Bacterial molecular mimicry in autoimmune diseases

Marco Palma *^ 
* Independent researcher, Torrevieja, Spain
^ Corresponding author: Marco Palma, phd@marcopalma.es

Bacterial molecular mimicry in autoimmune diseases is one of the leading mechanisms by which microorganisms may induce autoimmunity and survive in the host. The main purpose of the current study was to determine the main microbes that elicit autoimmune reactions through molecular mimicry and identify the most relevant approaches to investigate this mechanism. A classic example is the M protein of Streptococcus pyogenes, which induces antibody cross-reactivity with a cardiac protein and causes rheumatic fever. Another notable example is the protein from Porphyromonas gingivalis that closely resembles the human heat shock protein and accelerates atherosclerotic. There is evidence that antibodies against Helicobacter pylori CagA interact with different parts of smooth muscle and endothelial cells enhancing atherosclerotic vascular disease. Recently, one cause of infertility has been associated with Staphylococcus aureus molecular mimicry that triggers an antibody response that cross-reacts with human spermatozoa proteins. Further examples of bacterial molecular mimicry are associated with Chlamydia pneumoniae, Escherichia coli, Yersinia, and Salmonella. From the literature, the most widely used methods in this field are Basic Local Alignment Search Tool (BLAST), serological assays, and phage display. The subjects of particular concern are vaccine cross-reactivity and immunosuppressive drugs side-effects, therefore alternative approaches are needed. Such an approach is phage display where therapeutic antibody fragments obtained by this technique have been used in the treatment of autoimmune diseases by neutralizing the pathological effects of autoantibodies. Phage display libraries are constructed from the antibody repertoires of autoimmune disease patients. Antibody fragments without the Fc domain can not interact with Fc receptors and proteins of the complement system and trigger autoimmune diseases. Another approach is to block the Fc receptors. In conclusion, this review highlights key aspects of bacterial molecular mimicry to better understand the factors associated with autoimmune diseases and encourage further research in this field.

Keywords: molecular bacterial molecular mimicry, molecular mimicry, autoimmune diseases, autoantibody, cross-reactivity, phage display, blast.

Introduction

Bacterial molecular mimicry mechanisms are implicated in several types of autoimmune diseases. They are a frequent cause of morbidity and mortality affecting over 3–5% of our population (1). They are triggered by the loss of immunological tolerance to self-antigens, which can cause systemic or organ-specific damages. Microorganisms have often appeared as one of the main factors and on many occasions, an autoimmune disease is considered a consequence of infection (2).

One of the leading mechanisms by which infectious agents may induce autoimmunity is molecular mimicry. Several studies have demonstrated that
Microorganisms contain proteins that are similar enough to host proteins that make B and T cells respond to self-proteins. Production of large quantities of autoantibodies by B lymphocytes may be important in antibody and complement deposition in tissues, leading to inflammation and subsequently to tissue damage (3). Molecular mimicry has been implicated in the pathogenesis of many autoimmune diseases including multiple sclerosis, Guillain-Barré syndrome, type 1 diabetes, rheumatoid arthritis, and cardiovascular diseases (4). Many bacterial species can induce an autoimmune response by molecular mimicry mechanism, including Streptococcus pyogenes, Porphyromonas gingivalis, Helicobacter pylori, Chlamydia pneumoniae, Staphylococcus aureus, Escherichia coli, Yersinia, Campylobacter jejuni, and Salmonella. The main purpose of this study is to describe the main pathogenic bacteria that cause autoimmune diseases and their mechanisms of molecular mimicry. We comment on certain aspects of possible methods to identify immunogenic epitopes and therapeutic approaches.

Sources of information

An extensive literature review was conducted in PubMed’s databases on autoimmune diseases, autoantibodies, and molecular mimicry in combination with the keywords bacteria and pathogen.

Bacterial molecular mimicry as a cause of autoimmune diseases

Streptococcus pyogenes

Streptococcus pyogenes generally inhabits epithelial surfaces, especially of the throat and skin, but it can cause severe conditions, including rheumatic fever, which is a serious autoimmune sequel of pharyngitis (5). The onset of rheumatic fever usually occurs about two to four weeks after a streptococcal throat infection. It is estimated that around 30 million people are currently affected by rheumatic heart disease globally (6), with 300,000 deaths each year, of which 60% occurred prematurely.

