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Animal Models used to Examine the Role of the Environment in the Development of Autoimmune Disease: Findings from an NIEHS Expert Panel Workshop^a

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Abstract

Autoimmunity is thought to result from a combination of genetics, environmental triggers, and stochastic events. Environmental factors, such as chemicals, drugs or infectious agents, have been implicated in the expression of autoimmune disease, yet human studies are extremely limited in their ability to test isolated exposures to demonstrate causation or to assess pathogenic mechanisms. In this review we examine the research literature on the ability of chemical, physical and biological agents to induce and/or exacerbate autoimmunity in a variety of animal models. There is no single animal model capable of mimicking the features of human autoimmune disease, particularly as related to environmental exposures. An objective, therefore, was to assess the types of information that can be gleaned from the use of animal models, and how well that information can be used to translate back to human health. Our review notes the importance of genetic background to the types and severity of the autoimmune response following exposure to environmental factors, and emphasizes literature where animal model studies have led to increased confidence about environmental factors that affect expression of autoimmunity. A high level of confidence was reached if there were multiple studies from different laboratories confirming the same findings. Examples include mercury, pristane, and infection with *Streptococcus* or Coxsackie B virus. A second level of consensus identified those exposures likely to influence autoimmunity but requiring further confirmation. To fit into this category, there needed to be significant supporting data, perhaps by multiple studies from a single laboratory, or repetition of some but not all findings in multiple laboratories. Examples include silica, gold, TCE, TCDD, UV radiation, and Theiler's murine encephalomyelitis virus. With the caveat that researchers must keep in mind the limitations and appropriate applications of the various approaches, animal

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models are shown to be extremely valuable tools for studying the induction or exacerbation of autoimmunity by environmental conditions and exposures.

Keywords

autoimmunity; animal model; environmental factors; chemicals; biological

1. Introduction

Environmental factors have been reported to be associated with autoimmunity in humans. However a direct link is difficult to establish because of the inherent limitations of epidemiological studies to draw causal conclusions. A link between environmental exposure and autoimmune disease is made more difficult because human populations are rarely exposed to a single agent, there can be a significant delay between exposure and disease onset, and it is often not possible to identify all the agents to which individuals may have been exposed. Medications are exceptions because exposed populations can be identified and affected individuals can cease use of the suspected agent in order to determine if consumption is the cause of disease [1, 2]. Nevertheless, induction of autoimmune disease as a result of medications has established that contact with exogenous agents can result in autoimmunity. Animal models have played a significant role in investigations into the mechanisms of drug-induced autoimmunity [3–5]. Thus animal models have proven to be useful surrogates for identification of exogenous factors that affect autoimmune disease in humans.

Investigation of autoimmune disease has resulted in the development of several animal model approaches. Idiopathic disease mechanisms can be examined in inbred murine strains that spontaneously develop organ specific (e.g. diabetes [6]) or systemic (e.g. lupus [7]) autoimmunity. Autoimmunity can also be induced in animals by immunization with specific (auto)antigen (e.g. EAE [8]), or genetic manipulation [9, 10]. Examination of the role of environmental factors in autoimmunity most often involves exposure of healthy inbred mice to determine if the agent can elicit disease in a non-autoimmune-prone population. However, such research is hindered by the complexity of disease susceptibility loci that may or may not be present in these mice. Thus studies have examined exposure in autoimmune-prone strains as examples of genetically sensitive populations. In this later case, exposure may exacerbate or accelerate disease expression. A list of common rodent models for studying environmental effects on autoimmunity are listed in Table 1.

In 2010 the National Institutes of Environmental Health Sciences (NIEHS) convened a workshop to examine the role of the environment in the development of autoimmune disease. The authors of this report were charged with drawing conclusions regarding published data on animal models. This review is a condensed description of those deliberations and examines the roles that non-therapeutic chemical, physical and biological agents play in the induction and/or exacerbation/acceleration of autoimmunity in a variety of animal models. The more detailed and wider ranging white paper prepared following the NIEHS workshop is available from the corresponding author.

We did not examine drugs in this report because, although there is clear evidence that they can elicit autoimmune disease [11], they are most often taken under medical supervision and exposure is closely monitored and can be terminated at any time. This is often not the case with non-therapeutic chemical, physical and biological agents that humans may be exposed to during their lifetime.

Our review of the literature identified individual chemical, physical or biological factors that have been shown to either induce autoimmunity in non-autoimmune-prone strains, or exacerbate disease in inducible or spontaneous autoimmune models. Exposures for which multiple independent studies have found the same or similar results to provide confidence that the factor in question influences expression of autoimmunity are listed in Table 2. Those environmental factors where significant effects have been reported but multiple independent studies are lacking have been classified as appearing likely to affect autoimmunity but require further confirmation (Table 3). The tabulated studies should not be considered to encompass all published studies on animal exposure to any particular agent. Finally we identify several broad themes that should be pursued in future investigations to identify exogenous agents that affect expression of autoimmune disease in animals.

