CLINICAL IMPLICATIONS OF BASIC RESEARCH

Molecular Mimicry in Multiple Sclerosis

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Most experts believe that multiple sclerosis is an autoimmune disease in which T cells recognize and attack components of the axonal myelin sheath and other features of the central nervous system, destroying myelin and the underlying axon. Although self-reactive T cells are present in the immune system of people with multiple sclerosis, they are also found in a quiescent state in perfectly healthy people. Their pathogenic potential is realized only on acute activation, which can occur through different mechanisms. Recent work by Lang and colleagues focused on molecular mimicry, one of the presumed triggers of autoimmunity.[1]

Lang and coworkers investigated the antigen-specific T-cell receptor of a particular T-cell clone (Hy.2E11), originally isolated from the blood of a patient with multiple sclerosis. The clone was selected for its reactivity to a self antigen — the myelin basic protein (MBP) — but it was later found to cross-react with a peptide analogous to part of a viral antigen, the polymerase of the Epstein–Barr virus (EBV).[2]

The new work shows that this dual response is more complex than anticipated. The mimicry is not simply explained by the structural similarity of the two peptides, as posited by the original model of autoimmune mimicry,[3] in which a foreign antigen is sufficiently similar to a self antigen to trigger an autoimmune response. The MBP and EBV peptides share no obvious sequence similarities. Furthermore — and this is the most striking point of the study by Lang et al.[1] — the two peptides are presented by different major-histocompatibility-complex (MHC) HLA class II proteins. The EBV peptide is presented by HLA-DR2a, and the MBP peptide by HLA-DR2b (Fig. 1).

Lang et al.[1] introduced the genes encoding the T-cell–receptor chains of the human Hy.2E11 T-cell line into a lymphoid mouse-cell line that lacks T-cell receptors of its own, thus ensuring that the mouse-cell line expressed only the Hy.2E11 T-cell receptors. They then had to make sure that the antigen-presenting cells expressed only the relevant HLA-DR2 restriction molecules. Normally, in HLA-DR2–positive persons, antigen-presenting cells (which include dendritic cells, macrophages, and B cells) ex-

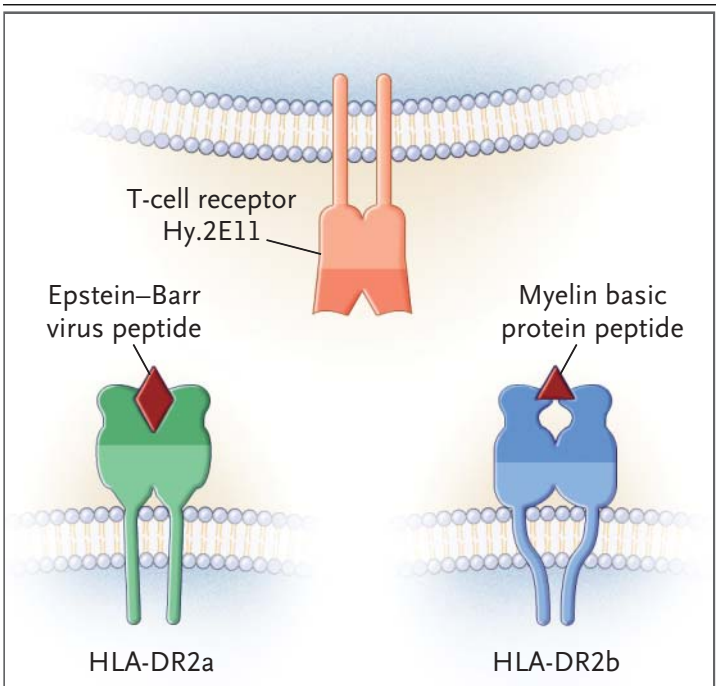

Figure 1. Modeling a Mimic.

