CHAPTER 3

Molecular Mimicry and Autoimmunity

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1 INTRODUCTION

The term *molecular mimicry* was originally defined by Damian as "the sharing of antigens between parasite and host".[1] The sequence similarity between foreign (a microorganism's peptides) and self-peptides (the host's antigen) enable pathogens that mimic self-epitopes to evade the immune system and lead to an immunological tolerance; in this way they gain an evolutionary advantage.[2–4] The mechanism by which pathogens have evolved or obtained by chance similar amino acid sequences or the homologous three-dimensional crystal structure of immune-dominant epitopes remains a mystery, yet there are many examples of common microorganisms that 'use' this mechanism: the *Vaccinia* virus protein A49 mimics nuclear factor κB inhibitor; *Neisseria meningitidis* recruits complement-soluble plasma regulatory protein factor H by mimicking host carbohydrates; and group B *Streptococcus* (GBS) mimics host sialoglycan, resulting in impaired neutrophil function.[5–7]

The phenomenon of molecular mimicry has, however, been just recently discovered as one of several ways in which autoimmunity can be evoked. Under certain circumstances, these infectious 'mimickers' can activate the immune system, initiate an immune response and lead to a breakdown in self-tolerance and autoimmunity.[8] Structural homology – meaning that a single antibody or T-cell receptor can only be activated by a few residues – is crucial for this immune system activation. Following the encounter with the pathogen, activated autoreactive B or T cells can cross-react with self-epitopes, thus leading to autoimmunity.[9] Autoimmunity is the result of a loss of immunological tolerance, the ability of the immunologic system to discriminate between self and nonself. Recent data show that autoimmune diseases affect approximately 1 in 31 people within the general population.[10] Growth also has led to a greater characterisation of what autoimmunity is and how it

can be studied and treated. With the increased amount of research, there has been tremendous growth in the study of several different ways in which autoimmunity can occur, one of which is molecular mimicry. Thus, nowadays the term *molecular mimicry* has been transformed and is used to define an autoimmune response elicited by a microorganism's antigenic determinants.[11]

Here we provide some examples of common infectious agents and their roll in creating autoimmune disorders. Later, we present the opposite, describing autoimmune disorders in which there was found a relation to infectious agents via a molecular mimicry mechanism. At the end of each paragraph, the data are summarized in two tables.

2 COMMON INFECTIOUS AGENTS AND THEIR ROLL IN SETTING AUTOIMMUNE DISORDERS

2.1 Viruses

Epstein–Barr virus (EBV), a member of the *herpesviridae* family, is estimated to infect more than 90% of the human population.[12] There is consistent evidence supporting the role of EBV in triggering many autoimmune diseases, particularly systemic lupus erythematosus (SLE).[13–15] The most relevant mechanism by which EBV has been suggested to induce autoimmunity is molecular mimicry. Epstein–Barr nuclear antigen-1 (EBNA-1) has regions bearing homology to SLE-associated antigens such as ribonucleoprotein Smith antigen (Sm) and Ro self-protein.[8,16–18] By tracing autoantibody response in SLE back in time, cross-reactivity was found between the Ro self-protein, the initial SLE autoantigen and EBNA-1, suggesting it is triggered by molecular mimicry.[19] Furthermore, in mice, expression of EBNA-1 may elicit antibodies to Sm and double-stranded DNA (dsDNA), and antibodies elicited in response to EBNA-1 were shown to cross-react with dsDNA.[20,21] Finally, in rabbits, immunization with EBNA-1 fragments containing the PPPGRRP sequence led to the development of antibodies with cross-reactivity to Sm and nuclear ribonucleoproteins; after immunization, most of the rabbits developed leucopenia or lymphopenia (or both), the features of which resemble those of SLE.[22]

Cytomegalovirus (CMV), also a member of the *herpesviridae* family, is an extremely common human pathogen worldwide.[23] Its role in triggering autoimmunity trough molecular mimicry has been pointed out in different autoimmune disorders. Immunoglobulin G antibodies from the sera of

patients with systemic sclerosis where found to recognize both autoantigens and human CMV late protein UL94 and to induce endothelial cell apoptosis.[24] Cross-reactivity also was found between glutamic acid decarboxylase (a major autoantigen in diabetes mellitus type 1 and stiff-man syndrome) and CMV major DNA-binding protein pUL57, which supports the role of CMV in triggering those two pathologies.[25] Regarding Guillain-Barré syndrome (GBS), it has been demonstrated that anti–GM2 antibodies cross-react with CMV–infected fibroblasts.[26] Finally, Hsieh et al.[27] demonstrated that most patients with SLE have antibodies to CMV phosphoprotein 65 when compared with controls and that immunization with CMV phosphoprotein 65 in mice elicited the production of antichromatin, anticentriole, antimitotic spindle type I/II and anti-dsDNA antibody, as well as deposition of glomerular immunoglobulin.

