HLA-Related Autoimmunity Whitepaper

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Introduction

Autoimmune diseases occur when the immune system fails to distinguish self from non-self, resulting in a breach of tolerance (1). The heterogenous group of diseases share common genetic risk factors and several pathophysiological mechanisms resulting in overlapping clinical manifestations which target specific organs or multiple organ systems, causing inflammation and tissue damage (2).

The immune system plays a key role in the defence against external pathogens, involving a multitude of diverse cell populations. The T and B lymphocytes are responsible for the innate and adaptive immune responses through regulated cell-cell interactions and secretion of cytokines, chemokines and other inflammatory mediators. The defence against external pathogens must occur without causing unnecessary harm to self. However, when the regulatory balance of the immune response is disturbed, autoimmunity follows (2).

Various genetic and environmental factors have been found to contribute to autoimmune disorders. In almost all patients presenting with an autoimmune disease, the prevalence is increased in first-degree relatives and is even higher in monozygotic twins (3). While an array of genes, involved in both the innate and adaptive immune response, have been linked to various autoimmune disease, one of the strongest associations has been with the major histocompatibility complex (MHC) region, on chromosome 6p21.3. This highly polymorphic, gene dense region displays strong linkage disequilibrium (4). The gene products of MHC are termed human leukocyte antigens (HLAs) and these play a pivotal role in the antigen presentation of self and non-self peptides and the regulation of innate and adaptive immune responses (5). The HLA profiles can influence autoimmunity risk or protection, by either binding pathogenic- or self-peptides more or less efficiently, resulting in the loss of tolerance (2). Various environmental factors, such as smoking, vitamin D deficiency and infections, have been implicated in the development of autoimmunity in genetically susceptible individuals, resulting in autoantigens. These antigens can be recognised by the immune system, triggering antibody production and the inflammatory process, resulting in the clinical manifestations of autoimmune diseases (6).

For the purposes of this HLA test, only those HLA-related disease phenotypes, most commonly seen in clinical practice, have been chosen and will be discussed below. There is compelling evidence confirming the association of HLA variants with these disease phenotypes.

Alopecia Areata

Description

Alopecia areata (AA) is one of the most prevalent autoimmune diseases. In AA, abnormal immune damage targeted to the hair follicle results in non-scarring hair loss that typically begins as patches, which can increase in size and progress to cover the entire scalp (alopecia totalis, AT) and body (alopecia universalis, AU) (7).

Genetics

Multiple lines of research, including the observed heritability in first-degree relatives, twin studies and family-based linkage studies have provided evidence supporting a genetic basis for AA. HLA-DR, a locus is found in the class II region of the human MHC, has been identified as a key etiologic driver of AA (7). A number of meta-analyses have been performed showing a significant increase in the *HLA-DRB1*04:01* and *HLA-DRB1*16* alleles in AA patients versus controls (7,8). Studies have also found protective HLA-DR alleles such as *HLA-DRB1*03*, *HLA-DRB1*09* and *HLA-DRB1*13* (8,9).

Pathogenesis

The pathogenesis underlying AA is complex. Anagen stage hair follicles (HFs) exhibit "immune privilege (IP)" from the level of the bulge downwards to the bulb. Both passive and active IP mechanisms protect HFs from physiologically undesired immune responses and limit immune surveillance. The normal anagen hair follicle expresses little or no MHC class I and no MHC class II molecules and is considered to be a site of relative local immune privilege. Collapse of this IP is a pre-requisite for the development of AA (10). This collapse can be induced by exogenous agents or inherent IP deficiencies which might confer increased susceptibility to AA for some individuals such as those with the HL-DRB risk alleles.

Several studies have found vitamin D deficiency as a risk factor for the development of AA, demonstrating significantly lower levels of vitamin D in the patients with AA than the control group (11,12). Vitamin D is known to significantly inhibit the production of interferon gamma (IFN-γ). Kokic et al. (2018) showed that lower levels of vitamin D are correlated with higher levels of IFN-γ, as much as 150% higher, in vitamin D deficient patients. These findings suggest that normally vitamin D might contribute to maintain the IP of HF by modulating the production of IFN-γ (13). In contrast, vitamin D

insufficiency might lead to over-secretion of IFN-γ and play a role in the collapse of IP, of the anagen hair bulb, due to the increased follicular expression of MHC class I and II molecules (14).

Vitamin D is known to exert its effect through the vitamin D receptors (VDR) which are present in skin-resident cells such as keratinocytes, dendritic cells, macrophages, B and T lymphocytes as well as epidermal keratinocytes and mesodermal dermal papilla cells. The two latter cell populations are present in the hair follicle. VDR is known for its importance in maintaining hair follicle integrity. Mutations in the VDR gene has been linked to familial 1,25-dihydroxyvitamin D-resistant rickets (HVDRR), which can be associated with alopecia (15). A study done by Daroach et al. (2018) found VDR expression to be reduced in all patients affected with AA versus the controls. In addition, they noted an inverse correlation of VDR expression with presence of inflammation but no correlation with serum Vitamin D levels, severity, pattern or duration of illness (16).

Improving outcomes

Since vitamin D plays a role in the pathogenesis of AA, it seems a reasonable therapeutic strategy to monitor serum 25(OH)D levels and introduce vitamin D supplementation in case of its deficiency or insufficiency in patients with AA (17,18). Vitamin D supplementation studies have shown beneficial effects of vitamin D on immune function, in particular in autoimmune diseases. There is currently no international consensus available on the optimal serum 25(OH)D levels for vitamin D supplementation, in particular on the safe upper level. While the tolerable upper daily limit given by the Endocrine Society is 10,000 IU, the more conservative Institute of Medicine (USA) considers a supplementation of up to 4000 IU/day to be safe. The European Food and Safety Authority currently recommends to stay below 4000 IU/day (100 μg) (19).

Treatment with calcipotriol 0.005% ointment (50 μg calcipotriol monohydrate/mL), a synthetic derivative of vitamin D, has shown promising results in a pilot study. Patches were treated twice daily with topical calcipotriol ointment or topical clobetasol, another topical corticosteroid ointment, for a period of 12 weeks. Calcipotriol showed greater and faster response rates than clobetasol. The latter showed a greater and faster tendency to relapse (20 weeks) versus patients treated with the topical vitamin D analogue (48 weeks) (20).

Ankylosing Spondylitis

Description

Ankylosing spondylitis (AS) is an immune-mediated inflammatory disease. The main symptom of AS is inflammatory spinal pain; with time, some patients develop spinal immobility as a result of the progressive ossification and fusion of the vertebral joints caused by inflammation (21). The pathology mainly affects the entheses, where ligaments, tendons and capsules are attached to the bone. It is important to note that patients with AS have an increased risk of developing inflammatory bowel disease, acute anterior uveitis, and psoriasis. They are also prone to cardiovascular disease and pulmonary complications (22).

Genetics

AS was the first rheumatic disease to be linked with an HLA locus (namely HLA-B27) and the association with HLA is stronger than in any other rheumatic diseases. *HLA-B27* is an allele of the HLA-B locus in the class I region of human major histocompatibility complex (MHC). In most populations of the world, *HLA-B27* is present in >90% of patients with AS, but in <10% of the general population. However, of the *HLA-B27*-positive individuals in the general population, only 5% develop AS. Hence, additional genes must be involved. To add to the complexity of the association, *HLA-B27* is not a single allele: it is a family of alleles with at least 60 subtypes. All these subtypes evolve from a parent allele designated the *B*27:05* allele (23). The subtypes are distributed unevenly among different geographical locations. The common ones (*B*27:05*, *B*27:04*, *B*27:02*, *B*27:07*) are associated with AS (24,25). The subtypes *B*27:06* and *B*27:09*, which are found in Southeast Asia and Sardinia, respectively, are much less common in patients with AS and could potentially play a protective role against AS (26).

Pathogenesis

The main natural function of HLA-B27 is to form a complex with β2 microglobulin which can bind short antigenic peptides such as those derived from intracellular microorganisms. Following presentation at the cell surface, the complexes are specifically recognised by cytotoxic lymphocytes which then kill the infected cell (27).

Due to the peptide-presenting function of HLA-B27 and other HLA molecules, one of the most popular hypotheses is the arthritogenic peptide theory or molecular mimicry hypotheses which states the

following: Normally, the host develops immunity to viruses by generating T-cell receptors (TCRs) specific for viral peptides carried by host HLA molecules. To prevent autoimmunity, the host is usually tolerant to peptides that are derived from self-proteins. It is, however, possible that tolerance to a self-peptide will be lost if an infectious pathogen activates the immune system through a pathogen-derived peptide that mimics the self-peptide (28,29).

In support of this theory, onset of AS is often preceded by infection with enteropathic pathogens (such as *Klebsiella pneumoniae*). HLA-B27-restricted cytotoxic T lymphocytes (CTLs) have been identified in the synovial fluid of AS patients, which recognise both bacterial epitopes and self-peptides (30). Moreover, two allelic variants of HLA-B27 (*HLA-B*27:06* and *HLA-B*27:09*), which are not associated with AS, contain polymorphisms ideally placed to alter the presented peptide repertoire. Absolute binding preferences do not explain disease association. However, quantitative changes in peptide presentation between disease-associated and non-associated subtypes may be relevant for disease pathogenesis by exceeding (or falling below) a threshold required for the activation of autoreactive T cells and thus for the onset of autoimmunity. A study has identified 26 peptides, which are presented in lower abundance by *HLA-B*27:06* and *HLA-B*27:09* compared with disease-associated HLA-B27 subtypes. Although these differences were observed to be very subtle, these 26 peptides might encompass the sought-after arthritogenic peptide(s) (31).

Serum vitamin D levels have been found associated with a risk of developing AS. Meta-analysis data found that there is a consistent and inverse relationship between 25-hydroxy vitamin D3 [25(OH)D] levels and AS activity (32). Osteopenia and osteoporosis are well-known complications of AS. Vitamin D is an important hormone that regulates osteoblast activity in osteocalcin synthesis. Altered vitamin D levels can suppress adaptive immunity by down-regulating antigen presenting cells and shifting the balance of helper T cells from Th1 to Th2 and T regulatory cells. The proliferation of T cells could exacerbate the inflammation, which in turn causes bone loss and leads to osteopenia and osteoporosis (19,32,33).

The main biological functions of vitamin D are mediated by its effect on binding to the nuclear vitamin D receptor (VDR). Therefore one must keep in mind that mutations in the VDR may also be associated with AS susceptibility (32).

Improving outcomes

Klebsiella has been linked to the development of AS. It appears that starch is the main source of *Klebsiella* growth in the colon. Increased consumption of starch-containing foods, by genetically

susceptible individuals, such as those possessing HLA-B27 genes could result in the initiation and development of AS. In conjunction with medical therapeutic measures to manage patients with AS, a low starch diet should also be recommended (34). This includes decreasing the intake of the following starch containing foods: bread and biscuits, pasta, rice and potatoes while increasing the intake meat, fish, milk and milk products, eggs, vegetables and fruits.

Vitamin D supplementation studies have shown beneficial effects of vitamin D on immune function, in particular, in autoimmune diseases. There is currently no international consensus available on the optimal serum 25-hydroxyvitamin D [25(OH)D] levels for vitamin D supplementation, in particular, on the safe upper level. While the tolerable upper daily limit given by the Endocrine Society is 10,000 IU, the more conservative Institute of Medicine (USA) considers a supplementation of up to 4000 IU/day to be safe. The European Food and Safety Authority currently recommends to stay below 4000 IU/day (100 µg) (19).

Non-pharmacological interventions are one of the mainstream treatment options for AS patients. This includes education, measures regarding joint protection, posture and rest, therapeutic exercise, physical therapy modalities, orthoses and acupuncture. A key component in the rehabilitation of patients with AS is therapeutic exercise which has been shown to reduce pain, maintain mobility, improve posture, increase aerobic capacity and improve quality of life (35).

Coeliac Disease

Description

Coeliac disease (CD) is a multi-organ, autoimmune disorder, affecting the small bowel and is triggered by gluten ingestion, in genetically susceptible individuals (36). It is one of the more common autoimmune disorders, affecting around 1% of the general population (37). Clinical manifestation of CD may present as classical or non-classical, extra-intestinal symptoms, while some individuals remain asymptomatic. Classical symptoms include those of malabsorption such as diarrhoea, steatorrhea, weight loss or growth failure, whereas non-classical symptoms present as iron-deficiency anaemia, neurological symptoms such as ataxia, dermatitis herpetiformis, dental enamel hypoplasia and low bone mineral density (38). Certain individuals are known to be at higher risk for developing CD, including those with Down syndrome, type 1 diabetes, autoimmune thyroid disease, an IgA deficiency, or with a first degree relative diagnosed with CD (38). Most patients respond well to treatment with a gluten-free diet (GFD), however, unrecognised or untreated CD is associated with increased mortality and risk for intestinal lymphoma (37).

Genetics

HLA-DQ is a class II molecule, of the MHC, that is responsible for binding peptides produced by the exogenous pathway. HLA-DQ is composed of an αβ chain, encoded by *HLA-DQA1* and *HLA-DQB1* genes respectively, which is a cell surface receptor located on antigen-presenting cells (APCs) (39).

Genome-wide association studies have identified more than 100 non-HLA-related genes associated with CD (38), however, the specific role of the *HLA-DQA1* and *HLA-DQB1* genes in the presentation of gluten peptides as antigens makes the MHC-HLA locus the most important genetic factor in the development of CD (36). In fact, being a carrier of two specific MHC class II molecules, called DQ2 and DQ8, is almost necessary in order to develop CD during one's lifetime, with research confirming that 95% of all CD patients are carriers of either the HLA DQ2 or DQ8 genotype or a combination thereof (40).

