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ETIO PATHOGENESIS OF AUTOIMMUNITY

Tracing environmental markers of autoimmunity: introducing the infectome

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Abstract We recently introduced the concept of the infectome as a means of studying all infectious factors which contribute to the development of autoimmune disease. It forms the infectious part of the exposome, which collates all environmental factors contributing to the development of disease and studies the sum total of burden which leads to the loss of adaptive mechanisms in the body. These studies complement genome-wide association studies, which establish the genetic predisposition to disease. The infectome is a component which spans the whole life and may begin at the earliest stages right up to the time when the first symptoms manifest, and may thus contribute to the understanding of the pathogenesis of autoimmunity at the prodromal/asymptomatic stages. We provide practical examples and research tools as to how we can investigate disease-specific infectomes, using laboratory approaches employed from projects studying the "immunome" and "microbiome". It is envisioned that an understanding of the infectome and the environmental factors that affect it will allow for earlier patient-specific intervention by clinicians, through the possible treatment of infectious agents as well as other compounding factors, and hence slowing or preventing disease development.

Keywords Autoimmunity · Autoimmune disease · Environment · Infection · Immunity · Microbiome

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Abbreviations

AMA	Anti-mitochondrial antibody
ANA	Anti-nuclear antibody
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
EBV	Epstein–Barr virus
EWAS	Environmental-wide association study
FDR	First-degree relatives
GWAS	Genome-wide association study
HHV6	Human herpesvirus 6
LC–MS/MS	Liquid chromatography–tandem mass spectrometry
MS	Multiple sclerosis
IBS	Irritable bowel syndrome
PBC	Primary biliary cirrhosis
PCR	Polymerase chain reaction
PDC	Pyruvate dehydrogenase complex
SLE	Systemic lupus erythematosus

Introduction

We recently introduced the concept of the infectome as a means of studying all infections throughout life which contribute to the development/progression of disease [1], as it is now viewed that the majority of diseases develop as a result of the interaction between genetic and environmental influences [2–4]. Autoimmune diseases are especially seen to be caused by this interaction [2, 3, 5]. It is now estimated that approximately 5–20 % of North Americans are affected by at least one autoimmune disease [6, 7]. The mosaic of autoimmunity is a concept which reflects the fact that many patients with one autoimmune disease have several concomitant autoimmune diseases at any given time with heterogeneous triggers and aetiological factors [8–15].

Much attention has been given to genetic research on the path to uncovering the underlying factors of autoimmunity [16]. In addition to molecular signalling pathways [17], genome-wide association studies (GWAS) have identified numerous gene–disease associations in several autoimmune diseases [3]. The essential number of associated genes needed for the maintenance of autoaggressive responses and the development of clinically overt disease has not been properly delineated [18]. However, environmental factors, possibly occurring even in utero, must be given equal attention in the study of the nature of autoimmune disease [2, 3, 19, 20]. Epidemiological and clinical studies using toxicological, microbiological, biochemical and immunological testing are now being used to identify these diverse environmental factors, which include infectious organisms, xenobiotics, chemical compounds and heavy metals, although the list of materials may be exhaustive [2, 21–24]. Autoimmune (autoinflammatory) syndrome induced by adjuvants (ASIA) is one example where vaccinations and heavy metals have been implicated as triggers of autoimmunity. Recent news regarding the role of prosthetic metal on metal hip replacements has also shown how immune dysfunction and damage can be caused in distant organs due to the release of metals such as chromium and nickel from such prostheses. Recent findings from the National Institute of Environmental Health Sciences workshop on autoimmunity and environment support these findings and have reported significant evidence linking particular autoimmune disease to specific environmental agents [25, 26].

The exact interaction of these exposures and their interplay with genes that confer susceptibility remains poorly defined. It should also be noted that some common mechanisms may underlie the development of all or most autoimmune diseases, with subsequent exposures differentiating one disease from the other [27].

The concept of an "exposome" is being used as a means of collating and measuring the effects of environmental factors, both internal and external. These factors may be responsible for increased susceptibility to a disease, or protection from developing the disease. The internal factors include the balance of the flora in the microbiome, the nutritional status of the individual such as vitamin D levels and balance of essential fatty acids, the state of the antioxidant pathways that protect against the deleterious effects of free radicals generated during infective episodes, as well as factors relating to immune function/balance such as the health of the endocrine axis. This review will emphasise the role of the "infectome" as the infectious component of the microbiome/exposome which contributes to the development of autoimmune disease. As the infectome could broadly describe the infectious components of the exposome responsible for the induction of non-autoimmune in addition to autoimmune diseases, we may need to differentiate the "autoinfectome" from that not related to autoimmunity. In other words, there may be particular components that are only seen in autoimmune disease, and possibly certain features common to all autoimmune diseases.

