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Mercury-Induced Inflammation and Autoimmunity

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Abstract

Background—Human exposure to mercury leads to a variety of pathologies involving numerous organ systems including the immune system. A paucity of epidemiological studies and suitable diagnostic criteria, however, has hampered collection of sufficient data to support a causative role for mercury in autoimmune diseases. Nevertheless, there is evidence that mercury exposure in humans is linked to markers of inflammation and autoimmunity. This is supported by experimental animal model studies, which convincingly demonstrate the biological plausibility of mercury as a factor in the pathogenesis of autoimmune disease.

Scope of the review—In this review, we focus on ability of mercury to elicit inflammatory and autoimmune responses in both humans and experimental animal models.

Major conclusions—Although subtle differences exist, the inflammatory and autoimmune responses elicited by mercury exposure in humans and experimental animal models show many similarities. Proinflammatory cytokine expression, lymphoproliferation, autoantibody production, and nephropathy are common outcomes. Animal studies have revealed significant strain dependent differences in inflammation and autoimmunity suggesting genetic regulation. This has been confirmed by the requirement for individual genes as well as genome wide association studies.

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Importantly, many of the genes required for mercury-induced inflammation and autoimmunity are also required for idiopathic systemic autoimmunity. A notable difference is that mercury-induced autoimmunity does not require type I IFN. This observation suggests that mercury-induced autoimmunity may arise by both common and specific pathways, thereby raising the possibility of devising criteria for environmentally associated autoimmunity.

General significance—Mercury exposure likely contributes to the pathogenesis of autoimmunity.

Keywords

mercury; inflammation; autoimmunity; human; animal model

1. Introduction

Mercury is a widely distributed environmental and industrial xenobiotic. Consequently, the risk of mercury exposure for human populations is substantial and occurs through diverse routes such as occupational, dietary contamination, overuse of therapeutic or cosmetic agents, and fossil fuel emissions, among others [1–4]. Exposure to all forms of mercury including elemental, organic and inorganic can lead to a variety of pathologies involving numerous organ systems [3]. In this review, we focus on the immune system and the ability of mercury to elicit inflammatory and autoimmune responses in both humans and experimental animal models. Using this information, we propose possible molecular and cellular pathways through which mercury-induced inflammation can lead to autoimmunity.

2. Mercury exposure and induction of inflammation

Mercury exposure leading to documented inflammatory or autoimmune outcomes include mining, skin whitening creams, and fish consumption. Mercury is used by small scale gold miners in 50 developing countries and is a major source of mercury contamination in the associated rural communities [5, 6]. It is believed that between 10-15 million people, including women and children, are directly involved in artisanal gold mining [5, 7] including over 400,000 in China alone [8]. Mercury containing skin care products are widely used, with one commercial product being available in 35 countries [9]. Although regulated in the USA, use of mercury containing skin lightening creams has been documented in Hispanic women on the Texas-Mexico border [10], and their use accounted for reportable levels of urinary mercury (≥20μg/L) in 9 of 13 individuals identified among 1,840 adult New Yorkers [11]. Consumption offish is one of the major, if not the major, sources of ingestion-related mercury exposure in humans. The levels of exposure can vary depending upon the type of seafood consumed [3], the extent of seafood consumption [12, 13], and proximity to sources of environmental mercury contamination [14].

The ability of metal ions to stimulate inflammatory responses in the absence of mitogens is well established [15], although the mechanisms involved remain to be resolved [16]. Much of our understanding of metal-induced inflammation comes from studies of beryllium exposure [16, 17] where the proposed cellular mechanism involves activation of the innate immune system via cell death, engagement of pattern recognition receptors, migration of

antigen presenting cells to secondary lymphoid organs and subsequent activation of the adaptive immune system including IFN-γ producing Th1 $CD4^+$ T cells [16, 17]. T cell responses in chronic beryllium disease (CBD) are not mediated by direct recognition of Be^{2+} ions but by beryllium ion-induced changes in the structure of preexisting self MHC-peptide complexes that are then recognized by specific T cell antigen receptors [18]. Adaptive immunity mediated by mercury exposure also requires components of the innate immune system [19] arguing that an understanding of the very early events in metal-induced immune cell activation are important for both inflammation and subsequent immuno-pathology [17, 20]. However, an important distinction is that mercury, in contrast to beryllium, exposure induces systemic rather than organ specific autoimmunity [20, 21].

