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Gender differences in autoimmunity associated with exposure to environmental factors

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Abstract

Autoimmunity is thought to result from a combination of genetics, environmental triggers, and stochastic events. Gender is also a significant risk factor with many diseases exhibiting a female bias. Although the role of environmental triggers, especially medications, in eliciting autoimmunity is well established less is known about the interplay between gender, the environment and autoimmunity. This review examines the contribution of gender in autoimmunity induced by selected chemical, physical and biological agents in humans and animal models. Epidemiological studies reveal that environmental factors can be associated with a gender bias in human autoimmunity. However many studies show that the increased risk of autoimmunity is often influenced by occupational exposure or other gender biased activities. Animal studies, although often prejudiced by the exclusive use of female animals, reveal that gender bias can be strain specific suggesting an interaction between sex chromosome complement and background genes. This observation has important implications because it argues that within a gender biased disease there may be individuals in which gender does not contribute to autoimmunity. Exposure to environmental factors, which encompasses everything around us, adds an additional layer of complexity. Understanding how the environment influences the relationship between sex chromosome complement and innate and adaptive immune responses will be essential in determining the role of gender in environmentally-induced autoimmunity.

Keywords

gender; autoimmunity; environment; human; animal

1. Introduction

Autoimmunity is thought to result from a combination of genetics, environmental triggers, and stochastic events. The multitude of susceptibility genes, symptoms and immunological abnormalities suggest the involvement of numerous pathogenic pathways [1-3]. Among the most striking of these is the contribution of gender (sex) as autoimmunity often occurs more frequently in women [4-8]; in this review gender is synonymous with biologically

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determined sex. The influence of gender on the development of autoimmunity is most often viewed from the standpoint of biological differences between males and females [9, 10]. However susceptibility to autoimmune disease can be impacted by environmental factors [11] which encompass everything around us including the air we breathe, the water we drink, the food we eat, synthetic and natural chemicals, microorganisms, radiation, industrial by-products, and physical factors [12]. The role of environmental triggers, especially medications, in eliciting autoimmunity has been well established in both humans and animal models [13]. However it is unclear if idiopathic and induced disease arise by common mechanisms [11, 14]. Additionally there is no clear understanding of the role that gender plays in the spectrum of environmentally-induced autoimmunity [15]. These deficiencies are significant barriers to our understanding of the totality of the autoimmune disease process.

In this review I examine the roles that gender plays in the development of autoimmunity elicited by exposure to environmental factors with emphasis on chemical, physical and biological agents. The definitions of chemical, physical and biological agents are based on wording contained in the mission statement of the National Institute of Environmental Health Sciences (NIEHS), viz. “The terms chemical, physical and biological agents, and social environmental are interpreted broadly to include chemical and physical agents found in the ambient environment to which humans are exposed as well as social and behavioral influences and lifestyle choices. Chemical factors may include industrial chemicals and solvents, air pollutants, pesticides, heavy metals, food additives, and dietary and nutritional factors. Physical factors may include electric and electromagnetic fields, sunlight, and radiation. Biological agents may include diet/nutrition factors, molds, mycotoxins, and marine toxins. Social, behavioral, and cultural factors may include socioeconomic status, neighborhood environments, psychosocial stress, social support systems, and community and institutional influences. Exposure may occur by absorption, inspiration, ingestion, transmission, or behavior.” Examination of all chemical, physical and biological agents that may contribute to autoimmunity is obviously beyond the space limitations of this review. Therefore I have selected agents where convincing data exists for autoimmunity in either human and/or animal studies in order to examine the contribution that gender bias plays.

2. Gender in idiopathic human autoimmunity

The prevalence of idiopathic autoimmune diseases ranges between 3.2-9.4% depending upon study parameters [16-18]. Gender ratios (Table 1) reveal that many autoimmune diseases have a striking female predominance [5, 6, 19]. This is particularly true for systemic autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren’s syndrome, and mixed connective tissue disease and organ specific diseases like primary biliary cirrhosis (PBC), chonic active hepatitis, and autoimmune thyroid diseases. However other conditions including inflammatory bowel diseases, immune-mediated (type 1) diabetes, and autoimmune myocarditis show little or no female predominance. Although several explanations have been proposed to explain gender differences in idiopathic autoimmune diseases, no consensus has been reached [4, 6, 7, 10].

3. Gender in drug-induced human autoimmunity

There is clear evidence that medications elicit autoimmune disease, most commonly a lupus-like syndrome [13, 20]. Identification of drug-induced lupus as a subset of lupus related diseases is strong evidence that exposure to exogenous agents can elicit autoimmunity. Such a clear association is often not the case with non-therapeutic chemical, physical and biological agents. This is due in large part to the fact that medications are most often taken under medical supervision and exposure is closely monitored and can be terminated at any time. Almost 100 drugs have been associated with lupus [20] but only two, procainamide