Parvovirus B19 (PB19), a single-stranded DNA (ssDNA) virus and ubiquitous human pathogen, is the etiologic agent of erythema infectiosum (the fifth disease) and is responsible for such diverse pathologies as transient aplastic crisis, hydrops fetalis and arthropathy.[28,29] Clinical resemblance of PB19 infection and some autoimmune disorders has raised the possibility of a linkage between the two.[30,31] Loizou et al.[32] compared sera of three groups of patients with acute PB19 infection, patients with other acute viral infections and patients with syphilis. He specified the antiphospholipid antibodies and further compared sera from those three groups with sera from patients with SLE trying to investigate the dependence of anticardiolipin binding on the presence of β2-glycoprotein I as a cofactor. Sera from patients with PB19 was found to have different antiphospholipid specificity when compared with sera from patients with other infections; like sera from patients with SLE trying but unlike sera from patients with other acute viral infections or syphilis, anticardiolipin antibodies of patients with PB19 were found to increase their binding ability in the presence of β2-glycoprotein I.[32] After synthesizing a PB19 viral peptide, Lunardi et al.[33] demonstrated that purified anti-PB19 antibodies cross-reacted with autoantigens such as keratin, collagen type II, ssDNA and cardiolipin. Afterwards, 8 mice were immunised with that same viral peptide, eliciting autoantibody production against keratin, collagen II, cardiolipin and ssDNA in 6 of them.[33]

2.2 Bacteria

Streptococcus pyogenes, a Gram-positive cocci, is the main etiologic agent of bacterial pharyngitis. One of the first and best established linkages between

a human pathogen and an autoimmune disorder was that of *S. pyogenes* and rheumatic fever (RF); molecular mimicry was proposed as trigger early on.[34] Evidence of antibody cross–reactivity between the streptococcal M protein and cardiac myosin has been presented in different publications.[35–37] Guilherme et al.[38] demonstrated that T-cell clones from hearts of patients with RF recognized both streptococcal M protein and heart proteins. Regarding Sydenham chorea, cross–reactivity between mammalian lysoganglioside and *S. pyogenes* N–acetyl-beta-D-glucosamine was observed.[39] Finally, Quinn et al.[40] reported that 3 of 6 Lewis rats immunized with recombinant streptococcal M protein developed valvulitis and focal lesions of myocarditis, whereas Bronze and Dale[41] showed that immunization of rabbits with streptococcal protein M elicited the production of antibodies with cross–reactivity to brain proteins, thus establishing a possible etiology for Sydenham chorea in patients with RF.

Helicobacter pylori, a Gram–negative bacillus estimated to infect about 50% of the world's population, is linked with disorders such as atrophic gastritis, peptic ulcer disease and gastric carcinoma.[42] Different autoimmune disorders have been associated with *H. pylori* infection, and molecular mimicry was proposed as a triggering mechanism in some of them. Appelmelk et al.[43] observed that immunization of mice and rabbits with *H. pylori* lipopolysaccharide elicited production of antibodies to Lewis blood group antigens, which recognized human and murine gastric glandular tissue. Amedei et al.[44] showed that cell clones of gastric T cells recovered from *H. pylori*–infected patients with autoimmune gastritis recognized both pathogen antigens and H^+, K^+ ATPase. Finally, Takahashi et al.[45] demonstrated that platelet-associated immunoglobulin G from the sera of patients with idiopathic thrombocytopenic purpura recognized *H. pylori* CagA protein.

