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PATHOGEN-BASED MOLECULAR MIMICRY AND AUTOIMMUNE DISORDERS: A CLOSE LOOK

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ABSTRACT

Our immune system is fighting off the foreign invaders trying to enter our body on a day-to-day basis. However, in some cases, this army of cells can start to malfunction and produce an abnormal immune response against self-cells. This condition gives rise to a plethora of diseases, collectively called the autoimmune disorders. There have been several studies in recent years to understand how infectious agents trigger autoimmune disorders, and the corresponding mechanisms involved. One of the most important mechanisms reported is based on molecular mimicry. In many cases, a foreign antigen sharing similarities with the structure or sequence of a self-antigen has led to the initiation of B-cell and T-cell responses, which as a result, makes the host vulnerable to the attack of the self-cells to cause autoimmune disorders. There are reports of bacteria and viruses linked to the occurrence of many autoimmune diseases, although the identification of specific pathogens and its antigenic components responsible for the initiation of the diseases has not been performed much. This review paper highlights the mechanism of molecular mimicry associated with several autoimmune disorders reported in recent years, which may also open new avenues in their treatment.

Keywords: autoimmune disorders, B-cell, infectious agents, molecular mimicry, self-antigens, T-cell

INTRODUCTION

The studies on molecular mimicry are at the forefront of present-day advanced research, considering which infectious pathogens can trigger autoimmune disorders **[1]**. The similarities between foreign, non-self-peptides and self-peptides can induce the auto-reactive B cells or T cells to get activated by the pathogenic antigenic components, leading to disastrous effects in an individual **[2, 3]**. The auto-reactive T cells that are produced in response to molecular mimicry, the production of the autoimmune B cell responses and the effects of immune system getting exposed to foreign antigens all point towards the importance of molecular mimicry as the chief underlying factor **[4]**.

Autoimmune diseases (ADs) affect roughly 5% of the global population **[5]**, which produces a range of auto-antibodies with a diverse spectrum of specificity **[6]**. The understanding of the role of infectious agents in ADs is on a constant rise. Rates of development of ADs take a leap post-infection, and this has been mostly observed in the case of Guillain-Barre Syndrome (GBS) **[7, 8]**. This is highlighted by observations which show a 3-fold increased risk for the initiation of the GBS in individuals receiving the H_1N_1 influenza immunization **[9]**. This report has been linked to the findings that there are similarities in some of the structures present in the influenza virus to that seen in the myelin sheaths of the affected individuals **[10]**. Studies recently have also investigated B cell responses which are found responsible to produce auto-antibodies **[11]**. There is an elevated generation of such auto-antibodies against glycoproteins present on the myelin sheath in patients affected with *Campylobacter jejuni* infections **[12]**. This mechanism of molecular mimicry has been reported in several cases, which includes those on both localised and systemic ADs **[12]**.

LOCALISED AUTOIMMUNE DISEASES

A) Autoimmune Thyroid Disease (AITD)

Recent studies have pointed out that human Autoimmune Thyroid Disease (AITD) affects nearly 5% of the population and is a result of intricate complex interactions between the genome and environment of an individual **[13]**. AITDs are broadly divided into two major classes, namely Hashimoto's Thyroiditis (HT) and Grave's Disease (GD) **[14]**. HT leads to gradual self-destruction of the thyroid gland, whereas in GD, auto-antibodies to human Thyroid Stimulating Hormone Receptor (hTSHR) cause the disorder **[14]**.

Amino acid sequence homology was identified not only between five proteins of *Borrelia burgdorferi* (flagellar motor

rotation protein A, outer surface protein A, DNA recombinase/ATP dependent helicase and two hypothetical proteins BBG02 and BBJ08) and 5 segments of hTSHR **[15]**, but also between 16 *Borrelia* proteins and human thyroglobulin (Tg) and Sodium Iodide symporter **[16]**. Besides molecular mimicry of hTSHR by *B. burgdorferi*, the other microbial peptides showing significant homology with hTSHR include SpyA, exopolygalactouronase, YopM and Ysp of *Yesinia* spp. **[15]**, Neurotoxin A of *Clostridium botulinum*, ATPase of *Rickettsia prowazekii*, and putative Type I and type III Restriction Enzyme and Urease Accessory Protein (UAP) of *Helicobacter pylori* **[16]**. Calcium binding EGF-domain containing protein of *Toxoplasma gondii* and mannan polymerase II complex of *Candida albicans* share significant amino acid homology with endogenous Thyroid Peroxidase (TPO) protein of humans **[16]**. On the other hand, a number of proteins of *Bifidobacterium* sp., *Lactobacillus* sp. and *Treponema pallidum* share considerable homology with Tg, making it a potential target of molecular mimicry by these microbes **[16]**. All these data suggest possible roles of molecular mimicry in the development of AITD.