Rheumatic fever is a classic example of molecular mimicry where S. pyogenes M-protein shares an α-helical coiled structure similar to a heart protein (e.g., myosin). The antibodies from patients with acute rheumatic fever (ARF) cross-react with both M-protein and the cardiac tissue (7). Variability in the N-terminal of M proteins generates distinct M serotypes which makes it difficult to make a vaccine with good protection. Of the more than 130 M-protein types identified, M types such as 1, 3, 5, 6, 14, 18, 19, and 24 have been associated with rheumatic fever (8).

Moreover, some antibodies recognize the N-acetyl-β-D-glucosamine (GLcNAc) of S. pyogenes and cross-react with myosin (9). Besides, S.pyogenes induces the production of collagen IV autoantibodies after that S. pyogenes binds to collagen IV, a major component of subendothelial basement membranes, intermediated by a collagen-binding octapeptide motif of M-protein (10). Cross-reactivity has been found of anti S.pyogenes antibodies with vimentin, laminin, tropomyosin (11), and fibronectin (12).

Even when comprehensive studies on ARF and autoantibodies exist, there is currently no single test to diagnose or prevent this disease. Diagnosis of ARF is done using clinical criteria (Jones criteria) and excluding other differential diagnostics. Possible future research areas may include a better understanding of the epidemiology of the disease to improve diagnosis and identify new avenues for therapeutic intervention and development of group A streptococcal vaccine.

Porphyromonas gingivalis

Porphyromonas gingivalis is a gram-negative oral anaerobe that is involved in the pathogenesis of periodontitis, an inflammatory disease that destroys the tissues supporting the tooth which eventually may lead to tooth loss. Several studies show inflammatory mechanisms that link periodontal diseases to cardiovascular diseases (13).

It was suggested that the progression of atherosclerosis can be explained in terms of the immune response to bacterial heat-shock proteins (i.e. HSP60 or GroEL) (14) from P. gingivalis (15–17), a protein that closely resembles human heat shock protein. Also, the immune system may not be able to differentiate between self-HSP and bacterial HSP which is resulting in an autoimmune response (18). 91% of the periodontitis patients were seropositive for P. gingivalis GroEL but only 61% were for human HSP60 (19). However, nothing is known about autoantibodies against GroEL and hsp60 in cardiovascular disease patients with a prior history of periodontitis.

P. gingivalis cardiolipin, a lipid found in the bacterial membrane, induces autoantibodies against protein β2glycoprotein 1 (β2GP1), a protein whose physiological function speculates to protect damaged surfaces of endothelial cells from promoting inappropriate coagulation. A variety of microbial pathogens are capable of inducing autoantibodies by cardiolipin due to its similarity to the peptide sequences in β2GP1 (i.e. TLRVYK). Other antibodies that link periodontitis to
cardiovascular disease include anti-phosphorylcholine (anti-PC) and the antioxidant LDL (anti-oxLDL) (20,21).

Helicobacter pylori
Helicobacter pylori infections have been suggested to be associated with atherosclerotic vascular disease (22). Many mechanisms underlying the molecular mimicry between H. pylori and the host have been proposed. Antibodies against CagA protein from H. pylori interact with different parts of smooth muscle and endothelial cells present in the thin-layer sections of atherosclerotic vessels (23). H. pylori UreB subunit, with a high number of epitopes recognized by anti-urease antibodies (24,25), exhibits similarity to the human CCRL1 protein (CC chemokine receptor-like 1) expressed in heart tissue (26). Antibodies against H. pylori Hsp B heat shock protein cross-react with human Hsp60 facilitating inflammation in the vascular endothelium (27).

