Vitamin D in Host Defense: Implications for Future Research

Vitamin D plays a key role in the human immune response to infections. Vitamin D induces the production of the antimicrobial polypeptide cathelicidin (hCAP18/LL37) (1), which has both bacterial and antiviral effects (2). Additional host defense mechanisms of vitamin D include regulation of autophagy (3, 4), regulation of pathways involved in oxidative stress (5), regulation of secretion of inflammatory cytokines and chemokines (3, 6), and stabilization of the endothelium (7). More recently, vitamin D status has been shown to be important in host-microbiome interactions in both respiratory and intestinal compartments (8, 9). Taken together, these actions of vitamin D lead to overall regulation of inflammatory responses, and suggest that vitamin D acts as a switch to both turn on an appropriate inflammatory response and turn it off, particularly if it is excessive or prolonged.

Although the actions of vitamin D as a regulator of acute inflammatory responses are recognized, it remains unclear whether vitamin D's effects remain in the presence of chronic inflammation. This brings us to the current study by Schrumpf and colleagues in this issue of the *Journal* (pp. 749–761), who assessed vitamin D's ability to provide adequate host defense in a model of chronic inflammation using cultured airway epithelial cells (10). In this work, Schrumpf and colleagues used expression of hCAP18/LL-37, as well as vitamin D receptor (VDR), cytochrome (CYP) 24A1, and CYP27B1 (enzymes that metabolize vitamin D), as readouts of the effect of chronic inflammation in cultured primary bronchial epithelial cells (BECs). When these cells were exposed to TNF- α /IL-1 β as an inflammatory stimulus, there was decreased antibacterial activity of hCAP18/LL-37 via increased induction of CYP24A1, the degrading enzyme for 1,25(OH)D, the active form of the vitamin. Of interest, expression of CYP27B1 and VDR was not affected. Thus, the inflammatory milieu led to an impairment of the vitamin D effects. At least part of these effects are mediated via the transcription factor specific protein 1 (Sp1) and the epidermal growth factor receptor-mitogen associated protein kinase pathway, as outlined in the paper.

The authors are very careful to elaborate on the potential deficiencies of this *in vitro* experiment. Precisely because the experiment was performed *in vitro*, we do not know how variation in tissue vitamin D levels might affect the results. Specifically, in this model of chronic inflammation in BECs, would the results have changed if the cells were replete with vitamin D? In acute-infection models of influenza A and respiratory syncytial virus in BECs, pretreatment with vitamin D decreased the inflammatory response of cytokine and chemokine secretions after viral infection, without affecting viral killing (3, 6). It remains to be determined whether cells exposed to adequate vitamin D would be more resilient to chronic inflammation. We have previously shown that improved vitamin D status abrogated the effects of cigarette smoke (a chronic inflammatory stimulus) on lung function decline in older men (11), suggesting that indeed an adequate vitamin D status may provide resilience against the stress of chronic inflammation.

Another critical issue is the relationship between serum levels and tissue levels of vitamin D. To understand this issue, a review of the biochemistry of vitamin D is critical. Vitamin D (cholecalciferol) is either ingested or made from 7-dehydrocholesterol in the skin upon exposure to ultraviolet light, and then is transported to the liver for hydroxylation at the 25 position and then further hydroxylated in the kidney at the 1 position. 25(OH)D3 is measured in blood as a measure of vitamin D status because its half-life is ~ 4 wk, whereas the half-life of cholecalciferol is ~ 4 d and that of 1,25(OH)D3 is ~ 4 h. Emerging data suggest that all three forms of the compound have activity at the cellular level (7). Remember, all of these immune cells have the ability to fully recapitulate the biochemistry described above without resorting to the liver or kidney.

Now let us consider what the impact of this biochemistry is on the intact human subject or patient. The blood levels of these metabolites provide an excellent biomarker for the endocrine effects of vitamin D, such as bone and mineral metabolism, because here the blood level is the determinant of physiologic effect, but they are not as good at reflecting the paracrine effects of vitamin D on the immune system in the tissue. Here the blood level is serving as a proxy variable for the tissue level, which is not directly measurable. Another question that the results of Schrumpf and colleagues do not answer is whether higher concentrations of 25(OH)D3 or 1,25(OH)D3 in cell cultures would be more effective in reversing the effects in this cellular model of chronic inflammation. The finding in their experiment that VDR expression was not affected by the addition of 25(OH)D3 in the context of the inflammatory stimuli (see Figure 3A in Schrumpf and colleagues) suggests that the concentrations of these vitamin D compounds may not have been high enough, because VDR expression is expected to be enhanced by sufficient vitamin D (12). If higher concentrations are more effective, the clinical implication is that higher doses of vitamin D may be needed in chronic inflammatory disorders such as chronic obstructive pulmonary disease, much like what is being studied in disorders such as multiple sclerosis (with vitamin D doses on the order of 10,000 IU/d) (13). This is fertile ground for further study.

More research is currently needed to determine what level of vitamin D in the blood optimizes the function of the human immune system in tissue. This is a critical question for human studies of autoimmune diseases. To a certain extent, this will depend on fat mass because vitamin D is a fat-soluble vitamin; however, we suspect, based on our own research, that serum levels of 40–60 ng/ml are likely to be necessary for optimal immune health in humans. Such levels are significantly in excess of the 20 ng/ml needed for bone health. Unfortunately, Schrumpf and colleagues do not allow us to relate these *in vitro* experiments to serum levels in intact humans. It would be exceedingly helpful if *in vitro* and animal models could report blood levels as well as levels in tissue, thus allowing comparisons to be made. More work is clearly needed to establish a blood–tissue equivalency with certainty, but if we are correct, the degree of vitamin D deficiency worldwide is far greater than previously thought. ■

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