Campylobacter jejuni, a Gram–negative, spiral–shaped bacillus, is one of the most common agents of bacterial gastroenteritis in the world.[46] Postinfectious GBS is one of the best examples of autoimmune disease triggered by bacterial infection; up to a third of cases are preceded by *C. jejuni* infection.[47] Structural homology between *C. jejuni* lipo–oligosaccharide (LOS) and human ganglioside GM1 was first demonstrated by Yuki et al.[48] and Willison and Yuki;[49] later, cross–reactivity between *C. jejuni* LOS and human antiganglioside antibodies was observed. Furthermore, animal studies have shown anti-GM1 antibody development and neurologic disorders resembling GBS upon immunization with *C. jejuni* LOS, thus supporting the role of molecular mimicry in this disease.[50]

2.3 Parasites

Trypanosoma cruzi, a flagellated protozoan parasite, is the etiologic agent of Chagas' disease, a disorder with protean clinical manifestations including digestive, nervous and cardiac involvement; the latter is the most important because of its frequency and clinical implications.[51–55] The contribution of molecular mimicry in triggering Chagas' disease cardiopathy has been suggested by a number of publications.[56,57] Immunization of mice with cruzipain, a parasitic antigen, elicited anticruzipain and antimyosin antibody production and was associated with heart conduction disturbances.[58] Cunha-Neto et al.[59,60] demonstrated cross-reactivity between a heart-specific epitope of myosin and *T. cruzi* antigen B13 and further identified simultaneous responsiveness of heart-infiltrating T-cell clones from patients with Chagas' disease cardiopathy to cardiac myosin heavy chain and *T. cruzi* antigen B13. Leon et al.[61,62] showed that mice immunized with *T. cruzi* protein extract emulsified in complete Freund's adjuvant developed antibodies and delayed–type hypersensitivity to cardiac myosin, whereas mice immunized with cardiac myosin developed antibodies and delayed-type hypersensitivity to *T. cruzi*. Induction of peripheral immune tolerance to *T. cruzi* or myosin led to a decrease in cellular immunity to myosin and *T. cruzi*, respectively. Finally, mice immunized with R13 synthetic peptide, corresponding to sequences in the *T. cruzi* ribosomal P1 and P2 proteins, generated antibodies to R13 as well as to H3, an autoantigen, followed by cardiac structure abnormalities[63] (Table 1).

Autoimmunity is believed to be the consequence of a breakdown in self-tolerance that induces an attack of the immune system on different organs and tissues. A combination of genetic, immunologic and environmental factors is required, comprising what is nowadays called 'the mosaic of autoimmunity'.[79]

Microbial antigens have the potential to initiate autoreactivity through molecular mimicry and other mechanisms such as polyclonal activation or the release of previously sequestered antigens.[80] Although the triggering event in most autoimmune diseases is unknown, the process of molecular mimicry between microbial and self-components (e.g., proteins, carbohydrates or DNA epitopes) is postulated to be the most likely mechanism of postinfectious autoimmunity.

Molecular mimicry is one mechanism by which infectious agents (or other exogenous substances) may trigger an immune response against auto-antigens. According to this hypothesis, a susceptible host acquires an

Table 1 Examples of molecular mimicry mechanisms of infectious pathogens in autoimmune disorders

	Pathogen	Associated autoimmune disorder	Mimicking pathogenic antigen	References
Virus	CMV	DM1	pUL94	24
		SS	pUL57	25
		APS	TIFI	64
	EBV	MS	LMP-1	65
		SLE	EBNA-1	16–22
		RA	BZLF-1, BMLF-1	66
	Enterovirus	DM1	Several viral peptides	67
	HBV	MS	HBV DNA polymerase	68
	HCV	AH	Core protein	69
		CryG	Core protein	70
		AT	HCV polyprotein	71
	HIV	SjS	p24 Capsid antigen	72
		SLE	p24 Capsid antigen	72
	HSV	MG	Glycoprotein D	73
	PB19	APS	VP1u	74
	Rubella	DM1	Several viral peptides	75
Bacteria	*Campylobacter jejuni*	GBS	LOS	48–50
	Clostridium tetani (toxoid)	APS	TLRVYK hexapeptide	76
	Chlamydia trachomatis	AS	DNA primase	77
	Hemophilus influenzae	MS	Protease IV	73
		APS	TLRVYK hexapeptide	76
	Helicobacter pylori	AG	LPS	43
		ITP	CagA	45
	Neisseria gonorrhoeae	APS	TLRVYK hexapeptide	76
	Streptococcus pyogenes	RF	M protein	35–38,40,41
			N-acetyl-β-D-glucosamine	39
Parasites	*Trypanosoma cruzi*	CD	Cruzipain	58
			B13	59,60
			R13 synthetic peptid	63
			F1-160	78