2. Factors that Induce Autoimmune Responses in Non-Autoimmune Prone Strains

2.1 Metals: Mercury, Gold, and Silver

Mercury has been implicated as an environmental trigger in the induction of autoimmunity in humans [4]. The extensive literature on mercury-induced autoimmunity in experimental animals has been recently reviewed [4, 12]. The response of non-autoimmune rats to mercury is strain specific, clearly implicated gene-environment interactions. Implantation of dental amalgams into molars of BN rats results in a polyclonal B cell activation, elevated IgE and kidney deposition of IgG while Lewis rats are unaffected [13]. Mice also exhibit strain specific responses to mercury [12]. Susceptible strains given HgCl₂ develop a polyclonal B cell activation with autoantibodies and tissue immune complex deposits [14, 15]. Exposure to mercury vapor increased serum immunoglobulins, autoantibodies and mesangial IgG deposits [16]. Dental amalgam resulted in hypergammaglobulinemia, autoantibodies and tissue immune deposits [17]. Murine mercury-induced autoimmunity is not transient as found in the rat but may last for many months [18].

Gold salts have been used to treat rheumatoid arthritis (RA), but this can lead to complications including nephropathy [19]. Therefore, animal models have been used to test the ability of gold to induce autoimmunity. The response to gold is strain-specific with BN rats developing polyclonal B cell activation, autoantibodies, increased IgE, immune complex nephritis and vasculitis, while Lewis rats show less immune activation and pathology [20, 21]. As with mercury, the humoral responses in rats are transient, peaking within the first few weeks [20, 22, 23]. Immunological responses induced by gold in mice are also strain-specific, with differences in serum immunoglobulin levels and ANA responses, and humoral responses in mice persist throughout the exposure period [24, 25].

Autoantibodies are induced in mice via exposure to silver nitrate in drinking water, subcutaneous injection, or intraperitoneal implantation of silver alloy [4]. The MHC class II restricted autoantibody response targets the nucleolar protein fibrillarin [26]. Non-MHC genes influence the response rate and titer [27]. ANA have also been reported in outbred strains exposed to silver [28] suggesting that genetically heterogeneous backgrounds are susceptible to silver-induced autoantibodies. Silver exposed mice express a limited set of autoantibodies, without immune-complex deposits [27]. Thus silver results in less aggressive features of autoimmunity than mercury [4].

2.2. Mineral oil

Constituents of mineral oil and related substances are potent proinflammatory agents and adjuvants [29]. Thus, exploration of its potential to induce autoimmune response in animal models was prudent. Intradermal injection of Freund's incomplete adjuvant and its

constituents, mineral oil and Aracel A, induces an acute T cell-dependent spontaneous inflammatory arthritis in DA rats resembling adjuvant arthritis [30, 31]. Subcutaneous injection of a component of mineral oil, 2,6,10,14-tetramethylpentadecane (TMPD or pristane) in rats leads to a chronic inflammatory arthritis, with signs similar to human RA, in certain strains [32]. Among the strains, DA is the most and E3 the least susceptible; therefore clues to susceptibility genes are provided by animal models [32].

Inflammatory arthritis is induced in BALB/c mice with i.p. injections of TMPD. Serological findings consistent with rheumatoid arthritis included rheumatoid factor and anti-collagen antibodies [33]. Similar to the rat, susceptibility in mice differed among the strains examined, with the DBA/1 being highly susceptible and developing chronic erosive arthritis 4–8 months after exposure [33, 34]. Interestingly, TMPD-treated mice also exhibit many of the clinical features of human SLE including female predominance, the expression of interferon induced genes (“interferon-signature”), anti-RNP and anti-Sm antibodies, arthritis, and glomerulonephritis [29]. Susceptibility is strain dependent, as TMPD can induce autoantibody production in most immunocompetent strains with substantial variability in the time of onset, frequency, and severity [35]. TMPD also enhances the susceptibility of spontaneous lupus-prone strains except those that are *Fas*-deficient [35–37] suggesting that the pathogenic mechanisms of induction involve apoptosis. This example demonstrates the ability of genetic manipulation of animal models to explore mechanisms involved.

