We are IntechOpen,
the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Trojans in Oral Environments: Evidence of Molecular Mimicry in Oral Immunity

Gustavo Obando-Pereda

Additional information is available at the end of the chapter

Abstract

Oral microbiome possesses more than 1000 microbial species that co-exist with human oral cavity. However, when there is an imbalance in microbial ecosystem, infection and inflammation occurs. Chronic inflammation produces constant antigen-cell presentation and reactivity T and B cell results in an adaptive immune response with high specificity cell-cell and antibody response producing an autoimmune disease by molecular mimicry. In this chapter, using just BLAST, shows self-epitopes (autoantigens) from different autoimmune diseases such as Systemic lupus erythematosus, Sjögren's syndrome, neuromyelitis optica, Stiff-Person syndrome, autoimmune diabetes, autoimmune thyroiditis, myasthenia gravis, autoimmune gastritis, autoimmune hepatitis, myositis and rheumatoid arthritis that possess similarities with microbial epitopes belonging to oral microbiome acting has a computer trojan occult in a software package.

Keywords: molecular mimicry, autoimmunity, autoantingens, inflammation

1. Introduction

Inflammation is a physiological response to any aseptic or septic injury to provoke the activation of immune response to enhance the healing [1]. This event began firstly by the recognition of pathogens-associated molecular patterns (PAMPs) [2], microbiota-associated molecular patterns (MAMPS) [3] or damage-associated molecular patterns (DAMPs) [4] by macrophages [1], mainly, leading the stimulation of innate immune response and the generation of acquired immune response producing a cellular and humoral immunity [5]. In this way, inflammation recognized pathogens via toll-like receptors (TLRs) to stimulate an immune response to remove these pathogens from the body [1] and acquired immunity memory by the antigen presentation mechanisms [6]. However, chronic inflammation can last for weeks, months, even

years, provoking cycles of injury and healing causing irreversible tissue damage, being a risk factor for the development of autoimmune disease [7, 8].

Oral microbiome contains innumerable epitopes similar to self-epitopes than cause cross-reactivity immune response provoking the kill of microbe and self-tissue injury generating an autoimmune disease [9–11]. This phenomenon is known as molecular mimicry [12] or epitope mimicry [13].

2. Molecular mimicry

Molecular mimicry, term proposed firstly by Damian, is the theoretical probability that exist similarities in the molecular structures (amino acid sequence or conformational structure) between pathogens and the host producing a cross-reactivity immune response turn a defensive immune response into autoimmunity [8, 12–16].

However, molecular mimicry has been demonstrated as a common mechanism by microbes to elude immune response and may modulate biosynthetic or metabolic pathway of the host involved in the regulation of apoptosis, cell proliferation, inflammation and immune response [14, 17]. Pathogens imitate host proteins and their interactions interfering with the cell functions at four different levels [18]:

- Full length protein or domain.

- Structure with apparently sequence similarity.

- Short motif.

- Interface mimicry.

The Toll/Interleukin-1 receptor (TIR) domain is an example of full length protein mimicry. When pathogens stimulate the TIR domain signalosome, a molecular pathway is activated to reach the NF-kB to produce inflammatory cytokines to modulate an immune response. In this manner, pathogens can interfere or inhibit this downstream pathway by the production of similar structures producing a negative regulation of TIR pathway, evading the host immune system neutralizing the TLR signaling for survival and proliferation [18].

In other way, structures with apparently sequence similarity can be interfered with the immune regulation, inflammation and wound healing [19]. In this manner, viral chemokine of Kaposi's sarcoma-associated herpesvirus is very similar to human chemokine CX3CL1 [20] causing the activation or inhibition of immune modulation in the host [21].

Pathogens have homologs of short amino acid sequences known as motif mimicry [22, 23] composed of 3–10 residues with the capability to altered immune molecular pathways of the host [18]. One example of this mimicry is the bacterial guanine nucleotide exchange factors (GEFs), as Map and EspM2 of E. coli than can activated GTPases in the host [24, 25], who regulates many cell function as proliferation, survival, differentiation, migration and apoptosis [18].

Interface mimicry is produced by short linear motif than may adopt altered conformations altering the global protein conformation, generating the pathogen evasion [18]. Human GTPases and Map of E. coli and SopE of Salmonella, can serve as an example of interface mimicry.

2.1. The molecular mimicry mechanism

During T cell development, naïve cells moved from the bone marrow to the thymus. In this organ occurs the positive selection, when T cell CD4 + CD8+ recognized the MHC on cortical thymic epithelial cells, they receive signals than let a CD4- and CD8- differentiation according to their affinity to MHC class I or II [26]. The process of thymic selection eliminates 99% of precursor cells by apoptosis, leaving 1% to reach the periphery [27].

In this case, if an external peptide (such as microbe) present similarity with the host peptides, activate T cells can be presented by dendritic or macrophages cells. And if the host peptide possesses similar structure, the T cell becoming autoreactive with self-antigen [27], could originate an autoimmune disease (**Figure 1**).

The importance of interaction of peptide-MHC-TCR cannot be underestimated, because, antigen presentation plays an important role for autoimmune disease. The MHC class I binding area is closed, limiting the length of the presented peptides to 8–10 amino acids [28], however, MHC class II binding site is open and led peptides with 14–18 aa in length [28], but under certain conditions shorter peptides can be presented [29].

3. Autoimmunity

Autoimmunity is defined as a condition of loss of immune tolerance to self-antigens causing an autoreactive immune T and B cells that attack own organs provoking an aseptic inflammation and comprised more than 80 chronic diseases characterized by inflammatory reactions that can either be systemic or organ specific [30] and no cure exist for the majority autoimmune diseases and the treatment is based by control disease symptoms [31].

The early event in autoimmunity is the presentation of self-antigen derived peptides in complex with MHC class II to self-reactive T cells in an inflammatory environment where antigen-presenting cell, dendritic cell mainly, is activated and drives co-stimulation and development of pathogenic autoreactive T cell and autoantibodies, playing a critical role in breaking tolerance to self during an autoimmune disease, leading tissue and organ damage [31, 32], produced by susceptible and aberrant genes, environment exposure, and failed immune regulation [30].

