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Burning Debate: B cells vs. T cells

Professor Wraith:
So, I'm Professor David Wraith. I'm Director of the Institute of Immunology and Immunotherapy at the University of Birmingham. And we're here today to discuss a debate that I chaired at the ACTRIMS meeting in Paris last year, and this was a debate between David Hafler from Harvard University and Steve Hauser from UCSF in San Francisco on the relative importance of B and T cells in multiple sclerosis.

So, first of all, I think it would be important just to talk a little bit about multiple sclerosis. So, MS is an autoimmune disease, considered an autoimmune disease. Autoimmune diseases are a group of diseases where the body's immune system attacks parts of or tissues within our own body. What are autoimmune diseases? Well, they are diseases that are commonly found more frequently in women, and they also have strong genetic associations. Most predominantly their association is with genes within the major histocompatibility complex, particularly the class II region with the MHC, and this links them to T cells because MHC class II presents antigen to T cells. There are also environmental influences on multiple sclerosis, and this has been revealed very clearly in studies of twins in Canada, but also on migration studies.

So, if we look at the genes associated with MS, as I mentioned before, the strongest association is with MHC class II, which implicates T cells. More recently, however, studies in immunotherapy have shown that depleting B cells has a profound effect on the disease, and this is very, very important because it implies what we previously thought about the importance of T cells may have been wrong and that B cells also play an important role. And this is what really made this such a topical event at the ACTRIMS meeting and so important for us to debate.

Much of the work in history pointed to a role of T cells, and I'd like to mention 1 scientist in particular. This is Elvin Kabat, who I believe did 2 pieces of work that were vitally important in leading us to our present understanding of the nature of the adaptive immune response in multiple sclerosis. So, one of the observations he made dated back to studies in rabies vaccination, and what people had noticed in rabies vaccination was that a small percentage of people immunized with the rabies vaccine developed an acute demyelinating disease called disseminated encephalomyelitis, an inflammatory disease of the myelin sheath, and this in some ways resembled what was seen in multiple sclerosis. Now, then turned out that that was caused by contamination of the rabies vaccine with brain material. And what Kabat did was to combine brain material with a strong adjuvant that had just been developed in the US by his colleague Freund. He combined the 2 and immunized animals with this material and reproduced a disease called experimental autoimmune encephalomyelitis. Now, this experimental model led to discovery of the role of many immune components in this MS-like disease, and particularly the role of T cells, because it was later shown that you could reproduce the symptoms of this disease with T cells alone, okay? and even with CD4 positive T cells. And these are the cells, of course, that are presented too by the MHC class II that had been previously associated through the genetic studies in MS.

Are there drugs targeting T cells that are effective in MS? Well, if we think about it, 2 of the current drugs that are currently used for MS directly block T cell entry into the brain. These include natalizumab, and this targets an adhesion receptor, an integrin, VLA-4 on T cells, and VLA-4 is required for migration of T cells through the blood-brain barrier and into the brain. The other drug is fingolimod, and fingolimod is an S1 phosphate antagonist because it down-regulates the S1 phosphate receptor on T cells, and this receptor is required

for T cells to migrate out of lymphoid organs. So, there are 2 drugs here, one of which prevents T cells getting out of lymph nodes and the other of which blocks T cells migrating into the brain, both of which influence or dampen down the symptoms of MS, and this strongly implicates a role for T cells in the disease.

If we go back again to Elvin Kabat, he showed that if you look in the cerebrospinal fluid of patients with MS, they had a band, a protein band, that was also seen in plasma of individuals but wasn't seen… This was only seen in patients with MS, and this band was a protein band specific for immunoglobulin. So, he showed that something like 85% of people with MS-like symptoms had immunoglobulin in the fluid bathing the brain. Subsequently, it was shown that this immunoglobulin, if separated out on a gel, would band in a way which was consistent with selection of particular antibody types within the brain. And actually, then it was shown later that people with MS had foci of B cells and T cells forming almost like-new lymphoid organs within the brain. So, if you take all that together, it implies that within the brain there is an immune response being driven through T cells and B cells.

This led to people testing antibodies against B cells in therapy. Similar antibodies have been used in other autoimmune diseases and shown to be effective, and these antibodies were really quite effective. So, rituximab, for instance, had been shown to reduce the burden of lesions and the number of relapses in patients with MS, and more recently, ocrelizumab, a recombinant humanized antibody against the CD20 molecule, has been shown to be very effective in relapsing MS and has even had some impact in primary progressive MS. So, this blocks the disease activity and reduces progression.

Everybody was expecting a big fight, of course. "The rumble in the jungle" they called this debate. But in reality, both Steve Hauser and David Hafler agreed to agree, and they agreed that both B cells and T cells are vitally important in this disease. And to some extent that is strongly supported by studies with other treatments. So, cladribine, for example, affects both B and T cells and has an impact on the disease, and alemtuzumab, a monoclonal antibody that depletes all white blood cells, equally has a profound effect on disease progression.

However, I think we all accept that we need to learn a lot more about how these cells play a role in the disease. And ultimately, I, among many, am striving to find a way of specifically deactivating those cells that cause the disease so as to leave the rest of the immune system, the rest of the adaptive immune system, to do what it has evolved for, which is to protect us from infection and cancer. So, I think as we progress, we will move away from the drugs that nonspecifically suppress the immune system to more selective, targeted treatments for diseases like multiple sclerosis.