2.1 Human studies

2.1.1 In vitro studies—Mercury-induced proliferation of human lymphocytes has been reviewed previously [15]. These studies primarily involved unfractionated PBMC making identification of the responding cell types difficult. However, several observations are noted here simply because of their relevance to similar studies, described below, using experimental animals. PBMC and thymocytes proliferate within 6 days of exposure [22, 23], and removal of adherent cells does not affect the response of PBMC [23, 24]. Expression of several cytokines including IL-6 and IL-8 [25] but not IL-1β or TNF-α [26] are increased in PBMC. These findings argue that mercury-induced proliferation does not require the structured cellular compartmentalization of secondary lymphoid organs, at least for the first few days of exposure.

Micromolar concentrations of $HgCl_2$ negatively affect several functional activities of neutrophils [27, 28] but enhance chemiluminescence and H_20_2 production [28], and increase release of lysosomal enzymes within hours [27]. Reactive oxygen species generation is also linked to mercury-induced formation of neutrophil extracellular traps [29]. These finding suggest early events following local tissue injury produced by mercury exposure require infiltrating neutrophils [30].

Intracellular tyrosine phosphorylation is increased in neutrophils [31] and lymphocytes [32] following exposure to mercury. This may be related to activation of $p56^{lck}$ [32, 33]. More detailed analysis of intracellular signaling has been done using Jurkat cells, a human T cell line. Mercury enhanced survival of Jurkat cells via blockage of CD95-induced caspase-3 activation [34] potentially via disruption of the death inducing signaling complex (DISC) [35] due to dissociation of preassembled Fas receptor complexes [36]. Low dose mercury exposure also inhibits T cell receptor mediated activation of Ras and ERK MAP kinase in Jurkat cells [37]. This appears due to hypo-phosphorylation of LAT via inactive tyrosine kinase ZAP-70 [38]. The failure to activate ZAP-70 is likely due to mercury-induced inhibition of phosphorylation of the protein tyrosine kinase Lck [39]. These findings with Lck conflict with those found for human PBMC where phosphorylated Lck was co-immunoprecipitated with anti-CD4 after treatment with $HgCl_2$ [32]. Whether these findings reflect differences in intracellular signaling in primary versus transformed cells, or differences in phosphorylation of different tyrosines in Lck remains to be determined.

2.1.2 Epidemiological studies—Elevated serum levels of the inflammatory markers IL-1β, TNF-α, and IFN-γ have been found in gold miners in Amazonian Brazil [40]. Among fish consumers in Amazonian Brazil, L-6, IFN-γ, IL-4 and IL-17 cytokine levels were increased with mercury exposure [41]. In contrast, long term occupational exposure to inorganic mercury was not associated with cytokine levels, except for a negative relationship with serum TNF-α [42, 43]. Studies of cohorts with lower levels of exposure including maternal mercury exposures in the Brazilian Amazon [44] and fish consumers on Long Island, New York [45], have not found associations between mercury levels and serum cytokines. These studies suggest a relationship between exposure level and increased cytokine expression however more studies are needed, particularly those in which care is taken to identify appropriately exposed cohorts, and which control for the complexity of confounding variables including culture and ethnicity, severity and length of exposure, source of exposure (occupational, dietary), biological fluids assayed, analytical procedures, and statistical analysis.

2.2 Animal studies

2.2.1 In vitro studies—Mercuric chloride elicits *in vitro* lymphoproliferation in guinea pigs, rats and rabbits [46], and mice [47–49]. Consistent with human PBMC studies (see above), $HgCl_2$-induced proliferation of murine splenocytes is dependent on mercury concentration, cell density and culture conditions [47–49]. Similar findings were reported for lymphocytes from rat, guinea pig and rabbit [46]. Mouse lymphocyte proliferation is dependent upon macrophages [47] or splenic adherent cells [48, 49] and involves mature $CD4^+$ and $CD8^+$ T cells as neither splenic B cells [48, 49] nor thymocytes respond [48]. In contrast, thymocytes and splenic lymphoid cells from guinea pigs proliferate even in the absence of adherent cells [50], a response more akin to that found for human PBMC [15]. Antibodies against co-stimulatory molecules, and particularly IL-1α, inhibit proliferative responses [48]. Although human and animal studies have used mixed cell populations (PBMC vs. spleen) they show that mercury induces a proliferative response in lymphocytes.

