Journal of Autoimmunity xxx (2015) 1–13

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

The immunogenetics of multiple sclerosis: A comprehensive review

Jill A. Hollenbach*, Jorge R. Oksenberg

Department of Neurology, University of California San Francisco, San Francisco, CA 94158, USA

ARTICLE INFO

Article history:
Received 19 June 2015
Accepted 23 June 2015
Available online xxx

Keywords:
Multiple sclerosis
Genetics
Human leukocyte antigen
Killer-cell immunoglobulin-like receptor

ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system and common cause of non-traumatic neurological disability in young adults. The likelihood for an individual to develop MS is strongly influenced by her or his ethnic background and family history of disease, suggesting that genetic susceptibility is a key determinant of risk. Over 100 loci have been firmly associated with susceptibility, whereas the main signal genome-wide maps to the class II region of the human leukocyte antigen (*HLA*) gene cluster and explains up to 10.5% of the genetic variance underlying risk. *HLA-DRB1*15:01* has the strongest effect with an average odds ratio of 3.08. However, complex allelic hierarchical lineages, cis/trans haplotypic effects, and independent protective signals in the class I region of the locus have been described as well. Despite the remarkable molecular dissection of the *HLA* region in MS, further studies are needed to generate unifying models to account for the role of the *MHC* in disease pathogenesis. Driven by the discovery of combinatorial associations of Killer-cell Immunoglobulin-like Receptor (KIR) and HLA alleles with infectious, autoimmune diseases, transplantation outcome and pregnancy, multi-locus immunogenomic research is now thriving. Central to immunity and critically important for human health, KIR molecules and their *HLA* ligands are encoded by complex genetic systems with extraordinarily high levels of sequence and structural variation and complex expression patterns. However, studies to-date of KIR in MS have been few and limited to very low resolution genotyping. Application of modern sequencing methodologies coupled with state of the art bioinformatics and analytical approaches will permit us to fully appreciate the impact of HLA and KIR variation in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disease associated with central nervous system (CNS) inflammation and neurodegeneration mediated by the adaptive and innate arms of an unregulated immune response [1,2]. MS pathology is characterized by well-demarked inflammatory infiltrates, breakdown of myelin sheaths, microglia activation, proliferation of astrocytes and gliosis, and variable grades of axonal degeneration linked to oxidative stress and mitochondrial injury [3,4]. Demyelinated lesions are disseminated through the CNS, involving both the white and gray matter. MS is a common cause of progressive neurological deficits in young adults, but disease expression is heterogeneous, varying from a mild illness to a rapidly evolving, incapacitating disease requiring profound lifestyle adjustments.

The individual and socioeconomic consequences of this debilitating and unpredictable disease are stunning. Fifteen years after diagnosis more than 80% of patients have functional and/or cognitive limitations, and approximately half require assistance to walk [5]. Twelve FDA-approved treatments for MS are now available, and several others are in late phases of development. However, the effects of these therapies on the long-term prognosis of the disease are largely unknown [6]. Furthermore, these therapies have diverse safety and toxicity profiles, and in effect no comparative data exist to guide when to initiate, change, or even how to select amongst the available options. Furthermore, no therapy exists for the progressive forms of MS, the subtypes most responsible for disability and debilitation [7].

2. MS epidemiology

In Europeans and their descendants, MS is the most common cause of non-traumatic neurological disability in young adults, affecting approximately 2.5 million people worldwide and more

* Corresponding author.
E-mail address: jill.hollenbach@ucsf.edu (J.A. Hollenbach).

http://dx.doi.org/10.1016/j.jaut.2015.06.010
0896-8411/

than 400,000 individuals in the US [8]. The prevalence of MS varies with geography and ethnicity. Indeed, with some notable exceptions, MS is more frequent in high latitude regions and northern European populations [9]. Notwithstanding difficulties in surveillance, MS is almost nonexistent in black Africans and native populations of the Americas and Oceania. Remarkably, the incidence of MS seems to have increased considerably over the last century, and this increase may have occurred primarily in women [10,11] and in populations traditionally considered to be at low-risk, such as Hispanics, Asians, and African Americans. For example, early estimates suggested that the disease is significantly less prevalent in African Americans than in European Americans (relative risk of 0.64 [12]). In contrast, contemporary incidence studies are challenging the long-held belief that African Americans are at a reduced risk for developing MS [13,14]. Remarkably, compared to individuals with predominately European ancestry, African Americans are more likely to have a more severe disease course, which at least in part appears to be genetically determined [15,16].

3. MS genetics

Evidence for a genetic component in MS pathogenesis is found in the clustering of affected individuals in families, high disease concordance rate in monozygotic twins, and differences in disease prevalence among different ancestral groups [17–21]. However, a simple model of inheritance for all MS is unlikely since neither the recurrence rate nor the twin concordance supports the presence of a Mendelian trait. On the other hand, there is a broad consensus that the disease is multifactorial and the MS-prone genotype results from multiple independent or interacting polymorphic genes, with risk alleles common in the population, and each exerting a small or at most a moderate effect to the overall risk. Several epidemiologic risk factors have been consistently reported; these include vitamin D deficiency, exposure to the Epstein Barr virus (EBV) during childhood with manifestations of infectious mononucleosis, and cigarette smoking, among others [22,23].