Specific HLA alleles confer varying degrees of risk for developing CD. The highest risk is represented by the HLA DQ2.5 homozygous genotype, which is determined by those who carry the *HLA-DQA1*05* (α-chain) and *HLA-DQB1*02* (β-chain) alleles on both respective loci (41), followed by the HLA DQ2.5 heterozygous genotype (42). It should be noted that HLA DQ2.5 homozygous individuals are associated with having earlier disease onset and a more severe disease phenotype, including greater

villous atrophy, lower haemoglobin at presentation, a slower rate of villous healing on a gluten-free diet, as well as a higher rate of complicated (refractory) CD (42). HLA-DQ8, encoded by *HLA-DQA1*03* and *HLA-DQB1*03:02*, contributes a moderate risk (42), and the HLA-DQ2.2 variant alone, encoded by the *HLA-DQA1*02* and *HLA-DQB1*02* alleles imparts a lower risk for CD. Lastly, *HLA-DQA1*05* and *HLA-DQB1*03:01*, without *HLA-DQB1*02* is associated with a low risk for developing CD (43). Importantly, if none of the abovementioned alleles are present, then CD as a diagnosis can be ruled out, emphasising the use of HLA testing for its high negative predictive value (44).

Pathogenesis

CD is triggered, in genetically susceptible individuals, by the ingestion of gliadin, a component of gluten (found in wheat), as well as other prolamins found in barley, rye and oats (39). Although approximately 30% of the world population carries HLA DQ2 or DQ8 risk alleles, the prevalence of CD is only 1-3%, thus other genetic and environmental factors such as female sex, a pro-autoimmune genetic background, viral infections, an inappropriate adaptive immune response and an imbalanced gut microbiome, may also play a role (45).

There are several mechanisms by which gliadin peptides exert damaging effects on the system:

1. They are resistant to gastrointestinal enzymes,
2. They have amino acid sequences that are specific for HLA-DQ2 and DQ8,
3. Gliadin proteins have preferred glutamine residues for tissue transglutaminase (tTG)-mediated deamidation and
4. These proteins affect intestinal permeability (40)

There are two gliadin amino acid sequences that are resistant to gastrointestinal enzymes, namely the 33-mer (P55–87) and the 25-mer (P31–55) and are thus well-suited substrates for deamidation by tissue transglutaminase (TG2) (46).

During gluten consumption, human tissue transglutaminase (TG2), a calcium-dependent protein-glutamine γ-glutamyltransferase, is activated and catalyzes the deamidation of specific gluten peptides, converting them into negatively charged glutamic acid residues that have a high affinity for binding to HLA-DQA1 and -DQB1 susceptible molecules, leading to enhanced immunogenicity in CD (47). Another important consideration is the crosslinking between gluten peptides and TG2 itself as lysine donor, leading to the formation of TG2-gluten peptide complexes. These complexes are thought to activate B cells causing the secretion of anti-TG2 autoantibodies (anti-TG2 IgA, IgG or IgM) that serve as diagnostic markers for CD (47). Extraintestinal CD symptoms may be associated with

immunoglobulin A (IgA) deposits on extracellular TG2 in the liver, kidney, lymph nodes and muscles of CD patients (40).

The 33 mer contains overlapping T cell epitopes and its deamidated form is a potent T cell stimulator, generating the glutamic acid residues essential for binding to HLA-DQ2 and/or HLA-DQ8, inducing a potent adaptive Th1 pro-inflammatory response, whereby the HLA molecules on antigen presenting cells (APCs) present gluten peptides to CD4+ T cells, resulting in the typical small bowel lesion formation found in CD (39,40).

The 25 mer gliadin peptide (p31-43/55) has the potential to directly activate the innate immune response. Besides TG2 activation, this peptide also activates the NF-kB pathway and induces IL-15, a proinflammatory cytokine that promotes the adaptive immune response and leads to the development of villous atrophy and the major modulation of the small-intestinal mucosal biology as seen in CD (48).

The innate and adaptive immune responses to gluten peptides leads to increased intestinal permeability via the release of zonulin, with subsequent paracellular gliadin passage to the gut mucosa, leading to further alterations in the adaptive and immune response (40).

Improving outcomes

A gluten free diet (GFD) is the only effective treatment for CD (49). A gluten free diet entails strict avoidance of all products containing the prolamin proteins from wheat (gliadin), barley and rye, while pure oats appear to be safely tolerated by the majority of people with CD, oats should be introduced into the diet with caution and patients (49,50). Following a GFD under the guidance of a registered dietician who is familiar with CD is strongly advised (50). Evidence suggests that an earlier and more accurate CD diagnosis, with strict compliance to a GFD, is associated improved outcomes and healing of the small bowel (37,51).

Follow-up after initial diagnosis should occur within the first 6 to 12 months (49), that includes a thorough biochemical evaluation as well as assessment of compliance to the GFD. Screening for nutritional deficiencies, including iron, vitamin B12 and folate, should be conducted and managed accordingly. It is also important to monitor for CD-related complications including osteopenia (to be treated with supplements containing calcium and vitamin D) and osteoporosis (additional bisphosphonates should be considered). CD is often accompanied by other related autoimmune diseases and screening for these is advised (38).

Patients with refractory, or non-responsive CD should be evaluated carefully to identify and treat the specific aetiology in each patient and treatment with medication, as an adjunct to the GFD, as well as a FODMAP free diet, should be considered (37,49).

Graves' Disease

Description

Graves' disease (GD) is an organ-specific autoimmune disease, typically presenting in patients between the ages of 40 and 60 years. It is the commonest cause of hyperthyroidism, affecting 1.0 – 1.6% of the general population and results from a failure to maintain immune tolerance to thyroid antigens (52). In addition to affecting the thyroid, GD is also associated with goiter, ophthalmopathy and dermopathy (53).

Genetics

Twin studies have found that genetic factors contribute 79% to the likelihood of developing GD. While a number of genes have been identified to contribute to developing GD, such as *CTLA-4*, *TNF*, *TG* and *TSHR*, genes in the HLA region have shown to be the most significantly associated with GD (54–56).

The following HLA alleles have been identified as risk alleles for GD:

- *HLA-B*08* in the Caucasian population (55)
- *HLA-B*35:01* in the Japanese population (57)
- *HLA-B*46* in the Asian population (52)
- *HLA-B*46:01* in the Japanese population (57)
- *HLA-B*46:01* in the Han Chinese population (58)
- *HLA-C*07* in the Caucasian population (55)
- *HLA-DRB1*03* in the Caucasian population (59–61)
- *HLA-DRB1*08* in the Caucasian population (62)
- *HLA-DRB1*14:03* in the Japanese population (57)
- *HLA-DRB1*15:01* and *HLA-DRB1*16:02* in the Han Chinese population (58)
- *HLA-DRB3*02:02* in the Caucasian and African American populations (62,63)
    - Not currently reported on
- *HLA-DPB1*05:01* in the Han Chinese and Japanese populations (57,58)
- *HLA-DQA1*05* in the Caucasian (59)
- *HLA-DQA1*05:01* in the African American population (63)

It is interesting to note that inheritance of the *HLA-DRB1*03* risk allele is correlated with the highest susceptibility to GD in the Caucasian population (59–61) . This risk allele, together with *HLA-DRB1*08,* has also been associated with earlier onset of GD (younger than 30 years of age) (60,62). In contrast, *HLA-DRB3*02:02* has been associated with later onset of GD (62). Another interesting point to note is that a pilot study done by Vejrazkova et al. (2018) found the *DQA1**05 risk allele to be associated with recurrence of GD following treatment (61). A study done by Chen et al. (2011) found *HLA-DPB1*05:01* to be a major gene of GD in the Han Chinese population and singly accounts for 48.4% of population-attributable risk (58).

In addition, the following HLA alleles have been found to be protective in nature:

- *HLA-A*33:03* and *HLA-A**24:02 in the Japanese population (57)
- *HLA-B*07:02, HLA-B*44:03* and *HLA-B*52:01* in the Japanese population (57)
- *HLA-C*03* and *HLA-C*16* in the Caucasian population (55)
- *HLA-C*12:02* and *HLA-C*14:03* in the Japanese population (57)
- *HLA-DRB1*07* in the Caucasian population (59,62)
- *HLA-DRB1*01:01*, *HLA-DRB1*13:02* and *HLA-DRB1*15:02* in the Japanese population (57)
- *HLA-DQA1*02* in the Caucasian population (59)
- *HLA-DQB1*03:02* in the Han Chinese population (58)
- *HLA-DQB1*05:01* and *HLA-DQB1*06:04* in the Japanese population (57)
- *HLA-DPB1*04:01* and *HLA-DPB1*09:01* in the Japanese population (57)

In individuals possessing the *HLA-DRB1*07* allele and the *HLA-DRB1*03* risk allele, the protective effect of the *HLA-DRB1*07* allele appears to cancel out *HLA-DRB1*03* susceptibility (59).

It should be noted that all of the protective alleles, in the Japanese population, are components of the 3 most common HLA haplotypes in that population:

- *HLA-A*24:02*, *HLA-C*12:02*, *HLA-B*52:01*, *HLA-DRB1*15:02*, and *HLA-DPB1*09:01* are on the most common haplotype (designated as HP-1; *A*24:02- C*12:02-B*52:01-DRB1*15:02-DQB1*06:01-DPB1*09: 01*);
- *HLA-A*33:03*, *HLA-C*14:03*, *HLA-B*44:03*, *HLA-DRB1*13:02*, *HLA-DQB1*06:04*, and *HLA-DPB1*04:01* are on the second most common haplotype (designated as HP-2; *A*33:03-C*14:03-B*44:03-DRB1*13:02-DQB1*06:04-DPB1*04:01*); and
- *HLA-B*07:02*, *HLA-DRB1*01:01*, and *HLA-DQB1*05:01* are on the third most common haplotype (designated as HP-3; *A*24:02-C*07:02-B*07: 02-DRB1*01:01-DQB1*05:01-DPB1*04:02*) (57)

While the primary protective allele could not be identified for HP-2 and HP-3, due to the strong linkage disequilibrium between the alleles, *HLA-DRB1*15:02* on HP-1 was shown to be a primary protective allele with GD (57). In addition, it is important to note that *HLA-DRB1*13:02*, in the Japanese population, is epistatic to *HLA-DPB1*05:01* in controlling the development of GD. In other words, the presence of *HLA-DPB1*05:01* is critical for the development of GD in the presence of the protective *HLA-DRB1*13:02* allele, while the susceptibility conferred by the other risk alleles are easily blocked by *HLA-DRB1*13:02* (57).

Pathogenesis

GD is triggered as a consequence of a break in immunological tolerance. In an individual, harbouring susceptibility alleles, GD may develop as a result of environmental influences that induce or exacerbate immune dysfunction, ultimately leading to the onset of autoimmunity (61).

One of the main hallmarks of GD is hyperthyroidism. This is caused by stimulatory anti-TSHR antibodies (TRAb, TSAb, TSI) which are directed towards thyrotropin (TSH) receptor (TSHR). Under normal circumstances, TSHR mediates the activating action of TSH to the thyroid gland, resulting in the growth and proliferation of thyrocytes and thyroid hormone production (64). It is important to note that TSHR undergoes cleavage and the resulting subunit A is shed into circulation. It is postulated that alternative splicing could convert the wild-type A subunit into a potent autoantigen (65). This TSHR-derived peptide serves as an epitope which binds to HLA-class II molecules on the surface of antigen-presenting cells (APC), eliciting a cytokine response and subsequent production of autoantibodies (64). These antibodies have the ability to mimic TSH, resulting in the stimulation of thyroid cells and an abnormal overproduction of thyroid hormone, resulting in a loss of tolerance (66). A study done by Jansson et al. (1984) looking at thyrocytes from patients with GD, found HLA class II molecule expression, similar to those normally found on APCs. It was concluded that these thyrocytes were serving as facultative APCs and could be responsible for initiating thyroid autoimmunity via direct thyroid autoantigen presentation (67).

A key environmental trigger for GD, is infection by Yersinia enterocolitica (YE). The membrane of YE has been shown to contain high-affinity binding sites for TSH as well as TSHR antibodies from patients with GD, due to regions of sequence homology (68). This supports the concept of molecular mimicry between YE antigens and self-antigens and the induction of cross-reactive TSHR antibodies, resulting in GD (69,70).

Vitamin D deficiency has been associated with increased risk for GD. A meta-analysis study, done by Xu et al. (2015), found that vitamin D deficiency was prevalent in patients with GD compared to the control group and that these subjects had lower levels of serum 25-hydroxyvitamin D [25(OH)D], which may play a role in the development of the disease (71). Lower serum 25(OH)D levels were also found to be associated with a higher incidence of GD recurrence, following anti-thyroid drug discontinuation (72). Vitamin D plays a significant immunomodulatory function. The most active form of vitamin D, 1,25-Dihydroxyvitamin D [1,25(OH)2D] or calcitriol, serves as a ligand for the vitamin D receptor (VDR) which is present on many immunocytes and has been shown to have multifaceted immunomodulatory effects (73). Active vitamin D induces B cell apoptosis thereby preventing B cell activation, proliferation and differentiation. Active vitamin D also reduces the maturation of dendritic cells and suppresses dendritic cell-dependent T-cell activation, by down-regulating the expression of MHC II molecules. T cells are another target of vitamin D action where active vitamin D inhibits the cytotoxic activity of T cells by reducing Th1 and Th17 cells, which play a key role eliciting the inflammatory response by the release of cytokines. Conversely, active vitamin D induces the differentiation of regulatory T cells (Tregs), which play a pivotal role in the regulation of immune responses and maintenance of self-tolerance and immune homeostasis (74,75). Vitamin D deficiency has an opposite effect, resulting in the hyperactivation of B cells, an increased production of autoantibodies and suppressing Treg function. The latter contributing to the loss of immune tolerance and activation of inflammatory cytokines, contributing in disease pathogenesis in genetically susceptible individuals (76).

Another environmental and life-style risk factor linked to GD is smoking. In a large prospective cohort study, done by Holm et al. (2005), the risk of GD, in women, was found to be time dependant, with the current smokers having a higher risk than past smokers. In addition, the relationship was found to be dose-dependent; with the highest risk of GD in women with the greatest number of pack-years of smoking and current smokers who smoked the most cigarettes per day. Among past smokers, the risk of GD decreased as the time since smoking cessation increased (53). The latter was also found from a meta-analysis done by Vestergaard (2002) where smoking cessation was found to be associated with a lower risk of GD than current smoking (77). Cigarette smoking is known to affect thyroid function and decrease the levels of TSH levels (78). The possible mechanism by which smoking can increase one's risk for developing GD is through the actions of thiocyanate (79). Thiocyanate is generated from cigarette smoking, as a detoxifying product of cyanide and serves as a potent inhibitor of iodide transport to the thyroid cells. This results in a decrease in thyroid hormone synthesis and an increase in goiter, which subsequently compensates for low thyroid hormone synthesis and overproduces TSH (80). In addition, other compounds found in cigarettes, such as nicotine might cause sympathetic

activation, which could increase thyroid secretion, while benzopyrene may have direct thyroid-stimulatory actions or stimulating effects on hepatic oxidative metabolism, which in turn may stimulate hepatic conversion of thyroid hormones; T4 to T3 (79).

