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Review

Infectome: A platform to trace infectious triggers of autoimmunity

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ABSTRACT

The "exposome" is a term recently used to describe all environmental factors, both exogenous and endogenous, which we are exposed to in a lifetime. It represents an important tool in the study of autoimmunity, complementing classical immunological research tools and cutting-edge genome wide association studies (GWAS). Recently, environmental wide association studies (EWAS) investigated the effect of environment in the development of diseases. Environmental triggers are largely subdivided into infectious and non-infectious agents. In this review, we introduce the concept of the "infectome", which is the part of the exposome referring to the collection of an individual's exposures to infectious agents. The infectome directly relates to geoepidemiological, serological and molecular evidence of the co-occurrence of several infectious agents associated with autoimmune diseases that may provide hints for the triggering factors responsible for the pathogenesis of autoimmunity. We discuss the implications that the investigation of the infectome may have for the understanding of microbial/host interactions in autoimmune diseases with long, pre-clinical phases. It may also contribute to the concept of the human body as a superorganism where the microbiome is part of the whole organism, as can be seen with mitochondria which existed as microbes prior to becoming organelles in eukaryotic cells of multicellular organisms over time. A similar argument can now be made in regard to normal intestinal flora, living in symbiosis within the host. We also provide practical examples as to how we can characterise and measure the totality of a disease-specific infectome, based on the experimental approaches employed from the "immunome" and "microbiome" projects.

Contents

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 herpes virus 6; LC–MS/MS, liquid chromatography–tandem mass spectrometry (LC–MS/MS); MS, multiple sclerosis; IBS, irritable bowel syndrome; PBC, primary biliary cirrhosis; PCR, polymerase chain reaction; PDC, pyruvate dehydrogenase complex; SLE, systemic lupus erythematosus.

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1. Introduction

It is widely accepted that the vast majority of diseases develop from the interaction between genes and the environment [1–3]. This concept has formed the basis for studying the pathogenesis of many diseases including autoimmune diseases [1,2,4]. There are now almost 100 categories of autoimmune diseases, both organ specific or systemic in nature. Although individual autoimmune diseases are relatively rare in any population that has been investigated so far, projected data estimate that approximately 5–20% of North Americans are affected by at least one autoimmune disease [5]. Some of the best known autoimmune diseases are type 1 diabetes, rheumatoid arthritis, multiple sclerosis, Grave's disease, Hashimoto's thyroiditis, myasthenia gravis, systemic lupus erythematosus, Sjögren's syndrome, scleroderma and autoimmune liver diseases such as autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis (PBC) [5]. The observation that many autoimmune diseases may affect one individual, has led to the concept of the Mosaic of Autoimmunity [6–13].

The study of genetic and epigenetic factors linking to autoimmunity is the focus of ongoing research [14]. Also, the exact signalling cascades that govern the perpetuation of inflammatory processes responsible for tissue destruction are poorly understood [15]. In recent years, genome wide association studies (GWAS) have identified numerous gene–disease associations, many of which include autoimmune diseases [2]. Although these associations are connected to genetic susceptibility, the genetic 'dosage' or number of associated genes required for disease development is not well defined [16]. Although GWAS have been instrumental in unlocking a pathogenetic starting point, exposure to environmental factors is also likely to contribute to the actual development of most diseases, and work with genetics in the induction of autoimmune disease [1,2,17]. For example, smoking has been indicated to increase the risk of developing MS in individuals with HLA-DRB1*1501 [18]. Epidemiological studies using toxicological, microbiological, biochemical, and immunological testing are important in order to identify these environmental agents, which include infectious organisms, xenobiotics, chemical compounds, heavy metals from prostheses and dental materials, radiation, vaccines, and foods to name but a few [1,19–22]. Heavy metals and vaccinations have also been implicated in the pathogenesis of autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA) [23–32]. In fact, siliconosis, Gulf war syndrome (GWS), macrophagic myofasciitis syndrome (MMF) and post-vaccination phenomena were linked with past exposure to adjuvants.

Since GWAS underlined the view that multiple genes are needed to induce autoimmunity [2], it is also likely that several environmental triggers either complement or substitute each other to provoke immune mediated processes which then lead to autoimmunity. The additive effects of these triggers, and their interaction with susceptible genes, remain poorly defined.

In recent years, the concept of an "exposome" has been introduced, as a means of collating, and possibly measuring the effects of environmental factors. The exposome takes into account all internal and external stimuli associated with a disease, and provides a potentially quantifiable way for the evaluation of environmental factors (Fig. 1). This review will examine the role of the exposome in relation to major exemplary autoimmune disease where genetics and environment most likely play key roles in pathogenesis. The role of the "infectome" as the infectious component of the microbiome/exposome that takes part (directly or indirectly) in the development of autoimmunity will also be introduced (Fig. 2).

2. The exposome: what is it, and how do we measure it?

The exposome represents the totality of all environmental exposures, both exogenous and endogenous, which begins from conception, and extends throughout our lives [33–37]. This differs from previous epidemiological studies, which have largely concentrated on the external environment, and specifically to air, water, soil and food [35]. In contrast to approaches limited to external triggers, the study of the exposome needs to address endogenous factors directly or indirectly related to the environment [36,37]. Endogenous sources include by-products of inflammation, lipid peroxidation, as well as oxidative stress [35]. Some of these components may act as nucleophiles or electrophiles, and as such, would be capable of DNA and protein modification [38]. Indeed, bacterial alterations in glycosylation patterns of immunoglobulins have been noted in several studies [39–41]. The collation of all these exposures may provide a fingerprint of a particular disease, which would likely complement data from GWAS [38].

