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Molecular mimicry and autoimmunity

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ABSTRACT

Molecular mimicry is one of the leading mechanisms by which infectious or chemical agents may induce autoimmunity. It occurs when similarities between foreign and self-peptides favor an activation of autoreactive T or B cells by a foreign-derived antigen in a susceptible individual. However, molecular mimicry is unlikely to be the only underlying mechanism for autoimmune responses; other factors such as breach in central tolerance, non-specific bystander activation, or persistent antigenic stimuli (amongst others) may also contribute to the development of autoimmune diseases. Host genetics, exposure to microbiota and environmental chemicals are additional links to our understanding of molecular mimicry. Our current knowledge of the detailed mechanisms of molecular mimicry is limited by the issues of prolonged periods of latency before the appearance of disease, the lack of enough statistical power in epidemiological studies, the limitations of the potential role of genetics in human studies, the relevance of inbred murine models to the diverse human population and especially the limited technology to systematically dissect the human T-cell repertoire and B-cell responses. Nevertheless, studies on the role of autoreactive T-cells that are generated secondary to molecular mimicry, the diversity of the T-cell receptor repertoires of auto-reactive T-cells, the role of exposure to cryptic antigens, the generation of autoimmune B-cell responses, the interaction of microbiota and chemical adjuvants with the host immune systems all provide clues in advancing our understanding of the molecular mechanisms involved in the evolving concept of molecular mimicry and also may potentially aid in the prevention and treatment of autoimmune diseases.

1. Introduction

Autoimmune diseases (ADs) are a chronic and clinically heterogeneous group of diseases that affect approximately 5% of the world population [1], with a steady rise throughout Westernized societies [2]. Although clinically diverse, autoimmune disorders share common immunopathogenic mechanisms and risk factors, coined as the autoimmune tautology [3]. Interestingly, one AD may coexist with others (i.e., polyautoimmunity) [4], which may exhibit several autoantibodies with diverse specificities. ADs are considered "complex" since their pathology is secondary to the interaction of host genetics (i.e., polygenic) and environmental factors [1]. The influence of environmental exposure on the risk of developing ADs is paramount (i.e., the autoimmune ecology) [5]. In this respect, infectious agents have often emerged as key factors for ADs and in some cases, the pathology is considered a "post-infectious" AD (e.g., Guillain-Barré syndrome - GBS) [6,7]. One of the leading mechanisms by which infectious or chemical agents may induce autoimmunity is molecular mimicry, which occur when similarities between foreign and self-peptides favor an activation of autoreactive T or B cells by foreign-derived peptides in a susceptible individual.

In 1966, Zabriskie and Freimer described the similarity between the *S. pyogenes* membrane and mammalian muscle [8], and subsequently a number of pathogens exhibiting structures that share homology with human proteins have been reported [9–12]. For example, in GBS, a homology between the polysaccharides of *Campylobacter jejuni (C. jejuni)* membrane with carbohydrate structures found in the myelin sheath of peripheral axons was reported [6,13]. Interestingly, GBS has also been associated with influenza vaccination [14] with a similar sharing of epitopes between host and microbe, thus further supporting

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Abbreviations

ADs	Autoimmune diseases
AIH	Autoimmune hepatitis
AITD	Autoimmune thyroid disease
AMAN	Acute motor axonal neuropathy
APC	Antigen presenting cell
AS	Ankylosing spondylitis
BCR	B-cell receptor
CMV	Cytomegalovirus
CNS	Central nervous system
CVB	Coxsackievirus B
CI	Confidence interval
EAE	Experimental autoimmune encephalomyelitis
EBV	Epstein–Barr virus
EBVNA1	EBV nuclear antigen 1
GAD65	Glutamic acid decarboxylase 65
GBS	Guillain-Barré syndrome
GD	Graves' disease
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GWAS	Genome-wide association studies
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBVP	Hepatitis B virus polymerase
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
HpmB	*Proteus mirabilis* hemolysin B
HPV	Human papilloma virus
HSV	Herpes simplex virus
HT	Hashimoto's thyroiditis
HTLV-1	Human T-lymphotropic virus 1
IFN	Interferon
IL	Interleukin
JCV	John Cunningham virus
LCMV	Lymphocytic choriomeningitis virus
LKM1	Liver kidney microsome type 1 antibodies
MBP	Myelin basic protein
MHC	Major histocompatibility complex
MOG	Myelin oligodendrocyte glycoprotein
MS	Multiple sclerosis
NOD	Non-obese diabetic
PBC	Primary biliary cholangitis
PDC-E2	E2 component of the pyruvate dehydrogenase complex
POTS	Postural orthostatic tachycardia syndrome
RA	Rheumatoid arthritis
RIP-LCMV	Rat insulin promoter-lymphocytic choriomeningitis virus
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
SSc	Systemic sclerosis
T1D	Type 1 diabetes
TCR	T-cell receptor
Tg	Thyroglobulin
Th1	T-helper type 1
Th17	T-helper type 17
Th2	T-helper type 2
TMEV	Theiler's murine encephalomyelitis virus
Treg	T regulatory cell
TSH	Thyroid-stimulating hormone
TSHR	Thyroid-stimulating hormone receptor
OR	Odds ratio
UreC	Urease C
UreF	Urease F
Yops	Yersinia outer proteins
YpOmpF	OmpF porin from *Yersinia pseudotuberculosis*

molecular mimicry in the induction of autoimmunity. Within this context, it is important to recall that substances such as adjuvants, may amplify the immune response, including molecular mimicry [15].

Although there are extensive studies on the homology between a large number of microbial peptides/proteins and human tissue peptides/protein, the details by which the microbial proteins are involved in the etiology of AD remains enigmatic. However, the fact that up to 99.7% of bacterial heptapeptides are shared between microbes and humans [9] suggests that such molecular identity between microbes and the human host cannot be the sole etiology in autoimmunity [16]. In fact, the balance between autoimmunity and self tolerance may be affected by other factors inherent in the hosts [17–24]. Moreover, the development of autoimmunity is associated with activation of previously autoreactive T cells, which may occur in response to hidden antigens (i.e., cryptic antigens) [25,26]. In addition, given the wide avidity of T-cell receptors (TCR) to recognize foreign antigens, diverse configurations of the TCR (e.g., heterodimers or homodimers of α and β chains) may play a central role in loss of tolerance [16]. Herein, a comprehensive review of molecular mimicry is presented.

2. "Molecular mimicry": an evolving concept

In 1964, Damian formally used the term "molecular mimicry" to denote that existence of similar antigens expressed by infectious agents and their human hosts may facilitate microbes to avoid the host immune response [27]. Two years earlier, Kaplan et al. [28] reported evidence of immune cross-reactivity in a patient with rheumatic fever by examining the sera reaction of rabbits immunized with group A streptococcal cells to human heart tissue. However, at that moment the precise homology between these structures was unknown. In 1966, Zabriskie and Freimer discovered that the membrane structures in group A streptococcus, shared structures with mammalian muscle [8]. Simultaneously, Damian proposed that parasites exhibit antigenic determinants similar to antigenic structures found in humans, which instead of inducing a parasite specific immune response, leads to the facilitation of parasitemia due to immune tolerance [27]. Although these two perspectives may appear contradictory, current evidence advocates that the two hypotheses could coexist in a complex network and suggest that other factors in addition to homology itself are necessary for triggering autoimmunity [29–31].

Thereafter, based on epidemiological and experimental evidence, there has been a growing awareness of the role of infectious diseases in autoimmunity via molecular mimicry and cross-reactivity. One of the first experimental models was described by Fujinami et al. [32] in 1983. They found that murine antibodies to measles virus and herpes simplex virus (HSV) were found to react against human cells. Furthermore, in 1985, these authors, using myelin basic protein (MBP) encephalitogenic peptide, which shares homology with the hepatitis B virus polymerase (HBVP), demonstrated that myelin basic protein MBP or HBPV sensitized rabbits developed encephalomyelitis [33]. These studies reflected the potential role of molecular mimicry in autoimmunity.

Although animal studies on infection and autoimmunity have provided convincing data supporting molecular mimicry, a question remained: why do most patients with infectious diseases not develop ADs? If molecular mimicry were sufficient to induce autoimmunity, ADs would have a higher prevalence than reported today (i.e., 5%). Trost and Kanduc et al. [9,34], addressed this question and demonstrated the existence of a large overlap of viral and bacterial peptides with the human proteome, up to 99.7%. Further questions on additional mechanisms associated with cross-reactivity have also emerged. For

instance, why do multiple sclerosis (MS) patients, who are infected with Epstein-Barr virus (EBV) and are HLA-DRB1*15:01 exhibit a higher risk for MS than those patients who express the HLA allele but not EBV infection or those who do not express the HLA allele but are infected with EBV? [35]. Because other factors such as chemicals, cosmetic and food additives (e.g., 2-octoynoicacid) have been shown to be associated with molecular mimicry and the development of ADs such as primary biliary cholangitis (PBC) [36]. Thus, the mechanism of cross-reactivity associated with molecular mimicry is more complex than previously described.

Additional striking data about the role of molecular mimicry in ADs comes from studies of individuals post standard vaccination. Thus, it has been suggested that patients receiving vaccines may develop ADs [37]. This is exemplified by a report that there is an approximate 3-fold increased risk for GBS after vaccination following immunization with the H1N1 Influenza vaccine [38]. This has been ascribed to the similarities between some structures of influenza virus with those found in the myelin sheaths [6]. However, since the incidence of influenza vaccine associated development of GBS is rare, it is reasoned to be influenced by host genetics. There is also a case to be made for the role of adjuvants that are used for such vaccinations [15]. These compounds added to vaccines increase the response of the immune system to antigens. It has thus been suggested that the homology between the human proteome and the adjuvanted-vaccine in a genetically susceptible host may increase the possibility for the induction of cross-reactive immune responses that lead to AD [15].