Iodine deficiency is another risk factor for developing GD. Iodine is a dietary micronutrient required for the production of thyroid hormone (81). Prior to 2000, Denmark was an area of iodine deficiency, which was associated with a high occurrence of goiter and hyperthyroidism in elderly people (82). In mild-to-moderate iodine deficiency, increased thyroid activity can compensate for low iodine intake and maintain euthyroidism in most individuals, however, chronic thyroid stimulation can result in an increase in the prevalence of hyperthyroidism in populations (83).

Improving Outcomes

GD hyperthyroidism is treated by reducing thyroid hormone synthesis, using anti-thyroid drugs (ATD), reducing the amount of thyroid tissue with radioactive iodine (RAI) treatment or total thyroidectomy (84).

The following recommendations on management and improvement of GD comes from the 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism (84):

- *Anti-thyroid Drugs*

The main ATD are propylthiouracil (PTU) and methimazole (MMI). The initial dose of MMI is usually 10–30 mg daily depending on the severity of hyperthyroidism, while PTU is given at a dose of 100 mg every 8 h. Thyroid function tests are reviewed 3–4 weeks after starting treatment. A substantial proportion of patients reach euthyroidism within 3–4 weeks of treatment. The usual daily maintenance doses of ATD are 2.5–10 mg of MMI and 50–100 mg of PTU. Alternatively, MMI daily doses of 30 mg may be given combined with levothyroxine (L-T4) supplementation to avoid drug-induced hypothyroidism. It is recommended that MMI be used in every non-pregnant patient who chooses ATD therapy for Graves' hyperthyroidism. This ATD can be administered for 12–18 months then discontinued if the TSH and TSHR antibody levels are normal. Patients with persistently high TSHR antibodies at 12–18 months should continue MMI therapy, repeating the TSHR antibody measurement after an additional 12 months, or opt for RAI or thyroidectomy.

- *Radioactive Iodine Treatment*

RAI therapy is often recommended for patients with side-effects to or recurrence after a course of ATD. If ATD are used before RAI therapy they should be paused around 1 week before and after therapy in order not to decrease the efficacy of RAI therapy. No dose calculation can secure long-term

euthyroidism and it is fully acceptable to offer a fixed dose of RAI. This form of treatment is not recommended if the patient is pregnant or breast feeding and it must be noted that conception should be postponed until at least 6 months after RAI in both males and females.

- *Surgery*

Thyroidectomy is the least commonly selected treatment with two main advantages; the absence of radiation risk and the rapid control of hyperthyroidism. However, if surgery is selected, total thyroidectomy is the procedure of choice and should be performed by a skilled surgeon. Euthyroidism should be restored by ATD prior to surgery to avoid peri- or post-operative exacerbation of thyrotoxicosis. In addition, vitamin D deficiency should be corrected to prior to surgery to reduce the postoperative risk of hypocalcaemia. A solution containing potassium iodide can be given for 10 days prior to surgery, in order to decrease thyroid vascularity and intraoperative blood loss.

A study done by Sundaresh et al. (2017) found RAI treatment demonstrated the best efficacy and safety profile. Surgery was also found to be very effective and relatively safe in the hands of experienced surgeons. While ATDs allow preservation of thyroid function, a high relapse rate combined with a significant adverse-effect profile was documented in the study (85).

Iodine deficiency, as a potential risk factor for hyperthyroidism, can be overcome by iodine fortification. This has been introduced to previously iodine-replete countries (82). However, it is important to monitor and adjust iodine intake, as excess iodine intake could lead to hypothyroidism (86).

Hashimoto's Thyroiditis

Description

Hashimoto thyroiditis (HT), also known as chronic lymphocytic thyroiditis or goitrous autoimmune thyroiditis, is the most common autoimmune thyroid disorder and is characterized by the destruction of thyroid tissue by antibody-mediated immune processes (87). It is the most common cause of hypothyroidism in developed countries and has a higher prevalence in females than in males (88). The resulting symptoms include fatigue, weight gain, constipation, increased sensitivity to cold, dry skin, depression, muscle aches and reduced exercise tolerance (89). The diagnosis of HT is challenging in that signs, symptoms and laboratory findings may show normal to hyperthyroid values, due the destruction of thyroid cells being intermittent early on in the disease.

Genetics

Epidemiological data from twin studies has shown that 73% of the susceptibility related to the development of antibody production, against thyroid-specific antigens, seems to be attributable to the genetic factors (90). To date a number of genes have been identified that contribute to HT susceptibility; *CTLA-4* and *PTPN22* and *VAV3* (91–93). In addition, HLA class II genes have also been shown to influence disease susceptibility in HT (94,95).

The following HLA class II risk alleles have been identified:

- *HLA-A*2* and *HLA-A*02:07* in the Japanese population (57,95)
- *HLA-DRB1*03*, *HLA-DRB1*04* and *HLA-DRB1*08* in the Caucasian population (94)
- *HLA-DRB1*04:03* in the Japanese population (95)
- *HLA-DRB4*, *HLA-DRB4*01:01* in the Japanese population (57,95)
    - Not currently reported on
- *HLA-DQA1* 03:011/12* and *HLA-DQA1*04:01* in the Caucasian population (94)
- *HLA-DQA1*03* in the Japanese population (95)
- *HLA-DQB1*03:01/4* and *HLA-DQB1*04* in the Caucasian population (94)
- *HLA-DQB1*03:03* in the Japanese population (95)

It is important to note that *HLA-DRB1*04:03*, *HLA-DQA1*03* and *HLA-DQB1*03:03* are in linkage disequilibria with *HLA-DRB4*01:01*, in the Japanese population. In addition, the combination of *HLA-A*2* and *HLA-DRB4*01:01* was strongly associated with susceptibility to HT (95).

The following protective alleles have been identified for HT:

- *HLA-B*44:03* in the Japanese population (57)
- *HLA-C*14:03* in the Japanese population (57)
- *HLA-DRB1*07* and *HLA-DRB1*13* in the Caucasian population (94)
- *HLA-DRB1*13:02* in the Japanese population (57)
- *HLA-DQA1*02:01* and *HLA-DQA1*01:02/3* in the Caucasian population (94)
- *HLA-DQA1*01:02* in the Japanese population (95)
- *HLA-DQB1*06* in the Caucasian population (94)
- *HLA-DQB1*06:04* in the Japanese population (57)
- *HLA-DPB1*04:01* in the Japanese population (57)

From all the following protective alleles, *HLA-C*14:03, HLA-B*44:03, HLA-DRB1*13:02, HLA-DRB3, HLA-DQB1*06:04*, and *HLA-DPB1*04:01* in the Japanese population, researchers could not pinpoint the primary protective allele, due to strong linkage between these alleles. Haplotype analysis, by Ueda et al. (2014) found a significant protective association between this haplotype and HT (57).

Pathogenesis

Similar to GD, several endogenous and environmental factors may trigger HT in individuals with susceptible genetic backgrounds, causing increased antigen presentation in the thyroid and consequent loss of immune tolerance (88).

HT is defined by the dramatic loss of thyroid cells (thyrocytes), an increase in circulating autoantibodies to two primary thyroid-specific antigens, thyroglobulin (TG), thyroid peroxidase (TPO), increased concentrations of serum TSH and lowered T4 levels (96). TG, the main protein synthesized in the thyroid gland, serves both in the synthesis and in the storage of thyroid hormones (87). Epidemiologic and experimental evidence has indicated that the iodine content may play an important role in its autoantigenicity (97). Iodine is a necessary component of normal thyroid hormonogenesis. Iodine is incorporated into the tyrosine residues of TG, ultimately producing T3 and T4 thyroid hormones (87). TPO plays a key role in catalysing the oxidation of iodine, making it capable of converting the tyrosine molecules to amino acids that make up the TG molecule. The presence of these amino acids in TG molecules, induces the refolding of TG and subsequent assembly and incorporation of thyroxine residues in the TG protein (98). External insults in the form of excess dietary iodine intake, vitamin D and selenium deficiency and intestinal bacterial dybiosis, can cause insults to

the thyrocytes, resulting in the exposure of new or cryptic epitopes on TG and TPO molecules, which then go on to serve as autoantigens (87,99). These autoantigens are taken up and processed by the antigen-presenting cells (APCs) and presented by the MHC class II molecules, eliciting a cytokine response and subsequent production of autoantibodies. It is interesting to note that thyrocytes can act as facultative APCs and have aberrant MHC class II expression (67). This results in a massive depletion of thyrocytes via antibody-dependent, cytokine-mediated mechanisms. In addition, interferon gamma (IFNγ), secreted by T-helper cells, have the ability to induce the expression of Fas and Fas-ligands on thyrocytes, resulting in immune-mediated apoptosis of these target cells (88). These mechanisms collectively result in the clinical manifestation of Hashimoto's thyroiditis and hypothyroidism.

One of the key environmental factors, influencing hypothyroidism and HT, is dietary iodine intake. Excess iodine can directly affect the TG molecule, creating new or cryptic epitopes, which may facilitate antigen uptake and processing by APC (87). These epitopes serve as auto-antigens in HT disease. Excess iodine can also induce oxidative stress by increased activation of TPO (100). The resulting reactive oxygen species (ROS) and free-radicals have the ability to damage thyrocyte cell membrane by oxidation of membrane lipids and proteins causing thyrocyte necrosis and apoptosis, resulting in hypothyroidism (101). Hypothyroidism tends to be more common in iodine-replete areas than in iodine-deficient areas. A population-based study, done in Denmark, by Pedersen et al. (2007) showed an increase in the incidence rate of hypothyroidism from 38.3/100 000 per year, increasing to 47.2/100 000 per year, 5–7 years after iodine fortification of salt (86).

Vitamin D deficiency has been associated with increased risk for HT (102–104). A meta-analysis study, done by Xu et al. (2015), found that vitamin D deficiency was prevalent in patients with HT compared to the control group and that these subjects had lower levels of serum 25-hydroxyvitamin D [25(OH)D], which may play a role in the development of the disease (71). A study done by Bozkurt et al. (2013), found a direct correlation between 25(OH)D levels and thyroid volume and an inverse correlation with anti-TPO and anti-TG levels (103). Vitamin D plays a significant immunomodulatory function. The most active form of vitamin D, 1,25-Dihydroxyvitamin D [1,25(OH)2D] or calcitriol, serves as a ligand for the vitamin D receptor (VDR) which is present on many immunocytes, and has been shown to have multifaceted immunomodulatory effects (73). Active vitamin D induces B cell apoptosis thereby preventing B cell activation, proliferation and differentiation. Active vitamin D also reduces the maturation of dendritic cells and suppresses dendritic cell-dependent T-cell activation, by down-regulating the expression of MHC II molecules. T cells are another target of vitamin D action where active vitamin D inhibits the cytotoxic activity of T cells by reducing Th1 and Th17 cells, which play a

key role eliciting the inflammatory response by the release of cytokines, such as the interleukins and IFNγ. Conversely, active vitamin D induces the differentiation of regulatory T cells (Tregs), which play a pivotal role in the regulation of immune responses and maintenance of self-tolerance and immune homeostasis (74,75). Vitamin D deficiency, might induce thyroid autoimmunity, by hyperactivating of B cells, up-regulating Th1 and Th17 cells and the expression of MHC II molecules on thyrocyte surface and suppressing Treg function. The latter contributing to the loss of immune tolerance and activation of inflammatory cytokines, contributing in disease pathogenesis in genetically susceptible individuals (76). This could explain the high anti-thyroid antibody titres seen in HT patients with vitamin D deficiency (103).

Selenium (Se) deficiency has been associated with HT. Se is an essential trace element found in various food sources and is vital for the proper functioning of both the thyroid and the immune system. The thyroid is the organ with the highest Se content per gram of tissue (105). It exercises its impact on thyroid regulation mainly in the form of selenoproteins, a large family of enzymes involved in the activation, proliferation and differentiation of cells that drive the innate and adaptive immune responses. In addition, these enzymes play a key role in regulation of the redox state and protect from oxidative damage (106). While the exact mechanisms behind the adverse influence of Se-deficiency in HT remains to be elucidated, it has been proposed that Se-deficiency may lead to an oxidant–antioxidant imbalance (107). The resulting increase in oxidative stress can damage membrane lipids, proteins and DNA and increase the risk of exposure of unusual epitopes which are recognised and reacted to by the immune system. This ultimately leads to cell death by apoptosis (107). A study done by Rostami et al. (2020) found the frequency of Se-deficiency to be higher in HT patients than the healthy controls. In addition, HT patients with Se-deficiency were found to have increased TPO- and TG-antibodies compared to Se sufficient participants (107). These findings suggest that Se-deficiency plays an important role in the immunological events leading to the induction of the deleterious cycle of oxidative stress and subsequent thyroid failure.