Overview of the exposome

The exposome represents all exogenous and endogenous environmental exposures which begin preconception and carry on throughout life [28–32]. The endogenous factors are unique to the exposome as compared to previous epidemiological studies [30]. The study of the exposome addresses both external triggers and endogenous factors directly or indirectly linked to the environment [31, 32]. By-products of inflammation, lipid peroxidation, as well as oxidative stress are examples of endogenous sources [30]. Several of these constituents serve as nucleophiles or electrophiles and are capable of DNA and protein modification [33], which may also occur due to bacterial infection [34–36]. It is likely that the collation of these components would be unique to a disease, much like GWAS [33]. Also akin to GWAS, quantification of exposure may be a critical piece of information.

It may be clinically useful to look at causes within an individual in terms of exposure, times of exposure, sequence of exposure, time-points of exposure events, as well as other risk factors (genetic, epigenetic and other) that induce or maintain an inflammation state and exposure to various stimuli that provoke further autoaggression. If these exposures could be examined independently, they may help identify the pieces of the jigsaw puzzle that lead to the breakdown of tolerance and the induction of pathological alterations as the result of the autoimmune attack. Components of the exposome may also serve as measurable biomarkers [33] in the blood or body fluids of affected

patients or individuals prone to develop autoimmune diseases [4, 31–33]. Technologies such as liquid chromatography–tandem mass spectrometry [37], DNA adducts [38], functional measurements of antioxidant capacity and breath analysis may be utilised in such instances [29].

Two methods of exposomal measurement have been proposed: the "bottom-up" method which measures the external factors [30] and the "top-down" method which measures internal factors. Both methods may provide the whole picture of a measurable exposome when they are used in conjunction with extensive questionnaires and other established epidemiological tools [30–32]. Frequent sampling could provide evidence of significant changes of these markers over time, especially during critical phases of the disease (sub-clinical course, remission, relapses) [30]. One such study indicated that breath analysis for particular biomarkers provides critical information as to whether one has been exposed, what the dosage was, and how rapidly the body is eliminating the toxicant [29]. The plausibility of the exposome has been demonstrated by Patel et al. [39]. These investigators conducted an "environmental-wide association study" on late diabetes mellitus, where epidemiological data were systematically assessed with methodologies comparable to those used in GWAS, and found associations with 37 environmental factors, including organochlorine pesticides, nutrients/vitamins, polychlorinated biphenyls and dioxins [39]. Other studies have demonstrated similar results on an immunological cross-reactivity level [40] [41]. The complexity and breadth of these components would suggest that breaking them down into multiple components may allow for more in-depth analysis [1].

There is no need to underline how difficult it would be to trace down all these highly heterogenous triggers. Homogenous technology platforms suffer from limitations, as all human biomarker measurements are subject to inter- and intra-subject variance. The creation of a uniform platform that will incorporate and analyse the obtained data would be a milestone, even in the age of ultra-fast computing. Breaking down the heterogenous and highly diverse components could be a more logical step. Screening for the presence of individual infections is routinely used in a small scale [31]. Medium-scale multi-parametric immunoassays for antibodies of various isotypes specific to bacterial or viral antigens, urine and stool cultures and polymerase chain reaction (PCR) are also used in larger laboratories and provide a wealth of information [31]. The ultimate step would be to go a step further and introduce technological platforms that enable high-scale testing of dozens—if not hundreds—of infectious agents at one time, similar to what has been achieved for genes through GWAS. Other functional tests that are available within the realm of scientific research may be brought into clinical and epidemiological use. Examples of these include functional assays of antioxidant pathways, tests of immune sensitivity designed for environmental factors as opposed to biological antigens, DNA adducts, assessment of methylation status and assessment of cellular membrane structure to name but a few.