Several studies have determined that *in vitro* exposure to mercury involves intracellular calcium accumulation and signal transduction [15]. These events, occurring within minutes, appear to be initiated at the plasma membrane [51, 52], possibly via oxidation of cell surface thiol groups [15, 33]. Tyrosine phosphorylation is observed in both primary and transformed lymphocytes [33, 53]. Non-toxic doses of $HgCl_2$ selectively affect tyrosine phosphorylation in the mouse B cell line WEHI-231 [54] including attenuation of B cell receptor (BCR)-mediated activation of ERK-MAPK [51]. Lyn, a protein tyrosine kinase, appears to be one target of mercury-induced B cell intracellular signaling [55] leading to defects in BCR signaling in immature B cells [56] and modulation of cytoskeletal protein phosphorylation [57]. It remains to be determined if these findings contribute to *in vivo* inflammatory and autoimmune responses, however the role that Lyn plays in regulating signaling pathways within B cells is known to be important in idiopathic autoimmunity [58].

2.2.2 In vivo studies—Mercury-induced lymphoproliferation *in vivo* has been documented in mice using the popliteal lymph node assay (PLNA) [59, 60]. As found for *in vitro* studies, responses are strain, dose and time dependent. Reactions peak between 4-8

days except for the DBA/2 strain which is unresponsive [59]. DBA/2 mice also fail to develop an inflammatory response following subcutaneous injection of $HgCl_2$ [61]. In contrast, sensitive strains show pronounced inflammatory cell infiltrates, and elevated proinflammatory cytokines together with increased cathepsin B activity [62]. It is unclear whether cathepsin B activity is responsible for, or a consequence of, proinflammatory cytokine expression as cytokines required for mHgIA (IFN-γ, IL-6) are not required for mercury-induced increase in cathepsin B activity nor inflammation at the site of exposure [61, 62]. However, the localization of mercury to lysosomes [63, 64], and subsequent lysosomal membrane destabilization [65] may be a mechanism of rapid cathepsin B release.

Inflammatory events in the first 2-3 days at the site of exposure have not been examined in detail, although increases in IL-1 expression [66] and IFN-γ+ cells [61] can occur within 24 hours. Consistent with *in vitro* studies, both CD4+ and CD8+ T cells and cytokine expression begin to increase within 3 days in spleen and lymph nodes [67–70]. In contrast to *in vitro* studies, B cell expansion also occurs [67, 68] together with production of IgE and IL-4 [71–73]. These studies argued that mercury-induced lymphoproliferation drives a type 2 helper CD4+ T cell response (Th2) [74–76]. However, induction of Th2 IL-4 and/or Th1 IFN-γ was found to be strain dependent, suggesting that a Th2 response does not predominate [69]. Subsequent gene deletion studies found that IFN-γ but not IL-4 is required for mercury-induced proliferation of CD4+ T cells and (auto)antibody producing B cells [77–79]. More recently, it was found that $HgCl_2$ exposure induced the expansion of hematopoietic stem cells and this required bone marrow-resident macrophages and FN-γ [80]. The effects of inorganic mercury exposure on myeloid and lymphoid lineage development might also impact inflammatory and autoimmune responses.

The early inflammatory response, and particularly proinflammatory cytokine expression, is most obvious at the site of exposure rather than the spleen [61, 62, 81]. Numerous proinflammatory mediators, including NLRP3, IL-1β, IL-4, IL-6, TNF-α, IFN-γ [61, 62, 81], and innate and adaptive immune cells [61], are increased within the first week after exposure. Although IFN-γ and IL-6 are not required for the early inflammatory response, they are necessary for the exacerbation of other proinflammatory cytokines as well as genes known to be regulated by either IFN-γ or type I IFN [61]. Pivotal among these may be IRF-1, because it appears to be at the nexus of the interplay between IFN-γ and IL-6 in exacerbating mercury-induced inflammation, regulation of interferon responsive genes and autoimmunity [61, 78]. These early inflammatory events are required for expression of mercury-induced autoimmunity although it remains to be determined which are essential for development of autoantibody production such as germinal center formation and polyclonal expansion of autoreactive B cells.

3. Mercury-Induced Autoimmunity

3.1 Human studies

A recent review of epidemiological data concluded that there is insufficient evidence to prove a causative role for mercury in development of autoimmune diseases [82]. This is due in large part to the paucity of epidemiological studies addressing this association, as well as lack of suitable diagnostic criteria to identify autoimmune disease phenotypes for which

such an environmental exposure plays a causative role [83]. However, a more recent review of the association between mercury exposure and autoimmunity concluded that while evidence of clinical disease remains elusive, mercury exposure in humans is linked to the presence of autoantibodies [84].