Most of the H. pylori vaccine clinical trials focused on the urease antigen with different adjuvants, routes, and delivery systems that are generally not been effective in humans (28). H. pylori has not a predominant outer membrane protein (OMP), rather multiple lower-abundance OMPs have been observed (29). The largest family is Family 1, comprised of the Hop (for H. pylori OMP, 21 members) and Hor (for Hop related, 12 members) proteins. Families 2 and 3 comprise the Hof (for Helicobacter OMP, 8 members) and Hom (for Helicobacter outer membrane, 4 members) proteins, respectively. Families 4 and 5 are composed of iron-regulated OMPs (6 members) and efflux pump OMPs (3 members), respectively. I need to check all these proteins closely to decide if there is a good candidate to be used in a vaccine.

Chlamydia pneumoniae
Chlamydia pneumoniae is a widespread respiratory pathogen responsible for sinusitis, pharyngitis, and pneumonia and its transmission occurs via the aerial route (30). The relationship between C. pneumoniae and cardiovascular diseases was first suggested in 1988 (31). Cardiovascular diseases are one of the main causes of death globally. It is expected to surpass infectious diseases as the leading cause of mortality and the number of deaths is estimated to reach 23.3 million by 2030 (32). The mechanism by which C. pneumoniae causes cardiovascular diseases is unknown, but it is speculated that it is through molecular mimicry. C. pneumoniae induces the expression of autoantibodies by producing proteins that have similarities with human proteins including hHSP60, a peptide of the alpha-myosin heavy chain molecule (M7Aα motif; SLKLMATLFSTYASAD). It will be interesting to analyze autoantibodies (i.e. against human HSP60 and myosin) in sera from cardiovascular disease patients with a history of C. pneumoniae infection.

Staphylococcus aureus
Infertility is a frequent health problem among 5-8% of couples in developed countries and 5.8% to 44.2% in developing countries (33). 30-40% of couples have female infertility while 60-70% of couples have male infertility. The immune reaction in spermatozoa causes 2-30% of infertility (34) and in 9-12.8% of infertile couples were found anti-sperm antibodies (35,36). Affected women of bacterial vaginitis caused by Staphylococcus aureus develop antibodies against S. aureus that cross-react with human spermatozoa proteins which could be a potential cause of infertility (37). A molecular modeling approach revealed 55 of 96 human spermatozoa proteins with homology to S. aureus proteins (identity 19-45%). The top five proteins that showed high sequence and structure homology, as well as high antigenicity, were Glyceraldehyde-3-phosphate dehydrogenase, L-lactate dehydrogenase C, protein deglycase Dj-1, sperm acrosome membrane-associated protein-4, and UDP-N-acetylhexosamine phosphorylase (38). Recently, it was demonstrated that amelioration of sperm immobilization factor-induced infertility by bacterial antigenic determinants cross-reacting with spermatozoa (39).

Escherichia coli
E. coli has been associated with several autoimmune diseases, including primary biliary cirrhosis (PBC), autoimmune hepatitis, rheumatoid arthritis (40). E.coli expresses several proteins that have homology with human proteins. Antimitochondrial antibodies, typically found in PBC, recognized E2 components of pyruvate dehydrogenase complex (PDC) that are localized in the mitochondrial inner membrane. These antibodies react well against PDC-E2 of E. coli (41). The E. coli type I Fim H that binds to GpI-anchored molecule CD48, thereby inducing bacterial phagocytosis, has homology to human CD2 (42). Rheumatoid arthritis is associated with the amino acid sequence QKRAA located in the third hypervariable region of the DR beta-1 chain of HLA-DR4 which is recognized by the T-cell antigen receptor. This motif has been identified in the E.coli dnaJ (43,44).

Yersinia
Graves’ disease is the most common type of autoimmune thyroid disease (AITD) distinguished by the presence of anti-TSH receptor (TSHR) autoantibodies (TRAb) in the serum of more than 90% of patients with Graves’ disease. Some of these autoantibodies stimulate the thyroid
resulting in hyperthyroidism. It was demonstrated that the outer membrane porin F protein (ompF) of Yersinia shared cross-immunogenicity with a leucine-rich domain of TSHR and these autoantibodies recognized the region between residues 190–197 of ompF (45). TSHR has also homology to Yersinia proteins YopM, Ysp, exopolygalacturonase, and SpyA(46). In addition, the envelope protein invasin from Yersinia pseudotuberculosis binds to the host-cell β1 integrin surface receptors leading to the internalization of Yersinia. The invasin protein has structural similarity to fibronectin (47).

