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Environmental factors acting during development to influence MS risk: insights from animal studies

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Abstract

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system with an increasing incidence in females. Epidemiological data strongly implicate environmental factors acting at the population level during gestation, childhood, and adulthood in the increasing incidence of MS. Several such factors have been implicated in disease risk, but their causality remains unproven, while other factors remain unknown. The understanding of risk factors acting during development is particularly limited. Animal studies could potentially bridge the gap between observational epidemiology and clinical intervention, providing not only direct evidence of causality for a given environmental agent, but also an opportunity to dissect the underlying molecular mechanisms. Given the short gestational and developmental period in rodents, effects of developmental exposure can also be readily addressed. Nonetheless, studies in this area have so far been few. In this review, we summarize the insights gleaned from studies that test environmental influences in animal models of MS, with a particular focus on gestational and early life exposures.

Pathogenesis of MS and its animal models

MS is a multifactorial inflammatory disease of the central nervous system (CNS) characterized by demyelination, gliosis, axonal loss, and progressive neurological dysfunction. The etiology of MS is not well-understood, but current evidence suggests that activation of myelin-reactive T cells triggers an inflammatory cascade in the CNS, recruiting other immune cells which mediate the subsequent tissue destruction and pathology.[1, 2] There are two animal models commonly used to study the immunopathogenesis of MS: experimental allergic encephalomyelitis (EAE) and Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEVD).[3] EAE is an autoimmune disease induced in several animal species (from rodents to primates) by active immunization with CNS homogenate or specific myelin proteins/peptides, or by adoptive transfer of CD4 T cells reactive to these antigens. Alternatively, spontaneous EAE in mice can be induced by transgenic expression of T cell receptors (TCRs) specific for myelin epitopes. As in MS, autoreactive CD4 T cells enter the CNS to initiate inflammation and pathology, leading to clinical signs. In contrast, TMEVD is induced by infection with TMEV, a neurotropic virus that triggers immune infiltration into the CNS and subsequent neural damage and dysfunction. Both of these models, in particular EAE, have been instrumental in the improved understanding of MS pathogenesis and the development of novel therapies.[4] We have in fact shown in mice that EAE recapitulates with high fidelity many of the elements

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underlying MS pathogenesis, including the genetic architecture and role for cellmediated immune mechanisms in disease pathogenesis.[5, 6] Moreover, all of the currently approved MS therapies are also efficacious in EAE, underscoring the relevance of this model. Unfortunately, many therapies that are effective in EAE have no clinical efficacy in MS, and some even exacerbate disease (e.g. interferon-γ therapy[7]). While it is likely that in some cases the EAE model has generated incorrect predictions for MS pathogenesis, it is also possible that the findings from this model have not translated due to other limitations, e.g. dose, bioavailability, bioactivity, timing of treatment, etc.[4] The EAE model clearly has its limitations in its predictive power for MS, and results from this model need to be interpreted cautiously and followed up with correlates in MS patients. However, when applied and interpreted correctly, this model can provide novel mechanistic insights into the etiopathogenesis of MS.

Environmental factors and MS susceptibility

The etiology of MS involves both genetics and the environment.[8] Epidemiological studies have documented a 3–6 fold increase in MS incidence in females over the last 50–70 years, while disease incidence in men has remained relatively stable.[9] This rate of change clearly implicates environmental variable(s) that are preferentially affecting MS incidence in the female population. The timing of increased MS incidence may also provide insight as to the identity of the environmental factors causing increased disease risk. The 20th century has brought about many rapid societal changes for both sexes, some of which may be responsible for increased MS risk in women. Many environmental factors have been associated with MS susceptibility and have been reviewed extensively elsewhere.[8] The most prominent of these are sunlight exposure/latitude, vitamin D_3 (VitD), and Epstein-Barr virus (EBV) infection. The effect of sunlight has been thought to be mediated by immunomodulatory effects of VitD, whose synthesis is catalyzed by UV exposure, although immunosuppressive effects of UV radiation independent of VitD are also well-documented.[10] Accordingly, recent epidemiological studies suggest that VitD and UV radiation exert independent effects on MS risk.[11, 12]

