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REVIEW ARTICLE

Potential Role of Bacterial Infection in Autoimmune Diseases: A New Aspect of Molecular Mimicry

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Molecular mimicry is an attractive mechanism for triggering autoimmunity. In this review, we explore the potential role of evolutionary conserved bacterial proteins in the production of autoantibodies with focus on granulomatosis with polyangiitis (GPA) and rheumatoid arthritis (RA). Seven autoantigens characterized in GPA and RA were BLASTed against a bacterial protein database. Of the seven autoantigens, proteinase 3, type II collagen, binding immunoglobulin protein, glucose-6-phosphate isomerase, α-enolase, and heterogeneous nuclear ribonuclear protein have well-conserved bacterial orthologs. Importantly, those bacterial orthologs are also found in human-associated bacteria. The wide distribution of the highly conserved stress proteins or enzymes among the members of the normal flora and common infectious microorganisms raises a new question on how cross-reactive autoantibodies are not produced during the immune response to these bacteria in most healthy people. Understanding the mechanisms that deselect auto-reactive B cell clones during the germinal center reaction to homologous foreign antigens may provide a novel strategy to treat autoimmune diseases.

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INTRODUCTION

Autoimmune diseases are complex immune-mediated diseases that involve both genetic and environmental factors in their pathogenesis. Infectious microorganisms have long been suggested to trigger an immune response to autoantigens by providing stimuli for the breakdown of self-tolerance and also by generating cross-reactive T cells and antibodies via molecular mimicry. Molecular mimicry is a mechanism that has a proposed role in many autoimmune diseases such as acute rheumatic fever, rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, type 1 diabetes mellitus, and Lyme arthritis. In autoimmune diseases, the concept of molecular mimicry has often been used to describe similar structures shared by molecules from dissimilar proteins, as illustrated by the α-helical coiled-coil streptococcal M protein and cardiac myosin in rheumatic fever. However, some proteins such as heat shock proteins are evolutionally highly conserved from prokaryotes to eukaryotes. In this review, we explore the potential role of the evolutionary conserved bacterial proteins in the production of autoantibodies with focus on granulomatosis with polyangiitis (GPA) and rheumatoid arthritis (RA).

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Abbreviations: GPA, granulomatosis with polyangiitis; RA, rheumatoid arthritis; ANCA, anti-neutrophil cytoplasmic autoantibodies; PR3, proteinase 3; MPO, myeloperoxidase; LAMP-2, lysosomal membrane glycoprotein 2; RF, rheumatoid factor; CII, type II collagen; BiP, binding immunoglobulin protein; G6PPI, glucose-6-phosphate isomerase; hnRNP, heterogeneous nuclear ribonuclear protein

Table I. Selected bacteria that contain human PR3-homologous proteins

Bacteria	Protein	Query cover (%)	Identities (%)	Similarities (%)
Myxococcus xanthus	S1A family peptidase	88	35	45
Actinosynnema mirum	S1 and S6 peptidase	92	34	47
Streptomyces clavuligerus	Trypsin	83	35	48
Pseudoalteromonas tunicata	Secreted trypsin-like serine protease	91	33	48
Saccharomonospora viridis	Secreted trypsin-like serine protease	93	31	44
Saccharopolyspora erythraea	Secreted trypsin-like serine protease	95	30	43
Vibrio cholerae	Serine protease	87	27	46
Vibrio parahaemolyticus	Trypsin family protein	78	31	46

GPA AND ANTI-NEUTROPHIL CYTOPLASMIC AUTOANTIBODIES (ANCA)

GPA (Wegener's) is a type of ANCA-associated vasculitis that affects small- and medium-sized vessels in many organs. Its clinical symptoms include fever, fatigue, weight loss, nasal discharge, sinusitis, cough, dyspnea, hematuria, and proteinuria. Pathologically, GPA is characterized by multi-focal granulomatous inflammation with central necrosis and necrotizing vasculitis. In addition, the presence of an ANCA in serum is used as a diagnostic marker. There are two types of ANCAs, *i.e.*, directed against either proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). The ANCA antigen specificity of GPA in European patients is predominantly PR3, whereas that in Japanese patients is predominantly MPO. The pathogenesis of necrotizing vasculitis is understood to involve infiltration of neutrophils into vessel walls and their subsequent activation. ANCA is known to mediate the activation of neutrophils and degranulation via crosslinking of the Fc receptor and antigens expressed on the membrane. However, what causes the production of ANCA and granulomatous inflammation, is not known.