There is a growing body of evidence suggesting that an alteration in the composition of intestinal bacteria (dysbiosis), bacterial overgrowth and increased intestinal permeability are associated with HT development (108). The gut microbiota have a key role in modulating the innate and the adaptive immune system, in the gut and other organs such as the thyroid gland and in so doing maintain the host homeostasis (109). In addition, the composition of the gut microbiota has an influence on the availability of essential micronutrients for the thyroid gland, such as iodine and selenium (110). This microbiota can also be affected by dietary changes, the environment, genetics and other diseases. The modulation of the microbiota, by diet, directly influences the inflammatory profile due to the resulting

metabolites and this can result in increased intestinal permeability and low-grade systemic inflammation. In a study done by Cayres et al. (2021), patients presenting with HT, were found to have significantly different dietary habits and as a consequence diminished beneficial microbiota compositions compared to the control patients and were found to exhibit higher levels of zonulin compared to the control patients (110). Zonulin is a physiological modulator of intercellular tight junctions, involved in macromolecule trafficking, epithelial and endothelial barrier integrity and immune tolerance in the gut mucosa (111). Intestinal dysbiosis can activate the zonulin pathway and stimulate the release and allow the traffic of luminal contents, not normally found circulation. This results in a breakdown in tolerance, activating immune cells which can remain in the gut mucosa or migrate to distant organs, resulting in chronic inflammatory and autoimmune diseases. One mechanism by which dysbiosis may lead to the development of HT, is that two microbial species found in the gut, *Lactobacillus* spp. and *Bifidobacterium* spp., have been shown to induce antibodies that cross-react with TPO and TG, through molecular mimicry. An increase in intestinal permeability would allow for these microbial species to "leak" through and cause an autoimmune response and subsequent loss of tolerance within the thyroid due to cross-reacting antibodies (108).

Improving outcomes

Medical management with thyroid hormone replacement is the fundamental treatment in HT, with levothyroxine (L-T4) treatment the established first choice as a standard of care. This hormone replacement therapy is for life. The main goal is to achieve a TSH level of 1 to 3 milliunits (mIU) per L. A starting dosage of 1.6 microgram (mcg) per kg per day can be initiated, with subsequent incremental changes made every 10 to 12 weeks to achieve this goal. Thyroid hormone therapy should resolve hypothyroid symptoms. This generally occurs within six months after achievement of euthyroidism. Treatment with thyroid hormone in patients with elevated TPO-antibody levels and subclinical hypothyroidism (TSH level greater than the upper limit of the reference range, but less than 10 mIU per L) is reasonable, especially if symptoms of hypothyroidism are present. Dosages of 25 to 50 mcg per day of levothyroxine can be initiated in these patients and titrated to the same TSH goals as in overt hypothyroidism.

Nutrition can support the medical treatment of HT and the impact of diet on thyroid function cannot be denied, as dietary micronutrients play a role in thyroid hormones synthesis and serve as defence elements of the immune system (112).

Foods to include in a diet plan would be:

Protein: Protein malnutrition intensifies iodine deficiency and thyroid gland damage. It is advised to increase the intake of whole meal protein from unprocessed products (meat, sea fish, especially fatty fish, eggs). This could assist in reducing the excessive body weight. Due to the possible need to eliminate milk and dairy products, this might not be a source of protein in HT, although vegetable substitutes like coconut, almond or rice milk also contain protein (112).

Zinc: Zinc is involved in the production of thyroid hormones, and its deficiency leads to an increase in antibody titres against thyroid antigens. Improvement of the nutritional status of this mineral in patients with Hashimoto's disease restores normal thyroid function caused by its deficiency. Among the products containing the largest amounts of zinc are pumpkin seeds, flax seeds, whole grain cereals, such as wholemeal bread, millet and buckwheat and mushrooms (112).

Magnesium: Magnesium plays an important role in normal immune function and serves as a co-factor for enzymes that regulate a variety of biochemical processes. A study by Wang et al. (2018) found that serum magnesium levels ≤0.55 mmol/L were associated with high levels of TG-antibody and a subsequent increase of HT prevalence and hypothyroidism (113). Low magnesium levels could abnormally activate immune cells and reduce the antioxidant response capacity in cells, resulting in an accumulation of free radicals. Foods containing a high-magnesium content include cocoa and bitter chocolate, nuts, pumpkin seeds, whole grain cereals and leafy greens (112,113).

Polyunsaturated fatty acids (PUFA): These are found in fish such as salmon, sardines and mackerel as well as from vegetable oil sources such as soybean oil, safflower oil, olive oil or flaxseed oil and avocados and can promote the quality of gut microbiota and maintain a steady state of these microbes, improving host metabolic functions. PUFAs also have the ability to modulate the gut microbes by promoting the production of anti-inflammatory mediators while inhibiting the pro-inflammatory markers (114,115).

Foods to avoid:

Lactose: Lactose intolerance is diagnosed in 75.9 % of the patients with HT (116). This intervention is important in patients taking L-T4, as lactose intolerance reduces the bioavailability of the drug and enforces the use of higher doses of L-T4. It is of importance to perform a lactose tolerance test, in patients on L-T4 treatment with elevated TSH levels (117).

Gluten: HT is the most prevalent co-existing autoimmune disorder in patients with celiac disease (CD). A study done by Hadizadeh Riseh et al. (2017) in patients with HT, found a high prevalence of anti-transglutaminase and IgA anti-gliadin antibodies, which serve as markers for CD, together with a positive significant relationship between anti-TPO and anti-TG antibodies (118). These results suggest that a CD diagnostic test should be carried out to identify if CD is present in the patient, with HT, prior to eliminating gluten from the diet (112).

Se supplementation: There have been many conflicting results relating to Se supplementation, in patients with HT. Data from a recent meta-analysis has suggested that SE supplementation should be discouraged (119).

Vitamin D supplementation: Meaningful concrete clinical data on impact of Vitamin D supplementation on hard clinical end points in this thyroid disorder is lacking (120).

Idiopathic Membranous Nephropathy

Description

Idiopathic membranous nephropathy (IMN) is the most common cause of nephrotic syndrome in adults and is now recognised as an organ–specific autoimmune disease. It is characterised by immune complex depositions on the extra-capillary side of glomerular basement membrane (121).

Genetics

The HLA class II genes are involved in stimulating autoantibody production by presenting antigens to antigen–specific CD4+ T cells (121). GWAS and high-throughput sequencing revealed that *HLA-DRB1*15:01*, *HLA-DRB1*03:01* and *HLA-DRB3*02:02* alleles each confer significant independent effects on the risk of IMN among the Asian population (121,122). A study done by Le et al. (2016) found that all Chinese patients with PLA_2R1-related IMN in the study cohort carried at least one of the two HLA risk alleles; *HLA-DRB1*15:01* and/or *HLA-DRB3*02:02* (122). To please note that *HLA-DRB3* is not currently reported on.

In addition to the high risk HLA alleles, a high risk SNP (rs2187668 – A risk allele) has also been identified by various studies, including a meta-analysis (123,121,124). This SNP is found in the *HLA-DQA1* gene and is known as a tag SNP of *DRB1*03:01* and is found to be associated with susceptibility to IMN in the Asian, European and Caucasian populations (124).

A study done by Qin et al. (2017), found that 5 IgA Nephropathy-associated SNPs in the HLA-DR-DQ region were also significantly associated with IMN pathogenesis in the Han Chinese (125):

- SNP rs9275596 was found to be the most significant SNP associated with susceptibility to IMN. This SNP rs9275596 maps to a linkage disequilibrium (LD) block constructed of rs9275224, rs2856717 and rs9275596 and the frequency of haplotype AAC for this block is higher in the IMN cases.
- rs2856717 in LD with rs927559
- rs9275224 in LD with rs927559
- rs7763262 in high LD with rs660895
- rs660895

It is worth noting that for these SNPs, the risk alleles confer a completely opposite effect in the pathogenesis of IgAN (125).

The following alleles have been found to be protective against IMN in the Han Chinese population:

- *DQA1*03:01*
- *DQA1*03:02*
- *DRB1*09:01*
- *DQB1*03:03* (121)

A genome-wide association study, on 3 Caucasian populations, by Stanescu et al. (2011) found 2 significant associations with IMN. The first was with rs2187668-A risk allele within *HLA-DQA1* (mentioned above) and the second was with rs4664308-A risk allele found in the *PLA_2R1* gene. The study found that the risk of developing IMN increased, in an additive fashion, with each additional copy of the risk allele at either locus (*HLA-DQA1* and *PLA_2R1)* (123).

Pathogenesis

M-type phospholipase A_2 receptor (PLA_2R1), expressed in normal podocytes, serves as a major target antigen in IMN disease (126). A study done by Beck et al. (2009) showed that 70% of patients with active IMN disease had antibodies, that are of IgG4 subclass, against PLA_2R1 (126). PLA_2R1 is a type I transmembrane protein member of the mannose receptor family. Receptors in this family are composed of a large extracellular segment containing an N-terminal cystine-rich ricin domain, a transmembrane domain and a short intracellular domain and can present either as a straight or bent conformation (127,128). A study done by Fresquet et al. (2015) found the cysteine-rich ricin domain as a major antigen epitope of PLA_2R1 (129). Beck et al. (2009) found that antigens exist only when PLA_2R1 is in a configuration dependent on intramolecular disulfide bonds and that the antibody response is restricted to this conformation (126).

There are several hypotheses regarding how PLA_2R1 may induce an autoimmune response in IMN patients. Oxidative stress can result in disulfide bond formation in cytoplasmic proteins. A study done by Xu et (2016) found that long term exposure to $PM_{2.5}$ was associated with an increased risk for IMN (130). Exposure to reactive oxygen species (ROS) produced by polycyclic aromatic hydrocarbons and transition metals in the PM (particulate matter) could lead to increased expression of PLA_2R1 conformation-dependant epitopes (131). It is postulated that this conformational change is

recognised by HLA-DQA1 which then facilitates the anti- PLA_2R1 production, in IMN patients carrying the risk alleles (132). The level of autoantibody to PLA_2R1 correlates with the severity of clinical manifestation and progression of this disease (133).

Sequence variations in the *PLA_2R1* gene could control both the conformational change of the protein resulting in it functioning as an antigen as well as the pattern of antigen-peptide processing. Sequence variations in *HLA-DQA1* and *HLA-DRB1* can alter the MHC Class II molecules conformation, consequently changing the shape of the peptide groove resulting in an altered specificity of antigen peptide presentation (134–136). This would ultimately trigger an autoimmune response. Lv et al. (2013) postulated that the co-existence of risk alleles in *HLA* and *PLA_2R1* in the same person may lead to the dysregulation of the tightly regulated adaptive immune system and allow for the development of IMN (136).

Another possible mechanism by which an immune response is elicited, is through bacterial infections. A study done by Fresquet et al. (2015) found that the a portion of the cysteine-rich ricin region, maintained by a disulfide bond, showed complete homology to part of the bacterial cell wall enzyme common to *Clostridium* species and other bacteria (129). In this instance, molecular mimicry could play a crucial role in activating an autoimmune response by triggering the innate and adaptive immune response, resulting in an abundance of anti- PLA_2R1 antibodies.

The resulting circulatory antibodies can bind PLA_2R1 antigens on podocytes, by entering the glomerular basement membrane, and form immune complexes. These complexes have the ability to activate the complement system which in turn induces the production of the membrane attack complex. These two processes are responsible for inflammatory mediator release and podocyte injury, proteinuria and ultimately kidney damage (137).

Improving Outcomes

Many non-disease specific treatments have been shown to improve the outcome of glomerular diseases. It is well established that a diet high in salt and protein can influence proteinuria and increase the risk for end stage renal disease (ESFD). Daily salt intake >14g is associated with an increase in ESRD in patients with chronic kidney disease (138). A high sodium diet was is also known to inhibit the antiproteinuric effects of angiotensin-converting enzyme (ACE) inhibitors in patients with chronic kidney disease. It is advised that patients decrease their sodium intake to 3 g per day (139). In terms

of dietary protein intake, a moderate dietary protein restriction of 0.8 g/kg body weight/day is found to reduce proteinuria by 15–25% and slow the progression of renal disease (140).

Hyperlipidemia is a known complication of nephrotic syndrome and almost always accompanies IMN patients with nephrotic-range proteinuria (141). The use of statins can assist in decreasing the risk of coronary disease in nephrotic patients (140).

Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARB drugs) are appropriate for all patients with MN. They have the ability to reduce proteinuria and slow progression of renal disease (142).

Rituximab, an anti-B cell monoclonal antibody (mAb), forms part of the disease specific therapy for IMN. This mAb binds to CD20 antigens on selective B cells, destroying them. It is important to note that CD20 antigens are not expressed on hematopoietic stem cells, normal plasma cells or other normal tissues. Destroying selective B cells can halt the production specific immunoglobulins directed against antigens present in the glomeruli. Intravenous administration of Rituximab, either 375 mg/m^2 at 4 weekly doses or 1 g at 2 doses 15 days apart has the ability to reduce proteinuria, while increasing serum albumin levels and improving hyperlipidemia in patients with IMN (142).

IgA Nephropathy

Description

IgA nephropathy (IgAN) is the most prevalent primary chronic glomerular disease worldwide. It represents the leading cause of end-stage renal disease (ESRD) in Asian populations. The diagnosis is made by kidney biopsy, which shows predominant deposition of IgA-containing immune complexes in the glomerular mesangium, leading to glomerulonephritis, glomerular sclerosis and progressive loss of kidney function (143).

Genetics

IgAN represents a genetically complex multifactorial trait. It may occur sporadically or follow a familial pattern. Its prevalence and clinical features vary geographically, across various ethnicities and race groups and the disease has a range of clinical presentations (144). A number of Genome-Wide Association Studies (GWAS) have been done looking at family-based and case-control association studies (143,145–148). The strongest association signals were observed in the MHC. The following HLA alleles have been identified as risks alleles for IgAN:

- *HLA-DQB*05:01* in the European population (145)
- *HLA-DQA1*01:01* and *DQB1*03:01* in the European and East Asian populations (143)
- *HLA-B*40:01, HLA-DQB*03:02 and HLA-A*11:01* in the Han Chinese (147)

The following HLA alleles have been found to be negatively associated with IgAN:

- *HLA-DQB*02:01* and *HLA-DQA1*01:02* in the European and East Asian populations (143,145)
- *HLA-DQB1*06:02* in the Chinese Han (146)

In addition to the HLA alleles identified as risk alleles, GWAS studies have also identified single nucleotide polymorphisms (SNPS) associated with susceptibility to IgAN. A strong association was found between rs7763262-C risk allele in the *HLA-DQ/DR* locus and age of diagnosis and greater risk of progression to end-stage kidney disease (143). The effect was stronger in Europeans than Asians. In addition, SNPs rs2523946 within *HLA-A*, rs660895 within *HLA-DRB1* and rs1794275 within *HLA-DQA/B* have all been found to be independently associated with IgAN in the Han Chinese (147). A study by Yu et al. (2012) found that the rs660895- G risk allele was associated with a mild subtype of IgAN, mild proteinuria but higher IgA level in cases (147). Another study done by Zhou et al. (2015)

looked at the cumulative effects of variants identified by various GWAS in IgAN and found the following SNPs to be independently associated with susceptibility to IgAN; rs9275224, rs2856717, rs9275596 and rs1883414 (148). It's important to note that rs660895 and rs1794275, mentioned above, are found to be in strong linkage disequilibrium with rs9275596 (147).