Dendritic cells are the responsible for the initiation of primary T cell responses imprinting the phenotype Th1, Th2, Th17, Treg population in response to environmental signals mediating the breach of T cell tolerance in many autoimmune conditions [31] involved in the activation of other autoreactive B cells [33]. Indeed, T cell help for antigens and can lead the activation of B
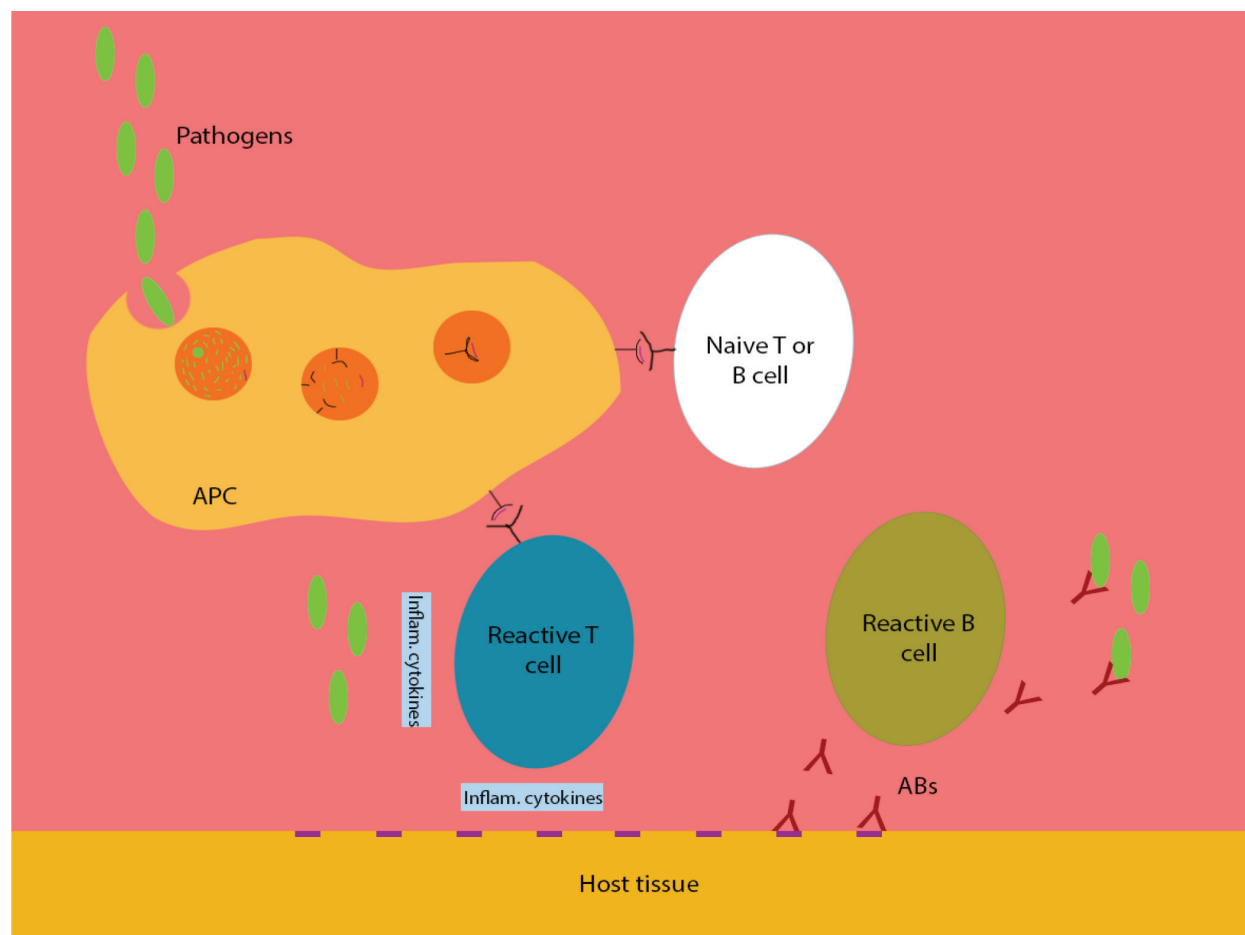
Figure 1. Molecular mimicry. Pathogens are recognized via TLRs by APC and they are phagocytosed in phagosome, digested and many microbial epitopes are exposed. MHC-II is mounted and microbial epitope is coupled in the MHC-II. In this case, epitope with similar characteristics with self-epitope (in violet) is mounted in MHC-II. The epitope is presented to naïve T or B cell, and a specific immune response is initiated. This immune response provokes the production of antibodies and cell-cell response by liberation of proinflammatory cytokines to the antigen presented. In this case, this immune response is addressed to pathogens and host tissue, with similar epitope, originating an autoimmune disease.

cells that recognized the foreign antigen but also cross-react with self-antigen [34] producing and autoimmune disease.

T cells, for example, are important for the pathogenesis of rheumatoid arthritis (RA), particularly in the initial phase of autoimmune response, inducing the joint inflammation of the joints [3]. The Th17 cells are very important because they promote the development of autoimmune diseases by producing IL-17 promoted osteoclastogenesis in RA by upregulating RANK-RANKL expression on osteoblast, macrophages and synovial fibroblast [3, 35] (**Figure 2**).

