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Review

Interaction between food antigens and the immune system: Association with autoimmune disorders

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ABSTRACT

It has been shown that environmental factors such as infections, chemicals, and diet play a major role in autoimmune diseases; however, relatively little attention has been given to food components as the most prevalent modifiers of these afflictions. This review summarizes the current body of knowledge related to different mechanisms and associations between food proteins/peptides and autoimmune disorders. The primary factor controlling food-related immune reactions is the oral tolerance mechanism. The failure of oral tolerance triggers immune reactivity against dietary antigens, which may initiate or exacerbate autoimmune disease when the food antigen shares homology with human tissue antigens. Because the conformational fit between food antigens and a host's self-determinants has been determined for only a few food proteins, we examined evidence related to the reaction of affinity-purified disease-specific antibody with different food antigens. We also studied the reaction of monoclonal or polyclonal tissue-specific antibodies with various food antigens and the reaction of food-specific antibodies with human tissue antigens. Examining the assembled information, we postulated that chemical modification of food proteins by different toxicants in food may result in immune reaction against modified food proteins that cross-react with tissue antigens, resulting in autoimmune reactivity. Because we are what our microbiome eats, food can change the gut commensals, and toxins can breach the gut barrier, penetrating into different organs where they can initiate autoimmune response. Conversely, there are also foods and supplements that help maintain oral tolerance and microbiome homeostasis. Understanding the potential link between specific food consumption and autoimmunity in humans may lay the foundation for further research about the proper diet in the prevention of autoimmune diseases.

1. Introduction

Autoimmune disease has seen a significant worldwide increase in the past few decades. Evidence continues to accumulate indicating that there is a close interactive relationship between genetic factors and environmental triggers such as food, toxic chemicals and infections in the pathogenesis of autoimmune diseases. The mechanisms for the induction of autoimmunity by environmental factors have been variously described as involving molecular mimicry or cross-reactivity, aberrant cell death, or the formation of neoantigens through the binding of toxicants to self-tissue proteins [1–3]. In this regard, there is a significant emphasis on the role of infectious pathogens in autoimmunity [4]. This may be due to an article that aroused great interest in 1962 about the cross-reaction between *Streptococcus* and heart tissue as the cause of rheumatic fever [5]. In any case, infections are used as examples of well-known and accepted causes of autoimmune disorders such as Guillain-Barré syndrome (GBS), type 1 diabetes (T1D) or multiple sclerosis (MS) [6–10].

In comparison with infections, the role of diet in autoimmunity has been relatively overlooked, although a great many instances linking food and autoimmunity have been reported. Patients with rheumatoid arthritis (RA) report not only an association between food intake and the severity of their symptoms, but also elevated serum IgG, IgA and IgM antibodies against food proteins such as milk, wheat, eggs, fish, pork, lectins and agglutinins [11–15]. Studies indicate that lifestyle choices such as adopting the Mediterranean diet appear to have beneficial effects for RA sufferers [16,17]. Interestingly, across 27 countries the incidence of MS correlated strongly (r^2 = 0.795) with the consumption of cow's milk [18]. Polyradiculoneuropathy, a normally slow-developing autoimmune neurologic disease, was thought to have been

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induced after only 4 weeks of exposure in abattoir workers by the aerosolized neural antigens coming from the pig brains they processed, thereby indicating that environmental exposure to food antigens via aerosol can induce similar autoimmune reactions as ingestion of food antigens [19]. A very recent systemic analysis of commonly consumed foods implicated in autoimmunity, such as meats, fish, soybean and grains, found hundreds of peptide epitopes that share homology with human tissue antigen [20]. Using a systematic data-driven approach, this study found that among the 14 different categories of foods that were tested, pig contained disproportionately more shared sequences with almost 70 unique human MS epitopes in different tissues from blood to kidney, thyroid and central nervous system [20]. One possible explanation is that the exposure of the immune system to exogenous molecules with a sufficiently similar structure either breaks tolerance to self-antigens or activates pre-existing but inactive immune system cells. These findings indicate that the interaction between diet and autoimmune disorders is much more extensive than earlier thought and lays the foundation for future studies to find the still undiscovered food peptide epitopes that are also implicated in the pathogenesis and progression of autoimmune diseases.

2. Oral tolerance failure

In the event of a breakdown in the oral tolerance mechanism, autoimmune diseases can be initiated or exacerbated by dietary proteins and peptides, especially those such as pig and others that share homology with human tissue antigens [20–23]. Oral tolerance is established a few months after birth upon the interaction of orally administered food antigens with the immune system in the gut, leading to the generation of food antigen-specific regulatory $CD4^+CD25^+$ cells. Oral tolerance established by Tregs is crucial to the body's health and immune system because it prevents inflammatory reactions towards necessary foods and elements while permitting the immune system to target and destroy pathogens and unwanted antigens.

Immunity and oral tolerance both start developing in the womb, but important tolerance development events can continue to occur throughout a person's life. Modern food production exposes consumers to chemicals and environmental toxins that assault the immune system, causing a failure in the oral tolerance mechanism, opening the barriers, and causing intestinal permeability to food antigens. This inflammation and gut permeability allows undigested food proteins and commensal bacteria or their toxins to enter the blood stream and be presented to the immune system. In this situation, Tregs may become dysregulated, thereby disrupting immune homeostasis and exacerbating inflammation, resulting in the loss of oral tolerance. These events and many other factors can affect a pregnant mother's health and immune system, can also affect the child in the womb (Fig. 1), and can affect adults throughout their lifetime. Therefore, the loss of oral tolerance against food peptide epitopes that share homology with human tissue proteins can result in food immune reactivity and autoimmunity [24–27].

3. Molecular mimicry between food antigens and human tissue

Molecular mimicry is defined as amino acid (AA) sequence similarity between foreign (food) and self peptides that is sufficient to result in the cross-activation of autoreactive T and B cells, and the production of antibodies that react with both foreign and self peptides. Molecular mimicry-based food immune reactivity occurs when a food protein or peptide has a sequence of amino acids that is significantly similar to the structure of a person's own tissue. Normally if the gut barriers are somehow breached and undigested food proteins are able to enter the circulatory system, the body's immune system will mount a response in the form of defensive antibodies against those food proteins. However, if the AA peptide sequence of the food particle is sufficiently similar to the structure of a human self-tissue, the immune system will also produce antibodies against the body's own tissue, resulting in autoreactivity and eventually autoimmune disease.

During the past decades, significant progress has been made in the search for peptide epitopes in food antigens that share similarities with autoantigens that are involved in autoimmune diseases. Milk, wheat, plant aquaporins, serpin from legumes, glycine-rich food proteins, glucans, pectins, shrimp tropomyosin, *Saccharomyces cerevisiae* and pork are some examples of foods that share a significant homology with different human tissue proteins [20,28–45]. The mechanisms for these molecular similarities and many others that are discussed elsewhere in this article are summarized in Fig. 2.

3.1. Molecular mimicry and glycosylphosphatidylinositols

It has been proposed that the glycosylphosphatidylinositols (GPI) initially present on some surface glycoproteins of *S. cerevisiae* participate in a transglycosylation reaction in which the glycoprotein becomes cross-linked to cell wall β-glucan. Several of the genes in the GPI sequence have been identified, and AA sequence similarity has been found in most yeast and mammalian GPI assembly proteins [29]. This similarity between *S. cerevisiae* AA sequences and human phosphatidylinositol *N*-acetylglucosaminyltransferase subunit P (PIG-P) implies that if the tolerance mechanism in an individual fails and the immune system reacts to yeast antigens, the resulting antibodies may attack the corresponding self-tissue, resulting in autoimmunity.

3.2. Molecular mimicry and gluten

Gluten has been linked to celiac disease (CD) and non-celiac gluten sensitivity (NCGS). Patients with CD have an immune system that may react to a wide range of peptides. Patients with NCGS and Crohn's disease react to a repertoire of wheat antigens, producing IgG and IgA antibodies against them [34]. Continued and untreated exposure to wheat brings about a worsening of NCGS and CD, and can lead to autoimmunity. In another of our previous studies [46], we examined the possible mechanisms behind autoimmune reaction to nervous system antigens in children with autism. We tested 50 autism patients and 50 controls and found that there was peptide sequence similarity between the wheat protein gliadin antibody (EQVPLVQQ) and cerebellar neural tissue antibody (EDVPLLED). We concluded that in a subgroup of autism patients, antibodies may be produced against both Purkinje cells and gliadin peptides, and that this may be responsible for some of the neurological symptoms of autism.