From exposome- to infectome-induced autoimmunity

Infectious and non-infectious agents comprise environmental triggers [5, 42–46]. Non-infectious triggers are numerous, and some examples from our literature search can be found in Table 1 [42, 47–75]. An infectious burden in autoimmunity has been documented and the triggers are numerous, including bacteria, viruses, parasites and fungi, with variations on particular organisms being found from one autoimmune disease to the next [5, 76, 77]. Geo-epidemiological, microbiological and immunological data indicate the existence of infectious burdens varying from one autoimmune disease to another. Autoantibody burdens in infected individuals have also been noted, but these individuals have not been followed-up for long and it is not know how many of those could develop autoimmune disease [78]. We define the group of disease-causing or disease-linked infections as the "infectome". Alterations in the presence of these organisms or the body's immune response to them would also be noted, such as in the case of treatment with antibiotics [79, 80] or exposure to xenobiotics [81–83]. Such exposures may alter the disease course or its progression by altering the flora present. In contrast to the hygiene hypothesis which supports a protective role played by infections [84–88], work on clinical biomaterial and experimental animal models of autoimmune diseases clearly demonstrates that infectious agents break immunological tolerance to self-antigens and can induce autoimmune disease [5]. Examples include acute rheumatic fever presenting several weeks after infection with *Streptococcus pyogenes* [89], *Helicobacter pylori* and autoimmune gastritis [90], as well as between *Trypanosoma cruzi* and Chagas' cardiomyopathy [91], and *Mycoplasma* with rheumatoid arthritis [92]. These exposures likely begin as early as the transfer of maternal antibodies via the placenta or via breast milk in the gastrointestinal tract, but it is important to identify which of these exposures contributes to the development of disease. It is also important to highlight differences with the microbiome, which identified all microorganisms in a particular region, but is unable to identify those which cause (or protect from) the development and/or progression of a disease. It is also a measure which occurs at a single time point, and thus, only gives a snapshot of which organisms are present throughout a lifetime. Likewise, environmental factors may

influence the development of autoimmunity by infectious agents through several routes. The co-expression of xenobiotics or metals, such as nickel, aluminium or mercury, for example, which are now ubiquitous in our environment and a constant part of the human exposome, may act as adjuvants to the immune system. If this occurs in anatomical positions, such as the oral cavity, which is key to the development of oral tolerance through various dental interventions, it may have vast ramification for the development of immunity and autoimmunity. Likewise, the effects of metals have not been fully studied on the human gut microbiome. Potential damage to the gut microflora has potentially extensive implications for the protective role of these floras against pathogen invasion as well as the interactions of the microflora with the mucosal-associated immune system. Mercury is well known for its immunomodulating effects and is frequently used in experimental models for inducing immune reactions (e.g. mercuric chloride model for vasculitis). It also is known to have immunosuppressive effects, and this in its own right may impair the immune system's response to infections (Fig. 1).

Moreover, induction of autoimmunity by viruses or bacteria is probably done by a "hit-and-run" mechanism when the causative agent has been cleared from circulation by the time of diagnosis. Tracking down each individual's exposure to infectious agents as well as anti-microbial immune responses may be important for the establishment of a causative link between infection and autoimmunity. The infectome allows for the analysis of affected tissue not only at the time of overt infection, but also allows for the analysis of humoral and cellular immune responses to that infection, possibly some time after the causative organism has been cleared. Hence, the infectome allows for the ongoing surveillance of infection, response and possible change in clinical course. When done in several individuals over time, a particular disease "fingerprint" may be established in relation to triggering infectious agents (Fig. 2).

It is envisioned that the infectome would be most helpful in autoimmune diseases with long subclinical stages and frequent remission–relapse states such as multiple sclerosis (MS), primary biliary cirrhosis (PBC), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [93]. Highly specific antibodies appear years before the onset of symptoms in most of these diseases [94–96]. Reasons underlying relapse–remission in these diseases are unknown, making them ideal candidates for the investigation of the infectome.

Table 1 Environmental agents associated with the development of autoimmune disease

Environmental triggers	Disease	Reference
Allopurinol	Immune haemolytic anaemia	[65]
Captopril	Autoimmune thrombocytopenia	[66]
Chlorpromazine	Anti-phospholipid syndrome, haemolytic anaemia, SLE, AiLD	[67–73]
Estrogens	PBC, SLE, RA	[149–152, 310–314]
Halothane	AIH	[72, 315, 316]
Iodine	Autoimmune thyroid	[57]
Penicillins	AiLD, immune haemolytic anaemia	[72, 317]
Rifampicin	AIH, autoimmune thyroid, immune haemolytic anaemia	[318–320]
Tetracyclines	AIH, DM, SLE	[74, 321–330]
Vaccinations	PBC, AIH, SLE, RA, MS, MG, DM, polyarteritis nodosa	[270, 331–343]
Smoking	PBC, COPD, RA, autoimmune thyroid	[149–152, 344–349]
Silicone and collagen implants	SLE, Sjogren's, SSc	[347, 350–356]

This table provides examples of several non-infectious agents which have been associated with the development of autoimmune disease. These agents are highly varied and range from pharmacological materials to waste products and cigarette smoke. Note that this list is not extensive, but serves to give examples from a variety of sources