Recent studies have focused on the B-cell response associated with the production of autoantibodies [39–42]. The recognition of antibodies against self-antigens has been used as a “signature” of autoimmunity. For example, patients with *C. jejuni* infection and GBS develop antibodies against GM1, which are glycoproteins located on the myelin sheath [43]. These findings suggest that the production of these autoantibodies was the primary mechanism related to the development of GBS [6]. However, some patients with GBS and *C. jejuni* infection do not produce autoantibodies [44]. These observations led to a change in the paradigm of molecular mimicry elicited B-cell response as the cornerstone in autoimmunity [16] and suggests that autoreactive T cells escape central and peripheral tolerance mechanisms, which if

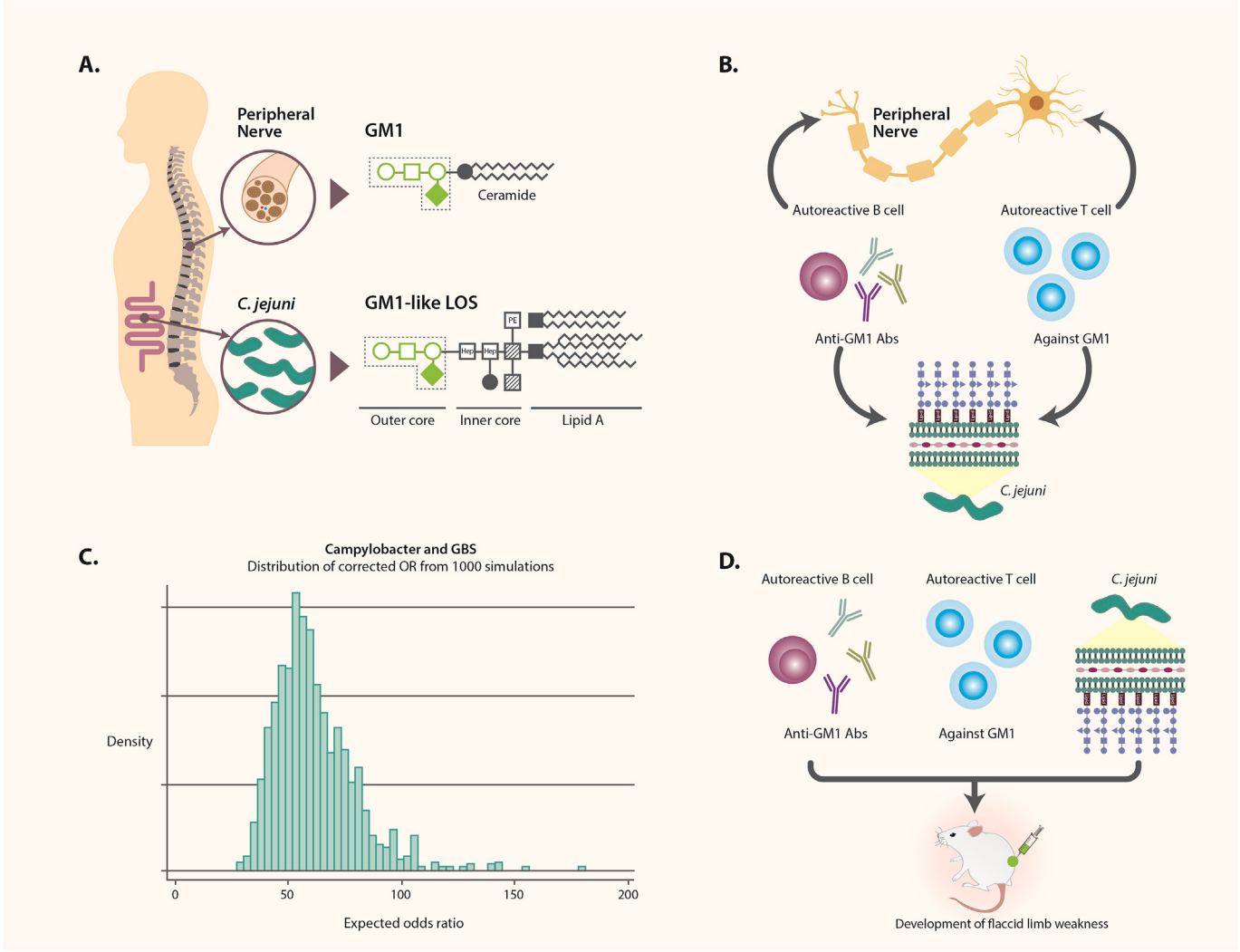

Fig. 1. Criteria for the identification of molecular mimicry. A. Evidence of homology between host epitopes and an epitope of the microorganism. *Campylobacter jejuni* (*C. jejuni*) shares homology on its membrane with the GM1 structure located on peripheral nerves. B. Detection of autoantibodies or autoreactive T cells against both epitopes in humans and the microbes. Either autoreactive T or B cells should be able to induce an immune response against GM1 or GM1-like LOS to consider a phenomenon of molecular mimicry. C. Epidemiological link between the exposure to the environmental agent and the development of autoimmunity. In this graph the OR for the development of GBS is 58.7 with a 95% confidence interval 36.9 to 105.2. Taken and adapted from Ref. [48]. D. Reproducibility of autoimmunity in an animal model. Mice inoculated with *C. jejuni* or transference of autoreactive T and B cells induce the development of flaccid limb weakness resembling GBS and confirming the role of molecular mimicry in this disease.

stimulated with "cryptic" or external antigens, could induce autoimmunity [25,26]. In addition, a TCR with either heterodimeric or homodimeric configuration (i.e., α and β chains) may also explain the heterogeneity in response to infectious agents in different populations [16].

Thus, the concept of molecular mimicry has evolved from just similarity between structures of microbes and the human proteome, to include genetic and environmental factors, as well as issues related to mechanisms associated with positive/negative selection of T cells that involve the leakage of clones of autoreactive T cells. In the future, the study of the different interactions between the different components of the immune system (i.e., systems medicine) [45], will improve our understanding of how molecular mimicry is linked to ADs, and personalized medicine may improve disease prognosis and outcome [46].

3. Molecular mimicry and autoimmune diseases

Currently, there are four major criteria that are reasoned to account for molecular mimicry (Fig. 1) [47,48]: 1) "similarity between a host epitope and an epitope of a microorganism or environmental agent", 2) "detection of antibodies or T-cells that cross-react with both epitopes in patients with AD", 3) "epidemiological link between exposure to the environmental agent or microbe and development of AD", and 4) "reproducibility of autoimmunity in an animal model following sensitization with the appropriate epitopes either following infection with the microbe or exposure to the environmental agent". The development of GBS following *C. jejuni* infection [49], and the role of bovine milk protein butyrophilin in the development of MS [50], both illustrate these criteria.

Although these criteria have existed for several years, they are challenging to demonstrate in humans for several reasons. These include the issues of latency, the lack of enough epidemiologic power, the limitations of genetic human studies, the relevance of inbred murine models to outbred humans and the limited technology to individually study the human T-cell repertoire systematically. Moreover, there are other concerns regarding these criteria [51]. For example, infection could have occurred years before the onset of disease, and not all infected subjects develop an AD [52]. Furthermore, humans are challenged with multiple infections across their life time but not all of these trigger autoimmunity, and some infectious agents may have the potential to abrogate the development of ADs [51].

Four types of molecular mimicry have been proposed (Table 1) [6,13,47,53–55], including: 1) Type 1: "complete identity at the protein level between a microorganism and its host" (e.g., A human protein hijacked by the virus and presented as antigen), 2) Type 2: "homology at the protein level between a microorganism and its host, of a protein encoded by the microorganism", 3) Type 3: "common or similar native or glycosylated amino acid sequences or epitopes shared between the microorganisms or environmental agents and its host", and 4) Type 4: "structural similarities between the microbe or environmental agents and its host". Although all the above-mentioned mechanisms have been studied [56], type 3 is the most common reported for AD because it is the easiest to study. The following is a partial listing of ADs in which molecular mimicry has been examined.

3.1. Multiple sclerosis

MS is considered the most common inflammatory demyelinating AD of the central nervous system (CNS) affecting over 2 million individuals worldwide. Classically, MS is characterized by motor and sensory disturbances associated with vision and cognitive impairment [57]. About 85% of those diagnosed with MS have the relapsing-remitting form of the disease and the disease is 2–3 times more common in women than men. Although the etiology remains unknown, both genetic and environmental factors have been associated with its development [57]. MS has been considered as a T-cell mediated disease [57]. The MBP, the myelin oligodendrocyte glycoprotein (MOG) and the proteolipid protein, are the main target host antigens of autoreactive $CD4^+$ T cells [58]. However, the production of inflammation and damage at the tissue level is produced principally by $CD8^+$ T cells [59,60]. The role of T helper type 1 (Th1) and T helper type 17 (Th17) sub-lineages of the $CD4^+$ T cells have been shown to play a major role and at the molecular level this has been ascribed to polymorphisms in host genes that encode for key regulators of the NF-κB signaling pathways [61], providing for the mechanisms by which these autoreactive $CD4^+$ T cells play a pivotal role of these cells in the development of MS.

Although the HSV-6 [62], herpes zoster virus [63], John Cunningham virus (JCV) [64], *Mycoplasma pneumoniae* (*M. pneumoniae*) [65], and *Chlamydia pneumoniae* [66] have all been associated with MS, EBV is considered the main infectious agent linked to this disease. EBV belongs to the *Herpesviridae* family, and it is best known as the cause of infectious mononucleosis [67]. In a recent meta-analysis conducted by Xiao et al. [35], either the EBV infection, inheritance of the *HLA-DRB1*15:01* gene or both were strongly associated to the development of MS. Fine analysis of the autoimmune response in MS patients has shown the existence of T cells with specificity for MBP that also react with the EBV nuclear antigen 1 (EBVNA1) [68,69]. In addition, structural homology between the MBP and the EBV peptides presented by DRB1*15:01 molecule that result in DRB5*01:01-restricted cross-reactive autoimmune responses has also been documented [54]. Interestingly, $CD4^+$ T cells isolated from the CNS of patients with MS, were capable of recognizing autologous EBV transformed B cells providing confirmatory evidence for such cross-reactivity [70].

The CNS can be considered as a secondary lymphoid organ, not just a potential immune privileged site [71]. This concept has led to the study of mechanisms associated with CNS and immune system communication [72]. It has been proposed that the CNS is capable of immune surveillance in which autoreactive T cells can induce autoimmune phenomena. Paroni et al. [73] found that Th1/Th17 central memory cells, which commonly migrate via chemokine gradients to the

Table 1
Types of molecular mimicry.

Type	Definition	Experimental scenario	References
1	Complete identity at the protein level between a microorganism and its host, of a protein not encoded by the microorganism.	CMV acquire the CD13 and incorporate it on the viral envelope. This CD13 has shown to induce an immune reaction against CD13-positive cells such as all mononuclear cells, fibroblast and smooth muscle which ultimately are associated with graft-versus-host disease.	[47,55]
2	Homology at the protein level between a microorganism and its host, of a protein encoded by the microorganism.	*Helicobacter pylori* codifies for α-carbonic anhydrase which share significant homology with the human carbonic anhydrase II. This mechanism gives an advantage to this microbe since can proliferate in the gastric environment.	[47,53]
3	Common or similar amino acid sequences or epitopes between the microorganisms or environmental agent and its host.	Polysaccharides on the *C. jejuni* membrane share homology with carbohydrates structures that are found in the myelin sheath of peripheral axons.	[6,13,47]
4	Structural similarities between the microbe or environmental agent and its host.	Structurally homology between the DRB1*15:01-restricted MBP and the DRB5*01:01-restricted EBV peptide were associated with cross-reactivity.	[47,54]

Table taken and adapted from Ref. [65]. CMV: cytomegalovirus; EBV: Epstein-Barr virus. MBP: myelin basic protein.

CNS from the peripheral immune system, were augmented in the blood of MS patients. These cells were shown to strongly react against both the JCV or the myelin-derived self-antigens from patients with MS. It was reasoned that the TCR of the autoreactive T cells must share similar affinity for MBP and the microbial peptide as a proposed mechanisms by which this cross-reactivity occurs [74]. However, interestingly, the affinity of the autoreactive TCR was low for the microbial antigens but high for MBP [74]. Thus, it is tempting to speculate that after initial activation in response to microbial antigens involving low affinity TCR bearing autoreactive T cells, the ensuing inflammation and CNS damage, driven by interferon-γ (IFN-γ), interleukin-17 (IL-17), and granulocyte-macrophage colony-stimulating factor (GM-CSF) [75] leads to the generation of higher relative affinity autoreactive T-cell clones.

3.2. Guillain-Barré syndrome

GBS is characterized by an acute inflammatory neuropathy, with distal-proximal progression of weakness, dysautonomia, and pain [76]. This illness is classified into two major groups: a) acute inflammatory demyelinating polyneuropathy, that is typically associated with immune injury at the myelin sheath, and b) acute motor axonal neuropathy (AMAN), which targets the axon membranes. To date, and as previously revised [6], there are no robust data on the role of host genetics for GBS. However, GBS can be considered as a post-infectious AD [6]. Thus, infections such as *M. pneumoniae* [77–79], *Haemophilus influenza* [80], CMV [81], HSV [82], EBV [83], Hepatitis E virus [84], and *C. jejuni* have each been reported to be associated with the development of GBS.

