Food allergy type III
What is the link to auto-immune diseases? **Camille Lieners PhD**

The National Institute of Health (NIH) estimates up to 23,5 million Americans suffer from Auto-immune diseases and that the prevalence is rising. According to the American Auto-immune Related Diseases Associations (AARDA) it affects up to 50 million Americans. This difference occurs because the NIH only include 24 diseases while the AARDA count 80-100 diseases related to auto-immune conditions.

The common definition of autoimmune disease relates the pathology to an abnormal immune response to normal body parts. The cause is generally unknown. All autoimmune conditions include chronic inflammatory processes which may improve at certain times but can flare-up at any time. According to epidemiologic data women represent 85% of the subjects suffering from auto-immune diseases (1).
A genetic predisposition seems to play a major role in most autoimmune diseases, particularly mutations in the HLA system may be linked to autoimmune diseases. (2). Certain HLA mutations are well described and their dominant role in celiac disease (HLA-DQ2 and -DQ8), rheumatoid arthritis (HLA-DR4), diabetes type 1 (HLA-DR3), Systemic Lupus Erythematosus (HLA-DR3 and HLA-DR2), Sjögren syndrome (HLA-DR-3), Ankolysing spondylitis (HLA-B27), just to name a few.

Auto-immune disease	HLA mutations
Celiac disease	HLA-DQ2 (80%) and -DQ8 (17%)
Rheumatoid arthritis	HLA-DR4 (35%)
Diabetes type 1	HLA-DR3/DR4
Systemic Lupus Erythematosus	HLA-DR3 (62%)and HLA-DR2 (41%)
Sjögren syndrome	HLA-DR3 (25%)
Ankylosing spondylitis	HLA-B27 (40-90%) depending on ethnics

But these mutations are just predispositions to acquire the disease. Other factors like environmental factors (3), infections (4), leaky gut (5), drugs (6), stress (7) or adverse food reactions (8) may trigger the disease. For many of these autoimmune conditions, having high-risk genes may be a necessary, but not sufficient a reason for a person to get the disease. There is something more than just genes.

The best explored example is celiac disease, being related to the consumption of gluten. A patient with HLA-DQ2 and HLA-DQ8 positive mutations runs a very high risk to develop celiac disease when consuming gluten (9). If this patient avoids gluten the disease and the symptoms will improve or never flares up.
So, it seems to be essential that certain genetic predisposition and environmental factors are necessary to induce the disease.

In most auto-immune diseases additional triggers are not known and for this reason no causal treatment or specific recommendations are available to prevent the appearance most of the diseases.

The diagnosis of auto-immune diseases mainly relies on the clinical picture, presence of inflammatory processes and the determination of organ specific antibody patterns. It is believed that these antibodies are responsible for the disease and sometimes correlate with the disease severity. It is not normal that the body produces antibodies against its own tissue. It is well known that antibodies are produced against non-self- HLAs via blood transfusion, or transplants. Most of the autoimmune antibodies found are directed against intra cellular targets.

Auto-immune disease	Target	Location
Hashimoto	TPO	Intra-cellular
Lupus	DNA, histones, ribosomes	Intra-cellular
Sjögren	Anti-nuclear antigen	Intra-cellular
Wegener's Granulomatosis	cANCA	Intra-cellular
Vasculitis	pANCA	Intra-cellular

So why are these auto-immune antibodies produced?

- Why should the immune system produce antibodies to intra-cellular structures?
- Intra-cellular structures are not accessible to the immune system, unless uncontrolled disruption of the cell integrity.
- What causes the cell disruption?

Leaky gut - a prerequisite for auto-immune diseases?

The intestinal epithelium is the largest mucosal surface in the human body, and provides an interface between the external environment and the host. In the gut, two key elements govern the interplay between environmental triggers and the host: intestinal permeability and intestinal mucosal defense. The permeability of the intestinal epithelium depends on the regulation of intercellular tight junctions. (10)

Zonulin signaling pathway regulates the TJ in a rapid, reversible, and reproducible fashion to enable paracellular pathways for the absorption of macromolecules (11)
Upregulation of zonulin has been reported to be linked to many auto-immune diseases, such T1D, CD, multiple sclerosis, rheumathoid arthritis.(10)

Another important factor is the gut microbiota itself. Dysbiosis may additionally trigger the leaky gut syndrome. Increased uncontrolled passage of non-self-antigens lead to increased immune reaction in the gut. Of particular interest is the regulation of antigen trafficking by the zonulin pathway and its activation by intestinal mucosa-microbiota/gluten interactions. These functions dictate the switch from tolerance to immunity and are likely integral mechanisms involved in the pathogenesis of inflammatory and neoplastical processes.