3.3. Molecular mimicry and milk

Despite the widespread acceptance of cow's milk as an essential part of child and adult nutrition, cow's milk is actually one of the most common foods that causes immune reactivity, affecting infants, children and adults. From an immunological perspective, it is critical to consider that cow's milk is a mucosal secretion from another species. The principal antigenic components of cow's milk are α-casein, β-casein, κ-casein, butyrophilin and β-lactoglobulin. The strong antigenicity of cow's milk means that drinking it early in life may compound the risks for developing autoimmune disorders such as Behçet's disease, celiac disease, Crohn's disease, MS, systemic lupus erythematosus (SLE), T1D, and uveitis in susceptible patients [29–31,33]. In almost all of these disorders, significantly higher levels of IgG and IgA antibodies against milk proteins are detected in disease sufferers compared to controls [47].

Molecular mimicry between cow's milk proteins and the islets of Langerhans cell proteins has been studied as one possible mechanism for the development of type 1 diabetes from the consumption of cow's milk [46]. Molecular mimicry between the milk protein αS2-casein and retinal S-antigen has also been identified as the cause of uveitis [36]. Molecular mimicry between the milk fat globule membrane called butyropholin (BTN) and the neural protein myelin oligodendrocyte

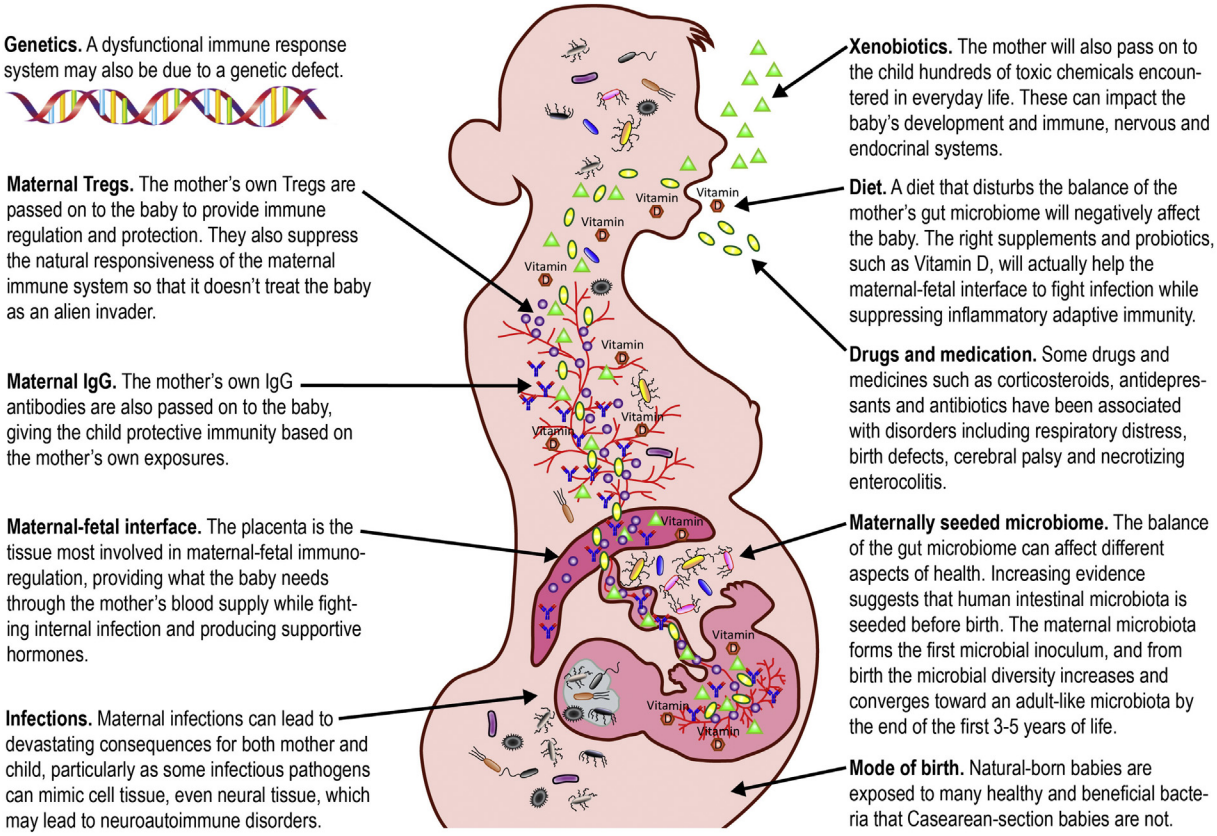

Fig. 1. Diet can affect immunity in the womb. Immunity and tolerance begin developing in the womb. The mother's diet and other factors can disrupt the homeostasis of her microbiome, affecting the immune system of both herself and her baby.

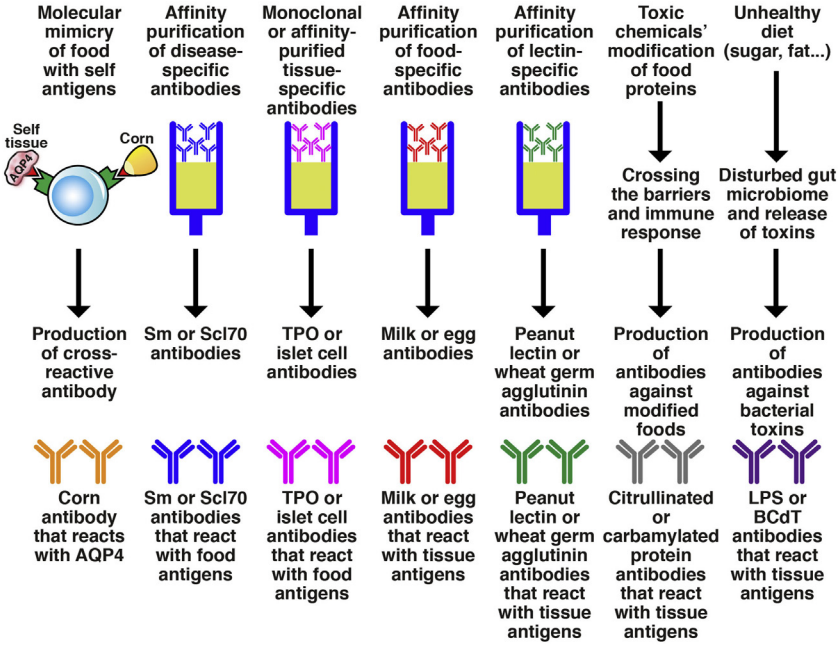

Fig. 2. Possible involvement of food antigens in different autoimmune diseases by the induction of cross-reactive antibody production and their reaction with different tissue antigens.

glycoprotein (MOG) may also be the mechanism for cow's milk causing MS, as multiple studies in the US, Europe, Japan and South Africa have shown a correlation between MS and cow's milk consumption [31,33,35].

3.4. Molecular mimicry and aquaporin

Aquaporin-4 (AQP4) is the predominant water channel in the central nervous system (CNS). It belongs to the aquaporin family of integral membrane proteins that conduct water through the cell membrane, and

is expressed in ependymocytes, endothelial cells, and astrocyte foot processes at the blood-brain barriers (BBB), but not in neurons. It can also be found in the epithelial cells of many organs, including sensory organs, throughout the body. In the brain it is believed to be involved in maintaining homeostasis and water exchange, electrical activity, and modulation of neuronal transmission and excitability. Aquaporins found in plant food sources are highly stable through food preparation, and may therefore reach the gastrointestinal system as intact proteins or peptides. Should the body's immunological tolerance fail, systemic aquaporins from foods may become antigenic, resulting in the production of anti-aquaporin.

Human aquaporin shows similarity with food aquaporins such as soy, corn, spinach, tomato, and with the legume serine proteinase inhibitors (serpins) found in beans, lentils, peas, peanuts, lupin, alfalfa and clover [37,38]. Therefore, human AQP4 may cross-react with these food aquaporins and serpins, leading to immune reactivity and the production of autoantibodies against human tissue aquaporins as well. If these antibodies cross the BBB in susceptible individuals, it could result in neuromyelitis optica (NMO) or Devic's disease, a severe neuroautoimmune inflammatory disorder that ultimately results in paralysis and sensory loss. Seventy-five percent of NMO cases are associated with the development of IgG1 antibodies that bind exclusively to AQP4 [49,50]. These IgG1 antibodies are produced in the blood, and when the BBB is compromised they are able to reach the AQP4 in the CNS. This can result in complications ranging from mild sensory disturbances to sensory impairment, paraplegia bladder-bowel dysfunction, and more [37,50,51].

3.5. Molecular mimicry and glycine-rich food proteins

Glycine-rich food proteins (GRPs) are found in meat, chicken, egg, fruits, vegetables, seeds, cereals, rice, soy protein and gelatin. Molecular mimicry and cross-reactivity between the GRPs from such foods and human collagen, keratin, actin, and ribonuclear protein exists, and thus can contribute to autoimmunity. Epitopes are the part of the peptide sequence recognized by |the immune system. The presence and repetition of these epitopes among divergent proteins may initiate or amplify an immune response. Thus, epitopes from different foods rich in GRPs can give rise to various autoimmune disorders, including RA, SLE, MS, T1D, and mixed connective tissue disease (MCTD), demonstrating a possible link between food antigens, gut mucosa and systemic immune response [43].

