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A molecular view of multiple sclerosis and experimental autoimmune encephalitis: What can we learn from the epitope data?

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ABSTRACT

An analysis to inventory all immune epitope data related to multiple sclerosis (MS) was performed using the Immune Epitope Database (IEDB). The analysis revealed that MS related data represent >20% of all autoimmune data, and that studies of EAE predominate; only 22% of the references describe human data. To date, >5800 unique peptides, analogs, mimotopes, and/or non-protein epitopes have been reported from 861 references, including data describing myelin-containing, as well as non-myelin antigens. This work provides a reference point for the scientific community of the universe of available data for MS-related adaptive immunity in the context of EAE and human disease.

1. Introduction

Multiple sclerosis (MS) is a progressive, debilitating neurological disorder characterized by central nervous system injury. The disease is largely regarded as autoimmune, primarily associated with genetic predisposition, though environmental factors have also been implicated (Lassman, 1983; Martin et al., 1992; Hafler et al., 2005; Sospedra & Martin, 2005). The main pathological features of MS are inflammatory infiltrates, destruction of the myelin sheath and oligodendrocytes, axonal and neuronal damage as well as glial proliferation. Adaptive and immune mechanisms are at the core of disease pathogenesis. While much of the downstream immunopathology has been characterized, the initiating event for the development of MS has yet to be elucidated. Current treatment options for MS are based on immunomodulation/suppression, and include type I interferons, a peptidic mixture of 4 amino acids, glatiramer-acetate, a sphingosine 1 phosphate receptor agonist, fingolimod, fumaric acid, teriflunomide and monoclonal antibodies against VLA-4 and CD52 (Wagner, 2012). Antigen-specific strategies have also been proposed and tested, and while this field has seen various setbacks (Hohlfeld & Wekerle, 2004), promising data have recently been published for at least two approaches, including the administration of seven myelin peptides coupled to autologous PBMCs and skin patch application using a mixture of three myelin peptides (Lutterotti et al., 2013; Walczak et al., 2013).

A great deal of what is now understood about MS was gained through studies using experimental autoimmune encephalomyelitis (EAE). EAE is the most common animal model used to simulate the human demyelination disease, MS, as it closely parallels key features of human disease, including inflammation, demyelination and gliosis (Rivers et al., 1933; Rao & Segal, 2012). EAE models have been used extensively as surrogates for characterizing MS immunopathology and to test candidate neuroprotective and reparative strategies. These models include primarily mice and rats, but also include rabbits and non-human primates (Constantinescu et al., 2011).

Despite its many merits, EAE differs from MS in several notable aspects. In most cases, EAE is experimentally induced (as the acronym implies) using antigens (peptides and proteins) along with bacterially-derived adjuvants; spontaneous disease is achieved using transgenic mice models (Madsen et al., 1999; Quandt et al., 2012). Moreover, while both humoral (B cells, plasma cells and antibody) and cellular ($CD4^+$ and $CD8^+$) mechanisms have been shown to contribute to MS immunopathology (Lassman et al., 2007; Simmons et al., 2013 May 21), EAE represents the prototype T cell-mediated autoimmune model, whereby $CD4^+$ T cells are the predominant effector cell in the disease, which is largely driven by a pro-inflammatory Th_1/Th_{17} cytokine milieu (Kroenke et al., 2008). Therefore, while many EAE models involve well-characterized B-cell responses, relatively fewer relevant B cell epitopes have been defined.

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At the antigenic level, MS and EAE share many of the same targets, including myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein (PLP) (Sospedra & Martin, 2005). While it is known that numerous other self-antigens are involved in MS, either as initiators or bystanders, it is the myelin-containing antigens that have been most frequently associated with the autoreactivity. Furthermore, there is a remarkable overlap, at least for MBP, with respect to immunodominant regions in the context of MS-associated HLA-class II alleles and those peptides that are able to elicit EAE in various susceptible rodent strains and species and in Rhesus monkeys (Sospedra & Martin, 2005). These same antigens serve as the immunogens in EAE induction (Rao & Segal, 2012) and therefore represent ideal targets for analysis and comparison of immune reactivity patterns between EAE and MS. As it is possible that the nature of immunological differences between these two models may be manifest at the molecular level, we propose that an analysis of all "MS-specific" and EAE-specific immune epitope data may reveal valuable insights similar to the above mentioned data on MBP. The dissection of immune reactivity at this level allows for direct comparative analysis of MS and EAE immunobiology using analogous self-antigens. Herein we provide a comprehensive analysis of all MS- and EAE-related epitope data and explore the relationship between MS and EAE as it relates to several key issues in MS immunobiology.

The goal of this analysis is to inventory all epitope data related to MS, as curated in the Immune Epitope Database (IEDB), to provide a reference point for the scientific community of the universe of available data, extract whenever possible general features of the data, and at the same time highlight areas for further research.

