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SPECIAL ARTICLE

Infectomics and autoinfectomics: a tool to study infectious-induced autoimmunity

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The exposome represents all exogenous and endogenous environmental exposures that begin at preconception and carry on throughout life, while the microbiome reflects the microbial component of the exposome. We recently introduced the concept of infectome and autoinfectome as a means of studying the totality of infections throughout life that participate in the induction as well as the progression of autoimmune diseases in an affected individual. The investigation of the autoinfectome could help us understand why some patients develop more than one autoimmune disease, a phenomenon also known as mosaic of autoimmunity. It could also explain the infectious and autoantibody burden of various autoimmune rheumatic diseases. The close interplay between infections and the immune system should be studied over time, long before the onset of autoaggression and autoimmunity. Tracking down each individual's exposure to infectious agents (as defined by the autoinfectome) would be important for the establishment of a causative link between infection and autoimmunity. *Lupus* (2015) **24,** 364–373.

Key words: Autoimmunity; autoimmune disease; environment; infection; immunology; microbiome; genome

General

Microbial pathogens have long been suspected as triggers of rheumatic diseases. In fact, gold salts used to treat infectious diseases in the 19th century were introduced to the treatment of rheumatoid arthritis (RA) based on the hypothesis that the disease was caused by mycobacteria. The significant role of environmental factors for the pathogenesis of autoimmune diseases[1–4] and in particular autoimmune rheumatic diseases[5] was established by genetic studies and epidemiological studies showing certain environmental factors in a proper genetic background can cause a disease.[6] An immune response to a microbial pathogen may result in an autoimmune disease by molecular mimicry, epitope spreading, bystander activation or pathogen persistence.[7,8] Another mechanism by which microbial agents may cause rheumatic diseases is through epigenetic changes.[9] Bacterial pathogens but also commensal bacteria can cause epigenetic modification of host genes, i.e. DNA modification without change in nucleotide sequence and post-translational histone modification, all of which change chromatin configuration and thus accessibility of genes to transcription machinery. For example, intestinal commensal bacteria affect DNA methylation of the Toll-like receptor 4 (TLR4) gene of the host that recognizes the lipopolysaccharide of Gram(−) bacteria.[10] Another means of epigenetic modification is through microRNAs (miRNAs). miRNA is a small (20- to 30-nucleotide long) non-coding RNA that silences the target gene by binding to its messenger RNA (mRNA).[11] Besides endogenous miRNAs, exogenous miRNAs can affect the expression of human genes. For example, miR168a from consumed rice can bind to human and mouse low-density lipoprotein (LDL) receptor protein-1 mRNA and inhibit its translation.[12]

A link between specific infectious agents and autoimmune rheumatic diseases has been established based on epidemiological, immunological,

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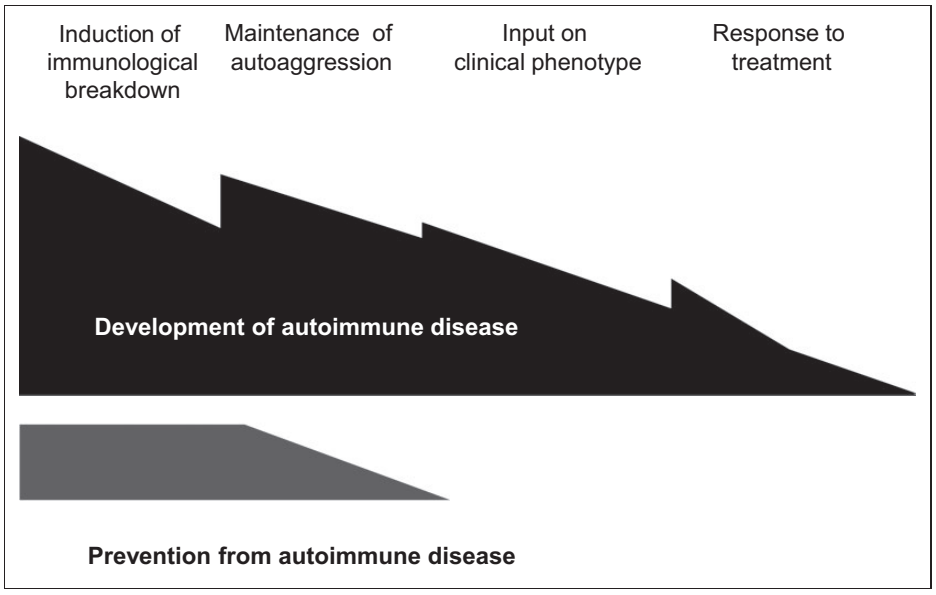