Interestingly, bacterial infection has been implicated in the initiation and relapse of GPA. Early observations suggested a potential role of infection in the relapse of disease. Chronic nasal carriage of *Staphylococcus aureus* is increased in GPA patients compared to healthy subjects (63% vs. 25%), and the carriage of *S. aureus* increases the risk of relapse by 7.16 fold (9). Furthermore, the addition of trimethoprim/sulfamethoxazole to maintenance treatment reduced the relapses by 60% (10). Although the underlying mechanisms for the increased relapse by *S. aureus* is not clear, potential roles in polyclonal activation of B cells, priming of neutrophils, and induction of anti-idiotypic antibodies to PR3-ANCA have been suggested (6). Kain et al. reported a new ANCA directed against lysosomal membrane glycoprotein 2 (LAMP-2) as a specific marker for focal necrotizing glomerulonephritis and showed that the autoantibodies to LAMP-2 can be induced by immunization with FimH, a bacterial fimbrial adhesin of Gram-negative bacteria (11). The eight amino acids of one LAMP-2 epitope (P_{41-49}) recognized by autoantibodies have a strong homology with the FimH of several common Gram-negative species, suggesting molecular mimicry between the two proteins.

We previously demonstrated that the membrane bound PR3 on neutrophils acts as a receptor for non-opsonic phagocytosis of bacteria and that the neutralization of PR3 with ANCA reduces both binding and phagocytosis of bacteria (12). It raised the possibility that ANCA may be induced by some pathogens possessing a PR3-homologous protein to avoid host immunity. When the bacterial protein database was searched using the PR3 protein sequence as a query, hundreds of bacterial proteases with 28% to 36% identity were indeed found. Among the bacteria containing PR3-homologous proteases, only *Vibrio cholerae, V. vulnificus, V. parahaemolyticus*, and *Saccharomonospora viridis* are known to infect humans (Table I). The spores of *S. viridis*, a gram-negative bacterium frequently found in hot compost and hay, can be readily dispersed in air. Prolonged exposure to those spores can cause farmer's lung, bagassosis, and humidifier fever that manifest symptoms such as fever, malaise, cough, and dyspnea similar to GPA (13). Granulomas are usually formed in an attempt to segregate foreign substances that are resistant to phagocytic clearance. If *S. viridis* induces ANCA production via molecular mimicry, the ANCA would inhibit phagocytosis of *S. viridis*. Furthermore, if *S. viridis* survives after phagocytosis, infection with *S. viridis* may also contribute to the formation of granulomatous inflammation.

AUTOANTIGENS CHARACTERIZED IN RHEUMATOID ARTHRITIS (RA)

A literature search revealed that Wegner et al. already proposed evolutionarily conserved antigens as stimuli to cause breakdown of tolerance and reported well-conserved bacterial orthologs for pyruvate dehydrogenase complex E2, glutamic acid decarboxylase, histidyl-tRNA synthetase, and enolase among seven major autoantigens examined (14). Therefore, we further explored the possibility that evolutionarily conserved bacterial proteins are involved in autoantibody production in RA, the most common systemic autoimmune disease.

RA is characterized by the presence of diverse autoantibodies in serum and synovial fluid. Rheumatoid factor (RF) is the first autoantibody described in RA, which is directed against the Fc portion of IgG, a major serum component (15). Together with the RF, anti-citrullinated protein antibodies are clinically important. The anti-citrullinated protein antibodies are a group of autoantibodies that recognize citrulline-containing peptides/proteins as common antigenic epitopes (16). Other antigens characterized as targets of autoantibodies in RA include type II collagen (CII), binding immunoglobulin protein (BiP), glucose-6-phosphate isomerase (G6PI), α-enolase, and heterogeneous nuclear ribonuclear protein (hnRNP) A2 (17). We searched the bacterial protein database using these human proteins as a query.