**Campylobacter jejuni**

*Campylobacter jejuni* is the major infecting agent in patients with the autoimmune condition SLE (systemic lupus erythematosus) which causes glomerulonephritis, arthritic changes, and neurological alterations. It was demonstrated the presence of antibodies against an epitope of the human ganglioside GM1 in SLE patients (48) which is mimicked by bacterial LPS (49).

**Salmonella**

Gram-negative enteric pathogens, including Salmonella, have been associated with the autoimmune disease reactive arthritis (ReA). ReA followed outbreaks of Salmonella food poisoning (50). The titer and profiles of autoantibodies in the sera of patients with acute salmonellosis due to *Salmonella enterica* serovar Typhimurium (*S. Typhimurium*) or *Salmonella enterica* serovar Enteritidis (*S. Enteritidis*) infection, as well as in convalescent patients, indicate that anti-smooth muscle antibodies (ASMA) were the most prevalent in all salmonellosis (51).

Recently, it was demonstrated that Curli, thin amyloid fibers expressed on the surface of enteric bacterial cells, can induce inflammatory responses by stimulating pattern recognition receptors. The study showed that curli is expressed by *S. Typhimurium* in the cecum and colon of mice after natural oral infection, in both acute and chronic infection models. The infected mice generated increased levels of anti-dsDNA autoantibodies and joint inflammation. They hypothesized that the study provided the relation between bacterial amyloids like curli and human amyloids and their association with diseases such as Alzheimer’s Disease (52).

**Methods to find similarity**

**Blast**

Probably many more candidates have been discredited in literature for molecular mimicry that so far remained unexplored. A suitable technique that can help to identify such molecules is to run BLAST at National Center for Biotechnology Information (NCBI) against the homosapiens database using pathogen sequences to find proteins with sequence similarities between two species.

**Serology studies**

It is necessary to analyze sera from patients with cardiovascular disease to study the profile of autoantibodies against human proteins (e.g. myosin) and bacterial proteins (e.g. *H. pylori* CagA, and UreB), and identify novel biomarkers by screening peptide libraries against patient serum. Serological studies can determine if patients with autoimmune diseases or individuals in the risk zone produce autoantibodies against human or bacterial proteins. The aim is to define these autoantibodies since there are studies that show that the specific autoantibodies are detected in asymptomatic individuals years before the presentation of autoimmune disorders (53–55). Therefore, they can be useful serological biomarkers to identify people with a predisposition to developing autoimmune diseases.

**Phage display**

The phage display technique consists of the expression of peptides, proteins, or antibody fragments on the surface of phage particles (56). The nucleotide sequence encoding the target protein is found in the phage genome fused to the gene sequence of a coat protein. This fusion ensures that during phage assembly, the target protein will be exposed on the surface of the mature phage while the sequence encoding it is contained in the same phage particle. Using phage display, the analysis of a library of nucleotide sequences with a diversity of millions or billions becomes the study of the corresponding population of exposed protein sequences that can be selected according to the desired properties.

Analysis of phage display libraries typically includes a panning selection step in which phage populations are exposed to the targets of interest to selectively capture the phages that have bound to them. Through successive rounds of binding, washing, elution, and amplification, the initial population made up of a great diversity of phages are enriched in those that can bind to the target in question. Since the phenotype of each protein carries its genotype inside the phage particle, once the proteins of interest have been isolated, the sequence encoding them can be easily determined and altered to manipulate or refine their binding properties. Currently, natural and synthetic peptides, proteins, and protein domains, as well as recombinant antibodies, are routinely expressed by phage display (56). The phage display technique constitutes...
a good system for the selection of antibodies or peptides with specific binding properties among a wide number of variants.

Novel biomarkers can be identified by screening phage-display peptide libraries with sera from autoimmune disease patients. A complementary strategy is to construct a phage display library from B-cells from autoimmune disease patients to identify antibody sequences that recognize human epitopes.