Figure 1 Infections participate in various phases of autoimmunity. This schematic illustration underlines the role of infection at various stages of autoimmunity. Infections are not only participating in the induction of autoaggression and autoimmunity but can also play a role in the maintenance of the loss of immunological tolerance in susceptible individuals. Following the development of full-blown autoimmune disease, infection with specific microbes may alter the clinical phenotype of the disease and its progression over time. Infections may also contribute to the extent by which an individual responds to immunosuppressive treatment. It is generally accepted that the major influence of infections is at the start of the development of autoimmune diseases rather than at later stages. Several studies have underlined the provocative role of infection in preventing rather than provoking autoimmunity, and this cannot be overlooked.

clinical and experimental data. Animal models of diseases have shed light on the role played by exogenous agents. Infection not only participates in the induction of autoimmunity but may also provide a significant input to the maintenance of immunological breakdown. It may also alter the state of disease progression after its onset, including the extent by which the patient responds to immunosuppressive treatment. Experimental studies have also made clear that depending on the timing and the microbe, infection prevents rather than exacerbates autoimmunity (Figure 1). This review focuses on the wealth of data reporting a connection between specific infectious triggers and autoimmunity. We also discuss the role of the infectome and the autoinfectome as tools to study microbial-induced autoimmunity.

RA and infection

RA is an inflammatory polyarthritis with extra-articular features, such as interstitial lung disease, and is associated with increased cardiovascular risk. The concordance rate of RA of around 13% in monozygotic twins and 4% in dizygotic twins suggests that environmental rather than genetic factors play a major role in the development of the disease.[13–16] Cigarette smoking has been linked to several autoimmune diseases,[17] and this as well as and periodontitis are two environmental risk factors known to be associated with RA.[13,14,18,19] Human leukocyte antigen (HLA) genes are the best-studied genetic factors in RA. RA is associated with HLA-DRB1 alleles carrying common amino acid sequences at position 70–74 of the β chain (shared epitope) (HLA-DRB1 SE).[20,21] This suggests that HLA-DRB1 SE alleles on antigen-presenting cells present an arthritogenic peptide to T cells to initiate a Th1 and Th17 immune response that culminates in a cytokine cascade with interferon (IFN)-γ, interleukin (IL)-17, tumor necrosis factor (TNF)-α, and IL-6.[22,23] Alternatively, the HLA-DRB1 SE itself may be the target of an immune response. The HLADRB1 SE is present in the Epstein-Barr virus (EBV) gp110 glycoprotein, and EBV has long been associated with RA.[24]

In recent years, citrullinated proteins have been shown to be the targets of B cells and T cells in RA. Citrulline derives from arginine residues by post-translational modification via the action of peptidyl arginine deiminase (PAD). Anti-citrullinated peptide antibodies (ACPA) appear up to 10 years

before the onset of clinical RA[25,26] and confer strong susceptibility to RA.[26–28] They are present in around 70% of patients with RA, are correlated with the severity of the disease[29,30] and they are associated with the HLA-DRB1 SE.[26–28]

HLA-DRB1 SE alleles recognize citrullinated peptides in RA as citrulline but arginine was not eluted from HLA-DRB1*04:01/04(SE) alleles.[31] Furthermore, increased frequency of CD4(+) T cells recognizing citrullinated vimentin and citrullinated aggrecan was found in the peripheral blood of HLA-DRB1*04:01 RA patients.[31] In addition, oligoclonal expansions of T cells were detected in synovial biopsies from ACPA(+) RA patients compared to ACPA(−) RA patients, as determined by the restriction of complementarity determining region (CDR) 3 length of T cell receptor (TCR).[32] The CDR3 of the TCR is involved in antigen binding.