The predominant problems in examining environmental exposures are the difficulties of quantification and normalisation as well as the determination of exposure sequences. This information is required, as alterations induced by one environmental agent may be necessary for a subsequent exposure to have its effect [2]. Moreover, environmental exposures within a population, as well as within an individual, are greatly varied. Given the myriad of causative possibilities in one individual, it may be useful clinically to look at causes within an individual in terms of exposure, sequence of exposure, hierarchy of exposure events, genetic and other risk factors that initiate or provoke exposure to various stimuli. Examined individually, these pieces may comprise the jigsaw puzzle that is loss of immunological tolerance, development of autoimmune disease and progression of

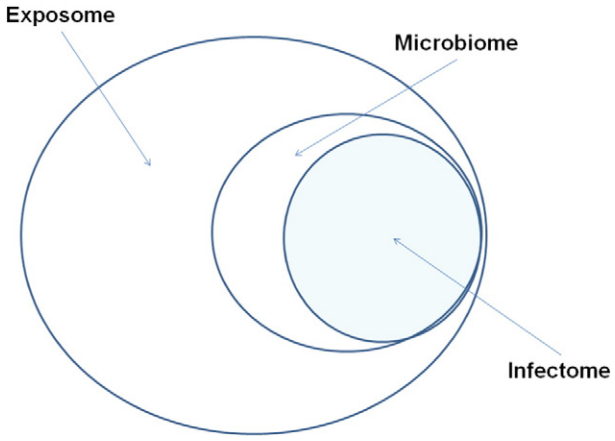

Fig. 1. From exposome to infectome via microbiome. "Exposome" describes all environmental factors which we are exposed to in a lifetime, both exogenous and endogenous, infectious and non-infectious. Environmental exposures are basically subdivided into infectious and non-infectious agents. The concept 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. 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.

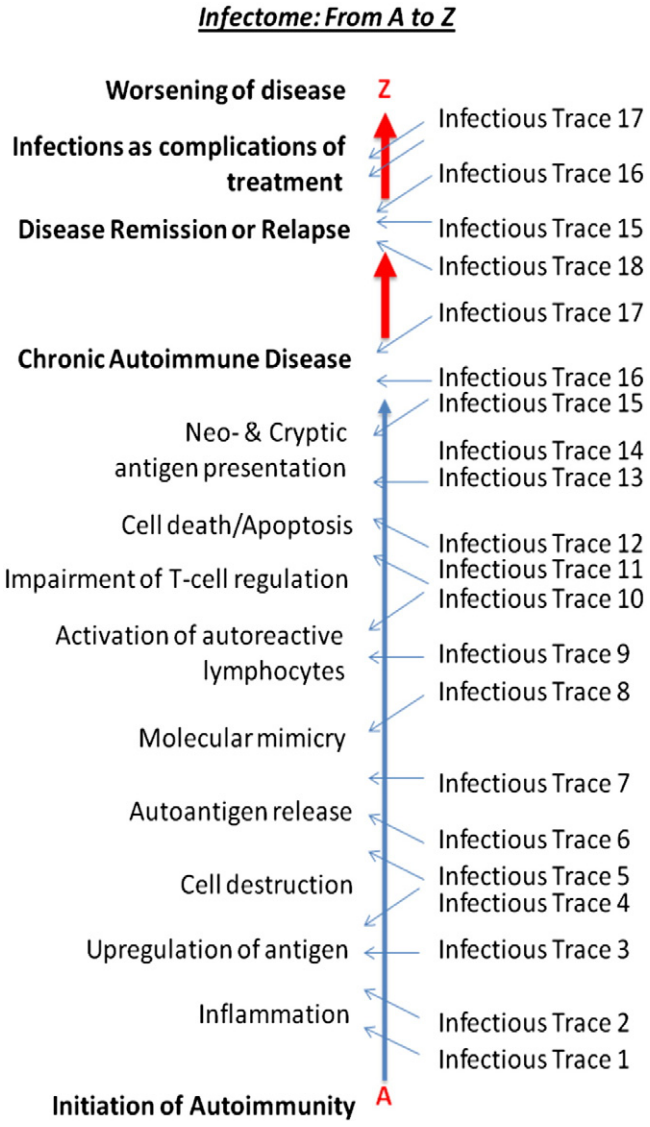

Fig. 2. Tracing infectious triggers of autoimmunity: the infectome from A to Z. Infectious agents participating in a series of events critical for the initiation of autoimmunity and the development of autoimmune disease can be traced at various time points. The traces of these infectious agents may help us to understand the extent of their involvement in the loss of immunological breakdown and/or the maintenance of autoreactive immune responses leading to self destruction. Infections, at times different of those responsible for the chain reaction of events that led to autoimmune disease, may participate in the remission/relapse clinical patterns seen after the onset of the disease.

clinically over disease and its complications. Although great variability may be seen from patient to patient, the overall collation of well-defined disease-related exposures individually may provide a picture of disease development in that patient. The exposome provides a potential platform by which these exposures may be measured. It has been suggested that their by-products in an individual, such as DNA and protein modification, can serve as biomarkers that are potentially measurable [38] in the blood or body fluids of patients [3,36–38] via technologies such as liquid chromatography–tandem mass spectrometry (LC–MS/MS) [42], DNA adducts [43], functional measurements of antioxidant capacity, and breath analysis [34].

Rappaport suggests two methods in which the exposome may be measured: the 'bottom-up' method measures chemicals in air, water and the external environment, but is limited in that it does not take into account the actual uptake of those substances nor the internal environment of a subject [35]. As an alternative, the 'top-down' method measures biomarkers in the patient's blood, however, this method does not indicate a potential source of the toxicant. It is likely that both complementary methods, in conjunction with refined questionnaires, will define the exposome in individuals, and larger populations [35–37]. Frequent sampling could demonstrate changes of these markers over time, especially during critical phases in the development of a disease [35]. A study by Pleil and colleagues [34] indicates that breath analysis for particular biomarkers is capable of identifying whether one has been exposed, what the dosage was, how rapidly the body is eliminating the toxicant, as well as possibly identifying the short and long term effects [34]. Finally, a recent study by Patel and colleagues [44] has provided evidence that the exposome can indeed be measured and characterised. That study conducted an environmental-wide association study (EWAS) on type 2 diabetes mellitus, where epidemiological data was comprehensively interpreted in a manner similar to GWAS [44]. Associations were found with 37 environmental factors, including organochlorine, pesticides, nutrients/vitamins, polychlorinated biphenyls, and dioxins [44]. Other studies have shown a potential crossreactivity between antigens within the pancreatic islet cells and cow's milk casein in siblings of type 1 diabetics [45], and multiple sclerosis's myelin oligodendrocyte glycoprotein with milk butyrophilin [46], highlighting the potential role for food antigens as triggers of autoimmune disease. Similar approaches can be used in future studies on the role of the exposome in the development of autoimmune diseases, especially those which develop in genetically susceptible individuals several years or decades following the initial insult.