Although GBS is clearly associated with molecular mimicry [7], AMAN is the only phenotype which has been confirmed to fulfil the four proposed molecular mimicry criteria described elsewhere [7]. First, Rees et al. [85] reported that a recent *C. jejuni* infection was more common in patients with GBS (26%) than in household controls (2%) and age-matched hospital controls (1%) through a case-control study. These data provided the first epidemiological evidence of *C. jejuni* in the development of GBS. Furthermore, Yuki et al. [86] *and* Ho et al. [87] demonstrated that patients with *C. jejuni* infections developed significant titers of IgG antibodies against GM1 and GD1a gangliosides that are known to be the key autoimmune targets in AMAN. In addition to epidemiological and immunological criteria, molecular mimicry between the bacterial lipo-oligosaccharides (the major glycolipids expressed on gram negative bacteria) and human GM1 ganglioside has also been reported [43]. In fact, experimental sensitization of rabbits with lipo-oligosaccharides was shown to produce an upsurge of anti-GM1 IgG antibodies and the subsequent development of limb weakness, resembling GBS presentation [88,89].

The role of T-cells in GBS has been extensively investigated as a central mechanism for autoimmunity [6]. Distinctive findings in GBS include infiltration of T cells [90], with parallel myelin swelling and demyelination [90–92]. In this case it is important to note that the gamma-delta (γδ) T-cells instead of the conventional α/β TCR expressing T cells have been shown to play a central role in the pathogenesis of GBS. In fact, they induce neural injury either by activating B cells and macrophages, or producing cytokines, secondary to the loss of self-tolerance [93]. Interestingly, the γδ T-cells were also shown to react to myelin proteins, such as P0, P2, PMP22 [94]. In this regard, it is important to note that *in vitro* stimulation of PBMCs with *C. jejuni* led to an increase in the production of γδ T cells that have been shown to selectively infiltrate peripheral nerves and are enriched for the Vγ5/Vδ1$^+$ subpopulation [95]. In a case control study, patients with GBS exhibited higher levels of Vδ1/CD8$^+$ (a subset predominantly present in the intestinal epithelium) than healthy subjects, thus suggesting that cytotoxicity could play a pivotal in the pathogenesis of GBS following *C. jejuni* infection [93,96].

3.3. Type 1 diabetes

Type 1 diabetes (T1D), an AD that is commonly diagnosed in children and young adults (previously known as juvenile diabetes) is characterized by a metabolic disorder caused by an autoimmune attack against the pancreas. The incidence varies, ranging from 0.1 cases to more than 40 cases per 100,000/year [97]. The autoimmune attack on the pancreas progressively leads to the destruction of β cells (the endocrine cell that is responsible for the production, storage and release of insulin), through production of autoantibodies against the β cell components, resulting in a reduction of insulin secretion, and the development of insulin-dependent diabetes mellitus [98–100]. The presence of CD4$^+$ and CD8$^+$ T cells, B cells, and macrophages has been documented among the infiltrating cells within the pancreatic islets [101–103]. The pathogenic role of autoreactive T cells is supported by the findings that the transfer of bone marrow cells from T1D patients to healthy predisposed subjects can induce the development of T1D in the recipients [104]. Interestingly, the administration of immunomodulatory/immunosuppressive drugs such as anti-CD3 monoclonal antibody and cyclosporine A have shown to be therapeutically beneficial in this disease [105], thus supporting the role of the immune system in the pathogenesis of this disease.

T1D is a polygenic disease, since its clinical risk and course are conditioned by the combination of different susceptibility genes [106–111]. A recent report on genotyping with 176586 SNPs in a cohort of 5806 patients led to the identification of six novel regions which were not previously reported in case control studies [112]. Among them, *PXK/PDHB* and *PPIL2* are associated with the development of islet autoantibodies. However, environmental factors have also been shown to play a decisive role in the appearance of T1D [113,114]. Maternal age, vitamin D deficiency, infant's diet, gut microbiota and exposure to chemicals are some of the environmental agents that have been considered as contributors to its development [115–117]. Infectious agents, especially those of viral origin, are considered the main triggers of T1D [118]. In fact, it has been reported that the risk to develop T1D in genetically predisposed children was significantly higher when they suffered viral respiratory infections in cold months, thus suggesting the seasonal pattern of the disease and the role of microbes in the development of T1D [119,120].

Among the other viruses associated with the appearance of T1D are those that belong to the genus enterovirus. Epidemiological data have noted an increase in the incidence of T1D after enteroviruses epidemics [121]. One study measured enterovirus RNA or viral protein in blood or stool, finding that the presence of infection was 10 times more common in children with T1D compared with controls, and the OR of infection was higher in patients with pre-diabetes than in healthy subjects [122]. In animal models, coxsackievirus has been associated with the development of T1D, as well as in patients with recent onset of the disease [123–125]. Rotaviruses, rubella, parechoviruses, influenza virus, Ljingan virus and mumps are examples of viruses other than enteroviruses that have also been associated with T1D [126–130].

Support for molecular mimicry in T1D comes from the finding of a similarity between epitopes of pancreatic β cells and viral components. The viral components are reasoned to initially trigger the activation of T cells in T1D patients that also have specificity (cross-react) against the pancreas [118]. This mechanism has been observed in experimental models designed to selectively express LCMV in pancreatic β-cells. Thus, infection with LCMV and its localization to the β-cells was associated with T1D development [131]. On the other hand, cross-reactivity has also been noted between the viral protein 1 of enteroviruses and the β cell antigen tyrosine phosphatase IA-2 [132], and epitopes of coxsackievirus, CMV and the pancreatic β-cell antigen glutamic acid decarboxylase 65 (GAD65) [133]. However, despite such well documented cross-reactivity between viral epitopesd and β cells, the role of molecular mimicry in T1D is still a subject of debate. The reason for such debate has been the finding that the inoculation of non-obese

diabetic (NOD) mice with coxsackievirus B3 was followed by long-term protection from T1D rather than the development of the disease [134]. In addition, infection of NOD mice with gammaherpesvirus-68 delayed the onset of T1D [135]. It is thus clear that further studies aimed at clarifying the role of viruses in the development of T1D are required [136,137].

3.4. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an AD clinically manifested by progressive joint damage, systemic complications and premature death [138]. Although this disease is chronic, the administration of adequate treatment and rehabilitation strategies, has led to a significant improvement in the quality of life and prognosis [139,140]. Autoantibody production, synovial tissue inflammation, cartilage and bone destruction, and cardiovascular compromise are some of the most frequent complications associated with this disease [141–144].

Several environmental factors, including infectious diseases, are the main factors associated with the development of RA in genetically susceptible individuals [145]. Clinical and experimental studies have reflected a role for microorganisms in the development of RA and among the most important ones are *Porphyromonas gingivalis (P. gingivalis), Proteus mirabilis (P. mirabilis), Escherichia coli* (*E. coli*), and EBV [146–150]. The list of other microorganisms that have been associated with RA include parvovirus, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) [151]. Although *P. gingivalis* is considered to be the main cause of periodontal disease, it is also most frequently associated with RA [152]. Several studies have described upto a two-fold increase in RA in patients who also have periodontal disease compared with controls [153–155]. In addition, a study found an association between DAS28 scores (i.e., disease activity score for RA) and severe periodontitis in patients with RA [155]. Several studies have documented a similarity (up to 82%) between *P. gingivalis* enolase and human α-enolase within the 17-amino acid immunodominant region [148]. In fact, antibodies against bacterial enolase can recognize human α-enolase promoting a possible role for cross-reactivity and disease. In addition, levels of antibodies to bacterial α-enolase were shown to correlate with anti-citrullinated human α-enolase antibodies [148]. Additionally, in animal models, arthritis was shown to be induced by experimental infection with *P. gingivalis* [156–158]. This was supported by a study that evidenced the development of arthritis in CIA mice through its unique bacterial peptidylarginine deiminase triggered by *P. gingivalis*, suggesting the important role of *P. gingivalis* in loss of tolerance to citrullinated proteins in RA [159].

In addition to *P. gingivalis*, the association between *P. mirabilis* and RA is widely documented. In fact, chronic infection by *P. mirabilis* could induce, through molecular mimicry, chronic inflammation of joints [160]. This view is supported by data from epidemiological studies that indicate a higher rate of *P. mirabilis* isolation in RA patients compared with controls [161]. Along with the establishment of a serological link. A study that evaluated the cross-reactivity between peptides from *P. mirabilis* hemolysin B (HpmB), urease C (UreC), and urease F (UreF) with elevated levels of IgM, IgG, and IgA antibodies against HpmB and UreC in RA patients supports this concept [162]. The presence of Anti-UreF antibodies that correlates with rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein in patients [162] also supports this general view. In addition, it has been noted that the HLA-DRB1*0401 molecule that is expressed by a high frequency of patients with the most severe form of RA naturally bears a peptide with a QKRAA motif that is shared with a motif present in *E. coli's* heat shock protein (i.e., DnaJ). This DnaJ QKRAA motif has been shown to bind bacterial hsp70's (Dna K proteins). Thus it is possible that exposure of HLA-DRB1*0401 expressing patients to enterobacteriacea leads to the binding of DnaK proteins to the QKRAA bearing HLA-DRB1*0401 molecules, which in turn triggers T-cell responses to hsp70's that shares a dominant epitope with human type II collagen [163].

A number of infectious agents have proteins that contain peptides with a high degree of similarity with the human proteome. In fact, mycobacterial heat shock proteins share extensive homology with human heat shock proteins. This is exemplified by the observation of a clonal expansion of T cells against mycobacterial HSP65 in blood samples and synovial fluids from RA patients [164,165]. Furthermore, the presence of T cell responses against CMV and EBV has been described in joints of patients with RA [166–168]. Similarly, EBV infection of mice was shown to induce erosive arthritis [169,170]. Thus, molecular mimicry appear to play a critical role in the development of RA. It should be noted that in sharp contrast, seronegative RA is enigmatic and distinct from seropositive RA.

3.5. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic AD with varied clinical manifestations and a wide profile of antibodies [171,172]. Several risk factors have been described that favor immune system dysregulation with autoantibody production and deposition of immune complexes [172,173]. B cell dysregulation is usually linked to the development of SLE as this lineage of lymphoid cells mediates the production of autoantibodies and present antigens to T cells [174]. In fact, autoantibodies in the form of immune complexes are fundamental players in SLE [175].

Most genetic factors identified as predisposition factors of SLE are within non-coding DNA regions of genes involved in the immune response [176–180]. These have included *ITGAM, TNSF4, TNFAIP3* and *STAT4* that have been associated with SLE based on population studies [181]. Other genes including *PTPN22, FCGR2A, TNSF4, IL10, LYST, STAT4, IL12A, BANK1, IRF5, ITGAM* and *BLK*, have been significantly associated with SLE in genome-wide association studies (GWAS) [181–186], and support a high burden of genetic factors in the development of SLE. However, twin studies strongly indicate an additional role of environmental factors [187–189].