and hydralazine, can be considered to pose a high risk [13] although both are seldom used today [21]. The clinical and laboratory features of procainamide and hydralazine-induced lupus overlap considerably with idiopathic lupus except that idiopathic disease is characterized by greater presence of anti-double-stranded DNA antibodies, hypocomplementemia, and glomerulohephritis [13]. The high female predominance observed in idiopathic SLE is not observed in drug-induced lupus [13, 20], nonetheless females are disproportionally represented. In procainamide-treated patients the male-to-female ratio of those with lupus–like symptoms was 2:1, while for asymptomatic patients the ratio was 5:1 [22], showing an increased presence of females in the symptomatic patients. In hydralazine-induced lupus the incidence at three years was higher in women (11.6%) than in men (2.8%) and was dose dependent, only occurring in men (4.9%) on the highest dose (200 mg daily). Women treated with 200 mg daily had a high incidence (19.4%) [23]. In a separate study the ratio of women to men with hydralazine-lupus was also 4:1 [24]. A male predominance has been observed for chlorpromazine-induced lupus but not for other drugs [25]. Surprisingly, proposed mechanisms of drug-induced autoimmunity do not include consideration of the sexually dimorphic nature [13, 20, 21].

4. Gender in environmentally-induced human autoimmunity

In the following sections studies of gender bias in autoimmune diseases associated with environmental exposures have been grouped according to the type of exposure (e.g. chemical, biological, or physical) and are summarized in Table 2.

4.1 Chemical

4.1.1. Silica—Silica exposure is associated with mining and the dusty trades, including sandblasting, rock drilling, granite cutting, construction work, bricklaying, and cement work. The linkage between autoimmune disease and silica exposure can be traced back to Bramwell's description of diffuse scleroderma in (male) stonemasons in 1914 [26]. In 2007 the US Occupational Safety and Health Administration (OSHA) estimated that almost 2 million individuals in the USA are occupationally exposed to respirable crystalline silica [27]. Epidemiologic data provides convincing evidence of the contribution of silica exposure to systemic autoimmunity including SLE [28-30]. Silica dust exposure is associated with high titers of anti-nuclear antibodies (ANA) [31]. Additionally both the presence of autoantibodies and clinical symptoms are positively linked with the intensity (e.g. concentration and frequency) of exposure [32, 33].

Three population based control studies in North America provided evidence that silica exposure contributes to development of SLE [28-30]. Only one of these examined the effect of gender and found that the association between SLE and silica exposure was seen in both sexes [30].

A meta-analysis of 16 studies examining the association between scleroderma and occupational exposure to silica (3 cohort studies, 9 case-control studies, and 4 other designs) determined a combined estimator of relative risk (CERR) of 3.02 (95% CI 1.24-7.35) for males with the CERR being much higher in the cohort studies (15.49, 95% CI 4.54-52.87) than case control studies (2.24, 95% CI 1.65-3.31) [34]. The CERR for studies in females was 1.03 (95% CI 0.74-1.44).

A meta-analysis of 10 studies examining the association between rheumatoid arthritis (RA) and exposure to silica (6 cohort studies, 2 case-control studies, and 2 proportionate mortality studies) showed significant positive associated between silica exposure and RA [35]. The relative risk was 3.43 (95% CI 2.25-5.22) for all studies, and 4.45 (95% CI 2.24-8.86) for the 4 male cohort studies. While gender differences could not be established due to

insufficient female studies it is interesting to note that the relative risk in the one female cohort study was 5.08 (95% CI 3.31-7.79).

These studies argue that the gender bias in autoimmunity associated with silica exposure suggests a male bias but this may be consistent with occupational exposure rather than a sex influenced bias.

4.1.2. Mercury—Epidemiological analysis has suggested that exposure to mercury in an occupational setting can be associated with increased risk of SLE [28]. Other studies suggest that exposure elicits aspects of systemic autoimmunity but do not document specific autoimmune diseases. Exposure to mercury during gold mining has been shown to result in the production of autoantibodies and pro-inflammatory cytokines [36, 37], The human populations at risk of exposure in artisanal mining communities are sizable and diverse. 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 [38, 39]. It is believed that between 10-15 million people, including women and children, are directly involved in artisanal gold mining [38, 40] including over 400,000 in China alone [41]. Among 98 Brazilian gold miners, 56% of whom were male, 51% had ANA and 37% had ANoA [36]; in comparison ANA and ANoA occurred in less than 3% of diamond and emerald miners. Anti-fibrillarin autoantibodies, a characteristic MHC-restricted response in murine mercury-induced autoimmunity (mHgIA) [42] were not identified in serum from ANoA positive individuals [37]. Twenty-five of the gold miners (16M/9F) had both high mercury exposure and were ANoA positive and in this group serum IL-1β, TNF-α, and IFN-γ were significantly higher compared to individuals with lower mercury exposures. The presence of autoimmune diseases was not documented.