Members of the immunoglobulin superfamily have also been found in bacteria (18). Homology search with the sequence of human immunoglobulin gamma-1 heavy chain constant region did not retrieve any bacterial proteins. When the CH2 and CH3 domains, the antigenic epitopes of RF, were searched separately, however, several bacterial proteins such as the cell wall binding repeat 2 family protein and cell surface protein of *Clostridium difficile* were found to share 46% similarities with the CH2 over 76% of the domain.

CII is a component of both articular and hyaline cartilage. RA patients often contain high titers of anti-CII antibodies in sera and synovial fluids (19). Because CII is exclusively expressed in the cartilage, autoantibodies against CII induce joint destruction. Surprisingly, a large number of bacterial species contain collagen triple helix repeat family proteins that share a high degree of identity (32～47%) and homology (36～52%) with human CII. Among those, important human

Table II. Selected human-associated bacteria that contain human CII-homologous proteins

Bacteria (Human association)	Protein	Query cover (%)	Identities (%)	Similarities (%)
Clostridium beijerinckii (gut)	Triple helix repeat-containing collagen	75	34	39
*Bacillus cereus** (infection in gut, eye, lung)	Collagen triple helix repeat domain protein	76	40	45
Bacillus thuringiensis (infection in gut, lung)	Triple helix repeat-containing collagen	92	40	46
Brevibacillus brevis (peritonitis)	Collagen like protein	65	42	49
*Clostridium difficile** (infection in gut)	Collagen triple helix repeat family protein	78	42	46

*Bacteria that have been reported to develop reactive arthritis, septic arthritis, or rheumatic symptoms.

Table III. Selected human-associated bacteria that contain human BiP-homologous proteins

Bacteria (Human association)	Protein	Query cover (%)	Identities (%)	Similarities (%)
*Bartonella rochalimae** (bacteremia)	HSP 70 DnaK	95	53	69
*Brucella abortus** (brucellosis)	DnaK	92	54	70
*Borrelia burgdorferi** (lyme disease)	DnaK	93	53	70
*Rickettsia felis** (spotted fever)	DnaK	95	52	68
Prevotella oralis (oral cavity)	DnaK	94	50	68
Atopobium parvulum (oral cavity)	DnaK	95	51	68
Prevotella veroralis (oral cavity)	DnaK	95	50	67
Prevotella nigrescens (oral cavity)	DnaK	94	50	67
Prevotella denticola (oral cavity)	DnaK	95	49	67

*Bacteria that have been reported to develop reactive arthritis, septic arthritis, or rheumatic symptoms.

pathogens such as *Clostridium difficile* and *Bacillus cereus* (20,21) and a member of normal gut flora *C. beijerinckii* (22) are included (Table II).

BiP (also known as 78 kDa glucose-regulated protein or heat shock 70 kDa protein 5), is a stress protein located in the endoplasmic reticulum. Stress proteins are evolutionally highly conserved from bacteria to human. Furthermore, microbial stress proteins are highly immunogenic (23). Therefore, cellular and humoral immune responses initiated by microbial stress proteins may target cross-reactive self proteins, resulting in autoimmunity (24). Among the hundreds of bacterial species that contain a BiP-homologous stress protein DnaK, human pathogens such as *Bartonella spp.*, *Brucella spp.*, *Borrelia spp.*, and *Rickettsia spp.* were found. In addition to the pathogenic bacteria, a number of bacteria in the human oral flora such as *Prevotella spp.* and *Atopobium parvulum* contained the BiP-homologous DnaK. Selective examples of bacterial DnaK listed in Table III have 49～54% identities and 67～70% similarities with the human BiP over 92% of the entire protein.