AG, autoimmune gastritis; AH, autoimmune hepatitis; APS, antiphospholipid syndrome; AS, ankylosing spondylitis; AT, autoimmune thyroiditis; CD, Chagas disease; CMV, cytomegalovirus; CryG, cryoglobulinemia; DM1, type 1 diabetes mellitus; EBV, Epstein-Barr virus; GBS, Guillain-Barré syndrome; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ITP, idiopathic thrombocytopenic purpura; LOS, lipo-oligosaccharide; LPS, lipopolysaccharide; MG, myasthenia gravis; MS, multiple sclerosis; PB19, parvovirus B19; RA, rheumatoid arthritis; RF, rheumatic fever; SLE, systemic lupus erythematosus; SjS, Sjögren's syndrome; SS, systemic sclerosis.

infection with an agent that has antigens that are immunologically similar to the host antigens but differ sufficiently to induce an immune response when presented to T cells. As a result, the tolerance to autoantigens breaks down, and the pathogen-specific immune response that is generated cross-reacts with host structures to cause tissue damage and disease. This model has persisted for more than three decades because it offers an attractive conceptual link between physiologic responses (defence against infection) and a pathologic process (autoimmunity).

Cross-reactivity between foreign (i.e., infectious) and self-antigens can be determined by different methods. One approach is to enable the detection of cross-reactive self-antigens and humoral response by identifying a suspected causative organism and its antigenic epitopes. Another method, when the causative organism is unknown, is identifying T-cell determinants capable of inducing autoimmunity and then searching for homologous microbial sequences that might activate the immune system in a major histocompatibility complex–dependent way.[81]

In recent years, the role of different infectious agents has been extensively studied, and several mechanisms were found to be associated with postinfectious autoimmunity pathogenesis, of which molecular mimicry is the dominant mechanism.[82] For example, it was found that several human monoclonal antibodies can react specifically with infectious agents as well as with human antigens.[83] These antibodies are believed to be at least partially responsible for initiating a pathogenic process that eventually results in autoimmunity. Those studies led to the suggested criteria for 'diagnosing' the role of molecular mimicry in autoimmune diseases.[50] The first requirement is that the suspected pathogen must be associated with the presence, onset or exacerbation of the autoimmune disease in a convincing number of patients. Second, the infectious agent must provoke either a T-cell-dependent or T-cell-independent immune response (i.e., autoantibodies) that cross-reacts with host antigens and is clinically relevant to the autoimmune disease. The proof of the causality between the mimic epitope and the autoimmune disease can be achieved by active immunization with the shared epitope in animal models and induction of the autoimmune disease or by passive transfer of the disease using autoreactive T cells or autoantibodies.

In conclusion, molecular mimicry has been linked to the pathogenesis of many autoimmune diseases. Here we review a few major examples of different autoimmune diseases that have been linked to this mechanism. The data of these examples as well as other autoimmune diseases and related

infectious agents that were found to be escaping the immune system through the roll of molecular mimicry are summarized in Table 2.

3 NEURO-AUTOIMMUNE DISEASE

Multiple sclerosis is a chronic human autoimmune disease characterized by mononuclear cell infiltration and demyelization within the central nervous system (CNS) and neurological dysfunction. In the case of multiple sclerosis, it has been hypothesized that the disease is initiated by an infection early in life by a virus that shares antigenic structures with the host's CNS tissue. The host immune response against EBV, influenza virus type A and human papillomavirus peptides cross-reacts with CNS self-antigens, such as myelin basic protein, leading to demyelization. Subsequent viral infections are thought to cause exacerbations of the disease by reactivating the immune response against viral antigens and autoantigens.[99]

4 ENDOCRINOLOGICAL AUTOIMMUNE DISEASE

Insulin–dependent diabetes mellitus (IDDM), or type I diabetes, is an auto-immune disease involving mononuclear cell infiltration of the pancreatic islets (insulitis), destruction of the beta islet cells and insulin deficiency. In autoimmune diabetes, T cells recognize both a peptide derived from the autoantigen glutamic–acid decarboxylase and a highly analogous peptide from the coxsackievirus P2–C protein (see Table 2).