The possible relationships between infectious agents and the development of SLE has been broadly assessed, suggesting a possible role of viruses such as EBV, parvovirus B19, HTLV-1 (Human T-lymphotropic virus 1), CMV, HCV and [174,190]. The association between EBV and SLE has been extensively studied [191]. Several studies have established a higher incidence of EBV infection among SLE patients as well as higher titers of antibodies against EBV among these patients [190,192,193]. A meta-analysis of the sero-epidemiological association between EBV and SLE, showed a non-significant difference between SLE and controls for anti-EBV nuclear antigen 1 (EBVNA-1) antibody seropositivity rates, while anti-viral capsid antigen IgG-seropositivity rates demonstrated a positive association with SLE (Odds ratio - OR = 5.05, 95% confidence interval - CI= 1.95–13.13, p = 0.0009) [194].

The immune response of SLE patients against EBV differs from healthy controls. Thus, the humoral response against EBVNA-1 generates cross-reactive antibodies in genetically susceptible individuals [191]. Murine models demonstrate that *in vivo* expression of EBVNA-1 antibodies favored the production of anti-dsDNA and anti-Sm antibodies [190,195]. A series of cross-reactivity patterns have emerged. This is highlighted by the specific cross-reactivity between PPPGRRP of EBVNA-1 that cross-reacts with PPPGMRPP of Sm [196] (amino acid residues 35–58 of EBVNA-1 cross-reacts with amino acids 95–119 of Sm). Similarly, the amino acids 58–72 of EBVNA-1 was shown to cross-react with amino acid residues 169–180 of Ro and associated with SLE-like disease in *in vivo* models [193,197,198]. These findings reinforce the hypothesis of molecular mimicry in the development of SLE. Nevertheless, the role of cellular profiles on autoimmunity driven by molecular mimicry in patients with EBV, remains to be defined.

3.6. Sjögren's syndrome

Sjögren's syndrome (SS) is an organ-specific AD that primarily affects the salivary and lachrymal glands but that can also affect any exocrine gland such as the eye and mouth leading to dry eye and dry-mouth symptoms (i.e., sicca-symptoms) [199]. The clinical spectrum of SS extends from sicca syndrome to systemic manifestations [200]. A progressive focal infiltration of exocrine glands composed of autoreactive T and B cells is described [179,199,201]. Murine models have demonstrated that the majority of T-cells infiltrating salivary and lachrymal glands are $CD4^+$, however, $CD8^+$ cells have also been observed, and both are able to produce pro-inflammatory cytokines [202]. The starting point in the pathophysiology of SS is considered to be epithelial cells lining the salivary gland [203–205].

Several environmental and genetic factors have been identified as risk factors for various ADs. Recently a GWAS identified both HLA and non-HLA susceptibility genes for SS. The non-HLA genes included *STAT4, CXCR5, TNIP1, GTF2I, TNFAIP3, PTPN22, IRF5, IL12*A, *BLK, BLK-FAM167*A, *BAFF*, and *EBF*. The HLA-genes associated with increased risk for SS include the MHC class I encoded *HLA-B8* and the MHC class II encoded *HLA-DR3, HLA-DRB1,* and *HLA-DQB1* [206–213]. In addition to genetic predisposing factors, infectious agents such as EBV, HTLV-1, HSV-6 and HCV are reported as risk factors for the development of SS [214]. A case-control study matching 82 SS patients with 139 healthy subjects found that the presence of anti-Ro/SSA was significantly associated with EBV-associated antibodies (Ig G anti-EBV early antigen and IgG anti-EBV capsid antigen). Moreover, a positive and significant association between anti-La/SSB and IgG anti-EBV early antigen was also found [215,216]. Another case-control study found an increased risk of SS with HCV (OR 2.49, 95%CI = 2.16–2.86) [217]. A recent meta-analysis included 10 studies (5 cohort and 5 cross-sectional studies) that examined the association between HCV infection and risk of SS, finding an overall OR of 3.31 (95% CI= 1.46–7.48) [218]. As far as molecular mimicry for SS, it is of interest to note that Haaheim et al. [219] found sequence similarities between the decapeptides of La/SSB with sequences present in HSV, HBV and polio viruses.

3.7. Systemic sclerosis

Systemic sclerosis (SSc) is characterized by fibrosis of the skin, internal organs, and vascular obliteration phenomena [220]. While this disease is associated with a predominance of Th1 and Th17 effector mechanisms during the early stages of disease, in the later stages when skin fibrosis occurs, a T helper type 2 (Th2) effector profile prevails [221]. The cytokines IL-6 and IL-13 have been associated with skin fibrosis ans severity of symptoms [222,223]; IL-5 and IL-17 are associated with interstitial lung disease [224,225], and reduced levels of IL-10 by the innate immune system after *in vitro* stimulation is characteristic of SSc [226]. Recent literature also suggest a decrease in functional capacity of peripheral T-regulatory (Treg) cells in SSc [227].

Endothelial cell apoptosis is the earliest skin event detected in SSc and the mechanisms involved in the apoptotic process have been thought to involve molecular mimicry between an “infectome”and host endogenous protein [228]. With regards to the nature of the “infectome”, Neidhart et al. [229] found that patients with SSc exhibited a higher prevalence of IgM, IgA, and/or IgG antibodies (74.4%) against CMV as compared with patients with RA (41.9%) and osteoarthritis (14.0%), providing limited epidemiological evidence about the role of CMV in the pathogenesis of SSc. Thereafter, in a study conducted by Lunardi et al. [230], using a random peptide library identified an immunodominant peptide (i.e., GGIGGAGIWLVV) which reacts with serum IgG isolated from patients with SSc. Of interest, this peptide shares homology with the UL94 protein of CMV. These autoantibodies were shown to induce apoptosis of endothelial cell by interaction with the cell surface integrin–NAG-2 protein complex [230] and a profibrotic phenotype [231].

An additional mechanism by which infection may mediate skin fibrosis is the activation of the AIM2 inflammasome, a sensor of cytosolic bacterial and viral DNA [232]. It is activated in skin fibroblasts from SSc patients and can contribute to collagen production [233]. In addition, the reactivity of antibodies against topoisomerase I present in sera of patients with SSc were localized to amino acid residues 121–126 of topoisomerase I that interestingly shares homology with the CMV late protein UL70 [234]. These findings provide evidence for the activation of autoreactive B-cells via molecular mimicry in patents with SSc. In a study conducted by Hamamdzic et al. [235], using a murine model of arteritis, triggered by murine CMV infection, mice infected with CMV and conditioned irradiation, developed severe vasculopathy characterized by extensive adventitial and medial infiltrate and significant neointima formation supporting a role for CMV in the pathology of this disease.

3.8. Autoimmune thyroid disease

Autoimmune thyroid disease (AITD) is an organ-specific AD that is initially mediated by T cells followed eventually by B-cell mediated autoimmunity [236], with a prevalence up to 10% [237,238]. The two main clinical presentations are Graves' disease (GD) and Hashimoto's thyroiditis (HT), characterized by a lymphocytic infiltration at the beginning of the disease to finally culminate in a production of autoantibodies against thyroid tissues [239]. Smith et al. [240] reported that a higher frequency of activated thyroid antigen activated B cells are present in recent onset compared to long standing AITD patients; suggesting that early loss of anergy contributes to the production and development of AITD.

There is a complex interaction between genetic susceptibility and environmental factors that alter the balance of immunological tolerance, leading to the generation of an autoimmune response. Smoking, radiation, microbial infections, drugs, Iodine substitution and stress are examples of environmental factors associated with this disease [241]. Several infectious agents have been implicated with the development of AITD. These include, *Yersinia* spp, *Helicobacter* spp, *Bartonella henselae*, influenza virus, herpesvirus, retrovirus, HCV, and staphylococcal infection [242–249].

As far as a role for infectious agents, it is known that there is a high prevalence of antibodies to *Yersinia enterocolitica* (*Y. enterocolitica*), in AITD patients [250]. In fact, in patients with GD, autoantibodies to TSH-receptor (TSH-R) have been shown to cross-react with the envelope proteins of *Y. enterocolitica*, due to the existence of common antigenic epitopes between *Y. enterocolitica* and the extracellular domain of human TSH-R [251,252]. Detailed analyses of the specificity of the auto-reactive antibodies has revealed that the antigenic epitopes of amino acid residues 22–272, 186–330, 319–363 and 684–749 from TSH-R have a high degree of homology with the YopM, Ysp, exopolygalacturonase and SpyA from *Y. enterocolitica* (identity 23–31%, similarity 40–48%) [253]. In addition, antibodies against the YopM, Ysp, exopolygalacturonase and SpyA of *Y. enterocolitica* have the same affinity for these epitopes compared with TSH-R in GD patients [250,254]. Other proteins associated with molecular mimicry between AITD and *Y. enterocolitica* are Yersinia outer proteins (Yops), which are related to the virulence of the bacteria [255]. Regarding the association between Yops and AITD, the prevalence of antibodies against these proteins is up to 14-fold higher in HT patients [256]. Of interest, these antibodies also shared epitopes with heat shock protein and were able to trigger lymphocytes of patients with GD [257]. Other reports have shown an association between other species of Yersinia, [i.e., *Yersinia pseudotuberculosis* (*Y. pseudotuberculosis*)] with AITD [258]. In this case, a study evaluated the serological cross-reactivity between OmpF porin from *Y. pseudotuberculosis* (YpOmpF) and TSH-R [246], and found that antibodies to TSH-R interacted similarly with thyroid antigens as with YpOmpF [258].

With respect to *Borrelia burgdorferi* (*B. burgdorferi*), a similarity

between amino acid residues 112–205, 127–150, 141–260, 299–383 and 620–697 of TSH-R, and the flagellar motor rotation protein A, outer surface protein A, and DNA recombinase/ATP dependent helicase of *B. burgdorferi* with an identity of 27–50%, and a similarity of 40–75% has recently been described [253]. Furthermore, homologies between thyroid autoantigens and 16 *B. burgdorferi* proteins (5 with hTSH-R, 2 with hTg, 3 with human thyroid peroxidase, and 6 with hNIS), suggest a role of this pathogen in the development of AITD via molecular mimicry. Thus, multiple infectious agents have the potential to induce immune responses that also show reactivity to antigens of the thyroid tissue making the case for distinct microbial etiologies for this AD. In support of this view is the suggested relationship between probiotic microorganisms and AITD and, in particular, homology between thyroid autoantibodies and proteins of bifidobacteria and lactobacilli [259]. Molecular structures of *Bifidobacterium bifidum 791 (B. bifidum)* that compete with antigens for the binding of thyroid autoantibodies were recently observed, along with evidence of homologies between glycopolymers of *B. bifidum* and thyroid autoantibodies [260].

Less common associations between infections and AITD have been reported. In a case report study using an *in silico* approach, the authors found a homology between botulinum neurotoxin and thyroid autoantigens, which exhibited regions that contained HLA-DR3 and/or HLA-DR7 binding motifs [261]. Other reports showed an association between HCV and AITD. One study described similarities between viral peptides and the thyroid gland in a range from 21.0% (31 identical residues out of 147 amino acid in the sequence) to 71.0% (5 identical residues out of 7 amino acid in the sequence) [262]. Clearly *in vivo* models are needed to clarify the mechanisms behind the multiple infectious agents, host genetics and this AD.

3.9. Autoimmune liver diseases

The term “autoimmune liver diseases” comprises different disease patterns that differ with regard to the degree of severity and clinical course, but have one important step in common with regard to the development of the disease: the autoimmune pattern of inflammation. The most important autoimmune liver diseases are autoimmune hepatitis (AIH), PBC, and primary sclerosing cholangitis; all are well-defined entities with diagnosis based upon a constellation of clinical, serologic, and liver pathology findings. Next, molecular mimicry in the context of AIH and PBC is discussed.