2. Materials and methods

2.1. IEDB queries

All queries were performed using the Immune Epitope Database and Analysis Resource (IEDB) home page search interface [www.iedb.org]. For more complex queries the advanced search interface (all fields) was utilized. Search criteria are provided in the figure legend or table notes. Results were downloaded in Excel format for detailed analysis, unless otherwise indicated. MS or EAE-specific queries were conducted using the disease finder, which selects only those data representing data generated in hosts with clinical disease. As such, these queries do not retrieve all data *associated* with disease, and therefore should be considered a subset of the entire MS-associated data captured by the IEDB, which considers clinical MS and EAE together. Antigen-specific queries include all data, regardless of the clinical state of a host. Unless otherwise indicated, antigen-specific queries were performed irrespective of disease status. Also, unless otherwise indicated, all reported data herein represent positive epitopes and/or assays only.

2.2. IEDB inclusion criteria

Our analysis includes all available data for antibody and T cell epitopes associated with MS (defined by clinical status of host and/or antigen association) in human and nonhuman (animal models) hosts. To identify MS-related data, we followed the process described by Davies et al. (2009). The data are derived from the peer-reviewed literature (PubMed), as well as data directly submitted to the IEDB. Epitope definitions (length and mass restrictions) and IEDB inclusion criteria can be found at http://tools.immuneepitope.org/wiki/index.php/Main_Page. For the purpose of this report, epitopes represent the unique molecular structures (minimal sequences, linear and discontinuous regions, as well as key residues) experimentally shown to react with a B cell or T cell receptor (no predictions). Peptidic as well as non-peptidic (*e.g.* lipids and carbohydrates) determinants are included in the IEDB.

2.3. Immunome browser

The Immunome Browser is a unique feature of the IEDB that allows the user to map the result of any query (in terms of epitopes) onto a reference genome or antigen. It does this by plotting the response frequency score (number respondents/number tested) of each epitope, by residue, along the entire length of the target protein. In this way, it is possible to visualize those regions on the antigen(s) that are more immunodominant or more frequently studied in a given population for a particular response (Ab, T, CD4, CD8, *etc.*). This provides the least biased way to analyze the cumulative data and allows for comparisons between hosts, disease states, as well as assay type (exacerbation *versus* tolerance), as examples. The reference human antigens used to compare response patterns between MS and EAE were the following: MBP [GI: 17378805], MOG [GI: 23270927] and PLP [GI: 41393531]. In order to accommodate all defined epitopes onto a reference antigen, full-length proteins are used. For this reason, residue numbering may be different than that of certain well-established protein isoforms.

3. Results and discussion

3.1. MS-related epitope data in the broader context

To put the MS-related epitope data into the broader context of all immune epitope data within the IEDB we first determined the relative proportion of autoimmune-specific data among all disease categories. The IEDB's categorization of all references containing epitope data from PubMed is done by disease association as previously described (Davies et al., 2009). Briefly, this categorization uses as a basis for disease association, the host's clinical status (including animal models that mimic human symptoms) and/or the epitope-derived antigens associated with disease(s). Fig. 1 shows that autoimmune (AI) diseases represent close to 30% of all epitope data housed within the IEDB, second only to infectious disease. Specific examination of the sub-categories within AI, reveals that references describing MS represent >20% of the total (Fig. 1b), making it the largest AI disease sub-category. Within this sub-category, studies of EAE predominate, with only 22% of references describing human data.

To date, there are more that 5800 unique molecular structures (peptides, analogs, mimotopes, non-peptidic molecules) reported as associated with MS (this includes all EAE studies as well) in 861 references, of which ~2400 have been found to be positive in the context of either B cell or T cell (or both) reactivity [data not shown]. Thus, MS is well covered at the molecular level by comparison to other AI disease categories. Because not all MS-related data are generated in the context of clinical disease (either MS or EAE), a secondary analysis was performed to specifically identify immune reactivity in the context of disease. Here we observed that when we filtered those data that specify MS or EAE as the disease state, there are 637 peer-reviewed papers describing a total of 1374 positive antibody/B cell and T cell epitopes, including those defined in MHC binding and/or from MHC ligand elution assays.

3.2. Analysis of the antigen composition of MS-associated epitope data for myelin-containing antigens

The main feature of MS immunopathology is antibody and T cell reactivity against self-antigens containing myelin, the chief component of white matter within the central nervous system (CNS). MS is classified into four phenotypes (I–IV); all involve T cells and macrophages, however, type II is specifically related to antibodies and complement (Lucchinetti et al., 2000). Numerous antigens derived from myelin proteins have been identified to date, and include myelin basic protein (MBP), proteolipid protein (PLP), myelin oligodendrocyte