3.1. Autoantigens

Autoantigens can be defined as antigens that can be assumed to be targeted in an autoimmune disease [28] by the production autoantibodies by autoreactives B cells. Indeed, autoantibody-producing B cell originated from T cell responses to foreign antigens thought molecular mimicry between microbial antigens and self-antigens [33].
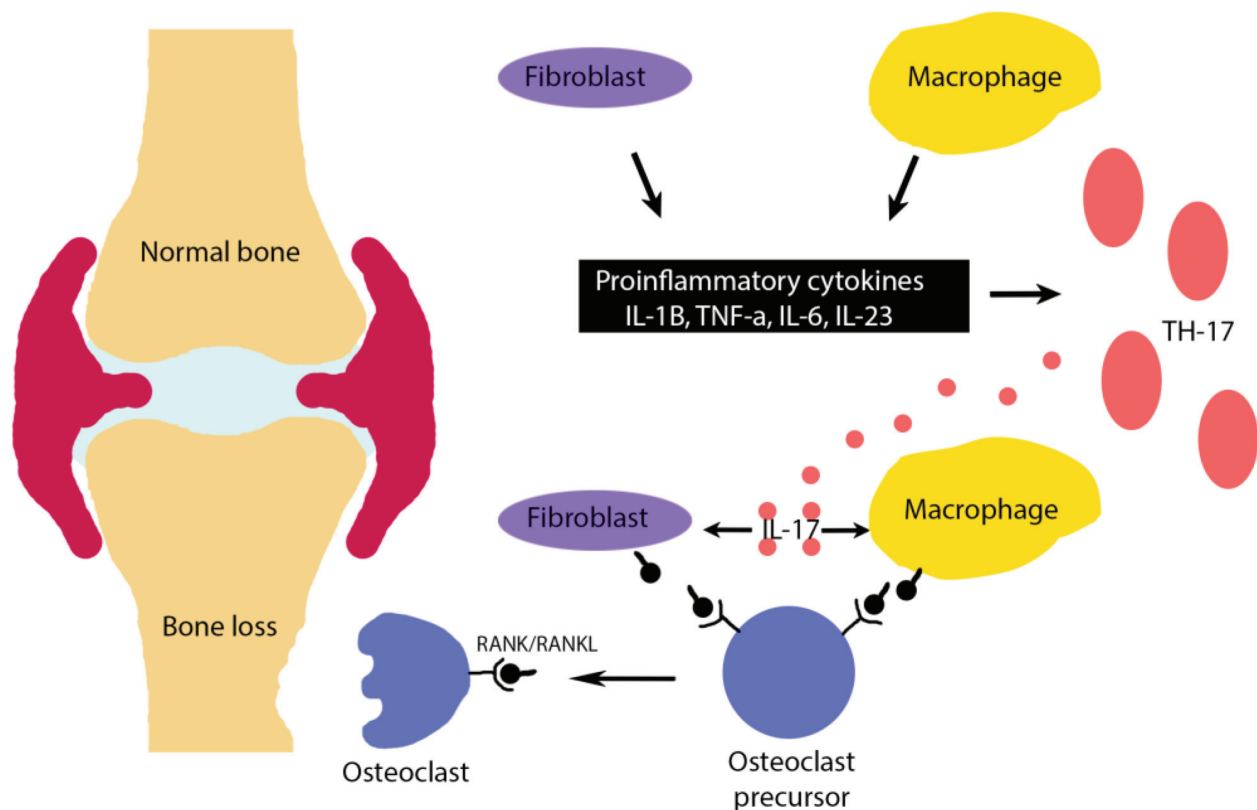
Figure 2. Synovial macrophages and fibroblast in a stress (aseptic or septic injury) released proinflammatory cytokines causing the production and release of IL-17 that provokes the overproduction of RANK by fibroblast and macrophages. RANK/RANKL stimulates osteoclast precursor to form an active osteoclast. The continued presence of RANK, produce the active form of osteoclast, reabsorbing bone.

The literature describes many autoantigens for each autoimmune disease. Type 1 diabetes mellitus (T1DM) is a metabolic disease that is explained as an autoimmune disease in which the B-cells in the Langerhans islands of pancreas are destroyed by autoreactive T and B cells resulting in a null production of insulin [28]. Zinc transporter 8 protein, pancreatic and duodenal homeobox 1, chromogranin A, islet amyloid polypeptide are new discovered autoantigens that explain the pathogenesis of T1DM [36].

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects connective tissue [37, 38], involved multiple systems, organs and autoantigens [38]. Autoantigens acidic ribosomal phosphoprotein (P0)-4, acidic ribosomal phosphoprotein (P0)-11, DNA topoisomerase 1 (full length)-1, and U1-SnRNP, were founded in clinical tests and are using as markers for clinical diagnoses [38].

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a strong autoimmune component that affect bones and joints with the concomitant destruction, associated with adverse morbidity, mortality, and socioeconomic consequences [39]. Autoantibodies such as rheumatoid factors (RFs) and anti-citrullinated protein antibodies (ACPAs) founded in serum samples obtained years before the onset of clinical disease [40, 41].

Autoantigens may cause a self-reactivity of T and B cells by dysregulation of homeostasis of immune response acting as a trojan horses harming own body producing an autoimmune disease.

3.2. Searching trojans in oral microbiome

Microbiome is defined by Lederberg as "the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease" [42]. *In silico* tools have provided a powerful means of understanding the contribution of the human microbiome to health and disease opening a great field for oral immunologist. In the era of computer trojan horse, microbial epitopes with high similarities (in sequence and structure) with the host, can act as little sequences for the evasion of host immune system, even more, this trojans may cause a T and B reactive cells provoking an immune response for the microbial elimination and the origin of an autoimmune disease [43].

3.2.1. Trojans against connective

Systemic lupus erythematosus (SLE) is an prototype of autoimmune disease, affecting the connective tissue [44], with a great spectrum of clinical symptoms such as joints, kidneys, skin, to other manifestation, in fact, SLE is a nonpreventable disease and may be life-threatening [45, 46]. Many autoantigens have been described to induce cross-reactivity immune response to SLE such as Ro52, Ro60, La, RNP-A, Sm-D3, and RNP-70 K. RNA-A and RNP-70 K, however, oral microbiome contain epitopes with similarities against SLE autoantingens (**Table 1**).

Ro ribonucleoprotein 60 KDa (Ro60) is an autoantigen most prevalent in systemic autoimmune diseases as SLE and Sjögren's syndrome, and exist in unabundant ribonucleoprotein complexes stabilizing small RNA to prevent degradation [47, 48]. This protein has a 6 aminoacids (aa) similarity against VWA domain-containing protein of *Prevotella denticola* (**Table 1**). Small nuclear ribonucleoprotein 70 kDa, another autoantigen in SLE, is a small protein conforming the spliceosome complex. This protein has a 7 aa similarity against *Bacillus cereus* (**Table 1**).