It is now well appreciated that various stimuli during gestation, development and early life can affect adult onset disease via epigenetic imprinting mechanisms.[13] A striking experimental example of this concept is the effect of maternal care on brain development and behavior in rats.[14] Similarly, epidemiological data indicate that some of the environmental exposures that determine MS risk take place not only in adulthood, but during early life or *in utero*, as reviewed by Burrell *et al.*[15]

Clearly, there are many putative environmental risk factors to which an individual is exposed during either development or adulthood which could explain the increasing incidence of MS. Some of these have been associated with disease in epidemiological studies, but their causality remains unproven. Others putative factors have not yet been explored. Over the last century, a vast amount of seminal epidemiological data on MS have been gathered, yet to date none has been successfully applied towards clinical intervention.[16] Animal studies can potentially bridge the gap between observational epidemiology and the clinic, providing not only direct evidence of causality for a given environmental agent, but also an opportunity to dissect the underlying molecular mechanisms.

In the following two sections, we describe how animal models of MS have been applied to study environmental risk factors and what has been learned from these results. We first briefly highlight studies using adult exposure to the most significant environmental MS risk factors, followed by a more expansive summary of the studies examining the effects of developmental exposure to these and other environmental risk factors.

Effects of environmental MS risk factors in animal models: adult exposure

Most of the animal studies of MS risk factors have been performed utilizing adult exposure. To date, the most well-studied factors are VitD and UV radiation. Treatment of animals with supra-physiological doses of the VitD metabolite, 1,25-dihydroxyvitamin D_3 which is thought to mediate most of the physiological actions of VitD, has long been known to suppress EAE.[17, 18] Supplementation with VitD itself also inhibited EAE selectively in female mice,[19] consistent with MS epidemiology.[20] However, dietary VitD deficiency suppressed rather than exacerbated EAE,[21] raising doubts as to whether VitD deficiency is a bona fide risk factor for MS. Moreover, while UV radiation has long been known to inhibit EAE,[22] recent studies show that this occurs in the absence of any detectable effects on VitD synthesis or metabolism.[23] In this regard, it has been reported that the persistence of systemic UV radiation-induced immunosuppression is associated with altered dendritic cell function and their induction of T regulatory cells, due to epigenetic changes in bone marrow dendritic cell progenitors.[24, 25] Lastly, we have shown that season influences EAE susceptibility independent of UV,[26, 27] further complicating the connection between sunlight, VitD, and month of birth effects in MS (which are thought to be mediated by sunlight exposure)[15], and strengthening the known connection between circadian biology and MS.[28]

Another well-studied putative MS risk factor is exposure to infectious agents, which is thought to play an adjuvant-like effect in triggering pre-existing autoimmunity. Consistent with this notion, early studies using TCR transgenic animals that spontaneously develop EAE showed that increased exposure to microorganisms promoted EAE incidence.[29] Moreover, infection of with a gamma-herpes virus homologous to EBV exacerbated EAE in mice and rats,[30, 31] in agreement with increased human MS risk in EBV-infected individuals. Studies in EAE in a marmoset model also indicate an involvement of gamma-herpes virus infection in augmenting disease pathogenesis.[32] Moreover, pertussis toxin and toll-like receptor ligands, two adjuvants used to potentiate spontaneous or induced EAE, are examples of environmental agents derived from infectious organisms.[3] In contrast, several parasitic microorganisms can skew and dampen the pathogenic immune response in EAE, and are being explored as potential therapy in MS.[33] Overall, it is likely that many different infectious agents may contribute to triggering of autoimmunity in MS, while others may be protective.

Effects of environmental MS risk factors in animal models: developmental exposure

The effects of environmental MS risk factors acting during development are less well studied in animal models, despite the short gestational period in rodents which allows for easily testing developmental effects. The factors that have been studied so far include VitD, microbial products, stress, environmental toxins, and endocrine influences.