**Therapeutic approaches**

Vaccinations are necessary to combat antibiotic resistance bacterial strains and more effectively control bacterial diseases. However, the increment of autoimmune diseases around the world raised the concerns of vaccination as one of the trigger factors.

An important example of this is the report of two cases with reactive arthritis associated with typhoid vaccination in travelers (57). This case reveals the need for further investigation in patients with autoimmune diseases related to vaccination.

Probably, some vaccines induce the production of antibodies against bacterial compounds that cross-react with compounds in the human body. This demonstrates the need for better therapeutic strategies for autoimmune diseases. Therefore, an alternative therapeutic approach is to neutralize the pathological effect of autoantibodies using antibody fragments isolated from phage display libraries constructed from B-cells from autoimmune disease patients. To accomplish this, Wang and colleagues used bullous pemphigoid (BP) as an example of a typical autoimmune disease. Specific Fab fragments to the non-collagenous 16th-A domain of type XVII collagen, the principal pathogenic target for autoantibodies in BP, were obtained from the antibody repertoires from patients with BP patients using phage display (58). The determination of the autoantibody profile represents a useful tool, not only helps to design neutralizing antibodies but also for both diagnosis and characterization of autoimmune diseases. Furthermore, peptides representing the epitopes identified by autoantibodies can be isolated from synthetic peptide phage display libraries. These peptides can then be used to neutralize autoantibodies and to design specific and safe vaccines that do not induce cross-reactivity.

**Declarations**

**Ethical approval**
Not required.

**Author contributions**
MP was the sole author of this article.

**Funding**
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Declaration of competing interest**
The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Discussion**

This study highlights the importance of understanding the antibody or biomarker profiles to develop diagnostic tools to identify people who are in an early stage of the disease or individuals with a predisposition to developing an autoimmune disease in the future. Furthermore, these profiles are useful to develop antibodies or peptides to treat such patients by blocking the pathological action of autoantibodies. Such molecules can prevent complement activation through inhibition of autoantibody binding to the corresponding pathogenic autoantigen. Therapeutic antibody fragments with no Fc portion necessary to activate the complement pathway fail to initiate autoimmune disease. Several clinical studies have shown correlative evidence between autoimmune diseases and autoantibodies. Despite this, no current therapeutic approaches are designed to improve many autoimmune disease outcomes by reducing autoantibody production or activity. Another approach consists in treating autoimmune diseases with molecules from phage display libraries that target the Fc receptors. An example of this is the study carried out by Bril et al. in which shown encouraging results in phase 3 trials by blocking the neonatal Fc receptor (FcRn) in myasthenia gravis (ClinicalTrials.gov Identifier: NCT03971422) with the therapeutic Rozanolixizumab (59). Furthermore, a peptide derived from a phage display library could inhibit IgG-neonatal Fc receptor interaction reducing the IgG levels in vivo (60).
References

1. Kim B, Kaitha SD, Rouse BT. Viruses and autoimmune disease. Autoimmunity [Internet]. 2006 Jan;73(1):71–7. Available from: http://www.tandfonline.com/doi/full/10.1080/08916930500484708. https://doi.org/10.1080/0891693940084708

2. Shahrizaila N, Yuki N. Guillain-Barré Syndrome Animal Model: The First Proof of Molecular Mimicry in Human Autoimmune Disorder. J Biomed Biotechnol [Internet]. 2011;2011:1–5. Available from: http://www.hindawi.com/journals/jbmt/2011/829129/

3. Abou-Raya A, Abou-Raya S. Inflammation: A pivotal link between autoimmunity and atherosclerosis. Autoimmun Rev [Internet]. 2006 May;5(5):331–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1568997706000036. https://doi.org/10.1016/j.autrev.2005.12.006

4. Rose* NR, Mackay IR. Molecular mimicry: a critical look at responses to streptococcal and tissue antigens in patients with rheumatic carditis. J Clin Invest [Internet]. 2000 Jul 15;106(2):217–24. Available from: https://doi.org/10.1172/JCI7132