Mercury exposure can also occur from skin care products and has been documented to lead to membranous nephropathy [43]. Mercury containing skin care products are widely used, with one commercially successful product being available in 35 countries [44]. Although regulated in the USA, use of mercury containing skin lightening creams has been documented in Hispanic women on the Texas-Mexico border [45]. More recently use of mercury containing skin-lightening creams accounted for reportable levels of urinary mercury (≥20 g/L) in 9 of 13 individuals identified during a screen of 1,840 adult New Yorkers [46]. All 13 were women and either Hispanic (N=11; 10 born in the Dominican Republic) or black (n=2) between the ages of 21 and 51. The presence of autoimmune diseases was not documented. A retrospective study of mercury-induced membranous nephropathy identified 11 individuals aged 15 to 45 years, 10 of which were women [43]; exclusion criteria included those with SLE and those with prior renal disease or abnormal urinary tests. Mercury exposure was due to mercury-containing pills (5 patients), skin lightening creams (4 patients), hair drying agent (1 patient), and mercury vapor (1 patient). Four of these patients, all female, were found to be ANA positive. Of these 2 were being treated for rheumatoid arthritis by mercury containing pills while the other 2 had no primary disease and were using skin-lightening cream.

Although these studies suggest that mercury exposure can elicit features of autoimmunity they fall short of a clear demonstration between exposure and specific diseases. The relationship between gender and induction of autoimmune features by mercury reveal no specific sex bias. Instead the reported effects fit with occupational, cosmetic or non-conventional therapeutic exposure.

4.1.3. Pesticides—Pesticides are known to accelerate systemic autoimmunity in murine models of systemic lupus [47]. ANA positivity was significantly associated with lifetime exposure to pesticides specifically to carbamate, organochlorine (including aldrin,

chlordane, dieldrin, endrin, heptachlor, and lindane, but excluding DDT and methoxychlor), and pyrethroid insecticides and to phenoxyacetic acid herbicides, including 2,4-D [48]. The relationship between ANA and exposure to the herbicide bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) was examined in a study of residents of a cereal-producing region in Saskatchewan, Canada. Female gender was found to be a positive predictor of ANA detection [49]. Analysis of data from the Women's Health Initiative Observational Study (post menopausal women, ages 50-79) concluded that insecticide exposure is associated with increased risk of autoimmune rheumatic diseases [50].

Although intriguing these studies fall short of demonstrating that a specific pesticide exposure is associated with a particular autoimmune disease. Further studies are also needed to clearly establish a link between pesticides and female gender bias in autoimmune diseases.

4.1.4. Solvents—Millions of workers are exposed to solvents on a daily basis. Health hazards may include toxicity to the nervous system [51], liver [52], kidney [53], lungs [54], and skin [55]. Scleroderma (SSc), a rare and severe connective tissue disease, is associated with solvent exposure [56]. A meta-analysis of seven case-control studies and one cohort study dealing with SSc and solvent exposure found a relative risk for all eight studies of 2.91 (95% CI 1.60-5.30), and a relative risk for the seven case-control studies of 3.14 (95% CI 1.56-6.33) [57]. A more recent study extended the meta-analysis to eleven studies and found that the relative risk was higher in men (odds ratio 2.96, 95% CI 1.89-4.64) than in women (odds ratio 1.75, 95% CI 1.48-2.09) although adjustment for publication bias reduced the difference between the sexes [58]. Meta-analysis of studies examining exposure to the industrial solvent trichloroethylene (TCE) and scleroderma found an odds ratio of 2.5 (95% CI 1.1-5.4) for men and 1.2 (95% CI 0.58-2.6) for women [59]. SSc is 3 to 5 fold more common in women than men (Table 1) arguing that occupational exposure to solvents is not a major risk factor in female SSc patients [56]. Whether occupational exposure to organic solvents is a risk factor for SSc in males will require additional studies of specific solvent exposures.

4.1.5. Smoking—A meta-analysis of recent studies that assessed the morbidity and mortality associated with smoking found a substantial gender effect with high-level use with the point estimate for females who smoked at high levels being 2.75 (95% CI 2.14-3.52), higher than the estimate of 1.95 (95% CI 1.70-2.24) for males [60]. An association with smoking has been found for RA, SLE, Graves' disease, multiple sclerosis (MS) and PBC [61]. Cigarette smoking is argued to be the most significant environmental risk factor for seropositive RA [61].

Review of 17 studies, including both case-control and cohort, concluded that the relative risk of RA is greater in men (odds ratio range 1.9-4.4) compared to women (odds ratio range 0.6-2.5) [61]. However several studies have noted an increased risk for RA in women. One study observed that the duration but not the intensity of smoking increased the risk in women [62]. Women who currently smoked (≥ 25 cigarettes/day) had 32% increased risk compared to women who never smoked (relative risk 1.32, 95%CI 1.19-1.46), while those who smoked for more than 20 years had a 27% increased risk (1.27, 95% CI 1.18-1.36). In a separate study heavy smoking (≥ 20 pack-year; a pack-year is smoking 20 cigarettes a day for one year) was associated with severity of RA in women including rheumatoid nodules (p=0.01) and joint damage (p=0.02) as well as a positive correlation between smoking and rheumatoid factor (RF) levels [63]. The relative risk of RA was found to be elevated for both current (1.43 95% CI, 1.16-1.75) and past (1.47, 95% CI 1.23-1.76) female smokers in the Nurses' Health Study [64]. Risk was also increased with increasing pack-years and longer duration and was greatest in those patients with RF positive RA. Past smoking has been

associated with increased risk of PBC (adjusted odds ratio 1.57, 95% CI 1.29-1.91) in a study of 1032 patients, 93% of which were female [65]. Comparison between male and female patients with Graves' disease suggested greater risk for female (odds ratio 2.82, 95% CI 1.18-6.73) than male (odds ratio 0.76, 95% CI 0.27-2.16) smokers [66].

