-cells, specific for gluten, were isolated from intestinal biopsies of patients with coeliac disease (Lundin et al 1993), but it was only in 1998 with the discovery that intestinal T-cells recognise deamidated gluten peptides in which specific glutamine residues have been converted to acidic glutamate residues, (Molberg et al 1998), that it became possible to define gluten peptides with T-cell stimulatory activities.

Deamidation by treatment with acid or by the action of transglutaminase (present in inflamed intestinal mucosa) of the most toxic portion of wheat gluten (the alcohol soluble fraction, gliadin) makes it a much more potent activator of gluten-specific intestinal T-cells (Molberg et al 1998). The explanation for enhanced T-cell stimulation by deamidated gliadin peptides is that HLA DQ2 and HLA DQ8 preferentially bind peptides with acidic amino acids at critical anchor positions (Molberg et al 1998; Quarsten et al 1999; van de Wal 1998b). Deamidation enhances the binding affinity of HLA DQ2 and HLA DQ8 for certain gluten peptides that would otherwise not trigger T-cell responses.

A series of mostly deamidated gluten peptides stimulate T-cells exclusively from patients with coeliac disease (Arentz-Hansen et al 2000, Vader et al 2002, Arentz-Hansen et al 2003). After a deliberate gluten challenge, certain gluten peptides are consistently recognised by substantial numbers of intestinal gluten-specific T-cells in blood (Anderson et al 2000, Anderson et al 2005). However, the peptides recognised in HLA DQ2 disease are not the same as in HLA DQ8 disease (Anderson et al 2003).

Several of the dominant gluten peptides in HLA DQ2 disease are unusually resistant to human digestive proteases (Shan et al 2003), but can be digested by treatment with specific enzymes that attack peptides rich in proline or glutamine (Shan et al 2004, Stepniak et al 2006).

Recent studies have indicated gluten also possesses inflammatory activity independent of classical T-cells, probably by damaging intestinal epithelial cells and activating intra-epithelial lymphocytes (Jabri et al 2005). Since disease is extremely rare in the absence of HLA DQ2 or HLA DQ8, the contribution of this 'innate' inflammatory effect of gluten to overall tissue damage is not sufficient to cause coeliac disease alone.

In summary, the properties of gluten that make it toxic in disease are:

1. Consumption of large amounts in the diet
2. Resistance to human digestive proteases
3. Absorption of protease-resistant gluten peptides
4. Susceptibility of protease-resistant peptides to deamidation by transglutaminase
5. Presentation of deamidated gluten peptides by HLA DQ2 and/or HLA DQ8
6. Recognition of gluten peptides bound to HLA DQ2 or HLA DQ8 by specific T-cells that stimulate and recruit additional inflammatory cells.

New therapeutic approaches

New approaches to treating coeliac disease involve changing gluten to being non-toxic, reducing the amount of intact toxic gluten reaching the immune cells, and changing the response of the immune cells to gluten (Sollid & Khosla 2005).

Redesigning gluten proteins to avoid the toxic sequences and then expressing these in grains by genetic modification is likely to be a lengthy but practical option. The anticipated result would be non-toxic gluten with baking properties similar to standard gluten.

Research is also underway to digest gluten before cooking, to inactivate toxic gluten sequences (Anderson et al 2005, Shan et al 2005). Whether gluten digestion to the level needed to make it non-toxic will destroy its baking properties is not yet resolved.

Gluten is partially degraded in the gut and fragments permeate into the intestinal tissues through leaky junctions between lining cells (Drago et al 2006). Absorbed gluten fragments are attacked and modified by an enzyme (transglutaminase) allowing them to be bound to HLA DQ2 or DQ8. When bound to DQ2 or DQ8, gluten fragments stimulate T-cells that damage the intestine.

The objective of enzyme supplements that degrade gluten, or drugs that reduce the leakiness of the gut (zonulin inhibitors) (<http://www.albatherapeutics.com/product-development/index.html>), inhibit transglutaminase (Choi et al 2005), or block binding of gluten to DQ2 or DQ8 (Xia et al 2006) is to limit T-cell exposure to gluten.

Given that 50mg of gluten is sufficient to cause intestinal damage (Catassi et al 2007), and the normal diet may contain up to one-thousand times this amount of gluten, these strategies would need to be highly (99.9%) effective to allow a normal diet.

A more achievable goal for these treatments may be to reduce inadvertent exposure to modest amounts of gluten. For example a 90% effective treatment could allow exposure to 500mg (1/10th of a slice of bread).

Immuno-suppressive drugs including steroids are already known to dampen the immune reaction to gluten in disease, but all have undesirable side effects and are not attractive as long-term treatments.

Therapeutic vaccines have been developed for immune diseases in animals and are under investigation in human asthma (Oldfield et al 2002). Such vaccines would target only a small proportion of the body's T-cells, the gluten-specific T-cells, with the aim of desensitising them to gluten. The treatment may not result in permanent tolerance to gluten after an 'induction' course of injections but would be likely to require periodic boosters to maintain tolerance to gluten.

By the end of 2006, clinical trials had been undertaken to assess pre-treatment of gluten with prolyl endopeptidase (Pyle et al 2005; and under commercial development by Alvine Pharmaceuticals, see <http://www.alvinepharma.com/index.asp?page=48>), and co-administration of prolyl endopeptidase with gluten cookies (Cornell et al 2005; under commercial development by Glutagen Pty Ltd, Australia). Neither study demonstrates clear-cut protection from the toxic effects of gluten.

Important messages from both studies are that endoscopic intestinal biopsy is a required endpoint for clinical trials in coeliac disease, that antibody responses to gluten were insensitive measures of in vivo toxicity, and that many of the volunteers on a long term gluten free diet who enrolled were not in remission when intestinal biopsies were performed prior to entry.

A successful Phase I/proof of concept study of a zonulin receptor antagonist AT1001 has also been completed and demonstrates the drug has acceptable safety (<http://www.medicalnewstoday.com/medicalnews.php?newsid=56565>), and that it did reduce permeability changes associated with gluten challenge in coeliac volunteers. AT1001 is now being assessed in Phase II trials (<http://www.medicalnewstoday.com/medicalnews.php?newsid=52442>).

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