One major obstacle to the complete analysis of all these triggers is their heterogeneity. It is unlikely to cover all such components by homogeneous technology platforms, as all human biomarker measurements are subject to inter- and intra-subject variance. This includes the composition of the received data into one model, which appears to be a Sisyphean task even in the age of ultra-fast computing. Therefore, the break-down of this multiversity of components into easier accessible, homogeneous realms of markers seems to be a reasonable next step. Techniques that can be utilised to detect infectious agents like multi-parametric immunoassays for antibodies of various isotypes specific to bacterial or viral antigens, urine and stool cultures and polymerase chain reaction (PCR) can be considered to be robust and integrateable [36]. Routine screening to detect the presence of an infectious causative agent is used clinically in a small scale and for individual microbial agents on an everyday basis [36].

3. Exposome, infectome and autoimmunity

Infectious and non-infectious environmental agents have long been considered important for the development of autoimmunity [4,47–51]. The list of non-infectious environmental factors which can trigger autoimmunity is vast, and includes tobacco smoke, pharmaceuticals, oestrogens, ultraviolet radiation, silica solvents, dietary components, heavy metals, dental materials, vaccines, and collagen/silicone implants (Table 1) [47,52–80]. Infectious triggers implicated in autoimmunity are also numerous and include bacteria, viruses, parasites and fungi. An infection burden corresponding to geo-epidemiological and serological evidence of the co-occurrence of anti-infectious agents has been observed and it is of interest that such an infection burden may differ from one autoimmune disease to another [4,81,82]. An analogous, autoantibody burden in non-autoimmune individuals during infection with various agents, further points towards the close relation of exposure to several infectious agents and the development of autoantibody reactivities [83]. From our point of view, it is helpful to define this subgroup of triggers as the "infectome" which is the part of the exposome referring to the collection of an individual's infectious exposures which are associated with disease, and in our case specific autoimmune diseases. It may also demonstrate the alteration in disease states, which are affected by alterations of the flora within the microbiome. Examples include

Table 1
Non-infectious environmental agents associated with the development of autoimmunity. This table provides examples of several non-infectious agents from a variety of sources, which have been associated with the development of autoimmune disease. 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.

Non-infectious environmental triggers	Disease	Reference
Occupational exposures		
Silica	RA, SLE, SSc, glomerulonephritis, small vessel vasculitis.	[52–56]
Solvents	SLE, AIH	[54,55,57,58]
Pesticides	Autoimmune thyroid, RA, SLE, SSc	[59–65]
Ultraviolet radiation	SLE, RA, DM, PM, MS, type 1 diabetes mellitus	[54,66–69]
Drugs		
Allopurinol	Immune haemolytic anaemia	[70]
Captopril	Autoimmune thrombocytopaenia	[71]
Chlorpromazine	Anti-phospholipid syndrome, haemolytic anaemia, SLE, AiLD	[72–78]
Estrogens	PBC, SLE, RA	[155–158,316–320]
Halothane	AIH	[77,321,322]
Iodine	Autoimmune thyroid	[62]
Penicillins	AiLD, immune haemolytic anaemia	[77,323]
Rifampicin	AIH, autoimmune thyroid, immune haemolytic anaemia	[324–326]
Tetracyclines	AIH, DM, SLE	[79,327–336]
Miscellaneous		
Vaccines	PBC, AIH, SLE, RA, MS, MG, DM, polyarteritis nodosa,	[279,337–349]
Cigarette smoke	PBC, COPD, RA, autoimmune thyroid	[155–158,350–355]
Collagen/silicone implants	SLE, Sjögren's, SSc	[353,356–362]

treatment with antibiotics [84,85], or exposure to toxic metals, silicone or other xenobiotics [30,86,87]. These exposures may very well alter the disease course or progression, by altering the flora within the microbiome, or by increasing the likelihood of infection with a disease causing infection. They may also increase the burden of oxidative stress. While the hygiene hypothesis underlines the protective role played by infections [88–92], clinical and experimental data in animal models implicate infections in the development of autoimmunity and autoimmune disease [4]. One of the best-studied examples of infection-induced autoimmunity is that of acute rheumatic fever presenting several weeks after infection with *Streptococcus pyogenes*. It is now well established that molecular mimicry between the bacterial M-protein and human lysoganglioside is responsible for the loss of immunological tolerance, and the development of autoimmunity in genetically susceptible individuals [93]. Other examples include the associations between *Helicobacter pylori* and autoimmune gastritis [94], as well as between *Trypanosoma cruzi* and Chagas' cardiomyopathy [95], and *Mycoplasma* with rheumatoid arthritis [96].

Although experimental models of autoimmune diseases and studies like those mentioned above provide data to support the role played by a single infectious trigger, the prevailing idea is that a multitude of infections from birth, in our term the infectome, contributes to the induction of autoimmunity [4]. In fact, Rolf Zinkernagel's hypothesis is that the increasing predisposition to autoimmune disease in the developing world may be due to the overall host–infection balance, beginning as early as the transfer of maternal antibodies via the placenta or via breast milk in the gastrointestinal tract. The question which then arises is how one can identify those specific infectious agents responsible for the initiation of an autoimmune disease. Studies in animals have provided some clues, but their resemblance to the human setting is poor in most cases.