These studies suggest that smoking is a risk factor for autoimmunity in both sexes and that both the degree of smoking (pack-years) and duration increase risk.

4.1.6. Cosmetics—Cosmetics exposure is very common, particularly among women. Relative risk for SLE was increased in occupations involved in applying nail polish or nail applications (odds ratio 10.2, 95% CI 1.3-12.3) [28]. An analysis of 1032 patients with PBC (93% female) reported use of hair dye ($p=0.044$) and nail polish ($p<0.0001$) was more frequent in patients than controls matched for sex, age group, race and geographical area [65]. A case controlled study found that women who were occupationally exposed to hairdressing chemicals had greater risk of developing RA (odds ratio 3.0, 95% CI 1.0-9.4) than unexposed women [67]. Greater attention needs to be paid to occupational exposures of women to cosmetic agents involved in hairdressing and nail polish and nail applications.

4.2 Biological

4.2.1. Infection—Infectious agents have long been considered one of the factors involved in autoimmunity [68-70]. Of 196 SLE patients 195 had previously been exposed to Epstein Barr virus (EBV) (odds ratio 9.3, 95% CI 2.4-57) [71]. In a case-control study of 87 Taiwanese SLE patients 82% were positive for EBV compared to 49% of 174 controls (odds ratio 4.64, 95% CI 2.5-8.62) [72]. In both studies over 90% of the SLE patients were female; however it is unclear if gender was a risk factor for the presence of EBV. EBV has also been associated with MS [73]. The mechanistic significance of these findings in SLE and MS are questionable given the lack of reproducibility in detecting the virus itself in tissue [70, 73].

4.2.2. Diet—Ingestion of L-tryptophan as a dietary supplement has been associated with eosinophilia-myalgia syndrome (EMS) [74]. The source of L-tryptophan appeared to be a significant risk factor in development of EMS [75]. Initial commentary suggested that EMS had a striking sex ratio with 80% of patients being female [74] and this was confirmed by a CDC study [76] and a study in Germany [77]. Other studies in the USA [75, 78] do not support a gender bias. EMS bears striking similarity to Toxic Oil Syndrome (TOS) as both include eosinophilia, severe myalgia and arthralgia [74, 78]. The TOS epidemic occurred in Spain in 1981 as a result of ingestion of adulterated cooking oil containing crude rapeseed oil denatured with 2% aniline [79]. The number of victims totaled over 20,000 with a female-to-male ratio of 1.5:1 [80]. Follow-up studies have supported the 2-to-1 predominance in females [80, 81] and have noted that the prevalence of severe scleroderma-like changes [81] and TOS-related deaths [80] are 2-to-3 fold higher in women than men.

Coeliac disease (CD) is triggered by ingestion of wheat gluten (gliadin and glutenin) and related prolamins from rye (secalin) and barley (hordein). CD is identified by the presence of gluten-dependent clinical manifestations, specific autoantibodies, enteropathy and genetic susceptibility [82]. In a study of Italian patients CD was found to be over 3 times more common in women than men, and was also diagnosed earlier and was more severe in women [83]. North American CD patients also have a female predominance [84]. Factors other than gluten ingestion may influence the incidence of CD. During a ten year period beginning in the mid-1980s there was a threefold increase in incidence of CD in Swedish children [85]. Moreover the two fold increased risk for CD in girls compared to boys (1.9, 95% CI 1.7-21) was constant throughout the epidemic. Possible causative factors for the epidemic include changes in infant feeding practices [86].

4.3 Physical

4.3.1. Ionizing radiation—Radiation therapy for treatment of Hodgkin's disease results in a number of thyroid diseases including hypothyroidism and Graves' disease [87]. In adult patients who developed hypothyroidism the chief risk factor was gender with women having a relative risk 1.6 times greater than men. In contrast, sex was not a risk factor in development of Graves' disease.

There is some evidence that environmental radiation may be associated with features of thyroid autoimmunity [88]. The presence of antibody positive hypothyroidism was found to be almost two fold greater in female atomic bomb survivors in the Nagasaki Adult health Study cohort [88]. Individuals presumed exposed to atmospheric releases of I^{131} from the Hanford nuclear site in southeastern Washington State showed an overall cumulative incidence of autoimmune thyroiditis of 18.2% with women affected (23.1%) more than men (13.1%) [89]. Autoimmune thyroiditis, which as defined by the presence of thyroid peroxidase antibodies or anti-thyroid microsomal antibodies, did not increase with increasing radiation dosage.