AIH autoimmune hepatitis, *AiLD* autoimmune liver disease, *COPD* chronic obstructive pulmonary disease, *DM* dermatomyositis, *MG* myasthenia gravis; rheumatoid arthritis, *SLE* systemic lupus erythematosus, *SSc* systemic sclerosis

SLE as an infectome model

Systemic lupus erythematosus is often characterised by a prodromal stage of anti-Sm and anti-Ro antibody responses with no clinical signs [97, 98]. Many first-degree relatives of SLE patients also have ANA reactivity, predominantly anti-dsDNA and anti-Ro/SSA antibody reactivity [99–101]. Published data have suggested that high ANA titre, anti-dsDNA, anti-Ro/SSA and anti-chromatin may be of prognostic relevance for the subsequent development of SLE [99]. It is unknown why some, but not all, individuals go on to develop clinical SLE, with disease flares [21]. Multiple infectious factors have been involved in the pathogenesis of SLE, ranging from EBV and cytomegalovirus (CMV) to parvovirus B19 [43, 97, 98, 100–106]. In the case of CMV, for example, one study found that all female patients with SLE are infected with CMV compared to 75 % of controls [104]. Another study reported that the pp65 antigen of CMV induces autoantibodies in SLE patients and mice prone to develop autoimmune disease [107]. It must be noted that the transient nature of these viruses may influence the detection rates within individuals. Hence, it is

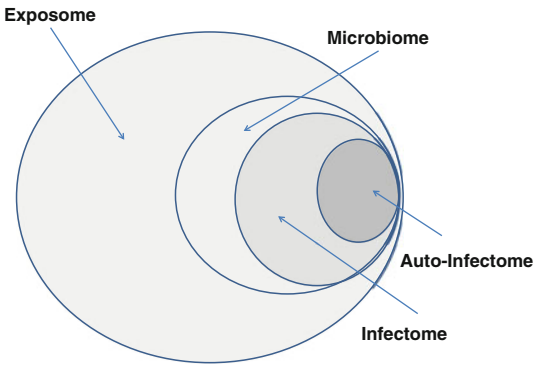

Fig. 1 From exposome to infectome via microbiome. "Exposome" describes all environmental factors which we are exposed to in a lifetime, both exogenous and endogenous, infectious and non-infectious. Environmental exposures are basically subdivided into infectious and non-infectious agents. The concept of "infectome" that we introduce describes the part of the exposome which refers to the collection of an individual's exposures to infectious agents participating in the pathogenesis of autoimmune disease ("auto-infectome"). The infectome can be considered a part of "microbiome", the collection of the microbial products which the human body is exposed to at a given time

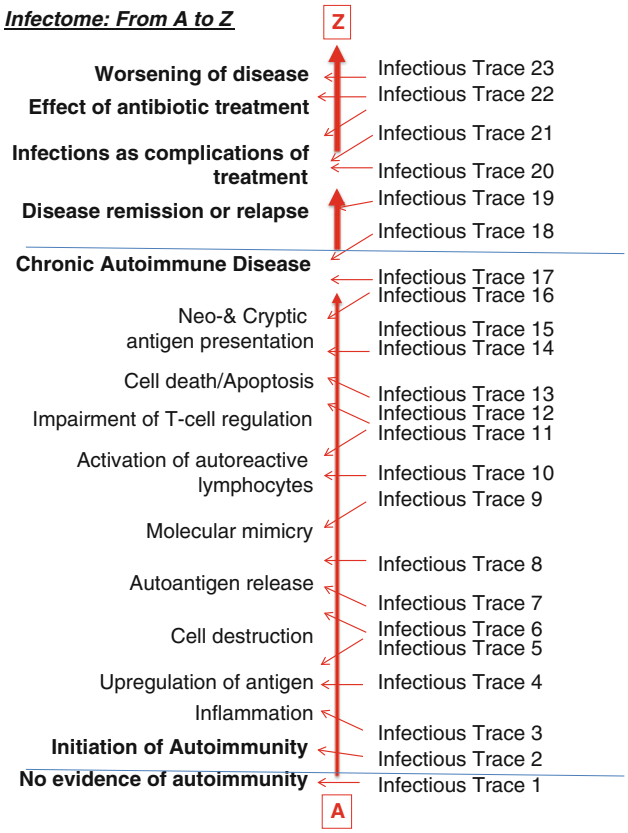

Fig. 2 The infectome from A to Z. The study of the infectome at various time-points in both sub-clinical and clinically overt disease can provide hints regarding the mechanisms leading to the loss of immunological tolerance. Infectious agents unrelated to the development of the induction of the disease may play a role in the appearance of concomitant autoimmune manifestations/diseases or specific clinical patterns (relapses/remission)

difficult to say whether the virus was present at a particular time frame of the disease. It is possible that SLE and/or SLE flares can develop after infection with specific agents, and the study of the infectome can serve as a model to study the role played by infections in such cases. First-degree relatives of SLE patients or other individuals at high risk to develop the disease such as those with autoantibody positivity may be screened at regular follow-ups. SLE patients would also be checked, and alterations of clinical phenotypes may be associated with exposure to particular infectious agents. Comprehensive analysis of the data initiated by the infectome may narrow-down the large list of organisms implicated in disease's development.