3.6. Molecular mimicry and tropomyosin

Tropomyosin (TM) is a protein found in the actin filaments in muscles that wraps around actin and prevents myosin from grabbing it, preventing muscle contractions until the proper signal arrives. As an antigen it can be found quite commonly in fish and shellfish. Shrimp tropomyosin is a cytoskeletal microfilamental protein that regulates actin mechanics. Tilapia TM has been shown to have 53.5% homology with shrimp TM and 87.7% homology to human TM isoform 5. The function of TM in muscle is well defined, but its function in epithelial cells is still unclear. Studies involving autoantibodies against human TM indicate that cross-reactivity between dietary tropomyosins and human epithelial tropomyosin may be a cause of inflammatory bowel disorders (IBDs) [44,52].

3.7. Interactions between diet and autoimmune disorders

Previous studies have shown a strong causal relationship between exposure to aerosolized pig antigen and neurological autoimmunity [19,53]. In the same vein, a very recent, very extensive study investigated the interaction between diet and autoimmune disorders, coining the term “immunodietica” [20]. This new term refers to the study of how the immune system reacts against food components and produces antibodies that react with human tissue, resulting in autoimmunity. The researchers analyzed shared epitopes in red meats (cow, sheep, goat, pig), poultry (chicken, turkey, duck), fish (tilapia, salmon), and grains (rice, quinoa, soybean, rye, wheat) in relation to autoimmune disease. Based on a very special index that reflected the similarity between the analyzed food and human autoimmune epitopes, red meat scored the highest, poultry and fish were intermediate, and grains scored the lowest. They then examined the relative similarity of the 14 chosen dietary epitopes and cross-referenced each organism's hit with 77 different autoimmune diseases. Overall, red meat scored between 8023 and 8524 hits, poultry and fish between 2762 and 4075 hits, and grains from 59 to 497 hits. Next, they isolated unique hits per food category and found that the number of unique disease-specific epitopes appeared in pigs 10–15 times higher than in any other tested organism. The diseases that shared unique epitopes with pig were MS, RA, autoimmune disease of the eyes, ears, nose and throat, Behçet's syndrome, and systemic autoimmune disease. These unique epitopes in pig were derived from proteins expressed in nervous tissue, such as MBP, MOG, myelin associated glycoprotein (MAG), proteolipid protein, AQP4, glial fibrillary acidic protein (GFAP), tubulin, and transaldolase [20]. Interestingly, 67 unique MS epitopes and 3 NMO epitopes were found in pig. Furthermore, pig epitopes matching MS epitopes such as MBP or MAG were derived not only from proteins expressed in the nervous system, but also in skeletal muscle, stomach, kidney, liver, heart, lung, and more. Additionally, some pig MS epitopes were found in ubiquitous proteins which are involved in basic metabolism. Aside from pig, cow was found to share unique epitopes with 5 different autoimmune diseases: GBS, demyelinating polyneuropathy, RA, antiphospholipid syndrome, and vitiligo [20]. These findings uncover a new link between autoimmune diseases in humans and the consumption of foods, i.e., pork and beef, etc. This lays the foundation for the importance of diet in the pathogenesis, progression, or even prevention of autoimmune diseases.

This amino acid sequence similarity between different food antigens and human tissue is summarized in Table 1.

4. Reaction of sera from patients with autoimmune disease with food antigens

Currently complete information about the possible cross-reactivity of every single food antigen with every human tissue is not available due to the limitless varieties of foods to test. Scientists, however, have devised a clever method for determining the involvement of foods in autoimmune diseases involving affinity purification of disease-specific serum with the disease-specific target antigen. Subsequent reaction of this disease-specific antibody with food antigens identifies the food antigens that cross-react with the disease-specific human tissue antigen. In one particular case, serum from lupus patients with high levels of antibody against small nuclear ribonucleoprotein (Sm) were passed through a column containing the Sm antigen. This affinity-purified anti-Sm antibody was then applied to many food antigens using ELISA assay. Of the numerous foods tested, the Sm antibody reacted strongly with soy, carrot, spinach and corn antigens [54]. This implies that these food antigens play a role in the production of anti-Sm antibody and may be involved in the etiology of lupus.

In a similar study involving patients suffering from scleroderma, the patients' sera were purified to homogeneity through a column containing Scl-70 and tested for reactivity to many food antigens. The Scl-70 affinity-purified antibody reacted strongly with the plant DNA topoisomerase or enzymes in wheat germ, peas, spinach and corn. The inflammation of the esophagus experienced by scleroderma patients may be connected to the throat's exposure to these four foods [55]. With triggering foods identified, clinicians can help their patients with disease-specific food avoidance protocols that could become part of their comprehensive treatment for autoimmune diseases, such as lupus, scleroderma, and possibly others.

Table 1
Sequence of food epitopes that share similarity with human tissue.

Food epitope	Tissue epitope	References
S. cerevisiae LTPPLDSLSTVTDAGGQL	Human PIG-P STSPLDSIHTITDNYAKN	[29]
Gliadin PQLQPQNPSQQQPQEQVPLVQQ	Human Cerebellar FLEDVPWLEDVDFLEDVPLLED	[34,46]
β-Casein Peptide GEIVESLSSSEESITR	Islet Cell Autoantigen GQQIGILISLEEENQR	[48]
αS2-Casein SEESAEVATEE	Retinal S-Antigen ELTSSEVATEV	[36]
BTN APFDVIGPQEPILAVVGEDAELPCRLSP	MOG GQFRVIGPRHPIRALVGDEVELPCRISP	[31,33]
Soy AQP4 FDGASMNPAVSFGPAVVSWTWSNHWV*	Human AQP4 YTGASMNPARSFGPAVIMGNWENHWI	[38]
Legume Serpin IMSAFEGVW	AQP4 N-Terminus IMVAFKGVW	[38]
Glycine rich food proteins GGYGDGGAHGGGYGG	Procollagen YDTYGGGRRGKGYKG	[43]
	hnRNP A2 GGYGGGPGYGNQGGG	
	Epidermal Keratin GGYGSGGGSGGRYGS	
Shrimp Tropomyosin DLDQVQESLLKFLAEEADRK	Human Tropomyosin DELDKYSKALKHIAEEADRK	[44,52]
Pig MBP ASQKRPSQRHGSKY	Human MBP ASQKRPSQRHGSKYLATAST	[20]
Pig AQP4 MVAFKGVWTQAFWKA	Human AQP4 MVAFKGVWTQAFWKA	[20]
Pig S100B AMVALIDVFHQYSGR	Human S100B MSELEKAMVALIDVFHQYSGR	[20]
Pig MOG ITVGLVFLCLQYRLRGKLRAE	Human MOG ITVGLVFLCLQYRLRGKLRAE	[20]
Pig GAD-65 AATHQDIDFLIEEIERLGQDL	Human GAD-65 AATHQDIDFLIEEIERLGQDL	[20]
Pig TPO AAGTACLPFY RSSAACGTGD	Human TPO AAGTACLPFY RSSAACGTGD	[20]
NFL Light LEQQNKVLEAELLVLRQKHS	Human NFL LEQQNKVLEAELLVLRQKHS	[20]

* Corn, spinach and tomato showed almost similar degree of cross reactivity with human aquaporin.

5. Reaction of tissue-specific antibody with food antigens

5.1. Thyroid

Another way of showing cross-reactivity between human tissue and food is affinity purification of a patient's serum with a target tissue antigen, followed by measuring its reactivity with different food antigens. Many different antigens have already been shown to specifically cross-react with thyroid tissue, triggering thyroid autoimmunity. The list of pathogenic organisms (viral, bacterial, fungal, spirochete, and protozoan antibodies) that may be involved in tissue-specific thyroid autoimmunity through molecular mimicry has become a growing field of study. In contrast, relatively little research has focused on the cross-reactivity of food protein antibodies with thyroid-specific antigens. There is existing research literature about gluten and endocrine autoimmunity, but the available information is limited about other dietary proteins and how they may affect thyroid function [56–58]. For this reason, in one of our studies [59] we applied monoclonal antibody made against T3 to 204 different food antigens and found 53 food proteins that reacted with this antibody: avocado, latex hevein, lemon and lime, orange juice, cooked Brussels sprouts, baked white potato, seaweed, radish, roasted almond, raw and roasted Brazil nut, cashew, roasted cashew, cashew vicilin, raw and roasted macadamia nut, mustard seeds, roasted peanut, peanut butter, raw and roasted pistachio, soy bean agglutinin, gluten-free soy sauce, tofu, roasted sunflower seeds, gelatin, cooked egg yolk, raw salmon, cooked tilapia, raw tuna, cooked tuna, cooked clam, cooked scallops, cooked squid, cooked shrimp, cow's milk, casein, sesame, hemp, rye, barley, kamut, buckwheat, sorghum, millet, spelt, amaranth, quinoa, yeast, oats, corn, and rice [59]. Of these 53 foods, 18 showed low reactivity, 16 moderate reactivity, and 19 showed high immune reactivity.