The Chernobyl disaster at the Chernobyl Nuclear Power Plant in Ukraine in April 1986 resulted in some 5 million individuals in Ukraine, Belarus and the Russian Federation being exposed to radioactive fallout [90]. In a study of a large Ukrainian cohort (of over 12,000 individuals with mild to moderate iodine deficiency who were under 18 years of age and had thyroid radioactivity measurements at the time of the disaster) it was found that in minimally exposed individuals (<0.14 Gy) females were 5 time more likely to have autoimmune thyroiditis than men. However at higher radiation doses men appeared to have higher risk (odds ratio 3.26, 95% CI 1.34-7.93 at 0.96-1.49Gy).

4.3.2. Ultraviolet radiation—Abundant evidence exists for a profound effect of the environment on the causality of multiple sclerosis [91, 92]. The latitude gradient is a unambiguous example of how the environment affects the risk of MS with prevalence increasing from 5–10 per 100,000 near the equator to around 200 per 100,000 at latitude 59°N, an increase of more than 20 fold [91]. In a New Zealand study the latitudinal gradient of MS prevalence was mostly driven by European females [93] while in Canada a rapid increase in female to male sex ratio for individuals born between 1931-1980 was suggested to have environmental origins [94]. The environmental differences responsible are suggested to include climatic factors, dietary characteristics, infectious agents, and/or gene-environment interactions. Another possibility is solar radiation. A study of prevalence data for six regions in Australia revealed a negative correlation between ultraviolet radiation (UVR) and MS prevalence [95]. In a meta-analysis of 650 prevalence estimates from 321 peer-reviewed studies the age standardized prevalence was 4.09 (95% CI 2.80-5.39) for male and 7.19 (95% CI 4.84-9.53) for female cases per 100,000 per degree of latitude. However this difference was not statistically significant, arguing that there is no distinguishable difference in the female/male ratio of age-standardized prevalence with latitude [92]. Although this global analysis conflicts with the increasing prevalence sex ratio over time in Canada [94] and over latitude in New Zealand [93], it has been argued that environment is more important than genetics (and sex) in the causation of MS [91]. Although sun exposure has an association with SLE [28] no SLE prevalence gradient has been found in relation to latitude around the world [96].

5. Gender in animal models of autoimmunity

Like their human counterparts animal models of autoimmunity can show gender bias (Table 3). Female predominance is found in lupus-prone strains including the prototypical (NZBW)F1 [97] and F1 hybrids of NZBxSJL [98] and SWRxSJL [99]. Sex bias in the

(NZBW)F1 has been associated with sex hormones [100] but can also be segregated by mixed breeding of the F1 progeny [101]. The resulting NZM strains show considerable phenotypic differences including presence or absence of female bias (Table 3). In the six surviving NZM strains only one, NZM2410, has no sex bias while the others show varying degrees of female bias NZM88>2328>391=2758>64 [102]; however sex bias does not predict disease severity [101, 102]. Modulation of single gene expression in different genetic backgrounds can also influence disease expression in a gender specific manner. For example, lupus-prone MRL-*Fas*^{lpr} and MRL-*Fas*$^{+/+}$ have no sex bias [97]. Rendering both strains C1q deficient does not modify disease expression in MRL-*Fas*^{lpr} mice while C1q deficient MRL-*Fas*$^{+/+}$ mice have accelerated disease which was more severe in females [103].

Disease in the lupus-prone BXSB mouse has a male predominance [97]. The sex bias in male BXSB mice is due to an abnormality in its Y chromosome, designated *Yaa* (Y-linked autoimmune acceleration) [104]. The *Yaa* mutation is due to translocation of the telomeric end of the X chromosome onto the Y chromosome resulting in duplication of the Toll-like receptor 7 (*Tlr7*) gene [105]. Interestingly, aged female C57BL/6 mice and young lupus-prone female (NZBW)F1 mice have TLR7 dependent CD11c^{+} B cells which produce autoantibodies [106]. The percentage of these B cells in blood correlated with the age of female RA patients [106]. Intriguingly plasmacytoid dendritic cells (pDCs) from women produce markedly more interferon-α (IFN-α) in response to virus-encoded TLR7 ligands than pDCs from men [107]. This suggests that gender may contribute to the vital role that pDCs and type I INF play in autoimmunity [108]. Another gene showing gender bias in lupus mice is interferon regulatory 5 (*Irf5*). *Irf5* is a human lupus susceptibility factor [109] and its expression is higher in autoimmune female mice than in strain and age-matched males and absence of the estrogen receptor was associated with reduced *Irf5* [110].

NOD mice, a model for diabetes mellitus type 1 [111], have significant female bias which is in contrast to the human disease [5]. This increased susceptibility may be due to estrogen activation of STAT4 leading to IL-12 induction and an enhanced Th1 immune response [112]. Experimental autoimmune encephalomyelitis (EAE), an animal model of MS, exhibits strain specific gender bias with female SJL, A.SW and NZW being more susceptible that males while B10.PL and PL/J have a male bias and the C57BL/6 and NOD have no sex bias [113].

In total these observations argue that genetic factors, in addition to gender, play a significant role in spontaneous expression of autoimmunity. However it is also becoming clear that sex-linked (*Tlr7*) and non-sex linked (*Irf5*) genes can confer susceptibility to autoimmunity and influence gender bias.