3.1.1 Association of mercury exposure and autoantibodies—Association between the presence of autoantibodies and mercury exposure has been found in several quite distinct populations. Epidemiological studies have described autoantibodies [40, 85, 86] in artisanal goldminers in South America. Other studies have observed a positive correlation between fish eating in Amazonians and the presence of anti-nuclear antibodies (ANA) [41], and the interactions of female gender with blood mercury and the presence of ANA in Cheyenne River Sioux Tribe members exposed to mercury through fish consumption [87]. In Faroese children, blood mercury was associated with multiple neural and non-neural IgM antibodies [12]. However, another study of mercury exposure from fish eating in the Amazon failed to find an association between hair mercury levels and ANA, although ANA positivity was more frequent in fish eaters and the only ANA positive individuals were those with ≥6 ppm of hair-mercury [88]. Separate studies of Colombian artisanal gold miners [89] and seafood consumers on Long Island, New York [45] failed to confirm a link between mercury exposures and ANA, however this may reflect the lower levels of mercury in these two study populations. In contrast, an association has been found between urinary mercury levels and anti-fibrillarin autoantibodies in scleroderma patients even though mercury levels were within the normal range [90].

The possibility of an association between autoantibodies and mercury levels has also been examined in various cohorts of the National Health and Nutrition Examination Survey (NHANES), a program designed to assess the health and nutritional status of adults and children in the United States. Using the 2007-2008 NHANES survey, an association was found between the upper quintile of blood mercury (>1.81 ug/L) in women 20 years and older and thyroglobulin autoantibody positivity [91], and hair and blood mercury levels were found associated with ANA in women 16-49 years old from the NHANES 1999-2004 survey [92]. However, analysis of men and women in the NHANES 1999-2004 survey failed to confirm this association [93] as did a comparison of blood levels of mercury and presence of ANA in men and women aged 12 – 85 using 2003-2004 NHAMES data [94].

These NHANES cohort studies suggest a relationship between mercury exposure and autoantibody induction particularly in cohorts with elevated exposure levels. However differences in study populations, study design and/or statistical analysis make establishing a convincing linkage difficult. Moreover, the lack of standardization of ANA testing [95] adds a further layer of complexity that is only likely to be resolved by more specific and sensitive autoantibody assays.

3.1.2 Mercury and nephrotic syndrome—An established outcome of mercury exposure in humans is nephrotic syndrome [96]. Associated exposures include mercury containing cosmetics such as skin whitening/lightening creams [9, 97] and hair dyes [98], occupational contact [99], and mercury-containing pills [98]. A literature review found 26 cases with renal biopsy of which 21 (72%) had glomerular diseases, with membranous

glomerulonephritis (15 patients) and minimal change disease (4 patients) being the major pathological observations [96]. Autoantibodies have been found in some patients [98, 100] but not others [96, 101]. The mechanisms leading to mercury-induced glomerular injury in humans are unknown. Mercury does exhibit significant renal tubular toxicity [102], and it has been suggested that this leads to release of self-antigen and an ensuing inflammatory response involving cytokine [103] and autoantibody production [98, 103].

3.2 Animal studies

The clear demonstration that mercury exposure can induce systemic autoimmunity in different animal species supports the biological plausibility of mercury as a factor in human autoimmune diseases. Numerous studies, predominantly in mice, have shown that mercury-induced autoimmunity can be elicited by a variety of exposure routes including subcutaneous injection [33] or oral ingestion of $HgCl_2$ [34], inhalation of mercury vapor [35], and dental [36] or peritoneal [37] implantation of mercury containing dental amalgam [37]. The expression of disease is influenced by dose [104–107], length of exposure [106], strain [108–110] and the presence or absence of specific genes [19, 77, 78, 111].

Although renal damage following inorganic mercury exposure in humans was known by the 1950s [112], it was not until the early 1970s that studies described glomerulonephritis mediated by immune complex deposits in rat based experimental models [113]. These observations were followed by reports of anti-glomerular basement membrane (GBM) autoantibodies in rats [114] and rabbits [115], and ANA in rats [116]. In mice, $HgCl_2$-induced ANA were found to include anti-nucleolar autoantibodies (ANoA) [117] subsequently identified as antibodies against fibrillarin, a 37-kDa protein component of box C/D small nucleolar ribonucleoprotein (snoRNP) particles [118, 119].