Similar to what we did with T3, we used monoclonal antibody against T4 and found 32 different food proteins that directly demonstrated immune reactivity with thyroxine antibody. These foods were avocado, lemon and lime, cooked Brussels sprouts, seaweed, cooked zucchini, raw almond, roasted almond, cooked black bean, raw and roasted Brazil nut, cashew, roasted cashew, cashew vicilin, raw and roasted hazelnut, raw and roasted macadamia nut, mustard seed, roasted peanut, peanut butter, raw and roasted pistachio, gluten-free soy sauce, tofu, gelatin, cooked egg yolk, raw salmon, cooked tilapia, raw tuna, cooked tuna, cooked clam, cooked scallops, cooked squid, cooked shrimp, amaranth and oats. In this case, the monoclonal antibody resulted in low reactivity with 7 foods, moderate reactivity with 7 foods, and high immune reactivity with 18 food antigens. Interestingly, anti-thyroglobulin and anti-deiodinase reacted with only one food each, while anti-TSHR, anti-thyroid binding globulin, and anti-TPO did not react at all with any of the 204 food items used in this study [59]. Because this immunoreactivity study was done in the laboratory, we are not certain if the consumption of potentially reactive food proteins alone would suffice to induce an inflammatory response on thyroid axis target sites. One should consider other possible contributing factors, such as inactive digestive enzymes in the face of oral tolerance breakdown, enhanced gut permeability to large molecules, composition of the gut microbiota, and a high salt diet. These, by themselves or in some combination, may increase the chances of developing immune reactivity to food and cross-reactivity with target tissue antigens [22,23,60–64].

5.2. Reaction of monoclonal antibody to pancreatic target sites with food antigens

It has been well-established that insulin, insulin receptors, islet cell antigen 2 (IA2), glutamic acid decarboxylase 65 (GAD-65), zinc transporter 8 (ZnT8) and the immune response against them all play significant roles in the pathophysiology of type 1 diabetes [64]. Antibodies reactive with islet cells are associated with T1D, and are considered early markers for the disease [65]. The antigen IA2, which was formerly called islet cell antigen 512, is a common tyrosine phosphatase-related autoantigen that is located in the insulin secretory granule membrane in beta cells [66]. ZnT8 is the most consistent zinc transporter expressed by beta cells, and has been found as an autoantigen in a high percentage of new-onset T1D patients [67,68]. Autoantibodies and T-cell responses against ZnT8 are produced in patients that develop autoimmune diabetes. Glutamic acid decarboxylase (GAD) exists in two isoforms (GAD-65 and GAD-67); both are found in pancreatic tissue, and both support the neuroendocrine modulation of insulin release [68–70].

We used ELISA to measure the immune reactivity of either target-specific monoclonal or polyclonal antibodies, insulin receptor alpha (IR-A), insulin receptor beta (IR-B), ZnT8, IA2, GAD-65 and GAD-67 antibodies against 204 commonly consumed food items. The results are discussed below.

5.2.1. Islet cell antigen 2 (IA2)

When we reacted monoclonal antibody made against IA2 with the 204 foods, 27 dietary proteins exhibited immune reactivity with specific target IA2 monoclonal antibody. Seaweed, guar gum and apricot were the most reactive (5+ on the scale), followed by pea lectin, spinach, cooked white and brown rice, cooked garlic, zucchini and

mackerel (3+), then by egg yolk, garbanzo bean, carrageenan, soy bean agglutinin, bell pepper and mint (2+), and then finally by cooked lima bean, gluten-free soy sauce, tofu, and mustard seed (1+). The reactions of rice, apple, melon, watermelon, clam, cooked cod, cooked halibut and cilantro were insignificant.

5.2.2. Zinc transporter 8 (ZnT8)

The antibody produced against ZnT8 reacted with 30 dietary proteins. Seaweed, cooked lentil and pea protein were the most reactive (5+), followed by guar gum, wheat, peanut oleosin and cooked pea (4+), garbanzo bean, soy bean oleosin, roasted peanut and cooked tilapia (3+), egg yolk, cooked lima bean, mustard seed, clam, goat's milk, roasted almond, cashew vicilin, tomato, cooked yam and sweet potato, banana and kiwi (2+), then, least of all, gluten-free soy sauce, tofu, pea lectin, spinach, carrageenan, macadamia nut, cherry and salmon (1+).

5.2.3. Insulin receptor (IR-A, IR-B)

While we did not find any reaction between insulin antibody and the tested food antigens, we did find that antibody specifically against insulin receptor alpha (IR-A) reacted with 8 dietary proteins: milk butyrophilin was the strongest (5+), followed by potato and amaranth (3+), then quinoa and tapioca (2+), and finally buckwheat, hemp and kamut (1+).

5.2.4. Glutamic acid decarboxylase 65 (GAD-65)

Polyclonal antibody produced against GAD-65 reacted with 9 dietary proteins: buckwheat, amaranth, rice, corn and yeast (3+), followed by potato, quinoa and oats (2+), then finally, tapioca (1+).

Many of the individual proteins in these groups may seem to have a low glycemic index or have insignificant scores. It is best to be cautionary, as the consumption of what may seem to be safe foods by a sensitive or predisposed individual may still trigger immune reactions or autoimmunity. Immune reactivity may develop if the gut immune system suffers a breakdown in its oral tolerance mechanism.

The early identification of potential immunoreactive food triggers may be of great aid to practitioners in designing protocols to reduce inflammatory sequelae and the progression of the disease process in susceptible, sensitive subgroups [65,71–74].

5.3. Immune reaction between antibody to amyloid beta peptide and food antigens

Amyloid-β (amyloid-beta, Aβ, Abeta, beta-amyloid) denotes peptides of the 36–43 amino acid sequence. It is a key protein that is considered one of the main components or inducers of the built-up plaque that is the characteristic feature of the brains of patients with Alzheimer's disease (AD). Amyloid-beta protein has many tetrapeptide sequences that are shared by a large number of foods, suggesting that cross-reactivity could have a role in AD [75]. We identified 10 dietary proteins that exhibited immune-reactivity with anti-amyloid-beta peptide 1–42 antibody: canned tuna was the most reactive (5+), followed by lentil lectin, hazelnut, squid, casein, and gluten and non-gluten proteins (4+), then egg yolk and pea protein (3+), and finally, pea lectin and cashew vicilin (2+) [76].

This indicates that certain undigested food proteins and the antibodies produced against them have a potential role in AD. It is important to consider that dietary proteins have no impact on antigenic-antibody models if properly digested. However, other factors, such as cellular immunity, immunological tolerance, human leukocyte antigen (HLA) allele and more are involved with pathogenic immune reactions to dietary proteins. Thus, the binding of antibodies to antigens may not always be pathogenic, but the ability of specific monoclonal and polyclonal antibodies to bind with purified proteins indicates that there is a potential for immunological cross-reactivity in a subgroup of susceptible individuals. Finally, the threat of these foods and their antibodies that cross-react with amyloid-beta should be considered in the context of their ability to transverse the circulatory system and cross the BBB to reach the brain tissue, where their homology with amyloid-beta peptide sequences may play a role in the development of Alzheimer's disease and other neurodegenerative disorders [77].

6. Reaction of food-specific antibody with human tissue

In studying the possible interaction between dietary components and the immune system, significant progress has been made in the theory that similarities between food antigens or peptides and autoantigens might be responsible for the induction of autoimmune diseases [2,42,78–82]. Following inciting events, the loss of oral, peripheral and central tolerance may result in the production of IgG, IgM or IgA antibodies against undigested food antigens and peptides [2].

In addition to antibodies, this autoimmune response is carried out by T-cell clones which are primed to be specific to particular food antigen epitopes that may arise in the gut mucosa. However, these primed T-cell clones may travel to particular sites, such as the joints, where they may proliferate in response to epitopes in the sequences of the joint's synovial proteins that are homologous with the epitopes of the priming food antigens. This causes local inflammation and the upregulation of major histocompatibility complex molecules (MHC) [82]. The resulting release of additional self-antigens and/or epitope spreading may generate a chronic self-perpetuating cycle of organ inflammation and cell destruction, leading to autoimmunity [79].