3.9.1. Autoimmune hepatitis

AIH is a progressive and chronic inflammatory liver disease with histologic evidence of lymphocytic infiltration of the liver. In addition to histological findings, elevated liver function tests, elevated serum IgG and the presence of specific and non-specific autoantibodies are characteristic [263–266]. T-cell mediated injury, imbalance in regulatory and effector cells, and loss of immune tolerance have been described to contribute to the pathogenesis of this disease [267–270].

Studies of genetic predisposition in AIH have identified several genes within the HLA region. While the MHC class II encoded HLA-DRB1 has been described as a susceptibility gene [271], HLA-DQB1 has been associated with the disease [272]. Of the infectious agents previous viral infections, specially hepatitis virus, EBV, varicella zoster virus, and CMV have each been described to increase the risk of AIH [273–280].

Evidence regarding the epidemiological association of viral infections, especially hepatotropic viruses support the theory of molecular mimicry in AIH [281]. Several case reports have described the occurrence of AIH after HCV infection [282–286]. Savage et al. [287] examined the paraffin-embedded biopsies of 19 patients with histologic, serologic and clinical characteristics of AIH, and found detectable HCV-RNA by polymerase chain reaction in five of them. In addition, autoantibodies such as anti-smooth muscle antibody, antinuclear antibodies, anti-liver kidney microsome type 1 antibodies (LKM1), and anti-liver cytosol antibody, have all been described in subjects with chronic HCV infection [269,277,288]. In addition, the HBV-DNA polymerase (HBV-pol) shares 7–9 amino acid sequences with nuclear and smooth muscle proteins (i.e., myosin and caldesmon) [289], reinforcing the data about the role of hepatitis viruses in the development of liver autoinmmunity. Interestingly, these autoantibodies appear to act against cytochrome P450db1 in the liver [290].

In support for a role of molecular mimicry, it has been shown that LKM1 antibodies directed towards CYP2D6 identified in HCV infection [277,279,291] cross-react with homologous regions of HSV-1, CMV and HCV [277,278]. Kerkar et al. [288] reported that an immunodominant epitope on CYP2D6 is recognized by LKM1-positive sera from both AIH and HCV patients and is the likely target of cross-reactivity. The dominant CYP2D 6193-212 peptide identified is located on the surface of CYP2D6, making it accessible to antibody recognition. The homologous HCV 2977–2996 peptide is identified as part of the HCV RNA-dependent DNA polymerase and an epitope on the native folded protein. In addition, a CMV encoded 121–140 homologous peptide has been also described to react with sera from AIH patients [288].

Molecular mimicry has also been assessed in murine models of AIH. Mice infected with adenovirus expressing human CYP2D6 develop hepatic infiltration, fibrosis and develop antibodies directed towards the CYP2D6 [292]. However, given the physiologically normal immune-tolerant state of the liver, the presence of an identical trigger to the target autoantigen in the liver is not enough to start the immune response [293,294]. Ehser et al. [293] demonstrated that mice that were immunized with a similar but not identical molecule of CYP2D6 developed robust T-cell responses and exacerbated clinical features of AIH, suggesting that molecular mimicry is involved with the etiology of AIH. The role of T cells has been broadly studied in AIH. Treg cells are described to be numerically reduced and functionally impaired in AIH as they are unable to regulate cytokine production from effector autoimmune $CD4^+$ and $CD8^+$ T-cells [295,296]. Further studies that focus on the role of T cells in the development of AIH through molecular mimicry are clearly important and warranted.

3.9.2. Primary biliary cholangitis

PBC, formally known as primary biliary cirrhosis, is characterized by biliary destruction, progressive cholestasis, and potentially liver cirrhosis [297]. The disease has a female predominance (i.e., fame/male ratio 10:1), with the highest incidence in USA (402 cases per million inhabitants) [298], and the lowest in Australia (19 cases per million inhabitants) [299]. Up to 57.4% of cases are asymptomatic [300], and symptoms appear to be most common in patients younger than 50 years old [297]. The most common symptomatology include fatigue, pruritus and jaundice, the latter frequently observed in end-stages of the disease [297].

PBC is characterized by immune-driven biliary injury and cholestasis [297]. The pathophysiology of disease is characterized by a loss of tolerance to mitochondrial antigens such as the E2 component of the pyruvate dehydrogenase complex (PDC-E2), which leads to an attack of biliary epithelial cells [301]. It is well known that $CD4^+$ and $CD8^+$ T cells infiltrate the portal triads [302]. Other studies have shown the role of NK [303], and autoreactive B cells [297]. Antimitochondrial antibodies (AMA) are highly specific for the diagnosis of disease, together with alkaline phosphatase over 1.5 times the upper limit for more than 24 weeks, and liver histology (i.e., interlobular bile duct destruction) [297].

As all ADs, genetic and environmental factors influence the development of the disease. A concordance rate of 63% in monozygotic twins indicates a strong participation of genetic factors [304], including *HLA* and non-*HLA* genes such as *IL12RB2* [305], *IRF5-TNPO3* [305], *DENND1B* [306], *TNFSF15* [307], and *TNFSF11* [308], among others. In addition, infectious agents such as *E. coli, Novosphingobium aromaticivorans, Lactobacillus delbrueckii and HIV* have been incriminated in the development of disease [309].

The evidence of *E. coli* as a plausible factor in the development of PBC comes from case-control studies of patients with urinary tract infections. Howel et al. [310] demonstrated that those patients with recurrent urinary tract infections had 2.4 odds to develop PBC than healthy controls. This fact was further confirmated by a study involving 1032 patients and 1041 healthy subjects [311]. However, the physiopathology of disease is not completely known. It was found that human PDC-E2 (i.e., KVGEKLSEGDLLAEIETDKATIGFEVQEEGY) shares a significant homology with the *E. coli* PDC-E2, especially in the region of immunodominant epitope of AMA (i.e., K-G————————L-EIETDK————————G) [312]. In addition, sera from patients with PBC react against both human PDC-E2 and *E. coli* PDC-E2 [312,313], suggesting molecular mimicry as a mechanism incriminated in the development of PBC. However, these observations await to be clarified by *in vivo* models.

3.10. Vaccines

Since the initial usage of cowpox vaccination by Edward Jenner in 1796 [314], to the eradication of smallpox in 1979 [315], it is undeniable that vaccines have had an immeasurable positive contribution to civilization. However, like most advances there also exist a small frequency of patients that manifest adverse reactions and in select cases there are also risks associated with vaccinations specially in immunosuppressed patients and those that involve live and/or attenuated organisms [316,317].

The influenza A virus, responsible for the Spanish flu in 1918, with an estimate of 100 million deaths [318], was isolated in 1930. Since then, this virus has been the model for development of vaccines. Following a pandemic attributed to the H1N1 strain, almost 30.5 million doses of the AS03-adjuvanted A (H1N1) vaccine were distributed [319]. This high number of doses distributed in a short period of time, allowed the study of several adverse events associated with autoimmunity (e.g., narcolepsy, GBS).

Narcolepsy is characterized by an excessive daytime sleepiness accompanied by impaired nocturnal sleep and hallucinations [320,321]. Although the pathogenesis of this disease is not clear, susceptibility with the inheritance of the MHC class II DQB1*06:02 gene, and the appearance of narcolepsy in mice injected with antibodies of narcoleptic patients, argue for a role of autoimmunity [322,323]. The first report that H1N1 vaccination has the potential for the development of narcolepsy, was provide by Han et al. [324] in 2011. They demonstrated a significant increase in narcolepsy diagnosis after systematic vaccination with the AS03 vaccine in a population of Beijing, China. Thereafter, in 2015, Ahmed et al. [325] identified a homology between the surface-exposed influenza nucleoprotein A and the extracellular domain of human hypocretin receptor 2, which are considered targets in the development of narcolepsy. In addition, antibodies derived from patients vaccinated with the pandemic Flu-vaccine demonstrated cross-reactivity with these two structures. Thus, molecular mimicry appears to be one key factor in the development of narcolepsy secondary to the administration of the vaccine.

The appearance of GBS following influenza immunization has also been reported. The first evidence arguing a role of influenza vaccination and the development of GBS, was reported by Schonberger et al. [326] in 1979, who showed a significant increased risk associated with the vaccine. This view is supported by the finding that there was a significant increased incidence of GBS in recipients of the vaccine during an outbreak of influenza in 2009 [38].

The most likely mechanism associated with the development of GBS is molecular mimicry, although there has been a lack of concrete evidence of any signficant homology between the molecular constituents of the influenza virus and in the human myelin sheath. There are studies such as the study conducted by Nachamkin et al. [327], that have reported that mice immunized with influenza vaccine developed an increase in anti-GM1 antibodies, which are critical in the development of GBS but does not prove that such antibodies are the cause of GBS. These data however do suggest that molecular mimicry may be a potential mechanism in GBS following influenza vaccination but clearly additional studies are needed.

Example of other vaccines that have been associated with the development of ADs, include the HBV vaccine, which is associated with demyelinating neuropathies, including encephalomyelitis, subphenotypes of GBS, MS and transverse myelitis [328–330]. Large scale studies have suggested up to a 5-fold increase of risk for MS associated with HBV vaccination [331,332]. However, their role in other neurologic conditions is based on case reports or studies with poor study designs and limited power calculations. Few studies have been conducted to find the mechanisms associated with HBV vaccine induced autoimmunity. One such study conducted by Bogdanos et al. [333] involved patients who received the vaccine who subsequently developed antibodies that cross reacted with MOG but lacked data to show cross-reactivity with the MBP. Of note, the HBV polymerase shares six consecutive amino acids with the encephalitogenic site of rabbit MBP [33].

The potential role of HBV and GBS, including a role for molecular mimicry, is interesting and, again, based upon case reports only. It has been thought that immune complexes formed between HBsAg and antibodies that are induced post HBV immunization (HBsAg-ICs) and may potentially bind to nerve structures that could result in inflammation and result in ischemic lesions. This view is supported by the finding that some patients with GBS and HBV infection have high levels of HBsAg-ICs [334–336]. Nevertheless, a homology between HBV and target proteins of GBS that may elicit molecular mimicry has not yet been described.

The human papillomaviruses (HPV) vaccine is another example of a vaccine that has been associated with autoimmunity. The HPVs comprise a family of small double-stranded DNA viruses that exhibit a preference for infection of epithelial tissues of the upper respiratory tracts and genital structures [337]. Although the vaccine is highly effective, there are reports on the potential role of this vaccine with the development of ADs and postural orthostatic tachycardia syndrome (POTS). A study conducted by Klumb et al. [338] involving SLE patients reported that these patients exhibited a significant increase in HPV infection, a view supported by the finding that patients with SLE have a relative risk for HPV infection of 7.2 despite immunomodulatory treatment [339]. Subsequently, in a comprehensive analysis of the sequences comprising the L1 antigen of HPV (HPVL1), Segal et al. [340] reported that the HPVL1 shared peptide sequence homologies with a mosaic of host proteins including lupus Ku autoantigen proteins (i.e., p86, p70), lupus brain antigen 1 homolog, natural killer cell IgG-like receptors, complement and complement receptor CD19 and others, thus, supporting the notion of molecular mimicry as one of the main mechanisms of SLE associated with HPV vaccination. Nonetheless, the evidence of HPV vaccine as a trigger for ADs is conflicting, and convincing studies supporting the role of molecular mimicry in their pathogenesis are lacking. Due to the low incidence of ADs, the studies performed so far looking at the association between ADs and HPV vaccination have been underpowered and biased. Therefore, “we need to look to follow-up of registry data involving millions of women to assess whether any relationship exists between vaccination and autoimmune conditions” [341].