5 INFLAMMATORY ARTICULAR DISEASE

Rheumatoid arthritis (RA) is a human autoimmune disease with an unknown etiology and is characterized by symmetrical persistent inflamma-tory synovitis of the peripheral joints. Rheumatic fever (RF) is the classical example of molecular mimicry resulting in postinfectious autoimmunity. A timely association between streptococcal infection and RF had been dem-onstrated in the majority of patients. Streptococcal epitopes such as N-acetylglucosamine or M-protein mimic cardiac myosin and a-helical proteins present in the valve, whereas N-acetyl glucosamine also mimics neuronal ganglioside. T-cell clones originating from human RF heart lesions recognize bacterial M-protein peptides and heart-derived peptides. These mimic peptides are clearly associated with major manifestations of RF that affect the heart valves and neuronal elements, among other organs.[100,39]

Table 2 Molecular mimicry mechanism in different autoimmune disorders

Autoimmune Disorder	Self-antigen	Pathogen	References
Rheumatic fever	Cardiac myosin, tropomyosin, laminin, vimentin, actin, keratin, N-acetyl-glucosamine	*Streptococcus pyogens* M protein and N-acetyl-glucosamine	84–86
Chagas cardiomyopathy	Humen β1-adrenergic receptor, cardiac myosin, Cha antigen, common glycolipid antigenson nervous tissue	*Trypanosoma cruzi* ribosomal PO, B13 protein, shed acute-phase antigen (SAPA); 160-kDa flagellum; trypomastigote stage specific glycoprotein	58
Rheumatoid arthritis	BZLF1, BMLF1	EBV	13,66
Ankylosing spondylitis	HLA B27 Type I, II, IV collagen	Klebsiella pneumonia, chlamydia	87
Systemic lupus erythematosus	Ro 60 kD, Sm, MDA, dsDNA	Mycobacteria, Klebsiella pneumonia Pneumococcal polysaccharide EBV, HERV, Coxsackie virus 2B, parvovirus, retroviruses	13,88–93
Sjögren's syndrome	Ro 60 kD	Coxsackie virus 2B	94
Antiphospholipid syndrome	β2 Glycoprotein I	*Hemophilus influenza*, *Niesseria gonorrhoeae*, tetanus toxin, parvovirus B12, CMV	64,76
Autoimmune liver diseases	Core protein	HCV	69,70
Inflammatory bowel diseases	Cruzipain	*Trypanosoma cruzi*	58
Type I diabetes mellitus	pUL94, viral peptides	CMV, enterovirus, rubella	67,75
Autoimmune thyroid diseases	HCV polyprotein	HCV	71

Continued

Table 2 Molecular mimicry mechanism in different autoimmune disorders—cont'd

Autoimmune Disorder	Self-antigen	Pathogen	References
Multiple sclerosis	Myelin basic protein Myelin oligodendrocyte glycoprotein 18–32	Corona virus, measles, mumps, EBV, human herpes Semliki Forest virus E2 peptide 115–129, *Acanthamoeba castellanii*, influenza virus type A, human papillomavirus	95,88,96,13
Myasthenia gravis	Acetylcholine receptor neurofilaments	Herpes virus, hemophilus influenza	97
Guillain-Barré syndrome	Gangliosides	*Campylobacter jejuni* lipo-oligosaccharide	98

CMV, cytomegalovirus; dsDNA, double-stranded DNA; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HERV, human endogenous retrovirus; HLA, human leukocyte antigen; MDA, malondialdehyde; Sm, Smith.