Because wheat, milk, corn, soy, egg and peanuts are among the most common sources of food allergens, in our very recent study [83], we applied affinity-purified anti-food antibody derived from these 6 foods to 65 different tissue antigens using ELISA. The data presented in Fig. 3A shows that the strongest reactions observed for wheat antibody were, in descending order, alpha-enolase, TPO, intrinsic factor, E-cadherin, and beta-NGF. An additional 10 tissue antigens reacted to a lesser degree, while 50 others were low or insignificant. In comparison to anti-wheat reaction with wheat antigens with an OD of 3.8 or 100%, this percent reactivity with alpha-enolase was 65.8%, with TPO 60%, with intrinsic factor 44.7%, with E-cadherin 36.8%, and with beta-NGF 34%.

Interestingly, when wheat antibody was replaced with α-gliadin 33-mer peptide, the number of tissue antigens that reacted with α-gliadin antibody increased to 20, in comparison to 15 with wheat antibody. Fig. 3B shows that anti-alpha-gliadin reacted very strongly with somatotropin with an index of 3.2 (82%) of anti-alpha-gliadin binding to alpha-gliadin, followed by elastin (index of 2.8 or 72%), α-myosin (index of 1.98 or 50%), hepatocyte and tyrosinase (index of 1.86 and 1.85 respectively, or 47%), intrinsic factor and insulin + islet cell (index of 1.6 or 41%), and 13 additional tissue antigens with reactivity ranging from ODs of 0.52 and 0.9 to 13.6 and 23% of anti-alpha-gliadin antibody binding to gliadin. This indicates that immunization with a single protein or peptide, such as purified alpha-gliadin 33-mer or wheat extract, results in more reactive antibodies than an administration of a mixture of antigens.

With regards to milk, although it has been shown that different milk components share homology with MOG, and the prevalence of MS has repeatedly been associated by epidemiological studies with dietary factors, including the consumption of milk and dairy products [31,82–85], analysis of our data showed a curiously low reaction (indices between 0.5 and 0.76) between milk antibody and neuronal antigens such as MOG and MBP. But this reaction to milk antibody was very strong with ASCA + ANCA (index of 3.1 or 84%), strong with hepatocytes (index 1.7 or 46%), with TPO and somatotropin (index 1.5 or 41%), and finally with α-enolase (index 1.4 or 38%) as shown in Fig. 3C. This lower reactivity between anti-milk antibodies with MOG could be related to the nature of antibodies used in our study. Instead of using antibodies made against pure components of milk such as BTN, alpha-, beta-or kappa-casein, we used whole milk for immunization.

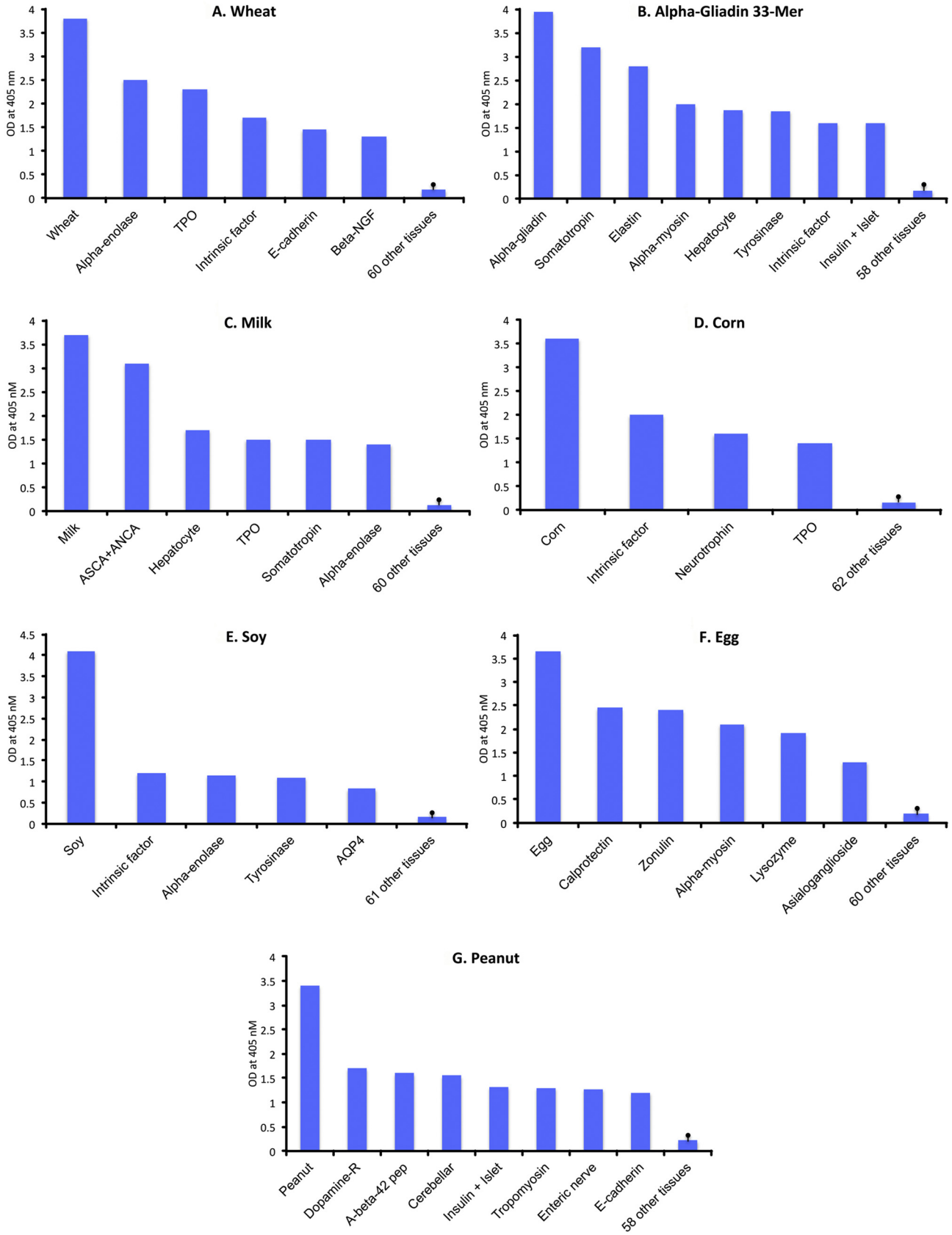

Fig. 3. Reaction of different food antibodies with different tissue antigens. Antibodies reacting with specific foods were tested against 65 different tissue antigens. For each food tested, only the tissues with the highest reactivity are shown in descending order.

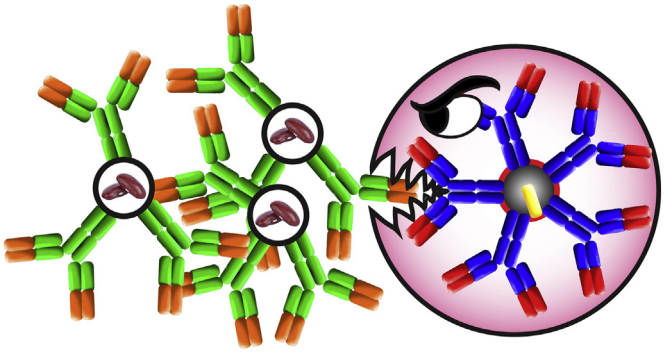

Fig. 4. Lectins bind to IgG, causing IgG aggregation and the formation of IgM anti-IgG antibodies known as rheumatoid factor (RF).

Still, the reaction of anti-milk antibodies with so many previously unnoticed tissue antigens may indicate that milk proteins do play a broader role in autoimmunity. Overall, milk-specific antibody reacted with 14 different tissue antigens with indices ranging from 0.5 (13.5%) for tyrosinase to an ASCA + ANCA index of 3.1 (84%) of anti-milk reaction with milk, and with the remaining 51 tissue antigens the reactions were low or insignificant.

The anti-corn antibody reacted with only 10 out of 65 tissue antigens. The lowest, but still significant reaction of anti-corn was with MBP with an index of 0.5 (13.9% of maximum reactivity); the highest reaction was with intrinsic factor with an index of 2.0 (55.5%), followed by neurotrophin with an index of 1.6 (44%), and then TPO with index of 1.3 (36%) (Fig. 3D).

Anti-soy antibody also reacted with only 10 out of 65 tissue antigens, but the strength of the reaction was low as well. For example, anti-soy reaction with alpha-myosin resulted in an index of 0.51 (12.4%), and the highest among the 10 tissues that reacted with anti-soy antibody was intrinsic factor with an index of only 1.2 (29.2%), followed by alpha-enolase (index 1.15, 28%) tyrosinase (index 1.1, 26.8%) and then AQP4 (index 0.83, 20.2%) as shown in Fig. 3E.