Pathogenesis

The various risk alleles and SNPS identified through the many GWAS are involved in the following pathways: adaptive immunity including antigen processing and presentation through the MHC region, complement system (*CFH*, *CFHR3-1*, and *ITGAM-ITGAX*), mucosal innate immunity against pathogens (*DEFA*, *CARD9*, *VAV3*, *ODF1-KLF10*, and *UBR5*) and regulation of mucosal IgA production (*TN*FSF13, *HORMAD2*, and *ST6GAL1*). Functional studies have confirmed and replicated the susceptibility loci involved in adaptive immunity and the complement system, thereby validating their role in IgAN pathogenesis (144).

The Asian populations have been shown to have higher frequencies of risk alleles compared to European populations (146). This could suggest local selective pressures which might have increased the frequency of risk alleles in some populations. The local helminth emerged as the strongest predictor of genetic risk. The enhanced IgA response, conferred by GWAS risk alleles, is likely a protective adaptation against mucosal invasion by helminth infection (149). In addition, it can also explain the known association of mucosal infections as a common trigger for IgAN (150,151).

The "four-hit" hypothesis is the most widely accepted hypothesis about the pathogenesis of IgAN, indicating that the development of IgAN requires 4 processes or "hits":

1. *Increased synthesis of poorly O-galactosylated IgA1 (also called Galactose-deficient IgA1, Gd-IgA1) in circulation.*

Abnormalities in IgA1 production and glycosylation leads to elevated levels of Gd-IgA1. The primary function of serum IgA in the mucosa is to neutralize toxins and maintain the mucosal epithelial barrier, preventing systemic infection. Aberrant glycosylation of IgA1 may reflect abnormal mucosal immune responses to infections of the upper respiratory tract in genetically predisposed individuals. Mucosal infections can up-regulate aberrant *O*-glycosylation of IgA1 by inducing the production of cytokines and growth factors and support survival of Gal-deficient IgA1-secreting cells in susceptible individuals (152).

2. *Production of autoantibodies against Gd-IgA1*

Aberrant glycosylation of IgA results in terminal GalNAc residues being exposed. Such IgA molecules are presented as autoantigens inducing the production of IgA autoantibodies which result in the formation of nephritogenic immune complexes. Some viruses (e.g. Epstein-Barr virus) and Gram-positive bacteria (*e.g.* streptococcus) display GalNAc-containing structures on their surfaces. These structures may mimic the glycan epitopes on galactose-deficient IgA1, triggering the formation of cross-reacting antibodies (153). MHC risk alleles may participate in this step by influencing the efficiency of antigen presentation, recognition, and processing, and subsequent activation of autoreactive B cells (149). High levels of anti-glycan antibodies correlates with proteinuria and disease severity (154).

3. *Formation of immune complexes containing pathogenic O-galactosylated IgA1*

The autoantibodies produced as a result of molecular mimicry of viral or bacterial structures and Gd-IgA1 form circulating immune complexes with these antigens. These complexes, being large in nature, cannot be cleared from the liver and enter renal circulation (154).

4. *Mesangial deposition of these immune complexes activating mesangial cells and subsequently impairing glomeruli*

The mesanguim cells of the kidney are prone to deposition of immune complexes. These immune complexes activate the mesangial cells to release inflammatory factors and complements. This results in glomerular inflammation and subsequent renal injury (154).

The bacterium species, *Staphylococcus aureus (S. aureus*), forms parts of the oral flora that is found to colonise at the surface of mucosal tissue and is kept in check by the mucosal and systemic immune system. This bacterium is known to cause post-operative wound infections, food poisoning and septicemia. Keeping the “four-hit” hypothesis in mind, bacterial invasion can occur after injury to the mucosal barrier. A study done by Koyama et al. (2004) showed that *S. aureus* cell envelope antigens were co-localized with IgA antibodies in the glomeruli of patients of IgAN, suggesting that *S. au- reus* plays a role in the immunopathogenesis of IgAN (155).

Being overweight has been associated with a number of chronic diseases, including chronic kidney disease. A study done by Wu et al. (2018) found that high BMI was linked to increased interstitial fibrosis frequency and consequently accelerated the progression and outcomes of IgAN (156). Interstitial lesions are strongly correlated with the density of interstitial inflammatory cells which cooperate with each other locally to accelerate renal inflammation, contributing to IgAN progression (157). A mouse model study done by Heymann et al. (2009) showed that renal interstitial dendritic cells were found to contribute to glomerulonephritis. They captured glomerular antigens and presented them to T-helper cells, which then recruited and activated cytotoxic T cells, driving renal lesions (158).

Improving Outcomes

Lifestyle modifications, including restriction of sodium intake, can lower blood pressure. Patients with IgAN exhibit sodium-sensitive hypertension as renal dysfunction progresses. A study done by Konishi et al. (2001) showed that a low sodium diet (≈5 g/d NaCl) was beneficial in patients with IgAN. The benefits of sodium restriction are thought to be related to sodium sensitivity of blood pressure, which correlates with renal ultrastructural damage. The low-sodium diet also resulted in reduced proteinuria levels (159).

Physical exercise is associated with a decreased risk of end stage renal function. Moderate activities (walking a mile without stopping, garden or yard work) for at least three times per week or vigorous physical activity (jogging, running or riding a bicycle or exercise bike, swimming, aerobics, dancing, calisthenics, and other activities) once a week, should be encouraged in patients with IgAN, especially males (160).

Lyme borreliosis

Description

Lyme borreliosis is an important emerging infectious disease which predominantly occurs in temperate regions of the northern hemisphere (161). The disease is caused by a bacterial agent, *Borrelia burgdorferi*, which is transmitted to the host by a bite from the *Ixodes* tick (162). Lyme disease is regarded a multi-system, inflammatory disease that affects the skin, nervous system, cardiovascular system, muscles and joints. Clinical signs may resolve or overlap with new manifestations as the infection progresses. While most patients present at an early stage of infection and can be treated with antibiotics, a subset of patients will go untreated and develop Lyme arthritis months after being infected (163). Lyme arthritis can be successfully treated with oral or intravenous (i.v.) antibiotic therapy, however in a small percentage of cases, persistent and excessive joint inflammation continues for several months to years after antibiotic therapy and this is termed antibiotic-refractory Lyme arthritis (161). The refractory outcome is likely an interplay between the pathogen, host genetic and immunologic factors (164).

Genetics

Several studies have identified the role of HLA and its association with Lyme disease and Lyme arthritis (161,165–168).

The following risk alleles have been identified in individuals infected by *Borrelia*, either suffering early-stage disease or late-stage disease in the form of Lyme arthritis:

- *HLA-DRB1*01:01* associated with early stage infection - erythema migrans and Lyme arthritis (161,168)
- *HLA-DRB1*01:02*, *HLA-DRB1*03:05*, *HLA-DRB1*04:01*, *HLA-DRB1*04:02*, *HLA-DRB1*04:04*, *HLA-DRB1*04:05* and *HLA-DRB1*16:01* (161,165)
- *HLA-DRB1*17* in the Latvian population associated with early stage infection (167)
- *HLA-DRB5*01:01* (161)
    - Not currently reported on

It is interesting to note that some of the risk alleles associated with Lyme arthritis overlap with those risk alleles associated with rheumatoid arthritis, such as *HLA-DRB1*01:01, HLA-DRB1*04:01 or HLA-DRB1*04:04* (161).

To date only a few protective alleles have been identified:

- *HLA-DRB1*08:01*, *HLA-DRB1*11:01* (161)
- *HLA-DRB1*13* in the Latvian population (167)

Pathogenesis

The risk of being infected by *B. burgdorferi* is dependent on the local abundance and infection rate of vector ticks as well as human behaviours that affect the likelihood of being bitten (169). Forestry workers such as hunters, natural science researchers, game managers or mushroom/berry pickers as well as individuals who enjoy hiking and gardening are at an increased risk of infection (170,171).

The onset of tick feeding initiates global changes in *B. burgdorferi* gene expression that are required for infection of the blood meal host. During transmission, pathogens bind a tick salivary protein to shield against host antibodies. In addition, the pathogen also evades the host immune response by expressing proteins that inhibit complement-mediated lysis. Despite these immune evasion techniques, *B. burgdorferi* is still recognised and killed by the host innate and adaptive immune response within a few weeks to months. However, some pathogens may remain in localized niches in untreated patients and cause persistent symptoms for several years. *B. burgdorferi* lacks virulent factors and toxins and relies on the host for its nutrient supply (163). As a consequence, the symptoms associated with Lyme disease are a result of the host inflammatory immune response against the pathogen rather than mediated by the pathogen itself (172).

Dendritic cells and macrophages are major drivers of the adaptive immune response against pathogens through their phagocytic and professional antigen-presenting functions (173). These are the first immune cells that interact with and phagocytose *B. burgdorferi*, allowing for the processing and presentation of *B. burgdorferi* antigens, on HLA molecules. This leads to the activation of CD4+ and CD8+ T cells and a cascade of pro-inflammatory responses that are responsible for controlling *B. burgdorferi* numbers in host tissues (173).

With Lyme arthritis, tissue damage and inflammation within the joint and synovial tissue persists long after successful bacterial clearance (164). A study done by Lochhead et al. (2019) found that genes related to the innate and adaptive immune activation such as those involved in antigen processing, cell mediated cytotoxicity and chemokine signalling, were up-regulated in patients with Lyme arthritis,

even in the absence of an active infection. The study also found that the gene expression profiles, in synovial tissue from patients with Lyme arthritis, showed a down-regulation of genes related to tissue repair and metabolism and a robust interferon gamma (IFNγ) profile. The latter prevents a return to tissue homeostasis, resulting in vascular damage, autoimmune, inflammatory processes, fibrosis and synovial hyperplasia lasting for months to several years, even in the absence of active infection (174). An in vitro study done by Lochhead et al. (2019) found that increased levels of IFNγ has the ability to stimulate fibroblast-like synoviocytes (FLS), the most common cell type in synovium, to differentiate into immune effector cells and express MHC Class II HLA-DR molecules and exhibit cytokine and chemokine responses similar to those observed in postinfectious synovial tissue. The altered role of FLS, a key cell type for tissue repair and wound healing, into a pro-inflammatory non-professional antigen presenting cell, is responsible for driving tissue-specific innate and adaptive immune responses seen in postinfectious Lyme arthritis (175). These two studies show that dysregulation of the immune response is a potential mechanism for the perpetuation of a chronic inflammatory state within the synovium of postinfectious Lyme arthritis patients.

A study done by Gutierrez-Hoffmann et al. (2020) found that *B. burgdorferi* has the ability to promote the processing and presentation of new sets of HLA-DR associated self-peptides derived from unique host protein sources (165). The following self-peptides have been identified to bind HLA-DR, in synovial tissues and serves as autoantigens in Lyme arthritis; endothelial cell growth factor (ECGF), matrix metalloproteinase- 10 (MMP-10), apolipoprotein B-100 (apoB-100) and Annexin A2 (165).

ECGF also known as thymidine phosphorylase, an IFN-γ-inducible protein and chemotactic factor, has a proliferative effect on endothelial cells and is known to induce angiogenesis. It serves as an autoantigen in many autoimmune diseases and has been found to be up-regulated in the synovial fluid of antibiotic-refractory Lyme arthritis and found to stimulate B and T cell responses (176). A study done by Londoño et al. (2014) found correlations between ECGF autoantibody reactivity with obliterative microvascular lesions, suggesting that these autoantibodies have specific pathologic consequences in synovial tissue antibiotic-refractory Lyme arthritis patients. Due to the high ECGF levels in the synovial fluid, it is presumed that antibodies to ECGF form immune complexes which activate the complement system and obliterate blood vessels. This immune process stimulates fibroblast activation, which may lead to fibrosis in the tissue (177).

Once in the host, *B. burgdorferi* is able to induce production of matrix metalloproteases (MMPs) which plays a role in degrading extracellular matrix proteins. An increase in MMP plays an important role in the dissemination of the organism through extracellular matrix tissues. A study done by Crowley et al.

(2016) showed a positive correlation between MMP-10 autoantibodies and synovial pathology. *B. burgdorferi* can indirectly induce the expression levels of MMP-10 and so too can increased pro-inflammatory cytokines (178). This increase in MMP-10 levels leads to the recruitment and activation of MMP-10-specific T cells and subsequent autoantibody generation. This, together with a combination of excessive inflammation and immune dysregulation, could contribute to joint inflammation and autoimmunity (179).

It is interesting to note that *B. burgdorferi* lacks the ability to synthesize cholesterol, an important component of the pathogen's membrane. As a result, this cholesterol is sequestered from the host cells resulting in the pathogens' lipid composition reflecting that of host (180). This structural similarity could aid in the loss of self-tolerance and autoimmunity to apoB-100 through 2 paths. First, the autoantibodies to apo-B-100 could be a result of this complex binding to the pathogen lipid membrane, leading to an increased uptake and presentation of apoB-100 peptides resulting T and B cell responses or antibodies against the pathogens' membrane glycolipids could cross-react with apoB-100 epitopes, leading to enhanced uptake and HLA-DR presentation of apoB-100 peptides (180).