Lang et al.[1] have demonstrated that molecular mimicry — the cross-recognition of foreign and self peptides — extends to complexes of peptide and peptide-binding major-histocompatibility-complex (MHC) molecules. They isolated a T-cell receptor called Hy.2E11 from a T-cell line from a patient with multiple sclerosis. This receptor recognizes MHC-bound myelin basic protein. They transfected mouse cells with the gene encoding this receptor and then stimulated the transfected cells with other cells engineered to express either HLA-DR2a or HLA-DR2b. The results indicate that the Hy.2E11 T-cell receptor can recognize two peptides, one derived from the Epstein–Barr virus, which is bound to HLA-DR2a, and one derived from myelin basic protein, which is bound to HLA-DR2b. This example of molecular mimicry is notable because it involves not only two peptides, but also two different HLA-DR molecules. In HLA-DR2–positive people, both HLA-DR2a and DR2b are expressed on the surface of all antigen-presenting cells.

press both HLA-DR2a and DR2b molecules on their surface. To separate the effects of these antigen-presenting molecules, Lang et al.[1] modified mouse fibroblasts so that they expressed only one of the two HLA-DR2 variants. Using these artificial antigen-presenting cells, they showed that HLA-DR2b presented the MBP peptide (but not the EBV peptide) to the T-cell receptor and that HLA-DR2a presented the EBV peptide, but not the MBP peptide (Fig. 1).

Are the findings relevant to events in vivo? The authors tried to address this question through the use of "humanized" transgenic mice that express the human MBP-specific T-cell receptor derived from Hy.2E11, together with human HLA-DR2a and DR2b and human CD4. Brain inflammation spontaneously develops in these mice under certain conditions, providing further support for the hypothesis that multiple sclerosis is an autoimmune disease.[4] As expected, both the MBP and EBV peptides activated spleen cells derived from these multitransgenic mice. In contrast, spleen cells from T-cell receptor–HLA-DR2a and T-cell receptor–HLA-DR2b double-transgenic mice responded solely to one peptide, as predicted by the experiments with HLA-DR–transfected mouse fibroblasts.

Molecular mimicry thus goes well beyond the simple structural resemblance of two individual peptides. It also embraces the peptide-presenting MHC class II proteins. Are the two peptide–HLA class II complexes sufficiently similar to stimulate the same T-cell receptor? X-ray crystallography had previously been used to delineate the structure of the MBP–HLA-DR2b complex,[5] and when Lang et al.[1] determined the structure of the EBV–HLA-DR2a complex, they discovered an astounding similarity between the two complexes (Fig. 1).

Although the study suggests that the mimicry of one complex by another may trigger an autoimmune response, it relied on synthetic peptides and genetically engineered cells and animals — a highly artificial setup. The extent to which this setup pertains to real life is not clear. For example, the mimicry response was elicited by synthetic peptides added to cultured cells. It is an open question whether the cross-reactive EBV peptide is generated during the natural processing of the whole virus, let alone during the course of EBV infection in vivo. That said, the study adds a new dimension of mimicry; it indicates that the search for structural mimics must be extended to molecular complexes — in this case, the peptide and the presenting HLA molecule. The new findings may also contribute to our understanding of the well-known association between the HLA genotype and multiple sclerosis. If, indeed, molecular mimicry can occur across different HLA proteins that are encoded by genes that, by virtue of being next to each other in the genome, are part of the same haplotype (as is the case for HLA-DR2a and DR2b in multiple sclerosis), the haplotype is more likely to be associated with the disease.

Finally, the study by Lang et al.[1] may help in designing better, more selective therapies for multiple sclerosis. Ideally, one would like to modulate or eliminate the autoaggressive T cells but leave the remaining immune system intact. This goal might be achieved by the use of altered peptide ligands derived from autoantigenic peptides — for example, an immunodominant peptide of MBP. The altered peptide ligand would bind to the same MHC and T-cell receptor as the autoantigenic peptide from which it derives, but it would fail to activate the T cell fully, thereby inducing a protective response. Preliminary clinical trials involving an altered peptide ligand derived from MBP indicated that low and intermediate doses of the ligand have some promise, whereas high doses stimulated allergic reactions and activated, rather than muted, the activity of MBP-specific T cells. A better understanding of the mechanisms of molecular mimicry should help to explain these puzzling observations and perhaps contribute to the development of new peptide ligands for the treatment of multiple sclerosis.

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