Glucose-6-phosphate isomerase (G6PI) is a ubiquitously expressed glycolytic enzyme that is also highly conserved through evolution. Selected bacterial G6PIs for several human-associated species present even higher identities (65～68%) and similarities (78～80%) than those observed in the stress protein BiP (Table IV). The human-associated bacteria include both commensals and pathogens that colonize the respiratory tract, urinary tract, or gastrointestinal tract. Given

Table IV. Selected human-associated bacteria that contain human G6PI-homologous proteins

Bacteria (Human association)	Protein	Query cover (%)	Identities (%)	Similarities (%)
Haemophilus sputorum (sputum, throat swab, blood)	G6PI	95	68	80
Providencia rettgeri (gut, opportunistic infection)	G6PI	97	67	79
*Yersinia pseudotuberculosis** (enteritis)	G6PI	97	66	78
Haemophilus parahaemolyticus (pharyngitis)	G6PI	98	66	78
Escherichia fergusonii (urinary tract infection)	G6PI	98	65	79
*Escherichia coli** (gut, urinary tract)	G6PI	98	65	79
Haemophilus haemolyticus (nasophaynx)	G6PI	95	65	80
*Haemophilus influenza** (pneumonia)	G6PI	96	65	79
*Serratia marcescens** (urinary tract infection)	G6PI	97	66	78
*Salmonella enteric** (enteritis)	G6PI	98	65	78
*Shigella flexneri** (enteritis)	G6PI	98	65	78

*Bacteria that have been reported to develop reactive arthritis, septic arthritis, or rheumatic symptoms.

Table V. Selected human-associated bacteria that contain human α-enolase-homologous proteins

Bacteria (Human association)	Protein	Query cover (%)	Identities (%)	Similarities (%)
Fusobacterium sp. CAG:439 (gut)	Enolase	97	55	72
Clostridium sp. CAG:306 (gut)	Enolase	97	55	71
Treponema denticola (oral cavity, periodontitis)	Enolase	99	54	70
Turicella otitidis (otitis)	Enolase	97	53	71
Bacillus smithii (gut)	Enolase	98	53	72
Propionibacterium sp. KPL1844 (Human microbiome project)	Enolase	97	55	70
Propionibacterium acnes (skin, gut)	Enolase	96	55	70
Actinomyces sp. Oral taxon 178 (oral cavity)	Enolase	97	55	69
Neisseria sicca (oral cavity)	Enolase	97	53	69
Clostridium botulinum (food-born infection)	Enolase	97	52	71
Acinetobacter sp. NIPH 542 (gut)	Enolase	97	52	69
*Bacillus cereus** (infection in gut, eye, lung)	Enolase	98	52	71
Brevibacillus brevis (peritonitis)	Enolase	97	51	70
*Neisseria meningitidis** (nasopharynx, meningitis)	Enolase	97	53	69

*Bacteria that have been reported to develop reactive arthritis, septic arthritis, or rheumatic symptoms.

Table VI. Selected human-associated bacteria that contain human hnRNP A2-homologus proteins

Bacteria (Human association)	Protein	Query cover (%)	Identities (%)	Similarities (%)
Variovorax paradoxus (oral cavity)	Rnp-1 like RNA-binding protein	22	34	54
Acidovorax avenae (catheter-related infection)	Rnp-1 like RNA-binding protein	17	38	56
Delftia acidovorans (catheter-related infection)	Rnp-1 like RNA-binding protein	17	38	56

the high degree of similarity between the human and bacterial G6PIs shown in Table IV, it can be speculated that a large body of human-associated bacteria, including those in the normal flora, may share significant homology (greater than 30%) in their G6PIs with the human protein. K/BxN mice spontaneously develop autoantibodies to G6PI and autoimmune arthritis (25). The serum autoantibody titer and autoimmune arthritis in the K/BxN mice are significantly attenuated under germ-free conditions, which are reinstated by the introduction of a single gut-residing species, asegmented filamentous bacteria (26). A homology search revealed that the G6PI of the segmented filamentous bacteria *Candidatus Arthromitus* sp. SFB-mouse-Japan has 40% homology with a mouse G6PI, supporting the role of this bacterium in anti-G6PI antibody production.

The α-enolase is another glycolytic enzyme ubiquitously expressed in the cytosol. It is also expressed on the surface of stimulated leukocytes, and then serves as a plasminogen-binding receptor, which assists in inflammatory cell invasion (27). The similar usage of enolase and plasminogen for the invasion of host tissue has been demonstrated by several pathogens (28). Interestingly, members of the normal flora in the oral cavity and gut express the enolase that shares a high degree of identity (51～55%) and similarity (68～72%) with the human α-enolase (Table V). The enolases of several important human pathogens such as *Treponema denticola, Turicella otitidis, Clostridium botulinum, Bacillus cereus*, and *Neisseria meningitidis* also have high degrees of homology with the human α-enolase.