PubMed ref	Organism	Epitopes
NP_001035828.1	*H. sapiens*	DVSASM
WP_036854258.1	*P. denticola*	DVSASM
NP_003080.2	*H. sapiens*	GYAFIEY
WP_061130177.1	*B. cereus*	GYAFIEY

P. denticola and *B. cereus* present epitopes with high similarities of self-autoantigens Ro60KDa and small nuclear ribonucleoprotein 70 KDa.

Table 1. Oral microbiome epitopes with similarities against connective.

3.2.2. Trojans against nerves

Aquaporin 4 is an integral membrane protein that conducts water through cell membrane founded in nervous system. It is presented as autoantigen in neuromyelitis optica, an auto-immune disease consisting of a chronic inflammation and demyelination of optical nerve and spinal cord. This protein has similarities against glycerol uptake facilitator protein 2 of *Strepto-coccus pneumoniae*, MIP family channel protein of *Prevotella oralis* and MIP family channel protein of *Enterococcus faecalis* (**Table 2**). Glycerol uptake facilitator protein 2 is a putative nonselective transport channel in the inner membrane of bacterium [49] and MIP family channel is a transmembrane protein transporting small molecules [50]. Both proteins are in external side of microbial cell membrane been more efficient form antibody-epitope complex.

Glutamate decarboxylase 2 is an autoantigen related in Stiff-Person syndrome, an autoimmune disease that affects nervous system. Glutamate decarboxylase of *Enterococcus spp*. possess 7 aa similarities against autoantigen (**Table 2**).

3.2.3. Trojans against diabetes

Type 1 diabetes is an autoimmune disease in which the B-cells in the Langerhans islands of pancreas are destroyed by T and B reactive cells lacking the insulin production [28], affecting children and latent autoimmune disease of adults [51]. One of characteristics of this disease is the recognition of beta cell proteins as autoantigens such as preproinsulin GAD65, islet antigen 2 (IA-2), ZnT8, nonspecific islet cell autoantigens (ICAs), imogen 38, pancreatic duodenal homeobox factor 1, chromogranin A, islet specific glucose-6-phosphatase catalytic subunit-related protein, heat shock protein 60 and islet cell antigen 69. IA-2, possess 6 aa with similar

PubMed ref	Organism	Epitopes
AAB26958.1	*H. sapiens*	ISG-HINPA-T
WP_004369577.1	*P. oralis*	ISG-HINPA-T
AAB26958.1	*H. sapiens*	G-IIGA-ILY
WP_004369577.1	*P. oralis*	G-IIGA-ILY
AAB26958.1	*H. sapiens*	S-NPARS-GPA
WP_004369577.1	*P. oralis*	S-NPARS-GPA
AAB26958.1	*H. sapiens*	SVNPARS
EFM77965.1	*Enterococcus spp*.	SVNPARS
NP_000809.1	*H. sapiens*	HVDAA-GG
WP_086305260.1	*Enterococcus spp*.	HVDAA-GG

P. oralis and *Enterococcus spp*. present epitopes with high similarities of self-autoantingens against aquaporin 4 and glutamate decarboxylase 2.

Table 2. Oral microbiome epitopes with similarities against nerves.

PubMed ref	Organism	Epitopes
NP_001186692.1	*H. sapiens*	PKAE-PA
WP_033676705.1	*S. mitis*	PKAE-PA

S. mitis presents epitope with high similarities of self-autoantigen against islet antigen A.

Table 3. Oral microbiome epitopes with similarities against diabetes.

PubMed ref	Organism	Epitopes
pir||B54197	*H. sapiens*	SFENP
CDB05904.1	*Prevotella sp.*	SFENP
pir||B54197	*H. sapiens*	FTNEDNP
EPH90635.1	*E. faecalis*	FTNEDNP
pir||B54197	*H. sapiens*	FENPVL
WP_002676716.1	*T. denticola*	FENPVL

Prevotella sp., E. faecalis., T. denticola., present epitopes with high similarities of self-autoantigens against Ku autoantigen 70 k.

Table 4. Oral microbiome epitopes with similarities against thyroiditis.

characteristics with LysM peptidoglycan-binding domain-containing protein of *Streptococcus mitis* (**Table 3**) that is present to bind noncovalently to peptidoglycan and chitin in cell wall [52].

3.2.4. Trojans against thyroiditis

Thyroiditis is an autoimmune disease that destroys thyroid cells by reactive T and B cells. This disease is also known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis. The pathology of thyroiditis involves the formation of antithyroid antibodies that attack thyroid tissue, causing progressive fibrosis [53]. One common autoantigen of many described in the literature is the thyroid autoantigen 70 k also known as Ku autoantigen [54]. Ku is an abundant protein in the body with multiple functions as replication, transcription and cell signaling [54]. Pilin isopeptide linkage domain protein of *E. faecalis*, ompA family protein of *Prevotella sp*. and aldo/keto reductase of *T. denticola* have small epitopes with high similarities with Ku autoantigen 70 k (**Table 4**).

3.2.5. Trojans against myasthenia gravis

Myasthenia gravis is an autoimmune disease that attacks neuromuscular junction where synapsis occurs between nerves and muscles causing muscle weakness in patients [55]. Auto-antibodies such as muscle-specific tyrosine kinase (MUSK), acetylcholine, agrin and low-density lipoprotein receptor–related protein 4 (LPR4) have been described in the literature [56, 57]. MUSK is a transmembrane protein that contains three IgG domains and one cyste-ine-rich domain in the extracellular region and a kinase domain in the intracellular region [56]

and possesses 6 aa similarity to Stk1 family PASTA domain-containing Ser/Thr kinase of *Lactobacillus sp.* (**Table 5**). This lactobacillus protein is present in cell wall in gram positives and negatives associated to penicillin-binding proteins [58].