2.3 Rapeseed Oil

Exposure in 1981 to an adulterated rapeseed oil manufactured for industrial use but denatured with 2% aniline, refined and sold as cooking oil, resulted in a disease termed toxic oil syndrome (TOS) [38]. Animal models helped to establish a component involved and confirm its ability to induce a similar disease in mice. Oleic acid anilide (OAA) exposure in B10.S and C57BL/6 mice resulted in a chronic polyclonal B cell activation together with autoantibodies [39, 40] while A/J mice have an acute and lethal wasting disease [39].

2.4 L-tryptophan

The eosinophilia-myalgia syndrome (EMS) associated with L-tryptophan ingestion was first recognized in the United States in 1989. EMS is characterized by eosinophilia, myalgia, joint pain, pruritus, edema, and sclerodermoid cutaneous manifestations [41]. Initial epidemiological studies implicated L-tryptophan from a single manufacturer, but other risk factors include increased dose of L- tryptophan, increased age and use of Ltryptophan as a sleeping aid [42]. High dietary tryptophan in rats amplified some of the pathological features of eosinophilia myalgia [43]. Exposure of Lewis rats resulted in inflammation of the fascia and perimysial spaces plus increased thickness of the fascia and the perimysial septae but no evidence of eosinophilia [44]. Ltryptophan and 1,1'-ethylidenebis (L-tryptophan) (EBT), a dimer of L-tryptophan found in greater concentration in case-associated L- tryptophan, failed to reproduce the inflammation of the fascia and perimysial spaces but did result in increased fascial thickness [45]. A study in C57BL/6 mice, using daily i.p. injections of L- tryptophan and/or EBT found inflammation of the fascia, fascial thickening and fibrosis but no eosinophilia [46]. Guinea pigs orally supplemented with non-case associated L- tryptophan for 14 days had decreased blood eosinophils and increased eosinophils in bronchiolar lavage but no skin changes [47]. In this case, animal models confirmed the pathogenic potential of L-tryptophan, while the variable responses suggest a complex, multi-genic susceptibility.

2.5 Iodine

The thyroid gland is frustratingly susceptible to autoimmune pathology, and yet the reasons and mechanisms behind this are not clear. Animal model studies also paint a complex picture, but are beginning to suggest mechanistic possibilities. Numerous studies have demonstrated that high dietary intake of iodine leads to increased incidence of thyroid autoimmunity in genetically predisposed NOD.H2h4 mice [48–52]. These studies have shown an increase in thyroiditis (characterized by lymphocytic infiltration) and antibodies to thyroglobulin, an iodoglycoprotein synthesized in the thyroid. Studies have indicated the presence of antithyroglobulin antibodies in mice with excess iodine may be due to increased iodination of thyroglobulin, and are able to separate disease phenotypes that are inflammatory or truly autoimmune [49, 51]. Evidence of exacerbated disease has also been observed in thyroiditis-prone BB rats follow excess dietary iodine [53]. BB/W rats injected with normal iodine content thyroglobulin showed an increased incidence of thyroiditis as opposed the rats injected with low iodine content thyroglobulin [54].

2.6 Infections

Animal models have been used to demonstrate that both genetics and infections are important in the co-morbidity of autoimmune disease and have been critical in the identification of the mechanisms and linkage with autoimmune pathology. Multiple infectious agents have been associated with autoimmune disorders that target the same tissues (i.e. streptococcus, Coxsackie B virus and Trypanosoma cruzi with myocarditis; Epstein-Barr virus (EBV) and mycoplasma with rheumatoid arthritis), and individual infectious agents have been associated with multiple autoimmune diseases (i.e. Hepatitis C virus with antiphospholipid syndrome, autoimmune hepatitis and vasculitis). The examples provided below are not all-inclusive, but rather highlight the pathogenic organisms that have been used to model some of the most common autoimmune diseases.

2.6.1. Bacterial Infections—Many features of the myocardial and vascular lesions observed in rabbits that received multiple cutaneous injections of group A streptococci [55] closely approximate the pathology observed in fatal cases of rheumatic fever [56]. While the Streptococcus organism has only rarely been isolated from affected tissues in humans, the bacterial antigens can induce myocarditis when injected into multiple strains of mice [57]. Monoclonal antibodies that recognize Streptococcal N-acetyl-glucosamine have been shown to deposit in the extracellular matrix of the myocardium in DBA/2 mice [58]. These antibodies generate T-cell dependent antibody responses that cross-react with cardiac myosin and the matrix protein laminin, resulting in inflammatory lesions in the muscle and valve endothelium [59]. Immunization with antibodies to streptococcal M protein also results in cardiomyopathy and valvular lesions in Lewis rats [60–62].

Immunization of susceptible rodents with heat shock proteins (HSP) from several mycobacterium strains can lead to pathology similar to rheumatoid arthritis in humans. When housed in a strictly controlled pathogenfree (SPF) environment, these mice failed to develop chronic arthritis, suggesting that infection may be a trigger for the induction of disease [63].