Ideally, investigations have to be carried out in affected individuals. However, when work is performed on biological material obtained from patients with a given autoimmune disease, it is difficult to single out disease-triggering microbes. Undoubtedly, information from the collection of the microbial genes in a particular region (such as the gut or the oral cavity), also known as "microbiome", can provide important hints for those potentially involved in the development of or protection against autoimmunity. However, this by itself cannot differentiate those with a pathogenic potential from the non-harmful ones, the latter representing the great majority. In fact, most of the isolated microbes have little to do with the initiation of immune-mediated inflammatory processes leading to a given disease. 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.

Studies attempting to investigate the role of the "infectome" in the induction or remission/relapse state of autoimmune disease may need to focus on autoimmune diseases such as multiple sclerosis or rheumatoid arthritis, as patients with these diseases experience frequent remissions and relapses as well as fluctuations in disease activities that are poorly understood. Systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis are three of the best studied diseases so far for which specific viral agents have been considered to be important for the development of the disease and the breakdown of immunological tolerance [4]. As well, exposure to metals and various other chemical components have also been linked with these two conditions, and it would be interesting to see how these exposures alter the presence of infectious agents. It may be the case that exposure to certain xenobiotics increases susceptibility to disease causing microorganisms, or possibly eliminates organisms that are determined to be protective.

Arguably, the ideal clinical setting for the study of the role of the "infectome" in autoimmunity would involve typical autoimmune diseases with long prodromal stages [97]. Serial testing of biological material from individuals who progress from an asymptomatic subclinical phase to clinical disease would be optimal for the study of the "infectome". Examples of this include systemic lupus erythematosus (SLE), multiple sclerosis (MS) and primary biliary cirrhosis (PBC) to name a few. All of those are characterised by highly specific antibodies that may appear years or even decades before the onset of symptoms [98–100]. These diseases also have long prodromal stages and their course highly varies among individuals. Relapse and remission states can be seen, but the reasons for this remain unknown. The characteristic features of these diseases and their reported pathogenic relationship with infectious agents make them ideal candidates for the study of the infectome.

4. SLE as an infectome model: known infections, stronger links

Systemic lupus erythematosus (SLE) is often characterised by a prodromal stage of antibody positivity (predominantly anti-Sm and anti-Ro) with no symptomatology [101,102]. A recent study has also found that a significant proportion of first degree relatives of SLE patients are positive for several autoantibodies, namely ANA (mostly anti-dsDNA), anti-Ro/SSA, and many other specificities [103–105]. In fact, ANA titre $\geq$ 1:160, anti-dsDNA, anti-Ro/SSA and anti-chromatin may have a high predictive value for SLE diagnosis [103]. The reasons underlying the development of and/or the progression to clinical disease, as well as the mechanisms underlying disease flares, remain elusive [19]. However, several infectious agents have been implicated including EBV, cytomegalovirus (CMV) and parvovirus B19 [48,101,102,104–110]. These features make SLE an ideal model for the

infectome, given the strong evidence for an infectious trigger, in addition to its unpredictable clinical course.

EBV appears to have an association with SLE, with variations and susceptibility based on demographical and genetic characteristics [111]. Harley and colleagues [101] propose a progression of EBV infection followed by Epstein–Barr virus nuclear antigen 1 (EBNA-1) antibody production, which predisposes to the development of cross-reactive autoantibodies, with progression to clinical SLE. Harley and James [102] indicated that the first lupus specific antibodies are directed against EBNA-1, which interestingly also binds lupus specific antigens such as Sm and Ro. As with many implicated viruses, the exact mechanisms in which they induce autoimmunity are not yet clear. However, one group which has indicated molecular mimicry as a mechanism with regard to EBV and SLE, notes similarities between the EBV peptide PPPGRRP and the PPPGMRPP peptide of Sm [109]. That same group tested 196 ANA positive adult SLE patients, and two age, race, and sex matched controls per patient, for evidence of previous infection with EBV, CMV, herpes simplex virus-1 (HSV-1), HSV-2, and varicella zoster virus (VZV) by ELISA [109]. Among the SLE patients, 195 out of 196 had previous EBV infection compared to 370 controls [109]. No differences were found in regard to the rate of infection with other viruses [109]. A study by Wang et al. [112] found that the EBV-encoded latent membrane protein 2A induced a heightened sensitivity to toll-like receptor (TLR) ligand stimulation, which increased proliferation of anti-Sm B-cells, and/or increased antibody secreting cell differentiation.

Parvovirus B19 has also been found to be associated with SLE, although the evidence is not as clear cut as that of EBV. The group of Bengtsson [106] tested 99 SLE patients and 99 age and sex matched controls for parvovirus IgG antibodies. No evidence of parvovirus B19 was found in SLE compared to controls, and in one analysis, the controls had a higher positivity than the SLE group [106]. As the symptoms of SLE and parvovirus B19 infection may be similar, a prospective study involving 42 patients with acute parvovirus B19 infection attempted to determine whether the symptoms persisted, and whether infection contributed to the development of SLE [110]. Clinical and laboratory investigations were performed at 1, 2, 6, 12, and 24 months from initial infection. Arthralgias persisted for 2–6 months in three female patients, for greater than two years in one female, but resolved in the remaining cases within 2 weeks [110]. One female with persistent arthralgia over two years was ANA positive and had hypercomplementaemia, but did not fulfil the diagnostic criteria for SLE or RA [110]. Despite the lack of evidence linking parvovirus B19 to the induction of SLE, one case report of a 26 year old female with SLE, who had a disease flare-up following parvovirus B19 infection, suggests that parvovirus B19 causes disease flares in SLE patients [107].