T_H17- a new player in autoimmune diseases.

In the past autoimmune diseases were considered to be mainly associated with a balance shifted to increased T_H1 reactivity and reduced T_H2 reactivity (12).
Newer evidence suggests a crucial role of T_H17 in the ongoing process of autoimmune diseases (13). $CD4^+$ T_H17 -cells are naïve cells and need a contact with the antigen to differentiate. After contact with the antigen, in most cases intra-cellular antigens, differentiated T_H17 induce specific antibody production to the respective antigen. They also have strong chemotactic properties for neutrophils and monocytes, not eosinophils. This means they attract phagocytes to the inflamed tissue and initiate the destruction of the formed immune complex by phagocytosis Th17 cells are active as well in the gut mucosa as well as in peripheral tissue affected by auto-immune reactions.
It is believed that a suppression of Treg cells, necessary for oral and self-tolerance by the induction of TGF-β and Il-10 may play a major role in autoimmune diseases, as well as in food allergy. (14). Reduced T_{reg} and T_H3 reactivity may also lead to increased gut permeability and influx of antigens.

Two possible theories to explain the role of these antibodies in the development of auto-immune diseases:

1. ***Antigen mimicry:***
   This approach assumes that certain peptide sequences from food, such as milk and gluten are similar or share common structures with human molecules or human tissue. So, antibodies produced against milk proteins or gluten may also bind to these structures. Known structures are human islet cell tissue, human aquaporin and myelin oligodendrocyte glycoprotein.(15) Consequently, these reactions could lead to Diabetes Type 1, neuromyelitis optica or multiple sclerosis.
   Vojdani (16) could show that antibodies to gliadin could cross-react with both, human tissue and other foods. This may explain why celiac patients being on a strict gluten free diet still experience celiac disease symptoms or do not improve their symptoms.
   Works of *Severance et al* (17) have proven that IgG antibodies to food can pass the blood-brain-barrier.
   Hadjivassiliou et al (18) could show that antibodies to gluten could also fix to Purkinje cells in the brain in cases of gluten induced ataxia. In this way antigen mimicry could enable food to be responsible for ongoing inflammation and active destruction of sensitized tissues.

Gluten as a major player inducing auto-immune disease

Significant immune reactivity with

- cow s milk,
- milk chocolate,
- milk butyrophilin,
- whey protein,
- casein,
- yeast,
- oats,
- corn,
- millet,
- Instant coffee
- rice.

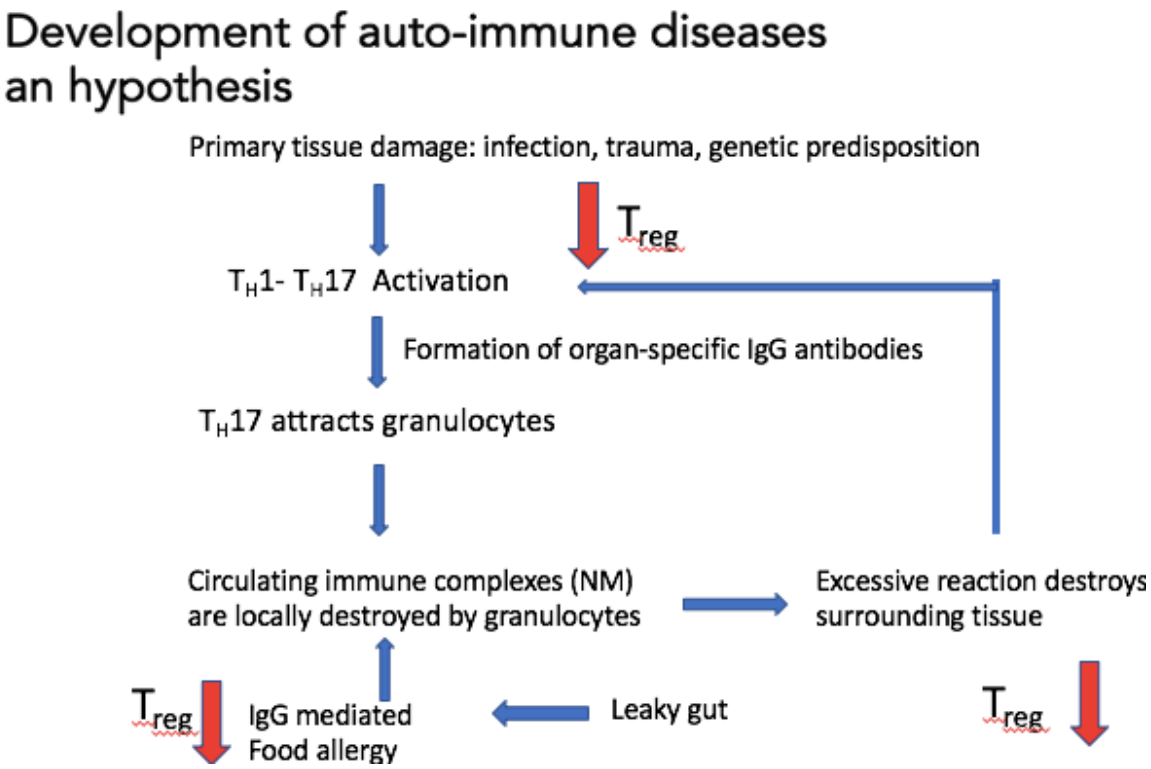
- cross-reactivity between -gliadin antibody and different tissue antigens:
- asialoganglioside,
- hepatocyte,
- GAD-65,
- adrenal 21-hydroxylase (adrenal),
- myelin basic protein (MBP), cerebellar,
- osteocyte,
- synapsin
- myocardial peptide,
- ovarian peptide,
- thyroid peroxidase (0.41).
- testes peptide,
- islet cell antigen,
- parietal and intrinsic factor

