Commentary

Experimental autoimmune encephalomyelitis (EAE) is an animal model of the human demyelinating disease, multiple sclerosis (MS). In this model, the autoimmune disease is manifested by the injection of proteins derived from the central nervous system (CNS), such as myelin basic protein (MBP) or myelin oligodendrocyte glycoprotein (MOG), into these animals or by direct transfer of MBP-specific CD4+ class II major histocompatibility complex-restricted T cells into these animals. Subsequently, inflammation and demyelination occurs in the CNS that is similar but not completely analogous to MS in humans. Various therapeutic treatment strategies and compounds have been tested on this "incomplete" model, with potential relevance to humans.

One such potential compound is Vitamin A. Vitamin A has bioactive compounds called retinoids (retinol, retinal and retinoic acid), most often obtained from certain plants, meats and fortified foods. Vitamin A has been found to regulate a wide range of biologic processes, including cell proliferation, differentiation and morphogenesis.[1]

The experimental administration of retinoids has had positive effects in various animal models of

autoimmune diseases, including EAE. Studies suggest that ligands bound to retinoid X receptors may play a role in the antiinflammatory effects on this mouse model.[2] It has been demonstrated that 9-cis-RA may inhibit the production of nitric oxide as well as pro-inflammatory cytokines TNF-a, IL-1B and IL-12-p40 by lipopolysaccharide-stimulated microglia.[3] Retinoids, like the synthetic AM80 with higher stability, increased half-life, higher potency and improved spectrum of actions with receptor specificity, have shown IL-6 inhibitory properties thus potentially mitigating the course of EAE animals.

Although it is unclear how much of the animal data may translate to human physiology, various attempts at closing the gap between theories developed in the lab and the reality of treatments to humans have been made. All-trans retinoic acid (tRA) was tested for its effects on proliferation and cytokine expression in human autoreactive T cells, and showed that tRA decreased human lymphocyte proliferation *in vitro* in a dose-dependent manner.[4] A study by Royal *et al.* suggests that there may be an association between plasma retinol levels and clinical disease activity in patients with MS. They assessed the circulating levels of retinol, the major dietary retinoid detectable in blood, and found some correlation with inflammatory neurologic processes.[5] Although this finding was not specific for MS patients, the studies have shown a possible benefit to Vitamin A supplementation in these patients. Furthermore, they also observed the expression of RXR-beta and gamma subtypes by immune cells treated with IFN-B1a, suggesting that there may be some therapeutic value and possible synergistic benefit when combined with Vitamin A.

There have been hypotheses that insufficient Vitamin A in the diets of young infants may lead to a higher incidence of MS in adulthood.[6] Although contrary at first glance, it is important to note that Vitamin A may play different roles in the immunomodulation process in the pre- and post-thymus maturation phase of human development. Vitamin A in higher doses in childhood may lead to decreased immunesurveillance and more autoreactive T-cells later in life, whereas, later in life, the immunosuppressive effects may contribute to a lessening of the disease.

Just as Vitamin D has been implicated in multiple immune-mediated phenomena, it appears that Vitamin A and its derivative retinoids, like all-trans and 9-cis retinoic acid or retinol, have immune-modulating effects as well. The role of retinoic acid, retinoids or their receptors in neurological disorders like MS continues to be worked out. There is increasing evidence suggesting that MS is IL-17 autoimmune inflammatory-mediated and that the IL-17/23 axis of inflammation and the role retinoic acid plays in this process further implicates Vitamin A as a possible critical component in MS physiology.[7]

However, some fundamental questions still remain. First, are retinoids or Vitamin A levels truly low in MS patients? There have been a few studies looking at Vitamin A and retinoid levels in MS patients. The results have been mixed with some studies showing differences in Vitamin A levels or derivatives while others have not. Although studies conducted by Royal *et al*. implied that inflammatory neurologic diseases in general, including patients with MS, resulted in low retinol levels; Zhang *et al*., analyzing the intakes of carotenoids among two large cohorts of women, showed that higher intakes did not reduce the risk of MS.[8]

Animal and cellular studies have demonstrated immunomodulating effects of retinoids. Changes in T-cell populations and levels of interleukins, such as IL-17 and IL-6, appear to be modulated by retinoic acid receptors such as ROR-gamma-t and RXR.[9] It remains to be seen if these findings are perpetuated in MS patients. It also appears that retinoic acid may play a role in remyelination, as seen in the EAE model.[10]

The article, "The Effect of vitamin A supplementation on stimulated T-cell Proliferation with Myelin Oligodendrocyte Glycoprotein in Patients with Multiple Sclerosis," by Jafarirad *et al.* demonstrates that Vitamin A may play a role in the proposed sentinel event in autoimmune-mediated demyelination of MS.[11] Although MOG may not be the antigen involved in autoimmune reactivity in MS patients, the fact that the EAE model and human-derived T-cells reacts with it may provide some parallel to the events leading to MS disease in patients.

The study demonstrated that MOG reactivity in combination with calf-derived serum by human T-cells was abated with the pre-treatment of Vitamin A. However, a similar reaction was not seen when MOG and human-derived serum was used. There was a reduction in the cell proliferation in the Vitamin A-supplemented group that was statistically significant. It was also unusual that PHA did not elicit a similar response.

This study is an interesting first step in determining whether Vitamin A and retinoids have a role in MS. However, it remains unclear if there are times when Vitamin A may be low in MS patients, such as during acute exacerbations. Secondly, it is unclear whether low serum Vitamin A levels in MS patients are associated with low levels of other retinoids like retinoic acid in these patients. Lastly, do high or low levels of each of these

retinoids correlate to disease severity or progression; and, do different retinoids have differing effects. Additionally, what co-interactions do these retinoids have with Vitamin D and the Vitamin D receptor (VDR), as certain retinoid receptors and VDR co-dimerize.[10,12] They may have combined roles in MS-associated gene expression and physiology. These questions remain to be answered.

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