5. Carapetis JR, Beaton A, Cunningham MW, Guilherme L, Karthikeyan G, Mayosi BM, et al. Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Prim [Internet]. 2016 Dec 22;2(1):15084. Available from: http://www.nature.com/articles/nrdp201584. https://doi.org/10.1038/nrdp.2015.84

6. Institute for Health Metrics and Evaluation. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle, United States [Internet]. 2016 [cited 2020 Mar 20]. Available from: http://ghdx.healthdata.org/gbd-results-tool

7. Sfriso P, Ghirardello A, Botsios C, Tonon M, Zen M, Bassi N, et al. Infections and autoimmunity: the multifaceted relationship. J Leukoc Biol [Internet]. 2010 Mar 1;87(3):385–95. Available from: http://doi.wiley.com/10.1189/jlb.0709517. https://doi.org/10.1002/pl.20000716

8. Stoller-Menz H, Rheumatogenic Group A streptococci and the return of rheumatic fever. Adv Intern Med [Internet]. 1990;35:1–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2405590

9. Adderson EE, Shikhman AR, Ward KE, Cunningham MW. Molecular analysis of polyclonal monoclonal antibodies from rheumatic carditis: human anti-N-acetylglucosamine/anti-myosin antibody V region genes. J Immunol [Internet]. 1998 Aug 15;161(4):2020–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9712075

10. Dinkla K, Nitsche-Schmitz DP, Barroso V, Reissmann S, Johansson HP, Frick I-M, et al. Identification of a Streptococcal Octapeptide Motif Involved in Acute Rheumatic Fever. J Biol Chem [Internet]. 2007 Jun 28(26):18668–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021925807037347. https://doi.org/10.1074/jbc.M701047200

11. Galvin JE, Henric ME, Ward K, Cunningham MW. Cytoxic mAb from rheumatic carditis recognizes heart valves and laminin. J Clin Invest [Internet]. 2000 Jul 15;106(2):217–24. Available from: http://www.jci.org/articles/view/7132. https://doi.org/10.1172/JCI7132

12. Martins TB, Hoffman JL, Augustine NH, Phansalkar AR, Fischetti VA, Zabriskie JB, et al. Comprehensive analysis of antibody responses to streptococcal and tissue antigens in patients with acute rheumatic fever. Int Immunol [Internet]. 2008 Mar 1;20(3):445–52. Available from: https://academic.oup.com/intimm/article-lookup/doi/10.1093/intimm/dxn004. https://doi.org/10.1093/intimm/dxn004

13. Schenken HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. J Clin Periodontol [Internet]. 2013 Apr;40:551–69. Available from: http://doi.wiley.com/10.1111/jpe.12060. https://doi.org/10.1111/jpe.12060

14. Yamazaki K, Ohsawa Y, Ichik H, Ueki K, Tabe K, Oda T, et al. T-cell clonality to Porphyromonas gingivalis and human heat shock protein 60s in patients with atherosclerosis and periodontitis. Oral Microbiol Immunol [Internet]. 2004 Jun;19(3):160–7. Available from: http://doi.wiley.com/10.1111/j.0902-0055.2004.00134.x. https://doi.org/10.1111/j.0902-0055.2004.00134.x

15. Lu B, McBride BC. Stress response of Porphyromonas gingivalis. Oral Microbiol Immunol [Internet]. 1994 Jun;9(3):166–73. Available from: http://doi.wiley.com/10.1111/j.1399-302X.1994.tb00005x. https://doi.org/10.1111/j.1399-302X.1994.tb00004x.