Cross-Reaction between Gliadin and Different Food and Tissue Antigens
Aristo Vojdani, Igal Tarash *Food and Nutrition Sciences*, 2013, 4, 20-32

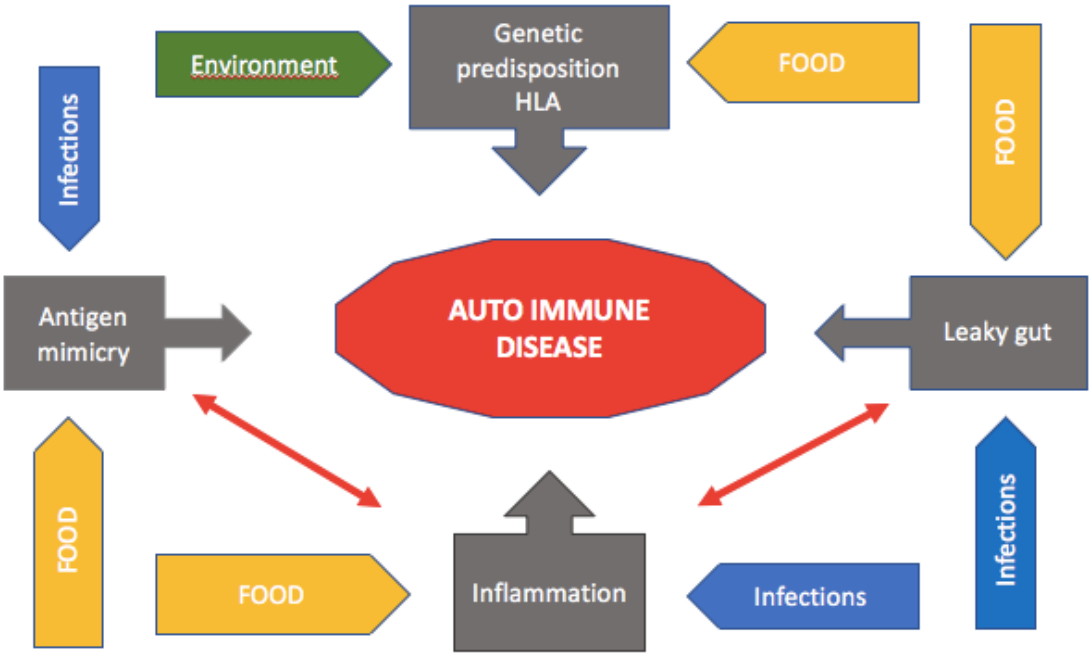
2. ***Active destruction of cell integrity***

Circulating IgG food immune complexes may fix to sensitized tissue and are destroyed by phagocytes locally. This induces cell damage to the tissue and provokes a washout of intra-cellular components, which activates T_H17. T_H17-$CD4^+$cells will attract further granulocytes and lead to the production of auto-immunes antibodies directed against these intra-cellular structures. Most of the autoimmune antibodies found are directed against intra cellular targets. Normally these structures are not present outside of the cells, so why should the immune system produce antibodies against them, if there is no contact. A cell going thru apoptosis or programmed cell death will not lead to immune response against intra-cellular particles. Only when these particles or molecules are liberated to the blood stream by active destruction of the cell by infections (19), trauma or any other circumstances the immune system would respond and initiate the production of antibodies. Food immune complexes would then fix to these tissues and continue damaging the tissue, even when the original cause have long disappeared. This way food hypersensitivity could maintain local inflammation, thus leading to auto-immune diseases. Lacking T_{reg} activity would further enable T_H17 to produces auto-antibodies.