The anti-fibrillarin response is MHC class II restricted unlike $HgCl_2$-induced responses to other nuclear antigens such as chromatin [109]. The response has similar properties to the anti-fibrillarin response in human autoimmunity including recognition of an epitope conserved from humans to yeast [120]. Although mercury binds fibrillarin at its two cysteines, this modification impairs both human and mouse anti-fibrillarin binding indicating that unmodified native fibrillarin is the dominant B cell antigen and arguing against the possibility that anti-fibrillarin neoantigens drive the B cell response [121]. Rather, mercury induced cell death results in proteolytic cleavage of fibrillarin to a 19-kDa fragment [122]. Proteolysis of fibrillarin lacking cysteines, and therefore unable to bind mercury, also produced the 19-kDa fragment which was capable of inducing anti-fibrillarin autoantibodies [122]. These observations suggest that mercury-induced cell death may generate novel protein fragments as sources of antigenic determinants for self-reactive T lymphocytes.

Additional evidence for the genetic regulation of autoimmune responses induced by mercury have come from comparison of inbred mouse strains. These studies have revealed a spectrum of responses ranging from non-responsiveness in the DBA/2, to the presence of autoantibodies without immune deposits in A/J and C57BL/6, to systemic disease with autoantibodies and immune deposits in tissues including the kidney in B10.S, A.SW and SJL [109]. The lack of response in the DBA/2 is due to the absence of inflammation at the site of exposure [30, 59, 61, 62], coincident with the lack of proinflammatory cytokines

IL-1β, TNF-α, and IFN-γ and cathepsin B activity [62]. In contrast, development of autoantibodies and immune deposits relies in large part on IFN-γ and genes affecting its function including IFN-γ receptor, IRF-1 and IL-6 [61, 78].

The molecular and cellular requirements for murine mercury-induced autoimmunity (mHgIA) have been investigated using a variety of approaches (Table 1, Figure 1). The most common approach has been to use mice lacking individual genes. These studies have identified four different types of genes, a) those required for autoimmunity, b) those not required, c) those that are partially required, and d) those that suppress autoimmunity. A fifth influence are autoimmune prone genotypes that result in exacerbation of mercury-induced autoimmunity. These studies have identified the essential roles that TLR trafficking and signaling (Ap3b1, Unc93b1, Slc15a4, Nfkb1, IL-6), IFN-γ response (IFN-γ, IFN-γR, IRF1, hemopexin), and T cell co-stimulation (CD28, CD40L, LAG-3, Daf1) play in mHgIA (Table 1). These observations also show that while genes such as CD40L and CD28 are required for mercury-induced T cell activation and autoantibodies [123], other genes, such as IFN-γ and IRF1, are not required for T cell activation but are necessary for production of autoantibodies [78].

An alternative approach has been to use antibody treatment to target specific immune components. Many of these studies have targeted molecules that regulate T cell responses including CD40L [74], CD80 and CD86 [124], CTLA4 [125], LAG-3 [126], ICOS [127], and 4-1BB [128] to confirm the importance of T cell co-stimulation in mHgIA. Another modality has been the use of recombinant molecules such as IL-10 to support findings with IL-10 deficient mice [129] and the fusion protein CTLA4-Ig [74] to confirm the importance of T cell co-stimulation in mHgIA. TACI-Ig fusion protein has been used to show the importance of BAFF in autoantibody production by B cells [130].

A less frequently used approach has been genome wide association studies. Hybrids between $HgCl_2$ sensitive Brown-Norway and resistant Lewis rats have found genetic linkages to MHC (RT1) for anti-glomerular basement membrane (anti-GBM) [131, 132], glomerulonephritis [132], and IgE [133]. More recent studies have found that a 117-kb interval on chromosome 9 from Lewis rats protects Brown-Norway rats from both elevated IgE response and nephropathy [134]. The region contains 4 genes, *C3, Gpr108, Cip4/Trip10* and exons 1-15 of *Vav1,* with non-synonymous polymorphisms in *C3* and *Vav1* [134]. However, the genetic element, or elements, responsible for the observed phenotype remain to be determined.

Genome wide scans using F2 intercrosses of the mHgIA resistant DBA/2 mouse with either of the mHgIA sensitive SJL or NZB strains were used to identify the genetic basis of resistance/sensitivity to mHgIA [135]. A single major QTL, designated *Hmr1,* and containing several lupus susceptibility loci, was identified on chromosome 1. *Hmr1* is linked to glomerular immune complex deposits but not autoantibody production [135]. Differential expression of genes within the *Hmr1* locus of DBA/2 and NZB mice identified decay accelerating factor 1 (,*Daf1* or CD55) which has a functional activity, inhibition of complement activation, that offered a rational explanation for the phenotype displayed by the *Hmr1* locus [136]. However complement is not required for mHgIA [137]. Nonetheless,