B) Guillain-Barre Syndrome (GBS)

Guillain-Barre syndrome (GBS) is the most common form of neuromuscular paralysis in the Western world, with an occurrence in about 1-2 individuals per 10,000 individuals **[17]**. In about 25% of the patients with acute demyelinating GBS, anti-ganglioside antibodies are found **[17]**. A much rarer variant of GBS is Miller-Fisher Syndrome (MFS) that does not usually involve motor weakness of the limbs **[18]**. There is enough available evidence that support the possible mechanisms of molecular mimicry involved in GBS and MFS.

Several microbes which are found associated with GBS include *Campylobacter jejuni* [19], *Mycoplasma pneumoniae* **[19]**, Influenza virus **[19]**, Zika virus **[19]** and SARS-CoV-2 virus **[20]**. One of the major components of the outer membrane of *C. jejuni* is the lipooligosaccharide (LOS) **[21]**. Bacterial isolates from patients suffering from GBS showed the presence of ganglioside GM1 and GD1a-mimicking LOS molecules from *C. jejuni* **[21]**, establishing the importance of molecular mimicry in the development of the disease. The major mechanism involved in GBS following Zika infection is molecular mimicry **[22]**. A recent study identified similarities in amino acid sequences associated with viral peptides and human auto-antibodies. Similarities between human heat shock proteins 90 and 60 and SARS CoV-2 has been found to cause GBS **[20]**. Multi-organ autoimmunity in COVID-19 has been attributed to

molecular mimicry of various human organs and tissues by SARS CoV-2 **[23]**. Molecular mimicry between SARS CoV-2 antigenic epitopes and three human proteins present in brainstem, namely SURF1, DAB1 and AIFM (catalogued at www.uniprot.org) can attribute molecular mimicry as the causative of respiratory failure associated with COVID 19 **[24]**.

In another study, *Haemophilus influenzae* isolated from patients suffering from MFS showed the presence of the bacterial LOS that mimics the human GQ1b gangliosides **[25]**.

C) Type-1 Diabetes Mellitus (T1D)

Type 1 diabetes (T1D) is caused due to autoimmune response against the beta (β)-cells of pancreas **[26]**. It is often found to co-exist with patients suffering from AITD, Idiopathic Addison's Disease and Pernicious Anemia **[27]**.

Evidence in the support of molecular mimicry triggering T1D come from the studies indicating similarities in sequences between viral peptides and pancreatic β-cell epitopes. The viral components initially trigger T-cell clones that have the capability to cross-react with pancreas against the shared epitopes **[28]**. Glutamic acid decarboxylase (GAD) is one of the most important auto-antigens involved in self-destruction of pancreatic β-cells **[29]**. Individuals with predisposition towards T1D or with recent development of T1D have elevated levels of anti-GAD antibodies in their sera **[29]**. Coxsackie Virus PC-2 protein, an 18 amino acid-peptide with distinctive resemblances to human GAD, provides for another evidence of molecular mimicry involved in T1D **[30]**. Notable sequence homology found between tyrosine phosphatase-like IA2 (Insulinoma Ag2) and GAD65 (Glutamic Acid Decarboxylase 65) islet auto-antigens with VP7, an important immunogenic protein of Rotavirus (RV) **[31]**, and antigenic epitopes of Cytomegalovirus (CMV) **[28]** has provided evidence of the mechanism of molecular mimicry underlying the development of T1D. Experimental models selectively expressing Lymphocytic Choriomeningitis Virus (LCMV) in the pancreatic β-cells also triggered T1D **[32]**.

Despite such promising evidence pointing to the fact that molecular mimicry is one of the major mechanisms in T1D development, it is still at a paradoxical state. The reason for such dispute is the finding that injection of Coxsackie Virus B3 in Non-Obese Diabetic (NOD) mice provided long-term protection against T1D instead of disease development and progression **[33]**. Thus, further studies are required to effectively support molecular

mimicry as the causative mechanism of T1D **[34, 35]**.

D) Myasthenia Gravis (MG)

Myasthenia Gravis (MG) is an autoimmune disorder characterized by muscle weakness and presence of auto-antibodies in the serum **[36]**, with a prevalence of about 10-20 cases per 100,000 individuals **[37]**.