16. Maeda H, Miymamoto M, Hongyo H, Nagai A, Kurihara H, Murayama Y. Heat shock protein 60 (GroEL) from Porphyromonas gingivalis: Molecular cloning and sequence analysis of its gene and purification of the recombinant protein. FEMS Microbiol Lett [Internet]. 1994 Jun;119(1–2):129–35. Available from: https://academic.oup.com/femsle/article-lookup/doi/10.1111/j.1574-6968.1994.tb06879.x. https://doi.org/10.1111/j.1574-6968.1994.tb06879.x

17. Vayssier C, Mayrand D, Grenier D. Detection of stress proteins in Porphyromonas gingivalis and other oral bacteria by Western immunoblotting analysis. FEMS Microbiol Lett [Internet]. 1994 Sep;121(3):303–7. Available from: https://academic.oup.com/femsle/article-lookup/doi/10.1111/j.1574-6968.1994.tb07117.x. https://doi.org/10.1111/j.1574-6968.1994.tb07117.x

18. Hinode D, Nakamura R, Grenier D, Mayrand D. Cross-reactivity of specific antibodies directed to heat shock proteins from periodontopathogenic bacteria of human origin. Oral Microbiol Immunol [Internet]. 1998 Feb;13(1):55–8. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/155.6.1307. https://doi.org/10.1093/infdis/155.6.1307

19. Tabeta K, Yamazaki K, Hohozekazusa H, Yoshie H, Hara K. Elevated humoral immune response to heat shock protein 60 (hsp60) family in periodontitis patients. Clin Exp Immunol [Internet]. 2000 May;120(2):285–93. Available from: http://doi.wiley.com/10.1046/j.1365-2249.2000.01216.x. https://doi.org/10.1046/j.1365-2249.2000.01216.x

20. Briales DE, Scott G, Gray B, Crain MJ, Blaese M, Nahm M, et al. Naturally Occurring Antibodies to Phosphocholine as a Potential Index of Antibody Responsiveness to Polysaccharides. J Infect Dis [Internet]. 1987 Jun 1;155(6):1307–14. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/155.6.1307. https://doi.org/10.1093/infdis/155.6.1307

21. Scott MG, Briales DE, Shackelford PG, Smith DS, Nahm MH. Human antibodies to phosphocholine, IgG anti-PC antibodies express restricted numbers of V and C regions. J Immunol [Internet]. 1987 May 15;138(10):3325–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3571975

22. Pasceri V, Cammarota G, Patt G, Cuoco L, Gasbarrini A, Grillo RL, et al. Association of Virulent Helicobacter pylori Strains With Ischemic Heart Disease. Circulation [Internet]. 1998 May 5;97(17):1675–9. Available from: https://www.ahajournals.org/doi/full/10.1161/01.CIR.97.17.1675.
33. Meng Q, Ren A, Zhang L, Liu J, Li Z, Yang Y, et al. Incidence of
defects in newly married couples in a Chinese population. Reprod Biomed
[Internet]. 2015 Jul;31(1):92–100. Available from:
https://linkinghub.elsevier.com/retrieve/pii/S147264831400546X.
doi:10.1016/j.rbmo.2014.10.002

34. Krause W, Naz RK. Immune infertility: impact of immune
reactions on human fertility. Second edit. Walter K.H. Krause,
Rajesh K. Naz E. editor. Switzerland: Springer; 2017. 302 p.

35. Ayvaliotis B, Bronson R, Rosenfeld D, Cooper G. Conception
rates in couples where autoimmunity to sperm is detected. Fertil
Steril [Internet]. 1985 May;43(5):739–42. Available from:
https://linkinghub.elsevier.com/retrieve/pii/S0015028216485572.
doi:10.1016/S0015-0282(16)48557-2

36. Collins JA, Burrows EA, Yeo J, YoungLi EV. Frequency and
predictive value of antisperm antibodies among infertile couples.
Hum Reprod [Internet]. 1993 Apr;8(4):592–8. Available from:
https://academic.oup.com/humrep/article/6/1/351/138102

37. Thayer D, Prabha V. Molecular mimicry: An explanation for
autoimmune diseases and infertility. Scand J Immunol [Internet].
2018 Aug;88(2):e12697. Available from:
http://doi.wiley.com/10.1111/sij.12697.

38. Ana M, Utomo DH, Widijanto E, Aulanià S, Wyssà IWA.
Molecular Modeling for Revealing Cross-Reaction Antibody with
Staphylococcus Aureus and Human Spermatozoa Protein. Int J
ChemTech Res. 2016;9(1):233–9.