Epidemiological data suggest that sunlight exposure and VitD intake during gestation and early childhood may influence MS risk[15, 34]. As described above, VitD supplementation or VitD deficiency in adult mice can both suppress EAE. Likewise, the findings in EAE on the role of VitD during development are also somewhat inconsistent. Using a model of dietary VitD deficiency, Feron and colleagues showed that depletion of VitD in the dams during gestation resulted in reduced EAE in the offspring,[35] contrary to the prediction based on MS epidemiology, but consistent with DeLuca *et al* who showed reduced EAE in VitD-deficient adult mice.[21] In contrast, the second generation of mice that were gestationally deficient in VitD developed more severe EAE.[36] Meanwhile, VitD supplementation from birth to weaning (pre-pubertal), reduced EAE.[37] In agreement with the latter results, a very recent study in rats directly compared the effects of VitD supplementation during gestation, early life, or adulthood and found that only early life VitD supplementation suppressed EAE, while the other treatment paradigms had no effect on disease.[38] Taken together, the results from these animal studies suggest that the critical window for VitD's effects on MS may be during early life/adolescence rather than gestation, and that some effects of VitD may be transgenerational. Further studies are needed to clarify these results, particularly using VitD deficiency or supplementation exclusively during the early life period or during gestation. Moreover, the effects of UV radiation independent of VitD during development need to be explored.

The effects of the human microbiome, i.e. the commensal microorganisms residing on skin or mucosal surfaces, on the immune system are now well appreciated. The microbiome has undoubtedly changed with diet, hygiene, and the use of antibiotics, and thus represents a putative factor behind increasing MS risk. Since the microbiome can potentially be manipulated in a targeted way, it represents an attractive avenue for altering MS risk or disease progression. Multiple studies in EAE have shown that modulation of gut microbiota composition can either promote or protect from disease, as has been reviewed in more detail elsewhere.[39] Typically, germ-free mice are resistant to EAE and become susceptible after colonization with different microbiota; however, the introduction of specific commensals (or their products) to existing microbiota can suppress EAE. However, no reports have directly examined the role of gut commensals during development or gestation, despite the findings that the presence or absence of different microbiota during early life can clearly affect CNS development.[40, 41] In previous EAE studies, the microbiome is typically manipulated after weaning of pups, i.e. post-puberty; thus this may be considered an early life, but not pre-pubertal exposure. Additionally, germ-free animals used in many of these studies are maintained as germ-free for several generations, thus this exposure (or lack thereof) includes adulthood and all developmental periods. Future studies will need to more clearly define whether the immunomodulatory effects of gut microbiota take place during gestation, pre-puberty, post-pubertal early life, or in adulthood. This would have important implications for potential preventative or therapeutic interventions aimed at modulating the microbiome in humans.

With regard to developmental exposure to microbial products, one report showed that early life exposure to lipopolysaccharide (LPS), a component of bacterial cell walls, ameliorated EAE in adulthood, accompanied by suppression of pro-inflammatory innate and adaptive responses.[42] In contrast, administration of LPS during pregnancy exacerbated EAE in the offspring.[43] Since in both of these models LPS is delivered systemically at relatively high doses (similar to models of septic shock), these systems more likely to mimic a general sickness/stress response to a systemic infection rather than natural exposure to commensal microorganisms e.g. via mucosal surfaces.