POTS is defined as a disorder of the autonomic nervous system characterized by heart rate changes secondary to a change in posture from a supine to an upright position, and orthostatic intolerance [342]. Some recent reports have suggested a role of the immunological system in the development of this condition, advocating an autoimmune phenomena in its development [343,344].

Blitshteyn et al. [345], described the first case report of POTS following HPV vaccination (i.e., Gardasil) in a 20-year-old woman. Thereafter, several other cases appeared with nausea, palpitations, fatigue and neuropathic pain as the most common symptoms [346–348].

Kanduc et al. [349] found that 34 pentameric sequences from the viral capsid protein of HPV shared sequences with human proteins that are associated with cardiovascular diseases. For example, the LPSEA sequence of the HPV16 shared homology with the human Q99959 protein, which has been associated with familial arrhythmogenic right ventricular dysplasia. Thus, it is tempting to speculate that POTS following HPV vaccination may also be secondary to molecular mimicry. Further studies exploring the role of this mechanism are needed.

The immunogenicity of native microbial formulations as candidate vaccines is usually low and one of the reasons forwarded is that the microbial product is rapidly removed from the body and therefore does not stay around long enough to sustain immune responses by the host [350,351]. Hence, organic compounds such as aluminum hydroxide, aluminum phosphate, and calcium phosphate [352,353], glycosphingolipid and oil emulsions [354], and products from bacteria (e.g., lipopolysaccharides and lectins) [355] have been incorporated with such poorly immunogenic vaccines to sustain a prolonged presence *in vivo* to address this issue. These additives are termed "adjuvants". These additives increase the response of the immune system against the antigens included in the vaccine. For example, beta-sphingolipid is added to the HBV vaccine. After treatment with this adjuvant it was found that beta-glucosylceramide, beta-lactosylceramide, and the combination of both increased the immune response of the vaccine and immunity against HBV. There is increasing interest in understanding how the genetic background influences the innate and adaptive responses to vaccines from the perspective of an individual and at the population level (i.e., vaccinomics) [356]. Data from such studies will allow defining how likely an individual responds to a vaccine challenge.

4. Molecular mimicry and cross-reactivity: what is necessary?

ADs are characterized by activation of T and B cells against self-antigens. T cells are considered as central players of "T-cell mediated" ADs [357–359]. Initially, T-cell recognition was assumed to be highly specific. Thus the cross-reactivity with infectious diseases was expected to be low [16]. However, further studies reflect that peptide binding by MHC II molecules that are presented to T cells are based on the sequence of 8–10 amino acids that are presented by MHC class I molecules, and 14–18 amino acids that are presented by MHC class II molecules to $CD8^+$ and $CD4^+$ T cells, respectively. Thus only a very small portion of an antigen is needed to be recognized by a TCR, and a specific TCR has specificity for the specific MHC bearing peptide, a phenomenon known as MHC restriction [360–362]. While there are critical residues of the peptide that are required to bind to a specific MHC molecule (anchor residues), there is a certain degree of plasticity in the other residues. This provides the ability to respond against multiple pathogens or chemical xenobiotics with certain specificity [52,363,364], a phenomenon known as "polyspecificity" [365].

A unique murine model study using the rat insulin promoter-lymphocytic choriomeningitis virus (RIP-LCMV) mice has been utilized that

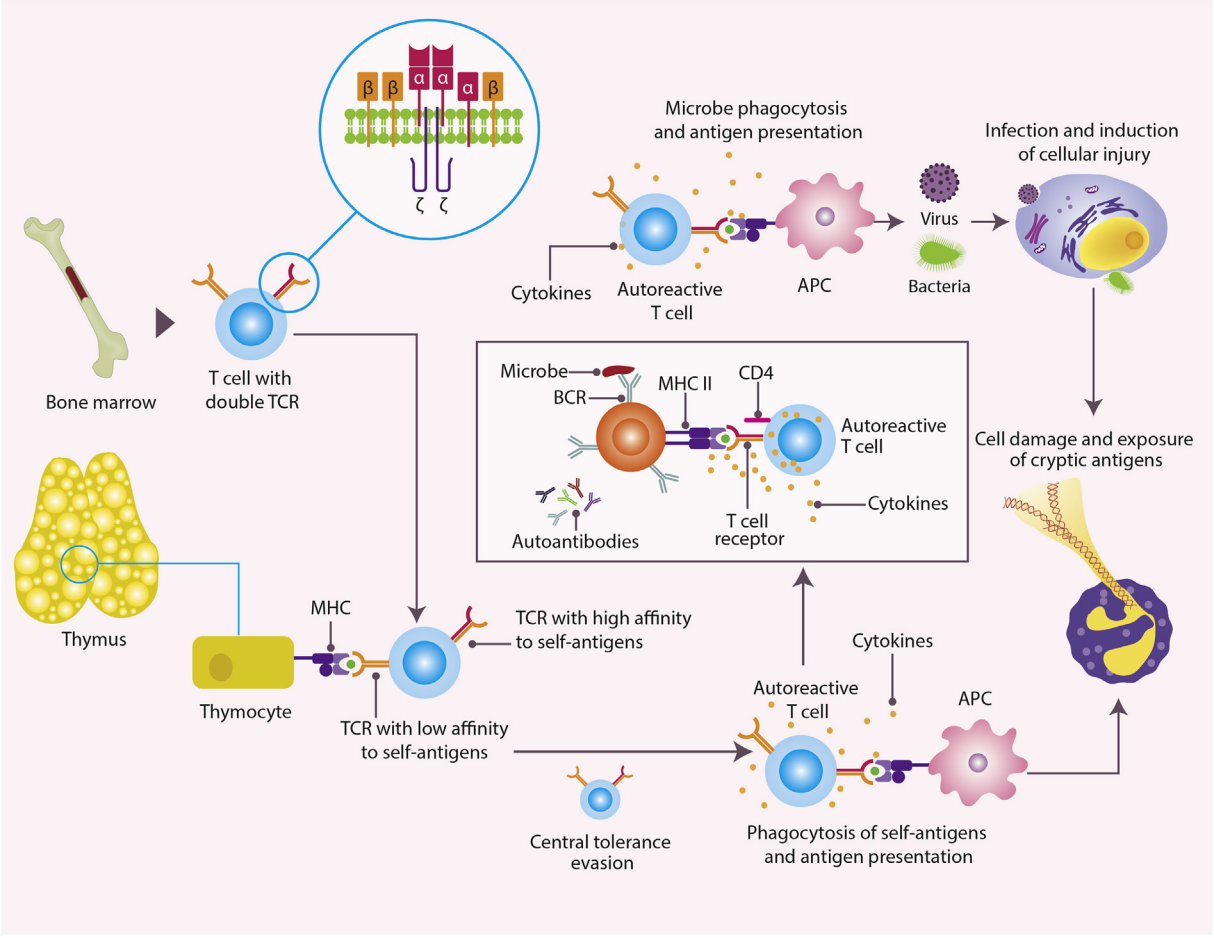

Fig. 2. Proposed mechanism for evasion of central tolerance, and development of autoimmunity secondary to molecular mimicry. T-cells from the bone marrow could have either a single TCR or double TCR with different α and β chains configurations. This scenario may help to avoid central tolerance, which eventually could aid the activation of T-cells, which are stimulated with foreign or self-antigens presented by APCs. This process may enhance the production of autoantibodies due to the activation of T-cells, or vice versa, since B-cells could present antigens to autoreactive T-cells which could increase the production of cytokines and direct damage of tissues through cytotoxicity. TCR: T-cell receptor; BCR: B-cell receptor; APC: antigen-presenting cell; MHC: major histocompatibility complex.

basically documents the fact that heterologous sequential viral infections can augment autoreactive cross-reactive T cells in the target organ above the disease initiating threshold so that major tissue injury and in this case diabetes develops much more rapidly [366]. Thus cross-reactivity between viral and self epitopes can augment but not initiate AD in this model. This model suggests that in humans, AD acceleration can be the result of the combined effect of a few to several immunologically cross-reactive viruses.

RIP-LCMV is a unique model to study the link between molecular mimicry and autoimmunity. These mice exhibit either the nucleoprotein or the glycoprotein of this virus in β cells in the islets of Langerhans [367]. In this model, von Herrath et al. [367] found that mice lacking thymic expression of LCMV-glycoprotein, developed T1D more rapidly than mice who expressed thymic LCMV-glycoprotein. This argues for a key role of central tolerance in the development of autoimmunity associated with molecular mimicry and supports the existence of T-cell cross-reactivity secondary to the existence of dual TCR [368,369]. This concept may be important in autoimmunity following vaccination.

Infectious agents that lyse or damage target tissues may in the process lead to the generation of neoantigens. Horwitz et al. [370] found that while Coxsackie virus B4 (CVB-4) infection of susceptible mice did not lead to any detectable disease, mice who were generated with a TCR transgene specific for a different islet autoantigen when infected with CVB-4 induced direct damage that produced inflammation in the islets leading to the release of islet neo-antigens which stimulated pre-existing resting autoreactive T cells (stimulation of cryptic antigens) resulting in diabetes. Thus, islet antigen sensitization is an indirect consequence of viral infection. We would argue for a complex network of events, that lead to the development of autoimmunity following infectious disease and/or immune challenges. First, as discussed above, infectious diseases may have a direct harmful effect on target tissues. For example, in the case of MS, viral infection can cause inflammation and damage to in the CNS. This phenomenon releases myelin tissue antigens that are recognized by autoreactive T-cells. This incites epitope spreading, where T cells recognize myelin antigens and produce more inflammation of the CNS [370]. Second, following the hypothesis of Cusick et al. [368], three ways of autoreactivity by molecular mimicry could take place (Fig. 2): 1) TCR, given the polyspecificity of this receptor, could recognize the microbe and self-antigens, 2) some T cells exhibit the presence of double TCRs on their surface. One TCR distinguishes the viral/bacteria peptides, and the other is reactive to self-peptides, and 3) the TCR is a “chimera” having 2 β chains and 1 α chain, or 2 α chains and 1 β chain, which, in different mixtures, may result in the recognition of self-antigens or foreign peptides inducing the development of autoimmunity.

Approximately 30% of human T-cells have two functional TCR α chains [371], and up to 15% of T-cells in mice express more than one TCR α chain [372,373]. In addition, approximately 1% of the T-cells express more than one TCR β chain in humans and mice [374,375]. In this context, the first proof of the potential of double receptors in the development of autoimmunity following an infection, was provided by Libbey et al. [376] who demonstrated that dual TCR were present on the surface of T-cells, following an infection by Theiler's murine encephalomyelitis virus (TMEV) in SJL/J mice which developed experimental autoimmune encephalomyelitis (EAE). In this study, Vβ3, Vβ6 and Vα were detected.