2.6.2. Viral Infections—Multiple sclerosis (MS) is characterized by inflammatory demyelination throughout the nervous system. Animal models of virally-induced demyelinating diseases have similar pathology to MS. Infection with Theiler's murine encephalomyelitis virus (TMEV) is used as a model of experimental autoimmune encephalomyelitis (EAE) [64, 65]. An initial virus-specific T cell response targets these virally infected cells leading to a transient meningo-encephalo-myelitis that resolves in mouse strains that are not genetically susceptible [66]. In SJL and other susceptible strains,

this inflammatory response leads to macrophage-mediated demyelination due to the release of pro-inflammatory cytokines and reactive oxygen species [67].

A number of viruses have been implicated in human myocarditis. Coxsackievirus B (CVB) is considered the dominant etiological agent, and infectious virus and viral RNA have been isolated from biopsy and autopsy specimens from patients with the disease [68, 69]. Resistant mouse strains eliminate the virus after an initial acute phase and do not develop autoimmune myocarditis [69, 70]. In susceptible mouse strains there is early injury to cardiomyocytes with an acute inflammatory response [71]. During the subacute phase of the infection, autoantibodies that target the myocardial proteins such as myosin, tropomyosin and actin develop, and correlate with disease severity and progression to cardiomyopathy and heart failure [68]. Mice with a cardiac-specific deletion of the Coxsackievirus–adenovirus receptor, which facilitates viral entry into cells, do not develop myocarditis [72], providing strong causative evidence.

Type 1 Diabetes (T1D) results from the destruction of pancreatic β cells by autoreactive T lymphocytes and/or inflammatory cytokines. Many viruses have been reported to be associated with T1D in humans, including CVB, rubella virus, mumps virus, cytomegalovirus, Epstein-Barr virus and rotavirus [73]. There is a strong genetic component to T1D and the most commonly used animal models for the disease, the Non-obese diabetic (NOD) mouse and the Bio-Breeding (BB) rat, develop spontaneous disease. However disease incidence and severity can be affected by the microbial environment in which the animals are housed, or by exposure to microbial stimuli and viral infection. The most compelling evidence for the role of viruses in T1D comes from studies with the encephalomyocarditis (EMC) virus in mice and the Kilham rat virus (KRV) in BB rats [74]. There is sequence homology between a Coxsackie B4 viral protein and human glutamate decarboxylase (GAD; [75]), and it has been suggested that CVB may act as a molecular mimic of the GAD and stimulate the production of anti-GAD autoantibodies.

2.6.3. Parasitic Infections—Chagas' disease cardiomyopathy is a consequence of infection with *Trypanosoma cruzi*, and is a major cause of cardiovascular related death in Latin America. In the century that has passed since the description of the disease, there has been (and still remains) considerable debate with regard to whether the pathogenesis of the disease is the result of parasite persistence or the development of auto-reactivity [76, 77]. Proponents of an autoimmune etiology for the disease suggest cross-reactivity between antibodies directed at the organism and myocardial or cardiac connective tissue and autoreactive cellular immunity as potential mechanisms [78]. Several animal species including dogs, monkeys, rabbits, guinea pigs, rats and mice have been used to model the disease, and there is evidence to suggest that the genotype of both the host and parasite are important in the outcome of the disease [79]. Murine models of *T. cruzi* infection are frequently used to study potential autoimmunity in Chagas disease. To investigate cardiac autoimmunity in the acute phase of infection, A/J mice have been infected with the Brazil strain of *T. cruzi* for periods ranging from 7–30 days [80]. Twenty-one days post-infection these animals demonstrated severe myocarditis, accompanied by IgG autoantibodies and delayed type hypersensitivity responses against cardiac myosin. Similarly infected C57Bl/6 mice, previously reported to be resistant to CVB-induced cardiac autoimmunity [81], generated lower levels of myosin-specific IgG and did not develop myocarditis [80].

3. Factors that Exacerbate Autoimmune Responses in Autoimmune Prone Strains

3.1. Silica

Autoimmune prone NZM2410 mice exposed to crystalline silica (SiO_2) had increased serum autoantibodies, proteinuria and reduced survival [82, 83]. Thus, silica can exacerbate autoimmunity in a lupus model, but there is limited data regarding induction in non-autoimmune strains, with only one study demonstrating the ability of silica to induce autoimmune responses in animal models that do not normally exhibit an autoimmune phenotype. Sodium silicate (NaSiO_4) exposure in Brown Norway rats resulted in increased serum autoantibodies [84]. Therefore, silica has been shown to affect the expression of autoimmunity, in terms of production of autoantibodies in both mice and rats, and other disease manifestations in mice. Now that exposure to crystalline silica has been confirmed as having a strong association with autoimmune disease in humans (Reviewed in paper by Miller, et al, in this issue), subsequent studies of silica exposure in animal models should focus on mechanisms of lost tolerance and pathogenesis, including genetic susceptibility loci. This type of data can be used to inform human studies, illustrating just one example of translational application of animal models.

