

UV radiation, vitamin D, and multiple sclerosis

Multiple sclerosis (MS) has a striking geographical distribution inversely paralleling that of UV radiation (1). The involvement of UV radiation in the formation of vitamin D led to the suggestion that vitamin D biology is the sun-related factor influencing MS risk (1). We thus read with interest the study showing that UV radiation could suppress experimental autoimmune encephalomyelitis (EAE) independent of vitamin D production (2). As this has significant implications for public health measures attempting to prevent MS, several points need to be considered.

MS susceptibility is determined by a complex interplay of genetic and environmental factors. Some environmental exposures influence the risk of MS many years before onset (1), and great strides have been made toward identifying risk factors (1). Without taking this knowledge of MS into account, EAE models cannot truly represent MS etiology, as highlighted by the failure of EAE to evaluate putative therapeutics (3). Studies in EAE models therefore cannot unequivocally be extrapolated to answer the question of whether UV radiation or vitamin D is more important in MS.

Disregarding the EAE caveat, the study conclusion is that UV treatment suppresses EAE independent of a biomarker for vitamin D status (25-hydroxyvitamin-D). However, what is meant by suppression? Neither continuous UV or 25-hydroxyvitamin-D treatment reduced the incidence of EAE by any significant degree, whereas the activated metabolite of vitamin D, calcitriol, reduced EAE incidence by 60%. Furthermore, the control mice, i.e., those not treated with UV and those not treated with vitamin D in the different experiment arms, had significantly different peak severities (difference of 1.1) and cumulative disease scores (difference of 29). Why control groups would differ this much is unclear and questions the meaning of “suppression.”

It is well known that many tissues express the calcitriol generating enzyme 1- α -hydroxylase, but the timing and tissue specific effects of the relationship among UV radiation, 25-hydroxyvitamin-D, and calcitriol is not yet conclusively known. Crucially, calcitriol levels in the central nervous system have previously been demonstrated to be important in protection against EAE (4), and thus we were surprised that detailed measurement of calcitriol levels in a number of tissues and at a wide range of time points was not performed.

In summary, we believe that the data from Becklund et al. (2) cannot be used to reliably inform us as to whether UV radiation exerts its protective effects in MS independently of vitamin D. An improvement to the study design would be to see if UV exposure exerts similar effects on EAE in 1- α -hydroxylase- or vitamin D receptor-KO mice. Regardless, the most conclusive answer for MS will come from prospective studies of vitamin D supplementation, although any trial will need careful thought and planning. Toxicity is one potential issue, but high doses of vitamin D (as much as 280,000 IU per week) have been shown to be safe in patients with MS (5) and sufficient to maintain individuals at circulating levels preliminarily indicated to protect against developing this devastating disease (1).

Lahiru Handunnetthi^a and Sreeram V. Ramagopalan^{a,b,1}

^aWellcome Trust Centre for Human Genetics and Department of Clinical Neurology, University of Oxford, Oxford OX3 7BN, United Kingdom; and ^bBlizard Institute of Cell and Molecular Science, Queen Mary University of London, Barts and The London School of Medicine and Dentistry, London E1 2AT, United Kingdom

1. Handel AE, Giovannoni G, Ebers GC, Ramagopalan SV (2010) Environmental factors and their timing in adult-onset multiple sclerosis. *Nat Rev Neurol* 6:156–166.
2. Becklund BR, Severson KS, Vang SV, DeLuca HF (2010) UV radiation suppresses experimental autoimmune encephalomyelitis independent of vitamin D production. *Proc Natl Acad Sci USA* 107:6418–6423.
3. Sriram S, Steiner I (2005) Experimental allergic encephalomyelitis: A misleading model of multiple sclerosis. *Ann Neurol* 58:939–945.
4. Spach KM, Hayes CE (2005) Vitamin D3 confers protection from autoimmune encephalomyelitis only in female mice. *J Immunol* 175:4119–4126.
5. Kimball SM, Ursell MR, O'Connor P, Vieth R (2007) Safety of vitamin D3 in adults with multiple sclerosis. *Am J Clin Nutr* 86:645–651.

Author contributions: L.H. and S.V.R. wrote the paper.

The authors declare no conflict of interest.

¹To whom correspondence should be addressed. E-mail: sramagopalan@gmail.com.