The mechanisms by which these cells evade central tolerance are unknown. Classically autoreactive T cells are deleted in the thymus, but the expression of double TCR on the surface of T cells may allow these cells to escape [40]. A study by Blichfeldt et al. [377] reported that dual transgenic-TCRs, required higher concentrations of antigens to generate T-cell proliferative response compared to single TCR T-cells. Sarukhan et al. [378] found that T-cells expressing double TCR were able to avoid tolerance to ubiquitously expressed antigens and produce autoimmune diabetes, if their target antigen was expressed in pancreatic tissue. This could explain the variability of response against self-antigens and external stimuli and may elucidate the mechanisms associated with molecular mimicry. However, further experimental evidence, including *in vivo* models, are required to confirm these hypotheses.

In order to fully understand the molecular mechanisms involved in host genetic susceptibility, it is reasoned that there is a mandatory requirement to characterize the TCR repertoire [379]. Currently, it is impossible to evaluate all TCRs but there are interesting estimates using the “unseen species problem” in ecology [379]. Genes coding the TCRs could produce up to 10^{13} TCR clonotypes [380]. However complete description of these receptors is unlikely given current technologies [379].

The process of TCR production requires recombination of the variable (V), joining (J) and the constant (C) regions which play a pivotal role in the diversity of T-cells [381]. Each of these regions is recombined, with extra nucleotides additions and/or deletions, to generate each rearranged TCR, which ultimately generates high T-cell diversity [381]. This process allows the recognition of thousands of self and non-self-antigens [382]. The identification of diversity of TCR is challenging since the variability of TCR due to rearrangement, reduces the odds to find a unique profile of TCRs. For example, Warren et al. [383] using massive parallel sequencing, found that two samples taken from the same subject obtained within 1 week of difference, showed only 35% identity; highlighting the difficult scenario of characterizing diversity of TCRs.

Three main problems have been considered in the characterization of TCR repertories. First, it is unlikely that the complete diversity of TCRs could be observed solely from blood sample obtained at a single time interval without considering age [384], viral infections [385], vaccination [386] and immunosuppressive processes [387]. Second, laboratory techniques used for the identification of T-cell diversity are technically challenging. For example, initial studies included the use of southern blots [388], and flow cytometry [389]. Nevertheless, these approaches only provide an indirect measurement of TCR diversity. Recently, the use of spectratyping has emerged as a useful laboratory technique to measure TCRs [390]. In this approach, the lengths of different CDR3 (a portion of the recombinant TCR) are used to calculate the number of T-cell clonotypes [379]. However, this method is low-throughput and highly labor-intensive [379,391]. Third, although the configuration of the TCR could be depicted (i.e., αβ, αα, ββ, γδ), the functional role of these combinations in the recognition of antigens is hard to prove, given the polyspecificity of the receptor [379].

Given this issue, several estimations of species richness (i.e. the number of species) have been utilized to estimate TCR diversity. In this scenario, parametric and non-parametric estimators have been used [392,393]. In the former, Poisson abundance models and power laws have been the most widely used to estimate a clonotype frequency distribution based on the assumption that T-cell diversity distribution follows an uniform predictable shape [379]. Non-parametric estimators include the Chao1, Chao2, abundance-based coverage estimator (ACE), and the capture–recapture strategies [379]. Although these strategies are thought-provoking, these estimators require true numbers of T-cell clonotypes to be validated, thus their usefulness in autoimmunity is limited [379]. Nevertheless, TCR diversity will be pivotal for our understanding of the development of autoimmunity. Improvement of current technologies, aimed at describing TCR diversity is warranted to further examine and define which agents may induce ADs via molecular mimicry. Advancements in our understanding of mechanisms associated with molecular mimicry will aid in the prevention and treatment of ADs associated with environmental agents.

5. Infections: a double-edge sword in autoimmunity

As previously reported in this review, there clearly appears to be a link between exposure to infectious disease agents and the role of immune tolerance. Thus, exposure to antigens of infectious agents leads to host immune responses that in some cases cross-react with normal

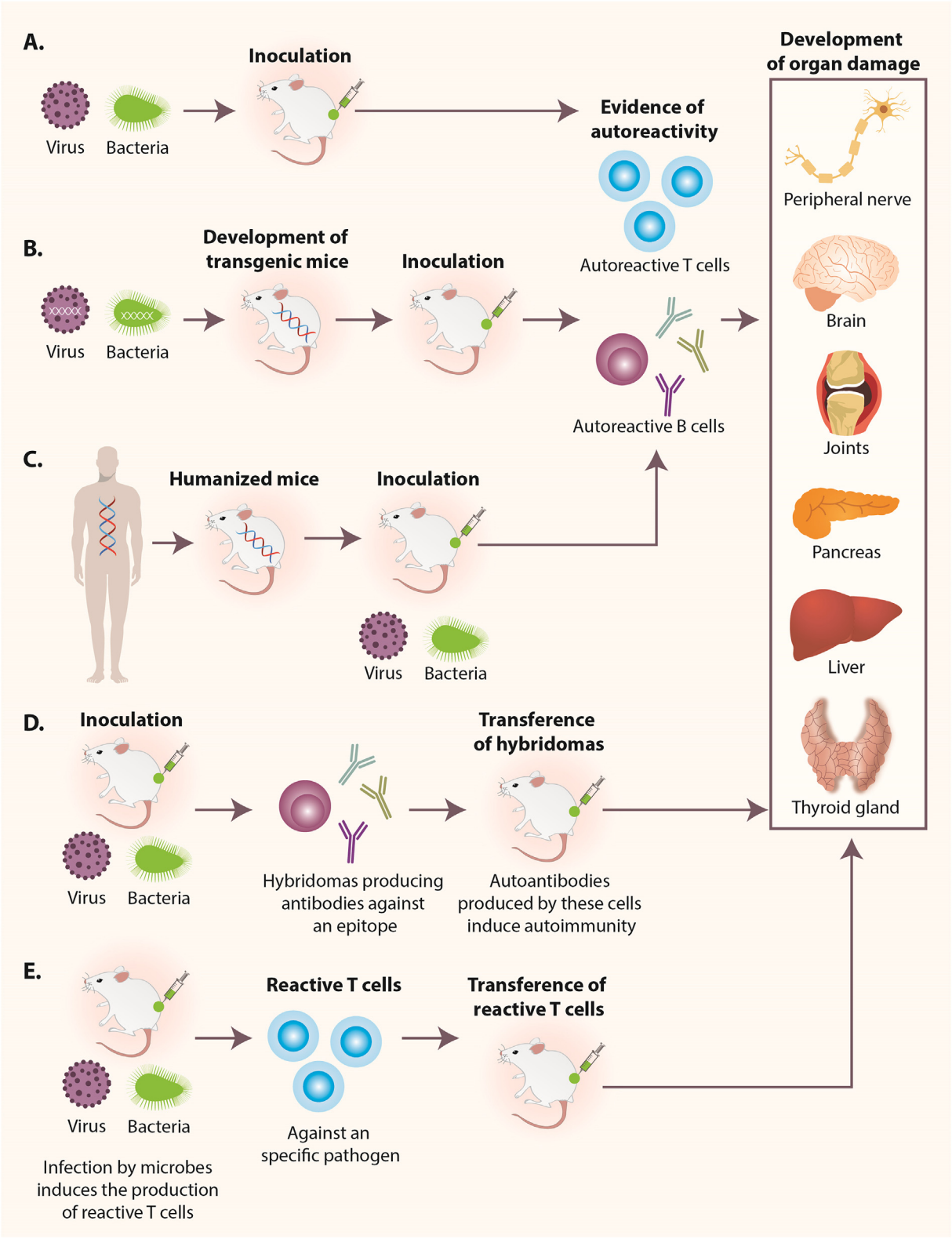

Fig. 3. *In vivo* models for the study of molecular mimicry. A. Mice are inoculated with either recombinant or wild virus encoding a self-protein or epitope, and the process is monitored for the appearance of autoreactivity or signs of autoimmunity. B. A microbe gene is converted in a "self-gene", then it is investigated to establish the development of autoimmunity secondary to molecular mimicry after inoculation of infectious agents. C. humanized mice are monitored to evaluate the development of cross-reactivity or autoimmune response in presence of microbes' epitopes. D. Transference of hybridomas producing autoantibodies against microbes' epitopes which are expected to induce autoimmunity in susceptible mice. E. Transfer of autoreactive T cells against microbes in naïve mice.

human tissue proteins and imply the breaking of self tolerance. Such responses are thought to be the genesis of select ADs as discussed above. It is also of great interest that the past century has seen a marked decrease and even eradication of parasitic worms and there is arguably a concurrent sharp increases in allergies and ADs. One logical interpretation of such phenomenon is that parasitic infection could have been the basis for decreased incidence of allergies and ADs leading to the concept put forth for the "hygiene hypothesis". These views have led some to believe that parasites can be utilized for therapeutic purposes against allergies and ADs. The rationale being that exposure to the parasitic antigens leads to highly effective immune-modulatory systems that can help prevent allergies/ADs [394]. Thus, in the case of infectious diseases, one is left with two ends of the spectrum. One set consisting primarily of viruses and bacteria that due to cross reactivity promote ADs as compared with parasitic infections that lead to inhibition of autoimmunity and thus having a beneficial role in humans [27].

There are some exceptions to this generalization. Thus, some infectious agents exhibit protective effects on ADs. *Helicobacter pylori* (*H. pylori*) is a microaerophilic gram-negative bacterium which is part of the normal flora in about 50% of the world population [395]. This bacterium has been associated with both deleterious and beneficial effects on autoimmunity [396]. In inflammatory bowel disease, using mouse models of dextran sodium sulfate-induced chronic colitis, exposure to *H. pylori* extracts produced amelioration of clinical and pathological status [397]. Furthermore, in patients with MS, *H. pylori* positivity was associated with better disability scores [398]. This was confirmed by Cook et al. [399] who found that C57BL/6 mice infected with *H. pylori* exhibited a lessened EAE, reduced levels of antigen-specific T-cell proliferative responses with lower levels of $CD4^+$ cells in the CNS, and a reduced proportion of $IFN\gamma^+$, IL-17^+, T-bet^+, and $ROR\gamma t^+$ cells from spleens and CNS.

On the other hand, *H. pylori* infection has also shown to be deleterious in ADs. Bai et al. [400] found that monoclonal antibodies against the urease B, an enzyme produced by the bacteria, can cross-react against the glycoprotein IIIa on the surface of platelets by a mechanisms of molecular mimicry, and may be associated with immune thrombocytopenic purpura.

Other bacterial agents that are included in these exceptions include *Klebsiella pneumoniae*. This microbe has been shown to promote protective effects for the development of T1D in murine models [401], whereas in those patients with ankylosing spondylitis (AS) and inflammatory bowel disease, this bacterium has been associated with deleterious effects [402,403]. Similarly, in T1D, infection either by group B coxsackie viruses or LCM have been associated with risk or protection for this disease [404–407]. These observations highlight the double-edged role of infection on autoimmunity and confirms that additional factors (e.g., genetics) are required to trigger autoimmunity.

One of the possible explanations that may elucidate the dual effects of infections on autoimmunity, is the role of the microbiota, which is defined as all those microbes which inhabit our bodies (part of our normal flora) and have evolved in a complex network of interactions with external microbes and the human body [408]. In a study conducted by Rosshart et al. [409], it was found that wild-gut microbiota had a positive influence on immune system homeostasis. In fact, microbiota may hinder the colonization of infectious agents competing for the same nutrients, inducing the production of mucus and antimicrobial peptides, and regulating virulent gene production [410–413].