3.2.6. Trojans against chronic autoimmune gastritis

Autoimmune gastritis represents approximately 5% of the whole spectrum of chronic gastritis and must be differentiated from the one associated with chronic *Helicobacter pylori* infection [59]. Gastritis is a chronic inflammatory disease involving gastric body and fundus, with the progressive reduction and/or disappearance of gastric glands that are sometimes replaced by intestinal or pyloric epithelium [60]. Autoantigens for the autoimmune gastritis has been related as Gastric ATPase α subunit, Gastric ATPase β subunit and Gastric intrinsic factor [61]. Gastric ATPase α subunit have three epitopes in different position in the same protein with a 6 aa, 7aa and 15 aa similarity, to Ca2 + −transporting ATPase of *Streptococcus pneumoniae* (**Table 6**).

3.2.7. Trojans against liver

Autoimmune hepatitis is a chronic and progressive inflammation of the liver from an unknown cause, whose pathology is explained by the failure of immune tolerance in a genetically susceptible individual leading to a reactive T-cell mediated inflammation caused by various environmental triggers including infections, medications, and toxins [62]. Autoantigens for autoimmune hepatitis have been related such as O-phosphoseryl-tRNA(Sec) selenium transferase (SLA), cytochrome P450 2D6 isoform 1 (CYP2D6) and formimidoyltransferase-cyclodeaminase isoform C (FTCD) [61]. FTCD epitopes have similarities with glutamate

PubMed ref	Organism	Epitopes
NP_001159752.1	*H. sapiens*	KIADFG
WP_083289611.1	*Lactobacillus spp.*	KIADFG

Lactobacillus spp. presents epitope with high similarities of self-autoantigen MUSK.

Table 5. Oral microbiome epitopes with similarities against neuromuscular junctions.

PubMed ref	Organism	Epitopes
NP_000695.2	*H. sapiens*	ICSDKTGTLTQN-MTV
CKF15123.1	*S. pneumoniae*	ICSDKTGTLTQN-MTV
NP_000695.2	*H. sapiens*	MIDPPR
CKF15123.1	*S. pneumoniae*	MIDPPR
NP_000695.2	*H. sapiens*	TGDGVND
CKF15123.1	*S. pneumoniae*	TGDGVND

S. pneumoniae present epitope with high similarities of self-autoantigen against gastric ATPase α subunit.

Table 6. Oral microbiome epitopes with similarities against gastritis.

PubMed ref	Organism	Epitopes
NP_001307341.1	*H. sapiens*	ECVPNFSEG
WP_054191567.1	*P. gingivalis*	ECVPNFSEG
NP_001307341.1	*H. sapiens*	GEHPRMGA-DVCPF
WP_010922735.1	*Streptococcus spp.*	GEHPRMGA-DVCPF
NP_001307341.1	*H. sapiens*	APGGGSV
WP_088387656.1	*F. nucleatum*	APGGGSV
NP_001307341.1	*H. sapiens*	PNFSEG
WP_010922735.1	*Streptococcus spp.*	PNFSEG

P. gingivalis., Streptococcus spp., F. nucleatum., present epitopes with high similarities of self-autoantingens FTCD and PDC-E2.

Table 7. Oral microbiome epitopes with similarities against liver.

formimidoyltransferase of *Porphyromonas gingivalis*, formimidoyltetrahydrofolate cyclodeaminase of *Fusobacterium nucleatum* and glutamate formimidoyltransferase of *Streptococcus spp* (**Table 7**).

Primary biliary cirrhosis (PBC) is now known as primary biliary cholangitis [63]. It is an autoimmune disorder which leads to gradual destruction of intrahepatic bile ducts resulting into periportal inflammation, cholestasis [63]. This disease is common among women of middle age worldwide. Primary biliary cirrhosis is associated with highly specific autoantibody [64]. The anti-mitochondrial antibody is found in 85% of the cases, other antibodies associated with disease is an antinuclear antibody (ANA), anti-multiple nuclear dot antibody (anti-MND), anticentromere antibody, pyruvate dehydrogenase complex E2 (PDC-E2) and antinuclear envelop antibody [61, 63] . PDC-E2, possess 7 aa with similarities to dihydrolipoyllysine-residue acetyltransferase of *Enterococcus spp*.

3.2.8. Trojans against muscle

Myositis is an autoimmune disease that attack muscles [65]. There are three types of this disease: polymyositis, dermatomyositis, and juvenile myositis and possess and autoimmune origin, meaning the immune system is attacking the muscle [66]. This disease is not present in etiology. Although myositis is often treatable, these diseases are poorly understood and do not always completely respond to current medications [66]. Autoantigens has been related in the literature: histidine–tRNA ligase, cytoplasmic isoform 2, threonine–tRNA ligase, cytoplasmic isoform 1, exosome complex component RRP45 isoform 1, exosome component 10 isoform 1, chromodomain-helicase-DNA-binding protein 4 isoform 1, interferon-induced helicase C domain-containing protein 1, MORC family CW-type zinc finger protein 3 isoform 2, signal recognition particle 54 kDa protein isoform 2, E3 ubiquitin-protein ligase TRIM33 isoform alpha and 3-hydroxy-3-methylglutaryl-Coenzyme A reductase isoform 1 [61]. Threonine–tRNA ligase, cytoplasmic isoform 1 autoantigen, possess many epitopes with high similarities with threonine-tRNA ligase of *Aggregatibacter actinomycetemcomitans* and threonine–tRNA ligase of *Streptococcus spp.* (**Table 8**).