The hnRNP A2 is an abundant RNA-binding protein that is predominantly expressed inside the nucleus and involved in pre-mRNA splicing, mRNA transport, and translation (29). Although bacteria do not make mRNA, a homology search using the hnRNP A2 retrieved 61 bacterial proteins that share 27～49% identities and 51～73% similarities with the first RNA recognition motif (RRM) superfamily domain of hnRNP A2. Indeed, all retrieved bacterial proteins were RNA-binding proteins. Among them, *Variovorax paradoxus* is a member of the human oral flora, and *Acidovorax avenae* and *Delftia acidovorans* are involved in catheter-related infection (Table VI).

Collectively, bacterial orthologs exist for almost all autoantigens characterized in RA. It is remarkable that most of the pathogenic bacteria listed in Table II～V have been reported to develop reactive arthritis, septic arthritis, or rheumatic symptoms (30-38). Furthermore, there is evidence for the possible involvement of *Clostridium spp.*, and *Prevotella spp.* in the pathogenesis of RA (39). Accumulating evidence suggests that not only infectious but also indigenous microorganisms may be involved in the initiation and perpetuation of RA (39). Increased epithelial permeability, loss of immune tolerance, and trafficking of both microbial components and activated immune cells to the joints have been suggested as underlying mechanisms for the involvement of the indigenous bacteria (39).

CONCLUSION

We explored seven autoantigens for the presence of evolutionary conserved counterparts in the bacterial protein database. Of the seven autoantigens, PR3, CII, BiP, G6PI, α-enolase, and hnRNP A2 have well conserved bacterial orthologs. Importantly, those bacterial orthologs are also found in human-associated bacteria. Although there are no bacterial orthologs for human immunoglobulin gamma-1 heavy chain constant region, proteins with an immunoglobulin superfamily domain are found in bacteria. The wide distribution of the highly conserved DnaK, G6PI, or enolase among the members of the normal flora and common infectious microorganisms rather raises the question on how cross-reactive autoantibodies are not produced during the immune response to these bacteria in most healthy people. Understanding the mechanisms that deselect auto-reactive B cell clones during the germinal center reaction to homologous foreign antigens may provide a novel strategy to treat autoimmune diseases.

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CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