The two risk factors for RA, cigarette smoking and periodontitis, are probably attributed to protein citrullination and ACPA production. Cigarette smoking is a strong inducer of protein citrullination in a proper genetic background. Tobacco exposure is also a risk factor for ACPA in RA patients carrying the HLA-DRB1 SE.[33] In transgenic mice carrying RA-susceptible HLA-DR alleles, tobacco exposure induces PAD.[34] *Porphyromonas gingivalis*, a microbe that is the major causative agent for periodontitis, possesses PAD that can cause citrullination of both bacterial and host proteins.[35] A citrullinated α-enolase peptide-1 (CEP-1) was identified as a dominant B cell epitope present in 36%–60% of RA patients.[36] Antibodies to human CEP-1 cross-reacted with antibodies to recombinant *P. gingivalis* α-enolase. CEP-1 is highly conserved in prokaryotes and eukaryotes, and there is 100% homology of a 9 amino acid span of the CEP-1 between human and *P. gingivalis* α-enolase.[36] Anti-citrullinated bacterial α-enolase antibodies are detected in ACPA(+) RA patients.[37] *P. gingivalis* DNA was also detected in synovial fluid from RA patients more frequently than controls (15.7% vs 3.5%).[38] Furthermore, *P. gingivalis* DNA can induce IL-1, IL-6 and TNFα production in a monocytic line through TLR9.[39] Therefore, it is plausible that cross-reactivity between bacteria and human citrullinated proteins can break tolerance and induce arthritis. Therefore, HLA-DRB1SE interacts with smoking for the development of ACPA-positive RA.[40–42]

Experimental data support the notion that citrullinated peptides are likely autoantigens for the development of arthritis in RA. Citrullination of proteins and the HLA-DRB1 SE both appear to be required for the development of arthritis: Citrullinated fibrinogen but not unmodified fibrinogen induced arthritis in transgenic mice carrying the HLA-DRB1 SE allele DRB1*0401. In contrast, citrullinated or unmodified fibrinogen could not induce arthritis in wild-type (B6) mice.[43] Also immune complexes with citrullinated fibrinogen stimulates macrophage TNFα production through TLR4 and Fcγ receptor.[44] In collagen-induced arthritis (CIA), a PAD inhibitor reduces the severity of arthritis, an effect that supports a pathogenic role for citrullination and ACPA production in RA.[45] In addition, *P. gingivalis* infection exacerbated CIA, a finding that was dependent on the expression of *P. gingivalis* PAD.[46]

ACPAs may be produced in lymphoid organs or local tissues. Higher expression of PAD2 was detected in bronchial mucosa and bronchoalveolar lavage (BAL) cells in healthy smokers compared to nonsmokers.[47] Levels of ACPAs were also elevated in synovial fluid compared with serum, suggesting antibody production locally in the joints.[27,48] In addition, the majority of synovial membrane immunoglobulin (Ig)G-expressing B cells were specific for citrullinated autoantigens in ACPA(+) RA patients.[49]

The gut microbiome may also affect the immune response in a proper genetic background, as HLA-DRB1*0401 (RA susceptible) transgenic mice do not exhibit the sex- and age difference in gut microbiome that HLA-DRB1*0402 (RA-resistant) transgenic mice exhibit, and have a differential Th17 cytokine gene network.[50]

Systemic sclerosis (SSc) and infection

SSc is a chronic disease characterized by fibrosis of the skin and internal organs, vasculopathy, and activation of the immune system. Vasculopathy takes the form of vasospastic episodes (Raynaud's phenomenon, RP) and fibrointimal proliferation of small vessels. Immune activation is exemplified by a plethora of autoantibodies (autoAbs) detected in sera of SSc patients, and the oligoclonal expansion of T cells in skin lesions.[51] The best known autoAbs in SSc are antinuclear antibodies (ANA), anti-topoisomerase I Abs that are associated with diffuse cutaneous disease, and anticentromere antibodies that are associated with limited cutaneous disease. RP and autoAbs appear years before clinical manifestations of fibrosis, while microvascular damage and autoAbs are independent predictors for the progression of RP to SSc.[52]