Which tissue is affected may again depend on various aspects, eventually again genetic predispositions.



Another interesting candidate to strengthen this hypothesis is anti-Saccharomyces cerevisiae or baker's/brewer's yeast. ASCA (anti-Saccharomyces cerevisiae antibodies) are long being used as a marker for Crohn's disease (20), strange enough that Crohn's disease patients are still recommended to eat yeast containing foods. But ASCA is also found to be linked to other immune diseases like antiphospholipid syndrome, systemic lupus erythematosus, type 1 diabetes mellitus, and rheumatoid arthritis.
Rinaldi M.et al. (21) could identify overlaps with common autoantigens ranging from 50-100%. The autoantigen U2 snRNP B″ was found to conserve a superfamily protein domain that shares 83 % of the S. cerevisiae mannan sequence. Furthermore, ASCAs may be present years before the diagnosis of some associated autoimmune diseases as they were retrospectively found in the preserved blood samples of soldiers who became affected by Crohn's disease years later. This means that antibodies recognizing Yeast could also recognize certain tissues.



Food allergy type III- What is the link to auto-immune diseases?

Autoimmunity is a multifactorial process in which genetic, immunological, environmental and hormonal factors play in concert, together representing what was termed years ago the 'mosaic of autoimmunity'(22,23).
Part of the environmental factors are food. Given the high degree of cross reactivity of food antibodies to human cell structures, it seems evident that the food triggering these antibodies should be avoided!
Several researchers could show the implication of casein as well as gluten in recent onset psychosis and schizophrenia (24, 25, 26) and bipolar disorders (27). There is also evidence that food hypersensitivities may play a role in Sjögren syndrome (28, 29). Increased incidence of autoimmune disorders as a late complication in children with early onset dermatitis and/or milk allergy (30).
Higher titers of anti-Saccharomyces cerevisiae antibodies IgA and IgG are associated with more aggressive phenotypes (31). But not only Saccharomyces cerevisiae is important in Crohn's disease. In a double-blind cross-over study, Bentz et al (32) could demonstrate the beneficial effect of an IgG guided diet determined by the Imupro test on Crohn's disease symptoms, such as reduced defecation, reduced abdominal pain, improved general well-being. In contrast Üzunismail et al (33) could induce Crohn's disease symptoms, both histologically and clinically by challenging Crohn's disease patients in remission with only 3 IgG positive foods (Imuprotest). Significant increase in faecal calprotectin, white blood cells and CRP demonstrated the pro-inflammatory action of the ingestion of IgG positive foods. Other studies (34,35) could show that high salt intake, sodium chloride, can drive autoimmune disease by the activation or induction of pathogenic 17 cells, thus promoting auto-immune diseases.

In house data showed a reduction of ANA (anti-nuclear antibodies) in patients with Lupus after the elimination of IgG positive foods, as well as the reduction of anti-TPO in cases of Hashimoto disease, going in hand with the improvement of the clinical picture.
Studies showing the detrimental effect of the sensitization to food in cases of asthma are supported by yet unpublished data showing a marked improvement of FEV1 in patients with asthma after a 3-week avoidance of IgG positive foods determined by the Imupro test. Indeed, an average increase of 20% of the initial forced expired volume (FEV1) and an increase of 100% of FEV1 after a bronchodilator shot could be observed after 3 weeks. Clinical picture of COPD also improved significantly.

Conclusion

Auto-immune diseases are complex diseases with in most cases a genetic predisposition triggered by external factors like stress, environmental agents, drugs, leaky gut, infections and food. Auto-immune diseases are linked to decreased oral tolerance associated with reduced Treg and T_H3. Furthermore, activation of T_H17 plays an essential role in maintaining inflammation in the concerned tissues.
Food is probably not the inducer of the disease, but may play an important role in maintaining and aggravating the progression of the disease, either by antigen mimicry or active contribution to tissue damage, or both. Hypersensitivity to food mediated by pro-inflammatory IgG (IgG1-IgG3) and not IgG4, is responsible for ongoing inflammation and destruction of the targeted tissue. Antigen mimicry of food antigens and tissue surface proteins, may aggravate the situation.
Therefore, it is important to identify the pro-inflammatory foods by the determination of specific IgG to food and eliminate these foods from the diet for a prolonged time, to reduce the inflammatory burden, to enable the body to eliminate the respective antibodies, and to repair the tissue.

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