The major histocompatibility complex and antibody-mediated limbic encephalitis

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Autoimmune encephalitides, including limbic encephalitis, represent an increasingly recognized and heterogeneous group of neurological disorders characterized by changes in behavior and cognition, and that is frequently associated with epileptic seizures. A possible association between remote neoplastic growths and pathologic changes of the limbic grey matter was first implied by Corsellis and colleagues in 1968 [1]. Fifteen years later, Greenlee and Brashear showed in this journal that CNS neurons, namely Purkinje cells, are cellular targets of an antibody-mediated paraneoplastic autoimmune disorder [2]. In this issue of the Annals of Neurology, work by Kim et al [3], and van Sonderen et al [4] further elucidate potential pathogenic mechanism underlying one form of limbic encephalitis, anti-leucine-rich glioma-inactivated1 (anti-LGI1)-encephalitis.

Specifically, Kim et al demonstrate that anti-LGI1 encephalitis is strongly associated with the major histocompatibility complex (MHC) II haplotype human leukocyte antigen (HLA) DRB1*07:01–DQB1*02:02, and to a lesser degree with the MHC I alleles HLA B*44:03 and C*07:06 in their cohort of 11 patients with anti-LGI1-encephalitis. van Sonderen et al show that HLA-DR7, which comprises the gene products of HLA DRB1*07:01, and HLA-DRB4 alleles are significantly more prevalent in a group of 25 non-paraneoplastic anti-LGI1-encephalitis. These investigators further performed an exploratory analysis in four patients with anti-LGI1 antibodies and different forms of cancer, in whom a MHC association could not be proven.

What is the biological significance of these observations? There are three possible answers. The most likely explanation is that an association of MHC alleles support the autoimmune hypothesis proposed for limbic encephalitis. An association with HLA

genes, in particular HLA-DR, has been established in many human immune-mediated disorders, and was first demonstrated in 1973 by Singal and Blajchman for type I diabetes mellitus [5]. Similar associations were subsequently shown for many other systemic and organ-specific inflammatory diseases, including for the human central nervous system (CNS) autoimmune disorder multiple sclerosis (MS) [6, 7]. MHC I molecules are expressed on all nucleated cells, whereas MHC II molecules are constitutively expressed on antigen-presenting cells (APC), including myeloid cells and B lymphocytes. The biological role of MHC I is to present linear peptide antigens to CD8^{+} cytotoxic T cells, and that of MHC II to present linear peptides to CD4^{+} T helper cells. An antigen-specific T cell receptor (TCR) recognizes peptide/MHC II complexes, requiring interaction with both the peptide and MHC molecule to initiate TCR signaling [8]. Thus, an association of a clinical disorder with a MHC I or MHC II haplotype implies a pathogenic involvement of an antigen-specific CD8^{+} or CD4^{+} T cell, respectively. There are three events that are required to trigger CNS autoimmunity: 1) The generation of autoimmune-prone T cells specific for CNS antigens, 2) the migration of autoimmune-prone T cells into the CNS, and 3) the re-activation of the autoimmune-prone T cells within the CNS, converting them to autoimmune T cells. The generation of autoimmune-prone T cells in secondary lymphoid organs is initiated when an APC presents an infectious or neoplastic antigen. In most tissues, foreign antigens are first recognized by tissue macrophages. The inflammatory response is than amplified to include other immune competent cells, and eventually antigenic peptides are presented in the context of MHC to T cells. Alternatively, pathogenic or neoplastic antigens may be recognized by a B cells through the B cell receptor (BCR), which is capable of

binding to conformational or linear antigenic determinants [9]. Once the naïve B cell is activated, the binding domain of the BCR generates the fragment antigen-binding (FAB) region of the secreted antibody [10]. Importantly, an antibody isotype switching from IgM to IgG typically does not occur without CD4^{+} T helper cell involvement [11]. Identifying an IgG antibody and a MHC association in patients with anti-LGI1-encephalitis suggests that LGI1 is recognized by a BCR, that a peptide fragment of LGI1 is subsequently presented to a T cells, and that this autoimmune-prone T cells in turn cross-activates the antigen-specific B cell.

An association of a disease with a specific HLA DR may also explain how autoimmune-prone CD4^{+} T cells might escape negative thymic deletion and trigger autoimmunity without exposure to a foreign antigen. Muraro and colleagues showed that a relatively weak MHC-binding antigenic epitope yields an immunodominant CD4^{+} T cell response, whose TCR repertoire presents specific structural constraints, both in variable gene segment usage (contributing the CDR1 and CDR2 regions) and in V-(D)-J junctional region sequences (representing the CDR3 region) [12]. These constraints may subsequently account for a limited heterogeneity observed in the TCR repertoire of cells detectable in the periphery of patients with autoimmunity.

Finally, in very rare cases an association of a human disorder with an MHC allele may be a misinterpretation, especially if low-to-medium resolution genotyping is performed. For instance, the HLA super-locus in the chromosomal position 6p21 encodes not only the six classical HLA genes, but also at least 132 protein encoding genes that regulate molecular and cellular processes pertinent to immune responses,

including myelin oligodendrocyte glycoprotein (MOG), a putative CNS autoantigen in MS.

The numbers of patients and controls studied by Kim et al and van Sonderen et al are too small to draw definite conclusions about disease phenotypes and associated genotypes. Also, in the study by Kim and colleagues, multiple HLA alleles were associated with anti-LGI1-encephalitis. The MHC II molecule HLA-DR is a heterodimer consisting of a membrane-anchored alpha (DRA), and a membrane-anchored beta chain (DRB). The beta chain contains all the polymorphisms that ultimately define the peptide binding specificities. Thus far, hundreds of DRB1 alleles have been identified. As occurs with other genes, there is a random association of alleles at different loci within the HLA locus. If such an association of their different alleles is higher or lower than expected if the loci were independent and randomly associated, geneticists speak of a linkage disequilibrium [13]. For instance, HLA-DRB1*07:01 is very commonly associates with HLA-DQB1*02: and HLA-DRB4. Haplotypes with these alleles are found in almost 10% of Caucasians [14]. HLA-B*44:03 is also known to infrequently pair with HLA-C*07:06, but this is very uncommon and possibly exclusive to native American and Asian/ Pacific Islander populations.

Ultimately, the observations made by Kim et al and van Sonderen et al may suggest that there are numerous potential molecular and cellular targets for therapeutic interventions in patients with anti-LGI1-encephalitis that are waiting to be explored.

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