The pathogenesis of SSc is incompletely understood.[53] Based on avian scleroderma, it has been suggested that endothelial cell apoptosis is the primary event in the pathogenesis of SSc.[54] The low concordance rate of SSc in monozygotic twins (4.7%) equal to dizygotic twins suggests that environmental factors play the major role in the development of the disease.[55] Molecular mimicry has been suggested as an early pathogenetic mechanism for SSc and several microbes have been implicated, including human cytomegalovirus (hCMV), EBV, endogenous retroviruses, and *H. pylori*.[56] The strongest data hold for hCMV and EBV. Increased levels of serum anti-hCMV antibodies are detected in SSc patients.[57] SSc patients also have Abs against an epitope of the late protein UL94 that shares homology with the novel antigen-2 (NAG-2), present on endothelial cells. Anti-UL94 Abs bind to NAG-2 on endothelial cells and induce apoptosis.[58] NAG-2 is also expressed on human fibroblasts and anti-UL94 Abs bind to fibroblasts, which then acquire a profibrotic phenotype.[59] Furthermore, anti-Topoisomerase I autoAbs share homology with the hCMV-derived UL70 protein. hCMV is associated with increased risk of graft-versus-host disease (GVHD), a condition that develops after bone marrow transplantation and that shares clinical and serological features with SSc.[60] Murine MCV (mMCV) can invade endothelial cells in mice and cause latency and intermittent shedding of the virus. mMCV-infected immunocompromised mice (irradiated IFN-γR−/− mice) exhibit neointima formation with myofibroblast proliferation,[61] a condition reminiscent of SSc vasculopathy.

EBV is another candidate agent. EBV is a lymphotropic virus infecting the vast majority of the adult population. EBV has been found to infect the majority of fibroblasts and endothelial cells in the skin of patients with SSc. Furthermore, EBV activates TLR, transforming growth factor beta 1 (TGFβ1), and endothelin in infected fibroblasts that acquire a profibrotic phenotype.[62] Finally, Parvovirus B19 DNA was detected in the bone marrow of SSc patients but not in controls.[63]

The role of infections was further supported by the inflammasome activation in SSc. In SSc skin fibroblasts there was increased expression of NLRP3 and AIM2 inflammasome proteins, and inhibition of caspace-1 abrogated the secretion of collagens, IL-1β, and IL-18.[64] It should be mentioned that the AIM2 inflammasome is a sensor for cytosolic double-stranded DNA (dsDNA), bacterial DNA and viral DNA.[65]

SLE and infection

Systemic lupus erythematosus (SLE) is a multisystem disease affecting mostly women in the reproductive years (women to men ratio, 9:1) and characterized by a plethora of autoAbs, including ANA, anti-Sm antibodies and anti-Ro antibodies. A 24% concordance rate of SLE in monozygotic twins and 2% in dizygotic twins suggests that both genetic and environmental factors interplay for the development of the disease.[66] EBV has long been suspected to play a pathogenic role in SLE. EBV-IgA antibodies, which are thought to reflect reactivation or re-infection with EBV, were associated with SLE particularly in African Americans.[67,68] Antibodies to EBV nuclear antigen-1 (EBNA-1) and EBNA-2 cross-react with SmD and 60 kD Ro. Furthermore, mice and rabbits immunized with EBNA-1 develop experimental lupus.[69,70]

Other candidate agents include retroviruses. The association of SLE with retroviruses is well recognized.[71] Retroviruses are small viruses that require reverse transcription for their replication. Human endogenous retroviruses (HERV) are retroviruses thought to be trapped in the human genome. Environmental factors, like infections, ultraviolet (UV) light, hormones, stress, and drugs may affect endogenous retroviruses.[71] In EBV latency-infected B cells, there is transactivation of HERV-K18. The *env* protein encoded by HERV-K18 is a T cell superantigen. T cell superantigens bind to the Vβ segment of the T cell receptor and activate a huge number of T cells. Another HERV, HERV3, encodes for an *env* protein expressed in the placenta and shares homology with the Ro antigen. It has long been known that mothers with anti-Ro Abs have an increased risk for fetal heart block (congenital heart block, CHB) and mothers of babies with CHB have anti-HERV3 Abs that bind to sections of the fetal heart.[72]

Epigenetic changes may be another pathogenetic mechanism in SLE. Environmental factors, such as infection, drugs, smoking, and UV light, cause oxidative stress and DNA demethylation of certain genes, such as genes of CD4+ T cells to become autoreactive, proinflammatory cells.[73] CD4+ T cells treated with a DNA methylation inhibitor (5-azacytidine, 5-azaC) overexpress CD11a, perforin, CD40L, CD70 (a B cell costimulatory molecule), and killer cell Ig-like receptor (KIR) and spontaneously kill autologous macrophages and stimulate autologous B cells. Similarly, CD4+T cells from SLE patients overexpress CD11a, perforin (not normally expressed in T cells), CD40L,