Multiple sclerosis and infectome

Multiple sclerosis, a chronic autoimmune neurological syndrome, serves as another prototype autoimmune disease in which the infectome model can be assessed, as it is characterised by periods of relapse and remission [108, 109]. It is likely that several risk factors accumulated over a long period of time are responsible for the development of the disease [110–112].

The relapsing–remitting form of MS is most common and is characterised by flares that include the worsening of previous/current symptoms and the development of new ones [113]. Flares are followed by complete or partial recovery, with a variable period of duration from one patient to the next, and several patients acquire secondary progressive MS. Primary progressive MS (PPMS) is a form of MS characterised by stable progression of the disease with worsening of the symptomatology over the course of time. Two further forms of the disease are also found: the benign form characterised by minimal or mild progression of disability and full recovery of sporadic sensory episodes [113], and the Marburg variant of MS, a rapidly progressive disease, which eventually leads to death. It is currently unknown as to why these clinically distinct variants exist within one disease [113].

Pathologically, MS is characterised by inflammatory lesions with areas of demyelination in the CNS, which consist of mononuclear cell infiltrates composed of T and B lymphocytes, plasma cells, macrophages and microglia in the perivascular spaces that develop into plaques [108, 114].

Multiple sclerosis has a strong genetic background, as identical twins are 100 times more likely to develop MS if their co-twin has MS, whereas non-twin siblings are 20 times more likely [115, 116]. Previous studies have demonstrated that the strongest genetic association of MS is

with HLA-DRB1*1501 [117], though GWAS studies [109] have also implicated non-HLA immunomodulatory genes, including IL7R, IL12RA, CLEC16 and CD226 [118, 119]. In support of a pivotal role for environmental influences in the development of MS is the fact that MS-related implicated genes have only demonstrated an odds ratio of less than 1.3 and that there is a 30 % concordance for MS twins [108, 109, 120, 121] (Table 2).

Vitamin D appears to be a non-infectious agent that is involved in the induction of MS and other autoimmune diseases [109, 122–134]. Vitamin D appears to play a role in the modulation of pro-inflammatory pathways and T cell regulation [109]. Increased distance from the equator has been correlated with low vitamin D, and interestingly, MS rates increase as distance from the equator increases [108]. As well, populations with increased dietary vitamin D intake have lower rates of MS [109]. An Australian study found a decreased risk of a first demyelinating event in those with increased sun exposure, who also had increased levels of serum vitamin D [135]. This has also been found in other studies [136]. As well, the effect of month of birth on MS development was more apparent in familial MS groupings, suggesting an influence on prenatal vitamin D levels, as well as an interaction between genes and environment [109]. Smoking has also been associated with MS development [137]. Smoking appears to have an interaction with genetic features (so-called gene–environmental interactions) and in particular with HLA-DRB1*15 and the absence of HLA-A*02, which appears to increase the risk of developing MS [138]. Heavy metals may also play a role in some MS patients [139]. Several bacteria and viruses have been implicated in MS (Table 3) [108, 109, 120, 121, 140, 141], including EBV [108, 109, 120, 121] and human herpesvirus 6 (HHV6) have been implicated. Interestingly, the relapse–remittance pattern of HHV6 is similar to the clinical phenotype of MS [109], and HHV6 reservoirs have been demonstrated in serum, CSF [142, 143] and CNS tissues of patients with MS [144, 145]. Molecular mimicry involving myelin basic protein and HHV6 encoded U24 mimics, and T cell cross-reactivity has been documented [146]. Other implicated viruses include coronaviruses, varicella zoster virus, Torque teno virus, retroviruses and JC virus [108, 109, 120, 121]. Reactivity to several viral peptides was found, which has led to the speculation that continual exposure to a variety of viruses can lead to T cell expansion reactive against highly conserved proteins, including self-peptides [147].

In addition to providing answers to the aetiology of autoimmune disease, it is also envisioned that the infectome may also identify the cause of certain disease characteristics, such as variable presentation and progression, disease flares, or relapse–remittance.