6. Gender in animal models of environmentally-induced autoimmunity

The female gender predominance in many human autoimmune diseases has resulted in many investigators using female animals, mostly mice, in studies of autoimmune disease induced by environmental factors. Although this severely limits identifying a gender bias, it does at least establish whether or not females are sensitive to the environmental factor under investigation. In the following sections I have identified as clearly as possible whether gender comparisons were done, or if a single sex was used. Environmental exposures have been grouped according to the type of exposure (e.g. chemical, biological, or physical) and are summarized in Table 4.

6.1 Chemical

6.1.1. Silica/Asbestos—Very few studies have examined induction of autoimmunity by silica and/or asbestos in animals. Male and female lupus-prone NZM 2410 mice exposed to crystalline silica had reduced survival, increased proteinuria, circulating immune complexes and autoantibodies [114]. Female C57BL/6 mice exposed to asbestos had a significantly higher frequency of ANA and renal IgG deposits compared to controls [115]. These studies do not allow determination of gender bias in silica/asbestos-induced murine autoimmunity.

6.1.2. Mercury—Although the role for mercury exposure in human autoimmune disease remains to be fully explored, there is clear evidence that mercury produces systemic autoimmunity in several animal models, especially mice [11, 116]. Murine mercury–induced autoimmunity (mHgIA) can be induced by numerous exposure routes and chemical forms including subcutaneous injection or oral ingestion of $HgCl_2$, inhalation of mercury vapor, and dental or peritoneal implantation of mercury containing dental amalgam [11]. The severity of disease is dependent upon strain [117, 118] and dose [119, 120]. Gender also contributes to susceptibility because although the A.SW strain develops the MHC class II restricted ANoA response at a lower body burden of $HgCl_2$ than the B10.S, the males of both strains are less susceptible than females [120]. This female bias is not universal because male (SJLxC57BL/6)F1 mice are much more likely to develop ANoA than females while (SJLxDBA/2)F1 mice show no gender preference in autoantibody development [117].

Mercury also influences autoimmune disease in spontaneous and induced animal models. Mercury exposure exacerbates autoimmune disease in female (NZBxNZW)F1 mice [121-123]. Both male and female BXSB mice showed evidence of accelerated disease following mercury exposure, although the severity was greater in male mice carrying the *Yaa* mutation [124]. Older female mice (8 weeks) proved more sensitive to mercury-induced acceleration of autoimmunity than younger (4 weeks) females [124]. Lupus-prone (SWRxSJL)F1 male and female mice showed no exaggeration of spontaneous autoimmunity following mercury exposure [125]. However, metal exposure did suppress the spontaneous the anti-Sm response and the serum IgG concentration in male mice. Mercury exposure in female NOD mice suppressed development of insulitis and postponed the onset of diabetes while inducing hypergammaglobulinemia and IgG renal deposits [126]. Mercury exacerbated myocarditis induced by coxsackievirus B_3 infection in male BALB/c mice [127].

These studies suggest that here is evidence for greater sensitivity of female mice to mHgIA. However it is possible that more significant gender bias in mHgIA may be obscured by the considerable differences in response among mouse strains.

6.2.3. Pristane—Tetramethylpentadecane (TMPD, or pristane)-induced lupus is a murine model of SLE [128]. In female mice a single i.p. dose of TMPD leads to antibodies against a number of autoantigens although the frequency, level, and time of onset can vary between strains [129]. Female SJL/J mice exposed to TMPD exhibit greater mortality, kidney disease and autoantibodies than their male counterparts [130]. Induction of autoimmunity has been examined in SJL mice in which the testes-determining *Sry* gene has been deleted from the Y chromosome [131]. Using both the pristane-induced lupus and EAE models it was determined that the XX sex chromosome complement confers greater susceptibility to autoimmune disease than XY. Whether female bias is common among other mouse strains exposed to pristane remains to be investigated.

6.2.4. TCDD—Dioxins are waste contaminants [132]. The most potent is the halogenated aromatic hydrocarbon 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) which is a known

contaminant in Agent Orange, a herbicide used in the Vietnam War. TCDD has significant but complex effects on autoimmunity. Chronic TCDD treatment suppresses the development of autoimmune diabetes in female NOD mice [133] and systemic autoimmunity in female (NZBW)F1 mice [134]. This suppression is likely mediated via the interaction of TCDD with its specific receptor, the aryl hydrocarbon receptor (AhR), leading to regulatory T cell (Treg) differentiation [135]. There is some indication that TCDD can promote autoimmunity when exposure occurs during fetal or early neonatal development. C57BL/6 mice that received TCDD mid-gestation showed signs of male biased autoimmunity with increased autoantibodies and immune deposits in 48 week old male mice compared to females [136]. These observations suggest that mid-gestation exposure to TCDD may provide a model for the age related increase of SLE in males. Gender differences in autoimmune parameters were observed following TCDD mid-gestation in both C57BL/6 and lupus–prone SNF1 mice at 24 weeks of age [137]. The mechanisms responsible for these complex gender biased outcomes following TCDD exposure at different life stages are unknown.