Annexin A2, another autoantibody found in patients with Lyme arthritis, acts as a receptor for plasminogen and tissue plasminogen activator on endothelial cells and plays a crucial role in the enzymatic breakdown of fibrin in blood clots (181). Anti-Annexin 2 antibodies can activate endothelial cells leading to loss of the anticoagulant phenotype and assumption of pro-inflammatory, prothrombotic properties (182). *B. burgdorferi* binds host plasminogen with borrelial surface proteins and subsequently digests the extracellular matrix and disseminates (183). Pianta et al. (2015) postulated that since annexin A2 binds both plasminogen and tissue plasminogen activator, the pathogen may also bind annexin A2, thereby acting as a conduit for phagocytosis of Annexin A2. The resulting cell debris, consisting of both pathogen and host antigenic peptides stimulates T and B cell responses. The inflammatory microenvironment of the joint, in patients with antibiotic-refractory Lyme arthritis, may lead to increased expression of Annexin A2. This would result in greater HLA-DR presentation of Annexin A2 peptides, suggesting that abundance of the Annexin A2 is a factor in antigenicity. In addition, high levels of annexin A2 protein in the antibiotic-refractory group may stimulate FLS proliferation, resulting in increased secretion of pro-inflammatory cytokines, this together with Annexin A2 autoantigen-autoantibody complexes may further accentuate the inflammatory response (181).

It is unlikely that immune responses, to the four autoantibodies mentioned above, can alone account for antibiotic-refractory Lyme arthritis. Retained *B. burgdorferi* antigens may have a role in

inflammation in an antigen-specific manner or as an adjuvant or both. In addition, immune reactivity with multiple autoantigens, as well as excessive inflammation and immune dysregulation are probably required for an antibiotic-refractory course (177).

Improving Outcomes

The Infectious Diseases Society of America has published guidelines for the treatment of Lyme disease (184). A single dose of doxycycline may be offered to adult patients (200 mg dose) and to children 8 years and older (4 mg/kg up to a maximum dose of 200 mg) when **all** of the following circumstances exist:

1. The attached tick can be reliably identified as an adult or nymphal *Ixodes* tick that is estimated to have been attached for more than 36 hours on the basis of the degree of engorgement of the tick with blood or of certainty about the time of exposure to the tick;
2. Prophylaxis can be started within 72 h of the time that the tick was removed;
3. Ecologic information indicates that the local rate of infection of these ticks with *B. burgdorferi* is greater than 20%; *and*
4. doxycycline treatment is not contraindicated.

Prophylaxis with single-dose doxycycline would be justified depending if the specific local area has an infection rate higher than 20%, provided that all other criteria mentioned above are met (184).

The first-line therapy for adult patients, with early localized or early disseminated Lyme disease associated with erythema migrans, should be the usage of oral antimicrobial agents such as doxycycline (100 mg twice per day), amoxicillin (500 mg 3 times per day) or cefuroxime axetil (500 mg twice per day) for 14 days (range, 10–21 days for doxycycline and 14–21 days for amoxicillin or cefuroxime axetil). Doxycycline is relatively contraindicated during pregnancy or lactation and in children younger than 8 years of age. Antibiotics recommended for children are amoxicillin (50 mg/kg per day in 3 divided doses [maximum of 500 mg per dose]), cefuroxime axetil (30 mg/kg per day in 2 divided doses [maximum of 500 mg per dose]) or if the patient is 8 years or older, doxycycline (4 mg/kg per day in 2 divided doses [maximum of 100 mg per dose]) (184).

Lyme arthritis can also be treated successfully with oral antimicrobial agents; doxycycline (100 mg twice per day), amoxicillin (500 mg 3 times per day) or cefuroxime axetil (500 mg twice per day) for 28 days. For children, amoxicillin (50 mg/kg per day in 3 divided doses [maximum of 500 mg per dose]),

cefuroxime axetil (30 mg/kg per day in 2 divided doses [maximum of 500 mg per dose]) or if the patient is 8 years or older, doxycycline (4 mg/ kg per day in 2 divided doses [maximum of 100 mg per dose]) is recommended. If joint swelling persists in patients, a second 4-week course of oral antibiotic therapy is recommended. If the arthritis fails to improve or worsens, a 2-4 week course of ceftriaxone, given intravenously, is recommended. If there is no resolution of arthritis despite intravenous therapy, nonsteroidal anti-inflammatory agents, intra-articular injections of corticosteroids, or disease-modifying antirheumatic drugs (DMARDs) is recommended for symptomatic treatment. A synovectomy may be recommended to reduce the duration of joint inflammation, if persistent significant pain or limitation of function continues (184).

As mentioned previously *Borrelia* cannot synthesize cholesterol, a key component of the pathogen's membrane and depends on the host to acquire it. It is logical to suspect that in hypercholesterolemic patients, where cholesterol is more accessible, it would be easier for *Borrelia* to acquire it and therefore to cause more severe symptoms or faster dissemination with poorer prognosis. Indeed, it has been demonstrated in an animal model of Lyme disease that deficiency of one of the key components of the efficient cholesterol transport and metabolism, ApoE protein or LDL receptor, leads to higher pathogen load in the blood and joints of the hypercholesterolemic animal and more severe inflammation (185). It would be important to note the cholesterol status of patients who present with *Ixodes* tick bite for disease outcome and management purposes.

Multiple Sclerosis

Description

Multiple sclerosis (MS), is a T cell mediated chronic autoimmune disease of the central nervous system (CNS), which is characterized by inflammation, demyelination and neurodegeneration. The course of MS is highly varied and unpredictable. In most patients, the disease is characterized initially by episodes of reversible neurological deficits, which is often followed by progressive neurological deterioration over time (186).

Genetics

MS is not caused by a single-gene defect, but rather by the effect of several genes that each contribute to the risk of disease. Following a number of genome-wide association studies, genes within the HLA region are now thought to exert a major genetic contribution to MS risk. The HLA class II alleles *HLA-DRB1*15:01*, *HLA-DRB1*03:01* and *HLA-DQB1*06:02* are associated with an increased risk of developing MS, while the HLA class I allele *HLA-A*02:01* as well as HLA class II alleles *HLA-DRB1*01*, *HLA-DRB1*09* and *HLA-DRB1*11* are associated with a decreased risk or protective role (187–189).

Compared to a lifetime risk of 0.2% in the general population, siblings of affected individuals have a 10- to 20-fold higher risk of developing the disease (2–4%), with monozygotic twins having an even higher risk (30%) (190). On the other hand, the fact that the relative risk does not reach 100% even in identical twins suggests that other factors beyond genetics leads to the dysregulation of the immune response associated with MS. These factors include environmental exposures (e.g., smoking, viral infections, vitamin D intake, diet, and microbiome) as well as epigenetic signatures (e.g., DNA methylation patterns, histone modifications, and non-coding RNAs).

Pathogenesis

HLA class II molecules present processed peptides to CD4+ T lymphocytes. The strongest genetic association for MS maps to the *HLA-DRB1* gene, specifically the *HLA-DRB1*15:01.* Consistent with the gene expression data, HLA-DRB1 protein expression is increased in *HLA-DRB1*15:01*-positive cases and has been associated with larger gray matter lesions in MS (191). These findings hint at a link between the strongest genetic risk factor for MS and an important pathologic hallmark, namely demyelinated lesions in the cerebral cortex. For CD4+ T cell activation to occur, an interaction between

the T cell receptor and MHC class II/peptide (pMHC) complexes is required. The amount of antigen loaded on MHC class II molecules of antigen-presenting cells and the level of MHC class II expression determines the activation of CD4+ T cell activation. Similar to the ectopic expression of HLA class II in autoimmune thyroid disease, higher HLA-DRB1 expression by microglia in the brain may therefore affect the pMHC concentration and consequently lead to an increased probability of T cell activation and brain inflammation (191).

Environmental factors, including exposure to viral agents such as Epstein Barr virus (EBV), exposure to nitric oxide through active or passive smoking, vitamin D deficiency and diet have all been associated with the onset of MS. The foreign agents may have a nuclear antigen that is structurally homologous with myelin sheet components. Thus, when immune cells are activated by these pathogens, myelin sheath lesions will form.

The combined effects of *HLA-DRB1*15:01* positivity and EBV infection result in an up to six-fold increased risk of MS (192). The one possible mechanism which could explain the interaction effects between *HLA-DRB1*15:01* and EBV infection on the occurrence of MS is that HLA class II molecules, are involved in the processing and presentation of foreign antigens in the immune defence process. *HLA-DRB1*15:01* may interfere with this process and prevent the presentation of EBV antigens to CD4+ Th cell receptor, thereby inhibiting immune defence recognition, leading to EBV accumulation in B cells. EBV-infected B cells distributed in the CNS can present CNS antigens to CD4+ T cell receptors under the influence of the virus and may activate cellular and humoral immune responses. These EBV-infected B cells provide survival signals to the T cells, thereby inhibiting the activation-induced T cell apoptosis that normally occurs when autoreactive T cells enter the CNS. The autoreactive T cells initiate an immune attack on the CNS, recruiting macrophages and B cells. CNS antigens released by this attack induce spreading of the immune response to other CNS antigens. Repeated T cell attacks on the CNS supported by local EBV-infected B cells can ultimately produce autoantibodies that cause demyelination and neuronal damage in the underlying cerebral and cerebellar cortex, leading to the progressive phase of MS (192,193).

Smoking is also known to play an important role in MS. Hedström et al. (2014) hypothesised that smoke-induced lung-irritation in the context of HLA- MS risk genes may post-translationally modify peptides cross-reactive with CNS antigens, promoting a CNS- directed auto-aggressive immunity that results in MS (194). In addition, nitric oxide (NO), a toxic soluble gas, in pathological concentrations can damage neurons and oligodendrocytes (cells that produce the myelin sheath). Lipid peroxidation and mitochondrial damage that result from NO can lead to oligodendrocytes apoptosis, axonal degeneration and demyelination (195).

It is widely known that the risk for MS increases with distance from the equator, suggesting that environmental risk factors related to latitude, such as decreased sunlight exposure and vitamin D levels, are involved (196). High circulating levels of vitamin D has been shown to decrease the risk of developing MS (197). Vitamin D is a steroidal hormone whose active metabolite 1,25-dihydroxyvitamin D [1,25(OH)2D] serves as a ligand and activates vitamin D receptors (VDR). The VDRs are present in many parts of the body including the central nervous system (CNS), microglia, activated monocytes and B and T lymphocytes. The activation of VDR plays a major role in adaptive immunity by inhibiting the maturation of dendritic cells. The functions of dendritic cells are tightly regulated, in this manner, such that protective immune responses are elicited and unwanted immune responses are prevented (198). The 1,25(OH)2D ligand has a number of crucial roles:

1. Suppressing interferon gamma (EFN-γ) production by Th1 cells, which is associated with potential tissue damage in the pathogenesis of autoimmune diseases (199)
2. Suppressing interleukin-17 (IL-17) synthesis, which is linked to tissue damage and inflammation (200)
3. Inducing T suppressor cells (T regs) and IL-10 secretion, both of which are believed to play key roles in promoting adaptive immunity (201)

It can be seen that a deficiency in vitamin D can affect the potent immunomodulator properties which can have a negative impact on the proinflammatory pathways.

Several previous studies have investigated the roles of homocysteine (Hcy), Vitamin B12, and folate in MS, since myelin replacement requires normal function of “folate-vitamin B12-methylation” pathway. This is vital to provide methyl groups for myelin regeneration. Hcy exerts direct effects on cell damage and the activation of macrophages. Increased Hcy levels in the circulation play an underestimated role in the process of MS. Folate and Vitamin B12 are needed in the process of methionine-synthase mediating the conversion of Hcy to methionine, lacking these may cause an increased level of Hcy. Increased Hcy plays a role in the myelin sheath degeneration through interfering methyl group donors, causing neuroinflammation, microglial activation and other biochemical reactions in the CNS (202).

Improving outcomes

Meta-analysis data suggests that exercise training is associated with a small improvement in walking mobility among individuals with multiple sclerosis (202). Exercise training is described as cumulative bouts of planned and structured physical activity that are repeatedly performed for an extended period of time with a specific external objective or goal of improved or maintained fitness. It has a

promising behavioural strategy with implications for disease progression, particularly for mitigating reductions in walking mobility among people with MS.

Muscle weakness and fatigue are common symptoms in MS. Green tea catechins such as (2)epigallocatechin-3-gallate (EGCG) are known to improve energy metabolism at rest and during exercise when given to patients with MS over a 12-week period (203). Experimental autoimmune encephalomyelitis (EAE) is a well-established animal model for human MS. A study done by Wang et al. (2012) showed that EGCG supplementation was effective in ameliorating the symptoms and pathological changes in EAE animals. The EGCG was also found to reduce the inflammatory infiltration in the CNS and had the ability to down-regulate T17 cell population while promoting the up-regulation of the regulatory T cells (Treg) population (204).

The association of low vitamin D concentration and MS suggests that vitamin D supplementation may play a beneficial role of as prophylactic and/or treatment agents. A study done by Kimball et al. (2007) found that large doses of 25(OH)D supplements are safe and well tolerated by MS patients. Patients who were in an active phase of MS were given 1200 mg elemental Ca/d along with progressively increasing doses of vitamin D_3: from 700 to 7000 μg/wk (from 28 000 to 280 000 IU/wk) for a 28-week period. Even though disease progression and activity were not altered by 25(OH)D, the vitamin supplementation led to a reduction in gadolinium-enhancing lesions per patient by the end of the study (205).

The polyunsaturated fatty acid (PUFA) composition of membrane phospholipids plays an important role in immune-related and non-immune-related inflammation. PUFA and antioxidant deficiencies, along with decreased cellular antioxidant defence mechanisms have been reported in MS patients. A randomised-trial found the PLP10 (formula containing a balanced mixture of specific Ω-3 and Ω-6 PUFAs, MUFAs, SFAs, vitamin A, vitamin E and γ-tocopherol) treatment can significantly reduce the annualised relapse rate and the risk of sustained disability progression without any adverse events (206).

Rheumatoid Arthritis

Description

Rheumatoid arthritis (RA) is a common chronic inflammatory autoimmune disease that is characterized by synovitis and the localized destruction of cartilage and bone. Affected individuals gradually develop articular damage and functional disability (207). The worldwide prevalence of RA is estimated to be around 1%, with more females being affected than males.