Table 2 Infectious agents implicated in multiple sclerosis

Strong evidence base		Weak evidence base	
Epstein–Barr virus	[357–372]	*Chlamydia pneumoniae*	[373]
Human herpesvirus 6	[142–146, 374, 375]	*Borrelia burgdorferi*	[376]
Varicella zoster virus	[377–379]	*Mycobacterium tuberculosis*	[380]
		Human cytomegalovirus	[381]
		Retroviruses	[382, 383]
		Coronavirus	[384, 385]
		Torque teno virus	[147]
		JC virus	[386, 387]
		Rubella virus	[388]
		Parainfluenza virus I	[389]
		Measles virus	[390, 391]
		Mumps virus	[392]

Several infectious agents have been implicated in the pathogenesis of multiple sclerosis (MS), but few have a strong evidence base. Interestingly, only viruses appear to be strongly linked with the disease, whereas several viruses and bacteria have weak or circumstantial associations. It may be the case that several of the infectious agents with a weak evidence base reflect the lack of investigation into these organisms. As well, it is unclear as to whether any of these infectious agents also play a role in the relapsing–remitting course of the disease. By applying the infectome model, it will likely be easier to define which of the organisms listed below (and likely more) are involved in the development and progression of MS, as well as possibly defining particular subtypes of the disease

Primary biliary cirrhosis and infectome

Primary biliary cirrhosis can also be used as a model disease to investigate the role of the infectome [148]. This is largely based in its relatively common (as far as autoimmune disease go) prevalence, its long preclinical phase with positivity for antimitochondrial antibodies (AMA) that are pathognomonic for the disease, its differing progression among patients, and growing evidence for an involvement of genetic, environmental and infectious pathogenetic factors [149–157]. Clinical, histopathological and experimental data support that the disease is autoimmune [94, 153, 158–178]. Infectious agents and xenobiotics mimicking the autoepitopic region of PDC-E2, the major PBC self-target, induce PBC-specific autoantibodies and bile duct destruction.

Primary biliary cirrhosis is characterised by a long preclinical phase of AMA positivity with no biochemical evidence of liver disease, which is followed by a period of

Table 3 Infectious agents implicated in primary biliary cirrhosis

Bacteria	*Escherichia coli*	[170, 172, 256, 258, 393, 394]
	Novosphingobium aromaticivorans	[172, 393]
	Mycobacterium gordonae	[395–397]
	Lactobacillus delbrueckii subsp. bulgaricus	[250, 270]
Viruses	*Betaretrovirus*	[263, 267, 398, 399]

This table provides examples of infectious organisms which have been implicated in the pathogenesis of primary biliary cirrhosis (PBC). Although several organisms have been implicated, we have only included those which appear to have strong evidence base so far, based on multiple studies and case reports. Many implicated pathogens have not been studied in any great depth so far

biochemical abnormalities and then clinically overt disease. The disease has a long preclinical phase which may take several years. Most sera from patients with PBC have AMA at diagnosis [95, 169, 178–204], which is also predictive of eventual disease development [205]. PBC is also characterised by disease-specific anti-nuclear autoantibodies (ANA) that identify patients with worst disease [206–221]. Familial PBC has been noted and the risk of developing PBC is high amongst family members of PBC patients [222–228]. Most patients with PBC also have other extra-hepatic disease, including autoimmune rheumatic diseases, and autoimmune thyroiditis.

An interesting feature of PBC is that it does not respond to immunosuppressive treatment, which eliminates the need to consider the effects of immunosuppressive therapy on relapse/remission states, thus making PBC ideal for an infectome study.

A "bottom-up" approach has been taken in various epidemiological studies examining associated risk factors and has identified several environmental factors [149–152] [153–156, 229]. This has been associated with animal models [153, 230–234].Genetic risks involve HLA [235, 236], non-HLA [237–243] and sex-linked genes [244–246]. It is likely that some genetic factors may influence the potential penetrance of infectious agents. For example, HLA-DRB1*11 and HLA-DRB1*13 have a negative association with PBC. It is of interest that such genes confer protection to hepatotropic viruses, such as hepatitis B and C. This highlights the notion that the infectome and GWAS (and likely all exposome components) cannot be studied in isolation. Various pathogens are linked with PBC including *E.coli* due to a link with UTI (Table 2) [158, 176, 244, 247–270]. Microbial/self-molecular mimicry has been proposed as a bridge linking infections and autoimmunity [158, 176, 247–251, 255, 265, 266, 270–276].

