Vitamin D and the HLA locus help to explain the relationship between autoimmune and allergic diseases

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Autoimmunity has been defined as a T-helper cell type 1 (Th1) immune phenomenon, which creates an inflammatory response in the body against normal body substances (tissues/proteins). Allergy on the other hand is a T-helper cell type 2 (Th2) immune response to foreign antigen that also leads to inflammation. Because these two classes of immune disorders involve different clusters of differentiation 4 (CD4+) T-helper cell subsets, hitherto they have been considered immunologically separate and distinct – i.e. not caused by the same underlying genetic and environmental factors. However, in this issue of the PCRJ, Maas and colleagues have studied the co-occurrence of these immune diseases in families in the general population of the Netherlands, and have found that a diagnosed autoimmune disease in the parents suggested a roughly 2-fold increased risk of allergic disease in the eldest child.1 Their data suggest that there may be more of a common aetiology for these two types of immune disorders than previously thought.2,3

Critical to the interpretation of the paper by Maas et al. is the issue of disease classification. The investigators used the International Classification of Primary Care (ICPC) diagnoses to define autoimmune disease in the parents. This system identifies the seven most common autoimmune diseases: psoriasis, rheumatoid arthritis/ankylosing spondylitis, ulcerative colitis/Crohn’s disease, diabetes mellitus type 1, and multiple sclerosis. There are many more autoimmune diseases that were excluded from consideration because they are rare and hence not included in the ICPC. Including these rarer disorders might have made the results of the study even stronger. The allergic diseases classified included allergic asthma, hay fever, atopic dermatitis, and atopic conjunctivitis. This disease classification was relatively complete and thus misclassification bias is unlikely to have occurred for this outcome. Another methodological concern is that non-paternity was assessed and judged to be at an acceptable level; again, more stringent criteria for non-paternity would only have strengthened the results.

As noted by the authors,1 epidemiological data suggesting familial aggregation of these types of immune disorders in families is conflicting, and for some studies, statistical power has been limited by the low prevalence of the autoimmune diseases. Again, as noted by the authors, small sample size was an issue in some of the prior studies, as well as incomplete ascertainment of autoimmune disease.4,5 In contrast to the autoimmune diseases, the prevalence of allergy is high, and thus familial aggregation can occur simply by high disease prevalence alone.

The central question is whether this disease co-occurrence is just due to the nonspecific “environmental and epigenetic and genetic effects” alluded to by Maas and colleagues,1 or is there a hypothesis that might explain the underlying co-occurrence of autoimmune and allergic diseases in families?

I think there is a hypothesis as to what has caused a rise in prevalence of both Th1- and Th2-mediated immune diseases. First, the rise in both Th2 and Th1 immune diseases suggests that the immunological defect is at the next level up from the CD4 +, Th1, and Th2 cell, namely at the level of the T-regulatory cell (T-reg); these cells control both Th2 and Th1 inflammatory responses. These T-reg cells are in turn under the control of vitamin D, corticosteroids, and the cellular cytokines Transforming Growth factor Beta one (TGFβ1) and
interleukin 10 (IL10). Higher levels of vitamin D lead to up-regulation of IL10 and TGFβ1, the subsequent up-regulation of effector T-regulatory cell activity, and the down-regulation of inflammation (both Th1 or Th2). In addition, higher levels of vitamin D lead to decreased dendritic cell signaling to the T-regulatory cells, which means a decreased antigenic input to these controller cells. Finally, vitamin D levels are important epigenetic activators that establish signaling between mother and fetus and induce downstream gene expression in over 5000 genes when comparing the sufficient and the deficient states of the mother.

There are several features that are attractive about this theory. First, it provides a plausible set of environmental factors – e.g. sun exposure, cod liver oil intake, and subsequent vitamin D levels – to explain the epidemiology of a rise in both Th1 and Th2 disease over the past 50 years, a time when vitamin D levels in the population have been decreasing. The causes of the epidemic of vitamin D deficiency and its role in fetal development and disease have been well documented.

However, whilst I believe that vitamin D is responsible for much of the fetal origins of disease, vitamin D deficiency alone cannot account for the wide variation in clinical disease phenotypes seen for both autoimmunity and allergy. As noted by Maas et al.,

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