3.2. Metals

Mercury exposure exacerbates the expression of systemic autoimmunity in NZBWF1, MRL-*Fas*^{+/+} and BXSB mice [85–87]. Mercuric chloride exacerbated the severity and onset of arthritis in a collagen-induced model [88]. In contrast HgCl_2 produced a significant reduction in insulinitis and delayed diabetes in nonobese diabetic (NOD) mice; however, these mice still developed a polyclonal B cell response and deposits of IgG in the kidney [89]. Similarly, tight skinned mice (C57BL/6 *Tsk1*/+), an animal model of scleroderma, showed no progression of skin fibrosis but developed a polyclonal B cell response and renal IgG deposits [90]. Thus, mercury appears to not only induce autoimmunity in non-autoimmune animals (discussed above), but also to exacerbate or ameliorate various autoimmune disease models.

3.3. TCDD

Dioxins are waste contaminants of industrial processes that persist in the environment and bioaccumulate [91]. Among the dioxins, the most potent is the halogenated aromatic hydrocarbon, 2,3,7,8- tetrachlorodibenzo-*p*-dioxin (TCDD). Epidemiological studies have implicated TCDD with a variety of generally modest immunological alterations, including immunodeficiency, but have not documented an association with autoimmune disease [91–96]. However, TCDD can induce autoimmunity if exposure occurs during fetal development or the early neonatal period. A single exposure of TCDD during mid gestation was shown to slightly enhance anti-DNA antibodies and/or glomerular immune complex deposits in non-autoimmune C57BL/6 or lupus-predisposed SNF1 mice [97, 98]. Neonatal exposure of NFS/*sld* mice to TCDD induced a Sjögren's syndrome-like disease along with increased anti-SS-A/Ro and anti-SS-B/La autoantibodies [99]. The extensive literature on TCDD exposure in animal models thus begins to explore the possibility of adult exacerbation of disease via pre-natal exposure.

3.4. Organochlorine pesticides

Several banned organochlorine pesticides have been shown to promote the development of autoimmunity in the lupus-prone NZBWF1 strain [100, 101]. These include *o*, *p*' - dichlorodiphenyltrichloroethane (DDT), methoxychlor, and chlordecone. Exposure to these compounds accelerated mortality in ovariectomized females, and for chlordecone,

exacerbated autoantibody production, glomerular immune complex deposition, and proteinuria [101]. Chlordecone also accelerated disease in ovary-intact female NZBWF1, but did not induce lupus-like disease in the non-autoimmune BALB/c strain [100], suggesting that the mechanism of action only exacerbates an already existing autoimmune disease.

3.5. Trichloroethylene (TCE)

Trichloroethylene (TCE) is an industrial solvent used in metal cleaning and degreasing and has been found to contaminate ground water. Studies on the induction and/or exacerbation of autoimmunity in humans and experimental animals by TCE and derivatives has been recently reviewed [102]. Using adult autoimmune prone MRL-*Fas*^{+/+} mice studies have demonstrated an accelerated autoimmune response including increased autoantibodies, T cell activation and inflammatory cytokines [103–106] following TCE exposure via different routes and a wide range of doses. Various metabolites of TCE, including dichloroacetyl chloride [104], trichloroacetaldehyde hydrate [107, 108] and trichloroacetic acid [107] produced similar results in MRL-*Fas*^{+/+} mice as TCE. Interestingly, MRL-*Fas*^{+/+} mice exposed to TCE from conception to adulthood had evidence of accelerated autoimmunity [109] as did those exposed from gestation day 1 to 6 weeks of age [110]. Therefore, as with TCDD, animal models provide data that suggest that early exposures may be very important in subsequent development of disease, and emphasize developmental effects of exposures on the young immune system.

3.6. UV radiation

Photosensitivity contributes to human autoimmune diseases, including cutaneous lupus erythematosus (CLE) [111]. Acute or chronic doses of UV radiation (UVA and UVB) increased mortality in male lupus-prone BXSB mice but not other lupus-prone strains including MRL-*Fas*^{lpr} and NZBWF1 strains [112]. The increased mortality was associated with autoantibodies and glomerulonephritis and was a direct result of UVB (320–290nm) radiation.