Genetics

Based on twin studies, the heritability of the disease is estimated at around 60% (208). A particularly strong association has been found for RA and HLA-DRB1 alleles that encode a HLA-DRβ chain, containing a five amino acid sequence motif called the 'shared epitope' (SE). Majority of RA patients share a 5 amino acid sequence motif (i.e. QKRAA, QRRAA, or RRRAA) (209). This SE confers a higher risk for RA and also increases the likelihood of developing earlier disease onset and more severe bone erosions (210). The associations of RA with HLA-DRB1 SE alleles have been observed in all racial and ethnic populations. The following HLA-DRB1 SE alleles have been identified as risk alleles:

- *HLA-DRB1*04:01*, *HLA-DRB1*04:04* and *HLA-DRB1*10* in the European population (211,212)
- *HLA-DRB1*01:01*, *HLA-DRB1*04:01*, *HLA-DRB1*04:04*, *HLA-DRB1*04:05*, *HLA-DRB1*04:10* and *HLA-DRB1*10:01* in the Asian population (213)
- *HLA-DRB1*01*, *HLA-DRB1*04* and *HLA-DRB1*10* in the Syrian population (214)

A number of studies have also identified HLA-DRB1 alleles which confer protection against RA. These are:

- *HLA-DRB1*13:01* in the European population (215)
- *HLA-DRB1*11* and *HLA-DRB1*13* in the Syrian population (214)
- *HLA-DRB1*04:02, HLA-DRB1*13:01 and HLA-DRB1*13:02* have been found to be dominantly protective (216)

In addition to the SE alleles, another HLA allele, *HLA-DPB1*, has been shown to be a novel genetic marker which could be used to assess susceptibility to RA. A meta-analysis study done by Jiang et al. (2018) showed that *HLA-DPB1*04:01* and *HLA-DPB1*06:01* allelic frequencies were higher in the RA group versus the control group and contributed to RA susceptibility, while the frequencies of *HLA-*

*DPB1*01:01*, *HLA-DPB1*04:02* and *HLA-DPB1*05:01* were lower in RA group, suggesting a potential protective role against developing RA in the Caucasian and Asian populations (207).

Two-thirds of the RA risk is attributed to genetic factors, of which the SE is the most significant one. The remaining one third of disease susceptibility is attributed to non-genetic mechanisms that are most likely triggered by environmental factors (217).

Pathogenesis

The best-known environmental risk-factor for RA is smoking. Several studies have reported a strong association between the SE alleles and smoking in RA risk (218–220). A popular model for the etiology of RA suggests that the association between smoking and RA is due to the ability of the former to enhance SE-dependent immune reaction to citrullinated proteins, which in turn, trigger disease. According to this model, smoking increases the abundance of citrullinated proteins in the lung, which in SE-positive individuals may provide an antigenic stimulus for anti-cyclic citrullinated peptide generation, a useful disease marker for RA (221). This hypothesis has been strengthened by demonstration that citrullination of certain peptides, in transgenic *HLA-DRB1*04:01* mice, increases binding to HLA class II molecules with the SE (222). This peptide-MHC interaction and subsequent T-helper cell activation, may be responsible for eliciting an auto-immune response.

Excess weight and obesity are less established RA risk factors. There are several potential mechanisms by which obesity or higher BMI could lead to RA. Obesity is considered a systemic inflammatory condition with increased levels of inflammatory cytokines which have been implicated in RA pathogenesis (223). Obesity is also associated with a relative increase in estrogen levels, which likely plays a major role in RA pathogenesis given female predominance and could explain potential differences by sex (224)

Infections by many microorganisms, such as *Porphyromonas gingivalis* (*P. gingivalis), Proteus mirabilis* (*P. mirabilis*), Epstein–Barr virus (EBV) have been found to contribute to the pathogenesis of RA (225–227). Protein citrullination is a post-translational modification catalyzed by the enzyme peptidylarginine deiminase (PAD) (228). *P. gingivalis* is the only prokaryotic organism that contains PAD and is thus capable of facilitating the citrullination process generating neo-antigens which may trigger the aberrant immune responses in RA.

Microbial infection can contribute to the cartilage loss in RA patients. It has been shown that *P. gingivalis* can directly promote early and later stages of apoptosis of human chondrocytes contributing to the joint damage seen in the pathogenesis of RA (228).

Diet has long been considered a potential environmental factor influencing the development and the course of the RA. Specific dietary choices, such as a high intake of red meat, saturated and trans fats, a low ratio of omega-3:omega-6 fatty acids and high consumption of refined carbohydrates, can have pro-inflammatory effects (229). Moreover, diet plays an important role in maintaining the intestinal microbial homeostasis related to the pathogenesis of several inflammatory diseases, including RA. RA patients present a reduced gut microbial diversity in comparison to healthy controls. The gut bacteria have important digestive roles such as vitamin synthesis, digestion and cleavage of fibre and other dietary components into metabolites such as short-chain fatty acids (SCFA). These SCFA act as anti-inflammatory molecules modulating macrophages and dendritic cells and enhancing regulatory T cells function (230). SCFA also has beneficial effects on the intestinal barrier by reducing intestinal permeability and bacterial translocation, limiting local and systemic inflammation. Changes in microbiota or dysbiosis, due to poor dietary patterns, may consequently promote increased intestinal permeability and local inflammation, causing a consequent spreading of inflammation to the joints (231).

Improving Outcomes

Since the central paradigm for RA pathogenesis is related to a gene-smoking interaction wherein individuals with HLA-DRB1 SE alleles and history of heavy smoking are at very elevated risk for RA, it would be intuitive to think that smoking cessation would decrease the risk of developing RA. A number of studies have provided moderate evidence that smoking cessation could reduce seropositive RA risk (232,233). Costenbader et al. (2006) suggested that a certain threshold amount of cigarette smoke exposure is necessary and that once attained, this exposure poses a latent, rather than an instantaneous hazard and that the risk of developing RA does not decrease with time until long after cessation of exposure, 20 years or more (234). It must be kept in mind that smoking cessation may reduce, and not remove, RA risk.

Physical activity can be an effective intervention on RA risk. Physical activity can modulate the Th1/Th2 and natural killer cells levels and produce hormones including epinephrine and norepinephrine. Together, these effects tend to lower systemic inflammation and provide a rationale that physical activity could protect against RA (235). A study done by Di Giuseppe et al. (2015) found a 35% lower

risk of RA among women in the highest category of leisure-time activity (combining more than 20 minute per day of walking/bicycling (median 40–60 minute per day) and more than 1 hour per week of exercise (median 2–3 hours per week)) as compared to women in the lowest category (less than 20 minute per day of walking/bicycling and less than 1 hour per week of exercise) (236). Another study confirmed a statistically significant trend for reduced RA risk with increasing cumulative average total recreational activity hrs/wk (237). These recreational activities included walking, jogging, running, bicycling, lap swimming, tennis/racquet sports, and aerobics/calisthenics. In addition, cumulative average walking hrs/wk among women with a brisk/very brisk walking pace was associated with a statistically significant reduction in RA risk.

Dietary intervention can significantly modify gut microbiota in people at risk of developing RA. Foods rich in fibres, such as those present in the Mediterranean diet, are degraded by gut microbiota into SCFA, which can result in a protective effect on the intestinal barrier by reducing its permeability and limiting inflammation (238). A Mediterranean diet provides antioxidant, anti-inflammatory and prebiotic effects. It is characterized by a significant amount of unrefined cereals, fruit, vegetables, legumes; a consistent intake of extra-virgin olive oil, fish; a moderate consumption of eggs, dairy products, alcohol and a low consumption of sweets and red meat. A study done by Häger et al. (2019) found that RA patients who received daily high-fibre bars (ingredients: ground flaxseed, oat flakes, psyllium husk, inulin, arrowroot flour, guar gum, coconut, and hemp flour) or cereals for 28 days had an increase in circulating regulatory T cell numbers, as well as decreased markers of bone erosion. Furthermore, patient-related outcomes of RA improved (239). More recently, Diamanti et al. (2020) demonstrated an inverse association between Mediterranean diet and disease activity. While the high adherence group displayed a healthier gut microbiota composition, a significant decrease in Lactobacillaceae and an almost complete absence of *Prevotella copri* was noted in the low/moderate adherence group. These findings support the protective role of a Mediterranean diet on disease activity and microbiota composition in RA patients (240).

Systemic Lupus Erythematosus

Description

Systemic lupus erythematosus (SLE) is a multi-system, chronic, autoimmune inflammatory disease. It affects women of child-bearing age, with a female to male ratio of 9:1 (241). SLE is a heterogeneous disease with diverse clinical manifestations ranging from autoimmune haemolytic anaemia, leukopenia and thrombocytopenia to nephritis, arthritis, dermatitis and neuropsychiatric involvement (242).

Genetics

SLE has a strong genetic basis with a concordance rate of 2–5% in dizygotic compared with 24–57% in monozygotic twins (243). Susceptibility to SLE is determined by multiple immunological abnormalities arising from genetic variation at multiple loci. Genome wide studies have found that markers within the HLA region are very strongly associated with SLE (243).

The following HLA class I and II alleles have been identified as risk alleles for SLE:

- *HLA-A*29* in the Saudi population (244)
- *HLA-B*51* in the Saudi population (244)
- *HLA-DRB1*03:01* and *HLA-DRB1*15:01* in European, Latin Americans, Korean and Asian populations (245–250)
- *HLA-DRB1*07*, *HLA-DRB1*08:03* and *HLA-DRB1*09:01* in the Korean population (250)
- *HLA-DRB1*08:01* in the European population (247)
- *HLA-DRB1*15* in the Caucasian and Saudi population (2,244)
- *HLA-DQA1*01:02* in the European population (247)
- *HLA-DQB1*02* and *HLA-DQB1*06:02* in the Asian population (246)
- *HLA-DQB1*06* in the Saudi population (244)
- *HLA-DQB1*03:01* in the Han Chinese population (251)

It is important to note that a study done in the European population observed that the risk association of *HLA-DRB1*15:01* was due to its correlation with the *HLA-DQA1*01:02* risk allele, whereas the association of *HLA-DQA1*01:02* allele could not be explained by its correlation with *HLA-DRB1*15:01* allele (247).

In contrast, only a few protective HLA alleles have been identified:

- *HLA-DRB1*11:01* in the Latin American and Korean populations (2,248)
- *HLA-DRB1*12:02* in the Korean population (2)
- *HLA-DRB1*13* in the Caucasian population (2)
- *HLA-DRB1*13:02* and *HLA-DRB1*14:03* in the Japanese population (249)
- *HLA-DRB1*16* in the Saudi population (244)

It should be noted that protective effects of *HLA-DRB1*13:02* and *HLA-DRB1*14:03* are dominant over the predisposing risk effects of *HLA-DRB1*15:01* in SLE (252).

It is important to understand that HLA susceptibility and protective alleles are dependent on physicochemical differences of certain amino acids residues, that are responsible for shaping the peptide-binding groove (248).

Another important genetic association with SLE, is mutations in genes linked to the complement system classical pathway (253).

Pathogenesis

SLE is known to develop through multiple steps with the loss of self-tolerance and development of autoantibodies occurring sometimes several years prior to the onset of the clinically symptomatic disease (254). While some first degree relatives, of patients with SLE, have a higher prevalence of SLE-related autoantibodies and are at a higher risk of developing SLE, other first degree relatives with a high prevalence of SLE-related autoantibodies do not develop clinical SLE, suggesting the potential influence and complexity of environmental factors (254).

A broad-profile of autoantibodies are present in patients with SLE and many of them develop prior to the clinical manifestation of SLE. These include anti-nuclear antibodies (ANA), anti-double strand DNA (anti-dsDNA) antibodies, anti-Ro antibodies, anti-La antibodies and anti-Smith or Sm antibodies (241). These antibodies are directed at several self-molecules found in the nucleus, cytoplasm and cell surface, in addition to soluble molecules such as IgG and coagulation factors. ANA are most characteristic of SLE and present in more than 95% of patients (255). The clinical manifestations of SLE are a result of the deposition of the autoantigen-autoantibody immune complexes in tissues, resulting in subsequent hypocomplementemia and multi-organ damage (256).

The complement system plays a key role in the innate and acquired immune response and contributes to the inflammatory response triggered by immune complex deposition in tissues in autoimmune diseases (253). A decrease in complement activity could promote disease susceptibility by impairing the neutralisation and clearance of self- and foreign-antigens. When the antigen burden overwhelms the clearance capacity of the immune system, autoimmunity may follow (255).

Several environmental factors have been suggested to be associated with the development of SLE, in genetically susceptible individuals. These include exposure to silica, current smoking, vitamin D deficiency and Epstein Barr Virus (EBV) exposure (242,257–259).

Crystalline silica exposure is an occupational hazard, with the highest exposure being in construction, mining, ceramics, stone masonry or tile work industries. Exposure to silica has been shown to be a risk factor for developing SLE (260,261). A study by Finckh et al. (2006) showed that longer exposure to silica dust was associated with greater risk of developing SLE, suggesting a dose response (260). Constant inhalation of silica can have a negative impact on many cell types, including the alveolar macrophages in the lungs, inducing cell death or apoptosis (262). This results in the extracellular release of host DNA, which together with the uncleared cellular debris, will be presented by the HLA molecules on the antigen-presenting cells, promoting the development of autoreactive B and T cells. These cells are responsible for the production of auto-antibodies against host antigens, forming DNA-containing immune complexes and initiating inflammatory autoimmune responses (262). A study done by Brown et al. (2003), looked at the natural progression of SLE, in genetically susceptible mice, following inhaled silica. The study found high titres of circulating immune complexes, proteinuria and immune complex deposition within the kidneys, resulting in glomerulonephritis and subsequent death of the mice (263). Animals models of SLE have demonstrated that mutations in genes involved in the complement pathway can impair the clearance of dead cell debris, which is shown to be strong risk factors for the development of SLE (264).

