

Memory T Helper Cells and Multiple Sclerosis

Ashton F. Embry

Multiple sclerosis is a cell-mediated, organ-specific autoimmune disease. This means that a person's immune system is doing the damage which results in disease. In an autoimmune disease like MS, specific self-proteins in specific tissue in a specific part of the body are being attacked by the immune system and hence the term organ-specific. T cells, which are part of the white blood cells, are the key immune cells which are driving the attack and that is why it is referred to as a cell-mediated disease. In MS, T cells direct an attack on self-proteins of myelin in the central nervous system whereas in rheumatoid arthritis T cells direct an attack on self-proteins of synovial tissue in the joints.

T cells are immune cells which have receptors on them and these receptors allow T cells to recognize protein fragments (antigens) derived from foreign, potentially harmful substances such as bacteria and viruses. Each T cell receptor recognizes a different string of amino acids which comprise the antigen. Essentially there will always be at least one T cell receptor in the total repertoire of T cells which will recognize any given antigen which is in the body.

There are two main types of T cells, T helpers(CD4+) and T killers(CD8+). T helpers (Th) are the ones which are the drivers of MS. The T helper receptor engages an antigen only when the antigen is displayed on the surface of an antigen-presenting cell (APC) by what is called a class 2 MHC molecule. Only through such engagement can the Th cell be activated which then allows it to lead the attack against that specific antigen.

Before a Th cell has reacted with an antigen on an APC, it is known as a naïve T cell. Once it is activated by an antigen displayed by an MHC molecule on a APC it becomes an effector Th cell and it then becomes part of the immune attack on the antigen. Importantly, a naïve Th cell can be activated only by antigen presented by a "professional" APC. These cells are mainly dendritic cells but may include macrophages. In such situations the naïve Th cell needs to receive a second signal when it has engaged the antigen being presented. This is known as co-stimulation. The Danger Model of immunity postulates that such co-stimulation only occurs when damage (ie infection) has occurred to cells. Such a system helps to prevent an attack on self-proteins because they are routinely engaged by T cells in a no damage (non-infectious) context. If a naïve Th cell does not receive the second signal it dies and this helps to maintain a tolerance of harmless self proteins.

After the antigen has been cleared, most of the effector Th cells die but some are maintained in a resting state. These are known as memory Th cells. These memory cells allow a swift and usually very effective attack on the reappearance of the same antigen which activated it in the first place. They quickly become effector cells because they can recognize antigen presented by "amateur" APCs such as B cells which are very common and which can activate the Th cell without a second signal (no co-stimulation). Such an easy, fast and large generation of effector cells allows the immune system to deal with the antigen in a very efficient manner. This is the reason why vaccines work. They result in the creation of various types of memory cells (T cells,B cells) to the virus or bacteria in the vaccine so that if the person is exposed to that infectious agent in the future the immune system can quickly get rid of it before any significant damage (ie. disease) occurs.

For some time now I have been convinced that memory Th cells are a key factor in MS. There are about half a dozen important references in the literature pertinent to this. Two studies have shown that the Th cells which are reactive with myelin basic protein (MBP), the most common protein in myelin and a probable target of attack in MS, are mainly memory cells in PwMS but are mainly naïve cells in healthy people. It is interesting to note that many healthy people also have some autoaggressive memory Th cells although in far lower quantities than that found in persons with MS. This might explain why about 15%

of healthy people have at least one lesion in their central nervous system. Other studies have shown that such MBP reactive cells in persons with MS do not need co-stimulation to be reactivated to effector status, again confirming their memory status and the relative ease with which they can be activated.

From this I infer the following:

1. Most people carry MBP reactive Th cells (and most probably carry Th cells which react with other proteins in the CNS such as PLP, MOG, MAG etc).
2. Healthy people have some activation of such autoreactive Th cells but not much (little activation and/or very rare activation). It is well established that autoreactive cells are produced in most people following infection and this is the likely source of CNS autoaggressive T cells in healthy people. Such autoimmunity is well controlled in most instances and results in little or no CNS inflammation.
3. These autoaggressive Th cells are most likely activated by cross reactions with foreign antigens (molecular mimicry, super antigens). Clearly, autoaggressive naïve Th cells have to be activated by cross-reactive antigens derived from infectious agents because they require co-stimulation. In persons with MS (PwMS) such reactions are likely more expansive and/or more frequent mainly due to genetics. This is readily inferred because PwMS have similar exposures to common infectious as healthy people do. Furthermore such reactions are not as effectively suppressed in those with MS as they are in others.
4. Food antigens are usually not thought of as possible cross-reactive antigens for Th cells which are reactive with myelin antigens. One of the main reasons for this is that food antigens usually are not presented by APCs in the context of damage and thus do not result in co-stimulation and activation of naïve Th cells. However food antigens can play a major role in MS by reactivating myelin-sensitive, memory Th cells which do not need co-stimulation. Thus as long as the myelin-reactive Th cells, which most people carry, have been previously activated by an infectious mimic (i.e. they are now memory cells), food antigens can also potentially activate such myelin-sensitive Th cells. Furthermore, this can occur on a near daily basis although the reactions will in most cases be small in magnitude due to the limited amount of antigen. Two main factors are in play here in terms of magnitude and frequency of these food-driven reactions—the amount of mimicking food proteins consumed and the flow rate of such protein fragments into circulation through a leaky gut. Such reactions also guarantee a relatively large pool of autoreactive memory cells is maintained because of daily restimulation of the cells.
5. Infectious agents also drive MS (molecular mimicry, upregulation of proinflammatory cytokines) and, as noted above, they are essential for precipitating cross reactions which result in the initial production of myelin-sensitive memory Th cells. Notably, because infectious agents replicate and thus potentially create a great deal of antigen, they can result in a much larger autoimmune reaction than non-replicating food antigens. On the other hand, exposure to them is much less common than to food antigens and such infection-driven reactions are very rare compared to the food-driven ones.
6. The frequent small reactions driven by food likely result in much larger than normal reactions by infectious agents because of the maintenance of a large pool of memory cells (memory cells slowly disappear if not restimulated). Due to this greater magnitude of response, such reactions are not controlled in genetically susceptible people (the well adapted suppressor mechanisms fail) and damage outstrips repair. This results in the onset of autoimmune disease, which is a different concept from autoimmunity.

In summary, I see MS progression being driven to a large extent by the reactivation of memory Th cells which are autoreactive with various self proteins in the CNS as well as with infectious and food antigens. This occurs in two ways; frequent, small, food-driven reactions and rare, large, ones driven by infections.

The big question is if we stop the numerous, small, food-driven ones (ie stop consumption of foods which contain mimicking proteins and/or which adversely affect intestinal permeability) and increase the intake of nutrients which suppress autoimmune reactions (eg vitamin D) will that allow the body to control the rare, large infection-driven ones?

It seems reasonable to assume that evolution has adapted us to the rare, big infection-driven autoimmune reactions because it had 2 million years plus to do so. Undoubtedly the suppressor side of the immune system developed and evolved in part to counteract infection-driven autoimmune reactions. In this regard it must be noted that one of the main evolved mechanisms for the suppression of autoimmune reactions is through the action of vitamin D hormone. Thus it is essential to have an optimal level of circulating vitamin D (25(OH)D) to allow sufficient vitamin D hormone to be produced when and where (eg CNS for MS) it is required. Recent studies have shown that an intake of 4000 IU/d of vitamin D3 is needed to ensure optimal levels of circulating vitamin D and effective suppressor reactions. The other nutritional factor which aids suppression of autoimmune reactions is an abundant supply of omega 3 essential fatty acids which are derived mainly from fish oil.

Thus, although evolution has allowed the development of strategies to offset infection-driven autoimmune reactions, we have not had enough time to adapt to the innumerable food-driven ones because such reactions to foods introduced by agriculture (dairy, grains etc.) have been going on for only a few thousand years. Furthermore due to migration and cultural changes we have a greatly decreased supply of the two main suppressor nutrients, vitamin D and fish oil. These new, food-driven reactions, for which we have no adaptation, in combination with a marked decrease in suppressor nutrients, have short-circuited our well adapted suppressor responses and have resulted in genetically susceptible people losing control of the rare, infection-driven autoimmune reactions. Such people contract one or more of a variety of autoimmune diseases with each specific disease being related to a specific combination of genes.

A clinical trial which monitors MS progression in people who have given up foods which potentially cause autoimmune reactions and who have increased their supply of suppressor nutrients to Paleolithic levels should allow a good evaluation of how effective such a strategy is for controlling MS.