Menke et al [113] found that UVB exposure increased skin lesions and levels of colony stimulating factor-1 (CSF-1) in MRL-*Fas*^{lpr} mice but not in CSF-1 deficient MRL-*Fas*^{lpr} mice (MRL-*Fas*^{lpr}/*csf1*^{-/-}) or BALB/c mice. In the MRL-*Fas*^{lpr} or MRL-*Fas*^{lpr}/*csf1*^{-/-} mice reconstituted with CSF-1, UVB was able to trigger an increase of macrophages in the skin and an increase in keratinocyte apoptosis, which led to an increase in CLE. Both CLE and nephritis in MRL-*Fas*^{lpr} mice requires the presence of CSF-1, and UVB accelerates onset of these lupus phenotypes by enhancing the production of CSF-1 and apoptotic keratinocytes. Dermal fibroblasts from lupusprone strains (MRL-*Fas*^{lpr} and NZBWF1) upon exposure to UVB produce more proinflammatory cytokines (IL-1 β , IL-6 and TNF α) than C57BL/6 or BALB/c mice, which may relate to the increase in cell damage and enhanced autoimmunity [114].

3.7. Gluten

Celiac disease (CD) is the result of lost tolerance to grain gluten, mediated by activated CD4⁺ T cells specific for peptides of gliadins presented on MHC Class II. Certain animals are particularly susceptible to gluten intolerance, including Irish Setters [115] and BALB/c mice [116]. In addition, strains susceptible to other endocrine-immune diseases, such as BB rats and NOD mice, also appear susceptible to CD, and in fact a diet containing gluten increases the incidence of diabetes in NOD mice in addition to small intestinal enteropathy [117]. A relatively new model is the gluten-sensitive HLA-DQ8 transgenic mouse. Loss of gluten tolerance appears to occur in the presence of gluten peptides bound to HLA-DQ2 or DQ8. This mouse strain is therefore susceptible to CD [118]. Animal models are thus

providing new evidence of gene susceptibility that may translate to our understanding of human susceptibility to this disease.

4. Summary of conclusions and levels of confidence

Two levels of consensus were identified. A high level of confidence was reached if there were multiple studies from different laboratories confirming the same findings. Any studies with data contrary to the majority were only excluded if there was evidence that the study and/or its interpretation were faulty. A second level of consensus identified those exposures considered likely to influence autoimmunity but requiring further confirmation. To fit into this category there needed to be significant supporting data, perhaps by multiple studies from a single laboratory, or repetition of some but not all findings in multiple laboratories.

4.1. Based on existing evidence, we are confident of the following, with supporting studies listed in Table 2

1. Forms of inorganic mercury induce systemic autoimmune disease in rats (transient) and mice, and exacerbates systemic autoimmune disease in lupus-prone mice.
2. Several mineral oil components and certain other hydrocarbons can induced an acute inflammatory arthritis in some rat strains.
3. The mineral oil component 2,6,10,14-tetramethylpentadecane (TMPD or pristane) can induce chronic lupus like disease and inflammatory arthritis in several strains of mice.
4. For a limited number of pathogens, there is a clear association between infection and the development of specific autoimmune diseases.
5. Excess iodine increases the incidence of autoimmune thyroiditis in genetically predisposed animal models.

4.2. Based on existing evidence, we consider the following likely but requiring conformation (Supporting studies listed in Table 3)

1. Gold causes (transient) nephropathy in rats. Gold and silver cause autoimmune responses, not autoimmune disease, in mice; but the ability of silver and gold to exacerbate spontaneous autoimmune disease requires study.
2. Silica exacerbates autoimmune disease but more studies are needed using more species/strains and a wider range of doses and exposure routes.
3. Trichloroethylene (TCE) exacerbates systemic autoimmunity although responses are often limited and transient. More studies are needed with additional species/strains to examine induction of autoimmune liver disease and in developmental studies.
4. There is some indication that TCDD can promote autoimmunity when exposure occurs during fetal or early neonatal development.
5. Organochlorine pesticides have been reported to enhance lupus-like disease in a predisposed mouse strain.
6. UV radiation exacerbates lupus in genetically prone mice.

4.3. We believe the following broad themes should be pursued in future investigations

Based upon the literature review and discussion points raised during the NIEHS *Expert Panel Workshop to Examine the Role of the Environment in the Development of*

Autoimmune Disease a number of broad themes were identified to be worthy of further study and/or consideration by investigators.

1. Responses of animals to environmental exposure should not be the only driving force for human studies. Studies should be “shaped by what is observed in humans, not by what is possible in mice” [119].
2. A single mouse strain is clearly unable to encompass the heterogeneity of the human population. Thus studies should not be restricted to the identification and/or use of a “gold standard” animal model. Rather models should be investigated that best reflect human genetic heterogeneity, and/or ask specific mechanistic questions that a particular model is able to address.
3. When using spontaneous disease models it is important to consider whether environmental exposures directly impacts idiopathic autoimmunity, or reflects environmental factor-specific autoimmunity.
4. More studies on the effects of environmental factor exposure on expression of autoimmunity during different stages of life (gestational to adulthood) are needed.