REFERENCES

1. Albert, L. J. and R. D. Inman. 1999. Molecular mimicry and autoimmunity. *N. Engl. J. Med.* 341: 2068-2074.
2. Libbey, J. E., L. L. McCoy, and R. S. Fujinami. 2007. Molecular mimicry in multiple sclerosis. *Int. Rev. Neurobiol.* 79: 127-147.
3. Ang, C. W., B. C. Jacobs, and J. D. Laman. 2004. The Guillain-Barré syndrome: a true case of molecular mimicry. *Trends Immunol.* 25: 61-66.
4. Guilherme, L., J. Kalil, and M. Cunningham. 2006. Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease. *Autoimmunity* 39: 31-39.
5. Hu, N., J. Westra, and C. G. Kallenberg. 2009. Membrane-bound proteinase 3 and its receptors: relevance for the pathogenesis of Wegener's Granulomatosis. *Autoimmun. Rev.* 8: 510-514.
6. Chen, M. and C. G. Kallenberg. 2010. The environment, geoepidemiology and ANCA-associated vasculitides. *Autoimmun. Rev.* 9: A293-A298.
7. Watts, R. A. and D. G. I. Scott. 2012. ANCA vasculitis: to lump or split? *Rheumatology (Oxford)* 51: 2115-2117.
8. Pinching, A. J., A. J. Rees, B. A. Pussell, C. M. Lockwood, R. S. Mitchison, and D. K. Peters. 1980. Relapses in Wegener's granulomatosis: the role of infection. *Br. Med. J.* 281: 836-838.
9. Stegeman, C. A., J. W. Tervaert, W. J. Sluiter, W. L. Manson, P. E. de Jong, and C. G. Kallenberg. 1994. Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. *Ann. Intern. Med.* 120: 12-17.
10. Stegeman, C. A., J. W. Tervaert, P. E. de Jong, and C. G. Kallenberg. 1996. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N. Engl. J. Med.* 335: 16-20.
11. Kain, R., M. Exner, R. Brandes, R. Ziebermayr, D. Cunningham, C. A. Alderson, A. Davidovits, I. Raab, R. Jahn, O. Ashour, S. Spitzauer, G. Sunder-Plassmann, M. Fukuda, P. Klemm, A. J. Rees, and D. Kerjaschki. 2008. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. *Nat. Med.* 14: 1088-1096.
12. Kim, Y. C., J. E. Shin, S. H. Lee, W. J. Chung, Y. S. Lee, B. K. Choi, and Y. Choi. 2011. Membrane-bound proteinase 3 and PAR2 mediate phagocytosis of non-opsonized bacteria in human neutrophils. *Mol. Immunol.* 48: 1966-1974.
13. Pati, A., J. Sikorski, M. Nolan, A. Lapidus, A. Copeland, T. Glavina Del Rio, S. Lucas, F. Chen, H. Tice, S. Pitluck, J. F. Cheng, O. Chertkov, T. Brettin, C. Han, J. C. Detter, C. Kuske, D. Bruce, L. Goodwin, P. Chain, P. D'haeseleer, A. Chen, K. Palaniappan, N. Ivanova, K. Mavromatis, N. Mikhailova, M. Rohde, B. J. Tindall, M. Göker, J. Bristow, J. A. Eisen, V. Markowitz, P. Hugenholtz, N. C. Kyrpides, and H. P. Klenk. 2009. Complete genome sequence of Saccharomonospora viridis type strain (P101). *Stand. Genomic Sci.* 1: 141-149.
14. Wegner, N., R. Wait, and P. J. Venables. 2009. Evolutionarily conserved antigens in autoimmune disease: implications for an infective aetiology. *Int. J. Biochem. Cell Biol.* 41: 390-397.
15. Artandi, S. E., K. L. Calame, S. L. Morrison, and V. R. Bonagura. 1992. Monoclonal IgM rheumatoid factors bind IgG at a discontinuous epitope comprised of amino acid loops from heavy-chain constant-region domains 2 and 3. *Proc. Natl. Acad. Sci. USA* 89: 94-98.
16. Schellekens, G. A., B. A. de Jong, F. H. van den Hoogen, L. B. van de Putte, and W. J. van Venrooij. 1998. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J. Clin. Invest.* 101: 273-281.
17. Song, Y. W. and E. H. Kang. 2010. Autoantibodies in rheumatoid arthritis: rheumatoid factors and anticitrullinated protein antibodies. *QJM.* 103: 139-146.
18. Bateman, A., S. R. Eddy, and C. Chothia. 1996. Members of the immunoglobulin superfamily in bacteria. *Protein Sci.* 5: 1939-1941.
19. Cho, Y. G., M. L. Cho, S. Y. Min, and H. Y. Kim. 2007. Type II collagen autoimmunity in a mouse model of human rheumatoid arthritis. *Autoimmun. Rev.* 7: 65-70.
20. Sammons, J. S., R. Localio, R. Xiao, S. E. Coffin, and T. Zaoutis. 2013. Clostridium difficile infection is associated with increased risk of death and prolonged hospitalization in children. *Clin. Infect. Dis.* 57: 1-8.
21. Bottone, E. J. 2010. Bacillus cereus, a volatile human pathogen. *Clin. Microbiol. Rev.* 23: 382-398.
22. Nakajima, N. and Y. Matsuura. 1997. Purification and characterization of konjac glucomannan degrading enzyme from anaerobic human intestinal bacterium, Clostridium butyricum-Clostridium beijerinckii group. *Biosci. Biotechnol. Biochem.* 61: 1739-1742.
23. Lindquist, S. and E. A. Craig. 1988. The heat-shock proteins. *Annu. Rev. Genet.* 22: 631-677.
24. Rajaiah, R. and K. D. Moudgil. 2009. Heat-shock proteins can promote as well as regulate autoimmunity. *Autoimmun. Rev.* 8: 388-393.
25. Schubert, D., B. Maier, L. Morawietz, V. Krenn, and T. Kamradt. 2004. Immunization with glucose-6-phosphate isomerase induces T cell-dependent peripheral polyarthritis in genetically unaltered mice. *J. Immunol.* 172: 4503-4509.
26. Fan, L. Y., M. Zong, Q. Wang, L. Yang, L. S. Sun, Q. Ye, Y. Y. Ding, and J. W. Ma. 2010. Diagnostic value of glucose-6-phosphate isomerase in rheumatoid arthritis. *Clin. Chim. Acta* 411: 2049-2053.
27. Wygrecka, M., L. M. Marsh, R. E. Morty, I. Henneke, A.