PubMed ref	Organism	Epitopes
NP_001245366.1	*H. sapiens*	TLPDG
WP_005555043.1	*A. actinomycetemcomitans*	TLPDG
NP_001245366.1	*H. sapiens*	NGFYYD
WP_005555043.1	*A. actinomycetemcomitans*	NGFYYD
NP_001245366.1	*H. sapiens*	CRGPHV
WP_005555043.1	*A. actinomycetemcomitans*	CRGPHV
NP_001245366.1	*H. sapiens*	RDHRKIG
WP_005555043.1	*A. actinomycetemcomitans*	RDHRKIG
NP_001245366.1	*H. sapiens*	KPMNCPGH
WP_005555043.1	*A. actinomycetemcomitans*	KPMNCPGH
NP_001245366.1	*H. sapiens*	QDDAHIFC
WP_005555043.1	*A. actinomycetemcomitans*	QDDAHIFC
NP_001245366.1	*H. sapiens*	LSTRPEK
WP_005555043.1	*A. actinomycetemcomitans*	LSTRPEK
NP_001245366.1	*H. sapiens*	GAFYGPK
WP_005555043.1	*A. actinomycetemcomitans*	GAFYGPK
NP_001245366.1	*H. sapiens*	TIQLDF
WP_005555043.1	*A. actinomycetemcomitans*	TIQLDF
NP_001245366.1	*H. sapiens*	HRAILGS
WP_005555043.1	*A. actinomycetemcomitans*	HRAILGS
NP_001245366.1	*H. sapiens*	GFYYD
WP_000591038.1	*Streptococcus spp.*	GFYYD
NP_001245366.1	*H. sapiens*	DLCRGPHV
WP_000591038.1	*Streptococcus spp.*	DLCRGPHV
NP_001245366.1	*H. sapiens*	RDHRK
WP_000591038.1	*Streptococcus spp.*	RDHRK
NP_001245366.1	*H. sapiens*	TSGHW
WP_000591038.1	*Streptococcus spp.*	TSGHW
NP_001245366.1	*H. sapiens*	SGALTGL
WP_000591038.1	*Streptococcus spp.*	SGALTGL
NP_001245366.1	*H. sapiens*	AFYGPK
WP_000591038.1	*Streptococcus spp.*	AFYGPK

A. actinomycetemcomitans, and *Streptococcus spp.*, present epitopes with high similarities of self-autoantingen Threonine—tRNA ligase, cytoplasmic isoform 1.

Table 8. Oral microbiome epitopes with similarities against gastritis.

PubMed ref	Organism	Epitopes
NP_110447.2	*H. sapiens*	GAKG-RGEKG
ZP_05918585.1	*Prevotella sp.*	GAKG-RGEKG

Prevotella sp. presents epitope with high similarities of self-autoantigen against collagen alpha-1(XXI) chain isoform a.

Table 9. Oral microbiome epitopes with similarities against collagen.

3.2.9. Trojans against collagen

Collagen is the most tissue presented in the body; it is associated with the skin, kidney, nerves, blood vessels and muscles protecting them against compressive forces [67, 68]. Rheumatoid arthritis (RA) is a progressive autoimmune disease that affects directly the collagen by the chronification of inflammation causing a tissue damage (specially cartilage and bone), functional impairment, severe disability and premature mortality [69, 70]. Periodontitis is a chronic disease by microbial multispecies insult. Microbiome of periodontal disease (PD) could be showed some bacteria such *P. gingivalis, P. intermedia, Tannerella forsythia. F. nucleatum* and *Aggregatibacter actinomycetemcomitans,* with epitopes that provokes autoreactivity against collagen [71]. Anti-citrullinated protein is an important autoantigen present in patients with RA having antibodies anti-Pg [72]. Obando-Pereda et al. showed that an epitope of *Prevotella sp.* has high similarity with human collagen report a positive antigen-antibody complex in RA and PD patient's sera [8] (**Table 9**).

4. Conclusion

The majority of autoimmune diseases possess an unknown etiology and can be explained from genetic factors to molecular mimicry. In silico, tools for biological purposes are important to determinate if external epitopes that possess similarities with epitopes from autoantigens. Epitopes for Systemic lupus erythematosus, Sjögren's syndrome, neuromyelitis optica, Stiff-Person syndrome, autoimmune diabetes, autoimmune thyroiditis, myasthenia gravis, autoimmune gastritis, autoimmune hepatitis, myositis and rheumatoid arthritis, possess microbial epitopes belong to oral microbiome with high similarities that can explain the possible etiology of autoimmune disease by molecular mimicry.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest in the present chapter.

Author details

Gustavo Obando-Pereda

Address all correspondence to: gobando@ucsm.edu.pe

Dentistry School, Universidad Católica de Santa María, Arequipa, Peru

References

[1] Yi YS. Role of inflammasomes in inflammatory autoimmune rheumatic diseases. The Korean Journal of Physiology & Pharmacology. 2018;**22**(1):1-15

[2] Tartey S, Takeuchi O. Pathogen recognition and Toll-like receptor targeted therapeutics in innate immune cells. International Reviews of Immunology. 2017;**36**(2):57-73

[3] Walsh MC, Takegahara N, Kim H, Choi Y. Updating osteoimmunology: Regulation of bone cells by innate and adaptive immunity. Nature Reviews Rheumatology. 2018

[4] Schaefer L. Complexity of danger: The diverse nature of damage-associated molecular patterns. The Journal of Biological Chemistry. 2014;**289**(51):35237-35245

[5] Twigg HL 3rd. Macrophages in innate and acquired immunity. Seminars in Respiratory and Critical Care Medicine. 2004;**25**(1):21-31

[6] Padovan E. Modulation of CD4+ T helper cell memory responses in the human skin. International Archives of Allergy and Immunology. 2017;**173**(3):121-137

[7] Kramer JM, Gaffen SL. Interleukin-17: A new paradigm in inflammation, autoimmunity, and therapy. Journal of Periodontology. 2007;**78**(6):1083-1093

[8] Obando-Pereda GA. GAKG-RGEKG an epitope that provokes immune cross-reactivity between *Prevotella sp.* and human collagen: Evidence of molecular mimicry in chronic periodontitis. Autoimmune Diseases. 2016;**2016**:5472320

[9] Burne RA. Getting to know "The Known Unknowns": Heterogeneity in the oral microbiome. Advances in Dental Research. 2018;**29**(1):66-70

[10] Chen B, Sun L, Zhang X. Integration of microbiome and epigenome to decipher the pathogenesis of autoimmune diseases. Journal of Autoimmunity. 2017;**83**:31-42

[11] Mira A. Oral microbiome studies: Potential diagnostic and therapeutic implications. Advances in Dental Research. 2018;**29**(1):71-77