As with parvovirus B19, the evidence linking CMV to SLE is scarce. Hrycek and colleagues found that 100% of female SLE patients have evidence of CMV infection, compared to 75% of controls [108]. As well, another study had found that the CMV pp65 antigen triggers humoral immunity in SLE patients and autoimmune prone mice [113]. The lack of evidence linking particular viruses to SLE does not infer non-involvement, but reflects the difficulty of detecting infectious organisms, which may be transient, in these patients. It is likely that diagnosis of SLE and/or SLE flares occurs after an infection. The infectome serves as a model in such cases. At-risk patients, such as first degree relatives of SLE patients, who are found to be positive for autoantibodies, may be screened at regular intervals. Likewise, SLE patients may be screened, and changes in clinical course, such as flares, may be correlated with infection. Several other diseases with a well defined connection such as that of *H. pylori*-induced idiopathic thrombocytopenic purpura could be explored. These methods are useful in that they not only indicate the who and when, but also provide a more narrowed-down list of organisms to evaluate in regard to the mechanism in which they induce autoimmunity.

5. Multiple sclerosis as an infectome model for relapse remittance clinical states

Multiple sclerosis (MS) serves as another example in which the infectome model may be applied. MS is a chronic autoimmune neurological syndrome characterised by chronic inflammation, demyelination and gliosis in the central nervous system (CNS) [114,115]. It is characterised by periods of relapse and remission [114,115], the reasons for which are not understood. Current evidence suggests that the risk for acquiring MS is spread over a long period of time, and is not limited to childhood or early adult life [116–118].

The most prevalent form of the syndrome is the so called relapsing–remitting MS, characterised by flares whereby pre-existing symptoms become more severe, or new symptoms develop [119]. These flares are followed by phases of complete or partial recovery and their duration is highly variably among affected individuals. A considerable proportion of these patients acquire progressive disability with or without disease relapses (secondary progressive MS). Another form of MS is characterised by a stable progression of the disease with worsening of the symptomatology over the course of the disease. This form is also known as primary progressive MS (PPMS). Two further forms of the disease are also found with totally contradictory outcomes. The benign form of MS usually presents with minimal or mild progression of disability, and is clinically characterised by full recovery of sporadic sensory episodes [119]. On the other hand, the Marburg variant of MS is characterised by rapidly progressive disease which leads to accumulating disability and eventually to death. The mechanisms responsible for the development of clinically distinct disease phenotypes are poorly understood [119].

The pathological hallmark of MS is inflammatory lesions (areas of demyelination) in the CNS composed of mononuclear cell infiltrates in the perivascular spaces that develop into plaques [114,120]. These mononuclear cells are largely composed of T and B lymphocytes, plasma cells, macrophages and microglia [114,120]. Positive staining for IgG is found in the peripheral regions of the plaques [114,120]. Additionally, approximately 90% of MS patients show intrathecal IgG synthesis in the cerebrospinal fluid (CSF) [114].

Environmental and genetic components are clearly involved in the aetiology of MS, with geographical and twin data indicating a greater environmental component [114,115,121,122]. However, identical twins are 100 times more likely to develop MS if their co-twin is affected, whereas non-twin siblings are 20 times more likely [123,124]. Genetic and GWAS have implicated several alleles, with the strongest association being with HLA-DRB1*1501 [125]. Seven GWAS studies have been conducted, which included nearly 10,000 MS patients and 15,000 controls [115]. Implicated genes include IL7R, IL12RA, CLEC16, and CD226 [126,127]. Nonetheless, implicated genes have only demonstrated an odds ratio of less than 1.3 [115], and MS twins only demonstrate a 30% concordance [114], indicating more of an environmental influence in the disease pathogenesis.

Non-infectious and infectious components have been implicated to be involved in the development of MS. Within the group of non-infectious agents, vitamin D is of particular interest, not only in MS but also in several other autoimmune diseases [115,128–140]. Vitamin D appears to play a role in the modulation of pro-inflammatory pathways and T cell regulation [115]. Increased distance from the equator has been correlated with low vitamin D, and interestingly, MS rates increase as distance from the equator increases [114]. As well, populations with increased dietary vitamin D intake have lower rates of MS [115]. 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 [141]. This has also been found in other studies [142]. 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 [115]. Like many

conditions, smoking has also been associated with MS development, and a recent meta-analysis overwhelmingly associated smoking with MS [143]. Gene–environment interactions have been suggested in regard to smoking and the presence of HLA-DRB1*15 with the absence of HLA-A*02 [144]. Smokers with this genetic combination appeared to have an increased risk of developing MS [144]. Whether this is due to the effect of the nitrosamines or the heavy metals in cigarette smoke is not clear. There is limited evidence for the role of heavy metals in some patients with MS [145]. Infectious agents investigated in regard to MS have included bacteria and viruses (Table 3) [114,115,121,122,146,147], and implicated viruses include EBV [114,115,121,122] and human herpes virus 6 (HHV6). The relapse–remittance pattern of the human herpes virus 6 (HHV6) is similar to the clinical pattern of MS [115] and HHV6 reservoirs have been found in CNS tissue [148,149], in addition to the CSF and serum of MS patients [150,151]. Molecular mimicry has been indicated, as sequence homology has been found between myelin basic protein and HHV6 encoded U24, and cross-reactive T cells responding to both protein types are found to be elevated in MS patients [152]. Varicella zoster virus, torque teno virus, retroviruses, coronaviruses and JC virus have also been implicated, but with limited evidence [114,115,121,122]. Reactivity to several viral peptides was found [153], 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.

An infectome for the above conditions (and others) may clarify questions regarding aetiology, but may also identify the cause of certain disease characteristics, such as variable presentation and progression among PBC patients, disease flares in patients with SLE, or relapse–remittance among MS patients. As such, these conditions serve as models for an infectomal analysis.