39. Thayer D, Rahi DK, Prabha V. Amelioration of sperm
immobilization factor-induced infertility by bacterial antigenic
determinants cross-reacting with spermatozoa. Reprod Fertil Dev
[Internet]. 2019;31(3).602. Available from:
http://www.publish.csiro.au/paper/RFD1300.
doi:10.1071/RD13000

40. Blount ZD. The unexhausted potential of E. coli. Elife [Internet].
2015 Mar 25;4. Available from:
https://elifesciences.org/articles/05826.
doi:10.7554/Elife.05826

41. Shimoda S, Nakamura M, Ishibashi H, Hayashida K, Niyo Y. HLA
DRB4 0101-restricted immunodominant T cell autoepitope of
pyruvate dehydrogenase complex in primary biliary cirrhosis:
evidence of molecular mimicry in human autoimmune diseases.
J Exp Med [Internet]. 1995 May 1;181(5):1835–45. Available from:
https://rupress.org/jem/article/181/5/1835/25325/HLA-DRB4-
0101-restricted-immunodominant-T-cell.
doi:10.1084/jem.181.5.1835

42. Abraham SN, Sun D, Dale JB, Beachey EH. Conservation of the
d-mannose-adhesion protein among type I fimbriated members of
the family Enterobacteriaceae. Nature [Internet]. 1988
Dec;336(6200):682–4. Available from:
http://www.nature.com/articles/336682a0.
doi:10.1038/3366820a

43. Roudier J, Petersen J, Rhodes GH, Luka J, Carson DA.
Susceptibility to rheumatoid arthritis maps to a T-cell epitope
shared by the HLA-Dw4 DR beta-1 chain and the Epstein-Barr
virus glycoprotein gp110. Proc Natl Acad Sci [Internet]. 1989 Jul
1;86(13):5104–8. Available from:
http://www.pnas.org/cgi/doi/10.1073/pnas.86.13.5104.
doi:10.1073/pnas.86.13.5104

44. Albani S, Tuckwell JE, Esparza L, Carson DA, Roudier J. The
susceptibility sequence to rheumatoid arthritis is a cross-reactive
B cell epitope shared by the Escherichia coli heat shock protein
dnaj and the histocompatibility leukocyte antigen DRB10401
molecule. J Clin Invest [Internet]. 1992 Jan 1;89(1):327–31.
Available from:
http://www.jci.org/articles/view/115580.
Diabetes in Relatives of Patients with Insulin-Dependent Diabetes. N Engl J Med [Internet]. 1990 Oct 25;323(17):1167–72. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199010253231704

Bonifacio E, Shattock M, Dean BM, Bottazzo GF, Bingley PM, Gale EAM, et al. Quantification of islet-cell antibodies and prediction of insulin-dependent diabetes. Lancet [Internet]. 1990 Jan 20;335(8682):147–9. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.4001944.

Rose NR, Bona C. Defining criteria for autoimmune diseases (Wirebsky’s postulates revisited). Immunol Today [Internet]. 1993 Sep;14(9):426–30. Available from: https://www.sciencemag.org/lookup/doi/10.1210/jc.2009-2184.

Smith G. Filamentous fusion phage: novel expression vectors that display cloned antigens on the virion surface. Science (80-) [Internet]. 1985 Jun 14;228(4705):1315–7. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.4001944.

Wang G, Ujiie H, Shibaki A, Nishie W, Tateishi Y, Kikuchi K, et al. Blockade of Autoantibody-Initiated Tissue Damage by Using Recombinant Fab Antibody Fragments against Pathogenic Autoantigen. Am J Pathol [Internet]. 2010 Feb;176(2):914–25. Available from: https://www.liebertpub.com/doi/10.1089/thy.2004.14.964.

Bril V, Benatar M, Andersen H, Vissing J, Brock M, Greve B, et al. Efficacy and safety of rozanolixizumab in moderate-to-severe generalised myasthenia gravis. Neurology [Internet]. 2020 Nov 20;10.1212/WNL.0000000000011108. Available from: https://doi.org/10.1212/WNL.0000000000011108.