it was found that exposure to $HgCl_2$ reduces Daf1 expression on activated $CD4^+$ T cells in mHgIA sensitive B10.S but not the resistant DBA/2, and that autoimmune prone NZB mice have reduced constitutive expression of Daf1 on T and B cells [138]. A unique pentanucleotide repeat variant in the second intron of Daf1 in DBA/2 mice was shown in F2 intercrosses to be associated with less severe renal immune deposits, however analysis of *Hmr1* congenics failed to show that this regulates *Daf1* expression [139]. A recent study used A.SW and B10.S mice, both with the same MHC class II ($H\text{-}2^s$), to investigate non-MHC genes involved in the development of ANoA [140]. A QTL on chromosome 3 was identified and candidate genes *Bank1* (B-cell scaffold protein with ankyrin repeats 1) and *Nfkb1* (nuclear factor kappa B subunit 1) proposed as key regulators of ANoA development in mHgIA. These studies argue that induction of autoimmune pathology by mercury is complex and likely requires multiple genetic elements.

4. Molecular and cellular mechanisms of mercury-induced immune activation and autoimmunity

In contrast to idiopathic models of autoimmunity, a notable feature of the induced models is that the initiating factor is known making it possible to identify and study the temporal and mechanistic course of events leading to autoimmunity. This is especially true for the mercury model where autoantibodies are detected within two weeks of initial exposure and the development of autoimmunity resembles to a large extent a classical T-dependent humoral immune response (Figure 1). Accordingly, mercury-induced autoimmunity is characterized sequentially by the development of an essential inflammatory reaction at the site of exposure; a T-dependent humoral response characterized by activation and expansion of $CD4^+$ T cells, hypertrophy of draining lymph nodes with new germinal centers, and IgG production; the generation of IgG ANAs; and immune complex deposits in glomeruli and blood vessels.

We recently proposed that the inflammation following exposure to mercury likely arises as a consequence of tissue damage leading to the availability of damage associated molecular patterns (DAMPs), resulting in the engagement of innate sensors including nucleic acid-sensing TLRs, the production of inflammatory cytokines and the induction of chronic inflammation [30]. Although mercury-induced TLR activation leading to proinflammatory cytokine production remains to be documented, the concept is supported by mercury-induced neutrophil extracellular trap (NET) activation and release (NETosis) as a source of TLR agonists [29], mercury-induced changes in TLR expression [141], and the requirement for TLR trafficking and signaling [19]. The localization of mercury to lysosomal compartments [64] and increased cathepsin B activity [62] likely contribute to the involvement of innate immune processes in mercury-induced inflammation and autoimmunity [19]. Importantly, several early inflammatory events including activation of cathepsin B [62], proinflammatory cytokines [61, 62, 81] and cellular infiltrates [61, 62] are linked to subsequent autoimmune responses. Taken together, these findings support a fundamental role for the local inflammation induced by mercury.

An additional contributing factor appears to be the relationship between persistence of mercury in tissues and autoimmunity [104]. The prolonged presence of mercury likely fosters chronic tissue damage and inflammation leading to secondary lymphoid organ hypertrophy and possibly formation of transient organized aggregates of lymphoid cells called ectopic lymphoid structures [30]. Several observations also show that the subsequent development of autoimmunity requires additional distinct pathobiologies from that of the local innate immune pathways. For example, inflammation at the site of mercury exposure occurs in the absence of many genes required for mHgIA [61, 62]. Accordingly, both *in vitro* and *in vivo* studies show that mercury-induced T cell proliferation requires "accessory cells" [25–27], the presence of inflammatory cytokines [25, 26, 87], and co-stimulatory molecules [123, 142] all of which is consistent with a T-dependent antibody mechanism. Other genes such as IFN-γ and IRF1 are not required for mercury-induced T cell proliferation, but are required for mHgIA [78] indicating the presence of additional autoAb-specific pathways.

Although it remains unclear how the mercury-induced innate immune response leads to an adaptive autoimmune response, it is most likely that TLR trafficking and signaling in antigen presenting cells (APCs and B cells) play a key role [19] as mercury-induced MHC class II expression is important for T cell activation [143] and autoantibody production [109, 144]. Remarkably, lack of endosomal TLR signaling associated with deficiencies in either UN93B1, AP3B1, or SLC15A4, blocks not only autoAb production in HgIA, but also $CD4^+$ T cell activation and polyclonal IgG production. This suggests that activation of the innate system required for even non autoAb T-dependent antibody responses to mercury is completely dependent on recognition of extracellular nucleic acid material. This contrasts to T-dependent humoral immune responses which are not dependent on nucleic acid TLR signaling [145, 146].