Anti-egg antibody reactions ranged from low to strong with 17 out of 65 tissue antigens, with the indices ranging from 0.6 to 2.45. In comparison to anti-egg reaction with egg antigens, the reaction was strongest with calprotectin, zonulin, alpha-myosin, lysozyme and asialoganglioside, with indices 2.45, 2.4, 2.1, 1.9 and 1.3, or 67, 66, 58, 52 and 36% of maximum immunoreactivity respectively. With the other 12 tissue antigens the indices ranged from 0.6–1.1. Reactivity with the other 48 tissue antigens in reaction with anti-egg antibody was insignificant (Fig. 3F).

Anti-peanut antibody reacted with 24 out of 65 tested tissue antigens, with the highest reaction being with dopamine receptor with an index of 1.7 (50%), followed by amyloid-beta-42 peptide with an index of 1.6 (49%), and then cerebellar with an index of 1.55 (45%). Insulin + islet cell, tropomyosin and enteric nerve had lesser reactions with an index of about 1.3 (38%), while E-cadherin had an index of 1.2 (35%) as shown in Fig. 3G. With the other 17 tissue antigens the reaction ranged from low to moderate. For example, with asialoganglioside this reaction resulted in an index of 0.71 (21%).

This extensive immunoreactivity between food-specific antibodies and human tissue antigens indicates that commonly consumed foods may share peptide epitopes which may possibly be involved in human autoimmune diseases. More studies are needed on antibody cross-reactivity from foods that are consumed by different demographics. Furthermore, epidemiological studies are needed to determine whether associations exist between human tissue cross-reactive foods and certain autoimmune diseases that exist in the populations that consume these foods more often. Finally, other mechanistic studies are required to dissect the contribution of food antigens to the pathogenesis and magnitude of autoimmune diseases [20].

7. Reaction of lectin antibody with human tissue

Lectins and agglutinins are carbohydrate-binding proteins found in microorganisms, plants and animals. They perform important functions on many biological levels. Plants produce toxic lectins as a survival mechanism against insects, molds, fungi and diseases. They are contained in many common food plants and thus are a large part of our diet. Unfortunately, lectins are somewhat resistant to digestion, and humans need the proper enzymes in sufficient quantity to digest them. Undigested lectins that manage to penetrate the digestive barriers can have devastating effects on the body, including indigestion, nutritional deficiencies, intestinal damage, and leaky gut, the gateway to autoimmunity [86–90]. Both gut bacteria and epithelial cells carry receptors for different lectins. By binding to gut bacteria, dietary lectins can induce the release of endotoxins such as lipopolysaccharides (LPS). This increases gut permeability and allows the passage of lectins, food antigens, and bacterial toxins into the circulation.

Because of the high affinity between lectins/agglutinins and human tissue, lectins and agglutinins can potentially bind to a number of tissues throughout the human body, setting the stage for various autoimmune disorders. For example, lectins can bind to the islet cells of the pancreas, which can result in autoimmunity against the islet cells and then to T1D. Lectins can also bind to the major joint components glucosaminoglycans and proteoglycans, which may lead to rheumatic conditions. Lectin injected into mice induces lectin binding to IgG, followed by IgG aggregation and the forming of IgM anti-IgG or rheumatoid factor (RF), thus inducing RA (Fig. 4). Lectins can also bind to glomerular basement membrane, resulting in glomerulonephritis. Additionally, lectins can bind to human endometrium, spermatozoa and ova, resulting in an autoimmune reaction that could cause infertility in men or women [91–98].

We reacted 4 lectin-specific antibodies (WGA, PNA, SBA, PHA) with 62 different tissue antigens using ELISA methodology. Of the food antibodies, wheat germ agglutinin (WGA) was the most reactive with 37 out of 62 tissues, followed by both kidney bean (PHA) and soybean (SBA) with 20 out of 62, and peanut agglutinin (PNA) with 15 out of 62 (Fig. 5). A cellular and/or antibody attack against lectin-bound tissue antigens or tissue antigens that share homology with food and bacterial antigens can significantly enhance the risks of developing autoimmune reactivity and autoimmune disease [91,94,96–98].

7.1. Comparison of IgM antibodies against different lectins in samples negative or positive for RF

IgM antibodies against six different lectins were measured in 48 sera with normal levels and 48 sera with high levels of rheumatoid factor (RF). When a comparison was made between the levels of IgM antibody against these six lectins in RF-negative sera versus RF-positive sera, the IgM antibody level against all six lectins was much higher in the RF-positive group than in the RF-negative samples ($p < .0001$). These results also showed significant correlations between IgM antibodies and lectins with elevated RF. This IgM correlation in RF-positive samples was the most significant with lentil lectin IgM ($r = 0.81$), followed by pea lectin ($r = 0.66$), SBA ($r = 0.62$), PNA ($r = 0.56$), WGA ($r = 0.48$), and PHA ($r = 0.46$). When we tested for simultaneous elevation of lectin antibodies, we found that 22 out of 48 or 46% of samples with elevated RF also exhibited elevation of IgM antibody against all six lectins used in the study. The other specimens either did not react or reacted to some lectins but not to others.

The detection of lectin IgM antibodies in the blood supports the idea that undigested lectins and agglutinins can cross the gut barriers; Once in circulation, the lectins and agglutinins can then bind to IgG and form IgG aggregations, leading to the production of IgM anti-IgG autoantibodies. The correlation shown between higher levels of IgM anti bodies in patients positive for RF indicates an association or interaction between the two. This indicates that lectins or the antibodies produced

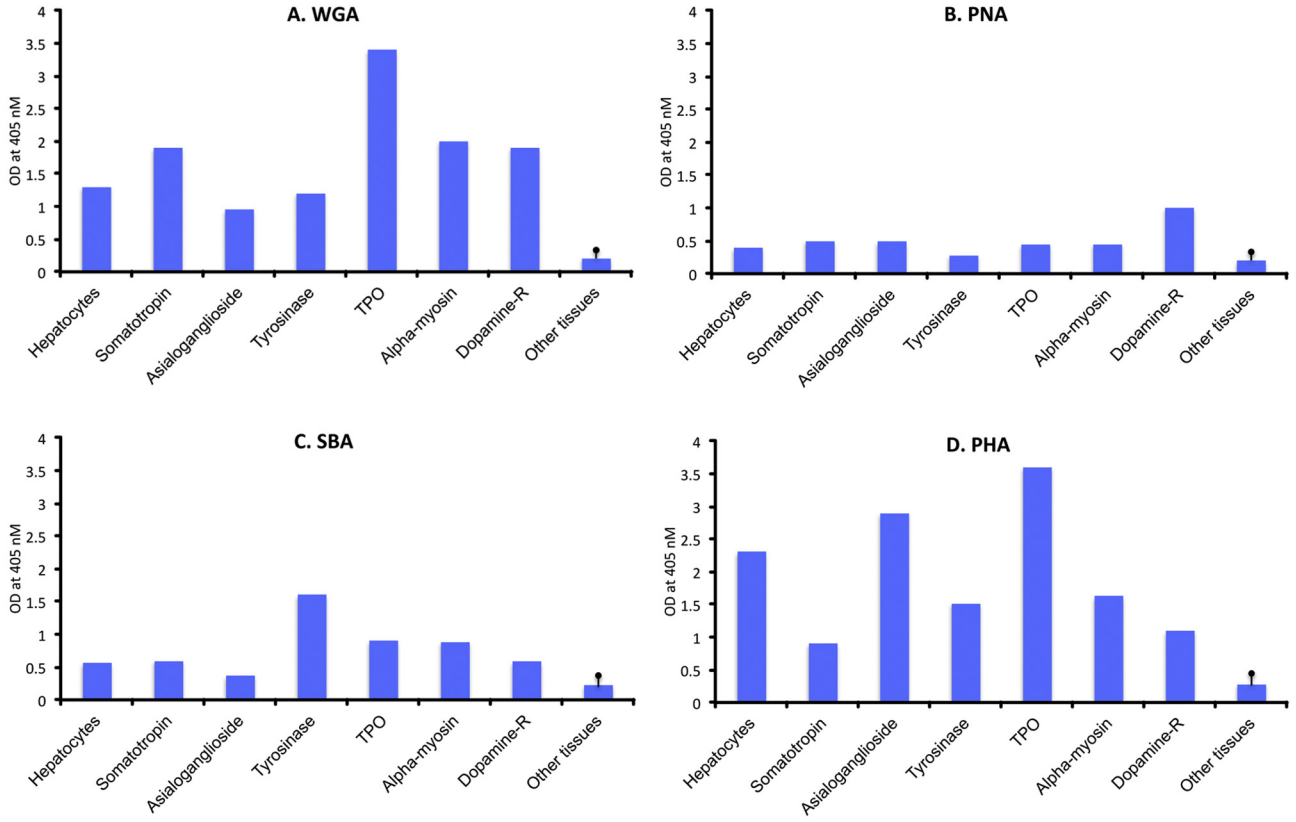

Fig. 5. Reaction of 4 lectin-specific antibodies with different tissue antigens using ELISA. Each anti-lectin antibody was tested for reactivity to 62 tissue antigens. WGA was the most reactive with 37 out of 62 tissues. Only a few representative tissue antigen reactions are shown for each lectin-specific antibody.

against them may be directly or indirectly involved in autoimmunity.