[12] Damian RT. Molecular mimicry: Antigen sharing by parasite and host and its consequences. The American Naturalist. 1964;**98**(900):21

[13] Rose NR. Negative selection, epitope mimicry and autoimmunity. Current Opinion in Immunology. 2017;**49**:51-55

[14] Benvenga S, Guarneri F. Molecular mimicry and autoimmune thyroid disease. Reviews in Endocrine & Metabolic Disorders. 2016;**17**(4):485-498

[15] Friedland RP. Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. Journal of Alzheimer's Disease. 2015;**45**(2):349-362

[16] Xie Z, Chang C, Zhou Z. Molecular mechanisms in autoimmune type 1 diabetes: A critical review. Clinical Reviews in Allergy and Immunology. 2014;**47**(2):174-192

[17] Grossman Z, Paul WE. Autoreactivity, dynamic tuning and selectivity. Current Opinion in Immunology. 2001;**13**(6):687-698

[18] Guven-Maiorov E, Tsai CJ, Nussinov R. Pathogen mimicry of host protein-protein interfaces modulates immunity. Seminars in Cell & Developmental Biology. 2016;**58**:136-145

[19] Burg JS, Ingram JR, Venkatakrishnan AJ, Jude KM, Dukkipati A, Feinberg EN, et al. Structural biology. Structural basis for chemokine recognition and activation of a viral G protein-coupled receptor. Science. 2015;**347**(6226):1113-1117

[20] Qin L, Kufareva I, Holden LG, Wang C, Zheng Y, Zhao C, et al. Structural biology. Crystal structure of the chemokine receptor CXCR4 in complex with a viral chemokine. Science. 2015;**347**(6226):1117-1122

[21] Finlay BB, McFadden G. Anti-immunology: Evasion of the host immune system by bacterial and viral pathogens. Cell. 2006;**124**(4):767-782

[22] Hagai T, Azia A, Babu MM, Andino R. Use of host-like peptide motifs in viral proteins is a prevalent strategy in host-virus interactions. Cell Reports. 2014;**7**(5):1729-1739

[23] Davey NE, Trave G, Gibson TJ. How viruses hijack cell regulation. Trends in Biochemical Sciences. 2011;**36**(3):159-169

[24] Bulgin R, Raymond B, Garnett JA, Frankel G, Crepin VF, Berger CN, et al. Bacterial guanine nucleotide exchange factors SopE-like and WxxxE effectors. Infection and Immunity. 2010;**78**(4):1417-1425

[25] Huang Z, Sutton SE, Wallenfang AJ, Orchard RC, Wu X, Feng Y, et al. Structural insights into host GTPase isoform selection by a family of bacterial GEF mimics. Nature Structural & Molecular Biology. 2009;**16**(8):853-860

[26] Takaba H, Takayanagi H. The mechanisms of T cell selection in the thymus. Trends in Immunology. 2017;**38**(11):805-816

[27] Leech S. Molecular mimicry in autoimmune disease. Archives of Disease in Childhood. 1998;**79**(5):448-451

[28] Riedhammer C, Weissert R. Antigen presentation, autoantigens, and immune regulation in multiple sclerosis and other autoimmune diseases. Frontiers in Immunology. 2015;**6**:322

[29] Oldstone MB. Molecular mimicry: Its evolution from concept to mechanism as a cause of autoimmune diseases. Monoclonal Antibodies in Immunodiagnosis and Immunotherapy. 2014;**33**(3):158-165

[30] Sudres M, Verdier J, Truffault F, Le Panse R, Berrih-Aknin S. Pathophysiological mechanisms of autoimmunity. Annals of the New York Academy of Sciences. 2018

[31] Benson RA, Brewer JM, Platt AM. Mechanisms of autoimmunity in human diseases: A critical review of current dogma. Current Opinion in Rheumatology. 2014;**26**(2):197-203

[32] Yang SH, Gao CY, Li L, Chang C, Leung PSC, Gershwin ME, et al. The molecular basis of immune regulation in autoimmunity. Clinical Science. 2018;**132**(1):43-67

[33] Suurmond J, Diamond B. Autoantibodies in systemic autoimmune diseases: Specificity and pathogenicity. The Journal of Clinical Investigation. 2015;**125**(6):2194-2202

[34] Galvin JE, Hemric ME, Ward K, Cunningham MW. Cytotoxic mAb from rheumatic carditis recognizes heart valves and laminin. The Journal of Clinical Investigation. 2000; **106**(2):217-224

[35] Liao C, Zhang C, Yang Y. Pivotal roles of interleukin-17 as the epicenter of bone loss diseases. Current Pharmaceutical Design. 2017

[36] Han S, Donelan W, Wang H, Reeves W, Yang LJ. Novel autoantigens in type 1 diabetes. American Journal of Translational Research. 2013;**5**(4):379-392

[37] Magro-Checa C, Zirkzee EJ, Huizinga TW, Steup-Beekman GM. Management of neuropsychiatric systemic lupus erythematosus: Current approaches and future perspectives. Drugs. 2016;**76**(4):459-483

[38] Wang L, Hao C, Deng Y, Liu Y, Hu S, Peng Y, et al. Screening epitopes on systemic lupus erythematosus autoantigens with a peptide array. Oncotarget. 2017;**8**(49):85559-85567

[39] Catrina AI, Joshua V, Klareskog L, Malmstrom V. Mechanisms involved in triggering rheumatoid arthritis. Immunological Reviews. 2016;**269**(1):162-174

[40] Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: A study of serial measurements in blood donors. Arthritis and Rheumatism. 2004;**50**(2):380-386

[41] Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis and Rheumatism. 2003;**48**(10):2741-2749

[42] Pollock J, Glendinning L, Wisedchanwet T, Watson M. The madness of microbiome: Attempting to find consensus "best practice" for 16S microbiome studies. Applied and Environmental Microbiology. 2018

[43] Devasundaram S, Deenadayalan A, Raja A. In silico analysis of potential human T cell antigens from *Mycobacterium tuberculosis* for the development of subunit vaccines against tuberculosis. Immunological Investigations. 2014;**43**(2):137-159