Most of the auto-antibodies are raised against the acetylcholine receptor (AchR), lipoprotein-related protein 4 (LRP4) and Muscle-specific kinases (MuSK) **[38]**. Studies have pointed at the sequence similarities between Human AchR α-subunit residues 160-167 and pathogenic Herpes Simplex Virus-1 (HSV-1) Glycoprotein D residues 286-293, thereby linking molecular mimicry to MG **[39]**.

Molecular mimicry between West Nile Virus (WNV) and host proteins has also been highlighted as a major cause of MG **[40]**.

Recently, there have been quite a few reports of patients suffering from MG shortly after COVID-19 **[41]**. For the activation of MG in such patients, two possible hypotheses have been provided. Like other virus, SARS CoV-2 can trigger the latent autoimmune disorders such as MG. Also, antigenic similarity between human AchR at the neuromuscular junction with SARS CoV-2 antigenic epitopes can lead to MG induction **[42]**.

Another finding identified a penicillin-binding protein and serine/threonine kinase associated (PASTA)-domain containing Serine-Threonine Kinase of *Lactobacillus* spp. showing a 6 amino-acid 'KIADFG' sequence identical to human MuSK protein, suggesting yet another possible role of molecular mimicry in AD development **[43]**.

However, the definite mechanism of molecular mimicry for the development of MG still needs to be established.

E) Immune Thrombocytopenia Purpura (ITP)

A hematologic autoimmune disorder called Immune Thrombocytopenia Purpura (ITP) is characterized by abnormal megakaryocyte maturation in the bone marrow and uncontrolled destruction of platelets by auto-antibodies **[44]**.

Many studies have highlighted the role of *Helicobacter pylori* (HP) in the development of chronic ITP (cITP), and the underlying mechanism is hailed as molecular mimicry **[45]**. A virulence factor of HP, called Cytotoxin associated gene A (CagA) shares similarity with platelet-associated Immunoglobulin G (IgG). The antibodies raised against CagA can cross-react with platelet surface glycoproteins, thereby accelerating the process of platelet destruction in the host and leading to gradual disease progression **[45]**.

ITP is a very common complication associated with Hepatitis C virus (HCV) and Human Immunodeficiency virus (HIV) infections **[46, 47]**. HCV and HIV contain protein sequences consensus to peptide sequence ranging from amino acids 49-66 in platelet membrane glycoprotein IIIa (GPIIIa) **[48]**, thus leading to production of antibodies that react with GPIIIa on host platelets to carry out destruction **[49]**. These antibodies induce enzyme-catalyzed generation of reactive oxygen species (ROS) that leads to complement-mediated platelet destruction **[50]**. All these findings suggest possible roles in molecular mimicry mediated autoimmunity.

SYSTEMIC AUTOIMMUNE DISEASES

A) Rheumatoid Arthritis(RA)

Rheumatoid arthritis (RA) has become a very common joint-damaging disease, affecting over 20 million people worldwide **[51]**. It is seen majorly in women, affecting the HLA-DR1/4 individual carrying the shared epitope of the amino acid sequence EQRRAA **[52]**. Using molecular mimicry, it was observed that *Proteus* also possesses an amino acid sequence ESRRAL in haemolysin, which show resemblance with the shared epitope on HLA-DR1/4 **[53]**. Computational analysis of the components of the *Proteus* was done to check for molecular mimicry to the EQRRAA sequence, which revealed the presence of a sequence in the *Proteus* haemolysin (ESRRAL) from the 32^{nd} to the 36^{th} amino acid position **[53, 54]**. This was identical in shape to the EQRRAA sequence present on the shared epitopes of the HLA-DA1/4 molecules **[54]**. This furthered established that such antibodies possess the ability to bind to the EQRRAA sequence in HLA-DA1/4, and result in inflammation due to the activation of the complement system, eventually causing tissue damage **[54]**. Hence, one of the major mechanisms of RA has been explained based on molecular mimicry between the *Proteus* and the self-antigens. RA has a significantly higher risk for women than men, which link the onset of the disease to upper urinary tract infections (UTIs). *Proteus* is the second most important cause of urinary tract infections (UTIs) after *E. coli* **[52, 53]**. It has been observed that the connection between *Proteus* and RA, triggered by UTIs, has increased the possibilities of the diagnosis of RA in the early stages **[55]**. The antibodies against *Proteus* bacteria in the serum of individuals were evaluated and compared to individuals with various other diseases which are linked to *Proteus* bacteria, and it showed no increase in the antibody level against *Proteus* in all the other chronic diseases, thereby indicating that antibodies to *Proteus* are specific to individuals affected by RA **[56-58]**.