8. Protein modification and the production of cross-reacting antibodies

In addition to the many cross-reactive peptide epitopes present in commonly consumed foods that have been implicated in human autoimmune diseases, the modification of food proteins by environmental toxins and their similarity to proteins modified inside cells could be another mechanism for food-associated autoimmunity. For example, the application of fertilizers, pesticides, herbicides and xenobiotics in the air and water means that these substances and their metabolites can enter the food chain and form bound residues with food proteins and other macromolecules (Fig. 6). According to the IUPAC Commission on Agrochemicals and Environment, "A xenobiotic bound residue is a residue that is associated with one or more classes of endogenous macromolecules. It cannot be disassociated from the natural macromolecule using exhaustive extraction or digestion without significantly changing the nature of either the exocon or the associated endogenous macro macromolecules [99]."

The formation of bound residues can occur through a number of processes that result in the formation of covalent bonds or through physical encapsulation within the macromolecular matrix. It has also been observed that food processing may increase the proportion of a bound residue above that found in the raw agricultural commodity. For example, the proportion of bound residue from four major organophosphorus insecticides was found to be greater in bread and certain extrusion breakfast cereals than was originally observed in the raw grain [99].

It has been hypothesized that interaction between food proteins, carbohydrates, fats and pesticides may partially remove the insecticide and reduce the concentration of pesticide absorbed into the blood

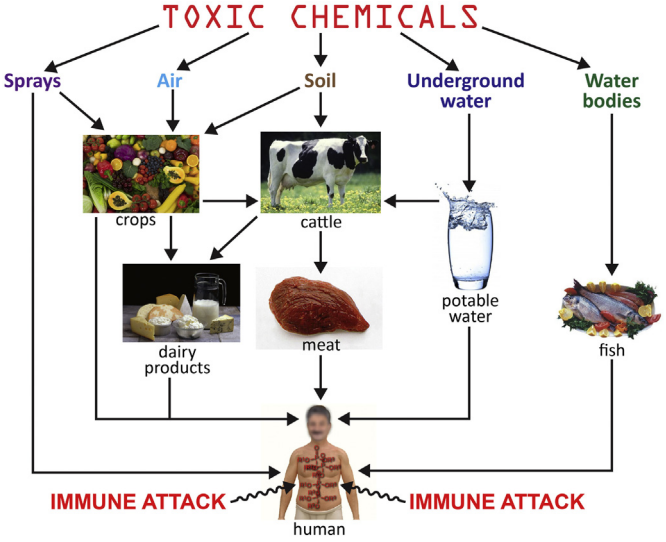

Fig. 6. How toxic chemicals get into food. Fertilizers, pesticides, herbicides and xenobiotics in the air, soil and water make their way into plant and animal foods and enter the body upon consumption.

[100]. If these food protein adducts are not digested properly, they may manage to enter the circulation, where they can be challenged by the immune system. Some researchers have concluded that even if pesticides manage to enter the blood, their binding to blood proteins such as albumin may decrease the concentration of these chemicals in the blood, consequently alleviating the intensity of their effect on the body [101–103]. However, these researchers are dismissing the basic principles of the immune function: that the formation of adducts or complexes between food proteins and xenobiotics and their entry into the

blood, in addition to the binding of haptenic chemicals to human tissue proteins, such as albumin, hemoglobin or actin, can initiate both cellular and humoral immune response against them, which may set the stage for autoimmune disease [104]. Therefore, this binding of pesticides to blood proteins may alleviate the corresponding toxicity [100–103], but in the process could enhance the process of autoimmunity.

8.1. Post-translational modification of proteins and the formation of adducts

In the field of autoimmunity, it is well-established that post-translational modification of proteins by citrullination, carbamylation, carbonylation, deamidation, glycation, oxidation or nitrosylation that results in neopeptides or proteins that are recognized by the immune system as non-self proteins, can induce the development of various autoimmune conditions [105–110]. Indeed, these protein modifications have been associated with a range of diseases, including MS, AD, RA, psoriasis, prion disease, liver fibrosis, chronic obstructive pulmonary disease (COPD), and cancers [111–113]. However, there is need for additional research on the associations between the consumption of foods that may contain similar modified proteins due to their exposure to environmental toxins and their relationship to the incidence of autoimmune diseases. For example, urea is used in many crops as fertilizer due to its conversion to ammonia and cyanate, which can react with lysine residues of peanuts, soy, corn, or other food proteins. The entry of these and other chemicals or their metabolites into the blood either directly or through food contamination can initiate this protein modification and antibody production against the modified protein, a process leading to autoimmunity [114]. It has been shown that about 3% of milk proteins formed adducts with chlorpyrifos that originated from the feed.

8.2. Glyphosate

Glyphosate is the active ingredient of the herbicide Roundup and many other products used for weed control. A 2017 study based in Germany involving 399 urine samples from adults not involved in agricultural work revealed glyphosate residues above the detection limit in the urine of 32% of the subjects [115]. This is despite the fact that a significant amount of the glyphosate binds to albumin and other tissue proteins, not only causing alterations in the proteins' secondary structure, but, as we've mentioned before, supposedly alleviating the detectable levels of glyphosate [101–103,116]. In addition, a remarkable correlation has been shown between the rising rate of glyphosate usage on corn and soy crops in the USA and an alarming rise in a number of different chronic diseases, including autoimmune disorders [117]. This is because glyphosate acts as a non-coding amino acid analogue of glycine, and thus could erroneously be incorporated into proteins in place of glycine, producing neo-antigens that could lead to autoimmune disease [118]. This study found support for this assertion when pigs and cattle were given glyphosate-contaminated feed; a significant amount of glyphosate was detected in the animals' collagen, the principle component of gelatin that contains very high levels of glycine [118].

8.3. Nanoparticles

In the past few decades, the production and biomedical application of nanomaterials have been on the rise. Nanoparticles are particles between 1 and 100 nm (nm) in size with a surrounding interfacial layer. They have a variety of commercial, industrial and even biomedical applications, such as controlled drug release. Most nanoparticles are prepared using nucleation material plus metals such as iron oxide, gold or platinum. Then porcine gelatin is added for the growth of maghemite thin film into porcine gelatin nuclei. The formed gelatin containing

Fig. 7. Nanoparticles. These are particles between 1 and 100 nm in size used for a variety of commercial, industrial, and medical/pharmaceutical applications.

nanoparticles are then coated with dextran followed by human serum albumin (HSA) to reduce its antigenicity (Fig. 7). Despite this, nanoparticles are recognized by the reticuloendothelial system, leading to the phagocytosis of foreign antigens and activation of B-2 cells, which results in the production of high-affinity antibodies that may lead to hypersentivity and autoimmunity. In addition, nanoparticles contribute to autoimmunity through the induction of protein citrullination [119]. In fact, previous studies have associated human exposure to environmentally presented nano-size and ultra-fine materials with various pathologic processes, such as chronic inflammation, pneumonia, COPD, and autoimmune conditions [114,120–122]. In a very elegant review article, Lerner and Matthias connected the increased use of industrial food additives to the rising incidence of autoimmune diseases [123]. They hypothesized that food additives such as nanoparticles, emulsifiers, organic solvents, extra salt and sugar, microbial transglutaminase (mTG) or gliadin cross-linked enzyme abrogate human epithelial barrier function, thus increasing intestinal permeability through the opened tight junction, resulting in the entry of foreign immunogenic antigens and activation of the autoimmune cascade [123,124].

8.4. Other environmental factors

In relation to specific autoimmune disease, there is growing scientific evidence that exposure to environmental factors such as cadmium, lead, mercury, antimony, crystalline silica and organic solvents correlate with the development of systemic sclerosis [125].

Finally, the interaction between genome and exposome in the development of autoimmune diseases should not be ignored. The exposome comprises the cumulative environmental influences on an individual and associated biological responses throughout one's lifespan. It has been shown that exposure to silica, smoking and exogenous hormones constitute environmental risk factors in systemic lupus erythematosus (SLE) [126].