Approaches to study the infectome

We have previously outlined how the infectome may be studied [1]. In brief, this would involve several steps, beginning with the determination of HLA class I and II, ideally at birth. This may allow for subgrouping individuals into high- or low-risk groups. Second, urine, oro-nasal swabs, saliva, faecal material and blood (for isolation of plasma, serum and peripheral blood mononuclear cells—PBMCs) would be collected, with once-yearly follow-ups with collection of samples. Meticulous recording of clinical data and collection of samples are needed when anti-infective treatment is applied for incidental/casual infections at the preclinical stages of the disease, as this may affect the final outcome of the underlying processes. All samples would be stored and then analysed for associated infectious agents and non-associated agents using multiplex technology (Table 4). This type of regular follow-up and sample collection with analysis would occur throughout the disease, paying close attention to the findings at times of change in clinical course, such as the development of symptoms.

It should be kept in mind that several patterns of infection may be seen in individuals with a particular disease characteristic or with a particular concomitant autoimmune disease. For example, a differing pattern of infection may be seen in patients with fast-progressing versus slow-progressing PBC. This of course applies to all autoimmune diseases.

Can we learn from the microbiome and immunome projects?

As described above, the microbiome and infectome are two distinct, yet complementary entities. The microbiome is region/organ-specific (such as the gut, oral cavity or inguinal crease), where microbial genes are found to be prevalent [277–286]. It provides a snapshot of the flora of that region in a particular state in time and often reflects what would be termed normal flora by performing metagenomic screens of bacterial populations in these regions. The microbiome is not necessarily limited to normal flora, but may also be applied to a disease-affected body site, such as the gastrointestinal tract in children with irritable bowel syndrome (IBS) [283]. Saulnier and colleagues [283] obtained 71 faecal samples from 22 children with IBS and 22 healthy children aged 7–12 years. Analysis showed an elevated percentage of γ-proteobacteria in the gut flora of children with IBS, with *Haemophilus parainfluenza* being a prominent component [283]. Although similar, the infectome relates only to those organisms

Table 4 Multiparametric systems for the diagnosis of autoimmune-related infectious agents can be based on the technology currently used for the multiparametric detection of systemic infections [290–292]

Molecular detection	
Multiplex real-time PCR	Real-time PCR and higly specific melting point analysis, e.g., LightCycler Septi*Fast* (25 pathogens)
Molecular hybridisation	Commercially available platforms are already in use, e.g., simultaneous detection of multiple viral types and subtypes from nasopharygeal swabs and simultaneous detection of viral, bacterial and protozoan parasites causing gastrointestinal diseases
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
	Post-PCR microbial identification by PCR-ESI
Integrated fluidic systems	
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

which are disease causing and is not limited to one body site.

It may be argued that the organisms of the human microbiome do not usually induce antigen-specific systemic humoral and cellular immune responses provoking local or systemic inflammatory response, while others believe that these organisms may not be pathogenic, but create disease through dysbiosis of the gut flora and participate in the induction of autoimmunity. This is a key difference between the microbiome and the infectome as the former appreciates the direct or indirect effect of immune responses against infectious agents as pivotal for the initiation of autoaggression and immune-mediated, self-targeting pathology. For the infectome, monitoring of the microbial/host immunity is as important as the isolation of potentially harmful bacterial products, since the host/microbe immunological interaction is the likely cause of the self-destruction in the case of non-cytopathic viruses and microbes. It may also be important to measure the degree to which normal flora may play in disease, as in the case of dysbiosis where beneficial bacteria become pathogenic, as with E. coli, clostridia and Klebsiella, for example.

Although separate, the infectome and microbiome complement each other in providing a micropathological profile (or profiles) of a particular disease. As well, the microbiome is essential to define the normal flora of a particular region and then collectively the entire body. Recent microbiome studies have been able to provide an idea of what "normal" may be in the gut by performing metagenomic screens of bacterial populations in these regions [279–282, 285]. What is normal in one individual may be abnormal for another and may vary from race to race and from one geographical location to the next. Likewise, studies of the gut flora of neonates over the past few decades have shown that the percentage of prevalent bacteria is changing from one generation to the next. An understanding of the normal flora of a particular region (as established by the exposome) is essential. For example, studying the microbiome of the urinary bladder and vagina may help us understand the role of UTI in PBC [149–152, 287, 288]. Investigation of multiple body sites would likely prove to be useful [266, 289].

Who to select for screening?