[44] Wolfe RM, Ang DC. Biologic therapies for autoimmune and connective tissue diseases. Immunology and Allergy Clinics of North America. 2017;**37**(2):283-299

[45] Barturen G, Alarcon-Riquelme ME. SLE redefined on the basis of molecular pathways. Best Practice & Research. Clinical Rheumatology. 2017;**31**(3):291-305

[46] Rose T, Dorner T. Drivers of the immunopathogenesis in systemic lupus erythematosus. Best Practice & Research. Clinical Rheumatology. 2017;**31**(3):321-333

[47] Deutscher SL, Harley JB, Keene JD. Molecular analysis of the 60-kDa human Ro ribonucleoprotein. Proceedings of the National Academy of Sciences of the United States of America. 1988;**85**(24):9479-9483

[48] Kurien BT, Dorri Y, Bachmann M, Scofield RH. Induction of anti-Ro60/anti-La by immunisation with spectrin and induction of anti-spectrin by immunisation with Ro60 and 4-hydroxy-2-nonenal-modified Ro60 immunisation. Clinical and Experimental Rheumatology. 2012;**30**(6):886-893

[49] Maurel C, Reizer J, Schroeder JI, Chrispeels MJ, Saier MH Jr. Functional characterization of the *Escherichia coli* glycerol facilitator, GlpF, in Xenopus oocytes. The Journal of Biological Chemistry. 1994;**269**(16):11869-11872

[50] Reizer J, Reizer A, Saier MH Jr. The MIP family of integral membrane channel proteins: Sequence comparisons, evolutionary relationships, reconstructed pathway of evolution, and proposed functional differentiation of the two repeated halves of the proteins. Critical Reviews in Biochemistry and Molecular Biology. 1993;**28**(3):235-257

[51] Patterson CC, Gyurus E, Rosenbauer J, Cinek O, Neu A, Schober E, et al. Trends in childhood type 1 diabetes incidence in Europe during 1989-2008: Evidence of non-uniformity over time in rates of increase. Diabetologia. 2012;**55**(8):2142-2147

[52] Visweswaran GR, Leenhouts K, van Roosmalen M, Kok J, Buist G. Exploiting the peptidoglycan-binding motif, LysM, for medical and industrial applications. Applied Microbiology and Biotechnology. 2014;**98**(10):4331-4345

[53] Mincer DL, Jialal II. Thyroid Hashimoto Thyroiditis. Treasure Island (FL): StatPearls; 2017

[54] Kelavkar UP, Wang S, Badr KF. Ku autoantigen (DNA helicase) is required for interleukins-13/-4-induction of 15-lipoxygenase-1 gene expression in human epithelial cells. Genes and Immunity. 2000;**1**(4):237-250

[55] Wang J, Xiao Y, Zhang K, Luo B, Shen C. Introducing autoimmunity at the synapse by a novel animal model of experimental autoimmune myasthenia gravis. Neuroscience. 2018

[56] Yan M, Xing GL, Xiong WC, Mei L. Agrin and LRP4 antibodies as new biomarkers of myasthenia gravis. Annals of the New York Academy of Sciences. 2018;**1413**(1):126-135

[57] Stathopoulos P, Kumar A, Heiden JAV, Pascual-Goni E, Nowak RJ, O'Connor KC. Mechanisms underlying B cell immune dysregulation and autoantibody production in MuSK myasthenia gravis. Annals of the New York Academy of Sciences. 2018;**1412**(1):154-165

[58] Turapov O, Loraine J, Jenkins CH, Barthe P, McFeely D, Forti F, et al. The external PASTA domain of the essential serine/threonine protein kinase PknB regulates mycobacterial growth. Open Biology. 2015;**5**(7):150025

[59] Toh BH. Diagnosis and classification of autoimmune gastritis. Autoimmunity Reviews. 2014;**13**(4–5):459-462

[60] Neumann WL, Coss E, Rugge M, Genta RM. Autoimmune atrophic gastritis—Pathogenesis, pathology and management. Nature Reviews Gastroenterology & Hepatology. 2013;**10**(9):529-541

[61] Burbelo PD, Iadarola MJ, Alevizos I, Sapio MR. Transcriptomic segregation of human autoantigens useful for the diagnosis of autoimmune diseases. Molecular Diagnosis & Therapy. 2016;**20**(5):415-427

[62] Linzay CD, Pandit S. Hepatitis, Autoimmune. Treasure Island (FL): StatPearls; 2017

[63] Pandit S, Samant H. Primary Biliary Cholangitis (Primary Biliary Cirrhosis). Treasure Island (FL): StatPearls; 2017

[64] Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. Lancet. 2015;**386**(10003):1565-1575

[65] Keller CW, Schmidt J, Lunemann JD. Immune and myodegenerative pathomechanisms in inclusion body myositis. Annals of Clinical Translational Neurology. 2017;**4**(6):422-445

[66] Mandel DE, Malemud CJ, Askari AD. Idiopathic inflammatory myopathies: A review of the classification and impact of pathogenesis. International Journal of Molecular Sciences. 2017;**18**(5)

[67] Lamande SR, Bateman JF. Collagen VI disorders: Insights on form and function in the extracellular matrix and beyond. Matrix Biology. 2017

[68] Cescon M, Gattazzo F, Chen P, Bonaldo P. Collagen VI at a glance. Journal of Cell Science. 2015;**128**(19):3525-3531

[69] Favalli EG, Biggioggero M, Crotti C, Becciolini A, Raimondo MG, Meroni PL. Sex and management of rheumatoid arthritis. Clinical Reviews in Allergy and Immunology. 2018

[70] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;**388**(10055):2023-2038

[71] Ogrendik M. Rheumatoid arthritis is an autoimmune disease caused by periodontal pathogens. International Journal of General Medicine. 2013;**6**:383-386

[72] Azzi L, Rania S, Vinci R, Spadari F, Croveri F, Scognamiglio C, et al. Periodontal microbioma and rheumatoid arthritis: The role of Porhyromonas gingivalis. Journal of Biological Regulators and Homeostatic Agents. 2017;**31**(2 Suppl 1):97-103