To date, the scientific evidence continues to accumulate that environmental factors have a significant impact on the modulation and alteration of the genome by the exposome in different autoimmune diseases [126]. This supports the proposal that occupational and

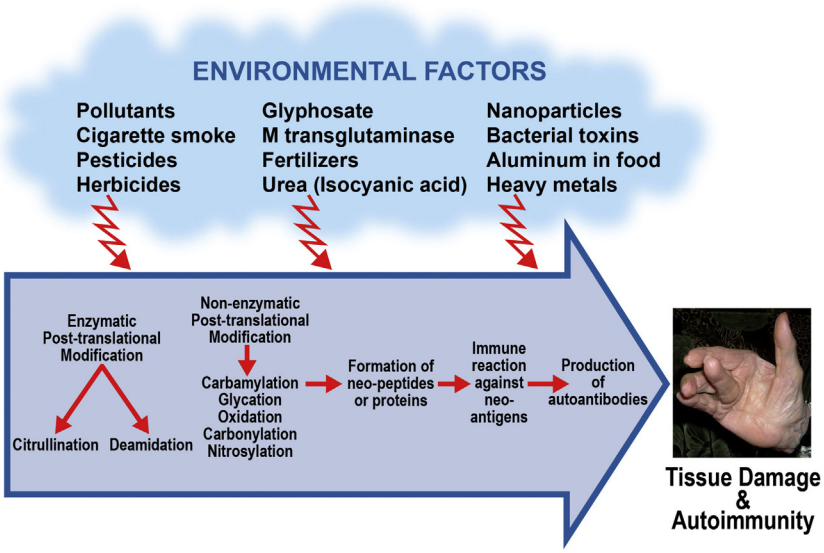

Fig. 8. The role of environmental factors in protein post-translational modification and their role in tissue damage and autoimmune diseases.*Modified from Marie* [125].

environmental exposure should be checked in all patients with autoimmune disease upon diagnosis. Fig. 8 shows this putative pathogenic mechanism of how enzymatic and non-enzymatic protein modification by environmental factors can result in neopeptides and proteins against which the body may mount immune responses, contributing to various autoimmune diseases. This identification of environmental and occupational toxic agents, whether in the surrounding environment or in food, will allow their removal or interruption, which may potentially result in the improvement of the autoimmune disease' outcome.

9. We are what our microbiome eats

In a microbiology laboratory, many types of growth media are used to grow and identify microbes. Nutrient agar, tryptic soy agar, egg yolk agar, potato agar, blood agar, and brain heart infusion agar are some examples of culture media. As these names show, microbes are choosy in their requirements for growth. Some like soy, some like potato or egg, and others may not grow unless blood or even brain proteins are added to the media. In essence, our gut environment, which contains about 4×10^{13} bacteria [127], is not that different from a microbiology lab. For example, the consumption of too much egg yolk encourages the growth of anaerobic bacteria, too much carbohydrates and sugar cause overgrowth of entrerobacteria, and too much potato may encourage the growth of fungi. Microbes have co-evolved with humans, depending on our diet for their survival, just as we depend on them for our well-being [128]. However, an unhealthy diet of saturated fats, high sodium diet, modified foods, sugar and corn syrup, and other bad heating habits can change this harmonious relationship, which may end with dysbiosis in the gut and the release of harmful bacterial toxins, such as lipopolysaccharides and bacterial cytolethal distending toxins. These bacterial toxins in the inflammatory environment can disrupt tight junction proteins and damage the enteric neurons through molecular mimicry. The breakdown of the barriers and tight junctions results in the release of self-tissue proteins and induces the production of antibodies in response to them. This breakdown facilitates the entry of different macromolecules, bacterial components and even the whole bacteria into the tissues, where they modulate the immune responses in a way that sets the stage for autoimmunity [129,130].

In support of this, very recently, researchers demonstrated that bacteria found in the small intestine of humans and mice can travel to different organs, where they trigger an autoimmune response. They discovered that *Enterococcus gallinarum*, an ordinary supposedly harmless gut bacterium, moved from the gut to the liver, spleen and lymph nodes in mice genetically prone to autoimmune disease. Once in these tissues, the bacteria induced production of autoantibodies that are biomarkers of autoimmunity [131]. Interestingly, they found this so-called harmless gut bacteria in the liver of patients with autoimmune liver disease and in patients with lupus, but not in healthy controls. Due to the molecular mimicry between these bacteria and human tissue antigens, T and B cells that attack proteins made by commensal bacteria may also attack the mimics of those proteins found in the human body.

Ro60 is an RNA binding protein found in the human body. Antibodies reacting with Ro60 are found in lupus patients and were shown to cross-react with *Propionibacterium propionicum* and *Bacteroides thetaiotaomicron*, which both share homology with Ro60. Filamin A (FLNA) is a widely distributed high molecular weight actin-binding protein that promotes orthogonal branching of actin filaments in non-muscle cells and links actin filaments to membrane glycoproteins. *Prevotella* spp. and *Butyricimona* spp. both share homology with FLNA. *Prevotella* spp. and *Parabacteroides* spp. both mimic *N*-acetylglucosamine-6-sulfatase, also known as glucosamine (*N*-acetyl)-6-sulfatase (GNS), an enzyme that is encoded by the human GNS gene. Antibodies against these bacteria are found in the blood and joint fluid of patients with RA but not in healthy controls. *Roseburia intestinalis*, which is prevalent in the human gut, cross-reacts with β2-glycoprotein, the antibody of which is found in patients with anti-phospholipid syndrome. T cells isolated from MS patients react to a component of *Akkermansia* spp. and *Prevotella* spp., as well as to the human enzyme guanosine diphosphate-L-fucose-synthase. Fusobacterial antigen, which mimics islet-specific glucose-6-phosphatase-related protein, activates the diabetogenic CD8 T cells that plays a role in the induction of T1D [132–137].

Identification of bacterial cross-reactive epitopes may guide researchers, some of whom suggest developing strategies for eliminating the microbiome that carries the autoimmune-associated mimicked protein (i.e., Ro60) in the earliest stage of the disease. Conversely, other researchers think that eliminating the microbiome is not the answer for treating autoimmune disorders, since resident bacteria have essential functions beyond their roles in the gut [135,138]. However, some immunologists believe that it is feasible to identify the specific bacterial triggers that cross-react with human tissue and either remove them or compete with them by using probiotics or prebiotics [131,132,135,139]. While there is as yet no clear vindication or resolution for these suggested strategies for treating autoimmune

diseases, we may need to consider a simpler method, and that is selective feeding of the microbiome using diet and nutrition. In this regard, evidence suggests that dietary factors, such as adhering to the Mediterranean diet with its increased consumption of fatty fish and reduced consumption of sugars, contributes towards reducing the risks of arthritis and osteoarthritis by enhancing the production of soluble mediators that are anti-inflammatory in nature [140–142].

As immunomodulatory agents, polyphenols are used for the management of different autoimmune disorders, such as ulcerative colitis, vitiligo, and MS. These natural products activate intracellular pathways that are involved in the regulation of immune response and induction of immune homeostasis [143]. Finally, regulators of the regulatory T cells in the gut, such as vitamins ABCD (retinoic acid, folic acid, ascorbic acid, 1,25-$(OH)_2D_3$), indole-3 carbinol, tryptophan, probiotics and others that maintain immune homeostasis in the gut and beyond, should also be considered as treatment options. These and many other factors that help regulate the $CD4^+CD25^+$ cells and maintain oral tolerance are reviewed in a chapter in this author's recent book [144–146].

10. Conclusions

Identification of dietary components that share epitopes with autoimmune diseases is extremely important for a subpopulation that is over-presented with incidences of those diseases. The study of the interaction between diet and autoimmune disorders which was very recently dubbed immunodietica [20] should not be limited to peptide epitopes from food that shares homology with human tissue, but should also investigate the reaction of affinity-purified sera from patients with different autoimmune disease with antigens from raw and modified foods. Immunodietica should also cover the study of the following:

1. Reaction of monoclonal or affinity-purified polyclonal antibodies made against different tissue antigens with raw and modified food antigens
2. Reaction of monoclonal or affinity-purified polyclonal antibodies made against different food proteins with human tissue antigens
3. Factors in the diet directly or indirectly involved in the post-translational modification of proteins, such as citrullination, glycation, oxidation and carbamylation, which are involved in various autoimmune diseases
4. The role in different autoimmune diseases of foods that contain lectins and agglutinins, and their possible binding to different tissues that carry lectin receptors
5. Finally, diet influences our microbiome. Certain foods can help maintain oral tolerance and a healthy digestive system, while detrimental foods can encourage the growth of harmful bacteria and lead to the release of bacterial toxins, weakening the gut barriers. By inducing gut permeability, the bacteria or their antigens can enter the circulation, where the immune reaction against them results in the production of antibodies. Because human tissue is mimicked by so many gut bacterial antigens, such as Ro60, FLN, GDP-L-fucose synthase, β2 glycoprotein 1, and *N*-acetylglucosamine-6-sulfatase, the antibodies and T cells reacting against the bacterial antigens may attack the bacteria-mimicking proteins found in the human tissue, and therefore trigger an autoimmune response

The avoidance of foods that contain autoimmune epitopes, or components that induce posttranslational modification of food proteins, or have the capacity to selectively change the gut microbiota, could improve symptoms in patients with the corresponding autoimmune disease.

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Declaration of Competing Interest

None.

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