CD70, and KIR (not normally expressed in T cells).[71,73] The procainamide and hydralazine drugs, known to induce lupus-like disease, inhibit the DNA methyltransferase Dnmt1 and cause demethylation of CD4+ T cells.[73] Serum proteins from SLE patients are modified by nitration, caused by reactive species of oxidative stress (peroxynitrite, ONOO−).[73] miRNAs also affect DNA methylation in SLE. miR-126 was found to be over-expressed in CD4+T cells from SLE patients and was inversely correlated with Dnmt1 protein levels. Furthermore, over-expression of miR-126 in CD4+ T cells from healthy donors caused hypomethylation and upregulation of CD11a and CD70 and thus over-reactivity of T cells and B cells.[74]

ANCA vasculitis and infection

Vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA-vasculitis) encompasses granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) microscopic polyangiitis, and pauci-immune glomerulonephritis (focal necrotizing glomerulonephritis, FNGN). The main manifestation of ANCA vasculitides is rapidly progressive glomerulonephritis, and the characteristic findings are the presence of ANCA in the sera and the absence of immune deposits in glomeruli (pauci-immune GN). The mechanisms responsible for the induction of these diseases are poorly understood but the role of molecular signaling pathways involving p38 mitogen-activated protein kinase (MAPK) and other kinases is under investigation.[75–77] Classical ANCA's target is the antimicrobial lysosomal enzyme proteinase-3 (PR3) or myeloperoxidase (MPO). A link between ANCA vasculitis and microbes first came from a clinical observation of increased frequency of nasal carriage of *Staphylococcus aureus* in patients with GPA.[78] This has led to antimicrobial treatment of GPA with beneficial results. Antibodies against complementary proteinase-3 (cPR3) was found in GPA and cPR3 has homology with *S. aureus* antigens.[79] A new ANCA recognizes a lysosomal membrane protein-2 (LAMP-2). Patients with FNGN have antibodies to LAMP-2 epitope 41–49 that has 100% homology with FimH, an adhesion molecule present on Gram(−) bacteria. Furthermore, immunization with FimH induced anti-LAMP-2 antibodies and FNGN.[80] Thus FNGN provides a direct link for a molecular mimicry between bacteria and host proteins. ANCA vasculitis is associated with increased formation of neutrophil extracellular traps (NETs). NETs are structures of chromatin with antimicrobial lysosomal proteins, such as PR3, MPO, lactoferin, elastase, and others. Neutrophils while dying (NETosis) extrude NETs to kill bacteria.[81] NETs can provide autoantigens to dendritic cells and activate B cells.[82] *S. aureus* is a strong inducer of NET formation and so are ANCAs.[83]

Revealing new triggers of autoimmunity: from infectome to autoinfectome

Geo-epidemiological, immunological and experimental data have led to the appreciation that specific infectious agents can trigger autoimmunity. However, more recent "out of the box" approaches suggest that more than one infection-inducing destructive immune responses over a period of time are pivotal for the development of autoimmunity. Also, the study of the "microbiome" has provided data to suggest that there is a significant patient-to-patient variability, suggesting that microbiomes are dynamic "fingerprints" that are distinctive for an individual but can change over time depending on environmental challenges. These may include among others microbe-to-microbe interplays. As most autoimmune diseases run long pre-clinical stages, alterations of the microbiome that potentially play a role in the development of autoimmunity need to be documented at various time points. What has not been considered by the approach to investigate the autoimmunity-associated microbiomes is that a better understanding of the infectious agents responsible for the induction of autoimmune diseases requires a better knowledge of the fine specificity of immune responses against infectious antigens. These infectious agents may fall within two categories: the first can be considered that of the "known suspects" while the second one consists of those that are identified only through an "out of the box" approach and can be considered as "unusual or unpredicted suspects." More recent data indicate that individualized infectious burdens are specifically linked to autoimmune diseases.[84–86] While these studies reported several of the suspected infectious triggers, they have also revealed some unexpected ones as potential inducers of autoimmunity. Autoantibody burdens in infected individuals have also been noted[87,88] and the concept of the mosaic of autoimmunity is well accepted in