Population screening is unlikely in the case of the infectome, from both a practical and financial standpoint. It is more logical to study individuals at high risk to develop autoimmune manifestations. These individuals are usually the family members or individuals with HLAs conferring susceptibility to the disease. In those individuals who are initially asymptomatic, or who are at high risk, ongoing

sampling and analysis may shed light as to whether the infections that induce the diseases are different to those that participate in the progression of the disease from early to advanced stages. Infectome profiling/burdens may play a decisive role in rapidly progressive patients or in patients who have frequent relapses. Common patterns may become apparent with particular disease subsets.

Screening methods and sampling sites

The easiest samples to obtain from patients include blood, urine or saliva. Analysis may be done by several methods and some of those are already in use. IgM, IgA and IgG antibody infectious serology testing is likely to be the most common method of detecting organisms, but also the most economical and efficient. Multiplex immunoassays such as ELISA and indirect immunofluorescence for the detection of antibodies against infectious agents are relatively inexpensive and provide valid information [290–292]. Large-scale multiplex technologies include protein microarrays and peptidome libraries, which are able to detect antibody responses to several hundred antigens [293–295].

A large German study used a PCR approach to detect a variety of organisms in archived liver tissues of PBC patients [296], which has been adopted in several other studies examining the role of mycobacteria in PBC [297–299], as well as beta-retroviral material in liver and lymph node tissue from PBC patients [267, 268]. Detection of viral and bacterial genetic material in tissues by a multiparametric approach may also prove to be promising. DNA sequencing technology, and specifically the so-called high-throughput DNA sequencers, can determine hundreds of megabases of DNA sequences per run, allowing for the analysis of a broad range of infectious agents [300–303]. Massive, parallel sequencing might be the next step of this approach for that it is the most sensitive procedure available and allows for the detection of a multitude of infectious agents at the same time [304]. Although immunohistochemical testing for several microbial agents in tissue samples can be applied [305], it is likely that tissue-based methods will be applied to the infectome, as they are time consuming, and tissue of the affected organ may not be readily available from all patients. The "top-down" approach suggested by other researchers may include the analysis of blood, faecal material, urine or saliva is more plausible and can be used for screening and reflecting [30]. Multiplex PCR is a useful tool for evaluating the presence of microorganisms from a variety of sample types. Other technologies include the use of 16S/18S rRNA gene sequencing, which allows for the mass analysis of samples [281, 283]. However, one drawback of this approach in comparison with immune profiles is the risk of missing the right time or site of sampling.

Multiple body sites may need sampling. In addition to the affected organ, general or systemic infections should be an indication for sampling and may include urine and stool samples in urinary and gastrointestinal tract infections, respectively, or blood cultures in febrile patients. Latent infections such as Lyme disease or mycoplasma may also be detected, in addition to chronic low-grade infections due to dental treatment. It is becoming more apparent that the oral cavity should be examined for infection in patients with autoimmune disease [306–308]. Alterations in the flora of the oral mucosa, which may lead to a dysbiosis in the gut microbiome, can also contribute to the pathogenesis of IBD [306]. On the other hand, the increased frequency of dental problems in IBD patients may be due to alterations in oral flora. Helenius et al. [308] indicate that patients with rheumatic conditions had various alterations in salivary flow and composition, and oral health. These findings warrant further investigation into the oral flora of patients with autoimmune conditions.

The infectome serves not only to characterise which infections lead to the development/progression of disease, but also provides clinicians an opportunity for early intervention and treatment. This could be achieved through the proper use of antibiotic or antiviral therapy, or supportive treatments to prevent damage through free radical stress, which would ideally be initiated early on in the management of these patients. It is envisioned that this intervention may allow for the slower progression of the disease or possibly the prevention of it in at-risk individuals. Guidelines for such treatment should be agreed upon in larger forums, to ensure best patient care and safety [263, 267, 268, 309].

Conclusion

It is now generally viewed that most diseases, including autoimmune disease, develop from an initial genetic susceptibility followed by several environmental exposures, including infections. GWAS is now characterising the genetic components to disease development, with the exposome serving to characterise all exogenous and endogenous environmental exposures. The complex nature of the exposome may require that it be broken down to several sub-components, such as the infectome, which reflects the characterisation and measurement of all infectious organisms that we are exposed to, and which contribute to the development and progression of disease. This characterisation will likely begin with at-risk individuals (such as family members), with further development as patients

develop disease symptoms or the progression of the disease changes. Many of these infectious exposures may be preventable or treatable and therefore represent a modifiable set of risk factors in their own right. On the other hand, it may be possible to modulate risk factors for the progression of disease such as the compounding effect of environmental exposures and the body's intrinsic protective pathways through supportive therapies.

Conflict of interest The authors declare that they have no conflict of interest.

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