Tissue pathology following mercury exposure involves both toxic [147] and immunological facets [96]. Continued exposure can be fatal, however this appears to be a toxic rather than immune mediated outcome as lethal proteinuria is rare in the absence of idiopathic autoimmunity [148]. Genes which are necessary for innate and adaptive immune responses are also required for immune-mediated pathology however there are genes, such as caspase 1 [78], that appear to contribute more to immune deposits than the proceeding immune responses.

An important consideration in defining the immunological and pathological criteria for mercury-induced autoimmunity, is that many of the genes required for disease are also required for idiopathic systemic autoimmunity. This is particularly true for genes required for TLR trafficking and signaling, IFN-γ signaling, and T cell co-stimulation (Table 1). A notable caveat to this is that mHgIA is a novel type I IFN-independent model of systemic autoimmunity [19]. Thus, mercury-induced autoimmunity arises by both common and unique pathways. This raises the possibility of identifying specific criteria for environmentally associated autoimmune diseases and applying this information to improve diagnosis, treatment and preventative strategies.

5. Conclusions

Human exposure to mercury in its various forms is associated with pathological outcomes including inflammatory markers, autoantibodies and renal pathology. However, definitive association with one or more diagnosable autoimmune diseases has not been documented due to the small number of small scale epidemiological studies and the lack of suitable diagnostic criteria. Nonetheless, our understanding of the mechanisms of mercury-induced inflammation and autoimmunity has benefited substantially from experimental animal studies. Such studies have recapitulated the presence of inflammatory cytokines, lymphoproliferation, autoantibodies and nephropathy that characterize human exposure. Moreover, they have allowed insight into the importance of genetics in the regulation of inflammatory and autoimmune phenotypes by demonstrating the significant spectrum of responses among inbred strains as well as the importance of single genes to disease expression. These studies have also demonstrated the importance of a susceptible autoimmune phenotype in disease severity, an observation that is reflected in the fact that many of the genes required for disease expression are also important for idiopathic autoimmune disease. Intriguingly, the caveat to this is the independence of mHgIA for type I IFN, a peculiarity which may explain the mild autoimmune disease features exhibited by both humans and mice exposed to mercury.

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Abbreviations

4-1BB	tumor necrosis factor receptor superfamily member 9 (TNFRSF9) (CD137)
AP3B1	adaptor related protein complex 3 subunit beta 1
CD	cluster of differentiation
Con A	concanavalin A
CTLA4	cytotoxic T-lymphocyte associated protein 4 (CD152)
DAF1	decay accelerating factor 1
ICOS	inducible T-cell costimulator (CD278)
IFN	interferon
IL	interleukin
IRF1	interferon regulatory factor 1
LAG	lymphocyte-activation gene
MHC	major histocompatibility complex

NFKB1	nuclear factor kappa B subunit 1
PHA	phytohaemagglutinin
SLC15A4	solute carrier family 15 member 4
TLR	Toll-like receptor
TACI	transmembrane activator and CAML interactor
TNF	tumor necrosis factor
UNC93B1	Unc-93 homolog B1

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Highlights

- Mercury exposure is linked with inflammation, autoantibodies, and renal pathology.
- Animal studies recapitulate the immune features of human exposure.
- Differences in inflammation and autoimmunity are genetically regulated.
- Required genes include those regulating innate and/or adaptive immunity.
- Unlike idiopathic autoimmunity type I IFN is not required.