4.4. General Conclusions

Our survey of the literature clearly shows that an autoimmune response following exposure to environmental factors is dependent upon genetic background of the host and can vary widely among species and strains. Our review also revealed that most animal models only recapitulate some features of human disease but that this provides useful information given the genetic heterogeneity of individual human autoimmune diseases. It is also clear that to establish the validity of any animal model of environmentally induced human autoimmunity there should be well defined markers of disease expression and pathology that are easily accessible in biological samples of both humans and the animals under investigation. We also believe that it is important that a catalog of animal models, along with their characteristics, be established to help investigators identify the most appropriate strains and/or species for their studies. The strength of animal models lies not only in the genetic homogeneity of inbred strains but also the ability to control experimental conditions.

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Research Highlights

1. Responses following environmental exposures in animals depend on genetic background.
2. Animal models have enough features of human disease to provide useful information.
3. Strengths of animal models: genetic homogeneity and control of experimental design.
4. Animal models provide strong data linking certain exposures to autoimmune disease.
5. Other exposures likely impact autoimmunity, but require confirmation.

Table 1**Common Rodent Models**

Mouse models	Name	Disease modeled	Notes
	EAE (Many strains)	Multiple sclerosis (MS)	Immunize with myelin
	NZM (New Zealand Mixed)	Systemic Lupus/nephritis	Polygenic, NZB/NZW cross
	NOD (non-obese diabetic) A.SW	Type I Diabetes	
	C57BL/6	Wild type inbred	
	B10.S		Derived from C57BL/6
	SJL/J	EAE/MS	Inducible with myelin or
	NZB/W F1	Systemic lupus	Polygenic, NZB/NZW cross
	BXSB	Systemic lupus	
	MRL- <i>Fas</i> ^{lpr}	Systemic lupus	
	MRL- <i>Fas</i> ^{+/+}	Systemic lupus	
	CD1	Wild type	Albino
	DBA/1	Arthritis	Immunize with collagen
	SNF1	Systemic lupus	
	NFS/sld	Sjögren's Syndrome	
	C3H/HeJ	Wild type	Endotoxin resistant
Rat models			
	Brown Norway (BN)	Some cancers	
	BB (BioBreeding)	Type I Diabetes, Thyroid	
	PVG/c	Resistant to disease induction	Complement 6 deficient
	Sprague-Dawley		Autoimmune resistant
	Wistar		Albino
	Lewis	Several (Arth, EAE, etc)	Induced by immunization
	DA (Dark August)	Several (Arth, EAE, Thyr, MS)	Induced by immunization
	E3	Resistant to induced arthritis	

Table 2

Environmental Factors that we are confident induce or exacerbate autoimmunity.

Agent (Form)	Species, strain	Sex	Age (weeks)	Exposure, Vehicle	Doses Tested, length of exposure	Endpoints	Reference
Chemical Factors							
<i>Metals</i>							
Inorganic Mercury (HgCl ₂)	Mouse, B10.S, SJL, others	M, F	6–8	Injection s.c., saline	1.6 mg/kg two to three times/week for 4 weeks	Disease induction: serum Igs, autoAb, immune deposits	Kono DH et al, 1998 [15] Abedi-Valugerti M et al 2001 [14]
Inorganic Mercury (HgCl ₂)	Mouse, NZBWF1	F	4–8	Injection s.c., saline	1.6 mg/kg two to three times/week for 4 weeks	Disease exacerbation: serum Igs, autoAb, immune deposits	Al-Balaghi S et al, 1996 [85] Pollard KM et al, 1999 [86]
<i>Adjuvants</i>							
TMPD (Pristane)	Rat, Dark Agouti, others	M, F	8–14	S.c. or intradermal, saline	150 ul X 1, up to 1 year	Disease induction: arthritis	Olofsson P and Holmdahl R, 2007 [32]
TMPD (Pristane)	Mouse, BALB/c, others	M, F	8–12	i.p., saline	0.5 ml, up to 9 months	Disease induction: serum Igs, autoAb, immune deposits, arthritis	Satoh M et al, 2000 [35] Clynes R et al, 2005 [34]
Biological Factors							
<i>Associated Infections</i>							
Streptococcus group A	Mouse, BALB/c,	M/F	4–8	s.c./PBS	0.5mg M protein peptides/8 weeks	Disease induction: AutoAbs, myocarditis	Cunningham MW et al, 2001 [57]
	Rat, Lewis	F	8–12	s.c. or i.p./CFA	0.5 mg recombinant M protein/17–21 days	Disease induction: Lymphocyte proliferation, Valvulitis/carditis	Gorton D et al, 2009 [62] Quinn A et al, 2001 [60]
Coxsackie B virus	Mouse, BALB/c, others	M/F	4–8	i.p./PBS	1×10 ³ PFU (Nancy strain) CVB3 up to 56 days	Disease induction: AutoAbs, myocarditis	Esfandiari M et al, 2008 [69]
<i>Dietary Factors</i>							
Iodine	Mouse, NOD-H2 ^{b4}	M, F	6–8	Oral, water	0.05% iodine for up to 8 weeks	Disease exacerbation: AutoAbs, thyroiditis	Rasooly L et al, 1996 [52] Hutchings PR et al, 1999 [51] McLachlan SM et al, 2005 [49]