Patients with RA carry a low proportion of *Bifidobacterium* and *Bacteroides* spp [414], with a relative abundance of *Prevotella copri* [415], *Lactobacillus salivarius, Lactobacillus iners* and *Lactobacillus ruminis* [416]. Wu et al. [417] found that the introduction of segmented filamentous bacteria in germ-free (GF) K/BXN mice exacerbates arthritis by activating Th17 cells. Furthermore, *Lactobacillus* could induce arthritis in IL-1rn$-/-$ mice, depending on Th17- and Toll-Like receptor 4 response [418]. In contrast, colonization of germ free mice with *E. coli,* resulted in an abrogation of experimentally induced arthritis, thus suggesting that *E. coli* may help to regulate joint inflammation [419].

Similarly, in patients with AS, Costello et al. [420] found that, *Bacteroidaceae, Ruminococcaceae, Rikenellaceae, Porphyromonadaceae,* and *Lachnospiraceae* species are copious, whereas *Veillonellaceae* and *Prevotellaceae* species are reduced in a subset of patients. In fact, the introduction of *Bacteroides* species in HLA-B27 transgenic mice, induced inflammatory responses, resembling colitis and gastritis, symptoms that could be found in those patients with AS [421]. Thus, the complex interaction between commensals, infectious agents, and the host should be considered as one explanation for the variability in AD.

As discussed above, not all cases of molecular mimicry trigger an autoimmune phenomenon. In this sense, the P2-C protein of CVB, shares an homology with the islet autoantigen GAD65 [422]. Nonetheless, infection with CVB did not influence the production of GAD65-specific T-cell response or the development of T1D by molecular mimicry [370]. Other factors such as magnitude of the generated cross-reactive immune response, and the overall pathogen history of the host, may contribute to the multitude of immunological response to infection [51].

In a study conducted by Ehser et al. [293] using transgenic mice expressing the human P450 2D6 (i.e., CYP2D6), infection with adenovirus carrying the identical CYP2D6 was less effective in triggering autoimmunity than those wild type mice that express similar CYP homologues. Thus, identical homology is not completely deleterious, and perhaps "almost identical" is more pathogenic than a "perfect fit" structure in the field of molecular mimicry.

6. Experimental models and molecular mimicry

Several experimental models have been developed to study the association between molecular mimicry and autoimmunity (Fig. 3). Five types of murine models have been commonly utilized [47]. In one model, mice are inoculated with either recombinant or wild type virus encoding a self-protein or epitope, and it is monitored for the appearance of autoreactivity or signs of autoimmunity [47]. One example for this model, comes from the study of Nachamkin et al. [327] who after inoculation of C3H/HeN mice with the A/NJ/1976/H1N1 "swine flu" vaccine, found that they developed anti-GM1 antibodies, which play a central role in the pathogenesis of GBS and are a prime example of the role of molecular mimicry (i.e., Type 3) [6]. This experimental model is similar to Koch's postulates, which argue for experimental evidence to demonstrate a causality nexus between an infectious agent and a disease [423]. These postulates include: 1) "The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms", 2) "The microorganism must be isolated from a diseased organism and grown in pure culture", 3) "The cultured microorganism should cause disease when introduced into a healthy organism", and 4) "The microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent". Research taken in count these postulates may provide high-quality evidence about the role of infectious agents in the development of autoimmunity, and may help to describe those particular characteristics associated with cross-reactivity following an infection by a specific agent.

In other murine models, a microbial gene is converted to a "self-gene" [47]. This is exemplified by studies by Evans et al. [424] who developed transgenic mice which expressed the nucleoprotein or glycoprotein of LCMV as a self-protein in oligodendrocytes. Subsequently, they inoculated these mice with an LCMV strain. In the first infection, mice developed peripheral damage but not CNS involvement. However, after the second viral inoculation, mice developed chronic CNS inflammation, loss of myelin and clinical motor dysfunction. This model provides experimental evidence of molecular mimicry in the development of autoimmunity in the CNS.

Table 2
Infections, autoimmune diseases and molecular mimicry.

Clinical setting	Infectious agent	Structural homology	Immunological mechanism	References
Multiple sclerosis	EBV	Similarity between the MBP and the EBVNA1. Homology between the DRB1*15:01-restricted MBP and the DRB5*01:01-restricted EBV peptide.	Activation of autoreactive T cells after infection of EBV.	[68,69,75]
Guillain-Barré syndrome	*C.jejuni*	Carbohydrate mimicry (Galβ1–3GalNAcβ1–4(NeuAcα2–3)Galβ1-) between the bacterial lipooligosaccharide and human GM1 ganglioside.	Activation of autoreactive γδ T cells. Increased production of autoantibodies by activation of B cells.	[43,95]
Type 1 diabetes	Enteroviruses and CMV	Homology between the viral protein 1 (PALTAVETGA/HT) of enterovirus and the β-cell antigen tyrosine phosphatase IA-2, and mimicry of the human CMV major DNA-binding protein with the glutamic acid decarboxylase 65.	Activation of autoreactive T and B cells after infection of enteroviruses.	[132,133]
Rheumatoid arthritis	*P. gingivalis*	Similarity between the *P. gingivalis* enolase and the human α-enolase at the 17-amino acid immunodominant regions. *P. gingivalis* may activate the citrullination of proteins through the bacterial peptidylarginine deiminase.	Cross-reactivity between the autoantibodies produced against the *P. gingivalis* and the human proteome. Induction of autoreactivity due to loss of tolerance to citrullinated proteins in RA.	[148] [159]
	P. mirabilis	Cross-reactivity between the enzymes hemolysin, urease C, urease F, and the human proteome.	Activation of B-cells with production of autoantibodies.	[162]
	E. coli	Heat shock protein (i.e., DnaJ) contains a QKRAA motif, present in the HLA-DRB1 shared epitope.	Activation of T cells by DnaJ.	[163]
Systemic lupus erythematosus	EBV	Cross-reaction between PPPGRRP of EBVNA-1 that cross-reacted with PPPGMRPP of Sm, amino acids 35–58 of EBVNA-1 that cross-reacted with amino acids 95–119 of Sm, and amino acids 58–72 of EBVNA-1 that cross-reacted with amino acids 169–180 of Ro.	Activation of autoreactive B and T cells.	[191,192,196–198]
Sjögren's syndrome	EBV, HTLV-1, HCV and HBV	Sequence similarities to SSB/La decapeptides with HSV, HBV.	Unknown, lack of experimental studies.	[217–219]
Systemic sclerosis	CMV	Mimicry between the CMV UL94 protein and human immunodominant peptide (i.e., GGIGGAGIWLVV). Topoisomerase I amino acid 121–126 share homology with the CMV late protein UL70.	Production of autoantibodies that can induce apoptosis of endothelial cell by interaction with the cell surface integrin–NAG-2 protein complex and a profibrotic phenotype. Activation of autoreactive B cells.	[230,231] [234]
Autoimmune thyroid disease	*Y. enterocolitica*	Mimicry between the TSH-R (residues 22–272, 186–330, 319–363 and 684–749) and the envelope proteins of *Y. enterocolitica* (YopM, Ysp, exopolygalacturonase and SpyA).	Trigger of autoreactive T cells.	[251–253]
	Y. pseudotuberculosis	Cross-reactivity between OmpF porin from *Y. pseudotuberculosis* and TSH-R.	Activation of autoreactive B cells.	[258]
	B. burgdorferi	Similarity between residues 112–205, 127–150, 141–260, 299–383 and 620–697 of TSH-R, and the flagellar motor rotation protein A, outer surface protein A, and DNA recombinase/ATP dependent helicase of *B. burgdorferi*.	Unknown, lack of experimental studies.	[253]
Autoimmune hepatitis	HSV-1, CMV, HCV and adenovirus	Mimicry between the CYP2D6 and viral proteins.	Trigger of autoreactive T cells.	[277,288,292,293]
Primary biliary cholangitis	*E. coli*	Mimicry between the human PDC-E2 and the *E. coli* PDC-E2	Unknown, lack of experimental studies.	[312,313]
Vaccines	Influenza vaccine	Homology between the surface-exposed influenza nucleoprotein A and the extracellular domain of hypocretin 2 receptor in narcolepsy.	Unknown, lack of experimental studies.	[325]
		Suspected homology between influenza proteins and peripheral nerve structures in GBS (unknown exactly homology).	Activation of autoreactive B cells producing anti-GM1 antibodies.	[327]
	HPV vaccine	Peptide homology between HPV with lupus Ku autoantigen proteins (i.e., p86, p70), lupus brain antigen 1 homolog, natural killer cell IgG-like receptors, complement and complement receptor CD19 in SLE.	Unknown, lack of experimental studies.	[340]
		34 pentamers from the viral capsid protein are shared with human proteins that are associated with cardiovascular diseases (i.e., PSEA sequence of the HPV16 shares homology with the human Q99959 protein). Likely associated with POTS.	Unknown, lack of experimental studies.	[349]

EBV: Epstein-Barr virus; CMV: cytomegalovirus; C. jejuni: Campylobacter jejuni; P. gingivalis: Porphyromonas gingivalis; *P. mirabilis*: *Proteus mirabilis*; *E. coli*: *Escherichia coli*; Y. enterocolitica: Yersinia enterocolitica; Y. pseudotuberculosis: Yersinia pseudotuberculosis; B. burgdorferi: Borrelia burgdorferi; MBP: Myelin basic protein; EBVNA1: EBV nuclear antigen 1; HSV: Herpes simplex virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TSH-R: Thyroid stimulating hormone receptor; GBS: Guillain-Barré syndrome; HPV: Human papilloma virus; SLE: systemic lupus erythematosus; POTS: Postural orthostatic tachycardia syndrome.

The third murine model includes the transfer of hybridomas producing autoantibodies against self-epitopes [47]. Antibodies against MOG (MOG92-106), which cross-reacts with milk protein [47], were produced from an A.SW mouse with progressive EAE. Transfer of hybridomas producing MOG mAb into naïve mice resulted in immunoglobulin deposition in kidneys and liver tissues, and induced EAE [425]. Another model utilized is one in which the mice are humanized with structures which are associated with immune response, i.e. TCR receptors, and then they are monitored to evaluate the development of cross-reactivity or autoimmune response in the presence of microbial epitopes. Harkiolaki et al. [74] in a humanized Ob TCR-HLA-DR 2β transgenic mice, found that T cells carrying these receptors reacted when incubated in vitro with MBP, Mycobacterium avium and developed a MS-like disease. Structural analysis revealed that this process was mediated by molecular mimicry (i.e., Type 4).

Another model used to study the role of molecular mimicry in autoimmunity is the transfer of autoreactive T cells in naïve mice. Tsunoda et al. [426] using TMEV which causes a demyelinating disease in infected mice, demonstrated that after intracerebral injection of TMEV-reactive $CD8^+$ T cells into naïve mice, degeneration of the brain and spinal cord was common, suggesting a role of molecular mimicry in neural damage [426]. Finally, *in vitro* models are also commonly used [427]. Lunemann et al. [68] using EBVNA1 reactive T cells in *in vitro* model, found that these cells were reactive to MBP and this response was associated with a high production of IFN-γ. Since immune responses involve multiple mechanisms, it is clear that *in vivo* models are likely to provide more reliable and useful results.

7. Conclusions

The mechanisms associated with cross-reactivity via molecular mimicry are complex and integrate genetic and environmental factors (Table 2). A systems medicine approach including the evaluation of changes in T cells in either the TCR or exposure to cryptic antigens will help to increase our understanding of molecular mimicry.

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