6. Primary biliary cirrhosis as an infectome model disease

PBC can be used as a model disease to investigate the role of the exposome, and indeed of the infectome [154], as A) it is an autoimmune disease and it is not as rare as many other such diseases, B) it has a long silent phase in which well-established biomarkers can be determined in high-risk populations, C) it presents with subgroups of patients who have differing disease progressions and/or concomitant other autoimmune diseases, D) it is not treated with immunosuppressive drugs that might deteriorate the immunological assessment of the infectome, and E) there is growing evidence in support of genetic, environmental, and infectious factors involved in the pathogenesis of the disease such as recurrent urinary tract infection (UTI), cigarette smoke, and oestrogen deficiency [155–163]. A plethora of experimental and clinical data clearly indicate that the disease is indeed autoimmune in nature [98,159,164–184]. Infectious agents and xenobiotics mimicking or modifying the core epitopic region of PDC-E2, the major autoantigen in PBC, appear to induce immune-mediated destruction of the bile ducts. As PBC affects the liver, access to the affected organ for research purposes is possible at the time of diagnosis via liver biopsy, and over the course of the disease from early to advanced stages. This is not possible in diseases such as diabetes mellitus type I.

In line with the already discussed ideal situation of a long prodromal period, PBC has a long pre-clinical phase, characterised by an asymptomatic period with evidence of autoimmune markers in the form of autoantibodies, followed by biochemical evidence of liver damage and finally clinically-evident disease. The progression from asymptomatic to symptomatic PBC may take years or decades. Virtually, all patients with PBC have high-titre anti-mitochondrial antibodies (AMA) at the time of diagnosis [99,175,184–210]. Also, the presence of AMA is predictive of eventual disease development [211]. PBC patients with disease-specific anti-nuclear autoantibodies (ANA) appear to have more advanced disease and poorer prognosis [212–227]. Individuals at the highest risk of developing PBC are family members of PBC patients. [228–234]. The vast majority of patients with PBC experience concomitant autoimmune diseases such as *Sicca* syndrome, autoimmune thyroiditis, rheumatoid arthritis, autoimmune hepatitis and systemic sclerosis. The reasons behind the fast pace of progression seen in some patients with PBC are unknown, and attempts to predefine those individuals which will progress faster than others have been largely unsuccessful.

PBC does not appear to respond to immunosuppressive treatment, making the disease perfect to study the involvement of infectious agents over the course of the disease without the need to consider the effects of immunosuppressive therapy on relapse/remission states. PBC patients are instead treated with ursodeoxycholic acid (UDCA) at adequate doses of 13–15 mg/kg/day [235,236]. It is not clear as to whether UDCA has immunomodulatory properties or not.

A number of environmental factors have been implicated in PBC by 'bottom-up' approaches in various epidemiological studies examining associated risk factors [155–158] including numerous xenobiotics and infectious agents [159–162,237]. Animal models have further supported this notion [159,238–242]. The genetics of PBC appear to include HLA [243,244], non-HLA [245–251] and sex-linked

Table 2
Examples of infectious agents implicated in multiple sclerosis. Several organisms have been implicated in the pathogenesis and clinical course of multiple sclerosis (MS), the vast majority of which are viruses.

Viruses		Bacteria	
Epstein Barr virus	[363–378]	*Chlamydia pneumoniae*	[379]
Human herpes virus 6	[148–152,380,381]	*Borrelia burgdorferi*	[382]
Varicella zoster virus	[383–385]	*Mycobacterium tuberculosis*	[386]
Human cytomegalovirus	[387]		
Retroviruses	[388,389]		
Coronavirus	[390,391]		
Torque teno virus	[153]		
JC virus	[392,393]		
Rubella virus	[394]		
Parainfluenza virus I	[395]		
Measles virus	[396,397]		
Mumps virus	[398]		

Table 3
Examples of infectious agents implicated in primary biliary cirrhosis. This table provides several examples of infectious organisms which have been implicated in the pathogenesis of primary biliary cirrhosis (PBC). Strong evidence exists for some organisms such as *Escherichia coli*, while weaker evidence exists for others. This may be due to the lack of investigation into the prevalence of some organisms in PBC.

Bacteria	*Escherichia coli*	[176,178,265,267,399,400]
	Chlamydia pneumoniae	[263,401]
	Mycobacterium gordonae	[402–404]
	Novosphingobium aromaticivorans	[178,399]
	Pseudomonas aeruginosa	[257,405]
	Lactobacillus delbrueckii subsp *bulgaricus*	[259,279]
	Yersinia enterocolitica	[260,406]
	Salmonella typhimurium	[407]
	Salmonella minnesota	[408]
	Haemophilus influenzae	[257,260]
	Streptococcus intermedius	[409]
	Paracoccus dentrificans	[410]
	Borrelia burgdorferi	[411]
	Propionibacterium acnes	[412]
	Mycoplasma pneumoniae	[413]
	Mycoplasma gallisepticum	[414]
Viruses	Betaretrovirus	[272,276,415,416]
	Cytomegalovirus	[257]
	Epstein Barr virus	[417]
Parasites	Trypanosomes	[418,419]
	Ascaridia galli	[419]
Other	*Saccharomyces cerevisiae*	[420]

genes [252–254]. Particular allelic associations may be indirectly relevant to the pathogenesis of the disease, as they may influence the penetrance of infectious agents. For example HLA-DRB1*11 and HLA-DRB1*13 have a negative association with PBC, and are protective for several viruses that affect the liver, such as hepatitis B and C. The lack of HLA alleles protective for PBC, which are associated with resistance to specific pathogens, may lead to susceptibility to infection responsible for the induction of the disease [244,255]. These findings underline the urgent need to investigate the infectome in parallel with GWAS. An infection burden involving EBV, CMV and *Toxoplasma* has been recently reported in patients with PBC.

However, the list of pathogens involved in PBC is vast, with some such as *Escherichia coli*, having a relatively strong evidence base (Table 2) [164,182,252,256–279]. Molecular mimicry has been considered a likely mechanism that could account for the initiation of liver autoimmune diseases, including PBC [164,182,256–260,264,274,275,279–285].