6.2.5.Pesticides—Chronic exposure to organochlorine pesticides such as *o,p'*-dichlorodiphenyltrichloroethane (DDT), methoxychlor, and chlordecone is known to exacerbate autoimmunity in ovariectomized female (NZBW)F1 mice [47]. Chronic chlordecone treatment also reduced time to onset of autoantibody and renal disease in a dose-related manner in ovary-intact (NZBW)F1 mice but not female BALB/c mice [138]. Because chlordecone has estrogenic effects it was hypothesized that chlordecone might increase circulating prolactin levels, and that prolactin might be an important mediator of chlordecone effects on autoimmunity [139]. However chlordecone decreased serum prolactin in ovariectomized female (NZBW)F1 mice in a dose dependent manner arguing that chlordecone exacerbates autoimmunity independent of prolactin [139].

6.2 Biological

6.2.1. Infection

Infection with Theiler's murine encephalomyelitis virus (TMEV) causes an immune-mediated demyelinating disease similar to human multiple sclerosis [140, 141]. The disease shows strain dependence and is biphasic with acute encephalitis in the first few weeks followed by chronic demyelination [142-144]. Although male mice are susceptible [142] many studies use female mice [145] with female SJL/J mice being susceptible while female C57BL/6 mice are not [146]. In SJL mice the early phases of the disease have been shown to have a female bias [145] with male mice having more severe neurologic deficits later in the disease [143]. This pattern of gender bias in SJL mice has been argued to closely resemble human MS where males have more severe deficits and deteriorate faster than females [143].

Myocarditis can be induced in mice with coxsackievirus B_3 virus [147]. Both strain and gender differences have been observed with susceptible mice being male 129/J and female SWR/J and C57BL/6 while both sexes of BALB/c and CD-1 are non-susceptible [148]. Using female mice another study also found variations in susceptibility to coxsackievirus B_3-induced myocarditis in a number of strains with A.BY, A.SW, A.CA and C3H.NB mice having late stage myocarditis and heart-specific autoantibodies [149]. In another study fulminant myocarditis occurred in male but not female BALB/c mice [150]. Female BALB/c mice given exogenous testosterone and progesterone had tenfold more virus in their hearts than mice given estradiol [151]. Increased inflammation in male BALB/c mice was not due to increased viral replication in the heart but to increased proinflammatory cytokines including IFN-γ [152]. The same group also found that sex related differences in BALB/c mice also included elevated TLR4 and reduced Treg in male mice and increased IL-4 and Treg in female mice [153]. Castration of male BALB/c mice reduced inflammation in the heart but IL-$4^+$$CD4^+$ T cells and $Foxp3^+$Treg were increased [154].

6.2.2. Diet (caloric restriction)

Caloric restriction (CR) ameliorates the clinical course of EAE in female SJL and C57BL/6 mice [155] and male Lewis rats [156, 157], reduces the histological severity of disease in salivary glands of female (NZBW)F1 mice [158], delayed onset of autoimmune disease [159], and improved survival in female (NZBW)F1 mice [160]. A common finding was reduction of proinflammatory cytokines [155, 158, 161] supporting the belief that one of the major benefits of dietary restriction is reduction of system-wide inflammatory processes [162].

6.3 Physical

6.3.1. Ultraviolet radiation

Ultraviolet radiation (UVR) dramatically increased mortality and accelerated autoimmunity in male compared to female BXSB mice [163]. No effect was seen with autoimmune prone MRL-*Fas*^{lpr} or (NZBW)F1 mice nor with nonautoimmune BALB/c or B10.A mice. Filtering out UVB negated the effect. Interestingly UVA was found to prolong survival and improve immune function in female (NZBW)F1 mice [164]. Why male BXSB mice are so exquisitely sensitive to UVB radiation in not known, but suspicion must fall on the *Yaa* mutation. It is also worth noting that mice lacking the autoantigen SS-A/Ro60 develop a lupus-like disease and can display increased sensitivity to UV radiation [165].

7. Conclusions

Autoimmunity in humans often, but not always, has a female bias. The mechanisms for gender bias in human autoimmunity are not clear and studies which further our understanding of sex differences will be highly rewarding. This will include an understanding of the contribution of sex chromosomes particularly the X chromosome in modulating the innate and adaptive immune pathways involved in autoimmunity [10, 113].

Numerous epidemiological studies have demonstrated an association between environmental factors and increased risk of autoimmunity in humans. This is most clearly demonstrated by drug-induced autoimmunity. For some environmental exposures there is a female gender bias (e.g. Toxic Oil Syndrome, eosinophilia-myalgia syndrome, coeliac disease), others show increased risk for both sexes (e.g. smoking and RA), and others increase the risk of gender biased diseases (e.g. cosmetics and increased risk of SLE, PBC, RA). However, underlying many of these studies is the likelihood that the presence or absence of gender bias is influenced by occupation (e.g. silica), sex biased activity (e.g. cosmetics) or non-conventional therapeutic/cosmetic exposure (e.g. mercury). Nonetheless the recognition of potential gender bias in autoimmunity associated with environmental factors identifies potential areas of investigation regarding possible mechanisms.