Furthermore, the connection between RA and the histocompatibility antigens was first introduced by Stastny who took leucocyte cultures from several people affected by RA in America **[59]**. Later, this observation was validated when it was seen that HLA-DR4 was present in a significantly higher amount in patients suffering from RA in England than the normal population **[54]**.

B) Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is a very dangerous demyelinating disease of the Central Nervous System (CNS), which causes loss of vision along with the impairment of the motor and sensory neurons **[60]**. Molecular mimicry has proven to be a key driver in the etiology and pathology of MS **[61]**. The role of environmental factors (like virus) in molecular mimicry to induce MS is supported by epidemiologic evidence **[62]**. Molecular mimicry is initiated when the T-cells specific for peptide epitopes obtained from the viral pathogens show cross-reaction with the self-epitopes, thereby causing autoimmune tissue destruction **[63]**.

The potential of a virus encoding a self-myelin mimic epitope to trigger an autoimmune response was validated by engineering a mouse model, where the myelin epitope PLP139-151expressed by the protease IV protein of *Haemophilus influenza*,were inserted into a non-pathogenic variant of the Theiler's Murine Encephalomyelitis Virus (TMEV) **[64]**. The mice model infected with the non-pathogenic TMEV virus, which possessed the PLP139-151, developed an initial progression of demyelinating disease that was linked with the activation of $CD4^+$ T-cells reactive with PLP139-151 **[64]**. This finding based on molecular mimicry was critical in emphasizing the requirement for mimic epitope processing, followed by subsequent presentation in case of an infection, and the need for the recognition of the T cell receptors (TCRs) and the MHC-binding of mimic epitopes **[65]**.

C) Sjogren's Syndrome(SS)

Sjogren's Syndrome (SS) is a systemic autoimmune disorder affecting the entire body. It causes dry mouth, dry eyes, excess fatigue and muscle pain **[66]**. The SS antigen A (SSA)/Ro60-reactive T cells have been shown to get triggered by the peptides present in the oral and gut bacteria, thereby indicating a role of molecular mimicry associated with SS **[67]**. A total of 3 regions on Ro60, having core epitopes mapped to amino acids positioned between228-238, 246-256 and 371-381 were recognised in the T-cell hybridomas obtained from HLA-DR3 transgenic mice **[67]**. BLAST analyses were also performed which further highlighted that several mimicry peptides were present in bacteria

originating from the oral and intestinal regions of man **[68]**.

Capnocytophaga ochracea, an oral microbe having the von Willebrand Factor type A (vWFA) domain protein, possesses a peptide which has been observed as a potent activator of SS antigen A (SSA)/Ro60-reactive T cells **[69]**. The Ro60-reactive T cells were also observed to be activated by the action of recombinant vWFA protein and a whole *E. coli* which expresses this protein. This led to the understanding that immune responses generated from the commensal microbiota should be further investigated as a trigger for causing SS **[69]**.

D) Psoriasis

Psoriasis is an autoimmune condition causing red, itchy patches, seen prominently on the knees, elbows and scalps. This is mainly triggered by infections, stress or cold. Psoriasis is linked to Streptococcal throat infection, with psoriasis patients having a heightened susceptibility to this infection **[70]**. The T-cell recognizing determinants are identical to the Streptococcal M-protein and Keratin (K) seen in patients diagnosed with psoriasis **[71]**.

ELISPOT technique performed on two sets of experiments with 31 chronic psoriasis patients showed an activation of the T cells by the M and K peptides to initiate IFN-γ response **[72]**. The two peptides sharing the amino acid sequence ALEEAN led to a heightened T cell response when compared to control patients with the streptokinase/streptodornase (sk/sd) antigen **[72]**. Further investigations also led to the observation that a single substitution of the alanine residue from the shared amino acid sequence led to the termination of the T cell response and IFN-γ production **[73]**. Hence, it can be concluded that the identification of the antigen factors that are recognised by the T cells in psoriasis patients can be used to create targets for a more specific immunotherapeutic treatment **[74]**.

CONCLUSION

The mechanism of molecular mimicry integrates the analysis of cross-reactivity using various genetic as well as environmental factors such as infectious agents. The alteration of T cell and B cell responses on exposure to foreign antigens sharing sequence similarities to self-antigens leaves us with the requirement of understanding molecular mimicry, and subsequently the vast area of immunotherapeutic treatments that can be further investigated.

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CONFLICTOF INTEREST

The authors have no relevant financial or non-financial interests.

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