Results from past studies focusing on the association between smoking and SLE have been conflicting, until recently (242,265). Meta-analysis data, together with a recent large cohort study, found an increased risk of developing SLE among current smokers and past smokers who had recently quit (within 4–5 years) (242,265). The toxic components of cigarette smoke is known to induce oxidative stress and directly damage endogenous proteins and DNA, leading to genetic mutations and gene activation, increasing B and T cell proliferation, reducing immune suppressive T regulatory (Treg) cell proliferation and activity, promoting autoantibody generation and enhancing the expression of pro-inflammatory mediators (266). This could induce inflammatory and autoimmune responses. A study

done by Freemer et al. (2006) found higher levels of dsDNA autoantibodies in the sera of SLE patients who were current smokers versus former or never smokers (267). A more recent study done by Barbhaiya et al. (2018) confirmed these findings (265). Reactive oxygen species, produced from the metabolism of tobacco smoke constituents can modify DNA and form DNA adducts. SLE patients tend to have higher levels of DNA adducts than healthy controls, and these adducts are found at high levels within immune complexes (268). This damaged DNA is more immunogenic than the undamaged dsDNA and serve as autoantigens, promoting the production of anti-dsDNA antibodies and subsequent immune complexes which induce serious inflammation (267,269). The autoantibodies are associated with a more severe phenotype of the disease; nephritis and vasculitis (270). The immune complexes have been shown to be deposited along the glomerulus basement membrane of the kidney (269).

A number of studies have found an inverse relationship between vitamin D levels and SLE disease activity (258,271–273). The most active form of vitamin D, 1,25-Dihydroxyvitamin D [1,25$(OH)_2$D] or calcitriol, serves as a ligand for the vitamin D receptor which is present on many immunocytes, and has been shown to have multifaceted immunomodulatory effects (73). Active vitamin D induces B cell apoptosis thereby preventing B cell activation, proliferation and differentiation. Active vitamin D also reduces the maturation of dendritic cells and suppresses dendritic cell-dependent T-cell activation, by down-regulating the expression of MHC II molecules. T cells are another target of vitamin D action where active vitamin D inhibits the cytotoxic activity of T cells by reducing Th1 and Th17 cells, which play a key role eliciting the inflammatory response by the release of cytokines. Conversely, active vitamin D induces the differentiation of regulatory T cells, which play a pivotal role in the regulation of immune responses and maintenance of self-tolerance and immune homeostasis (74,75). Vitamin D deficiency has an opposite effect, resulting in the hyperactivation of B cells, an increased production of autoantibodies, in particular those directed against nucleic acids (ANA) and suppressing Treg function. The latter contributing to the loss of immune tolerance and activation of inflammatory cytokines, contributing in SLE pathogenesis in genetically susceptible individuals.

Viral infections may be involved in the pathogenesis of SLE. The Epstein–Barr virus (EBV) is of particular interest and many studies have demonstrated a link between EBV and SLE (259,274,275). EBV has the ability to shift between an active lytic cycle and a latent state from which it can reactivate, depending on its interaction with host immune cells (276). Elevated viral loads have been noted in SLE patients compared to healthy controls, suggesting that viral reactivation is associated with the development of SLE (259,274). EBV is known to efficiently infect B cells via a complement receptor (CD21) and HLA class II molecule. This is followed by a vigorous CD8+ T cell response, which is responsible for

controlling the latently infected B cell population, which falls to a low steady state level, which is then maintained for life. A primary infection with EBV leads to an IgG response to viral capsid antigen (VCA). These VCA IgG antibodies are maintained throughout the life span of the individual. Following VCA IgG response, IgG responses toward early antigen (EA) are detected. These antibodies are detectable for 6 months to up to two years. Occasionally, EBV can be reactivated in these B cells and switch to a lytic cycle, allowing for viral transmission, the trigger for reactivation is unknown. During EBV reactivation, EA IgG levels are detectable and there is an increase in VCA IgG levels (276). Draborg et al. (2012) hypothesized that genetic predispositions in components of the classical complement pathway, certain HLA alleles and other immune-regulatory pathways could lead to frequent reactivation of EBV (277). EBV IL-10 (vIL-10) is a late viral gene expressed during the lytic phase of viral replication and is highly homologous to the human IL-10 (hIL-10) gene but displays functional differences to hIL-10. VIL-10 is known to inhibit induction of anti-inflammatory gene expression, in the host, and stimulate the differentiation of monocytes to cells with an increased antigen presentation capability while reducing their ability to clear apoptotic cells (278). An increase in cell debris from ineffective clearance of apoptotic cells results in increased autoantigen presentation and an amplification of autoimmune responses in SLE patients. Another mechanism by which EBV could add to SLE pathogenesis is through molecular mimicry. EBV nuclear antigen-1 (EBNA-1), displays high sequence homology to host nuclear components such as histones, Ro52, Ro60, La, and Sm and as a result antibodies to EBNA-1 have been found to cross-react with nuclear autoantigens due to these structural similarities (276,279). Immune complexes consisting of autoantigen-antibody complexes are internalized by antigen presenting cells resulting in the antigen being processed and peptides presented, by HLA molecules, to T cells resulting in the loss of tolerance. This loss of tolerance is responsible for contributing to an autoimmune response and clinical presentation of SLE (276).

Improving Outcomes

Vitamin D supplementation has the ability to increase serum 25-hydroxyvitamin D levels [25(OH)D] levels. A prospective study done by Terrier et al. (2012), found that oral vitamin D supplementation (100,000 IU of cholecalciferol per week for 4 weeks, followed by 100,000 IU of cholecalciferol per month for 6 months) had a beneficial impact on SLE patients displaying vitamin D deficiency (73). The supplementation was well tolerated and was found to induce a preferential increase of naïve CD4+ T cells, an increase of regulatory T cells, a decrease of effector Th1 and Th17 cells, and a decrease of memory B cells and anti-DNA antibodies. Another similar study done by Lima et al. (2016) administered oral cholecalciferol of 50,000 IU/week for 6 months to juvenile-onset SLE patients. The results showed that vitamin D supplementation was effective in decreasing disease activity and

improving fatigue. A significant reduction in anti-dsDNA antibodies was also noted (280). Elevated anti-dsDNA titres have been associated with moderate-to-severe SLE flares (281). Since vitamin D supplementation has the ability to decrease anti-dsDNA antibodies, it may be a beneficial therapeutic strategy for patients with high anti-dsDNA positivity, possibly assisting with reducing clinical flares.

A recent meta-analysis by Islam et al. (2020) found that a diet low in calories and protein but high in fibre, polyunsaturated fatty acids, vitamins (A, B, C, D, and E), minerals (calcium, zinc, selenium, iron and copper) and polyphenols has sufficient potential to regulate the activity of the overall disease by modulating the inflammation and immune functions of SLE (282). A traditional Mediterranean diet, consisting of vegetables, fruits, nuts, grains, olive oils and fish with limited meat consumption, may be a reasonable approach in SLE patients suffering from nephropathy. A high protein intake contributes to reduced renal filtration, directly leading to the progression of kidney damage (282). An adequate intake of dietary fibre could have a beneficial impact on decreasing disease activity by decreasing serum levels of autoantibodies and inflammatory cytokines, as seen in a prospective Japanese study (283). Polyunsaturated fatty acids, in particular, omega-3 fatty acids, have been shown to lower serum anti-dsDNA antibodies, IgG deposition in kidneys, and proteinuria (284). Vitamin A supplementation, in the form of retinoic acid, has been shown to modulate Th17 and Treg balance in the SLE patients, by inhibiting Th17 differentiation and enhancing Treg population, respectively. A daily vitamin A supplementation of 100,000 IU daily must not be exceeded (285,286). Approximately 15% of SLE patients have increased serum homocysteine levels, which is also associated with atherosclerosis in women affected by SLE (287). Intake of vitamins B6, B12 and folate can decrease the levels of homocysteine and subsequently retard the development and progression of atherosclerosis in SLE (283,287). Vitamin C is an antioxidant vitamin and has the ability to relieve oxidative stress and suppress the production of autoantibodies, in SLE patients, and in so doing could prevent the occurrence of active SLE disease (288). Vitamin E supplementation has also been shown to decrease antibodies, alleviating the severity of SLE (282).

Vitiligo

Description

Vitiligo, being autoimmune in nature, is a common depigmenting skin condition, characterized by a loss of melanocytes, which results in the appearance of milky white patches on the skin (289,290). The disease has an worldwide estimated prevalence of 0.1–2%, affecting both males and females equally (291). Vitiligo frequently occurs with other autoimmune diseases, such as rheumatoid arthritis, adult-onset type 1 diabetes mellitus, psoriasis, Addison's disease and systemic lupus erythematosus (292). These associations indicate that vitiligo shares common genetic etiologic links with these other autoimmune disorders.

Genetics

Epidemiological studies have found that 20% of probands have at least one first degree-relative affected with vitiligo, while monozygotic twins show a concordance rate of 23% (293,294). To date, GWAS studies have identified 50 loci associated with vitiligo susceptibility, in cases of European ancestry (295). These findings indicate that vitiligo is a complex, polygenic, multifactorial trait.

Being autoimmune in nature, many studies have been done looking at the MHC region of the genome (289,295–297). A number of associations have been found with both MHC class I and class II genes and susceptibility and protection to and from vitiligo, respectively. The following alleles were found to be positively associated with vitiligo:

- *HLA-A*02*, *HLA-A*33* and *HLA-A*33:01* – a strong association has been found between *HLA-A*02* and susceptibility to vitiligo in multiple studies and meta-analyses (289,297,298)
- *HLA-B*13*, *HLA-B*27*, *HLA-B**44:03 (289,296)
- *HLA-DRB1*07:01* (289)

In contrast, only a few alleles have been found to decrease susceptibility to vitiligo:

- *HLA-A*09* (298)
- *HLA-B*18*, *HLA-B*35* and *HLA-B*52* (296)

A genome-wide association study done by Jin et al. (2019) found a very strong association between an insertion/deletion (indel) polymorphism, rs145954018, and early age of vitiligo onset (299). The high-risk rs145954018del allele is in almost complete LD with another SNP, which is generically associated with both early- and late-onset vitiligo. Together, the rs145954018del-rs9271597A

haplotype carrying the risk alleles of both variants confers an 8-fold elevation of vitiligo risk and accelerates vitiligo onset by about 9 years (299).

Pathogenesis

Vitiligo is a disease associated with the skin and the skin is the first point of contact for one's interaction with the external environment (295,300,301). In those individuals who are genetically susceptible, exposure to phenols or having some form of skin injury has the ability to disrupt melanogenesis resulting in autoimmunity and melanocyte destruction.

Melanocytes are responsible for synthesizing melanin through a multi-step process which involves tyrosinase as the key enzyme (302). Even though the primary function of melanocytes is protection from UV irradiation, it also plays a role in the immune system and is found to express MHC class I and II molecules (303,304).

The pathogenesis of vitiligo is complex and only partially understood. However, the interaction of oxidative stress with the immune system clearly appears to be the key pathway that initiates and/or amplifies the loss of melanocytes.

The sera of patients with vitiligo has shown the presence of anti-tyrosinase antibodies which are targeted against tyrosinase, the key enzyme involved in melanin synthesis (305). Air pollutants can induce oxidative stress in human skin (306). A study done by Eskandani et al. (2010) revealed that oxidative stress and tyrosinase activity were inversely correlated with a decrease in tyrosinase activity in lesional skin of vitiligo patients compared to the controls (307). Chronic oxidative stress can alter the structure of tyrosinase which then serves as a neoantigen. This neoantigen, being sufficiently homologous to the host antigenic protein, can elicit an autoimmune response through molecular mimicry (308). There are two functional components in the MHC class I region that drives vitiligo susceptibility; increased HLA-A expression due to variants in the transcriptional regulatory region and antigenic specificity of HLA-A*02:01. These two features collectively increase cell-surface presentation of target antigens, resulting in an autoimmune attack on the melanocytes by cytotoxic T-cells (309). In this regard, the melanocytes are responsible for their own demise.

Chemical-induced depigmentation of the skin, through occupational hazards and household commercial skin-care products, has been recognised for over half a decade (300). Depigmenting chemicals, particularly phenols, share a chemical structure with tyrosine which serves as a key building

block for melanin. Tyrosinase makes key modifications to tyrosine during melanin synthesis. Phenols, due to their structural similarity to tyrosine, can serve as a substrate for tyrosinase and covalently binds to tyrosinase, creating a neoantigen (300). This stimulates the production of autoantibodies which activate an inflammatory cascade resulting in an autoimmune destruction of melanocytes.

Early onset vitiligo is dependent on whether an individual carries the rs145954018del-rs9271597A haplotype. The two polymorphisms, rs145954018 and rs9271597, are both located within lymphoid-specific transcriptional enhancers and have the ability to increase the expression of the HLA-DQ proteins on the surface of professional antigen presenting cells. Increased surface presentation of triggering antigens by HLA-DQ molecules may increase the probability of autoreactive T cell activation and thus may both increase overall vitiligo risk and accelerate vitiligo onset (299).

Improving Outcomes

Oxidative stress plays a key role in initiating melanocyte loss in vitiligo. Ginkgo biloba extract (EGb761) is a well-known antioxidant and has shown positive therapeutic effects in a variety of oxidative stress-related diseases (310,311). A study done by Zhang et al. (2018) found EGb761 to have a protective effect on melanocytes against oxidative stress damage by activating the Nrf2 signalling pathway (312). The exact mechanism of protection has not yet been elucidated.

Certain foods contain naturally occurring plant phenols and polyphenolic compounds (tannins), which have the ability to exacerbate and aggravate vitiligo through the mechanism mentioned above (313). These foods include mango, cashew, pistaschio, oak, cassava, areca nut, red chillies, cherry, raspberry, cranberry, blackberry and tea.

Circulating levels of vitamin D (as measured by 25-hydroxyvitamin D3 or 25(OH)D3) have been shown to be inversely related to the activity of various autoimmune diseases (12,32,197). Vitamin D has a stimulatory and protective effect on melanocytes and acts through its vitamin D receptor (VDR) on target cells. A case-control study done by Hassan et al. (2019) found a number of single nucleotide polymorphisms in the vitamin D receptors (VDR), resulting in potential VDR dysfunction in the vitiligo cases versus the controls, which could lead to vitamin D deficiency. The circulating vitamin D levels were markedly lower in the cases, suggesting that vitamin D deficiency may play a role in the vitiligo susceptibility (314). A study done by Finamor et al (2013) found that a daily oral intake of vitamin D3 (35,000 IU), together with partial dietary calcium restriction and a daily hydration of at least 2.5 L, was beneficial for patients with vitiligo and resulted in 14 of 16 patients having 25–75% re-pigmentation

(315). This pilot study showed that a high dose of vitamin D3 is a safe and effective therapeutic approach for reducing disease activity.

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