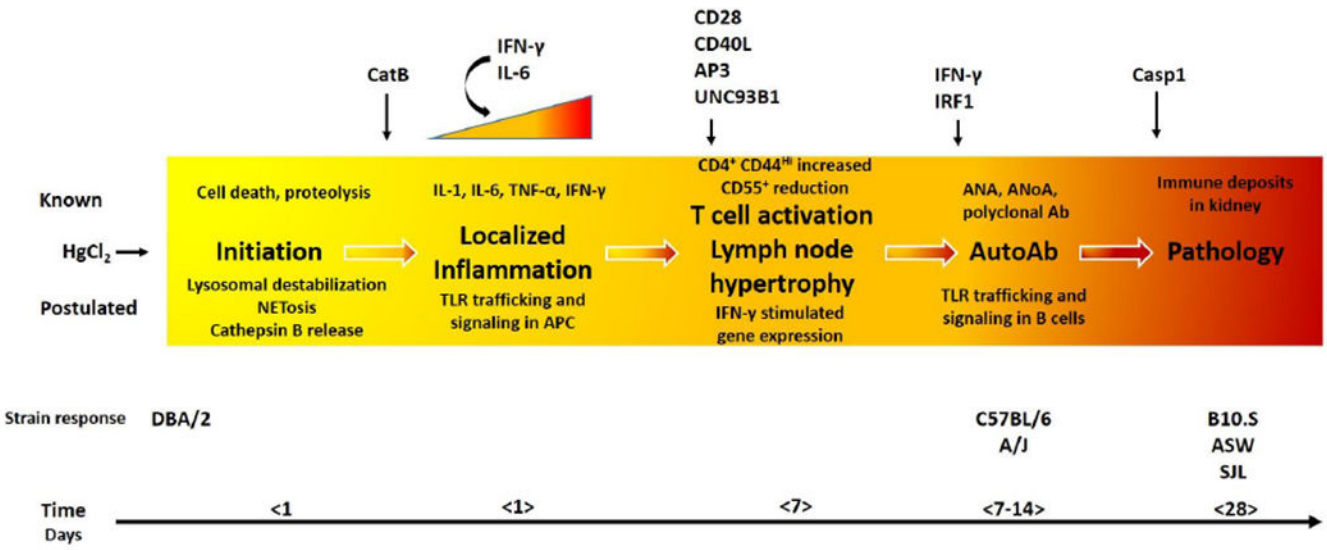

Figure 1.

The pathogenesis of inflammatory and autoimmune responses induced by subcutaneous mercury exposure in mouse models. The earliest events occurring within minutes to hours (Initiation) involve a toxic response that includes cell death and tissue damage with the release of lysosomal constituents such as cathepsin B (CatB), NETosis, and phagocytosis of cellular material. Proteolysis of self-proteins such as fibrillarin to autoantigenic forms also likely begins at this time. The ensuing Localized Inflammation occurs within hours after initial exposure and is associated with elevated CatB activity and proinflammatory cytokine expression, which is exacerbated by IL-6 and IFN-γ. Within the first 7 days, there is T Cell Activation and hypertrophy of draining Lymph Nodes dependent on co-stimulation (e.g. CD28, CD40L) and associated with concomitant reduced CD55 expression on CD4+ T cells. The subsequent B cell activation and generation of polyclonal and autoantibodies (AutoAbs) including the MHC-restricted anti-fibrillarin occurs by 7-14 days and requires IFN-γ, and likely B cell endosomal TLR signaling. Pathology, occurring within the first month, is characterized by immunoglobulin and complement deposition in the kidney. Known and Postulated events are indicated based on the literature and current understanding of inflammatory and autoimmune processes. Mouse strains that typify specific levels of response, such as resistance (DBA/2), autoAbs without pathology (C57BL/6, A/J) and autoAbs with immune deposits (B10.S, ASW, SJL) are shown.

Table 1.

Genetic requirements for murine mercury-induced autoimmunity

Effect	Genes or genotype	Reference (No.)
Required	IFN-γ	Kono et al, 1998 (82)
		Havarinasab et al, 2009 (117)
	CD28, CD40 ligand (CD154)	Pollard et al, 2004 (129)
		Havarinasab et al, 2009 (117)
	Hemopexin	Fagoonee et al, 2008 (142)
	IFN-γ receptor, IRF1	Pollard et al, 2012 (83)
	Ap3b1, Unc93b1, Slc15a4, Nfkb1, IL-6	Pollard et al, 2017 (19)
		Havarinasab et al, 2009 (117)
Not required	IL-4	Kono et al, 1998 (82)
		Bagenstose et al, 1998 (84)
		Havarinasab et al, 2009 (117)
	Icam1	Pollard et al, 2004 (129)
	Nlrp3, IL-12p35, IL-12p40, Stat4	Pollard et al, 2012 (83)
	IRF7, IFN-α/β receptor	Pollard et al, 2017 (19)
Partially required	β_2-microglobulin (B2m)	Pollard et al, 2011 (86)
	Casp1	Pollard et al, 2012 (83)
Suppressive	IL-10 **	Haggqvist et al, 2005 (137)
	Daf1	Toomey et al, 2010 (147)
	LAG-3 *	Jha et al, 2014 (134)
	CTLA4 *	Zheng et al, 2003 (133)
Exacerbate (Autoimmune prone mice)	NZBWF1	al-Balaghi et al, 1996 (130)
	NZBWF1, MRL-*Fas*^{lpr}, MRL-*Fas*+/+	Pollard et al, 1999 (115)
	BXSB	Pollard et al, 2001 (131)

* Confirmed by specific antibody

** Confirmed by specific recombinant protein