Much as the exposome reflects the collation of all exposures, an infectome may reflect all those bacterial, viral, or parasitic exposures which may contribute to the development of an autoimmune disease.

7. How to study the infectome

The study of the infectome needs to be customised taking into account the disease to be investigated. The type of the sample to be collected largely depends on the disease under investigation.

A generic, step-wise approach of infectome analysis at presentation would be the following:

1) Determination of HLA class I and II is performed in all individuals under investigation. Ideally, this could be performed at birth, or at the baseline when the individual/patient presents for the first time in the clinic. This information is important in order to sub-group the individual into high or low risk.
2) Collect urine, oro-nasal swabs, saliva, faecal material, and blood (for isolation of plasma, serum, and peripheral blood mononuclear cells — PBMCs).
3) Regular follow-up (once yearly) with collection of samples;
4) Meticulous recording of clinical data and collection of samples are needed when anti-infective treatment is applied for incidental/casual infections at the pre-clinical stages of the disease, as this may affect the final outcome of the underlying processes.
5) Store samples until patient has laboratory and/or clinical features related to the disease;
6) Analysis of collected samples for infectious agents with a known association with the disease, and "out of the box" analysis using multiplex technology for other infectious agents (see section "How to screen?" below). The analysis will provide information regarding the infection burdens at various-time points;
7) Associations are analysed, providing evidence for known/unknown infectious agents in the development of symptomatic disease.
8) Continuous analysis over the course of the disease, as it may reveal a close link between a specific agent and the clinical phenotypes of the disease.

The study of the role of infectious agents in the development of an autoimmune disease, whether RA, SLE, MS or PBC, may reveal which agents are involved in the development of the disease as well as other concomitant autoimmune diseases. It is likely that the combination of particular genes and particular infectious exposures is responsible for the development of an autoimmune disease, with or without a particular concomitant autoimmune disease. In other words, there may be several infectomes for SLE, some of which define SLE with a particular concomitant autoimmune disease. This of course applies to other autoimmune diseases.

8. Lessons that can be learned from the microbiome and immunome projects

The recently described microbiome concept can be separated from that of the infectome. The microbiome defines the collection of microbial genes in a particular region, such as the gut, inguinal crease, oral cavity, or virtually any body site [286–295]. The microbiome may be reflective of the normal or pathological profile of organisms. For example, the microbiome of the gut has been analysed in healthy individuals [288–291,294], which identified three distinct profiles or clusters, known as enterotypes [287,293]. Similar studies have been performed for the oral cavity as well [286,295]. The microbiome may also be applied to a disease-affected body site, such as the gastrointestinal tract in children with irritable bowel syndrome (IBS) [292]. A study by Saulnier and colleagues [292] obtained 71 faecal samples from 22 children with IBS and 22 healthy children, all aged 7–12 years. These samples were analysed by 16S rRNA gene sequencing, which showed an elevated percentage of γ-proteobacteria in the gut flora of children with IBS, with *Haemophilus parainfluenza* being a prominent component [292].

So how does the infectome differ from this? First, the infectome relates to those infectious organisms which are associated with the disease in question, as opposed to a totality of all organisms, both pathological and non-pathological within the human microbiome. Second, the infectome reflects all sites of infection, as opposed to one body site usually represented by the microbiome. As well, microbiome studies to date have largely concentrated on bacterial species, whereas the infectome takes into account all pathological bacteria, viruses, parasites, and fungi. The infectome is not limited to the affected site or organ but includes biological fluids as well as sampling of various body-sites including the oral cavity. Some argue 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 directly pathogenic, but create a 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.

Although the infectome and microbiome are distinct entities, they may be used symbiotically to provide a micropathological profile (or profiles) of a particular disease. As well, the microbiome is essential to define what "normal" actually is. 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 [288–291,294]. For example, in the case of PBC it may be pertinent to understand the normal microbiome of the urinary bladder and vagina, as infections in these sites have been associated with PBC [155–158,296,297]. Other body sites may also need investigation, as inhalation or consumption of potentially pathogenic organisms has also been implicated [275,298]. All associated organisms located in all potential body-sites, would comprise the infectome. The establishment of what is normal as well as infectious may contribute to the understanding of the network of events or exposures which lead to disease development. It is possible that a series of exposures leads to increased susceptibility to further exposures, which could be defined by the infectomal model.

9. Who to screen?

Unlike GWAS and the microbiome, it is unlikely that population screening of infectomal components could be performed due to the

lack of integrated analysis platforms. It may be more reasonable to screen particular groups of individuals who are at risk of developing autoimmune disease, like family members or individuals with an HLA profile conferring risk for a given disease. Further monitoring may reveal whether additional infections play a role in the progression of the disease to a symptomatic stage. Additionally, particular exposome/infectome profiles may be found among patients with rapidly progressive diseases (as in a subset of PBC patients), or in relapse remittance states in MS, and flares in SLE. This approach may delineate which infectious agents are responsible for disease development and/or progression, as well as identifying those that are associated with rapid versus slow progression, remittance, and flares.

10. How to screen?

The establishment of the infectome would have to rely on the detection of microbiological materials in patients, favourably in ease-to-sample material like blood, urine or saliva. There are several methods by which this may be done, and some of those have already been used for research purposes. Serological detection of IgM, IgA and IgG antibody responses to microbes, viruses, and fungi is likely to be the most common, fastest, and most cost effective method and independent of the actual presence of a respective infectious agent. Monitoring for seroconversion of antibody responses and isotype class switching from IgM to IgG is imperative for the identification of newly acquired infectious triggers over time. To this end, the part of the immunome which relates to infections is an integral part of the infectome and its primary goal to identify microbial triggers of autoimmunity. Immunoassays for the determination of antibodies against most of them, e.g. ELISA, are broadly available, have a high degree of robustness and standardisation and are comparably cheap. Furthermore in some diagnostic scenarios, multi-parametric immunoassays, e.g. lineblots for the detection of antibodies against tick-borne diseases exist that facilitate the determination of antibodies against several or even multiple entities at the same time with a limited amount of sample. The highest complexity up-to-date can be reached by using protein microarrays that allow for the screening of several thousand antibody entities at the same time [299,300]. However, such platforms have so far only been used to screen for immune profiles of individuals, and small numbers of similar infectious agents and commercial solutions with a similar degree of standardisation as those containing human proteins are not available. A major breakthrough might result from the development of high-density peptidome libraries of relevant microbes and viruses similar to the concepts of peptidome libraries covering human proteins, e.g. T7-Pep library for the human peptidome [301].