The polygenic model of MS genetics provided the rationale and drive for assembling large DNA datasets to pursue genome-wide association studies (GWAS), which have been highly successful in uncovering variants influencing susceptibility. Currently, a total of 110 polymorphisms in 103 discrete loci outside the major histocompatibility complex (MHC) have been firmly associated with susceptibility (Summarized in Ref. [24]). In aggregate, the proportion of the genetic variance accounting for disease risk explained by these polymorphisms is roughly 30%, but the mapping of additional risk variants is likely to proceed rapidly through ongoing multicenter initiatives utilizing dense, specialized arrays and very large sample collections. It is not inconceivable, however, that the potential for the discovery of additive risk variance extractable from large DNA screens will be quickly exhausted. Similar to other complex genetic diseases, multiple explanations for the missing heritability in MS have been proposed, including gene by gene and gene by environment interactions, cis/trans regulators of allelic expression, unidentified rare and penetrant semi-private variants, population and/or disease heterogeneity, neglecting the analysis of sex chromosomes, and hidden epigenetic effects. Regardless, genes encoding antigen-presenting molecules within the MHC region account for the largest component of the genetic risk for MS.

4. The human leukocyte antigen [HLA] region and MS

A search for “multiple sclerosis” and “HLA” in Pubmed reveals over two thousand entries. The HLA (Box 1) association with MS, which was first described several decades ago [25,26], is consistent with the idea that MS is, at its core, an antigen-specific autoimmune disease. The association of the *HLA* locus with MS risk has been observed across all populations studied, and in both primary progressive and relapsing-remitting patients. The primary signal within the MHC maps to the *HLA-DRB1* gene, or more specifically to the *DRB1*15:01* allele, in the class II segment of this locus. Complex allelic hierarchical lineages, cis/trans haplotypic effects, and independent protective signals in the class I region of the locus have been described as well and are summarized below.

Box 1
The human Major Histocompatibility Complex

Located on the short arm of chromosome 6p21, the human Major Histocompatibility Complex (MHC) is a remarkably gene-dense region with numerous immune response loci. These include the *HLA* genes, which were first recognized with respect to their critical role in histocompatibility, and are the major determinants of transplant outcome. Additionally, more than 100 infectious, autoimmune, inflammatory and pharmacological disease phenotypes and cancers are associated with HLA variation. The classical *HLA* class I and class II loci are the most polymorphic loci in the human genome and serve as a model for the study of genetic variation in human health and disease [27]. The extensive allelic diversity seen at these loci has been well documented [28,29], with more than 10,000 alleles identified to date, and their critical role in disease predisposition and transplant outcome has long been recognized.

There are two major classes of HLA-encoding genes. The telomeric region contains the *class I* genes, whereas the centromere proximal region encodes *HLA-class II* genes. *HLA class I* and *class II* encoded molecules are cell surface glycoproteins whose primary role in an immune response is to display and present short antigenic peptide fragments to peptide/MHC-specific T cells. The classical HLA-class I molecules, HLA-A, -B, and −C, are found on most nucleated cells as heterodimers, and bind and present peptides primarily derived from endogenous synthesized proteins (e.g. viral and tumor peptides) to CD8+ T cells; HLA class I also serve as ligands for the killer immunoglobulin-like receptors (KIR) on the surface of natural killer cells (Box 3). These heterodimers consist of an HLA-encoded alpha chain associated with the chromosome 17-encoded monomorphic polypeptide, β_2 microglobulin. The classical class II molecules, HLA-DR, -DQ, and DP consist of an alpha and beta chain, both *HLA* encoded, associated as heterodimers on the cell surface of antigen presenting cells such as B cells, dendritic cells, and macrophages. Class II molecules also serve as receptors for processed peptides; however these peptides are derived predominantly from membrane and extracellular proteins (e.g. bacterial peptides), and they are presented primarily to CD4+ T-lymphocytes. A third group of genes collectively known as *class III*, cluster between the *class I* and *II* regions and include genes coding for complement proteins, 21α-hydroxylase, tumor necrosis factor and heat shock proteins.

4.1. Association with DRB1*15:01~DQA1*01:02~DQB1*06:02. An historical perspective

The influence of *HLA* in MS susceptibility was first recognized prior to the molecular description of the class II molecules, and

Please cite this article in press as: J.A. Hollenbach, J.R. Oksenberg, The immunogenetics of multiple sclerosis: A comprehensive review, Journal of Autoimmunity (2015), http://dx.doi.org/10.1016/j.jaut.2015.06.010