Animal model studies have proven of great use in defining disease mechanisms in environmentally-induced autoimmunity [11]. However examination of gender bias has been limited because many studies have been restricted to female animals because of the known female bias in human autoimmune diseases. Restriction of gender and/or strain in animal model studies does not help confirm gender bias and may actually obscure gender effects. This is because it is clear that gender bias can be strain specific [163] suggesting an interaction between sex chromosome complement and background genes [113]. This observation has significant implications for human studies as it suggests that even within gender biased autoimmunity there may be individuals in which gender does not contribute to disease and vice versa. Environmental exposure likely adds an additional layer of complexity. Determining the interaction between environmental factors and sex hormones

and sex chromosome function will be essential in defining the contribution that sex differences play in environmentally-induced autoimmunity.

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Gender is a significant risk factor with many autoimmune diseases.

Increased risk of autoimmunity is influenced by gender biased activities.

Gender bias may result from the interaction between sex chromosomes and background genes.

Table 1

Gender ratios in human autoimmune diseases.

Autoimmune Disease	Ratio (female/male)
Sjögren's syndrome	9:1 - 20:1
Primary biliary cirrhosis	9:1 - 10:1
Systemic lupus erythematosus	9:1
Antiphospholipid antibodies	9:1
Mixed connective tissue disease	8:1
Chonic active hepatitis	8:1
Autoimmune thyroid diseases	8:1
Systemic sclerosis (scleroderma)	3:1 - 5:1
Rheumatoid arthritis	3:1 - 4:1
Myasthenia gravis	2:1 - 3:1
Multiple sclerosis	2:1 - 3:1
Autoimmune thrombocytopenic purpura	2:1
Diabetes mellitus type 1	1:1 - 2:1
Ulcerative colitis	1:1
Autoimmune myocarditis	1:1.2

See text for details.

Table 2

Gender in human environmentally-induced autoimmunity

Environmental Agent	Autoimmune Disease	Gender Predominance
Silica	SLE	None
	SSc	Male (occupational?)
	RA	None
Mercury	ANA, inflammatory cytokines	None
	Membranous nephropathy	Female (cosmetic or non-conventional therapeutic)
Pesticides	ANA	Female
Solvents (TCE)	SSc	Possible male (occupational?)
Smoking	RA	Increased risk for both sexes, higher in males
	PBC	Increased risk (female predominant disease)
	Graves' disease	Female
Cosmetics	SLE	Increased risk (female predominant disease)
	PBC	Increased risk (female predominant disease)
	RA	Increased risk (female predominant disease)
Infection (EBV)	SLE	Increased risk (female predominant disease)
Diet		
-L-tryptophan	EMS	Female or none
-Adulterated cooking oil	TOS	Female
-Gliadin	CD	Female
Ionizing radiation	Hypothyroidism	Female
	Graves' disease	None
Ultraviolet radiation	MS	Global none; Canada female, New Zealand female

See text for details.

Table 3

Gender in animal models of autoimmunity

Animal Model	Autoimmune Disease	Gender Predominance
Spontaneous		
MRL-*Fas*^{lpr}	SLE	None
MRL-*Fas*$^{+/+}$	SLE	None
(NZBxNZW)F1	SLE	Female
(NZBXSJL)F1	SLE	Female
(SWRxSJL)F1	SLE	Female
NZB	SLE, Autoimmune hemolytic anemia (AIHA)	Female (moderate)
NZM	SLE	Female NZM88, 2328, 391, 2758, 64
		No sex bias NZM2410
BXSB	SLE	Male
NOD	Type 1 diabetes	Female
Genetically modified		
C1q deficient MRL-*Fas*$^{+/+}$	SLE	Female
C1q deficient MRL-*Fas*^{lpr}	SLE	None
Induced		
EAE	Multiple sclerosis (MS)	Female SJL, A.SW, NZW Male B10.PL, PL/J No sex bias C57BL/6, NOD

See text for details.

Table 4

Gender in animal models of environmentally-induced autoimmunity

Environmental Agent	Animal Model/Strain	Autoimmune disease	Gender Predominance
Silica	NZM2410	SLE	None
Asbestos	C57BL/6	Silica-induced (lupus-like)	Only female tested
Mercury	B10.S	Mercury-induced (lupus-like)	Female
	A.SW	Mercury-induced (lupus-like)	Female
	(NZBxNZW)F1	SLE	Only female tested
	BXSB	SLE	Greater severity in male mice
	BALB/c	Coxsackievirus B_3 induced myocarditis)	Only male tested
Pristane	SJL	Pristane-induced (lupus-like)	Female
TCDD	C57BL/6 (mid-gestation exposure)	TCDD-induced (lupus-like)	Male
Pesticides	(NZBxNZW)F1	SLE	Only ovariectomized females tested
Infection	SJL	TMEV-induced MS	Greater severity in male mice
	BALB/c	Coxsackievirus B_3 induced myocarditis)	Greater severity in male mice
Caloric restriction	SJL, C57BL/6	EAE (suppression)	Only female tested
	(NZBxNZW)F1	SLE (suppression)	Only female tested
Ultraviolet radiation	BXSB	SLE	Male

See text for details.