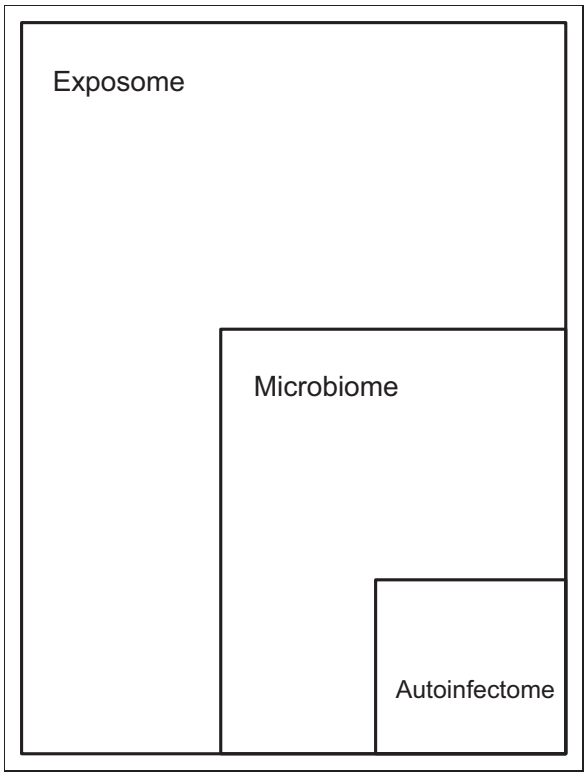

Figure 2 From exposome and microbiome to autoinfectome. Exposome is composed of the infectious (microbiome) and non-infectious (exogenous and endogenous) environmental factors that we are exposed to during our lifetime. The autoinfectome describes the minor part of the microbiome that includes the infectious agents inflicting self-damage and tissue destruction leading to the development of autoimmune disease.

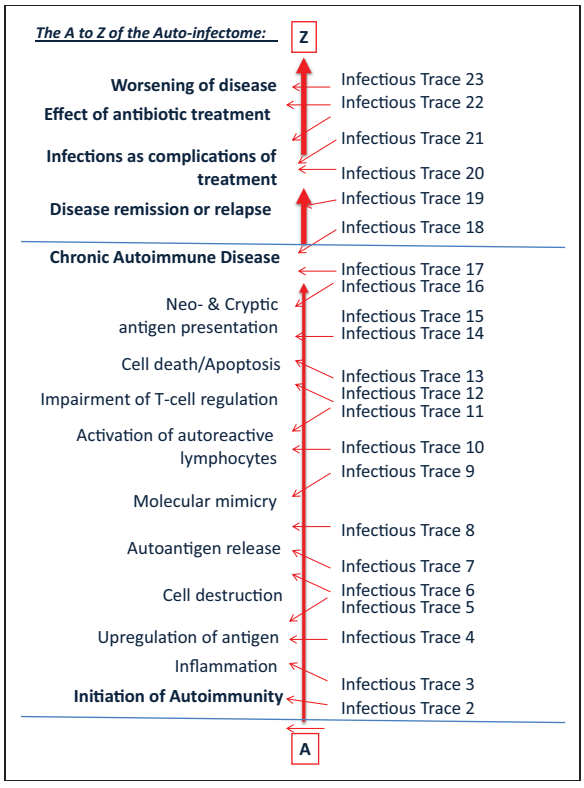

Figure 3 The A to Z of the autoinfectome. The study of the autoinfectome must be performed at various time points over the progression of the autoimmune disease. Ideally, the study must be performed before the onset of the disease, at pre-clinical stages of the disease. At these stages, the investigation of the autoinfectome may reveal the exact agent that is closely linked with an autoimmune disease. For example, the investigation could lead to the recognition of antimicrobial response that cross-reacts with a self-antigen. Such findings could help us to understand whether molecular mimicry is involved in the development of the disease, especially if these cross-reactive responses did not exist in previous assessments. Soon after the development of the autoimmune disease, specific infectious agents unrelated to the development of the induction of the disease may play a role in the appearance of specific clinical manifestations or the presentation of concomitant autoimmune diseases (mosaic of autoimmunity). Infectious traces can be identified at various time points originating from the same or different microbial infections. Other mechanisms leading to autoimmunity such as epitope spreading and others can be linked with specific infectious agents at the time of investigation compared to previous time points, leading to the understanding of the evolution of the autoimmune response and its connection with infections.