Stress has long been known as a potent immunosuppressant, and, not surprisingly, experimentally induced chronic stress in adult animals (e.g. restraint stress) suppresses EAE.[44] This is in line with a study showing decreased MS relapses in patients exposed to chronic stress during the Gulf War.[45] However, the vast majority of epidemiological studies indicate that chronic or acute stress may instead precipitate disease onset or exacerbate symptoms in relapsing–remitting MS.[46] Similarly, acute stress, unlike chronic stress, in adult animals accelerated EAE onset.[47] With regard to developmental exposure, early life stress induced in neonatal pups exacerbated EAE in adult rats[48–50] and mice,[51] with more profound effects observed in males compared to females in both species. In agreement with this, we have shown that changing the postnatal maternal environment can also exacerbate EAE.[52] In contrast, postnatal handling decreased clinical signs in the TMEVD model, although in this model the immune response against the virus was significantly affected by this treatment,[53] making it difficult to acertain whether this is an indirect effect due to differential viral clearance. The effect of gestational exposure to stress on EAE has not been studied directly, but a recent study in mice showed that maternal stress altered the fetal transcriptome and modulated expression of microRNAs associated with MS and other neurologic diseases.[54] Moreover, as mentioned above, systemic administration of LPS during pregnancy exacerbated EAE in the offspring.[43] Taken together, these results indicate that early life stress can exacerbate EAE in a sex-specific fashion, and suggest that MS risk in adulthood may be influenced by stressful events in childhood or *in utero*, differentially in males versus females.

The petrochemical revolution brought with it exposure to many synthetic compounds, some of which have profound physiological effects. Two examples of this are bisphenol A (BPA), a chemical compound used in the manufacture of plastics, and diethylstilbestrol (DES), a drug originally given to reduce pregnancy complications, both of which have estrogenic activity and exert endocrine disrupting effects during development.[55] In fact, developmental exposure to BPA was found to exacerbate asthma in mice,[56] and recent epidemiological studies show a positive correlation between maternal BPA levels and asthma incidence in the offspring.[57] Based on these findings, and the chronological concurrence between BPA exposure and increasing MS risk in females, we examined the effects of developmental exposure to this chemical in two different models of EAE, but found no effect on disease severity or progression.[58] Similarly, no effect of developmental BPA exposure was found in a model of colitis, another tissue-specific autoimmune disease,[59] suggesting that BPA exposure may have selective effects on allergic, but not autoimmune diseases. With regard to DES, no animal studies to date have confirmed the possible association between MS and developmental DES exposure.[60]

Many other potential environmental toxins and endocrine disruptors exist, and their effects should be examined in animal models of autoimmunity.[61] Particularly interesting are different environmental toxins or compounds that can serve as ligands for the aryl hydrocarbon receptor, given the findings that adult exposure to such compounds can modulate EAE.[62] Another intriguing possibility is equol, an estrogen-like molecule which is produced from dietary soy by certain commensal bacteria that are present in about 25% of the human population,[63] which could provide a potential mechanistic link between diet, the endocrine system, the microbiome, and autoimmunity. Furthermore, evidence for the role of gestational endocrine imbalance in autoimmunity comes from a study showing that decreased thyroid hormone levels during pregnancy exacerbated EAE in the offspring.[64] In addition, we have observed a Y chromosome-dependent parent-of-origin effect on EAE in female offspring, consistent with the possibility that the intrauterine hormone environment can influence EAE.[65] Taken together, these studies indicate that endocrine factors acting during development can influence EAE in adulthood, and that other environmental endocrine disruptors could potentially influence MS risk.

Conclusions and perspectives

MS is a highly complex and multifactorial disease that is profoundly impacted by the environment during gestation, childhood, and adulthood. The understanding of risk factors acting during development is particularly limited. Animal models provide a potential way to systematically delineate and/or validate putative risk factors for MS and, perhaps more importantly, to define the underlying molecular mechanisms of how these factors contribute to the etiopathogenesis of this disease, including epigenetic and gene-by-environment interactions. Findings from animal models can be further verified and validated in the MS population, either using epidemiology and/or biomarkers, similar to how the findings of the role BPA in promoting experimental asthma[56] were later confirmed in human studies.[57] Improved understanding of the mechanisms of environmental risk factors may provide an opportunity for public health strategies aimed at preventing MS, or personalized and targeted therapeutic interventions for individuals with MS, an approach that could one day become the standard of care for this highly heterogeneous and complex disease.

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