Table 3
Chemical Factors that we believe are likely to induce or exacerbate autoimmunity but require confirmation.

Agent (Form)	Species, strain (Source)	Sex	Age (weeks)	Exposure/Vehicle	Doses Tested and length of exposure	Endpoints	Reference
<i>Silica</i>							
Silica (Crystalline)	Mouse, NZM2410	M, F	6	Intranasal, PBS	1mg, two weeks apart	Exacerbation: serum Ig, autoAb, immune deposits, survival	Brown JM et al, 2003 [83] Brown JM et al, 2004 [82]
<i>Metals</i>							
Gold	Rat, Brown Norway	M, F	8–12	Injection s.c., acidified water	Multiple injections of 1mg/kg for up to 9 weeks	Disease induction: serum Igs, autoAb, immune deposits	Toumade H et al, 1991 [20] Qasim FJ et al, 1997 [21]
Gold	Mouse, A.SW, others	F	6–12	Injection im, saline	10mg–22mg/kg/week for 12 weeks,	Disease induction: autoAb,	Havarnasab S et al, 2007 [25]
Silver nitrate (AgNO ₃)	Mouse, B10.S, SJL/N, A.SW	F	4–12	Oral, tap water or Injection sc, saline	0.5 gm/liter, 10 weeks or 2.5 mg/kg every 3 rd day for 4 weeks	Disease induction: autoAb	Hultman P et al, 1995 [27] Hansson M and Abedi-Valagerdi M, 2003 [26]
<i>Halogenated Aromatic Hydrocarbons</i>							
TCDD	Mouse, C57BL/6	M, F	Mid - gestation	Gavage	5 ug/kg (once)	Disease induction: AutoAb, immune deposits	Holladay Sj and Gogal RM, 2011 [97]
TCDD	Mouse, NFS/sld	Not Stat ed	0–3 days	Injection ip,	0.1–10 ng (once)	Disease induction: Sjogren's Syndrome	Ishimaru U et al, 2009 [99]
<i>Pesticides/Herbicides</i>							
Organochlorine pesticides: DDT Methoxychlor Chlordecone	Mouse, NZBWF1 (ovariectomi zed)	F	6–8	Sc, slow release pellet, Control pellets (matrix only)	DDT 0.35 mg/kg/d Methoxychlor 1.2 mg/kg/d Chlordecone 0.2 mg/kg/d, up to 7 months	Disease exacerbation: Survival, autoAb	Sobel ES et al, 2005 [100] Sobel ES et al, 2006 [101]
<i>Solvents</i>							
Trichloroethyl ene (TCE)	Mouse, MRL- <i>Fas</i> ^{+/+}	F	5	Oral, drinking water	2.5mg/ml for up to 32 weeks	Disease exacerbation: autoAbs, T cell activation, cytokines	Griffin JM et al, 2000 [105] Griffin JM et al, 2000 [106]

Agent (Form)	Species, strain (Source)	Sex	Age (weeks)	Exposure/Vehicle	Doses Tested and length of exposure	Endpoints	Reference
Trichloroethylene (TCE)	Rat, Lewis	F	8–12	s.c. or i.p./CFA	0.5 mg recombinant M protein/17–21 days	Disease induction: Lymphocyte proliferation, Valvulitis/carditis	Gorton D et al, 2009 [62] Quinn A et al, 2001 [60]
Biological Factors							
<i>Associated Infections</i>							
Theiler's murine encephalomyelitis virus	Mouse, SJL/J	F	4–7	Intracerebral infection/DMEM	3×10 ⁵ PFU, up to 9 weeks	Disease induction: CNS inflammation, T cell activation, paralysis	Mohindru M et al, 2006 [65] Pope JG et al, 1996 [67]