modern times.[89–92] Such data have led us to introduce the concepts of ''infectome'' and ''autoinfectome''[93,94] (Figure 2). Autoinfectome is a holistic approach to study and recognize the totality of autoimmune disease-causing infectious agents for a given disease, including the mechanisms that can cause the disease (Figure 3).[94] This approach is entirely different from that usually applied, limited to the concept of a ''single infection causing a single autoimmune disease.'' We are now in a unique position to design studies investigating the role of the microbiome and those infectious agents that can play a role in the development of autoimmunity. Thus, the microbiomes of patients with autoimmune gastrointestinal diseases such as Crohn's disease or ulcerative colitis are well defined. It is also known that the microbiomes of patients with inflammatory bowel disease (IBD) considerably differ from those noted in patients with insulin-dependent diabetes mellitus.[95] These studies can be used as a reference tool to study the role of infection in the induction of autoimmune disease. We may also have a unique opportunity to identify infectious agents that play a protective role conferring resistance to autoimmunity.[96] We need, however, to take into account that gut and oral microbiomes identify all microorganisms in the intestine and in the oral cavity, respectively. Autoinfectomes on the other hand will be the

Table 1 An overview of multiparametric systems that can be used for the study of the autoinfectome-related infectious agents using multiparametric technology[97–99]

Immunological assays	• Multiparametric ELISA, line blots/dots • Multiparametric IFA chips • Magnetic and non-magnetic bead multiplex immunoassays • Lateral flow immunochromatographic assays • Triplex lateral flow immunoassay • Optical immunosensor systems • Electrochemical-based ELISA
	Molecular detection
Multiplex real-time PCR	• Real-time PCR and highly specific melting point analysis (approximately 25 pathogens)
Molecular hybridization	• Simultaneous detection of multiple viral types and subtypes from nasopharygeal swabs and simultaneous detection of viral, bacterial, and protozoan parasites causing gastrointestinal diseases are commercially available
Nucleotide sequencing	• Nucleotide (pyro)sequencing • Next-generation sequencing (highly massive pyrosequencing technology, sequencing by synthesis (SBS), sequencing by oligonucleotide ligation and detection (SOLiD) system
Mass spectrometry	• Post-culture microbial identification by MALDI-TOF
Integrated fluidic systems	• Post-PCR microbial identification by PCR-ESI

ELISA: enzyme-linked immunosorbent assay; IFA: immunofluorescence assay; PCR: polymerase chain reaction; MALDI-TOF: matrix-assisted laser desorption/ionization-time of flight; PCR-ESI: polymerase chain reaction-electrospray ionization.

minor parts of the respective microbiomes that are specifically associated with individual autoimmune diseases such as IBDs or autoimmune rheumatic diseases including RA and SSc.

Autoinfectome: who to screen—how to test

Ideally, studies investigating the autoinfectome must be performed using serum samples or peripheral blood mononuclear cells collected over time, long before the onset of overt autoimmune disease. Also, groups that could be screened are those including individuals who are at risk of developing autoimmune disease, like individuals with an HLA type conferring risk for a given disease or siblings and other family members of affected individuals. This assessment can delineate which microbial agents are responsible for disease development and/or progression. It could be possible to identify those agents that are associated with specific clinical phenotypes. Thus, studying those diseases that are characterized by frequent relapses/remissions could be a good start for the investigation of the autoinfectome.[94] Investigation of infectious agents would be based on biological material stemming from blood as well as urine, saliva or stools. Isolation of tissue-specific lymphocytes from the affected tissue would be an ideal source for the study of the infectome. Serological tests for IgA, IgM and IgG antibody detection against microbes, viruses, and fungi could reveal infectious burden linked to specific autoimmune rheumatic diseases. Particular interest must be given to the monitoring of seroconversion of antimicrobial antibody responses from IgM to IgG over time. Antibody tests widely used for such testing are now based on multiparametric analysis protein micro-arrays as illustrated in Table 1. Detection of viral and bacterial genetic material in tissues by a multiparametric approach is currently in use and can be useful for this type of studies. High-throughput DNA sequencers allow the determination of hundreds of megabases of DNA sequences per run and can assess a broad range of infectious agents. Massive, parallel sequencing is a very sensitive technology and permits the detection of various infectious agents. Multiplex polymerase chain reaction (PCR) technologies have become available and their cost is reducing over time. Also, 16S/18S ribosomal RNA (rRNA) gene sequencing allows the mass-analysis of biological samples.

In the near future and with the advent of new technological platforms, the study of the infectome will become less costly, leading to a new era of studies investigating infectious-triggered autoimmunity. Genome-wide association studies are a good example of how cutting-edge technology has changed the way that we understand the influence of genetic parameters in autoimmunity. The time has come for ''microbe-wide association studies.''

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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