Moreover, active immunization with these cross-reactive peptides induces myocarditis in mice, and passive transfer of purified antibodies from rats immunised with cardiac myosin resulted in immunoglobulin G deposition and apoptosis, leading to cardiomyopathy.[101,102]

6 VASCULITIDES

SLE is a multisystem human autoimmune disease characterized by multiple autoantibodies: anti–dsDNA, anti–Ro/La, antiribonucleoprotein complex, antihistone and other nuclear components. Among autoimmune diseases, SLE was linked to several viral and bacterial agents, especially the EBV, which is a ubiquitous pathogen associated with many autoimmune diseases. The interaction between EBV and SLE is not unidirectional. EBV may trigger autoimmunity (the appearance of SLE-associated autoantibodies and clinical manifestations), but it can also affect the immunologic system in patients with SLE, who seem to have an impaired anti-EBV immune response and dysregulation of the viral latency period compared with controls.[103,104] In recent years, several other viruses have been linked to SLE as well, and molecular mimicry was suggested as the responsible mechanism. For the majority of them, however, only antigenic cross-reactivity had been demonstrated so far. The first example for cross-reactivity is the peptide derivative from Coxsackie virus 2B protein (pepCoxs), which has 87% amino acid homology with the 222–229 region of the major linear antibody binding site of the Ro 60-kD autoantigen. The Coxsackie virus was suggested to have a potential role in the autoimmune response against Ro/SSA and La/SSB as well.[94] The second example of cross-reactivity is the PB19, which has been implicated as a causative agent of several autoimmune disorders, including SLE. A peptide that shares homology with the parvovirus VP1 protein and with human cytokeratin (the transcription factor GATA1) and that plays an essential role in megakaryopoiesis and erythropoiesis was identified and was suggested to have a role in the induction of cross-reactive autoantibodies.[88] Furthermore, endogenous retrovirus elements and nonendogenous elements were found to be linked with autoimmunity, and molecular mimicry between those retroviruses and a host antigen was proposed.[89] The complex interplay between infections, genetics and autoimmunity regarding retroviruses in SLE patients is reviewed elsewhere.[90]

    A molecular mimicry mechanism in lupus was studied in bacterial infections as well (i.e., mycobacteria, Klebsiella pneumonia), mainly with

anti–dsDNA antibodies, and has been documented in animal models and in humans.[91,105] For example, in healthy individuals, elevated titers of anti–dsDNA antibodies can be detected following different bacterial infections.[92] Furthermore, sera from patients infected with the Gram-negative pathogen *Klebsiella pneumoniae* were found to have high titers of a common anti–DNA idiotype (16/6ID). Another example is the similarity found between the B 561 peptides from *Burkholderia* bacteria and anti–dsDNA antibodies.[106] The cross-reactivity between anti–dsDNA and *Burkholderia* peptides points to the possible role of bacterial infection in inducing the production of autoantibodies.

6.1 Summary and Suggestions for the Future: 'Control' of Molecular mimicry

The complex causes of autoimmune diseases not only present a challenge to the development and testing of new therapies but also offer a framework that allows the identification of subgroups of patients who might benefit from particular approaches. Molecular mimicry is one of the most logical explanations for the linkage between infection and autoimmunity, and its concept is a useful tool in understanding the etiology and pathogenesis of autoimmune disorders. The examples detailed in this chapter supply evidence for the role of specific pathogens in triggering particular autoimmune disorders by molecular mimicry. However, a definite direct causality between this mechanism and autoimmunity is yet to be established.

Understanding the mechanism of molecular mimicry in autoimmune disorders, one cannot avoid thinking that autoimmunity caused by molecular mimicry can be avoided. Control of the initiating factor (pathogen) via vaccination seems to be the most common method of avoiding autoimmunity. Inducing tolerance to the host autoantigen in this way may also be the most stable factor. The development of a downregulating immune response to the epitopes shared between the pathogen and the host may be the best way of treating an autoimmune disease caused by molecular mimicry.[107] Unfortunately, this method is not straightforward. Recently, a large number of published case reports of immunologic late reactions to vaccines raised the hypothesis that specific vaccines containing adjuvants are responsible for autoimmune diseases, especially in genetically susceptible patients. The entity autoimmune/auto-inflammatory syndrome induced by adjuvants describes the role of various environmental factors in the pathogenesis of immune-mediated diseases. Of these factors, those entailing immune adjuvant activity, such as infectious agents, silicone, aluminium salts and others,

were associated with defined and nondefined immune-mediated diseases both in animal models and in humans.[108]

Understanding the mechanisms of molecular mimicry may allow future research to be directed towards uncovering the initiating infectious agent as well as recognizing the self-determinant. Willingly, future research may be able to design strategies for the treatment and prevention of autoimmunity.

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