The complex immunology of multiple sclerosis

The immunology of multiple sclerosis (MS) is at once well-understood and not at all well-understood. This paradox derives in part from our not knowing the etiology of MS and in part, from misconceptions about immunity itself. That MS is an immunological disease is without doubt, but whether the immune response initiates MS or is itself triggered by underlying neurological dysfunction that later persists as progressive MS, is not resolved.1

In this issue of MS Journal, Johannes Van Noort advances a viewpoint that addresses two aspects: whether pre-inflammatory oligodendrocyte stress signals act as a stimulus for entry of T cells to the central nervous system (CNS) and the role of the cytokine interferon gamma (IFNγ) in MS. The former issue also embraces a deeper question: whether a normally-constituted immune response should have the ability to initiate an autoimmune attack on the CNS, or whether this reflects an aberrant immune response.

The word aberrant has become quite widely used in this context and it is important to understand what is meant when it is used. It can possibly describe autoimmunity per se, where the outcome is undesired and so, ‘aberrant.’ It can also be used to mean that there is something fundamentally ‘different’ about the immune response in MS.

Van Noort addresses the latter possibility and argues that there is nothing intrinsically ‘different’ about the immune response in MS. This view is in fact shared by many immunologists. Autoimmune attack on an organ or tissue does not represent a deviant immune system, but one that is blindly following orders to respond wherever the T-cell receptor is engaged, with appropriate costimulation. The latter is a movable feast and primed T cells that have, for instance, recently encountered viral epitopes presented by a professional antigen-presenting cell (APC) are relatively easily triggered. Whether or not T-cell priming involves actual molecular mimicry, what is required for encephalitogenicity is that the T cell recognize MHC-associated peptides that are also presented in the CNS.2 As Van Noort reminds us, it has been amply demonstrated that myelin-specific T cells can be isolated from peripheral blood, even of healthy individuals. As befits a perfectly normal immune system, such primed T cells then patrol the body in a surveillance mode. Recognition of CNS antigen would then induce an autoreactive response. Although the outcome may not be desired, this does not represent an aberrant immune response.

Where does such recognition occur? Current consensus holds that dendritic cells (DC) in the subarachnoid and post-capillary venule perivascular space present a sampling of intra-CNS antigenic peptides. Because they are accessible to primed or activated T cells, this can initiate subsequent trans-glia limitans migration and T-cell entry.2 Of course, there is a chicken-and-egg problem here. The extent to which myelin peptides should normally be presented by perivascular DC, or whether such presentation represents a sequela of CNS inflammation, is not well understood. What Van Noort suggests is that such DC might present entities deriving from stressed oligodendrocytes. Oligodendrocyte stress may precede frank MS-related inflammation.3 The proposal that the small heat-shock protein HSPB5 or alpha-B-crystallin might recruit T cells has some attractive aspects, but not the least that HSPB5 has already been shown to induce experimental autoimmune encephalomyelitis (EAE). This would represent a working example of ‘Inside-Out’ MS.1

Some aspects need to be considered. One is whether normal myelin turnover can generate the necessary DC-associated peptides. The balance of reported evidence suggests that DC from unmanipulated CNS do not present endogenous peptides even to cell lines, and a prior event such as inflammation, demyelination or pre-active white matter lesions seems to be required. One must be cautious in extrapolating from this to initiation of MS, because neither a mouse nor normally appearing MS white matter can tell us the status of CNS DC in an individual prior to their MS diagnosis.

Another potential issue is tolerance. Although of enormous immunological interest, the significance for MS that all of the usual suspect myelin proteins (myelin basic protein, myelin oligodendrocyte glycoprotein, proteolipid protein) are expressed in the thymus5 remains uncertain, as (presumed) autoimmune disease was not averted. Even though central tolerance may not be absolute, thymic selection likely acts as a checkpoint. Whether this also holds for HSPB5, and whether that makes any difference to eventual autoimmunity, are unanswered but important questions. Nevertheless, regardless of whether HSPB5-specific T cells are subject to central tolerance, or are primed by cross-reactive recognition of pathogens, Van Noort argues persuasively that the immune response against them is not intrinsically aberrant.
A second focus is whether the T cells that initiate MS should secrete a select profile of cytokines, and which ones they are. The Th1/Th17 paradigm is by now well-established, but it needs to be kept in mind that the possibilities for polarizing a T-cell response that exist in experimental rodent systems likely do not apply in the human patient. Indeed, crossover T cells are described in MS as well as in EAE, and a decade of binary positions on this topic is giving way to more nuanced perspectives. Van Noort argues for a role for IFNγ, a classical pro-inflammatory cytokine that is the hallmark of Th1 responses. Despite this cytokine showing an equivocal effect in rodent models, it is the only cytokine whose pathogenicity is directly demonstrated in MS. Perhaps no further case need be made. At the same time, an appreciation is growing of the complexity underlying the role of IFNγ; specifically, the possibility that it may exert a regulatory role when expressed within the CNS, versus a pro-inflammatory role in the periphery (where it was applied to MS patients), which is extrapolated from the fact that IFNγ exerts different effects at different stages of disease. A benefit for MS patients from antibody blockade of IFNγ has been reported, which by the previous logic would be more consistent with a peripheral effect. The role proposed by Van Noort would be in initiation of CNS inflammation and so, arguably more peripheral than parenchymal.

These are not novel topics for MS immunologists. The fact that they still provoke debate reflects the complexity both of MS and of immunology itself.

**Conflict of interest**

The author declares that there is no conflict of interest.

**References**


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