Guenther, J. Lohmeyer, P. Markart, and K. T. Preissner. 2009. Enolase-1 promotes plasminogen-mediated recruitment of monocytes to the acutely inflamed lung. *Blood* 113: 5588-5598.
28. Pancholi, V., P. Fontan, and H. Jin. 2003. Plasminogen-mediated group A streptococcal adherence to and pericellular invasion of human pharyngeal cells. *Microb. Pathog.* 35: 293-303.
29. Hoffmann, M. H., K. Skriner, S. Herman, C. Baumann, C. W. Steiner, C. Ospelt, B. Meyer, A. Gleiss, J. Pfatschbache, B. Niederreiter, J. Tuncel, G. Zanoni, and G. Steiner. 2011. Nucleic acid-stimulated antigen-presenting cells trigger T cells to induce disease in a rat transfer model of inflammatory arthritis. *J. Autoimmun.* 36: 288-300.
30. Prati, C., E. Bertolini, E. Toussirot, and D. Wendling. 2010. Reactive arthritis due to Clostridium difficile. *Joint Bone Spine.* 77: 190-192.
31. Cuchacovich, R., S. Japa, W. Q. Huang, A. Calvo, L. Vega, R. B. Vargas, R. Singh, D. Flores, I. Castro, and L. R. Espinoza. 2002. Detection of bacterial DNA in Latin American patients with reactive arthritis by polymerase chain reaction and sequencing analysis. *J. Rheumatol.* 29: 1426-1429.
32. Maggi, R. G., B. R. Mozayeni, E. L. Pultorak, B. C. Hegarty, J. M. Bradley, M. Correa, and E. B. Breitschwerdt. 2012. Bartonella spp. bacteremia and rheumatic symptoms in patients from Lyme disease-endemic region. *Emerg. Infect. Dis.* 18: 783-791.
33. Hasanoglu, I., T. Guven, Y. Maras, R. Guner, M. A. Tasyaran, and Z. C. Acikgoz. 2013. Brucellosis as an aetiology of septic arthritis. *Trop. Doct.* in press: doi: 10.1177/0049475513512645.
34. Steere, A. C., E. E. Drouin, and L. J. Glickstein. 2011. Relationship between immunity to Borrelia burgdorferi outer-surface protein A (OspA) and Lyme arthritis. *Clin. Infect. Dis.* 52 Suppl 3: s259-s265.
35. Chaudhry, M. A. and R. H. Scofield. 2013. Atypical rocky mountain spotted Fever with polyarticular arthritis. *Am. J. Med. Sci.* 346: 427-429.
36. Leo, J. C. and M. Skurnik. 2011. Adhesins of human pathogens from the genus Yersinia. *Adv. Exp. Med. Biol.* 715: 1-15.
37. Bonet Llorach, M., D. Arnam Fernandez, J. Valles Daunis, J. Maymo Guarch, and H. Carbonell Abelló. 1989. Haemophilus influenza septic arthritis in the adult. *Clin. Rheumatol.* 8: 292-293.
38. Acar, J. F. 1986. Serratia marcescens infections. *Infect. Control* 7: 273-278.
39. Yeoh, N., J. P. Burton, P. Suppiah, G. Reid, and S. Stebbings. 2013. The role of the microbiome in rheumatic diseases. *Curr. Rheumatol. Rep.* 15: 314.