A large German study used a PCR approach to detect a variety of organisms in archived liver tissues of PBC patients [302]. This approach has also been adopted in several other studies examining the role of mycobacteria in PBC [303–305], as well as in another group which used this method to detect beta-retroviral material in the liver and lymph node tissue from PBC patients [276,277]. Similar studies have been conducted in other autoimmune diseases. Multi-parametric detection of viral and bacterial genetic material in tissues may be another promising approach. In recent years, DNA sequencing technology has undergone an outstanding upgrade, and the so-called 'high-throughput DNA sequencers' can determine hundreds of megabases of DNA sequences per run, enabling the analysis of a broad range of infectious agents [306–309]. 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 [310]. However, the considerable costs of this testing limit its wide use. Immunohistochemistry detecting several microbial agents in tissue samples can be applied [311], though it is likely that tissue based methods are not ideal in the establishment of the infectome, as they are time consuming, and tissue of the affected organ may not be readily available from all patients. The analysis of blood, faecal material, urine, or saliva is more plausible, and can be used for screening, reflecting the 'top-down' approach suggested by other researchers [35]. As mentioned, multiplex PCR is a useful tool for evaluating the presence of microorganisms from a variety of sample types. Microbiome studies have also highlighted the use of 16S/18S rRNA gene sequencing, which allows for the mass-analysis of samples [290,292]. However, one drawback of this approach in comparison to immune profiles is the risk of missing the right time or site of sampling.

11. Where to screen?

The question also remains as to which body sites should be sampled. In addition to the affected organ, general or systemic infections should be an indication for sampling. This may include urine and stool samples in urinary and gastrointestinal tract infections respectively, or blood cultures in febrile patients. In addition to clinically overt infections, many patients with autoimmunity may have latent infections such as Lyme disease or *Mycoplasma*. Examples of this include hidden chronic low grade infection associated with dental treatments. In fact, the oral cavity is not commonly examined for infection in patients with autoimmune disease, and it would most likely be useful to examine and sample the oral cavity for such overt infections [312–314]. Accumulating evidence indicates that oral hygiene practices may induce alterations in the flora of the oral mucosa, which leads to a dysbiosis in the gut microbiome, and thereby contributes to the pathogenesis of IBD [312]. On the other hand, the increased frequency of dental problems in IBD patients may be due to alterations in oral flora. Complementing these findings, a study by the group of Helenius [314] indicates that patients with rheumatic conditions had various alterations in salivary flow and composition, and oral health. It remains to be seen whether the increased incidence of bacterial infections is common among all autoimmune diseases, and if so, which oral microorganisms are common among those conditions.

The proposed model of screening is not only useful in characterising the components which lead to autoimmune disease development/progression, but may also provide further evidence as to preventative measures. For example, if it is demonstrated that progression of an autoimmune disease is dependent upon infectious triggers, the proper use of antibiotic or even antiviral therapy may be initiated early on in the management of these patients. Antibiotic treatment for infectious agents associated with autoimmune disease may slow the progression of the disease in some individuals, and possibly prevent the development of the disease in individuals found to be at risk. If exposure to a particular microbe is proven to be critical in a particular autoimmune disease development, measures may be taken to reduce the exposure to this microbe, regardless of whether it is exogenous or endogenous. Such treatments can only be incorporated in the routine management of these diseases through consensus statements and authoritative position papers/guidelines; otherwise are potentially dangerous for the wellbeing of the patient [272,276,277,315].

12. Conclusion

Genetic and environmental components are involved in the pathogenesis of most diseases. The GWAS have contributed greatly to the understanding of the genetic basis of disease. The theory of the exposome complementing GWAS is now evolving. The complexity of the exposome may require that it be broken down to several subcomponents such as the infectome, which reflects the characterisation and measurement of all infectious organisms that we are exposed to. The relationship of the exposome/infectome to the development of a disease, in individuals with particular genetic characteristics, may also help us characterise disease initiation and progression.

Given the growing knowledge of the genetic basis of disease, it may one day be possible to screen newborns for HLA and genetic characteristics which infer susceptibility to autoimmune disease, which may be done as routinely as the current newborn screening. Infants with a particular susceptibility profile can then be monitored closely for exposure to environmental triggers that may contribute to the development of a particular autoimmune disease. It is therefore essential that we establish not only the genetic basis of the disease (via GWAS), but also the environmental component of the disease, which must be established through an exposomal model. The covalent binding of xenobiotics to genomic DNA has been extensively explored and should be re-visited in this context in the light of more recent findings. As there is a clear delineation between organic and inorganic materials, the establishment of the infectome will represent the infectious component, comprised of all potential infections that initiate the disease, or alter the disease course. It is important that the subgroups of the exposome are considered together alongside the detailed investigation of each component part. It is likely that the methods used to establish and analyse the infectome will be simple modifications of technology already in use. It remains to be seen how this approach may be applied to other potential subgroups of the exposome, such as xenobiotics.

Take-home messages

- The infectious/host immunological interactions in autoimmunity are poorly understood.
- A direct link between infection and autoimmunity is difficult to obtain.
- Infectome refers to the collection of an individual's exposures to infectious agents.
- Infectome can be characterised with approaches employed for the "immunome" and "microbiome" projects.
- The study of the infectome can help us to delineate the triggers of autoimmunity.

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